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Recent advances in transition-metal-catalyzed carbene insertion to C–H bonds

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C–H functionalization has been emerging as a powerful method to establish carbon–carbon and carbon–heteroatom bonds. Many efforts have been devoted to transition-metal-catalyzed direct transformations of C–H bonds. Metal carbenes generated *in situ* from transition-metal compounds and diazo or its equivalents are usually applied as the transient reactive intermediates to furnish a catalytic cycle for new C–C and C–X bond formation. Using this strategy compounds from unactivated simple alkanes to complex molecules can be further functionalized or transformed to multi-functionalized compounds. In this area, transition-metal-catalyzed carbene insertion to C–H bonds has been paid continuous attention. Diverse catalyst design strategies, synthetic methods, and potential applications have been developed. This critical review will summarize the advance in transition-metal-catalyzed carbene insertion to C–H bonds dated up to July 2021, by the categories of C–H bonds from aliphatic C(sp^3)–H, aryl (aromatic) C(sp^2)–H, heteroaryl (heteroaromatic) C(sp^2)–H bonds, alkenyl C(sp^2)–H, and alkynyl C(sp)–H, as well as asymmetric carbene insertion to C–H bonds, and more coverage will be given to the recent work. Due to the rapid development of the C–H functionalization area, future directions in this topic are also discussed. This review will give the authors an overview of carbene insertion chemistry in C–H functionalization with focus on the catalytic systems and synthetic applications in C–C bond formation.

1. Introduction

Bond formation and cleavage lead to diverse compounds in organic chemistry. Chemists have been devoting continuous efforts to pursuing direct bond formation in a concise manner. Carbon–carbon bonds are among the most important chemical bonds and many methods have been developed to construct them. Recently, much attention has been paid to C–H functionalization as a promising route to direct formation of C–C and carbon–heteroatom (C–X) bonds, without prefunctionaliza-tion

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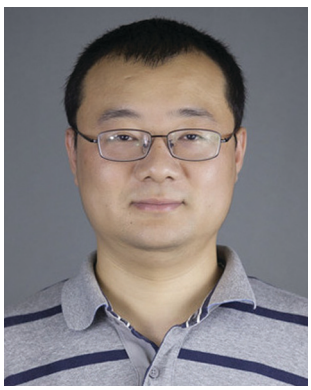
of the starting materials, demonstrating a high atom economy.[1–3] In this area, transition-metal-catalyzed carbene insertion to C–H bonds has attracted rapidly increasing interest. In the early related literature, "C–H insertion"[4,5] instead of the terminology "carbene insertion (in)to C–H bonds"[6] was used to describe the formal C–H substitution by carbene species. "Carbene migratory insertion"[7,8] and "carbene transfer"[9,10] were also used. Although "C–H insertion" is not considered to be strictly termed,[11] it is acceptable with the terminology "carbene insertion" at the same time by organic chemists, and both of them have been used in the recently published reports on such C–H functionalization reactions through transition-metal carbenes. In the presence of a transition-metal catalyst, carbenes are usually generated *in situ* as the transient reactive intermediates by the interaction of the transition-metal and carbene precursor compounds, furnishing a catalytic cycle. As for those carbenes capable of insertion to C–H bonds their precursor compounds can be typically classified into three categories, that is, diazo compounds,[12–20] *N*-tosylhydrazones,[21] and *N*-sulfonyl-1,2,3-triazoles[22] (Scheme 1). Other precursor compounds such as alkynes, *etc.* can also interact with a transition metal compound to generate metal carbenes to undergo carbene insertion reactions.[7] *N*-Tosylhydrazones and their unprotected hydrazone analogs,[23] and *N*-sulfonyl-1,2,3-triazoles are transformed to the corresponding diazo intermediates under basic, oxidative, and/or thermal conditions, which then undergo the carbene insertion reactions (Scheme 2).

Diazo compounds have been widely employed as versatile reagents for synthetic purposes in academic laboratories and industry.[12–20] To modulate the reactivity and applicability of diazo compounds functional groups with different electronic properties are introduced to the diazo carbon atom, which enhances the reactivity of the resultant metal carbenes or stabilizes the metal carbene species during the reaction. Based on the electronic features of such functional groups, the reactivities of diazo compounds or the corresponding metal carbenes can be differentiated as follows: acceptor, acceptor/acceptor, acceptor/donor, donor, and donor/donor (Scheme 3).



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Kaikai Wu studied pharmacy at Inner Mongolia Medical University, Huhhot, China, and received his BSc degree in July 2006. Then he joined Prof. Zhengkun Yu's group at DICP of CAS as a research associate. In July 2016, he completed his MSc degree thesis under the supervision of Prof. Zhengkun Yu. His current research interest is synthetic methodolo-gies and organometallic catalysis.

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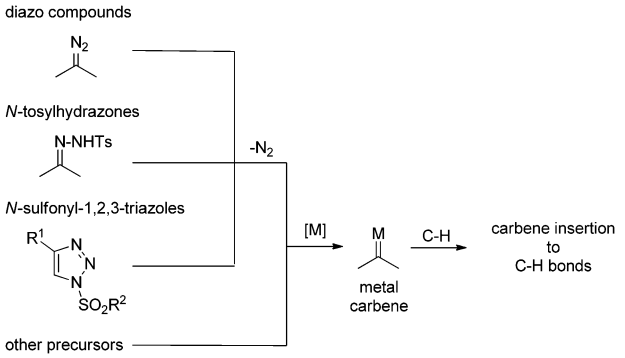
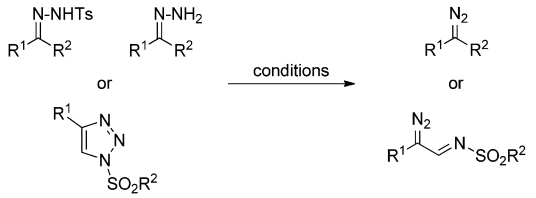
Zhengkun Yu

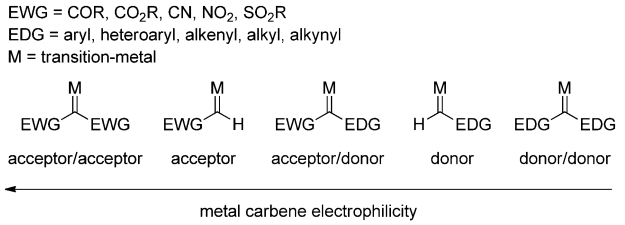
Zhengkun Yu obtained his PhD degree at Dalian Institute of Chemical Physics (DICP), CAS in July of 1995. During October 1995-January 2003 he worked as a post-doctoral fellow or research associate in the labs of Prof. Rudolf Aumann (University of Münster, Germany), Prof. John G. Verkade (Iowa State University, USA), and Prof. Chuck Winter (Wayne State University, USA), and in Waseda University/Japan Corporation of Science and Technology (Japan). He returned to DICP as a professor in early 2003 and has been working on organometallic catalysis.



Scheme 1 Three major categories of carbene precursors for carbene insertion to C–H bonds. M = Transition-metal.



Scheme 2 Diazo generation from (*N*-tosyl)hydrazones and *N*-sulfonyl-1,2,3-triazoles.



Scheme 3 Types and reactivity of metal carbenes for carbene insertion to C–H bonds.

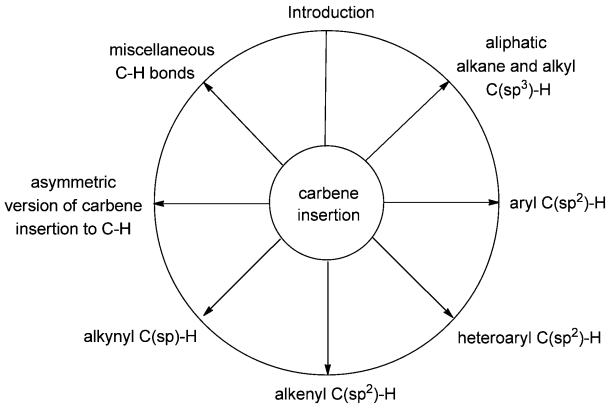
The first two types of metal carbenes are very reactive because the acceptor groups (EWG = electron-withdrawing group) can not stabilize the electrophilic carbene center, which are usually employed in intramolecular insertion reactions *via* formation of a four, five or six-membered cyclic intermediate, resulting in highly selective formation of the target products. An electron-donating group provides extra stability to the carbene center and thus adjusts the reactivity of diazo compounds. The last two types are usually generated from (*N*-tosyl)hydrazones and *N*-sulfonyl-1,2,3-triazoles. Introduction of an EDG (EDG = electron-donating group) to the carbene center dramatically diminishes dimerization of the carbene species during the reaction that EDG-bearing diazo precursor compounds can be used for intermolecular carbene insertion to C–H bonds.

Carbene insertion to C–H bonds, as one of the hot topics in C–H functionalization area, has aroused rapidly increasing interests. Due to the leading contributions by Davies,[24–26] Doyle,[4,6] Wang,[7,27] Fox,[28] and others, important advances have recently been achieved, some of which were highlighted,[11,29–31] and commented in prospects,[32–35] book chapters,[36,37] books,[38,39] and personal accounts.[24–28,40–43] In the recent reviews regarding C–H functionalization and diazo compounds, carbene insertion to C–H bonds is usually composed as an important section. For example, fragmentary summary was made in the following reviews: transition-metal-catalyzed cross-coupling through carbene migratory insertion,[7,8] C–H functionalization *via* iron-catalyzed carbene transfer (insertion) and other reactions,[9,10,44,45] transition-metal-catalyzed insertion reactions with donor/donor carbenes,[23] Co(III), Rh(III), and Ir(III)-catalyzed direct C–H alkylation/alkenylation/arylation with carbene precursors,[46] palladium-catalyzed bridging C–H activation by using alkenes, alkynes, and diazo compounds,[47] Tp^xM-catalyzed (Tp^x = scorpionate ligand, M = Cu, Ag, Au) C(sp^3)–H bond functionalization,[48–50] photocatalytic reactions with diazo compounds,[51] metal-carbene mediated alkylation of unactivated C(sp^3)–H bond,[52] gold-catalyzed transformations of α-diazocarbonyl compounds[53] and C–H activation processes,[54] catalytic C–H functionalization by metal carbene and nitrene insertion[55] and related dirhodium complexes,[56,57] and direct C(sp^3)–H bond activation adjacent to nitrogen in heterocycles.[58] In a limited number of recent focus reviews, topics on specific catalyst systems or catalytic reactions are described. Gold-catalyzed site-selective C–H bond functionalization with diazo compounds,[59,60] Rh(III)/Ir(III)-catalyzed C–H functionalization/annulation *via* carbene migratory insertion,[61] Tp*M-catalyzed C–H bond functionalization of alkanes by carbene insertion,[62] catalytic C(sp^3)–H bond functionalization *via* metal-carbene insertions,[63] site-selective and stereoselective intermolecular C–H functionalization by donor/acceptor rhodium carbenes,[64] synthesis of natural products *via* donor/acceptor carbenes,[65] and dirhodium complex catalysts for selective or enantioselective C–H functionalizations[66–68] were contributed as the focus reviews in this area. It should be noted that in this review only "carbene" is used for the relevant mechanism description in order to avoid confusion although in some reports "carbenoid" is also used for the same purpose.[55]

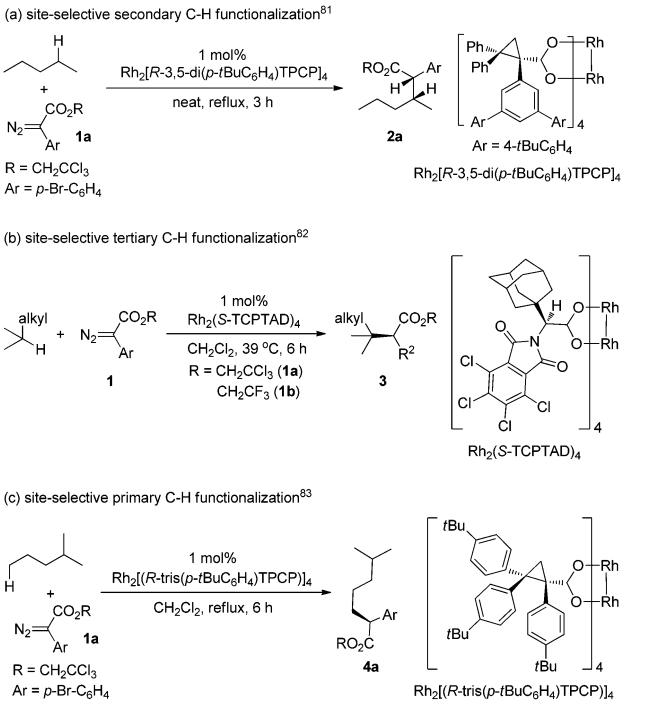
As such a research area develops quickly, it seems quite necessary to make a comprehensive summary of the work achieved *via* transition-metal-catalyzed carbene insertion to C–H bonds. The recent advances in this area may help to guide chemists to seek deep insights into the reaction mechanisms, broaden the protocol generality, and develop suitable catalyst systems for potential applications in organic synthesis. This critical review will be arranged by the C–H reaction types as shown in Scheme 4. In the major sections the content will be presented by the catalyst systems or C–H bond categories from the dominant to the minor, and more attention will be given to the recent work.

2. Carbene insertion to C(sp^3)–H bonds

Carbene insertions involving diazo compounds have been known since 1885.[69–72] Elemental metal catalysts or photo



Scheme 4 Carbene insertion to C–H bonds.



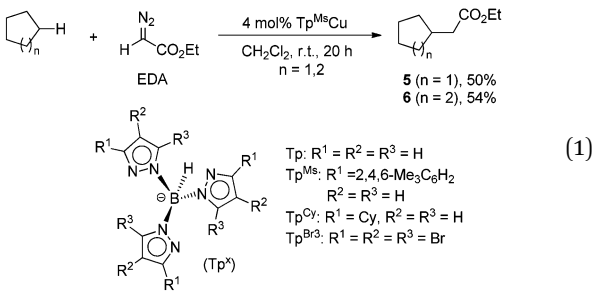
Scheme 5 Recent breakthrough work on transition-metal-catalyzed site-selective C–H functionalization *via* carbene insertion by Davies, *et al.*

irradiation conditions were employed for the decomposition of diazo compounds to be reacted with other reagents.[73] Although homogeneous transition-metal complex catalysts were developed for the same purpose,[74,75] the advance in carbene insertion to C–H bonds staggered over the time.[76,77] Since more and more attention has been paid to the rapidly increasing need for hydrocarbon transformation, the research in C–H functionalization booms into a golden era. Considerable efforts have been devoted to the direct functionalization of non-activated and substituted hydrocarbon derivatives by diazo compounds.[73,78–80] However, highly efficient and selective direct functionalization of C–H bonds in hydrocarbons and derivatives has been challenging. Gratifyingly, breakthrough work has recently been made in this area by Davies and co-workers.[81–83] By means of both the catalyst-control and substrate-control strategies using the donor/acceptor carbenes, bulky chiral Rh(II)-catalyzed highly site-selective, diastereoselective, and enantioselective secondary,[81] tertiary,[82] and primary[83] C–H functionalizations of non-activated alkanes were achieved, respectively (Scheme 5). Immobilization and flow reactor technology has also been successfully developed for the same purpose.[84] These results have provided promising strategies for relevant catalyst design and process development.

In this section, the traditional version of transition-metal-catalyzed carbene insertion to aliphatic C(sp^3)–H bonds in non-activated alkanes and substituted alkane derivatives with diazo compounds and surrogates is summarized. A few examples of enantioselective carbene insertion to aliphatic C–H bonds are presented only for demonstrating the related concepts, and the asymmetric version of transition-metal-catalyzed carbene insertion to C(sp^3)–H bonds will be reviewed in Section 7.

2.1. Carbene insertion to C(sp^3)–H bonds of non-activated alkanes

2.1.1. Tp^xM and related catalysts. In 1974, Scott, *et al.* reported the carbene insertion reaction of the C–H bond of cyclohexane with ethyldiazoacetate (EDA) and diazoacetophenone in the presence of copper sulfate or copper chloride as the catalyst, giving the C–H insertion products in 9–25% yields for the first time.[85] Similar results were obtained with $Cu(acac)_2$ and $P(OMe)_3CuCl$ as the catalysts and dimethyl diazomalonate as the carbene source.[86] In 2002, Pérez, *et al.* reported copper-catalyzed carbene insertion to C–H bonds of cycloalkanes by using a scorpionated-copper(I) complex (Tp^xCu) (Tp^x = homoscorpionate ligand) as the catalyst.[87] The complex catalyst $Tp^{Ms}Cu$ was generated *in situ* from the reaction of the thallium salt of the hydrotris(3-mesityl)pyrazolylborate ligand (Tp^{MS})[88] and copper(I) iodide. In the presence of such a catalyst (4 mol% $Tp^{Ms}Cu$) at ambient temperature, the reaction of cyclopentane with EDA gave the corresponding C–H insertion product ethyl 2-cyclopentyl acetate (**5**) (50%), and cyclohexane reacted to form the desired product ethyl 2-cyclohexyl acetate (**6**) (54%) (eqn (1)). It should be noted that dichloromethane was added to enhance the solubility of the catalyst, the measured relative reactivity of cyclohexane to cyclopentane was 1.00/0.34 by means of competition experiments, and the catalytic system also enabled carbene insertion to the C–H bonds of cyclic ethers.

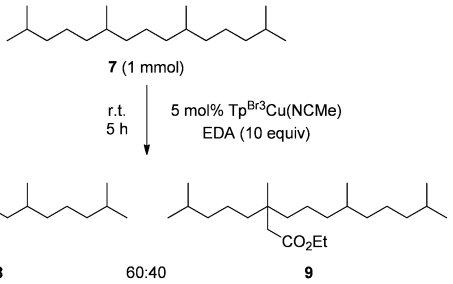


(1)

In order to increase the catalytic activity of the Tp^xCu catalysts for the reaction of cyclohexane with EDA, the

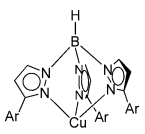
perbromo ligand Tp^{Br3}, which contains nine bromine atoms in the Tp framework ($R^1 = R^2 = R^3 = Br$ in Tp^x), was investigated.[89] It has been known that electron-withdrawing groups on ligands in the coordination sphere can favor the insertion reactions due to the enhancement in the electrophilicity of the metal-carbene intermediates.[90,91] Cu(I) complex $Tp^{Br3}Cu(NCMe)$ was thus prepared from the reaction of $TlTp^{Br3}$ and CuI in acetonitrile in a fashion similar to the synthesis of $Tp^{Ms}Cu$.[87] With 5 mol% loading of $Tp^{Br3}Cu(NCMe)$ as the catalyst, the reaction of cyclohexane with EDA gave the target product ethyl 2-cyclohexyl acetate (**6**) in 90% yield.[92] In a view of application acyclic alkanes are more interesting substrates. Unfortunately, only low conversions (<10%) were reached for acyclic alkanes by using $Tp^{Ms}Cu$ as the catalyst in the reaction with EDA, but $Tp^{Br3}Cu(NCMe)$ exhibited much higher catalytic activity for the C–H functionalization of acyclic alkanes by carbene insertion (Table 1).[92] No primary C–H functionalization occurred in all the cases. With 2-methylbutane as the C–H substrate, the relative reactivities of primary, secondary, and tertiary C–H bonds were differentiated. ^1H NMR analysis showed a 80 : 20 tertiary : secondary molar ratio of products. The carbene insertion product yields ranged from 50–73%. The normalized tertiary selectivity for 2-methylbutane reached 89%. For other branched alkanes the tertiary selectivities 87–>99% were obtained. This tertiary reaction site exhibits the weakest C–H bond as well as the highest steric hindrance, and the electronic effect seems to dominate in this system. Given the similar electronic property, steric factors play the crucial role. The methylene groups adjacent to terminal methyls underwent the reaction in all the cases, while internal CH_2 groups were functionalized to a less extent in linear alkanes or did not react when they were directly linked with a tertiary carbon atom. For 2,5-dimethylhexane no secondary C–H functionalization was observed in the central CH_2–CH_2 unit. The catalytic preference of complex $Tp^{Br3}Cu(NCMe)$ for tertiary C–H functionalization by carbene insertion was then applied to modify higher alkanes such as 2,6,10,14-tetramethylpenta-decane (**7**) with EDA under similar conditions (Scheme 6). The reaction worked well to reach 85% conversion of the alkane and favored formation of the terminal tertiary C–H carbene insertion product **8** with a molar ratio of 60 : 40 for **8** : **9** (**9**: the internal carbene insertion product), and it is noteworthy that carbene insertion to the methylene C–H did not occur. These results have suggested that catalyst control combined with the electronic and steric properties of the aliphatic C–H bonds play the crucial role in the insertion selectivity. Similar regioselectivity order (tertiary > secondary ≫ primary) was also observed with several rhodium catalyst systems.[91] The intramolecular relative reactivities of alkanes *vs.* the catalyst structures of $Tp^{Ms}Cu$, $Tp^{Br3}Cu(NCMe)$, and $Tp^{Cy}Cu$ were investigated in the reaction with EDA.[93] The following catalytic activity order $Tp^{Br3}Cu(NCMe)$ > $Tp^{Ms}Cu$ > $Tp^{Cy}Cu$ was observed in the reactions of alkanes, that is, *n*-hexane, 2,3-dimethylbutane, 2-methylpentane, and methylcyclohexane.

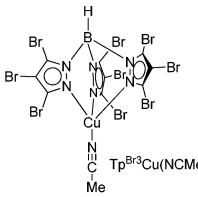
Tp^xAg complexes were also employed to catalyze carbene insertion to the C–H bonds of alkanes. By means of 5 mol% complex $Tp^{(CF3)2}Ag(THF)$[94] as the catalyst the reaction of cyclopentane with EDA as the carbene source at room temperature afforded ethyl 2-cyclopentylacetate (**5**) in 88% yield (Table 2), and the same result was obtained from the reaction of cyclohexane and EDA.[95] In this case, enhancement of the electron-withdrawing capability of the ligands favored the reactivity of the metal-carbene intermediates. Thus, introduction of six trifluoromethyl groups to the Tp^x ligand remarkably improved the catalytic activity of the Ag(I) complex catalyst $Tp^{(CF3)2}Ag(THF)$ compared to that of $Tp^{Br3}Cu(NCMe)$.[92] Notably, the carbene fragments of the remaining EDA ended up as

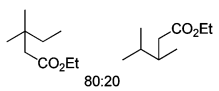
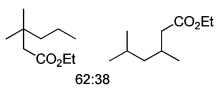
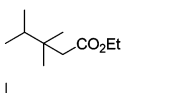
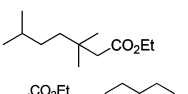
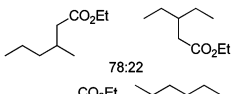
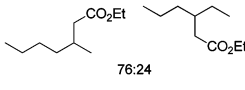


Scheme 6 Selective carbene insertion to the tertiary C–H bonds of 2,6,10,14-tetramethylpentadecane (**7**) with EDA.

Table 1 Insertion of ethyl diazoacetate (EDA) to C–H bonds of acyclic alkanes catalyzed by $Tp^{Br3}Cu(NCMe)$[a]





Alkane	Products[b]	Yield[c] (%)	Selectivity (%)
	 80:20	53	89[d]
	 62:38	73	76[d]
		56	>99[d]
		71	>99[d]
	 78:22	50	74[e]
	 76:24	60	76[e]

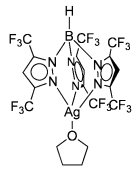
[a] Conditions: alkane (20 mL), CH_2Cl_2 (5 mL), EDA (1 mmol) in the same alkane (10 mL), r.t., in a drybox, 5 h. [b] Product distribution observed by ^1H NMR analysis. [c] EDA-based, determined after total consumption of EDA. [d] Selectivity for tertiary sites, normalized for the relative number of hydrogen atoms. [e] Selectivity for C2 secondary sites, also normalized.

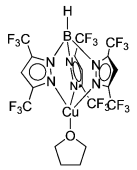
the carbene dimerization products diethyl fumarate and maleate, and the catalyst only showed poor or no catalytic activity for the carbene insertion reaction of cyclic ethers. In a similar fashion, the Cu(I) analog, that is, $Tp^{(CF3)2}Cu(THF)$, only exhibited a moderate catalytic activity for the reaction of cyclopentane or cyclohexane with EDA under the same conditions, giving the corresponding target products **5** and **6** in 58–60% yields. From the reactions of the three acyclic alkanes with EDA in Table 2 the selectivity order for carbene insertion to CH bonds was observed as tertiary ≈ secondary » primary. Similar results were obtained from Dias group.[96] Complexes F_n-$Tp^{4Bo,3Rf}Ag(L)$ (F_n-$Tp^{4Bo,3Rf}$ = a perfluorinated hydrotris(indazolyl)-borate ligand, L = acetone or THF) efficiently catalyzed carbene insertion to hexane, 2,3-dimethylbutane, and 2-methylpentane with EDA, and in the case of hexane the primary C–H functionalization reached a high selectivity (36%) when the Tp^x ligand bears 21 fluorine atoms.[97] A trinuclear cluster $Ag_3(\mu_2\text{-}3,5\text{-}(CF_3)_2PyrPy)_3$ (L = 2-(3,5-$(CF_3)_2$-pyrrol-2-yl)pyridine) was also used for the same purpose.[98]

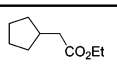
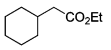
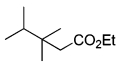
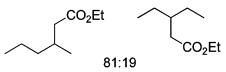
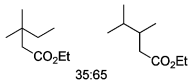
Encouraged by the high catalytic activity of complex $Tp^{(CF3)2}Ag(THF)$ for the carbene insertion reactions of alkanes with EDA as discussed above, the $Tp^{Br3}Ag$ complex catalysts $Tp^{Br3}Ag$(0.5 acetone) and $Tp^{Br3}Ag(THF)$ were then prepared (Scheme 7), and used to catalyze the carbene insertion reaction of the saturated C–H bonds of C4–C6 and C8 linear and branched alkanes (Table 3).[99] In addition to the tertiary and secondary sites, the primary C–H bonds of the studied alkanes could also be inserted with EDA. The primary to secondary ratio of the carbene insertion products for *n*-pentane (29 : 71) is similar to those obtained in the metal-free, photochemical (32 : 68), and thermal (33 : 67) processes.[90] A similar behavior was observed for 2,3-dimethylbutane, where the primary to tertiary ratio is 60 : 40. In other cases, primary C–H functionalization of the alkane substrates significantly proceeded. These results have suggested that elaborate design of ligands with specific electronic and steric effects may facilitate activation of the primary sites in alkanes.

N-Heterocyclic carbenes (NHCs) were applied for constructing the (pre)catalyst (IPr)CuCl (IPr = 1,3-bis(diisopropylphenyl)-imidazol-2-ylidene) for carbene insertion reactions of alkanes, amines, and alcohols with EDA.[100] A gold(I)–NHC complex which was generated from the corresponding (NHC)M′X complex and $AuCl(SMe_2)$, that is, (IPr)AuCl, exhibited a potential for the functionalization of benzene and benzylic C–H bonds by carbene insertion.[101] Thus, complex (IPr)AuCl and its analogs of type (NHC)AuCl were explored for carbene insertion to the C–H bonds of non-activated alkanes (Scheme 8 and Table 4).[102] It was found that complexes (NHC)MCl (M = Au, Cu)

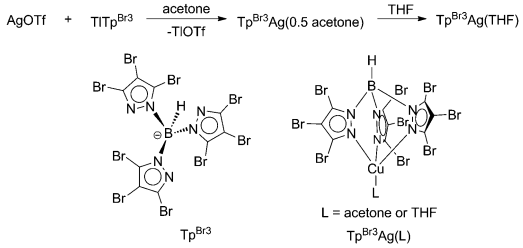
Table 2 $Tp^{(CF3)2}Ag(THF)$-catalyzed carbene insertion to C–H bonds of alkanes with EDA[a]


$Tp^{(CF3)2}Ag(THF)$


$Tp^{(CF3)2}Cu(THF)$

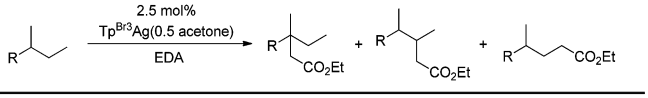
Alkane	Products	Yield[b] (%)
		88
		88
		85
	 81:19	81
	 35:65	87

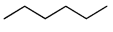
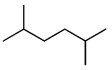
[a] Conditions: alkane (5 mL), EDA (1 mmol) in the alkane (5 mL) was added by an automatic syringe over 1 h to a stirred solution of the catalyst (0.05 mmol) in the alkane, N_2 atmosphere in the absence of light, room temperature, overnight. [b] Isolated yields.



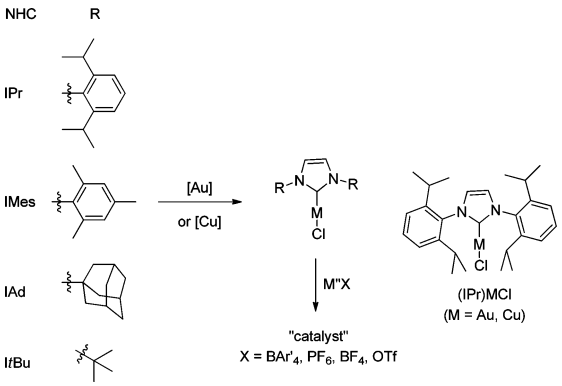
Scheme 7 Preparation of $Tp^{Br3}Ag(L)$ catalysts.

Table 3 Regioselectivity for carbene insertion to C–H bonds of alkanes using $Tp^{Br3}Ag$(0.5 acetone) as the catalyst[a,b]

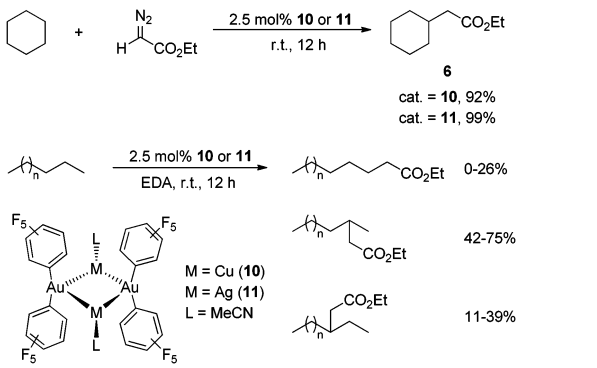


Alkane	Primary sites	Secondary sites	Tertiary sites
	1	2.44	—
	1	2.59	—
	1	—	3.97
	1	1.13	4.8
	1	1.33	1.8
	1	3.95	4.17
	1	1.76	3.71
	1	0.45	0.98

[a] Conditions: alkane (5 mL), EDA (0.75 mmol) added in one portion, $Tp^{Br3}Ag$ (0.5 acetone) (0.019 mol%), room temperature, 2–4 h, N_2, in the absence of light. [b] Values normalized for the relative number of C–H bonds of each type.



Scheme 8 (NHC)MCl precatalysts.



Scheme 9 Heterobimetallic coinage metal-catalyzed C–H functionalization of alkanes with EDA.

Table 4 (NHC)AuCl/NaBAr′$_4$-catalyzed carbene insertion to the C–H bonds of 2,3-dimethylbutane with EDA[a]

NHC ligand	EDA consumed (%)	EDA incorporated to alkane[b] (%)	CO_2Et	CO_2Et
IPr	>99	85	83	17
IAd	>99	74	66	40
I*t*Bu	>99	61	53	47
IMes	>99	25	32	68

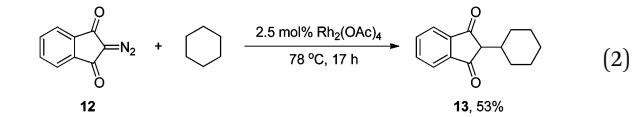
[a] Conditions: alkane (5 mL), EDA (0.5 mmol), catalyst (0.025 mmol), CH_2Cl_2 (5 mL), room temperature, N_2, 12 h. [b] The dimerization products accounted for the total amount of initial EDA.

could only act as the efficient precatalysts for such insertion reactions with EDA in the presence of a suitable counterion such as BAr′$_4$ (Ar′ = 3,5-bis(trifluoromethyl)phenyl)borate, PF_4, BF_4, or OTf. (IPr)AuCl favored carbene insertion to the primary C–H bonds, while (IPr)CuCl precatalyst facilitated carbene insertion to the tertiary C–H bonds of alkanes, and the former precatalyst demonstrated a much higher catalytic activity than the latter. With the well-known non-coordinating anion BAr′$_4$ as the counterion, the tertiary and primary sites were activated in 2,3-dimethylbutane, but the regioselectivity was reversed from Cu (12 : 88, primary/tertiary) to Au (83 : 17, primary/tertiary). Complex (IPr)AuCl was employed in the reactions of other branched alkanes such as 2- and 3-methyl pentanes, and 2,4-dimethylpentane with EDA to render C–H functionalization of the primary sites to be the major reaction. This work has demonstrated the effects from the central metals, stereoelectronic properties of the ligands, and the counterions on the catalytic activity and regioselectivity.

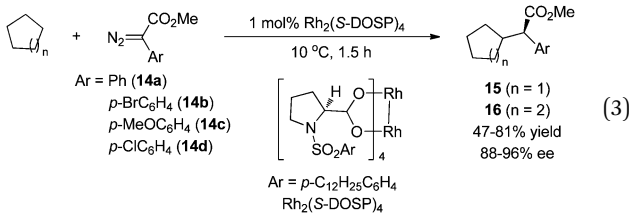
Using a unsymmetrical NHC ligand, that is, the NHC ligand with a pendant CH_2CO_2Et group attached to one nitrogen atom of the NHC ligand backbone, the resultant (NHC-CH_2CO_2Et)AuCl/NaBAr′$_4$ catalyst systems also effected carbene insertion to the C–H bonds of hexane with EDA, giving a primary/secondary regioselectivity of 5/95.[103] When one of the R groups is mesityl and the other is 2,6-i$Pr_2C_6H_3$ in the NHC ligand, the corresponding (NHC-CH_2CO_2Et)/NaBAr′$_4$ catalyst enhanced such a regioselectivity to 31/69, remarkably improving the primary C–H functionalization in hexane. With bimetallic Au(I)-based complexes $[Au_2M_2(C_6F_5)_4(NCMe)_2]$ [(M = Cu(10)), Ag(**11**)] as the catalysts the carbene insertion reactions of alkanes with EDA were also realized (Scheme 9).[104] In the presence of 2.5 mol% **10** or **11** as the catalyst, the reaction of cyclohexane (neat) with EDA at room temperature formed ethyl 2-cyclohexylacetate (**6**) in 92% and 99% yields, respectively. In the case of using the Au–Ag catalyst (**11**), EDA could be added in one portion, avoiding use of the slow addition device (72% yield). When linear pentane and hexane were applied as the C–H substrates, catalyst **10** favored the secondary C–H functionalization without insertion reaction occurring at the primary sites, and catalyst **11** activated all the sites for the carbene insertion reaction to reach 25–26% regioselectivity for the primary sites. Notably, the primary site regioselectivity was up to 45% in the reaction of 2-methylpentane by means of **11** as the catalyst. It is clear that the complex containing the Au-Ag unit induced not only the insertion at those secondary sites but also at the primary sites of these alkanes.

2.1.2. Rhodium and iron complex catalysts. Diazo compounds have been well-known to react advantageously in the presence of $Rh_2(OAc)_4$ and related rhodium catalysts for decades.[105,106] In 1988, Shechter, *et al.* reported $Rh_2(OAc)_4$-catalyzed reaction of 2-diazo-1,3-indan-dione (**12**) with cyclohexane and alkenes.[107] By means of **12** as the carbene source and 2.5 mol% $Rh_2(OAc)_4$ as the catalyst, a mixture of **12** and the catalyst in cyclohexane was refluxed for 17 h to give 2-cyclohexyl-1,3-indandione (**13**) in 53% yield (eqn (2)). As a matter of fact, in the area of transition-metal-catalyzed carbene insertion to C–H bonds of non-activated alkanes chiral Rh(II) complexes have recently been used as the dominant catalysts for these reactions. Herein, only several relevant early examples are briefly presented.[108–110] The majority of examples of chiral rhodium and other metal-catalyzed carbene insertion to C–H bonds of non-activated alkanes will be summarized in the section ''Enantioselective carbene insertion to C–H bonds'' (Section 7). With chiral Rh(II) complex Rh_2(*S*-DOSP)$_4$ as the catalyst, cycloalkanes such as cyclopentane and cyclohexane reacted with methyl aryldiazoacetates (**14**) to afford the carbine insertion products (**15**) (eqn (3)). Under refluxing conditions 55–96% yields with 60–89% ee were obtained.[108] However, the

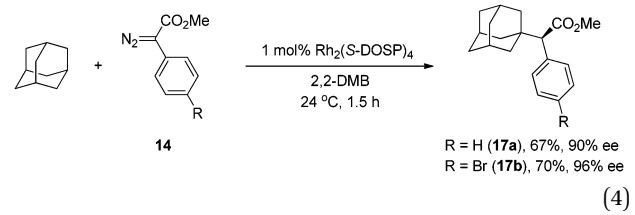
enantioselectivity could be remarkably increased to 88–96% ee when the reactions were conducted at 10 °C.[109] This method was also used to functionalize isobutane (20% yield, 75% ee at −12 °C), 2,3-dimethylbutane (2,3-DMB) (27% yield, 66% ee at 58 °C), and 2-methylbutane (60% yield, 68% ee at 24 °C), exclusively giving the tertiary C–H functionalization products inserted by carbene from methyl (*p*-bromophenyl)diazoacetate (**14b**). In the case of 2-methylpentane at 62 °C, the reaction afforded a mixture of both the tertiary and secondary C–H functionalization products by carbene insertion in a 75% total yield with a molar ratio of 58/42, and 26–86% ee for these isomeric products. It is noteworthy that the reaction of adamantane in 2,2-dimethylbutane (2,2-DMB) produced the target carbene insertion product at the tertiary site in 67% yield with 90% ee. Introduction of a *para*-Br substituent to the aryl moiety in the diazo compound improved the yield and enantioselectivity of product **17b** to 70% and 96% ee, respectively (eqn (4)). Because 2,2-dimethylbutane could not react under the stated conditions, it was chosen as the reaction solvent. This procedure was successfully applied for the synthesis of chiral adamantane-based ligand precursors **19** by using vinyl diazoacetates **18** (eqn (5)).[110]



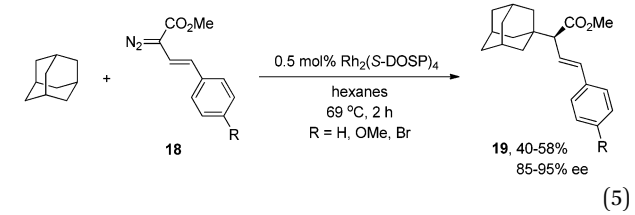
(2)



(3)

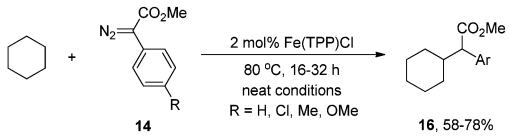


(4)



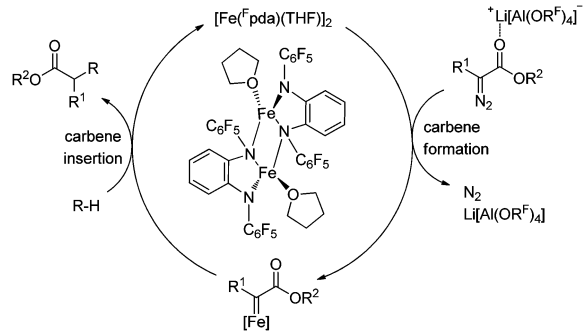
(5)

With 2 mol% Fe(TPP)Cl (TPP = 5,10,15,20-tetraphenylporphyrinnato) as the catalyst, hexane was functionalized by carbene insertion from methyl aryldiazoacetates (**14**) in the neat alkane under refluxing conditions (eqn (6)).[111] Yields of the target products were enhanced about 20%, and fewer unidentified side products could be detected when the reaction was performed under anaerobic conditions at 60 °C compared to the reaction run in air. The target products **16** were obtained in 58–78% yields, which are comparable to those obtained by using the dirhodium tetracarboxylate catalyst Rh_2(*S*-DOSP)$_4$.[109] The rate of Fe(TPP)Cl-catalyzed insertion reaction of hexane was found to be first-order in the concentration of methyl 2-(*p*-chlorophenyl)-diazoacetate, suggesting that generation of a metal carbene complex species is the rate-determining step. Zhu, *et al.*, developed a catalyst system consisting of 1 mol% $Fe(ClO_4)_2$/1.2 mol% N_4 ligand bpmen/1.2 mol% $NaBAr_4$ for the same purpose.[112]



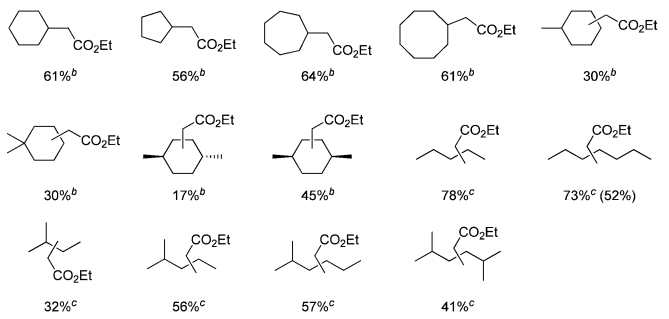
(6)

The combination of an electronic iron(II) complex catalyst and a lithium aluminum-alkoxy salt as the Lewis acid promoter facilitated the C–H functionalization of non-activated alkanes under relatively mild conditions. Such a combination of $[Fe(^{F}pda)(THF)]_2$ (^{F}pda = *N*,*N*′-bis(pentafluorophenyl)-*o*-phenylenediamide) and Lewis acid $LiAl(OR^{F})_4$ (OR^{F} = $OC(CF_3)_3$) was found to be catalytically efficient for the intramolecular carbene insertion to the strong alkyl C(sp^3)–H bonds in α-alkyl-α-diazo esters,[113] and was thus envisioned to enable the C–H functionalization of non-activated alkanes due to the preactivation of the carbene precursor *via* coordination of the Lewis acid to the carbonyl group, facilitating formation of the iron-carbene intermediate, and enhancing the highly electrophilic nature of the iron(II) catalyst (Scheme 10 and Table 5).[114] By using 2.5 mol% $[Fe(^{F}pda)(THF)]_2$ as the catalyst in CH_2Cl_2 or CH_2Cl_2/alkane at 40 °C, cycloalkanes and linear alkanes were functionalized with EDA through carbene insertion (Table 5). For cyclohexane its carbene insertion product (**6**) was obtained in 61% with comparable formation of the dimerization products from EDA. 62% yield was achieved for the reaction of linear hexane when 10 equiv. of it was used. It should be noted that this is the first example of iron-catalyzed intermolecular carbene insertion to the C–H bonds of non-activated linear alkanes. Other alkane substrates were subject to the stated conditions to give the corresponding carbene



Scheme 10 Carbene insertion to C–H bonds using the combination of an Fe(II) complex and $LiAl(OR^{F})_4$ as the catalyst.

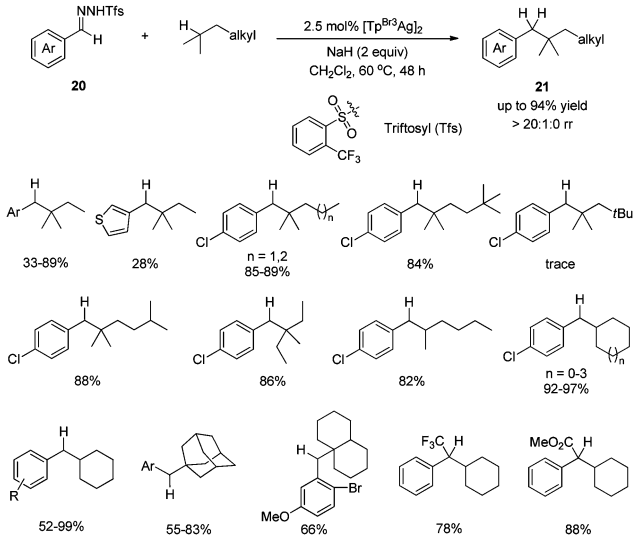
Table 5 $[Fe(^{F}pda)(THF)]_2/LiAl(OR^F)_4$-catalyzed carbene insertion to C–H bonds of non-activated alkanes[a]



[a] Conditions: catalyst (2.5 mol%), EDA (1–2 equiv.), $Li[Al(OR^F)_4]$ (1 equiv.), CH_2Cl_2 (0.08 M), 40 °C, 18 h. Yield obtained by ^1H NMR analysis. Isolated yield in parentheses. [b] Alkane (1 equiv.), EDA (2 equiv.). [c] Alkane (10 equiv.), EDA (1 equiv.).

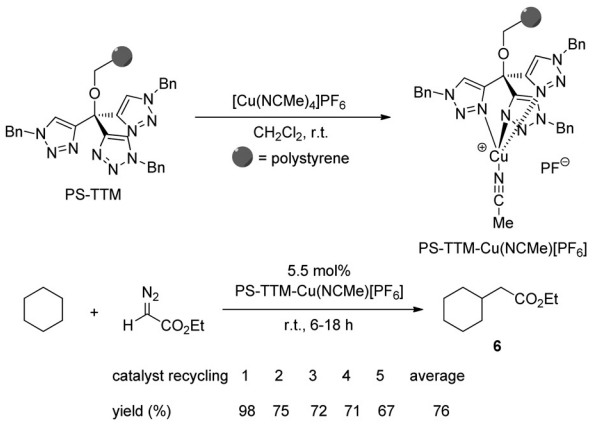
insertion products. In the case of cycloalkanes, the present catalytic system exhibited comparable efficiency and was compatible with various ring size substrates. Substituted cycloalkanes and fused bicycloalkanes showed a lower reactivity. For linear alkanes of different chain lengths they were functionalized by EDA in 32–78% yields, and the steric hindrance had a negative impact on the product yields. Overall, carbene insertion at tertiary sites is preferentially over secondary sites. Among the available secondary C–H bonds the iron(II) catalyst targeted preferentially those less sterically hindered, and carbene insertion can not be induced at the primary sites by this catalyst.

2.1.3. Non-diazo carbene sources, Tp^x analogs, and non-conventional reaction media. In order to realize carbene insertion to the C–H bonds of various non-activated alkanes diverse carbene source compounds, instead of diazo compounds, heterogenized transition-metal catalysts, and reaction media have been explored. In 2020, Bi, *et al.* reported silver(I)-catalyzed selective $C(sp^3)$–H benzylation of simple alkanes by means of *N*-triftosylhydrazones as the carbene source compounds.[115] With 5 mol% $[Tp^{Br3}Ag]_2$ as the catalyst, *N*-triftosylhydrazones **20** of benzaldehydes as the donor carbene precursor, the reaction with non-activated alkanes proceeded in the presence of NaH in CH_2Cl_2 at 60 °C, efficiently affording benzylated alkane products **21** (Scheme 11). The reaction regioselectively occurred at the tertiary sites of the linear alkanes as well as at the secondary sites of cycloalkanes. Up to 94% yields were obtained with >20 : 1 : 0 (tertiary : secondary : primary) regioselectivity. In most of the cases, only minor reactions occurred at the secondary sites in the linear alkane substrates, and no carbene insertion at the primary sites. The insertion reaction was also successful by a one-pot, two-step process through *in situ* preparation of the hydrazones from benzaldehydes and *N*-triflosylhydrazide. DFT calculations reveal three roles of the catalyst: modulating the carbene reactivity, inhibiting carbene dimmerization, and avoiding over insertion of the products. This work represents the first example of site-selective intermolecular insertion of donor carbenes to the $C(sp^3)$–H bonds of non-activated alkanes although the corresponding donor/acceptor carbene (Ph/CF_3 and Ph/CO_2Me) insertion could also be realized (Scheme 11).



Scheme 11 $[Tp^{Br3}Ag]_2$-catalyzed carbene insertion to tertiary C–H bonds of non-activated alkanes.

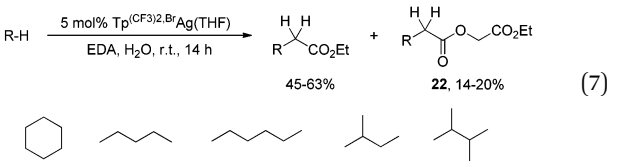
Complex (TTM)CuCl bearing a tris(triazolyl)methane (TTM) ligand is an efficient catalyst for alkyne-azide cycloaddition (CuAAC). Polystyrene-supported versions of TTM, that is, PS-TTM, have also been documented as ligands by modification with Merrifield resins through etherification and can be recycled unlimitedly in CuAAC reactions.[116] The reaction of PS-TTM (f = 0.495 mmol g^{-1}) with $[Cu(NCMe)_4]PF_6$ in CH_2Cl_2 at room temperature led to the formation of complex PS-TTM-Cu(NCMe)$[PF_6]$ bearing a labile acetonitrile ligand (Scheme 12).[117] This heterogenized Cu(I) complex catalyst was applied in the reaction of cyclohexane with EDA under batch conditions. In the first cycle, the target product ethyl 2-cyclohexylacetate (**6**) was formed in 98% yield. After being reused for five times 67% yield was still obtained with an average yield of 76%. This catalyst was also successfully employed for the reaction of ethanol in a continuous flow



Scheme 12 PS-TTM-Cu(NCMe)$[PF_6]$-catalyzed carbene insertion to the C–H bond of cyclohexane.

reactor, Büchner reaction of benzene, and cyclopropanation of phenylacetylene with EDA, respectively, exhibiting diverse catalytic activity.

Reaction media usually play a crucial role in the formation of products and reaction efficiency. Pérez, *et al.* reported the first example of carbene insertion to the C–H bonds of non-activated alkanes by using water as the reaction medium.[118] With 5 mol% $Tp^{(CF3)2,Br}Ag(THF)$ ($R^1 = R^3 = CF_3$, R^2 = Br in Tp^x ligand) as the ligand in water at room temperature, non-activated alkanes such as cyclohexane, pentane, hexane, 2-methylbutane, and 2,3-dimethylbutane were functionalized by carbene insertion with EDA (eqn (7)), respectively. In the case of hexane, 2-ethoxy-2-oxoethyl 2-cyclohexylacetate (**22a**)[119] was formed in 20% yield in the reaction mixture. In other cases, the side products α-(acyloxy)acetates (**22**) were also concurrently formed. It is noted that Lipshutz surfactant TPGS-750-M[120] could be used as an additive to diminish formation of these side products. Generation of **22** is attributed to the silver-catalyzed incorporation of a second carbene unit onto the ester moiety of the functionalized alkane product, which is a consequence of the elevated concentration of the nascent product (RCH_2CO_2Et) in the micelle that favors its further interaction with the catalyst, EDA, and H_2O. It is noteworthy that in neat cyclohexane, a >95% yield was reached for ethyl 2-cyclohexylacetate (**6**). In other cases, the regioselectivity for primary/secondary/tertiary sites are similar to those obtained in neat alkanes (as both the reactants and reaction media).[121] Such a consecutive transformation may be the result of the micellar nature of this catalytic system, which opens an alternative route to transforming non-activated alkanes. In an ionic liquid medium ([bmim]PF_6) at room temperature $Tpm^xCu(NCMe)$ (Tpm^x = tris(pyrazol-1-yl)methane) catalyzed carbene insertion to the C–H bonds of cyclohexane, hexane, and 2,3-dimethylbutane with EDA, affording the corresponding target secondary and tertiary insertion products with similar efficiency and regioselectivity for both the homogeneous and biphasic catalytic systems.[122] However, the two Cu(I) complex catalysts bearing a ligand Tpm^{Ms} (tris(3-mesitylpyrazol-1-yl)methane) or Tpm^{Ms*} (bis(3-mesitylpy-razol-1-yl)(5-mesitylpyrazol-1-yl)methane) could be recovered and reused for several times without loss of catalytic activity in the biphasic medium (ionic liquid/alkane).



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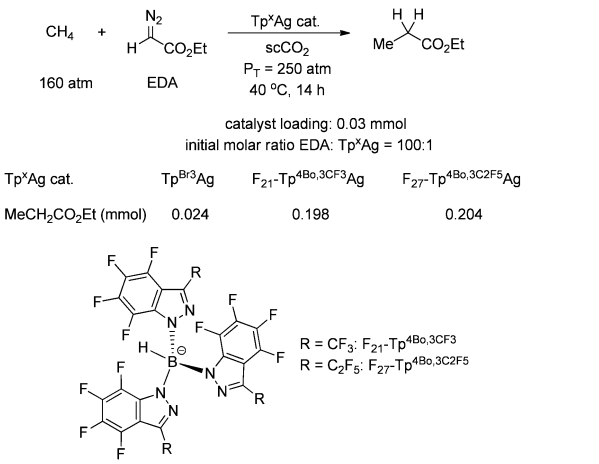
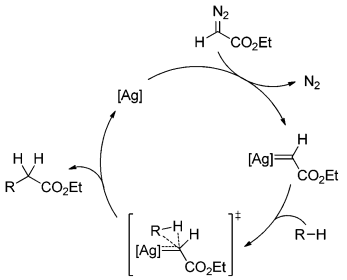
Direct functionalization of the most stable organic molecule, that is, methane, has been challenging.[123,124] In homogeneous systems it is very difficult to transform methane due to its gaseous nature, low solubility in organic solvents, and poor solvating ability. Methane can be transformed to methyl bisulfate *via* C–H activation under very harsh conditions such as in sulphuric acid and at high temperature, or converted to acetic acids by means of palladium and vanadium-based catalysts, respectively.[125,126] As discussed above, carbene insertion to the C–H bonds of non-activated alkanes has been demonstrated a potential to directly functionalize methane in the same way. However, homogeneous functionalization of methane should overcome its volatility and strong C–H energy because insertion to any C–H bond present in the reaction medium would be faster than the reaction of the stronger bonds in methane.

To overcome this problem, Pérez, *et al.* developed a silver-catalyzed carbene insertion process to functionalize methane in supercritical carbon dioxide.[127] Using Ag(I) complexes bearing a perfluorinated indazolylborate ligand to catalyze the reaction of methane with EDA led to 19% yield for the target product ethyl propionate ($MeCH_2CO_2Et$) in supercritical carbon dioxide ($scCO_2$) at 40 °C over a period of 14 h (Scheme 13). The comparative experiments of the reaction of pentane with EDA demonstrated a catalytic activity order to render carbene insertion at the primary sites F_{27}-$Tp^{4Bo,3C2F5}Ag$ > F_{21}-$Tp^{4Bo,3CF3}Ag$ > $[Tp^{Br3}Ag]_2$ (Bo = benzo). With all the three complexes the carbene insertion product ethyl propionate was formed along with diethyl fumarate and maleate from dimmerization of EDA as the by-products. Use of $[Tp^{Br3}Ag]_2$ led to almost stoichiometric formation of the ester product (0.03 mmol catalyst was applied), while complexes F_{21}-$Tp^{4Bo,3CF3}Ag$ and F_{27}-$Tp^{4Bo,3C2F5}Ag$ as the catalyst precursors afforded 0.198 and 0.204 mmol of the target product, respectively, reaching a up to 478 of TON. Herein, it was also demonstrated the higher catalytic activity of F_{21}-$Tp^{4Bo,3CF3}Ag$ than $[Tp^{Br3}Ag]_2$.[128] The control experiments reveal that the solubility of the silver catalyst was enhanced by increasing the portion of CO_2 in the fluid, in good agreement with the well-know capacity of $scCO_2$ to dissolve fluorinated compounds. However, enhancing the CO_2:CH_4 ratios reduced the conversion to the target product because a higher catalyst concentration not only facilitated the formation of ethyl propionate but also promoted the dimerization of EDA to the by-products. The present strategy provides a new protocol to functionalize non-activated alkanes by carbene



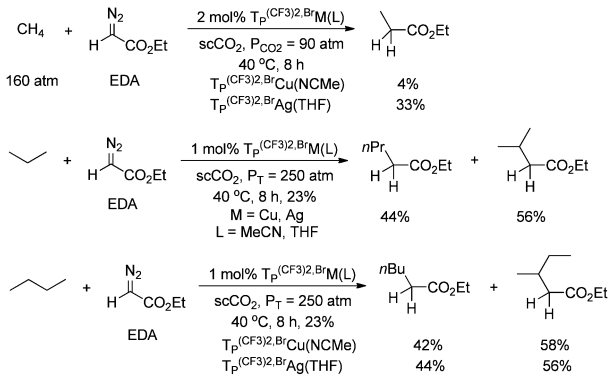
Scheme 13 Ag(I)-catalyzed methane functionalization by EDA. P_T = total pressure.



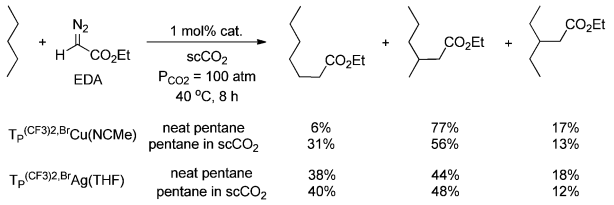
Scheme 14 Proposed mechanism for Ag(I)-catalyzed alkane C–H functionalization by EDA.

insertion. With 2 mol% F_{27}-$Tp^{4Bo,3C2F5}Ag$ as the catalyst and 155 atm of CH_4 and 95 atm of CO_2, formation of the ester product was improved (29%) from the reaction of CH_4 with EDA under the same conditions.[129]

Supercritical carbon dioxide ($scCO_2$) can be used as a promising reaction medium for the C–H functionalization of non-activated alkanes by carbene insertion.[127,129] The relevant protocol using $scCO_2$ as the reaction medium was applied to functionalize other alkane substrates. Using 1 mol% F_{27}-$Tp^{4Bo,3C2F5}Ag$ as the catalyst, the reaction of ethane with EDA gave the corresponding carbene insertion product ethyl butanoate ($EtCH_2CO_2Et$) in 30% yield (eqn (8)).[127] The lower hydrocarbon pressure (35 atm) is in agreement with the lower bond dissociation energy of the ethane C–H bond (≈101 *versus* 104.5 kcal mol^{-1} in methane). For the C–H functionalization of pentane in $scCO_2$, a mixture of insertion products, with a regioselectivity nearly the same as that obtained under the homogeneous conditions (eqn (9)), suggesting that the insertion mechanism operates the same in both medium (homogeneous/$scCO_2$) systems. A plausible mechanism is proposed for the alkane C–H functionalization by EDA (Scheme 14).[127] It involves metal-catalyzed N_2 elimination from the diazo compound followed by carbene insertion. The reactivity of Ag(I) carbene species toward C–H bonds gives a product distribution that is governed, maybe partially by the dissociation energy of the C(sp^3)–H bonds. The Cu(I) and Ag(I)-based catalysts bearing [hydrotris[3,5-bis-(trifluoromethyl)-4-bromo]pyrazol-1-yl]borate ligand ($Tp^{(CF3)2,Br}$), that is, $Tp^{(CF3)2,Br}Cu(NCMe)$ and

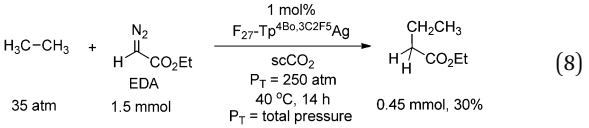


Scheme 15 C–H functionalization of propane and butane with EDA and $Tp^{(CF3)2,Br}M$-based catalysts (M = Cu, Ag). P_T = total pressure.



Scheme 16 Influence of the reaction media in the regioselectivity of alkane C–H functionalization with EDA.

$Tp^{(CF3)2,Br}Ag(THF)$, were successfully used for the functionalization of methane and other light alkanes in $scCO_2$ (Scheme 15),[121] and the same catalytic systems were comparatively investigated in $scCO_2$ and neat alkanes under the same conditions (Scheme 16).[130] These two complexes exhibited different regioselectivities for the reaction of EDA in neat pentane or $scCO_2$ as the reaction medium. Functionalization of the primary sites with Ag(I) complex $Tp^{(CF3)2,Br}Ag(THF)$ remained nearly the same, while Cu(I) complex $Tp^{(CF3)2,Br}$-Cu(NCMe) remarkably increased the regioselectivity of the primary sites from 6% to 31%. Both the complexes behaved the same for the C–H functionalization of 2-methylbutane and hexane with EDA.



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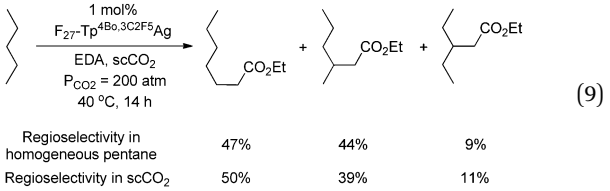

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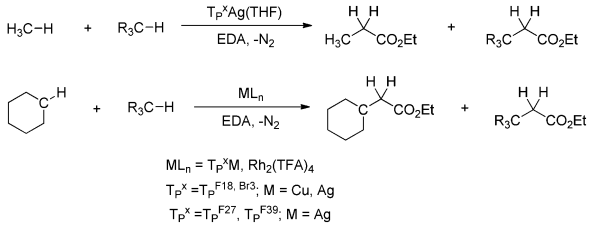
2.1.4. Mechanistic studies. Considerable attention has been paid to the mechanistic aspects of transition-metal-catalyzed C–H functionalization of alkanes by carbene insertion.[131] All the factors such as nature of the metals and their complexes, electronic and steric properties of the carbene source compounds, ligands, reaction media, and reaction parameters have impacts on the catalytic efficiency of alkane C–H functionalization. Olah and coworkers extensively studied the aliphatic electronic substitution of alkanes with a strong electrophile, giving a qualitative σ-donor ability order of the C–C and C–H bonds in alkanes, that is, methane C–H < primary C–H < secondary C–H < C–C < tertiary C–H.[132] In a quantitative fashion, Pérez, *et al.* measured the relative reactivities of the C–H bonds of alkanes as nucleophiles.[133] The reactions of gaseous or liquid alkanes C_nH_{2n+2} (n = 1–8, 29 different C–H bonds) with *in situ* generated electrophiles (silver, copper, and rhodium carbenes) were conducted with methane as a reference (Scheme 17). Such a protocol overcomes the drawback of previous model reactions of alkanes with strong electrophiles

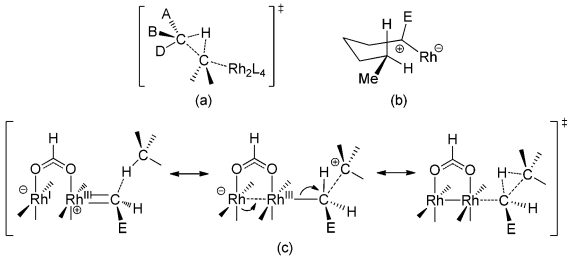


Scheme 17 The competition experiments.

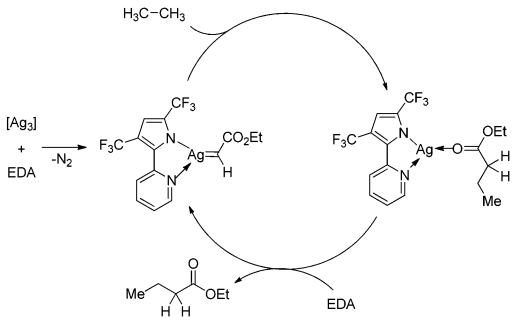
suffering from C–C bond cleavage that precludes direct comparison of the relative reactivities of alkane C–H bonds.

Nakamura, *et al.* investigated the reaction mechanism of alkanes with diazo compounds to form C–C bonds through carbene insertion catalyzed by dirhodium(II) tetracarboxylate.[134] The DFT studies reveal that the reaction is initiated by complexation of the rhodium catalyst and the diazo compound. Driven by the back-donation from the Rh $4d_{xz}$ orbit to the C–N σ*-orbit, nitrogen extrusion occurs to generate a rhodium carbene species. The carbene carbon is strongly electrophilic ue to its vacant 2p orbit. The C–H activation/C–C formation proceeds in a single step *via* a three-centered hydride transfer-like transition state with a small energy barrier. The transition state is proposed in Scheme 18c. Only one of the two Rh atoms acts as the carbene binding site throughout the reaction, and the other Rh atom assists carbene insertion to the C–H bond of the alkane substrate. The second Rh atom behaves as a mobile ligand for the first one to enhance the electrophilic capacity of the carbene unit and thus facilitate formation of the target C–C bond forming product by Rh–C bond cleavage.

The ligand effect was investigated by DFT calculations, suggesting that formation of a silver(I) carbene complex from the trinuclear $Ag_3(\mu_2\text{-}3,5\text{-}(CF_3)_2PyrPy)$ complex[98] and EDA is the rate-determining step for the functionalization of ethane and propane (Scheme 19). For methane, carbene insertion to the C–H bond is overall rate-determining. Theoretical analysis of the charge flow demonstrates that change from separated reagents to the transition state involves charge flow from alkane to the silver carbene atom with the bridging H as a conduit, which is in agreement with the 3e-centered transition state proposed by Doyle.[4] The computational studies of alkane C–H functionalization of methane, ethane, propane, and butane by



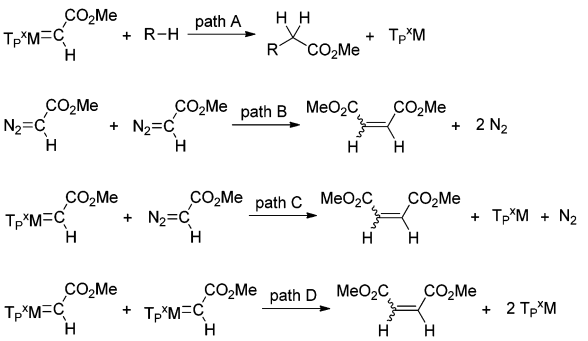
Scheme 18 Transition state models of C–H functionalization with diazo compounds and Rh_2L_4. (a) Doyle's 3e-center model.[4] (b) Taber's model.[135] (c) One metal center-dominating model.[134]



Scheme 19 $[Ag_3]$-catalyzed C–H functionalization of alkanes with EDA.

metallocarbene complexes TpAg = C(H)(CO_2Et), Tp^{Br3}Ag = C(H)(CO_2Et), TpCu = C(H)(CO_2Et), Tp^{Br3}Cu = C(H)(CO_2Et) were conducted.[136] It was found that the reactions were under kinetic control, and the regioselectivity was determined in a step with a low-barrier transition state where the key bond cleavage and formation processes took place in a concerted manner. Based on the DFT and multi-configurational self-consistent field (MCSCF) calculations, Cundaric, *et al.* found that cyclic (alkyl)(amino)-carbenes might be used as the ligands to construct transition-metal complex catalysts for methane C–H functionalization.[137]

In the carbene insertion reactions with ethyl diazoacetate (EDA) or other diazo compounds as the carbene source, dimerization of the diazo compounds concurrently occurred during the C–H functionalization process. In the case of EDA, ethyl fumarate and maleate were always obtained upon the decomposition of EDA during the reaction. Maseras and Pérez, *et al.* conducted theoretical studies on such side reactions.[138] DFT calculations were applied to the mechanistic study of the formation of fumarate and maleate derivatives in a solution containing an alkane substrate, a Tp^{Br3}M catalyst (M = Cu, Ag), and methyl diazoacetate. Such a solution is subject to the experimentally reported conditions for carbene insertion to the C–H bonds of alkanes (Scheme 20). Path A is the generally accepted pathway for carbene insertion to a C–H bond. Paths B-D represent three possible mechanisms for the competitive formation of fumarate and maleate derivatives as the side products. Formation of the side products can be considered



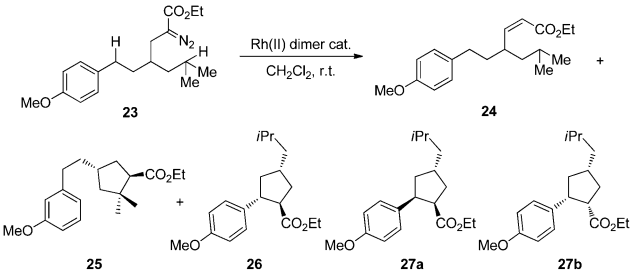
Scheme 20 Transition-metal-catalyzed C–H functionalization of alkanes *via* metal carbene intermediates.

as a formal dimmerization process of the diazo compound. Path B shows a direct reaction between two diazo compound molecules, while in path C the reaction occurs between a metal carbene and a diazo compound. For path D, a transition state between two metal carbene complexes was elusive. Due to the steric hindrance between the Tp^{Br3} ligands, this pathway is precluded. Path B is included in the analysis for the sake of completeness and is expected to have a high barrier. Otherwise, EDA would spontaneously dimerize in the reactor, which is experimentally known not to be the case. In path C, the reactants approach to each other to generate an intermediate which evolves through a concerted transition state to form a C–C bond between the carbene fragment of $MeO_2C(H)C{=}N_2$ and $Tp^{Br3}M$ = $C(H)CO_2(Me)$. Overall, the preferred mechanism proceeds through a direct reaction between a metal carbene complex intermediate and a diazo molecule (path C), which is in agreement with the experimental observations.[127]

2.2. Carbene insertion to alkyl C(sp^3)–H bonds

C–H functionalization by carbene insertion to C–H bonds with diazo and other carbene source compounds has been paid more and more attention. In this area, more efforts have been devoted to transition-metal-catalyzed carbene insertion to alkyl C(sp^3)–H bonds compared to the studies on the functionalization of other types of C–H bonds.[24,52,55,63] Because the dominantly applied catalysts are rhodium complex catalysts with occassional reports using gold, iridium, iron, ruthenium, cobalt, palladium, and other transition-metal compounds as the catalysts, the context herein is arranged by the categories of C(sp^3)–H bonds such as non-activated alkyl C–H bonds, alkyl C–H bonds adjacent to a heteroatom such as oxygen or nitrogen, allylic and benzylic C–H bonds, as well as the relevant mechanistic studies.

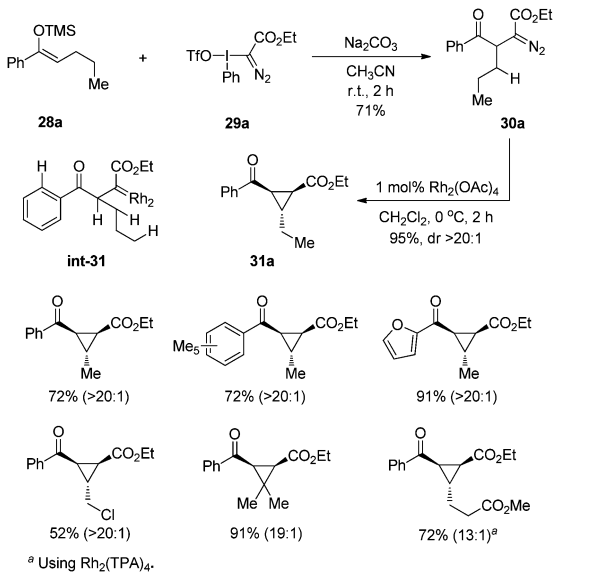
2.2.1. Non-activated alkyl C(sp^3)–H bonds. A non-activated alkyl C(sp^3)–H bond is defined as an aliphatic C–H bond in a functionalized alkyl moiety which is not vincinally linked by an activating group such as an EDG or EWG, a directing group, or a hetroatom (oxygen, nitrogen, and sulfur, *etc.*), which usually assists its activation by a transition-metal. The early development of alkyl C–H functionalization by carbene insertion was focused on the construction of carbocycles such as cyclopentanes, and heterocycles through Rh(II)-catalyzed intramolecular alkyl C–H functionalization with diazo carbonyls or esters.[135,139–144] To achieve highly efficient and site-selective alkyl C–H functionalization, diverse strategies related to catalysts and substrates have been developed. Taking the reaction of alkyldiazoacetate **23** under Rh(II) catalysis as an example,[145] there are at least four potential reactivities: β–H elimination to form **24**, and carbene insertion to various alkyl C–H bonds to result in cyclopentanes **25**, **26**, and **27a**/**27b**, as well as dimmerization of the diazo compound (Scheme 21). With a series of Rh(II) carboxylates and carboxamidates, and the bridged Rh(II) carboxylate (Lahuerta catalyst) as the catalysts the disappearance rate of diazo compound **23** was determined. The observed relative rate constants (k_{ob}) for the reaction of **23** with the Rh(II) complex catalysts varied over a range of $>10^7$.



Scheme 21 Potential reactivity of alkyl C–H bonds to carbene insertion.

The reactivity of the Rh(II) carbene intermediate was investigated by means of the ratio of the sum of (**25** + **26** + **27**) to **24** (insertion *vs.* elimination), the ratio of **25** to the sum of (**26** + **27**) (chemoselectivity), and the ratio of **26** to **27** (diastereoselectivity). It was found that these four measures of reactivity were independent of each other, and the catalyst or ligand-control of the reactivity was remarkable. Thus, continuous efforts have been made to enhance the selectivity for carbene insertion to C–H bonds, and explore highly efficient carbene insertion processes.

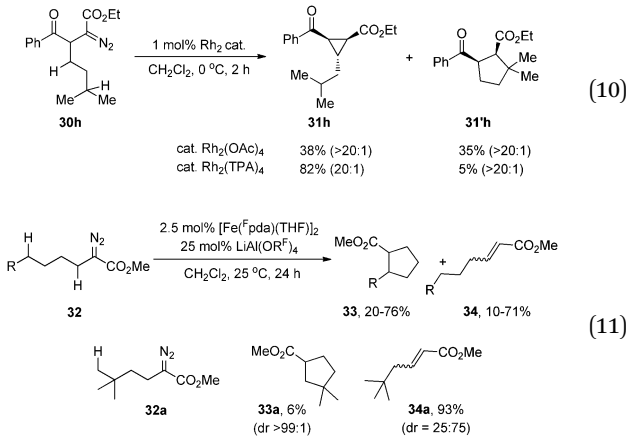
The cyclization strategy using carbene insertion to alkyl C–H bonds was used to construct cyclopropanes. In 2021, Suero, *et al.* disclosed the first electrophilic diazomethylation of ketone silyl enol ethers (**28**) with diazomethyl-substituted hypervalent iodine reagents (**29**) to afford unusual β-diazocarbonyl compounds (**30**) which then underwent intramolecular 1,3-carbene insertion to alkyl C–H bonds, forming multisubstituted cyclopropane derivatives (**31**) with excellent stereocontrol (Scheme 22).[146] In the presence of 1 mol% $Rh_2(OAc)_4$ catalyst, diazo compound **30a** reacted at 0 °C for 2 h to give the target product **31a** (95%, dr > 20 : 1). The analogs of **28a** underwent the same type of 1,3-carbene insertion



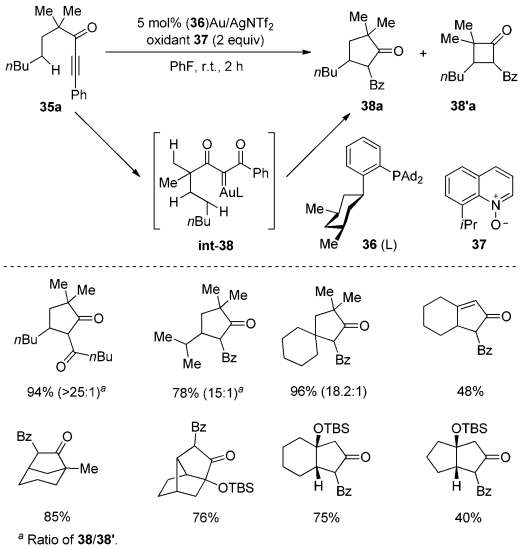
Scheme 22 Cyclopropanation *via* Rh(II)-catalyzed intramolecular C–H functionalization by carbene insertion to alkyl C–H bonds.

reaction to afford cyclopropanes **31** in 35–91% yields. $Rh_2(TFA)_4$ (TFA = trifluoroacetate) and $Rh_2(TPA)_4$ (TPA = triphenylacetate) could also behave effectively in some cases. It is noted that the diazo compound **30h** substituted by a longer carbon chain led to an almost equimolar ratio of 1,3- and 1,5-carbene insertion products **31h** and **31′h** (35%), while use of the bulkier catalyst $Rh_2(TPA)_4$ remarkably hampered the 1,5-insertion reaction and favored formation of the 1,3-carbene insertion product **31h** (82%) (eqn (10). This transformation might proceed *via* a Rh(II) carbene intermediate of type **int-31**.

A combination of electrophilic iron(II) complex $[Fe(^{F}pda)(THF)]_2$ with Lewis acid $LiAl(OR^F)_4$ (OR^F = $COC(CF_3)_3$) effected the intramolecular C–H functionalization of strong (non-activated) alkyl C–H bonds in diazo compound **32** by carbene insertion at room temperature (eqn (11)).[113] The target products **33** were obtained in up to 76% yields with concurrent generation of the β-H elimination products **34** (10–71%). The most challenging primary C–H bond present in **32a** was functionalized to give **33a** in a nearly stoichiometric yield (6%) with major formation of the β-H elimination products **34a** (93%). It is noteworthy that the reached activity and selectivity levels are similar to those of the rhodium carboxylate complex catalysts.

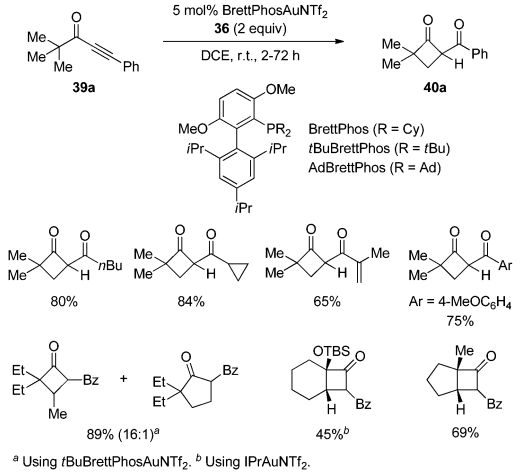


Other carbene source compounds have also been known to participate in C–H functionalization.[147,148] By means of *in situ* generation of the reactive α-oxo gold carbene intermediates *via* gold-catalyzed oxidation of alkynes in replace of diazo compounds as the carbene source, Zhang, *et al.* reported the first intramolecular transformation of ynones **35** (Scheme 23).[149] Cyclopentanones **38** were obtained in up to 96% yields. Substrate conformation control *via* the Thorpe-Ingold effect was attributed to the generally good to excellent efficiencies, enabling synthesis of spiro-, bridged, and fused bicyclic cyclopentanones with a catalyst system consisting of 5 mol% (**36**)AuCl/$AgNTf_2$ in PhF in the presence of the bulky phosphine ligand **36** and an oxidant such as 8-isopropylquinoline (**37**) at room temperature. Ynone **35a** reacted to give the target product **38a** in 70% isolated yield (**38a**/**38′a** = 13.7/1), forming cyclobutanone **38′a** as the byproduct. It was found that acetophenone (8%) was generated as the side product in this transformation. Species **int-38** is assumed to be the reactive intermediate to result in products **38a** and **38′a**. Although three kinds of alkyl

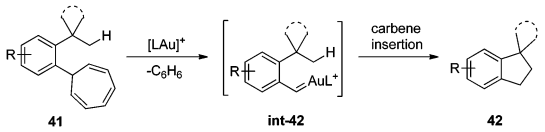


Scheme 23 Au(I)-catalyzed carbene insertion to non-activated alkyl C–H bonds.

C–H bonds are present in **int-38**, the most challenging primary (methyl) C–H bonds kept unchanged under the stated conditions. Using the same strategy with a sterically more hindered Au(I) complex $BrettPhosAuNTf_2$ or $tBuBrettPhosAuNTf_2$ enabled the intramolecular primary (methyl) C–H functionalization by carbene insertion (Scheme 24).[150] In the presence of 5 mol% $BrettPhosAuNTf_2$ as the catalyst, *tert*-butyl alkynyl ketone (**39a**) was transformed to the desired cyclobutane (**40a**). The variants of **39a** also efficiently afforded the products of type **40a** in yields up to 84%. When the methyl group(s) was replaced by other alkyl(s), cyclopentanone derivatives might be formed as the side products. These results have demonstrated catalyst control of the substrate reactivity. By means of $(IPr)AuNTf_2$ as the catalyst the non-activated primary, secondary, and tertiary alkyl C–H bonds in diynes could be intramolecularly functionalized by carbene insertion.[151]

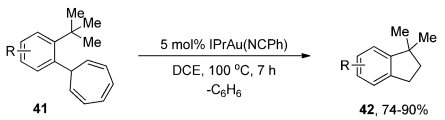


Scheme 24 Au(I)-catalyzed carbene insertion to non-activated primary alkyl C–H bonds.



Scheme 25 Au(I)-catalyzed intramolecular carbene insertion to alkyl C–H bonds with cycloheptatrienes as the carbene source.

Cycloheptatrienes were documented as the carbene source to enable Au(I)-catalyzed cyclopropanation with alkenes,[152] and they were also applied for intramolecular alkyl C–H functionalization.[153] In the relevant investigation of cyclopropanation, indane was detected as the side product (8%) *via* intramolecular carbene insertion to the benzylic C–H bond.[152] A strategy to place the alkyl C–H bond closer to the reactive gold(I) center was used to render such an intramolecular C–H functionalization process (Scheme 25).[153] In the presence of 5 mol% (IPr)Au(NCPh) in dichloroethane (DCE) at 100 °C, 7-(2-*tert*-butyl)phenylcyclohepta-1,3,5-trienes (**41**) reacted to form the target products **42** in 74–90% yields (eqn (12)). However, an adjacent oxygen atom did not benefit the transformation (eqn (13)). When the R groups were TIPS and TBS, only formed in 44–51% yields and the starting materials could not be completely consumed. In the case of TMS, the substrate did not undergo the reaction. Construction of six-membered rings was achieved in a similar fashion by modifying the substrates. Methyl ethers were found to be the suitable substrates for this purpose (eqn (14)). This protocol has demonstrated the application of gold(I) carbenes generated from retro-Büchner reaction (decarbenation) in intramolecular alkyl C–H functionalization.



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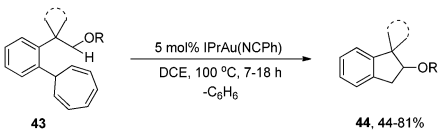

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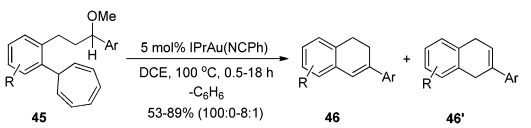
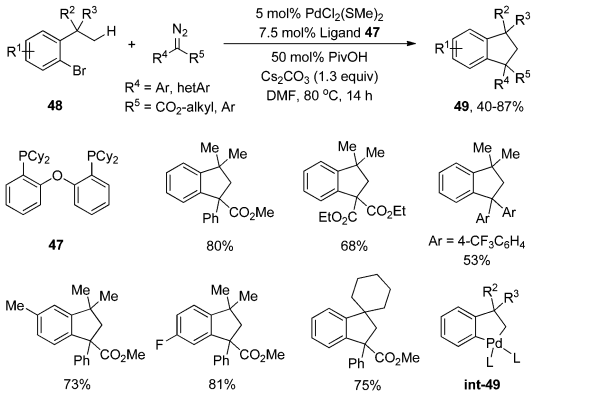


(14)

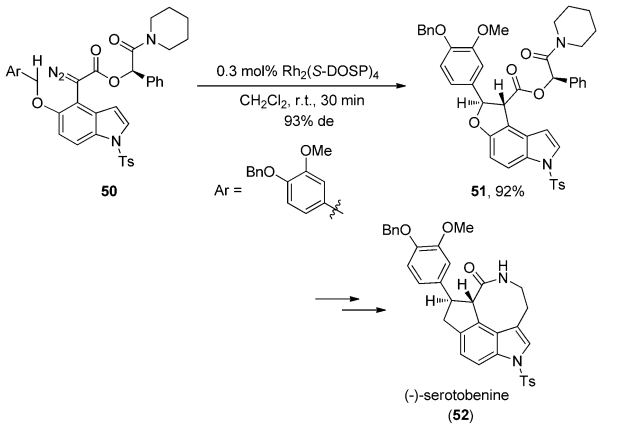
Intermolecular functionalization of non-activated alkyl C–H bonds is more challenging.[154] In the presence of 5 mol% $PdCl_2(SMe_2)_2$ as the catalyst, diphosphine **47** as the ligand, PivOH as the additive in DMF at 80 °C, *ortho*-alkyl-substituted arylbromides **48** reacted with diazo compounds to afford indane derivatives **49** in 40–87% yields (Scheme 26).[155] The protocol features wide substrate scopes of the diazo compounds and bromoarenes. A cyclopalladated complex is proposed as the possible reactive intermediate, which interacts



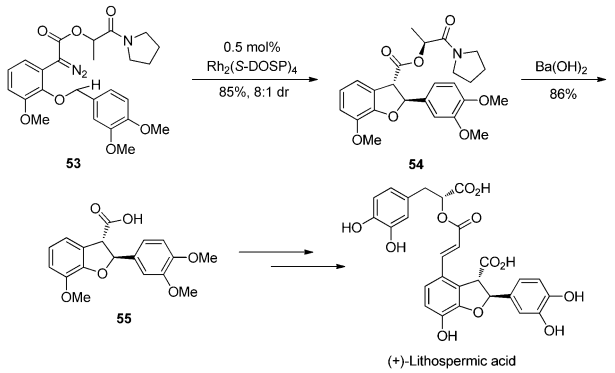
Scheme 26 Pd(II)-catalyzed intermolecular carbene insertion to alkyl C–H bonds.

with the diazo compounds to enable the intermolecular carbene insertion process. It is noteworthy that more discussion/examples will be given in Section 7 for the relevant asymmetric reactions.

2.2.2. Alkyl C(sp^3)–H bonds adjacent to an oxygen atom. Transition-metal-catalyzed intramolecular alkyl C–H functionalization by carbene insertion can offer a direct route to selective construction of O-heterocycles such as furan scaffolds in complex molecules by elaborate design of both the substrate and catalyst systems. The related strategy has been successfully applied for the total synthesis of some natural products and biologically active molecules in which carbene insertion to alkyl C–H bonds is usually used as a key early or late-stage step of the synthetic sequence.[156,157] When intramolecular carbene insertion occurs at the alkyl C–H bond which is activated by an adjacent oxygen atom, a furan unit may be formed in a regio- and/or stereoselective manner. In the presence of 0.3 mol% $Rh_2(S\text{-DOSP})_4$ in CH_2Cl_2 at room temperature, diazo compound **50** smoothly underwent the intramolecular carbene insertion reaction to exclusively afford *trans*-dihydrobenzofuran **51** (92%) in a completely stereoselective manner (Scheme 27).[158] Compound **51** was applied for the synthesis of pentacyclic indole



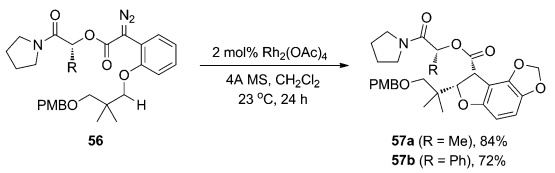
Scheme 27 Rh(II)-catalyzed construction of dihydrobezofuran motif by intramolecular carbene insertion to benzylic C–H bond adjacent to an oxygen atom.



Scheme 28 Rh(II)-catalyzed construction of the key intermediate for the synthesis of (+)-lithospermic acid.

alkaloid (−)-serotobenine (**52**). The same strategy with the catalytic system was employed for the total synthesis of (−)-ephedradine A (orantine).[159] Rh_2(*S*-DOSP)$_4$ efficiently facilitated the intramolecular carbene insertion process to access the dihydrobenzofuran intermediate for the total synthesis of (+)-lithospermic acid.[160] To achieve this goal, the key step is to prepare the crucial intermediate of type **55** (Scheme 28). In a similar fashion and by means of 2 mol% $Rh_2(OAc)_4$ as the catalyst in CH_2Cl_2, the reaction of diazo compounds **56** afforded the starting materials **57** which could be used for the construction of the key dihydrobenzofuran intermediates for the synthesis of (−)-maoecrystal V and its analogs (eqn (15)).[161]

Rh(II)-catalyzed carbene insertion to the anomeric C–H bonds of carbohydrates has been reported to access ketopyranosides and derivatives.[162–165] Due to the presence of multiple functional groups in a carbohydrate molecule, its further functionalization becomes very difficult. In general, modification of a sugar (carbohydrate) backbone requires a multistep and time-consuming approach involving: (a) selective protection/deprotection of a specific position; (b) oxidation of the resultant alcohol; (c) addition of an organometallic reagent. In this context, direct functionalization methods have been strongly desirable, and direct quaternarization of a given position may expand chemical tools for glycobiology. Taking the lactonization of diazo sugar compound **58** as an example, a direct functionalization strategy is demonstrated in eqn (16).[162] This protocol features a perfect stereocontrol to construct an anomeric quaternary center after the glycosylation step. Ring-opening of the lactone unit enables further functionalization of compound **59**. It is noteworthy that acceptor diazo-sugars were used as the substrates for such transformations.



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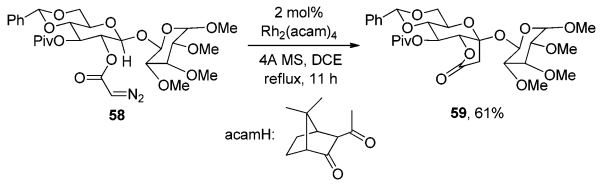


(16)

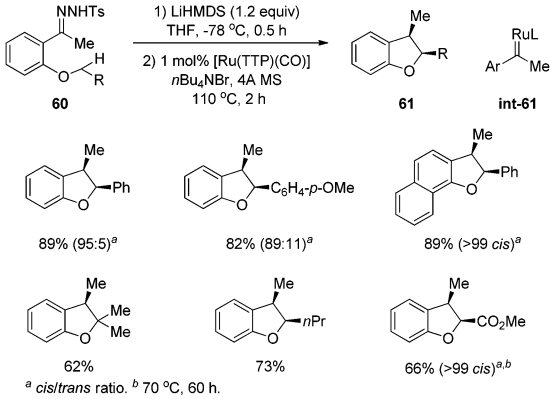
Other transition-metal complex catalysts have also been documented for intramolecular carbene insertion to alkyl C–H bonds activated by an adjacent oxygen atom. Both $Tp^{Br3}Cu$ and $Tp^{Ms}Cu$ exhibited a high catalytic activity for the intramolecular carbene insertion to primary and tertiary C–H bonds to afford the desired lactone products, but a low catalytic activity was observed for the secondary C–H bond functionalization.[166] Notably, $Rh_2(OAc)_4$ behaved much less efficiently for the same transformation (Table 6). Tp^xCu nearly showed no catalytic activity for the desired reaction, and $Tp^{Cy,4Br}Cu$ only effected the transformation of *tert*-butyldiazoacetate with a low efficiency. In the case of using 2 mmol of the diazo compound, $Tp^{Ms}Cu$ led to quantitative formation of the target products. Ir(III)[167] and other transition-metal complexes can also act as the catalysts for the same reactions.

N-Tosylhydrazones have been well known as the coupling partners in transition-metal-catalyzed cross-couplings,[21] and they can also be used as the carbene precursor compounds for direct C–H functionalization by carbene insertion.[7] With 1 mol% Ru(II) complex [Ru(TTP)(CO)] (H_2TTP = *meso*-tetrakis(*p*-tolyl)porphyrin) as the catalyst, a one-pot, two-step process was developed to establish dihydrobenzofuran scaffolds (Scheme 29).[168] The Ru(II) carbenes of type **int-61** were proposed as the reactive intermediates to enable the transformation. In a similar fashion the alkyl diazomethanes generated *in situ* from *N*-tosylhydrazones **62** efficiently underwent intramolecular carbene insertion to alkyl C–H bonds, affording substituted tetrahydrofuran derivatives **63** in up to 99% yields with up to 99 : 1 *cis*/*trans* selectivity (Scheme 30).[169] In most of the cases, the *cis*/*trans* ratios of the product isomers are > 95 : 5. The protocol features good tolerance of many functionalities,

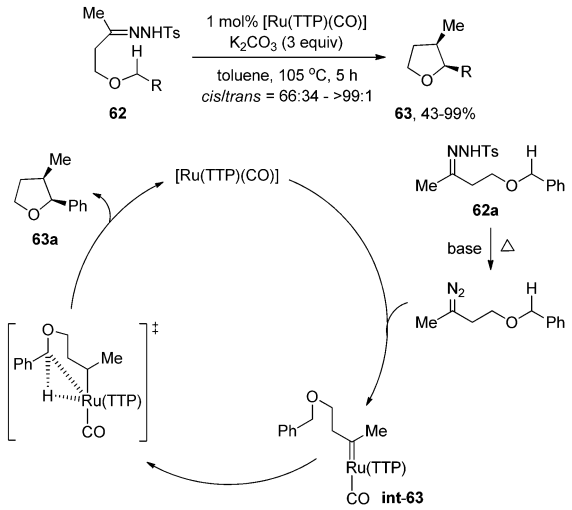
Table 6 Tp^xCu-catalyzed intramolecular carbene insertion to alkyl C–H bonds adjacent to an oxygen atom[a]

Catalyst				
$Tp^{Br3}Cu$	81%	71%	11%	22%
$Tp^{Ms}Cu$	98%	87%	5%	17%
$Rh_2(OAc)_4$	87%	40%	15%	0%

[a] Conditions: 1.25 mol% catalyst, 1 mmol diazoester, CH_2Cl_2, room temperature, 6 h.



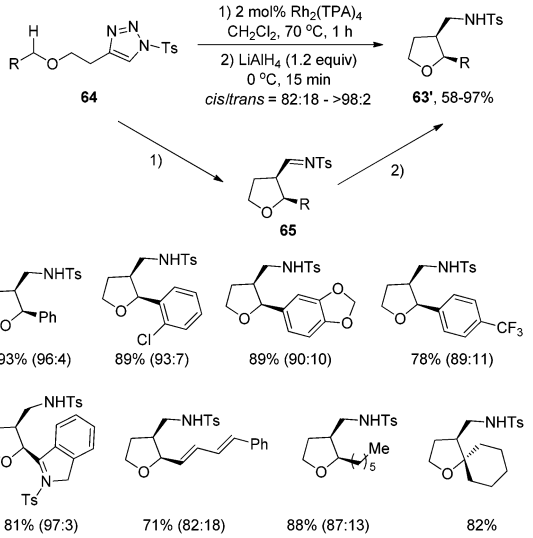
Scheme 29 Ru(II)-catalyzed intramolecular carbene insertion to alkyl C–H bonds adjacent to an oxygen atom.



Scheme 30 Ru(II)-catalyzed intramolecular carbene insertion to alkyl C–H bonds to access tetrahydrofurans.

and the procedure is simple. In the mechanistic studies, the stoichiometric reaction of **62a** (R = Ph) with [Ru(TTP)(CO)] gave **63a** (R = Ph) in 81% yield with 83% of the catalyst recovered, which showed a strong band at ν = 1937 cm^{-1} in the IR spectrum. This result supports formation of metal carbene complex [Ru(TTP)(CO)(CR^1R^2)] (**int-63**) as the reactive intermediate enabling the intramolecular carbene insertion.

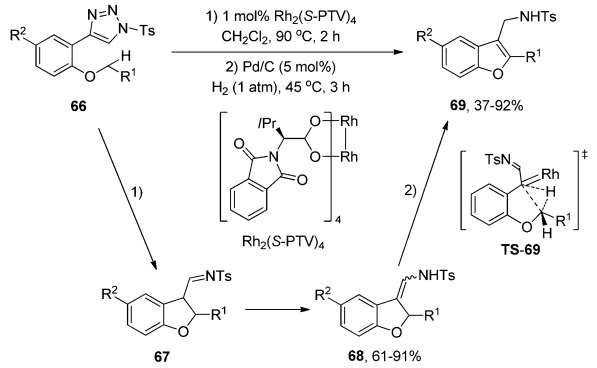
N-Sulfonyl-1,2,3-triazoles can act as the precursors to azavinylcarbenes which have been utilized for C–H functionalization. In the presence of 2 mol% $Rh_2(TPA)_4$ as the catalyst in CH_2Cl_2 at 70 °C, alkyl-substituted *N*-sulfonyltriazoles **64** were efficiently transformed to the desired 3-iminotetrahydrofurans **65** which were reduced to the corresponding tetrahydrofurans **63′** (58–97%) in a one-pot, two-step manner (Scheme 31).[170] Compounds **63′** can be applied as the important intermediates for the synthesis N-heterotricycles by intramolecular C–H amination or Pictet–Spengler cyclization. This protocol features the efficient synthesis of saturated O-heterocycles and fused N-heterocycles. Use of aryl-substituted *N*-sulfonyltriazoles **66** led



Scheme 31 Rh(II)-catalyzed intramolecular carbene insertion to alkyl C–H bonds with azavinylcarbenes.

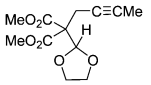
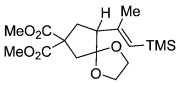
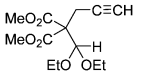
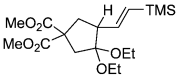
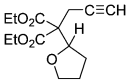
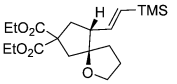
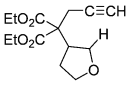
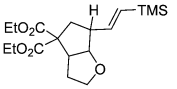
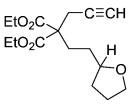
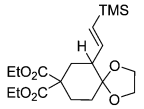
to hydrobenzofurans **68** which were formed from the 1,3-H shift of the less stable desired dihydrobenzofuran products dihydrobenzofuran **67** (Scheme 32).[171] In a one-pot, two-step manner, *N*-sulfonyltriazoles were transformed to benzofurans **69**. The second-step procedure was a palladium-catalyzed dehydrogenation/hydrogenation sequence. The reaction is proposed to proceed *via* a 3e-centered transition state **TS-69**.

Metal carbenes *in situ* generated from alkynes were documented for intramolecular alkyl C–H functionalization. Ruthenium-catalyzed carbene addition to terminal alkynes/insertion to C(sp^3)–H bonds in alkynyl acetals, ethers, and amines resulted in complex spiro and fused bicyclic structures by 1,*n*-H shift/cyclization cascades.[172] Ruthenium carbenes generated from alkynyl-based dioxalanes, linear acetals, acyclic ethers, cyclic tetrahydrofuryl/tetrahydropyranyl ethers (**70**), and diazo compound N_2CHTMS in the presence of complex catalyst [Cp*Ru(cod)Cl] could intramolecularly insert to the adjacent oxygen-activated alkyl C–H bonds, forming cyclopentane or cyclohexane derivatives (**71**) substituted by a vinyl group (Table 7).[173] The reaction smoothly proceeded *via* the possible



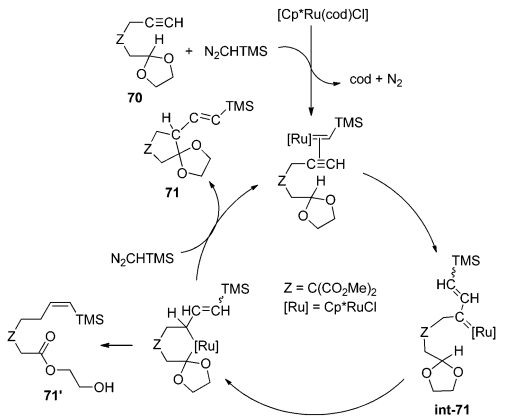
Scheme 32 Rh(II)-catalyzed intramolecular carbene insertion to alkyl C–H bonds to access benzofurans with azavinylcarbenes.

Table 7 Ru(II)-catalyzed 1,5-H/1,6-H shift cyclization sequence in alkynyl acetals and ethers[a]

Substrate (**70**)	Product (**71**)	Yield (%)
		25
		61[b]
		79
		87[b]
		90

[a] Conditions: [Cp*Ru(cod)Cl] (10 mol%), N_2CHTMS (1 equiv.), r.t., 0.5–2 h, Et_2O. [b] Dioxane, 60 °C, 10 h.

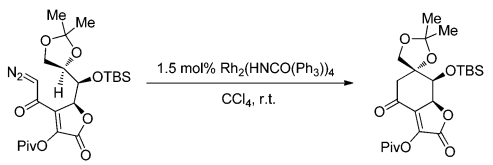
in situ generated ruthenium carbene species from the alkynyl moiety in the C–H substrates. A 1,5-H or 1,6-H shift/cyclization sequence was furnished to give the target products in decent yields (Scheme 33). A Ru(II) carbene species **int-71** is considered to be the reactive intermediate leading to the target product **71** as well as the acyclic side product **71′**. The strategy was used for the construction of a cyclohexane motif. As a key step in the synthesis of (−)-tetrodotoxin, diazo compound **72** was treated by 1.5 mol% $Rh_2(HNCOCPh_3)_4$ in CCl_4 at room temperature (eqn (17)).[174] The product was not isolated and directly used for the next step reduction by $NH_3{\cdot}BH_3$, reaching 75% yield for the two-step transformation. It is noteworthy that modified myoglobins containing an Ir(Me) site were also applied for the intramolecular carbene insertion to adjacent oxygen-activated alkyl (methyl) C–H bonds (eqn (18)).[175] When the phenyl group was substituted by 3-OMe, TON was reached 7260, while for the C–H functionalization of the secondary C–H bonds in OEt only a TON of 92 was obtained.



Scheme 33 Ru(II)-catalyzed 1,5-H/1,6-H shift cyclization sequence in alkynyl acetals and ethers with N_2CHTMS.

Although intermolecular C–H functionalization has been demonstrated its potential for constructing new chemical bonds, 1,3-carbene insertion to alkyl C–H bonds adjacent to an oxygen atom usually leads to cyclopentane, dihydrobenzofuran or tetrahydrofuran derivatives. As discussed in eqn (18),[175] artificial metalloenzymes containing an iridium–porphyrin cofactor such as Ir(Me)-P450s was used to enable intermolecular adjacent oxygen-activated alkyl C–H functionalization with EDA.[176]

By means of a substrate-control strategy carbene insertion to alkyl C–H and C–C bonds can be altered. In the presence of 0.5 mol% $Rh_2(esp)_2$ as the catalyst, vinyl diazo compounds **76** were treated in THF for one hour, resulting in a mixture of two kinds of intermolecular carbene insertion products **77** (carbene insertion to alkyl C–H bond) and **78** (carbene insertion to C–C bond) (eqn (19)).[177] Iridium-porphyrin-based metal–organic framework (MOF) was employed as a dual metallo- and photocatalyst for intermolecular carbene insertion to alkyl C–H bonds adjacent to an oxygen atom (eqn (20)).[178] The Ir(III) tetrakis(4-carboxyphenyl)porphyrin (TCPP(Ir)) moiety was used as the building block to integrate the metallo- and photocatalysis into one metal–organic framework. Elemental analysis and powder XRD analysis of the Ni-TCPP(Ir) framework indicate that the bulk sample consists of a single phase. The structural characterization reveals that the Ir(III)-carbene was formed and isolated to be confined in the pores of MOF without stabilization by a heteroatom. Such a catalyst also effected the C–H functionalization of ethyl ether and THF with diazo compounds such as EDA and quinone diazide (**79a**). Heterogeneous Cu/SiO_2–Al_2O_3 catalyst was also used for the intermolecular C–H functionalization of THF with diazo compounds.[179] Regarding the relevant carbene insertion mechanism,[180] it is generally accepted that the reaction proceeds *via* a three-electron-center transition state as proposed by Doyle.[9,134]



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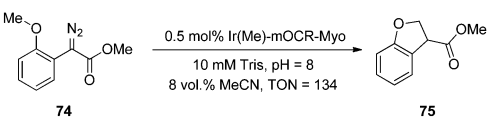
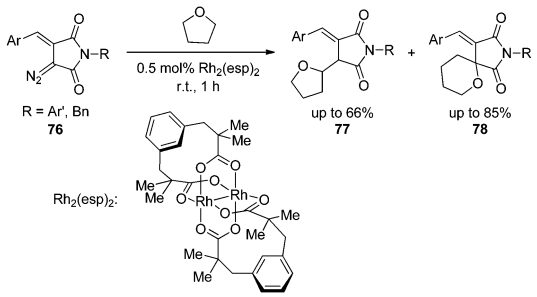
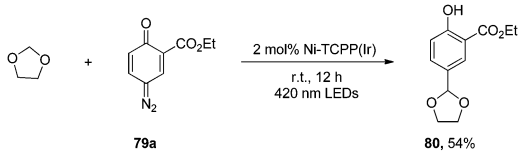


(18)

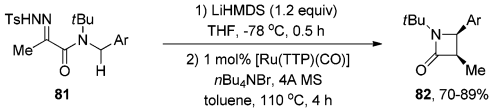


(19)



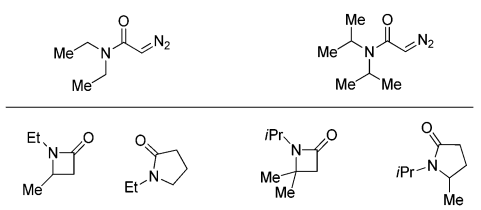
(20)

2.2.3. Alkyl C(sp^3)–H bonds adjacent to a nitrogen atom. A nitrogen atom can activate its adjacent alkyl C–H bonds to enable their functionalization by carbene insertion.[166,168–170,173] Tp^xCu complexes catalyzed the intramolecular C–H functionalization of *N*,*N*-diethyl and *N*,*N*-diisopropyldiazoaceta-mides through carbene insertion, giving the corresponding β- and γ-lactams (Table 8).[166] The sterically less hindered substrates favored formation of γ-lactams (47–61%) in all the cases, while the sterically hindered *N*,*N*-diisopropyldiazo-acetamide was preferentially converted to the β-lactams (66–87%). As compared to $Tp^{Ms}Cu$ and $Rh_2(OAc)_4$, complex $Tp^{Br3}Cu$ exhibited the highest catalytic activity for such transformations. In a one-pot, two-step manner, *cis*-β-lactams **82** (70–89%) were prepared *via* the *in situ* generated diazoacetamides from *N*-benzyl-*N*-*tert*-butylacetamide *N*-tosylhydrazones (**81**) under Ru(II) catalysis (eqn (21)).[168] Treating *N*,*N*-dibenzyl-2-aminoacetophenone *N*-tosylhydrazone under the same conditions afforded the corresponding dihydroindole in 78% with a >99% *cis*-selectivity. A similar strategy using *N*-tosylhydrazones as the carbene precursor was applied to access pyrrolidine derivatives.[169] The *in situ* generated ruthenium carbenes were also employed to enable intramolecular C–H functionalization of piperidine to produce fused bicyclic piperidines.[173] Azavinyl-carbenes generated from *N*-sulfonyltriazoles were suitable for the same process, producing *cis*-disubstituted pyrrolidine derivatives.[170]



(21)

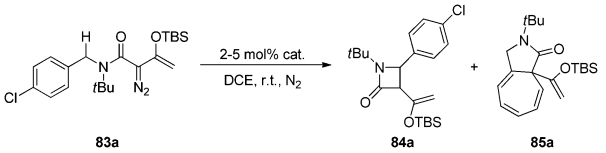
Table 8 Tp^xCu-catalyzed intramolecular carbene insertion to alkyl C–H bonds adjacent to a nitrogen atom[a]



Catalyst				
$Tp^{Br3}Cu$	21%	61%	87%	13%
$Tp^{Ms}Cu$[b]	41%	47%	82%	15%
$Rh_2(OAc)_4$	6%	63%	66%	27%

[a] Conditions: 1.25 mol% catalyst, 1 mmol diazoacetamide, CH_2Cl_2, 6 h. [b] 70 °C.

Table 9 Intramolecular carbene insertion to alkyl C–H bonds adjacent to a nitrogen atom[a]



Catalyst (mol%)	Temp. (°C)	Time (h)	Yield (%)	**84a : 85a**
$Rh_2(OAc)_4$ (2)	r.t.	4	92	88 : 12
$Rh_2(esp)_2$ (2)	r.t.	4	91	>95 : 5
$AgSbF_6$ (5)	r.t.	2	90	8 : 92
AgOTf (5)	r.t.	16	68	<5 : 95
$Cu(acac)_2$ (5)	r.t.	16	50	30 : 70
$[Pd(allyl)Cl]_2$ (2)	r.t.	0.5	96	>95 : 5
$[Ru(p\text{-Cymene})Cl_2]$ (2)	r.t.	2	97	>95 : 5
$[Rh(COD)Cl]_2$ (2)	r.t.	6	94	>95 : 5
$[Cp^*RhCl_2]_2$ (2)	r.t.	6	92	>95 : 5
$ZnCl_2$[b] (5)	r.t.	12	75	8 : 92
JohnPhos-Au(NCMe)-SbF_6 (2)	r.t.	24	19	50 : 50

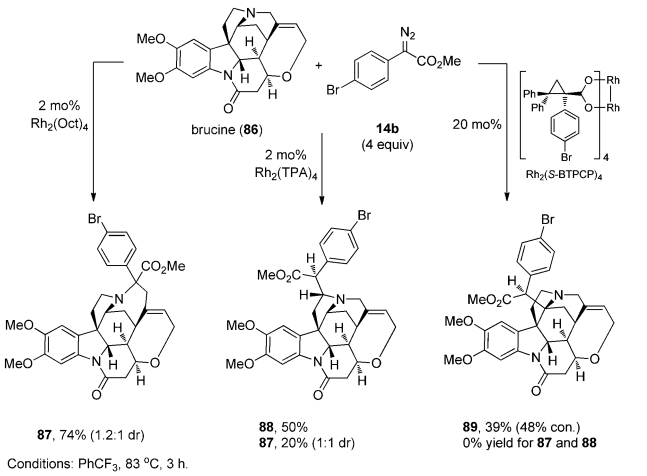
[a] Conditions: substrate (0.2 mmol), DCE (4 mL). [b] $ZnCl_2$ solution.

Doyle, *et al.* investigated the reactivity and selectivity in the catalytic reaction of enoldiazoacetamides (**83**) by means of various Rh(II), Ru(II), Ag(I), Cu(I), Cu(II), Co(II), Ir(I), Au(I) complexes, and Zn(II) salts as the catalysts.[181] The results were obtained in the case of 4-chlorobenzyl-substituted enoldiazoacetamide (**83a**) (Table 9). The rhodium complex catalysts always gave the β-lactam product **84a** in high yields (92–94%) with a molar ratio of 88 : 12–>95 : 5 for the products **84a**/**85a** (carbene insertion to alkyl C–H bond/Büchner reaction). Both Pd(II) and Ru(II) complexes also efficiently facilitated formation of β-lactam **84a** in up to 97% yields with a >95 : 5 chemoselectivity. However, the Ag(I), Cu(I), and Cu(II) catalysts as well as $ZnCl_2$ favored the Büchner reaction to form **85a**, and the Au(I) complex exhibited a lower catalytic activity for both the reactions. It should be noted that $PtCl_2(PhCN)_2$, $Fe(TPP)Cl_2$, Co-porphyrin, $[Ir(COD)Cl]_2$, and $PyAuCl_3$ did not work for such transformations. These results have suggested that carbene insertion to alkyl C–H bonds is usually concurrently accompanied by Büchner reaction when an aryl group is present at a specific position in the C–H substrates. Catalyst- or substrate-control may alter the reaction pathway. The reaction of the analogs of **83a** usually gave a mixture of types **84**/**85**. It was found that β- and γ-lactams were formed as the side products in Ag(I)-catalyzed dearomatization of phenols with α-diazoacetamides.[182] DFT calculations have suggested that substituent(s) at the α-site has an impact on the chemoselectivity of the intramolecular Büchner reaction of diazoacetamide catalyzed by $Rh_2(OAc)_4$.[183]

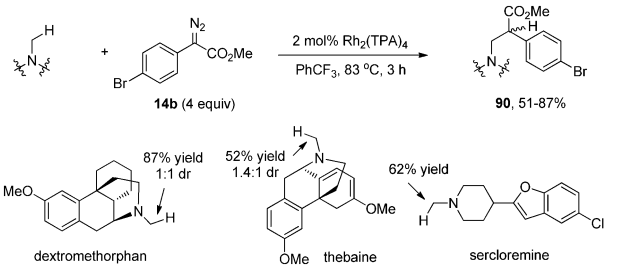
Carbene insertion to adjacent nitrogen-activated C–H bonds can be used as a direct strategy for the late-stage C–H functionalization of complex alkaloids and drug molecules in an inter- or intramolecular way. In 2015, Beckwith and Davies, *et al.* reported the first example of dirhodium(II)-catalyzed intermolecular carbene insertion to complex natural products bearing nucleophilic tertiary amino motifs, building a new C–C bond (Schemes 34 and 35).[184] As for the late-stage C–H

functionalization, alkaloids remain a great challenge due to the presence of basic amino and other functional groups. Brucine (**86**) contains 22 C–H bonds in different chemical environments with presence of two doubly activated allylic sites, a complex multi-ring architecture, a lactam motif, an electron-rich phenyl group, methyl ethers, as well as the basic tertiary amine scaffold, representing a challenging target molecule for direct C–H functionalization. In the presence of 2 mol% Rh_2(*S*-DOSP)$_4$ in trifluorotoluene at 83 °C for 3 h, brucine **86** reacted with the donor/acceptor diazo compound methyl *p*-bromophenyl diazoacetate (**14a**) to form Stevens rearrangement product **87** (58%) with 1.2 : 1 dr as well as the carbene insertion (to secondary C–H bond) product **88** as a single diastereomer in 20% yield. Use of the bulky dirhodium(II) catalyst Rh_2(TPA)$_4$ led to **88** (50%) and **87** (20%), respectively. Screening of other achiral rhodium catalysts revealed that Rh_2(Oct)$_4$ favored the exclusive formation of Stevens rearrangement product **87**(74%), and Rh_2(TPA)$_4$ is the most effective catalyst for carbene insertion to the adjacent nitrogen-activated alkyl C–H bonds to form **88**. Although the catalytic activity is low, the other carbene insertion (to tertiary C–H bond) product **89** was obtained in 39% yield (Scheme 34). The primary C–H bonds adjacent to a tertiary amine nitrogen atom in securinine was also functionalized in the same fashion with Rh_2(TPA)$_4$ as the catalyst and diazo compound **14a** as the carbene precursor.

Carbene insertion to primary C–H bond of the methyl group in a tertiary amine scaffold of natural products and drug molecules was explored as shown in Scheme 35. Under the same conditions for functionalizing brucine (**86**) by means of Rh_2(PTA)$_4$ catalyst and aryldiazoacetate **14b**, *N*-methyl-containing natural products and drug molecules such as dextromethorphan, thebaine sercloremine, noscapine, and bicuculline, were functionalized by carbene insertion to the *N*-methyl C–H bonds. Although secondary C–H bonds adjacent to a nitrogen atom, to aryl groups, and/or to an oxygen atom, doubly activated C–H bonds in the 1,3-dioxolane moiety, and the primary C–H bonds in methyl ether moieties are present in these molecules, C–H functionalization of the *N*-CH_3 moiety proceeded efficiently to give the target products in 51–87% yields.

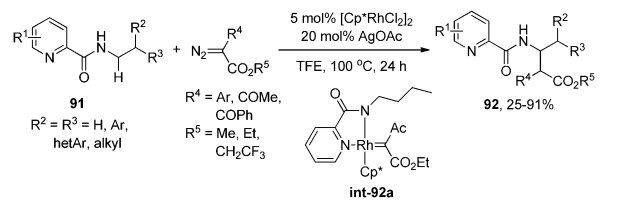


Scheme 34 Catalyst influence on site-selective C–H functionalization of brucine (86) by intermolecular carbene insertion.



Scheme 35 Rh(II)-catalyzed carbene insertion to primary C–H bonds of the *N*-CH_3 moiety in *N*-methyl-containing natural products and drug molecules.

Directing groups play a crucial role in many transition-metal-catalyzed site-selective C–H functionalization reactions. A Rh(III)-catalyzed regioselective intermolecular carbene insertion to the *N*-methylene C–H bonds of acyclic aliphatic amides (**91**) was achieved in the presence of 5 mol% $[Cp^*RhCl_2]_2$ as the precatalyst and 20 mol% AgOAc as the additive in 2,2,2-trifluoroethanol (TFE) at 100 °C under an inert atmosphere (eqn (22)).[185] *N*-Butylpyridine-2-carboxylic acid amide (**91a**) and ethyl α-acetyl-α-diazoacetate reacted to give the C–H alkylation product **92a** in 89% yield with 8 : 1 dr. The solvent and temperature effects were obvious. The directing group 2-pyridyl plays a crucial role in enabling the transformation. The control experiments revealed that the reaction did not occur when 2-pyridyl in **91a** was replaced by a phenyl group. In air the reaction did not occur either. When a substrate with the deuterated *N*-methylene was treated under the stated reaction conditions one deuterium was transferred to the β-position of the β-aminoester product. This result indicates that a two-electron carbene insertion to the C(sp^3)–H bond occurred with the bidentate chelation assistance. DFT calculations have suggested that rhodium carbene **int-92a** is the reactive intermediate enabling transformation to form the desired product **92a**. This protocol features a wide substrate scope of linear and branched-chain *N*-alkylamides, providing an alternative route to diverse β-amino esters.



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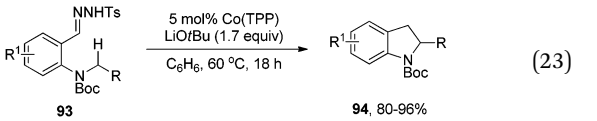

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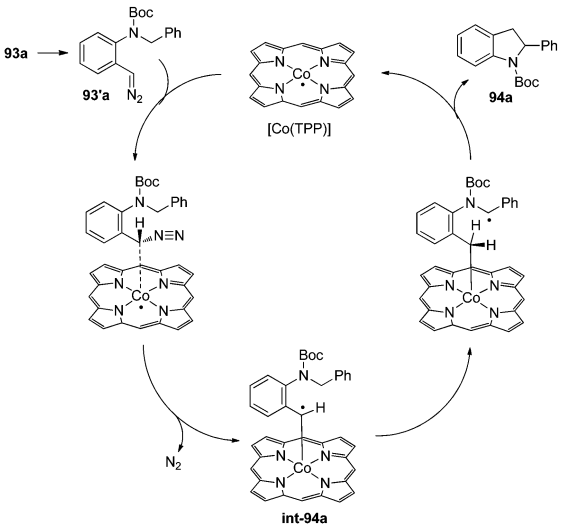
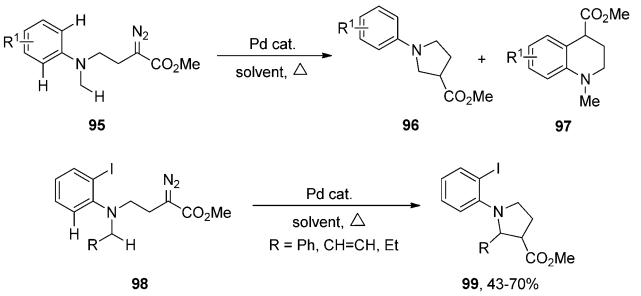
Ru(II) complex catalysts have been documented to catalyze the intramolecular carbene insertion to alkyl C–H bonds.

However, ruthenium carbenes usually insert to the alkyl C–H bonds β to the diazoacetamide nitrogen atom, forming γ-lactam products.[186,187] The β-lactam products which can be generated from intramolecular carbene insertion to the alkyl C–H bonds adjacent to a nitrogen atom were only formed as the side products under Ru(II) catalysis.[187] Under Co(II) catalysis, *o*-aminobenzylidine *N*-tosylhydrazones (**93**) underwent intramolecular carbene insertion to the benzylic C–H bond adjacent to the nitrogen atom *via* a cobalt(III)-carbene radical intermediate, affording indolines **94**.[188] In the presence of the Co(II) complex catalyst, that is, Co(TPP) (H_2TPP = tetraphenylporphyrin), and LiO*t*Bu base in benzene, the intramolecular insertion reaction occurred at the secondary C–H position adjacent to the nitrogen atom, giving the target indoline products in 80–96% yields (eqn (23)). When the R group is H or methyl, the reaction did not occur. In the cases of R = 2-furyl, 2-pyridyl, or allyl (R ≠ H, Me), the corresponding indoline products were obtained in 95%, 95%, and 80% yields, respectively. Co(III) carbene radicals of type **int-94a** were proposed as the reactive intermediates to furnish the catalytic cycle (Scheme 36).

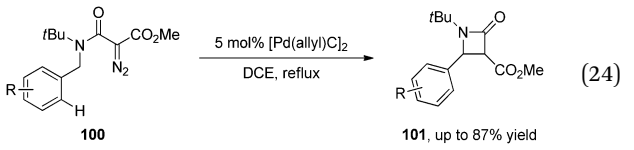
Palladium catalysts have been extensively reported for intermolecular cross-coupling of *N*-tosylhydrazones. They were also applied for intramolecular carbene insertion to alkyl C–H bonds. In general, electron-rich C–H bonds usually exhibit a higher reactivity toward a carbene center than their electron-deficient analogs and show an activation order: tertiary > secondary ≫ primary C(sp^3)–H. Although carbene insertion to tertiary and secondary C(sp^3)–H bonds has been well developed, less attention has been paid to the functionalization of primary C(sp^3)–H bonds by carbene insertion. In the case of *N*-methyl C–H bonds, palladium enabled the Intramolecular functionalization by carbene insertion when other reactive sites existed in the *N*-methyl-containing diazo compounds (Scheme 37).[189] By means of 10 mol% $Pd(OAc)_2$, 2.5 mol% $Pd_2(dba)_3$, or 2.5 mol% $Pd_2(dba)_3$/5 mol% dppf (dppf = 1,1′-bis(diphenyl-phosphino)ferrocene) as the catalyst in refluxing chloroform or dichloroethane at 80 °C, *N*-methyl-containing α-diazoesters **95** underwent intramolecular carbene insertion to both methyl and aryl C–H bonds, giving pyrrolidines **96** as well as tetrahydroquinolines **97** as the byproducts. When the substituent on the aniline moiety was 2-halo or 2-methyl, products **96** (49–89%) were exclusively formed. In the cases of 4-OMe and 4-Cl as the substituents, the yields of **96** were decreased to 25–38%. When 3-Cl and 3-OMe were the substituents, a mixture product of **96** and **97** was obtained in each case (39–47%, **96**/**97** = 1.5 : 1–2.7 : 1). The protocol was not limited to *N*-methyl-containing substrates, and also worked well for substituted *N*-alkyl-bearing diazoesters (Scheme 37). *N*-Benzylaniline (**98a**) regioselectively afforded the target product **99a** in up to 66% yield with a best *cis*/*trans* ratio of 5.5 : 1. In other cases, the *cis*/*trans* mixture products were also obtained. A Pd(II) complex catalyst enabled construction of β-lactams **101**, usually as mixtures of *cis* and *trans* isomers from diazo compounds **100** (eqn (24)).[190] Other transition-metal complex catalysts can also effect such transformations.[168,181]



Scheme 36 Co(III)-catalyzed intramolecular carbene insertion to adjacent nitrogen-activated alkyl C–H bonds.

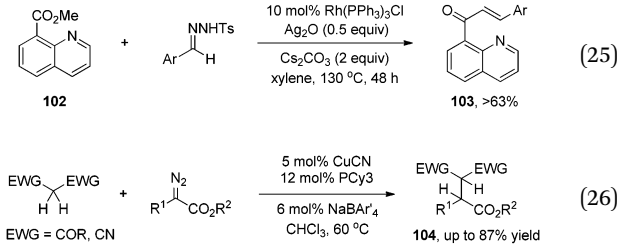


Scheme 37 Palladium-catalyzed intramolecular carbene insertion to adjacent nitrogen-activated alkyl C–H bonds.



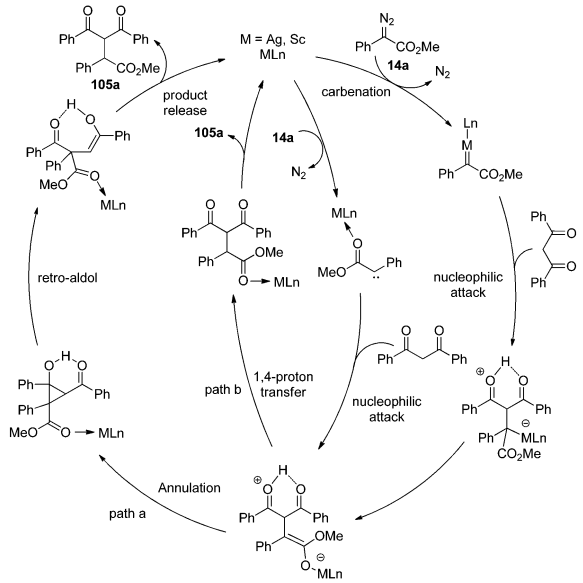
2.2.4. Alkyl C(sp^3)–H bonds adjacent to a carbonyl group. Carbene insertion to C(sp^3)–H bonds α to a carbonyl group has proved to be a useful method to formally functionalize enolic C–H bonds. As discussed above, carbene insertion to electron-rich C(sp^3)–H bonds have relatively been well studied, but similar carbene insertion to electron-deficient C(sp^3)–H bonds has been underdeveloped. A few reports were scattered in this direction of carbene insertion. With 10 mol% $Rh(PPh_3)_3Cl$ as the catalyst, Ag_2O (0.5 equiv.) as the oxidant, Cs_2CO_3 as the base in xylene at 130 °C (quinoline-8-yl)methanone (**102**) reacted with *N*-tosylhydrazones of benzaldehydes to afford the arylvinylation products **103** in >63% yields (eqn (25)).[191] A combination of 5 mol% CuCN/12 mol% PCy_3/6 mol% $NaBAr'_4$ promoted the reaction of donor/acceptor diazo compounds with 1,3-diesters, β-ketoesters, β-ketonitriles, and malononitriles (eqn (26)).[192] This

protocol offers a concise and straightforward route to synthetically important multisubstituted succinic acid derivatives.

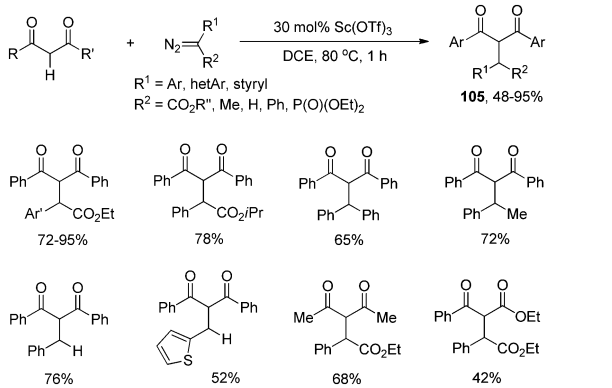


Catalyst-controllable chemoselective carbene insertion to alkyl C–H and C–C bonds was developed to functionalize 1,3-diketones and analogs (Scheme 38).[193] In the presence of 30 mol% $Sc(OTf)_3$ as the catalyst in dichloroethane at 80 °C, 1,3-diketones reacted with donor/acceptor, donor/donor, and donor diazo compounds to give the corresponding carbene insertion 2-alkylated products **105** in 48–95% yields. Acetoacetone and the β-ketoester underwent the same type of reaction to form the corresponding products in 68% and 42% yields, respectively. However, when 10 mol% AgOTf was used as the catalyst in CH_2Cl_2 at 40 °C, the 1,3-diketone substrates underwent carbene insertion to the C(C═O)–C bond, leading to 1,4-dicarbonyl products featuring an all-carbon α-quaternary center. The DFT calculations have revealed the Brønsted basicity *versus* nucleophilicity-controlled chemoselectivity.[194] The theoretical results have shown that scandium(III) salt behaves as a Lewis acid to generate free carbene, which is followed by conjugate addition of the free carbene to produce an enolate intermediate. Subsequent 1,4-proton transfer to a monoalkylation product is more favored than the nucleophilic addition process to form the 1,4-dicarbonyl products. With a silver(I) salt as the catalyst, the reaction starts with carbenation of the silver(I) catalyst to afford a Fischer-type silver carbene which is nucleophilically added to the 1,3-diketone substrate to afford an enolate intermediate. Subsequent annulation/retro-aldol reaction produces a dialkylation product. Both pathways are proposed as shown in Scheme 39.

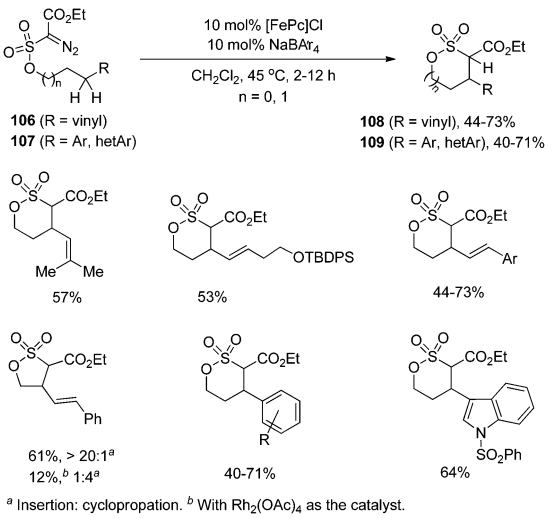
2.2.5. Allylic and benzylic C(sp^3)–H bonds. Allylic C–H bonds bearing no adjacent activating heteroatoms such as oxygen and nitrogen, and benzylic C–H bonds attached by an aryl group are considered as relatively activated C(sp^3)–H bonds. However, a challenge is confronted when they participate in transition-metal-catalyzed carbene insertion reactions because the vinylic C═C bonds readily undergo cyclopropanation with a metal carbene. Elaboration of the catalyst systems and/or allyl-containing substrates is usually required to achieve intra- and intermolecular carbene insertion to an allylic C–H bond.[195,196] In the presence of an Fe(III) complex catalyst, that is, iron(III) phthalocyanine chloride [FePc]Cl (Pc = phthalocyanine), and the non-coordinating counterion $BAr'_4{}^-$ in CH_2Cl_2 at 45 °C, diazo sulfonate esters **106** bearing an allyl motif and **107** containing a benzyl group underwent intramolecular carbene insertion to the allylic or benzylic C–H bond to give δ- or γ-sultone products **108** and **109**, respectively (Scheme 40).[197] Iron carbenes are usually



Scheme 39 Proposed mechanism for Sc(III)-catalyzed carbene insertion to C(sp^3)–H bonds α to a carbonyl group.



Scheme 38 Sc(III)-catalyzed carbene insertion to C(sp^3)–H bonds α to a carbonyl group.

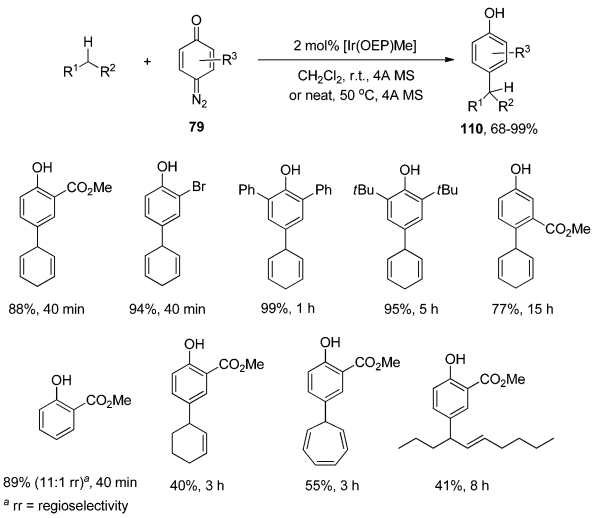


[a] Insertion: cyclopropation. [b] With $Rh_2(OAc)_4$ as the catalyst.

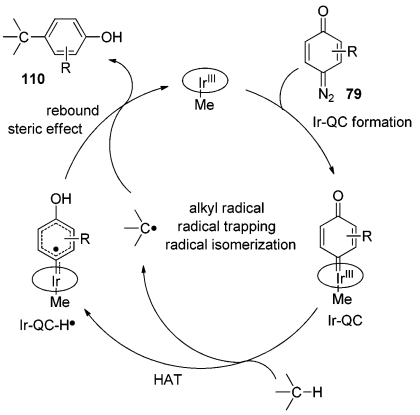
Scheme 40 Fe(III)-catalyzed intramolecular carbene insertion to allylic and benzylic C–H bonds.

inert, and they have been shown to favor olefin cyclopropanation and heteroatom-hydrogen insertion. In the present case, introduction of a sulfonate moiety to the diazo carbene center increased the electrophilicity of the resultant acceptor/acceptor diazo compounds, which thus enhanced the electrophilicity of the iron carbene intermediates generated *in situ* during the reaction, enabling the intramolecular carbene insertion reaction. The non-coordinating counterion helped to render the iron catalyst more electrophilic. The mechanistic studies suggest that the reaction proceeds *via* an iron bound carbene that promotes homolytic cleavage of the allylic or benzylic C–H bond, followed by recombination with the resulting carbene-centered radical to form a new C–C bond and establish the six or five-membered ring. Although the products were obtained in moderate to good yields, these results have demonstrated the potential of an iron carbene to facilitate the carbene insertion reaction of relatively strong aliphatic C(sp^3)–H bonds.

An Ir(III)-porphyrin complex was documented to mediate intermolecular carbene insertion to allylic C–H bonds *via* a metal-quinoid carbene (QC) intermediate through a radical mechanism (Scheme 41).[198] With 2 mol% [Ir(OEP)Me] (OEP = octaethylporphyrin) as the catalyst in CH_2Cl_2 at room temperature (conditions A) or in neat aliphatic substrates such as 1,4-cyclohexadienes and other cyclic monoalkenes or cycloheptatriene, quinone diazides (**79**) reacted with the aliphatic C–H substates to afford the aliphatic C–H arylation products **110** in 36–99% yields. 1,4-Cyclohexadienes usually reacted efficiently to give the target products in 68–99% yields. When the diazo compounds are substituted by 2- or 2,6-positioned electron-withdrawing groups such as ester, bromo, fluoro, and phenyl, the reaction was complete within one hour to reach 88–99% yields. 2,6-Di-*tert*-butyls and 3-alkoxy or 3-ester diminished the reactivity of the diazo compounds, and the arylation products derived from benzo-fused *p*-quinone diazide or *ortho*-quinone diazide hardly underwent the reaction.



Scheme 41 Ir(III)-catalyzed intermolecular carbene insertion to allylic C–H bonds.

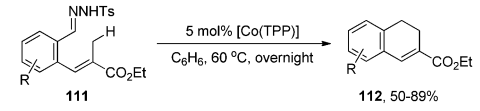


Scheme 42 Ir(III)-catalyzed intermolecular carbene insertion to allylic C–H bonds.

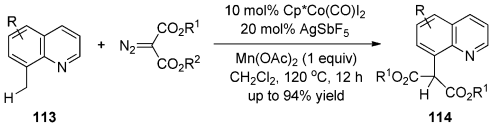
Under the stated conditions, cyclic and acyclic monoalkenes only exhibited a moderate reactivity to form the arylation products in about 40% yields. Interestingly, cycloheptatriene underwent the same type of reaction to result in the desired product (55%). The proposed radical mechanism was confirmed by the radical-trapping experiments. In the cases of 1,4-cyclohexadiene and cyclohexene as the aliphatic C–H substrates, addition of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) led to a remarkable yield drop of the corresponding arylation products from 88% to 16%, and from 40% to 13%, with obvious formation of the TEMPO-trapped products (19% and 28% yields), respectively. A simplified mechanism is demonstrated in Scheme 42. This method tolerates various functional groups on the carbene precursor and can install functionalized phenol moieties onto the 1,4-cyclohexadiene backbone. It is the hydrogen-atom transfer (HAT) reactivity of resultant metalloquinoid carbene intermediate that enables the intermolecular arylation.

Co(II) complex Co(TPP) can act as an efficient catalyst for the intramolecular carbene insertion to C(sp^3)–H bonds next to a nitrogen atom *via* a Co(III)-carbene radical intermediate.[188] The same strategy was used to intramolecularly functionalize the allylic (methyl) C–H bonds in *ortho*-styryl *N*-tosylhydrazones (**111**) for the synthesis of 1,2-dihydronaphthalene derivatives (**112**).[199] The reaction was carried out in benzene at 60 °C by means of 5 mol% [Co(TPP)] catalyst, giving the target products in 50–89% yields (eqn (27)). When the electron-withdrawing group CO_2Et was replaced by acetyl, an alkyl or phenyl, the product yields were dropped to 17–50%. Replacement of the methyl group in **111** led to a completely different reaction to afford the (*E*)-aryl dienes in 83–95% yields, instead of the desired 1,2-dihydronaphthalenes. Theoretical studies strongly support a mechanism proceeding *via ortho*-quinodimethane (*o*-QDM) intermediate. Radical-trapping experiments using TEMPO has confirmed that Co(III)-carbene radical intermediates were involved in the reaction. A Co(III)-catalyzed alkylation of primary (benzylic) C(sp^3)–H bonds with diazo compounds was also achieved (eqn (28)).[200] In the presence of 10 mol% Cp*Co(CO)I_2/20 mol% $AgSbF_6$/$Mn(OAc)_2$, 8-methylquinoline (**113a**) and its analogs reacted with acceptor/acceptor diethyl

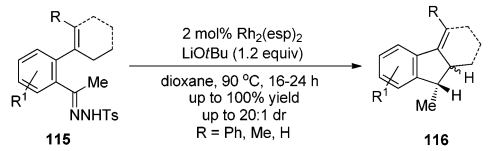
diazomalonate and derivatives to give the alkylation products **114** through insertion of the *in situ* generated cobalt carbenes to the primary (benzylic) C(sp^3)–H bond. The protocol is highly efficient and scalable, tolerant of various functional groups, which is potentially useful for the synthesis of azatricyclic antibiotic compounds.



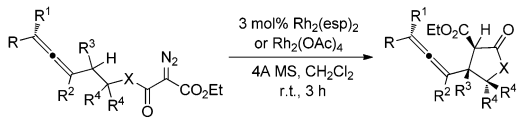
111 **112**, 50-89% (27)



113 **114** (28)

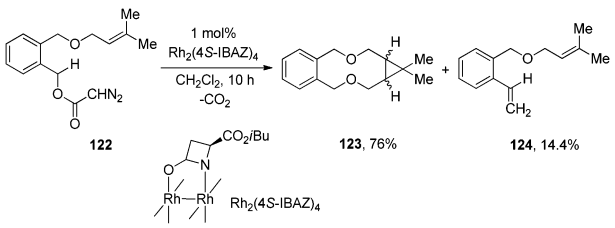


115 **116** (29)



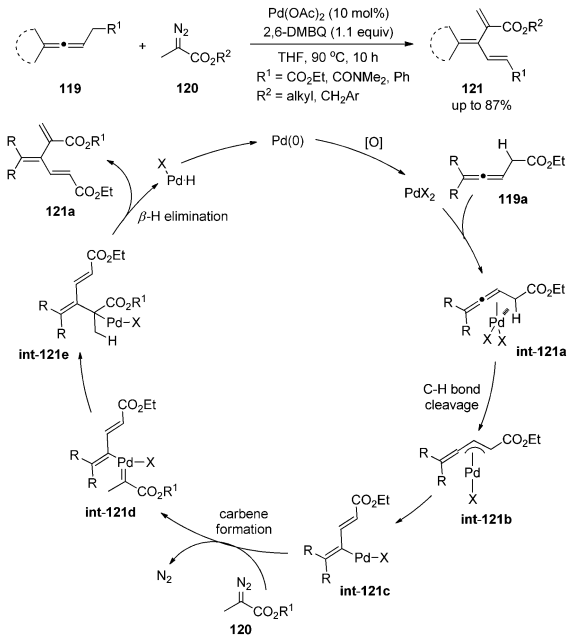
117 R = $BnCH_2$, C_5H_{11}, *n*Pr, Ph, etc.
R^1 = H, *n*Pr, Me; R^3, R^4 = H, Me
X = O, CH_2

118, 34-97% (30)



122 **123**, 76% **124**, 14.4% (31)

A Rh(II) catalyst control of the site-selectivity of electron-rich alkyl and aryl-disubstituted (donor/donor) carbenes generated *in situ* from *o*-alkenyl-substituted *N*-tosylhydrazones (**115**) was realized to access 1*H*-indene derivatives **116** in excellent yields with high diastereoselectivities (eqn (29)).[201] However, when the substrates were treated under Cu(I) catalysis the *in situ* generated carbene species were added to the β-carboxylate to establish a six-membered carbocycle, forming 2-alkoxy 2*H*-naphthalenones. These results have demonstrated an efficient catalyst system for intramolecularly functionalizing allylic C–H bonds. With a similar catalyst system intramolecular allenic C–H functionalization was achieved through Rh(II)-carbene insertion (eqn (30)).[202] A palladium-catalyzed formal allenic C–H functionalization was also realized by means of donor/acceptor α-diazo esters (Scheme 43).[203] With 10 mol% $Pd(OAc)_2$ as the precatalyst and 2,6-dimethylbenzoquinone (DMBQ) as the oxidant, ethyl 5-methylhexa-3,4-dienoate (**119a**) and its ester or amide analogs reacted with the stated diazo compounds **120** to give the desired [3]dendralene derivatives **121** in up to 87% yields. The plausible mechanism suggests that $Pd(OAc)_2$ initially reacts with the allene substrate to generate species **int-121a**. The allenic C–H bond cleavage then selectively occurs to form allylpalladium(II) complex **int-121b**, which may readily transfer to the vinylpalladium species **121c**. α-Diazo compound reacts with **int-121c** to form Pd(II)-carbene intermediate **int-121d**. Subsequent migratory carbene insertion proceeds to produce allylpalladium(II) intermediate **int-121e**, which undergoes β-H elimination to result in the [3]dendralene product. The catalytically active Pd(II) species is regenerated by oxidation with 2,6-DMBQ for the next catalytic cycle.

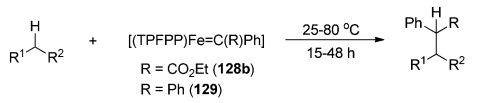


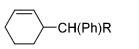
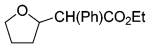
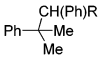
Scheme 43 Pd(II)-catalyzed formal allenic C–H functionalization *via* carbene insertion.

Intramolecular decarboxylative carbene insertion to benzylic C–H bond was observed as the side reaction in Rh(II)-catalyzed cyclopropanation of methallyl diazoacetates (**31**).[204] In the case of **122** using $Rh_2(4S\text{-IBAZ})_4$ as the catalyst, the target cyclopropanation product **123** was obtained with formation of the decarboxylative carbene insertion product **124** (14.4%) as the side product.

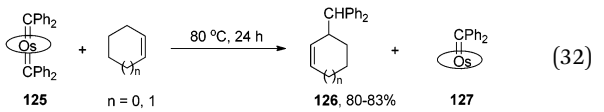
2.2.6. Mechanistic studies. Preparation, isolation, spectral and structural characterization, catalytic and stoichiometric reactions, of transition-metal carbene complexes, and the relevant theoretical calculations have been employed for the mechanistic studies of carbene insertion to aliphatic C(sp^3)–H bonds. An osmium(II) biscarbene complex **125** was prepared from the reaction of a simple osmium porphyrin complex [Os(TPFPP)(CO)] (TPFPP = *meso*-tetrakis(pentafluorophenyl)prophyrinato dianion) and excess of $Ph_2C{=}N_2$ in CH_2Cl_2.[147] This biscarbene complex underwent a stoichiometric reaction with cyclopentene and cyclohexene to give the corresponding alkylation products **126** at the allylic C–H sites as well as the osmium monocarbene complex **127** (eqn (32)). Complex **125** could efficiently catalyze the cyclopropanation of

Table 10 Stoichiometric reactions of iron(II) carbene complexes with C–H substrates



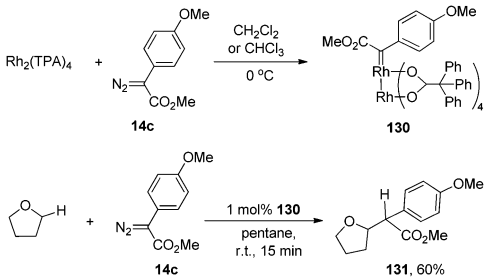
Complex	C–H substrate	Temp. (°C)	Time (h)	Product (yield %)
128b		80	24	 64
129		80	36	24
128b		65	24	 88
128b		80	15	 83
128b		25	48	15
129		80	20	59

styrene with diphenyldiazo-methane ($Ph_2C{=}N_2$). These results have revealed the reactive intermediates in metal-catalyzed cyclopropanation of alkenes and the potential for metal carbenes to insert into aliphatic C(sp^3)–H bonds. Reactions of [Fe(TPFPP)] with diazo compounds R(Ph)C=N_2 gave Fe(II) carbene complexes [Fe(TPFPP)(C(Ph)R)] (R=Ph (**128a**), CO_2Et (**128b**), $CO_2CH_2CH{=}CH_2$ (**128c**)) in 65–70% yields. Interaction of **128a** with *N*-methylimidazole (MeIm) afforded the adduct [Fe(TPFPP)(MeIm)] (**129**) which was structurally confirmed by X-ray single crystal crystallographic analysis.[148] Complexes **128b** and **129** were stoichiometrically reacted with allylic, tetrahydrofuryl, and benzylic C–H bonds to form the corresponding carbene insertion products (Table 10). This study suggests that the stable iron carbene complexes can be used as the potential catalysts for the C–H functionalization process through carbene insertion to C–H bonds. A stable structurally identified dirhodium(II)-NHC tetracarboxylate carbene complex was tested as the catalyst for intramolecular carbene insertion to C–H bond adjacent to a nitrogen atom to give a β-lactam product with an acceptor/acceptor diazo compound.[205]



(32)

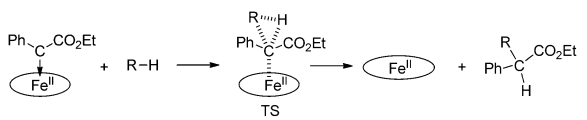
A metastable Rh_2-carbene intermediate bearing a donor/acceptor carbene fragment was synthesized, spectrally characterized, and tested its catalytic activity (Scheme 44).[206] The stoichiometric and catalytic C–H functionalization and cyclopropanation reactions gave the same products, respectively, which indicates that the reactions proceed *via* a rhodium carbene intermediate. The adduct $Rh_2(PTA)_4{\cdot}2CH_2Cl_2$ with excess of donor/acceptor methyl aryldiazoacetate (**14c**) in CH_2Cl_2 or $CHCl_3$ at 0 °C afforded the Rh_2 carbene complex **130** which could be stable over a period of about 20 hours in chloroform solution at 0 °C, allowing for studying its physical



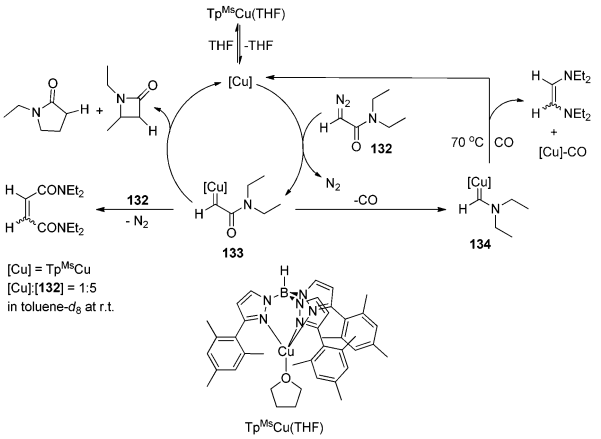
Scheme 44 Synthesis and its catalytic activity of a metastable Rh_2 carbene complex for carbene insertion to C(sp^3)–H bond.

and chemical properties. These results have revealed the possible intermediacy of highly reactive, electrophilic carbene intermediates that could not be directly observed in dirhodium(II) complex-catalyzed reactions. Fortunately, the first crystal structure of a reactive dirhodium complex, that is, Ar_2C = $Rh_2(PTA)_4$ (Ar = 4-$MeOC_6H_4$), an analog of complex **130**, was obtained from the reaction of $Rh_2(PTA)_4{\cdot}CH_2Cl_2$ with bis(4-methoxyphenyl)-diazomethane.[207] This result is very important for the mechanistic study involving dirhodium catalysis.

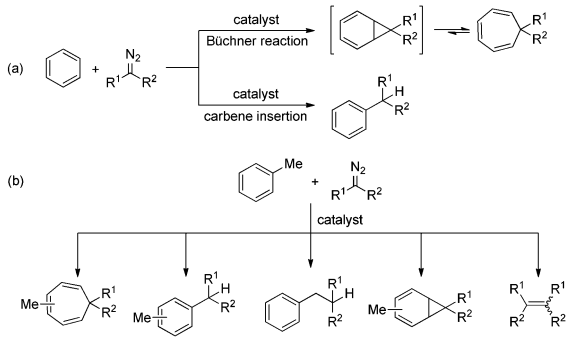
As reported by Che, *et al.*, iron(II) carbene complexes can undergo stoichiometric reaction with aliphatic C–H substrates by carbene insertion.[148] DFT calculations have suggested that iron(II) complexes supported by a bis(imino)pyridine ligand can act as the catalysts for aliphatic C–H functionalization by carbene insertion.[208] Ir(II) porphyrin carbene insertion to C–H bonds was theoretically investigated by Zhang, *et al.*, and the results have revealed an Fe^{II}-based, concerted, hydride transfer mechanism, which is different from the Fe^{IV}-based, stepwise hydrogen atom transfer mechanism for C–H functionalization by native heme enzymes (Scheme 45).[180] A computational approach was investigated to understand the role of metals (Fe and Ir) and the axial ligands in artificial heme enzyme-catalyzed intramolecular carbene insertion to C(sp^3)–H bonds.[209] These results provide the first theoretical evidence that carbene formation is the overall rate-limiting step and suggest a key role of the formation of strong electrophilic heme carbene in developing heme-based C–H functionalization by carbene insertion. Theoretical studies also reveal that both short-distance and long-range electronic effects strongly affect the mechanism and stereoselec-tivity of Rh(II)-carbene mediated C–H functionalization processes.[210] The reaction efficiency of diazoacetates in the presence of cyclohexane is highly dependent on the structure of the rhodium-stabilized carbene interemdiates.[211] The mechanistic studies on Michaelis–Menten kinetics in dirhodium(II) carboxylate-catalyzed carbene insertion reactions suggest that the rate-determining step



Scheme 45 Fe(II)-Catalyzed carbene insertion pathway. (Oval represents porphyrin dianion. TS = Transition state.)



Scheme 46 Unusual generation of a stable Cu(I) carbene complex.



Scheme 47 Possible reactions of a non-activated arene with a diazo compound.

is the generation of the rhodium carbenes.[212] The mechanism of rhodium-catalyzed C–H functionalization and cyclopropanation with methyl phenyldiazoacetate (**14a**) and methyl diazoacetate was studied computationally with DFT.[213] Based on the available experimental data, it has been demonstrated that donor/acceptor rhodium carbenes display potential activation barriers consistent with the much higher selectivity in both the reactions compared to the traditionally used acceptor metal carbenes derived from unsubstituted diazo esters. Other physical methods can also be applied for the theoretical studies. For example, IR vibrations were used to quantitatively describe and predict site-selectivity in rhodium-catalyzed C–H functionalization reactions.[214]

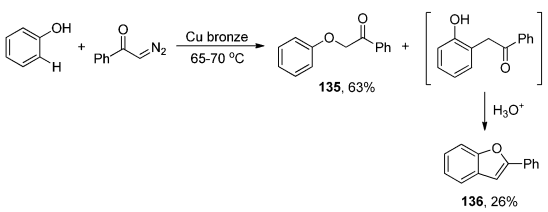
Almost in all the previous work on metal-carbenes $L_nM = CR^1R^2$ generated from transition-metal complexes L_nM and diazo compounds $N_2 = CR^1R^2$, the CR^1R^2 fragment at the metal-carbene remains intact from the parent diazo compound. Very recently, Pérez, *et al.* reported the detection and isolation of a monosubstituted copper carbene where the CR^1R^2 ligand had undergone a modification from the initial diazo compound (Scheme 46).[215] Complex $Tp^{Ms}Cu(THF)$ (Tp^{Ms} = hydrotris(3-mesitylpyrazol-1-yl)borate ligand) reacted with *N*,*N*-diethyldiazoacetamide (**132**) to give the stable copper carbene complex $Tp^{Ms}Cu = CH(NEt_2)$ (**134**), resulting from a decarbonylation process from the initially generated carbene intermediate **133**. Such a copper carbene can undergo intramolecular carbene insertion to C(sp^3)–H bond to afford lactams at room temperature. Such a process could be monitored by NMR analysis, and the molecular structure of **134** was further confirmed by X-ray single crystal structural characterization.

3. Carbene insertion to aryl C(sp^2)–H bonds

3.1. Carbene insertion to aryl C(sp^2)–H bonds of non-activated arenes

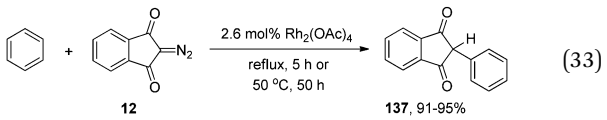
Although carbene insertion to an arene molecule can be used to functionalize aromatic C–H substrates, application of this strategy has not been well developed for decades due to the multiple reactivities of the non-activated arene substrates to a carbene source compound.[73] As a matter of fact, carbene insertion to C(sp^2)–H bonds of activated and functionalized arenes has recently been well documented, but it is not the case for non-activated arenes. In general, non-substituted benzene can undergo two kinds of competition reactions (Scheme 47a): The first is Büchner reaction[69] through addition of the carbene group from a diazo compound or other carbene source compounds to the C=C double bond of the aryl ring to generate a norcaradiene intermediate which spontaneously decomposes to the corresponding cycloheptatriene. These two species are usually in equilibrium, but the latter is dominantly favored in the reaction system. Under transition-metal catalysis, carbene can also insert to the aromatic C–H bonds of benzene to form the C–H functionalization product. For a functionalized arene such as toluene bearing different C(sp^3)–H and C(sp^2)–H bonds, its reaction with a carbene source diazo compound can produce at least four types of carbene insertion and addition products as well as the side products from the decomposition (dimmerization) of the carbene source compound (Scheme 47b). In order to functionalize the C–H bonds of a non-activated arene, the competition and side reactions should be surpassed. Notably, toluene is defined as a non-activated arene in this section when it is functionalized at the aromatic C–H bonds.

In the pioneering work by Yates,[70] carbene insertion to the aromatic C–H bond of phenol was reported as a side reaction (Scheme 48). Copper bronze promoted the reaction of phenol with α-diazoacetophenone in benzene at 65–70 °C to give α-phenoxyacetophenone (**135**) (63%) and 2-phenylbenzofuran



Scheme 48 The pioneering work by Yates.

(**136**) (26%) after acidification of the basic extract, which can be considered as the first example of intermolecular carbene insertion to an aryl C(sp^2)–H bond. However, the first example of intermolecular carbene insertion to non-activated aryl C–H bonds of benzene and toluene only appeared in 1988.[107] With $Rh_2(OAc)_4$ as the catalyst, the reaction of 2-diazo-1,3-indandione (**12**) in refluxing benzene for 5 h or at 50 °C for 50 h gave 2-phenyl-1,3-indandione (**137**) in 91% and 95% yields, respectively (eqn (33)). At 96–100 °C toluene reacted with **12** to afford a mixture of 2- and 4-insertion products by carbene in 86% yield with the 2-/4-site selectivity of 20–30/70–80. For such transformations the early reports only applied the simple dirhodium(II) tetracarboxylate complexes $Rh_2(OAc)_4$ and $Rh_2(TFA)_4$ as the catalysts.[107,216] By means of dimethyl diazomalonate as the carbene source and $Rh_2(OAc)_4$ as the catalyst, the reaction in refluxing benzene afforded two fractions of products after silica gel column chromatographic workup (Scheme 49).[216] Fraction A contains products **138** from the Büchner reaction, **139** from the cyclopropanation (**138** + **139** = 19%), and **140** (80%) from carbene insertion to benzene C–H bond. Fraction B is the double cyclopropanation product **141** (58%). The ratio of (**138** + **139**)/**140** depended on the refluxing time and ranged from 2.3 to 3.0 over a period 4–8 h. Interestingly, use of $Rh_2(TFA)_4$ instead of $Rh_2(OAc)_4$ as the catalyst remarkably altered the product distribution: (**138** + **139**), 64%; **140**, 32%; **141**, 4%. Such a low yield of the double cyclopropanation with $Rh_2(TFA)_4$ is comparable to the carbene insertion reaction of other aromatic compounds, in which double cyclopropanation was seldom observed. These results have demonstrated the influence of the steric and electronic properties of the diazo compounds as well as the catalysts on the efficiency of carbene insertion reactions.



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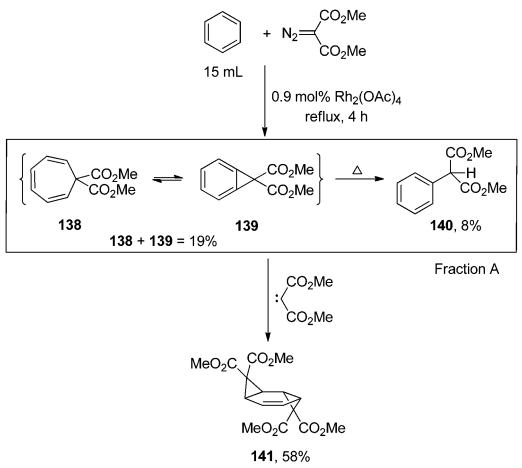
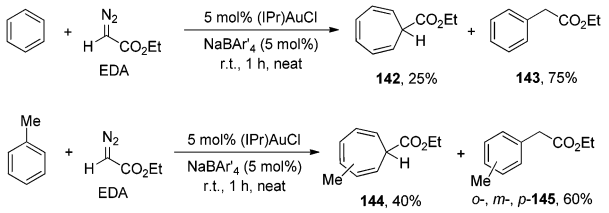
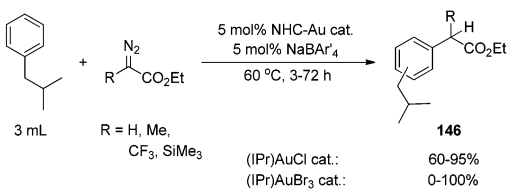


Scheme 49 Reactions of dimethyl diazomalonate in refluxing benzene with $Rh_2(OAc)_4$ catalyst.



Scheme 50 Au(I)-catalyzed reaction of benzene and toluene with EDA.

In 2005, Pérez and Diaz-Requejo, *et al.* found the Au–NHC complex, that is, (IPr)AuCl could be used for the C–H functionalization of benzene and toluene by carbene insertion with the simple acceptor carbene source EDA (Scheme 50).[101] The reaction of benzene afforded the expected Büchner product **142** (25%) and the carbene insertion product **143** (75%). In the case of toluene, carbene insertion occurred as the major reaction to give a mixture of the *o*-, *m*-, and *p*-isomers of the tolylacetate (**145**, 60%). It should be noted that these carbene insertion products were usually formed as the by-products with other metal catalysts.[217] The Au(I) and Au(III)–NHC complexes, that is, (IPr)AuCl and (IPr)$AuBr_3$, were comparatively studied in the reaction of isobutylbenzene with various diazo compounds (eqn (34)).[218] When acceptor and donor/acceptor diazo compounds were used, the reaction with catalyst (IPr)$AuBr_3$ exclusively gave the carbene insertion products **146** (100%), while the reaction with catalyst (IPr)AuCl afforded the target insertion products in 60–88% yield with considerable formation of the Büchner products (12–40%). Complex (IPr)AuCl efficiently catalyzed the reaction of CF_3-substituted acceptor/acceptor diazo compound to almost exclusively form the desired C–H functionalization product (selectivity 95%), whereas catalyst (IPr)$AuBr_3$ exhibited no catalytic activity under the stated conditions. With the Me_3Si-substituted diazo compound both the catalysts showed a decent catalytic activity to result in **146** (81%) and the Büchner product (19%) by using catalyst (IPr)AuCl, and yield **146** (95%) and the Büchner product (5%) in the presence of (IPr)$AuBr_3$. The discussed reaction may proceed *via* the gold carbene intermediates [NHC-Au=C(R)(CO_2Et)]$^+$ (**int-146a**) and [NHC-$(Br)_2$Au=C(R)(CO_2Et)]$^+$ (**int-146b**). These results have demonstrated that Au–NHC complexes can remarkably surpass the Büchner reaction of an arene substrate with suitable acceptor, donor/acceptor, and acceptor/acceptor diazo compounds. Au(I) and Ag(I) complexes bearing a N-heterocyclic carbene ligand with a pendant CH_2CO_2Et group attached to one N atom of the NHC ligand were also applied to catalyze the C–H functionalization of benzene with EDA, but only poor to moderate site-selectivities were obtained.[103]



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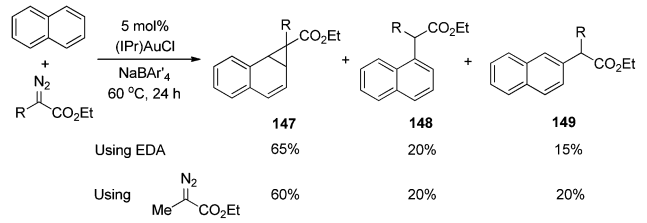
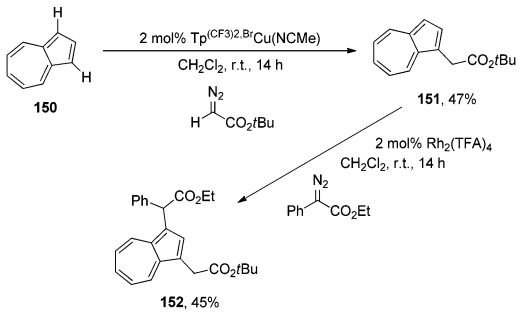
Both the NHC-M complex catalysts (IPr)AuCl and (IPr)CuCl were used to functionalize naphthalene by carbene insertion



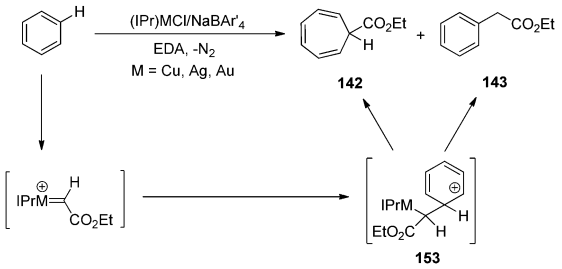
Scheme 51 (NHC)Au-catalyzed C–H functionalization of naphthalene by carbene insertion.



Scheme 52 Cu(I)/Rh(II)-catalyzed C–H functionalization of azulene by double carbene insertion with diazo compounds.

with EDA, giving the carbene insertion products in 35–40% yields in the presence of (IPr)AuCl as the catalyst, depending on the diazo compounds (Scheme 51),[219] while the Cu(I)–NHC catalyst[17] only induced the cyclopropanation to form product **147** (>99%). However, a Cu(I) complex, that is, $Tp^{(CF3)2,Br}Cu(NCMe)$, could be employed to doubly functionalize azulene (**150**) in a combination manner with $Rh_2(TFA)_4$ catalyst (Scheme 52).[220] This catalytic system was then applied for the synthesis of unsymmetrically disubstituted azulenes (**152**) *via* the monosubstituted intermediates **151**. It is noteworthy that functionalized azulene derivatives can be used as the building blocks for the preparation of degradable azulene-based materials.

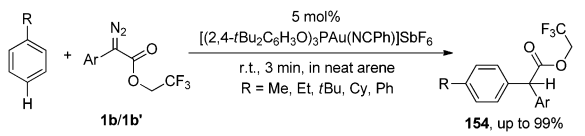
The mechanistic aspect of gold-catalyzed direct arene C–H bond functionalization by carbene insertion was explored and the coinage-metal effect was demonstrated by Cu, Ag, and Au.[221] A combination of (IPr)MCl with $NaBAr'_4$ was used to facilitate the reaction of benzene with EDA by insertion of the $CHCO_2Et$ group to the aromatic $C(sp^2)$–H bond. For Cu, Ag, and Au, the reaction with EDA gave ethyl cyclohepta-2,4,6-triene-carboxylate (**142**) as the by-product from the Büchner reaction. In the case of methyl-substituted benzenes, the reaction exclusively occurred at the aromatic ring and the $C(sp^3)$–H bonds remained unchanged in the presence of the Cu or Ag complex catalyst. A significant coinage-metal effect was observed since the gold catalyst favors formation of the carbene insertion product **143**. Both the experimental studies and DFT calculations can explain the observed selectivity in terms of formation of a common Wheland intermediate (**153**), behaving like an electrophilic aromatic substitution, from which the reaction pathway evolves into two separate routes to the different



Scheme 53 Mechanistic aspect of (NHC)M-catalyzed direct arene C–H functionalization by carbene insertion.

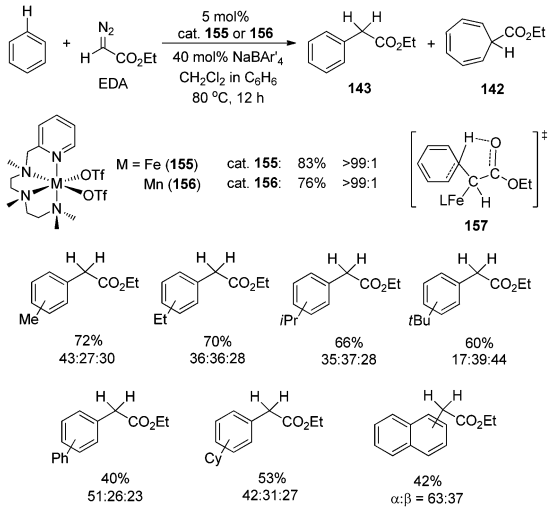
products (Scheme 53). It is proposed that the *in situ* generated metal carbene originates a Wheland intermediate (**153**) that undergoes a 1,2-H shift to give the final products.

In 2017, Zhang and Liu, *et al.* disclosed a non-NHC ligand, that is, $(2,4\text{-}tBu_2C_6H_3O)_3P$, supported Au(I) complex catalyst $[(2,4\text{-}tBu_2C_6H_3O)_3PAu(NCPh)]SbF_6$ which was successfully applied for *para*-selective C–H alkylation of toluene and its derivatives by carbene insertion with 2,2,2-trifluoroethyl α-aryl-α-diazoesters **1b** (Ar = p-BrC_6H_4) and its analogs **1b′** (eqn (35)).[222] The highly *para*-selective alkylation of toluene and its non-activated derivatives was achieved to give the target products **154** in up to 99% yields without applying a directing group in the arene C–H substrates. In such a transformation both the gold catalyst bearing a bulky triaryl phosphite ligand and a CF_3 group on the ester group of the diazo compounds play a crucial role for the high efficiency and regioselectivity. The electron-withdrawing substituents on the aryl ring of the diazo compounds were systematically explored as induced groups which could be used for further transformations.[223]

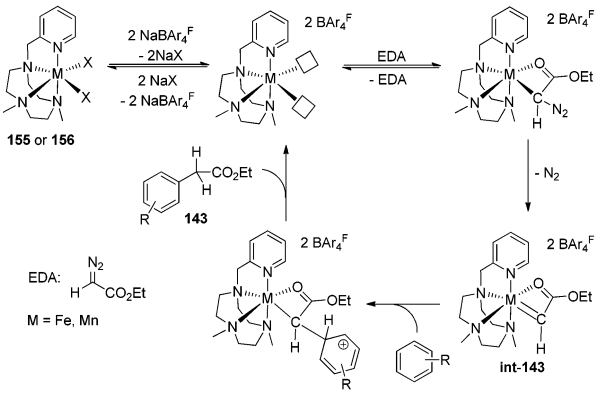


(35)

For the direct C–H functionalization of non-activated arenes by carbene insertion, Fe–N_4 and Mn–N_4 complexes $M(N_4)X_2$ (N_4 = 1-(2-pyridylmethyl)-4,7-dimethyl-1,4,7-lriazacyclononane; M = Fe (**155**), Mn (**156**); X = Cl, OTf) were demonstrated high catalytic activity when EDA was used as the carbene source compound (Scheme 54).[224] The concurrently formed cycloheptatriene products from the competing Büchner reaction were not observed with a >99 : 1 selectivity of insertion/Büchner reaction. In the case of benzene 76–83% yields were obtained, and the iron catalyst (**155**) exhibited a higher catalytic activity than its Mn analog **156**. The counterions Cl^- and OTf^- had no obvious impact on the catalytic behavior, and 40 mol% $NaBAr'_4$ was required. Other non-activated benzene derivatives were subject to the reaction conditions by means of the Fe–N_4 catalyst, affording the carbene insertion products in 42–72% yields with various *o*-, *m*-, and *p*-regioselectivity. This is the first example of transition-metal-catalyzed chemoselective



Scheme 54 Fe–N_4 and Mn–N_4 catalyzed C–H functionalization of non-activated arene by carbene insertion with EDA.



Scheme 55 Proposed mechanism for Fe–N_4 and Mn–N_4 catalyzed C–H functionalization of non-activated arene by carbene insertion with EDA.

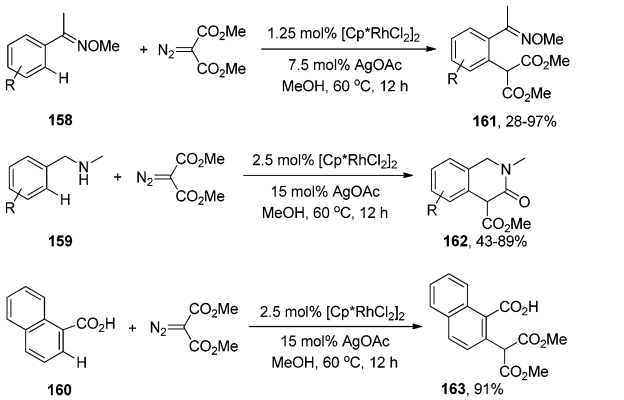
functionalization of benzene. The combined experimental and computational mechanistic studies have explained this exceptional selectivity for the direct C–H functionalization of benzene by carbene insertion with EDA ($>99:1$) without formation of the Büchner product. A plausible mechanism is proposed as shown in Scheme 55 involving anion dissociation/diazo coordination/metal carbene generation/migratory carbene insertion. Metal carbene species **int-143** is considered to be the reactive intermediate leading to the final product. Theoretical studies have revealed that the key step is the formation of an enol-like species **157**, which is the precursor to the final insertion product.[225]

3.2. Carbene insertion to aryl C(sp^2)–H bonds of functionalized arenes

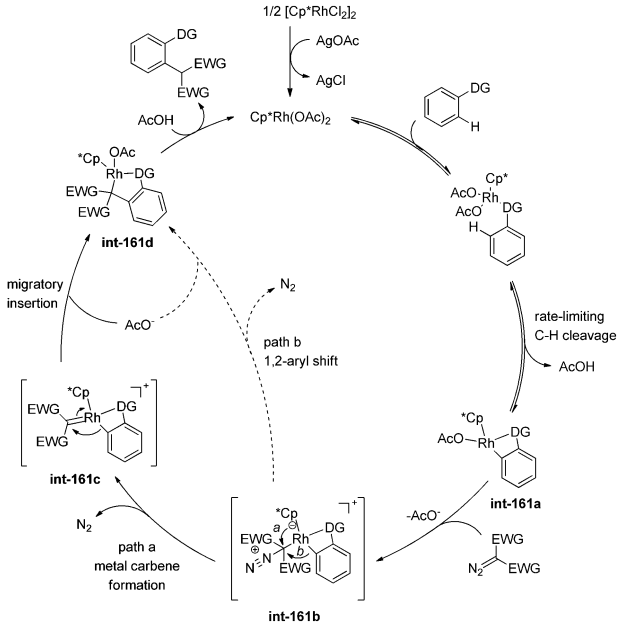
3.2.1. Rhodium complex catalysts

3.2.1.1. Rhodium(III) complex catalysts. Rhodium catalysts have been well known to decompose diazo compounds to induce their reactions with diverse reagents.[5–7] However, the reaction of monosubstituted arene, that is, toluene, with 2-diazo-1,3-indandione (**12**) by means of $Rh_2(OAc)_4$ as the catalyst,[107] only gave a mixture of 2- and 4-carbene insertion products. Without a directing group on the aryl moiety or specifying the electronic property of the aryl unit regioselective aryl C–H functionalization of an aromatic substrate by carbene insertion can not be achieved although intramolecular aryl C(sp^2)–H functionalization can be realized at specific sites. In a view of applicability, direct intermolecular aryl C(sp^2)–H functionalization by carbene insertion is more useful in organic synthesis, which has recently attracted much attention. The strategy using a directing group on the aryl moiety with Rh(III) complex catalysts has recently been well documented, and diverse *O*- and *N*-bearing directing groups were successfully applied for this purpose.

In 2012, Yu, *et al.* reported Rh(III)-catalyzed aromatic C–H functionalization by carbene insertion with dimethyl diazomalonate.[226] Such an intermolecular coupling was achieved with $[Cp^*RhCl_2]_2$ as the catalyst, and AgOAc as the co-catalyst in methanol at 60 °C (Scheme 56). In most of the cases, arenes with oximes (**158**), amines (**159**), and carboxylic acids (**160**) as the directing groups reacted well with dimethyl diazomalonate with excellent regioselectivities and functional group tolerance. This protocol offers a new route to α-aryl carbonyl derivatives. Other types of acceptor/acceptor (donor) diazo compounds such as $MeO_2C(C{=}N_2)SO_2Ph$, $MeO_2C(C{=}N_2)PO(OEt)_2$, and $MeO_2C(C{=}N_2)CF_3$, $MeO_2C(C{=}N_2)Ph$, and $MeO_2C(C{=}N_2)CONHR$ were also applied in the reaction. In the case of aryl ketone oximes (**158**), 28–97% yields of **161** were obtained and an obvious *o*-position steric effect was observed. When benzyl methylamines **159** were used, a condensation process was followed the carbene insertion reaction to give isoquinolones **162** in 43–89% yields. 2-Naphthoic acid (**160**) was functionalized by the Rh(III)-catalyzed carbene insertion process to afford **163** (91%) which could be efficiently transformed to the corresponding isocoumarin. A plausible mechanism is proposed (Scheme 57). Initially, the precatalyst $[Cp^*RhCl_2]_2$ reacts with AgOAc for ligand exchange to form the cationic acetate-ligated species, which undergoes electrophilic C–H activation to generate rhodacycle **int-161a**. Coordinationn of the diazo compound with **int-161a** may

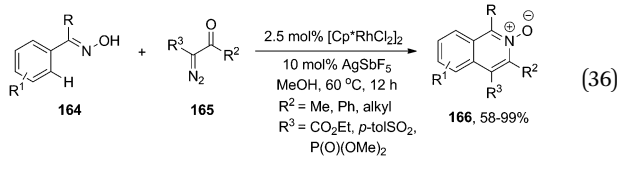


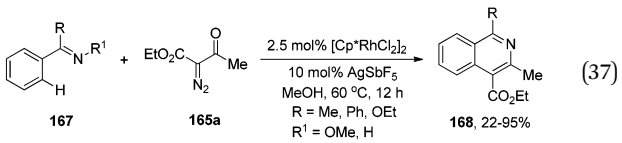
Scheme 56 Rh(III)-catalyzed aryl C(sp^2)–H functionalization by carbene insertion.



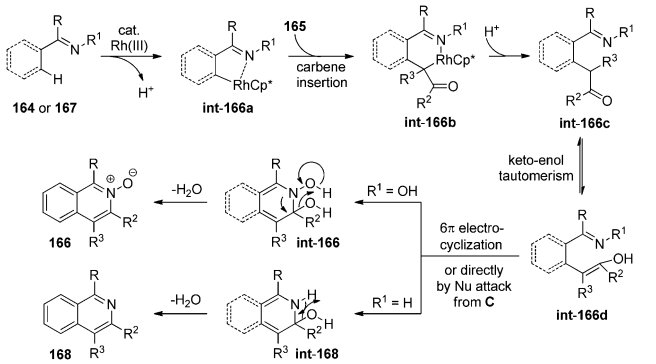
Scheme 57 Proposed mechanism for Rh(III)-catalyzed directed aryl C(sp^2)–H functionalization by carbene insertion.

produce the diazonium species **int-161b**. There may be two possibe pathways to form the final product from **int-161b**. In patway a, extrusion of dinitrogen forms Rh-carbene intermediate **int-161c**, which then undergoes migratory insertion to produce intermediate **int-161d**. Such an intermediate may also be formed by 1,2-aryl shift from **int-161b**. Protonolysis of **int-161d** gives the desired alkylated product and regenerates the catalytically active Rh species.





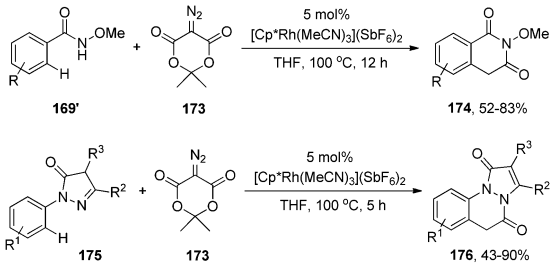
In a similar fashion, Glorius, *et al.* disclosed Rh(III)-catalyzed synthesis of multisubstituted isoquinoline *N*-oxides from oximes and diazo compounds (eqn (36) and (37), and Scheme 58).[227] Donor/acceptor diazo compounds (**165**) (R^2 = Me, Ph, alkyl; R^3 = CO_2Et, *p*-$tolSO_2$, $P(O)(OMe)_2$) and EDA could be applied in the reaction. The target isoquinoline *N*-oxides (**166**) were produced in 58–99% yields (eqn (36)). Under the stated conditions, the reaction of acetophenone *O*-methyl oxime (**167a**) reacted with diazo compound **165a** afforded isoquinoline **168a** (28%) with N–O bond cleavage (eqn (37)). Although such an oxime ether was not the suitable substrate, diphenylmethanimine (**167b**) and ethyl benzimidate (**167c**)



Scheme 58 Rh(III)-catalyzed aryl C(sp^2)–H functionalization of oximes by carbene insertion.

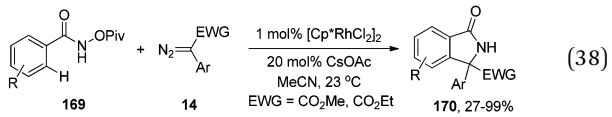
reacted well with **165a** to form **168b** (88%) and **168c** (95%), respectively. The proposed mechanism suggests that initial interaction of **164** or **167** with the Rh(III) catalyst ($[Cp^*RhCl_2]_2$) to generate five-membered rhodacycle **166a** which undergoes the carbene insertion reaction to form the six-membered rhodacycle **166b**. Subsequent protonolysis gives the alkylated intermediate **166c** which may tautomerize to produce the enol species **166d**. 6π-Electrocyclization then occurs to afford the final product **166** or **168** *via* intermediates **int-166** and **int-168**, respectively (Scheme 58).

The Rh(III) catalytic system was also applied for the C–H functionalization of benzhydroxamic acid derivatives (**169**) by carbene insertion with donor/acceptor diazo compounds (**14**) at room temperature (eqn (38)).[228] In the presence of 1 mol% $[Cp^*RhCl_2]_2$ as the precatalyst and 20 mol% CsOAc in acetonitrile at room temperature, the reaction of *O*-pivaloyl benzhydroxamic acids (**169**) with diazo compounds **14** afforded isoindolones (**170**) in 50–99% yields. In the case of using benzofuranyl- and indolyl-based diazo compounds the target products were only obtained in 27–37% yields. Aryl trifluoromethyldiazo compounds were successfully employed for the same purpose to reach 77–99% yields except in the case of using 4-MeO-phenyl CF_3-diazo compound as the donor/acceptor carbene source. The mechanistic studies have suggested that C–H activation is turnover-limiting and irreversible, and that carbene insertion favors the electron-deficient substrates. With the *in situ* generated hydrazones from arylketones, hydrazine, and MnO_2 as the donor/donor carbene source compounds, *N*-(pivaloyloxy)benzamides underwent the same type of Rh(III)-catalyzed carbene insertion reaction to form products of type **170**.[229] By means of the same catalytic system as depicted in eqn (38), substrates **169** underwent Rh(III)-catalyzed carbene insertion/[4+3] cycloaddition to give azepinone derivatives **172** (43–97%) (eqn (39)).[230] In most of the cases, the target products were obtained in good to excellent yields. Use of complex $[Cp^*Rh(MeCN)_3](SbF_6)_2$ as the catalyst the reaction of *N*-methoxybenzamides (**169′**) reacted with α-diazotized Meldrum's acid (**173**) gave isoquinolinediones (**174**) in 52–83% yields.[231] In the same manner, edaravone derivatives **175** were efficiently functionalized by carbene



Scheme 59 Rh(III)-catalyzed carbene insertion to aryl C(sp^2)–H bond with α-diazotized Meldrum's acid.

insertion to the aryl C(sp^2)–H bond with diazo compound **173** (Scheme 59).



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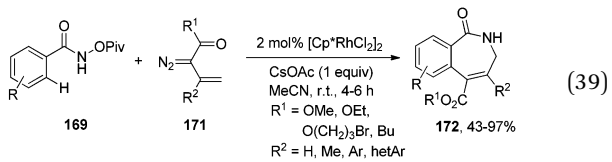
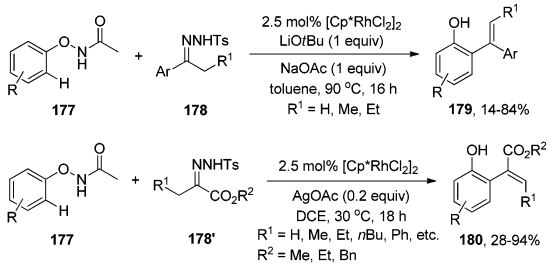


(39)

The aryl C(sp^2)–H bond in the aroxy moieties of *N*-aroxyacetamides (**177**) was also functionalized by carbene insertion under Rh(III) catalysis (Scheme 60).[232] In this case, the donor/donor carbene sources, that is, *N*-tosylhydrazones (**178**) of aryl ketones, reacted with *N*-phenoxyacetamides (**177**) and analogs to give *ortho*-alkenylated phenols (**179**) in 40–84% yields.

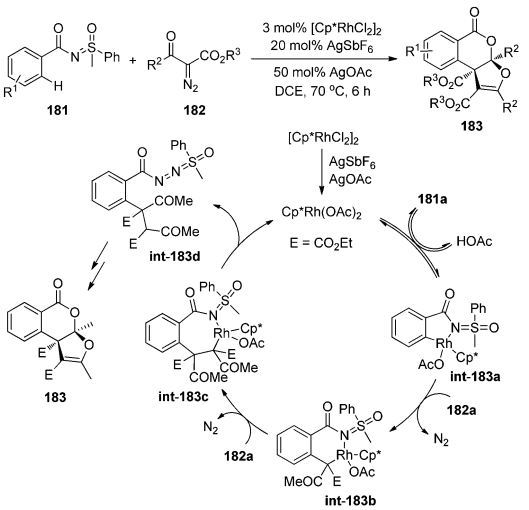
A 2-methyl group in the aryl moiety of the *N*-tosylhydrazone substrate exhibited an obvious negative impact on the reaction efficiency, leading to the target product in 14% yield. A wide range of functional groups such as alkyls, halogens, methoxy, cyano, CO_2Me, and furyl were tolerated. When donor/acceptor diazo compounds were used in the absence of *t*BuOLi base and by replacing NaOAc with AgOAc, the reaction of **177** produced the target products **180** in 28–94% yields. The same strategy was applied for the synthesis of polyaryl-substituted olefins by using the *in situ* generated hydrazones of aryl alkyl ketones and hydrazine as the carbene source compounds.[233]



Scheme 60 Rh(III)-catalyzed carbene insertion to aryl C(sp^2)–H bonds of *N*-aroxyacetamides.

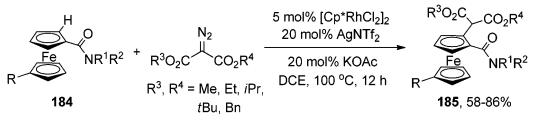
A Rh(III)-catalyzed formal carbene insertion to aryl C(sp^2)–H bond/diannulation sequence was developed to access furo[2,3-*c*]isochromenes (**183**) from the reaction of sulfoximine benzamides (**181**) and α-diazo carbonyl compounds (**182**) (Scheme 61).[234] Rh(III)-catalyzed double carbene insertion to C(sp^2)–H and C(sp^3)–H bonds successively occurred, followed by the diannulation process. Mechanistic studies reveal that the alkyl-rhodium intermediate **int-183b** formed by carbene insertion to aryl C–H is directly trapped with the other molecule of the carbene species to undergo carbene insertion to the alkyl C(sp^3)–H bond, followed by subsequent intramolecular cyclization reaction of **int-183b**. Sulfoximine is released *in situ*, which features a traceless directing group.

An amino moiety and its variants can act as effective directing groups for other Rh(III)-catalyzed intermolecular aryl C(sp^2)–H functionalization with diazo compounds. Ferrocenyl amides **184** reacted well in 1,2-dichloroethane with acceptor/acceptor diazo compounds, that is, dimethyl diazomalonate and its analogs, to give the target products **185** (58–86%) (eqn (40)).[235] However, the donor/acceptor diazo compound Ph(C=N_2)CO_2Me and acceptor/acceptor diazo compound MeCO(C=N_2)CO_2Et could not undergo the same type of reaction. With [Cp*$RhCl_2$]$_2$/NaOAc as the catalyst system C–H functionalization of aryl C(sp^2)–H bond with 4-diazoisochroman-3-imines enabled the synthesis of tetracyclic isochromeno[3,4-*c*]isoquinoline derivatives.[236] Sulfoximines acted as the directing groups to facilitate Rh(III)-catalyzed C–H functionalization by carbene insertion/annulation cascade to access 1,2-benzothiazines (**187**) (eqn (41)).[237] In most of the cases, the products were obtained in >90% yields. It is scalable, and the byproducts are dinitrogen and water. This protocol provides a highly regioselective and functional group-tolerant route to benzothiazine derivatives. A similar catalyst system was used to promote sulfonamide-directed *ortho*-C–H functionalization of aryl sulfonamides by carbene insertion with acceptor/acceptor diazo compounds,[238] and with the



Scheme 61 Rh(III)-catalyzed double carbene insertion/diannulation sequence for C–H functionalization of aryl C(sp^2)–H bond.

$[Cp^*RhCl_2]_2$/NaOAc combination in refluxing toluene aryl sulfonamides (**188**) reacted with pyridotriazoles **189** to form pyridylmethyl-functionalized aryl sulfonamides **190** (eqn (42)).[239] In this reaction, pyridotriazoles acted as the carbene precursor.



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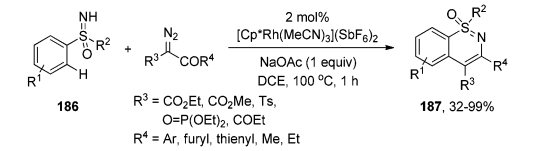

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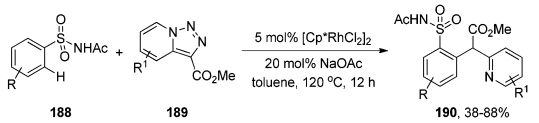

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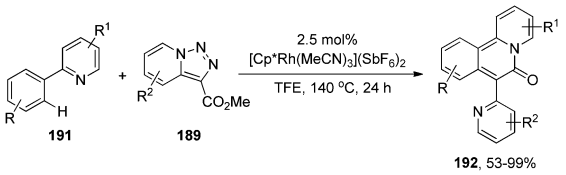
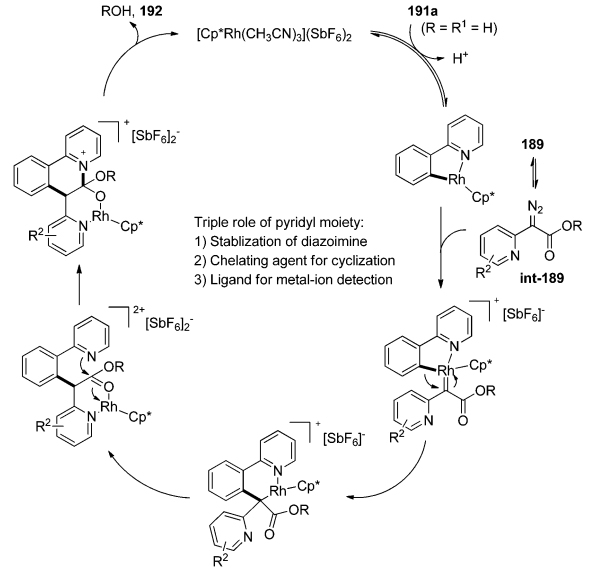


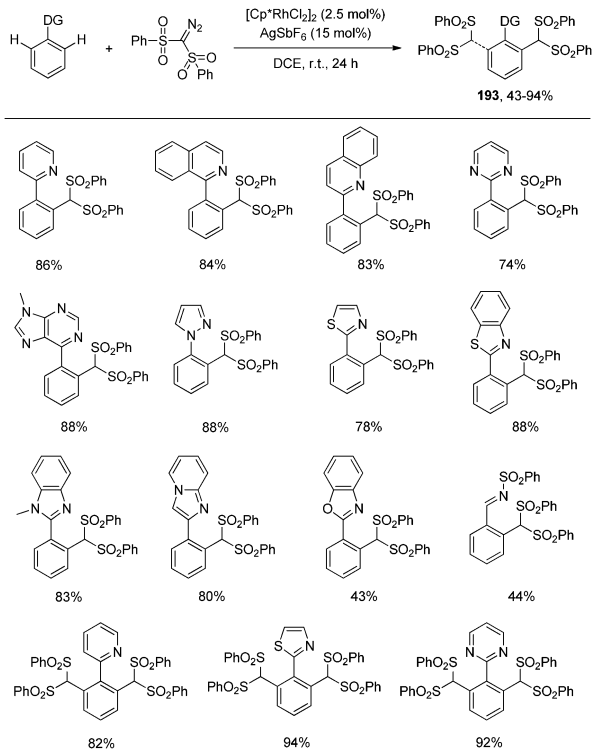
(43)

As extensively reported in transition-metal-catalyzed C–H activation, N-heterocyclic moieties have been used as the effective directing groups due to the good coordinating capability of nitrogen atom.[1–3] In order to achieve regioselective C–H functionalization of aryl C(sp^2)–H bonds by carbene insertion, the directing group strategy has been successfully applied in this area. N-Heterocyclic directing groups can play a crucial role in enabling efficient carbene insertion to C–H bonds. With 2-pyridyl as the directing group, 2-arylpyridines (**191**) were efficiently functionalized by Rh(III)-catalyzed carbene insertion with pyridotriazoles (**189**) as the azavinyl carbene precursor of type **int-189** (eqn (43) and Scheme 62).[240] With 2.5 mol% Rh(III) complex $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ or $[Cp^*RhCl_2]_2$/AgOAc as the catalyst in 2,2,2-trifluoroethanol (TFE) at 140 °C, the reaction gave the polycyclic N-heterocycle products (**192**) (53–99%). In most of the cases, the target products were produced in >90% yields, which exhibited novel UV/Vis absorption and emission properties in the presence of Cu^{2+} and Zn^{2+} ions. The mechanistic studies have elucidated that C–H bond activation is the first step before rhodium carbene insertion. The pyridyl moiety of pyridotriazoles plays three vital roles: (a) stabilization of the *in situ* generated diazo species; (b) acting as a chelating ligand for coordination with the catalyst, facilitating cyclization; (c) as a ligand for detection of metal ions with the products (Scheme 62). Pyridyls,[241–244] pyrazolyls and oxazolyl,[245] pyrimidyls,[245–247] indolyl,[248] and triazolyls[249] can play the same role in regiose-lective aryl C(sp^2)–H functionalization by carbene insertion.



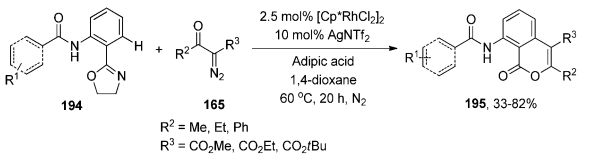
Scheme 62 Rh(III)-catalyzed, 2-pyridyl-directed C–H functionalization of aryl C(sp^2)–H bond.

With acceptor/donor diazo compound bis(phenylsulfonyl)-diazomethane as the carbene precursor under Rh(III) catalysis, aromatic C–H bonds were efficiently functionalized by N-heterocycle-directed carbene insertion.[244] An array of directing N-heteroaryl groups could be applied in the process (Scheme 63).



Scheme 63 Rh(III)-catalyzed, *N*-heteroaryl-directed C–H functionalization of aryl C(sp^2)–H bonds with bis(phenylsulfonyl)diazomethane.

In the presence of equimolar amounts of the C–H substrates and the diazo compound, the target monoalkylated products **193** were obtained in 43–94% yields. When excess of the diazo compound (>2 equiv.) was used, the double alkylation products were also efficiently accessed (82–94%). The di(phenylsulfonyl)-methyl group(s) in the products could be effectively transformed to methyl(s), giving the corresponding mono- or dimethylated arenes. In the assistance of an carboxylic acid, Rh(III)-catalyzed, oxazolyl-directed formal aromatic C–H functionalizetion by acceptor/acceptor carbene insertion was achieved.[250] The reaction of **194** and diazo compounds **165** in the presence of adipic acid in dioxane at 60 °C afforded the isocoumarin products of type **195** in moderate to good yields (33–82%) (eqn (44)). When the solvent was changed to THF at 80 °C, isoquinolines **196** were obtained in 46–80% yields (eqn (45)).



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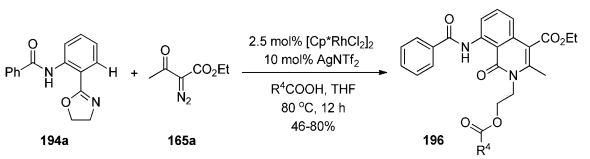

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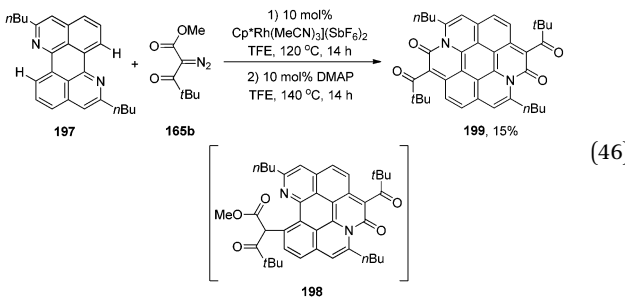
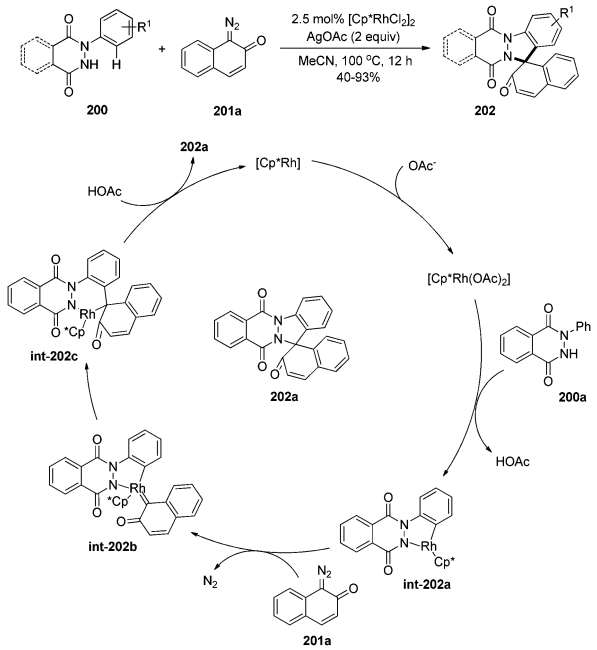


(46)

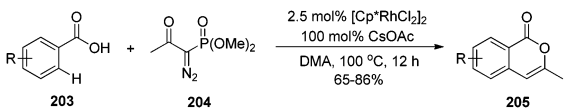
The diazaperylene precusor **197** was doubly functionalized by acceptor/acceptor diazo compound **165b** under Rh(III) catalysis *via* carbene insertion to the C–H bonds of the aryl moieties followed by treatment with DMAP (4-dimethylaminopyridine) (eqn (46)).[241] Unfortunately, the Rh(III)-catalyzed carbene insertion reaction only gave a mixture of the target product **199** and a monoalkylated, monoannulated product **198** due to the insufficient nucleophilicity of the heteroaromatic nitrogen atom to the electrophilic carbon of the ester group. However, simple addition of 10 mol% DMAP to the reaction mixture at 140 °C led to **199** in 15% isolated yield. This protocol provides a route to soluble amide-embeded coronenes which may be bestowed with specific photophysical properties.

By means of 2-phenyl-2,3-dihydrophthalazine-1,4-dione and derivatives **200** as the C–H substrates, a Rh(III)-catalyzed



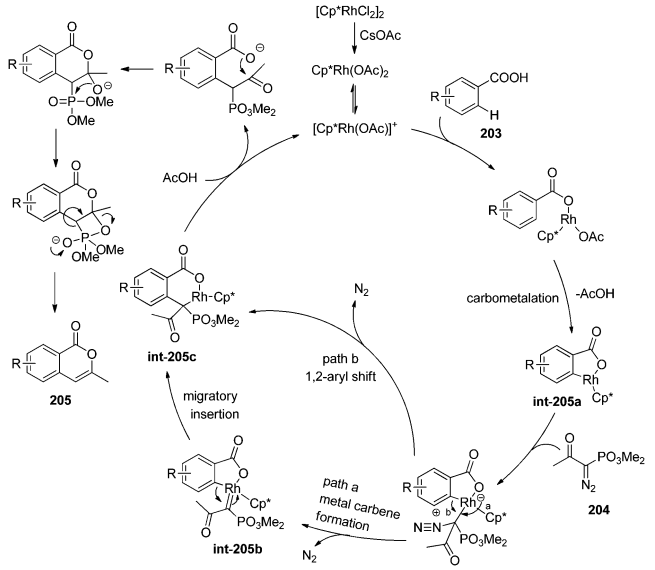
Scheme 64 Rh(III)-catalyzed, 2-pyridyl-directed carbene insertion to aryl C(sp^2)–H bond/annulation cascade.

carbene insertion to aromatic C–H/annulation cascade occurred to form spirocyclic indazole derivatives **202** in moderate to excellent yields (40–93%) (Scheme 64).[251] Initially, the active catalyst $Cp^*Rh(OAc)_2$ is possibly generated through *in situ* anion exchange of the precatalyst in the presence of AgOAc, followed by N-heterocycle-directed C–H cleavage to produce the five-membered rhodacycle intermediate **int-202a** as well as one molecule of acetic acid. Subsequent coordination and release of dinitrogen of 1-diazonaphthalen-2(*1H*)-one (**201a**) forms the rhodacycle carbene species **int-202b**. Migratory insertion of the *R*h-carbene generates the six-membered rhodacycle **int-202c**. Reductive elimination in the presence of HOAc delivers the final product. It is noteworthy that **int-202b** and **int-202c** were detected by HRMS spectroscopy.



(47)

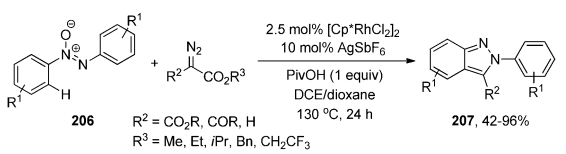
As shown in Scheme 56,[226] *ortho*-carbene insertion to the aromatic C–H bond of 2-naphthoic acid could be achieved under Rh(III) catalysis. In a similar fashion, a Rh(III)-catalyzed formal carbene insertion to C–H bond of benzoic acid/dephosphonylative annulation sequence was established with α-diazo-β-keto phosphonates (**204**) (eqn (47)).[252] With a combination of $[Cp^*RhCl_2]_2$ (2.5 mol%)/CsOAc (100 mol%) as the catalyst in DMA at 100 °C, the reaction efficiently proceeded to afford the target products **205** in good to excellent yields. Electron-donating and withdrawing groups such as methyl, methoxy, aryls, OCF_3, CF_3, halogens, and OH could be tolerated. However, in the case of using 4-nitrobenzoic acid, the



Scheme 65 Rh(III)-catalyzed carbene insertion to C–H bond of benzoic acid/dephosphonylative annulation sequence.

reaction did not happen. There are two possible pathways for the C–C bond formation between the *ortho*-positioned carbon atom of benzoic acid and the diazo carbon atom: (i) stepwise metal-carbene formation followed by migratory insertion, and (ii) concerted 1,2-aryl shift (Scheme 65). DFT calculations have suggested that the concerted pathway has a lower activation energy compared to the stepwise pathway by 1.5 kcal mol^{-1}. The five- and six-membered rhodacycles **int-205a** and **int-205c** are considered as the key intermediates to the target products.

Azoxy groups have recently been used as the directing groups for palladium-catalyzed *ortho*-C–H functionalization of azoxyarenes (**206**). The substrate scope is mostly limited to symmetrical azoxybenzenes, and the incorporated oxygen atom is always kept in the products. However, a Rh(III)-catalyzed carbene insertion/annulation sequence was realized with EDA and other acceptor/acceptor diazo compounds, that is, diazoesters, to give 3-acyl-2*H*-indazoles (**207**) (eqn (48)).[253] The azoxy instead of the azo group enabled the carbene insertion/[4+1] annulation rather than a classical [4+2] cyclization. The azoxy oxygen atom acted as a traceless directing atom, and its removal from the final products is not necessary. It is noteworthy that methyl 2-diazo-3-oxo-3-(pyridin-2-yl)propanoate, methyl 2-diazo-2-(pyridin-2-yl)acetate, and methyl 2-(benzo[*d*]thiazol-2-yl)-2-diazoacetate failed to undergo this type of reaction. The present protocol enables regioselective access to unsymmetrical azoxybenzenes.



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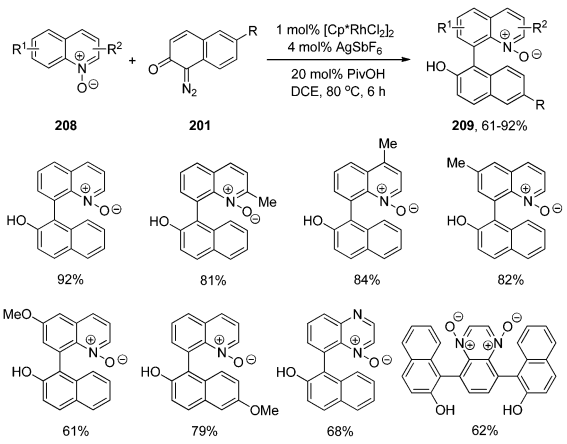
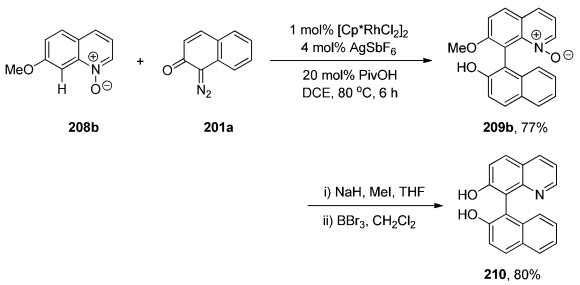
Rh(III)-catalyzed direct C(8)-arylation of quinoline *N*-oxides was documented by using diazonaphthalen-2(1*H*)-ones (**201**),



Scheme 66 Rh(III)-catalyzed C(8)-arylation of quinoline *N*-oxides.

offering a practical approach toward 8-aza-BINOL (Scheme 66).[254] In the presence of 1 mol% $[Cp^*RhCl_2]_2$ catalyst, 4 mol% $AgSbF_6$, and 20 mol% PivOH as the additives in dichloroethane at 80 °C, quinoline *N*-oxides **208** reacted with diazo compounds **201** to exclusively form C(8)-selective β-naphthol coupled compounds **209** through a Rh(III)-catalyzed carbene insertion to the C(8)–H bond of **208**/tautomerization sequence.[255] Diverse functional groups such as methyl, methoxy, alkoxys, cyclic alkyl, phenyl, F, Cl, Br, and NO_2 were tolerated on the aryl moiety of **208**, as well as methyl and Br on the pyridyl unit. Alkyls, methoxy, ester, amide, phenyl, acetyl, and Br could be tolerated on the aryl backbone of the diazo compounds. Interestingly, quinoxaline *N*-oxide also provided regioselective introduction of a β-naphthol moiety (68%). Bis(β-naphthol) groups were further introduced to the aryl moiety of quinoxaline by double arylation (62%). Notably, this protocol can be used for the late-stage modification of cinchonidine derivatives, and practical synthesis of 8-aza-BINOL (**210**) (Scheme 67).

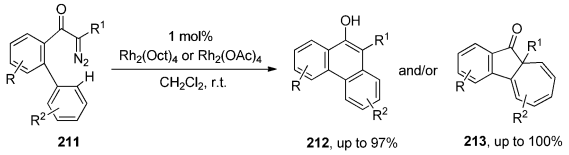
3.2.1.2. Rh(II) and Rh(I) complex catalysts. Rh(II) complex catalysts have been known to facilitate C–H functionalization of aryl $C(sp^2)$–H bonds by carbene insertion with diazo or other carbene source compounds. However, only very limited efforts have been devoted to this direction because a Rh(II) complex catalyst usually leads to poor regioselectivity, low reaction efficiency, and side reactions such as Büchner reaction, requires specific electronic features for the aromatic C–H substrates, and/or use combined bi- or trimetallic catalyst



Scheme 67 Practical synthesis of 8-aza-BINOL from quinoline *N*-oxides.

systems to quickly transform the *in situ* generated carbene insertion products in a reaction sequence.

Biphenyl 2-diazoketones (**211**) containing various electron-withdrawing groups (EWG = COMe, CN, CO_2Et, COPh, SO_2Me, and SO_2Ph) on the diazo carbon were treated in CH_2Cl_2 at room temperature in the presence of a Rh(II) complex catalyst, undergoing aryl C(sp^2)–H functionalization by carbene insertion followed by tautomerization to give phenanthrol derivatives **212** and/or by Büchner reaction to afford benz[α]azulenone derivatives **213** (eqn (49)).[256] Distribution of both the products depended on the electronic property of the reactive aryl moiety as well as the EWG. Both of the products could be formed as the major products. When two reactive aryl groups were present in a diaryl-substituted diazosulfonamide (**214**), two types of aryl C(sp^2)–H functionalization products by carbene insertion were concurrently formed (eqn (50)).[257] With 2 mol% $Rh_2(esp)_2$ as the catalyst substituted arenes reacted with diazo quinones (**79**) to give a mixture of *p*/*o*-C–H functionalization products (**217**) (Scheme 68).[258] When the substituent on the arene substrates was an EDG, up to *p*/*o* > 20 : 1 selectivity was obtained. When the substituent was an EWG such as Br and F, the *p*/*o* regioselectivity ranged from 1 : 1 to 2.5 : 1. When other Rh(II) complexes such as $Rh_2(OAc)_4$, $Rh_2(TFA)_4$, $Rh_2(Piv)_4$, and $Rh_2(TPA)_4$ were applied as the catalysts, only 14–40% yields could be reached, whereas use of $Rh_2(esp)_2$ as the catalyst gave the target products in 35–89% yields. This method may be employed for the late-stage modification of drugs and organic materials.



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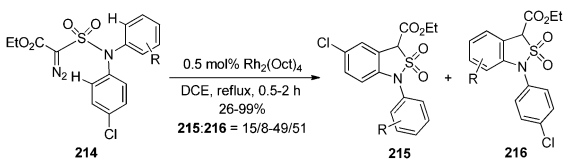
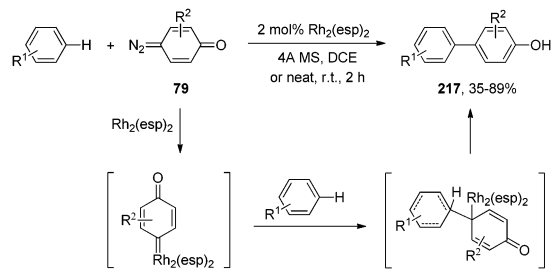
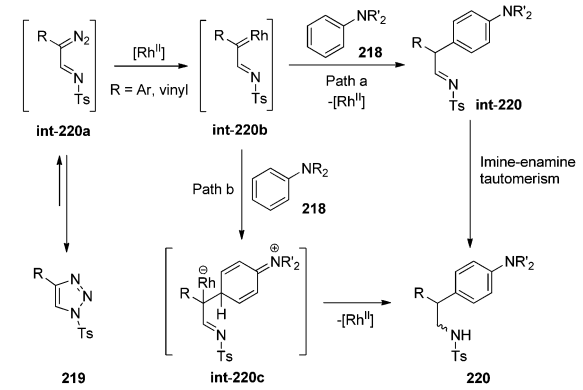


(50)

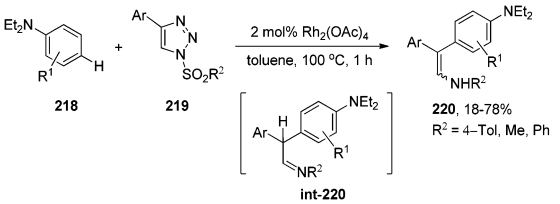
Direct arylation of 2-diazoimines, that is, precursors to azavinyl carbenes, generated from readily accessible *N*-SO_2R substituted 1,2,3-triazoles was realized by means of *N*,*N*-diethylanilines (**218**) as the C–H substrates through carbene insertion to the aryl C(sp^2)–H bond under Rh(II) catalysis (eqn (51)).[259] Using 2 mol% $Rh_2(OAc)_4$ as the catalyst in toluene at 100 °C, anilines **218** reacted with 4-aryl triazoles **219** to give 2,2-diaryl enamides **220** in moderate to good yields (50–70%). The reaction initially formed the carbene insertion product **int-220**, which then underwent imine–enamine tautomerism to afford the enamide product **220** (Scheme 69). Vinyl and heteroaryl-functionalized *N*-tosyl-1,2,3-triazoles could also be applied in the reaction. The electron-donating NEt_2 group is required to enable this transformation, and the reaction involves the chemo- and regioselective insertion of rhodium azavinyl carbene to the aryl C(sp^2)–H bond. **int-220a** and **int-220b** are considered as the key reactive intermediates to the target product **220** *via* intermediates **int-220** and **int-220c**, respectively. In the presence of a third reactant such as an imine of benzaldehyde, and chiral phosphoric acid as the cocatalyst, $Rh_2(OAc)_2$-catalyzed the enantioselective aryl C(sp^2)–H functionalization of electron-rich anilines of type **218** with diazo compounds also occurred.[260] A combination of three complexes ($Rh^{II}/Au^{I}/Cu^{II}$) was used to achieve an intramolecular aryl C(sp^2)–H functionalization by carbene insertion with diazo/Conia-ene cascade for the synthesis of spirocarbocycles.[261]



Scheme 68 Rh(II)-catalyzed aryl C(sp^2)–H functionalization by carbene insertion.

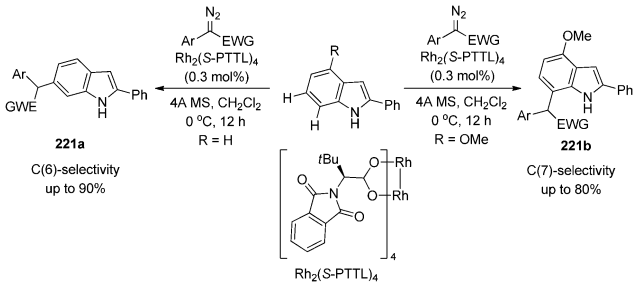


Scheme 69 Rh(II)-catalyzed aryl C(sp^2)–H alkylation by carbene insertion with substituted 1,2,3-triazoles.



(51)

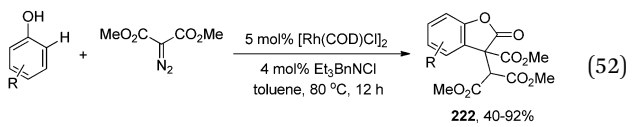
By modulating the steric and electronic properties of both the heteroaromatic and aromatic rings of an indole backbone, site-selective C–H functionalization by carbene insertion underwent at the aromatic C–H positions instead of the electron-rich heteroaryl C(3) position in indole derivatives (Scheme 70).[262] The regioselectivity and reaction efficiency were well controlled by introduction of an aryl group at C(2) position and an electron-donating group such as methoxy at C(4) position



Scheme 70 Rh(II)-catalyzed regioselective aromatic C–H functionalization of protic indoles by carbene insertion.

under bulky Rh(II) complex ($(S$-PTTL)$_4$) catalysis with donor/acceptor diazo compounds as the carbene precursor. The target C(6) and C(7)-alkylation products **221a** and **221b** were also obtained in up to 90% and 80% yields, respectively.

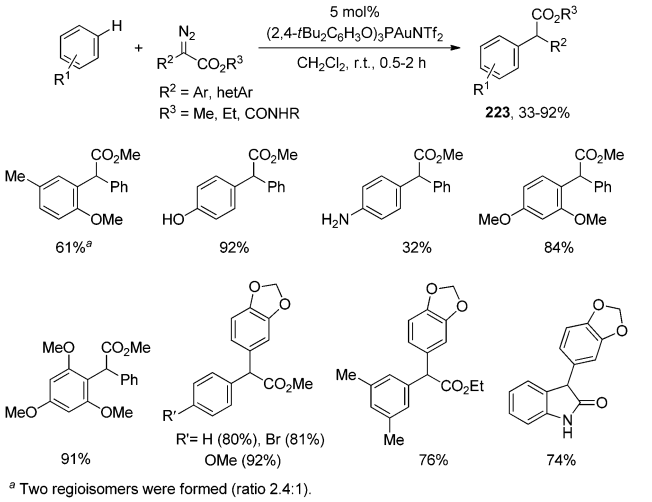
DFT calculations have revealed that a Rh(II) complex catalyst usually leads to carbene insertion to the O–H bond of phenol with a diazo compound,[263] suggesting that Rh(II) catalysts are not suitable for the phenolic C(sp^2)–H functionalization by carbene insertion. However, Rh(I) complex [Rh(COD)Cl]$_2$ was successfully used for this purpose, which represents a rare example of a Rh(I) complex catalyst enabling aryl C(sp^2)–H functionalization by carbene insertion with diazo compounds (eqn (52)).[264] The *ortho*-C–H functionalization of substituted phenols occurred with dimethyl diazomalonate in the presence of 2 mol% [Rh(COD)Cl]$_2$ as the catalyst. Formation of the target products **222** proceeded *via* a pathway different from that as proposed in Scheme 61,[234] in which sequential carbene insertion to the aryl C(sp^2)–H, cyclization, and carbene insertion to newly formed alkyl C(sp^3)–H bond enable generation of compounds **222** (40–92%). It is noteworthy that use of [Rh(ethylene)$_2$Cl]$_2$ as the catalyst in the presence of a chiral diene ligand enantioselective version of this transformation was realized.



(52)

3.2.2. Gold, copper, and silver complex catalysts. As investigated in gold-catalyzed reactions of phenol with diazo compounds, Au(I) complexes were found to favor the aryl C(sp^2)–H bond functionalization by carbene insertion.[263] Zhang and Liu, *et al.* reported that Au(I) complex [(2,4-tBu$_2$C$_6$H$_3$O)$_3$-PAu(NCPh)]SbF$_6$ could efficiently catalyze the *para*-C–H functionalization of mono-alkyl-substituted benzenes with donor/acceptor diazo compounds.[222]

With a similar Au(I) complex, that is, (2,4-tBu$_2$C$_6$H$_3$O)$_3$-PAuNTf$_2$ as the catalyst, Me/OMe, OH, NH$_2$, and OMe-substituted benzenes reacted with phenyldiazoacetate to give the carbene insertion products **223** in 32–92% yields, while these arenes usually undergo Rh-catalyzed carbene insertion to

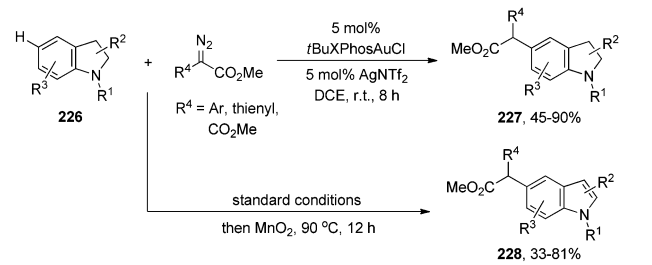


[a] Two regioisomers were formed (ratio 2.4:1).

Scheme 71 Au(I)-catalyzed aryl C(sp^2)–H functionalization of activated arenes by carbene insertion.

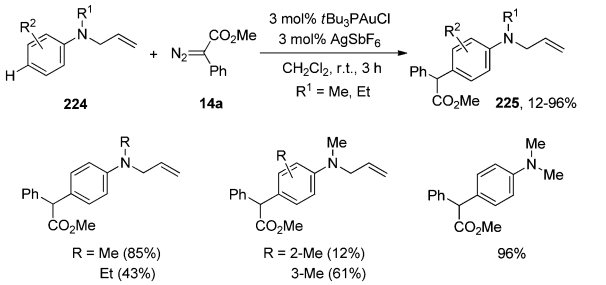
alkyl C–H bonds, Cu-catalyzed carbene insertion to O–H or N–H bond, or Fe-catalyzed Büchner reaction.[265] For other functionalized arenes their reactions with methyl phenyldiazoacetate (**14a**) and its derivatives afforded the target products in 64–92% yields (Scheme 71). It is noteworthy that this catalytic system was also applicable to 2-methylbenzofuran and 1,2,5-trimethylpyrrole, and their reactions with phenyldiazoacetate **14a** gave the corresponding benzylation products (74–86%), although they usually undergo Rh-catalyzed cyclopropanation. Such a protocol is potentially useful for further direct functionalization of the substituted aryl moieties in a complex molecule.

In a fashion similar to those Rh(II) complex catalysts facilitating the *para*-C–H functionalization of aniline derivatives with diazo compounds,[259,260] Au(I) complex tBu$_3$PAuCl effected the C–H functionalization of allyl(alkyl)amino-substituted benzenes **224** with phenyldiazoacetate **14a** at room temperature, giving the target products **225** in low to excellent yields (eqn (53)).[266] An obvious negative steric effect was observed on the reaction efficiency. By means of 5 mol% tBuXPhosAuCl as the catalyst in dichloroethane at room temperature, aryl C(sp^2)–H functionalization of indolines (**226**) with donor/acceptor diazo compounds proceeded efficiently to form the



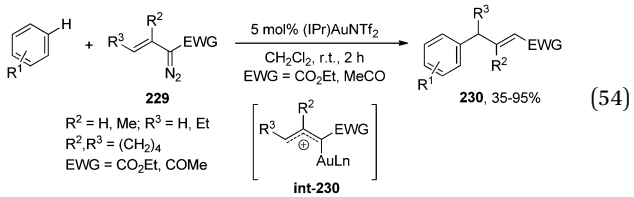
Scheme 72 Au(I)-catalyzed aryl C(sp^2)–H functionalization of aniline and indoline derivatives by carbene insertion.

corresponding products **227** in 45–90% yields[267] (Scheme 72). When acceptor/acceptor diazo compound dimethyl diazomalonate was used, the product was obtained in 42% yield. A one-pot, two-step process was developed to get indole derivatives **227**. After the first step reaction was complete, MnO_2 was added, and the resultant mixture was then stirred at 90 °C for another 12 h to afford the corresponding indole products **228** (33–81%).



(53)

Stabilized vinyl diazo compounds were applied to NHC–Au(I)-catalyzed C–H functionalization of substituted arenes, heteroarenes, and olefins by carbene insertion. By means of vinyl diazo compounds **229** as the carbene source, 5 mol% (IPr)AuNTf$_2$ as the catalyst in CH_2Cl_2 at room temperature the reaction of electron-donating group(s)-substituted benzenes gave the allylation products **230**, which were formed from the formal carbene insertion to the aryl C(sp^2)–H bond *via* the possible metal vinylcarbene species **int-230** (eqn (54)).[268] With Au(I) complex [(2,4-*t*Bu$_2$C$_6$H$_3$O)$_3$PAuNTf$_2$] as the catalyst, a carbene insertion to aryl C(sp^2)–H bond/aldol annulation sequence was enabled access of indanol and tetrahydronaphthalenol derivatives **232** through construction of two adjacent quaternary stereocenters from keto-functionalized arenes **231** (eqn (55)).[269] The present protocol features use of readily available starting materials, good diastereoselectivity, and versatile functional group tolerance. It is noted that this method is potentially applicable for the enantioselective synthesis of the chiral products.



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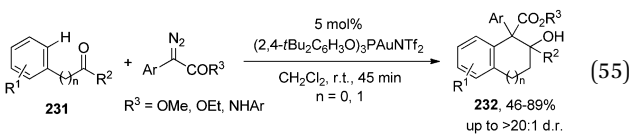
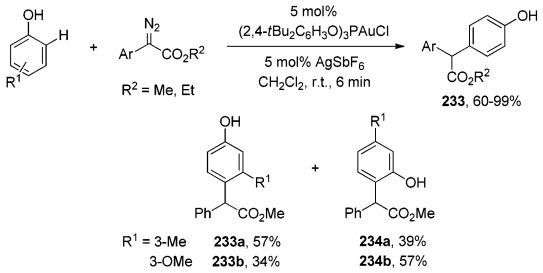


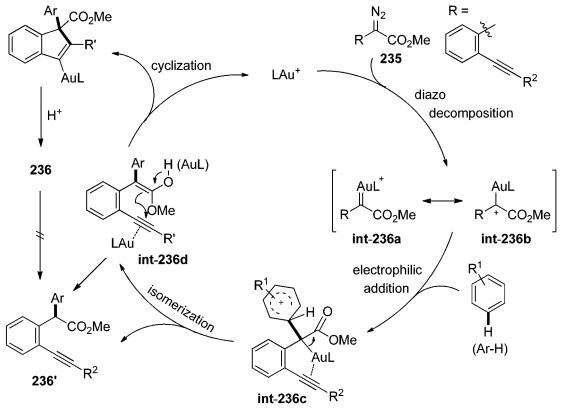
(55)

In 2014, Zhang and Liu, *et al.* reported *para*-selective aryl C(sp^2)–H functionalization of phenols by carbene insertion with diazo compounds under gold catalysis (Scheme 73).[270] Direct C–H functionalization of phenols with diazo compounds



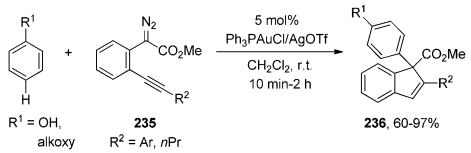
Scheme 73 Au(I)-catalyzed aryl C(sp^2)–H functionalization of phenols by carbene insertion with diazo compounds.

has been highly challenging due to the competitive chemoselective carbene insertion to O–H bond by using various transition-metal catalysts such as Rh, Cu, Ru, Fe, and Pd.[271,272] In the presence of 5 mol% (2,4-*t*Bu$_2$C$_6$H$_3$O)$_3$PAuCl/5 mol% AgSbF$_6$ in CH_2Cl_2 at room temperature, phenols reacted with donor/acceptor diazo compounds 2-aryl-2-diazoacetates of type **14** and their carbonyl analogs efficiently afforded the *para*-C–H functionalization (alkylation or benzylation) products **233** (60–99%). In most of the cases, the yields were >85%. It was found that use of the bulky phosphite ligand (2,4-*t*Bu$_2$C$_6$H$_{30}$)$_3$P completely compressed carbene insertion to the phenolic O–H bond compared to the case using PPh_3 and $(EtO)_3P$ as the ligands (carbene insertion to O–H yields: 46% and 27%, respectively). The regioselective C–H functionalization always occurred at the *para*-sites except in the case of using 3-methyl or 3-methoxy-substituted phenols as the arene substrates which formed two isomeric products **233a**/**234a** (57%/39%) and **233b**/**234b** (34%/57%), respectively. This methodology enables the unprecedented aryl C(sp^2)–H functionalization rather than carbene insertion to the phenolic O–H bond, featuring wide substrate scopes, good functional group tolerance, mild conditions, and high efficiency. This report can be considered as the first example of C–H functionalization of unprotected phenols with diazo compounds. The mechanistic studies have revealed that the ligands have an important impact on the carbene insertion to the aryl C(sp^2)–H bond, and the reaction proceeds through a pathway *via* the formation of an enolate-like intermediate.[273] The DFT calculations support that two water molecules serve as a proton shuttle, which favors the chemoselective C–H functionalization. With *o*-alkynylaryl-2-diazoesters (**235**) as the carbene source compounds, Ph_3PAuCl/AgOTf as the catalyst system in CH_2Cl_2 at room temperature aryl C(sp^2)–H functionalization through a carbene insertion/Conia-ene reaction sequence was efficiently achieved to construct indene scaffolds **236** (eqn (56)).[274] As shown in the proposed mechanism (Scheme 74), the electrophilic gold(I) carbene intermediate **int-236a**/**int-236b**, which is formed *in situ* from an *o*-alkynylaryl-2-diazoester (**235**) in the presence of the gold complex catalyst, reacts with the nucleophilic arene substrate to generate gold zwitterionic species **int-236c** which undergoes isomerization involving 1,4-H shift to give the enol intermediate **int-236d**. Subsequent 5-endo-*dig*



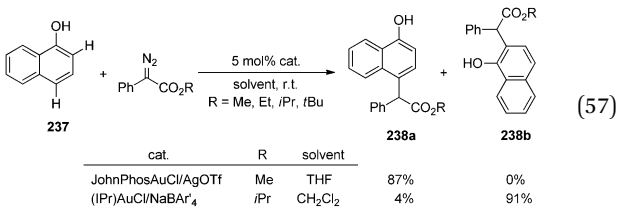
Scheme 74 Au(I)-catalyzed aryl C(sp^2)–H functionalization *via* a carbene insertion/Conia-ene reaction sequence.

carbocyclization onto the internal alkyne activated by the gold catalyst followed by protodeauration affords the target product **236**. The direct C–H functionalization products of type **236′** from carbene insertion might be formed as the side products.



(56)

The direct C–H functionalization of naphthols has also attracted interest among organic chemists. Encouraged by the above-discussed results for direct C–H functionalization of phenols, Zhang and Liu, *et al.* investigated the aryl C(sp^2)–H functionalization of naphthols by carbene insertion with diazo compounds (eqn (57)).[275] Taking the reaction of 1-naphthol (**237**) with phenyldiazoacetate (**14a**) by means of 5 mol% JohnPhosAuCl/AgOTf as the catalyst at room temperature as an example, the *para*-site C–H functionalization product **238a** was obtained in 87% yield without formation of the *ortho*-C–H functionalization product **238b**. It was envisioned that enhancement of the coordination between the catalyst and hydroxy group might elevate the *ortho*-selectivity by using the weakly coordinating BAr'_4 anion as the counterion, such an action remarkably increased the yield of **238b** to 91% with only minor formation of **238a**. Both the catalyst systems were applied for the synthesis of these two kinds of aryl C(sp^2)–H functionalization products from substituted naphthols. This switchable C–H functionalization of unprotected naphthols was enabled by tuning the ligands, counterions, and solvents. The mechanistic studies have revealed that interaction between the gold catalyst and the hydroxy group plays a crucial role in switching the site-selectivity by carbene insertion. The $Ph_3PAuCl/AgSbF_6$ catalyst system was documented for the C(sp^2)–H functionalization of 2-naphthols with methyl phenyldiazoacetate (**14a**).[276] The 1-site C–H functionalization occurred by carbene insertion and was followed by intramolecular lactonization.



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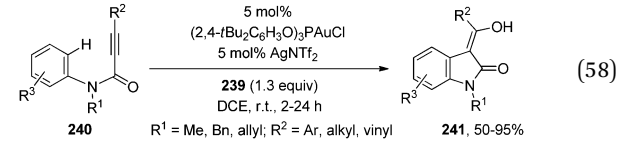
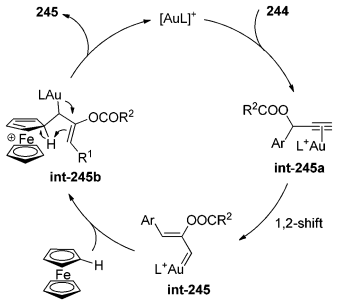


(58)

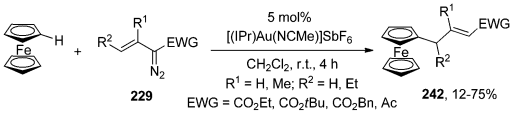
Functionalized alkynes can be used as the carbene source compounds for transition-metal-catalyzed carbene insertion to C–H bonds. In the presence of Au(I) complex $(2,4\text{-}tBu_2C_6H_3O)_3$-PAuCl/$AgNTf_2$ and 2-bromopyridine *N*-oxide (**239**), *N*-arylpropiolamides (**240**) underwent formal intramolecular carbene insertion to aryl C(sp^2)–H bond by gold carbene generated *in situ*/oxygen atom transfer to form 3-acyloxindole derivatives (**241**) in 50–95% yields (eqn (58)).[277] In most of the cases, the yields were >85%, and notably, when the *N*-protecting group was acetyl, the reaction did not occur. Such a reaction proceeded with an extremely good substrate scope, exhibiting a great potential for further structural diversification. Other examples of aryl C(sp^2)–H functionalization by insertion of *in situ* generated gold carbenes from alkynyl-containing aromatic substrates and Au(I) complex catalysts were also documented.[278,279]

Direct functionalization of ferrocence has attracted much interest because functionalized ferrocenes have been demonstrated for a wide range of applications in organometallic chemistry, homogeneous catalysis, materials science, and medicinal chemistry. However, the direct methods to functionalize ferrocence are very limited and dominantly involve: (a) initial Friedel–Crafts acylation followed by subsequent transformations of the resultant acylferrocenes, and (b) initial formation of ferrocenyl lithium by treating it with aryllithium reagents followed by coupling with suitable carboelectrophiles. Although ferrocene is more active than benzene, it can not be directly functionalized by the recently well-developed C–H activation methods.[1–3] As the representative of non-substituted metallocenes, ferrocene was applied in the carbene insertion reaction systems.[280–282] In the presence of the NHC–Au(I) complex catalyst, that is, [(IPr)Au(NCMe)]SbF_6, ferrocene was functionalized by donor/acceptor diazo compounds vinyldiazoacetates (**229**) (eqn (59)).[280] The reaction formally proceeded as a carbene insertion reaction *via* an electronic aromatic substitution pathway, giving the target products **242** in 12–75% yields. The catalytic system was also applicable for the direct C–H functionalization of ruthenocene by elevating the reaction temperature to 50 °C, affording the target products **243** (25–44%) with vinyldiazoacetates as the carbene source compounds (eqn (60)). When α-aryl-α-diazoacetates featuring electron-withdrawing substituents on the aryl moiety were



Scheme 75 Au(I)-catalyzed aryl C(sp^2)–H functionalization *via* a carbene insertion/Conia-ene reaction sequence.

used, the C–H bond at the α-position of the carbene insertion products were readily oxidized to O–H during work-up in air.[281] By means of 5 mol% $(2,4\text{-}t\text{Bu}_2\text{C}_6\text{H}_3\text{O})_3\text{PAuNTf}_2$ as the catalyst, treatment of propargylic esters (**244**) as the carbene source compounds in dichloromethane at room temperature for 15 min resulted in vinylated ferrocene derivatives **245** *via* formal carbene insertion to ferrocenyl C(sp^2)–H bond (eqn (61)).[282] *In situ* generated gold carbene species **int-245** is presumably inserted to the ferrocenyl C(sp^2)–H bond *via* a cyclic transition state **TS-245** to control the *E*-configuration of the final product (Scheme 75). Coordination of the gold catalyst to the alkyne motif triggers a 1,2-acyloxy rearrangement to generate the vinylgold carbene intermediate **int-245** *via* Au(I) complex **int-245a**. Attack at the ferrocenyl C–H bond by the carbenic electrophilic carbon atom of intermediate **int-245** forms allylgold(I) intermediate **int-245b**. Susequent demetalation and intramolecular 1,4-H transfer affords the final product **245**.



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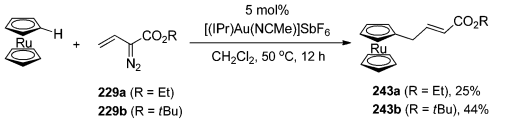
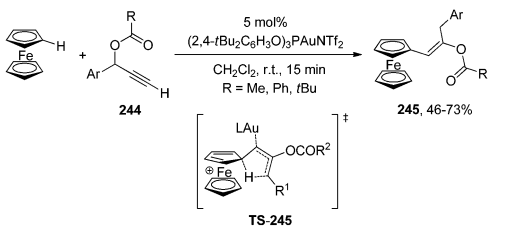
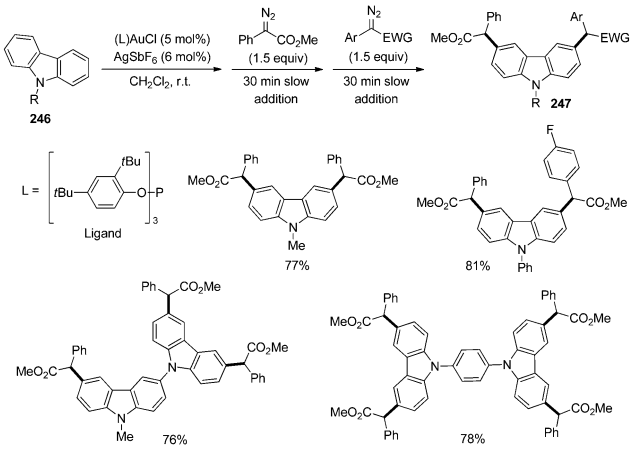


(60)



(61)

It should be noted that Au(I) complex catalysts can also facilitate C(sp^2)–H functionalization of the aryl moieties in carbazoles,[283] phenothiazines,[284] and unprotected NH-heterocycles[285] by carbene insertion to the aromatic C(sp^2)–H bonds with donor/acceptor diazo compounds. For example, multiple C–H functionalization of the aryl moieties in carbazoles **246** was achieved with $(2,4\text{-}t\text{Bu}_2\text{C}_6\text{H}_3\text{O})_3\text{PAuCl}$ as the

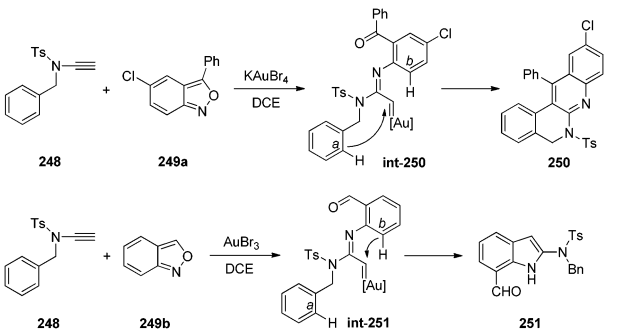


Scheme 76 Au(I)-catalyzed multiple aryl C(sp^2)–H functionalization of carbazoles by carbene insertion.

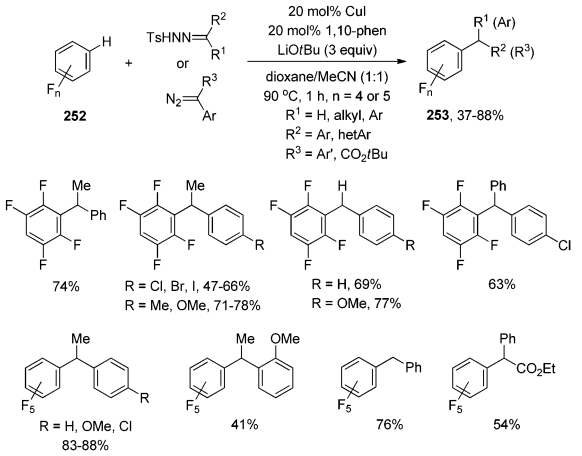
catalyst, giving multiply alkylated carbazoles **247**. Such a one-pot stepwise approach enables introduction of two different carbene fragments to allow orthogonal deprotection and straightforward derivatization (Scheme 76).[283]

Using $KAuBr_4$ as the catalyst, the reaction of *N*-benzyl ynamide **248** with substituted antranil **249a** is proposed to undergo C^a-nucleophilic attack to generate quinoline-fused polyazaheterocycle **250**,[286] while annulation of unsubstituted antranil **249b** with ynamide **248** under $AuBr_3$ catalysis results in unprotected 7-acylindole **251** where C^b attack is favored (Scheme 77).[287] For these transformations, a unified rationale for Br-migration on α-amino gold(III)-carbene is proposed by DFT calculations.[288] A N-donation/abstraction substitution mechanism is established for the substituted anthranils, and direct C–H nucleophilic attack is considered to be involved with the substituted anthranils. The computational studies provide insight for developing new α-amino gold(III)–carbene-catalyzed reactions.

Compared to Au(I) complex catalysts copper and silver complex catalysts have been paid much less attention for the aryl C(sp^2)–H bond functionalization by carbene insertion due to the above-mentioned side reactions such as carbene insertion to C(sp^3)–H bonds, cyclopropanation, and Büchner reaction. Only in the cases satisfying the electronic and steric



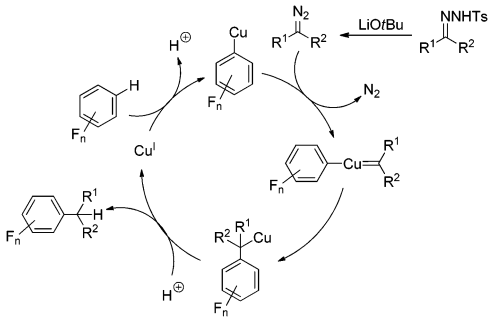
Scheme 77 Au(III)-catalyzed annulation of *N*-benzyl ynamides with anthranils *via* carbene insertion to aryl C(sp^2)–H bonds.



Scheme 78 Cu(I)-catalyzed aryl C(sp^2)–H functionalization of polyfluoroarenes by carbene insertion.

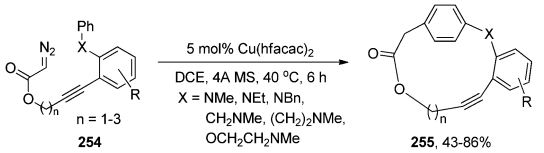
requirements of the substrates and catalysts, specific reactions can selectively occur. Wang, *et al.* reported Cu(I)-catalyzed carbene insertion to activated aryl C(sp^2)–H bonds by means of *N*-tosylhydrazones or diazo compounds as the carbene source (Scheme 78).[289] By means of 1,2,4,5-tetrafluorobenzene (**252a**, n = 4) as the C–H substrate, 20 mol% CuI/20 mol% 1,10-phenanthroline (1,10-phen) as the ligand, and *N*-tosylhydrazones as the donor/donor carbene source, the C–H functionalization process proceeded smoothly in dioxane at 90 °C to afford the desired alkylation products **253** (42–84%). Various *N*-tosylhydrazones (R^1, R^2 = alkyl, aryl, or H) were applicable in the reaction. In the case of pentafluorobenzene (**252b**, n = 5) the reaction with *N*-tosylhydrazones proceeded more efficiently than the former. It is noted that use of 2-furyl or vinyl-based *N*-tosylhydrazones led to the low yields (37–42%). Donor/acceptor diazo compounds were also the effective carbene source in the reaction. The reaction is initiated by deprotonation of the relatively acidic C–H bond of the polyfluoroarene substrate followed by transmetalation with the Cu(I) catalyst to generate the polyfluoroaryl-copper species. Subsequent interaction with the diazo species generated *in situ* from a *N*-tosylhydrazone forms a copper carbene intermediate which then undergoes a migration insertion process to result in an alkyl carbene species. Protonation of such an alkyl carbene species produces the final product and furnishes a catalytic cycle (Scheme 79).

A Cu(II) catalyst system was established for macrocycle construction through intramolecular carbene insertion to aryl C(sp^2)–H bonds in alkynyl-functionalized diazoacetates (eqn (62)).[290] With 5 mol% $Cu(hfacac)_2$ as the catalyst, 4A molecular sieves as the additive in dichloroethane at 40 °C, the alkynyl-embodied diazoacetates (**254**) underwent intramolecular carbene insertion to aryl C(sp^2)–H bond of the labile aryl moiety, establishing O,N-macroheterocycles (**255**). In the presence of a copper catalyst, the insertion took place dominantly with the tethered nucleophilic aniline species, resulted in the macrocyclic alkyne products **255** (43–86%). The substituents on the *ortho*-disubstituted phenyl unit only exhibited a



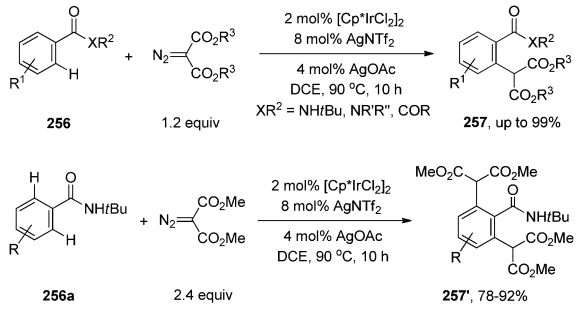
Scheme 79 Proposed mechanism for Cu(I)-catalyzed aryl C(sp^2)–H functionalization of polyfluoroarenes with *N*-tosylhydrazones.

slight impact on the reaction efficiency to form the target products (77–82%). It was found that the reactivity or chemo/regioselectivity of **254** was diminished as the linker chain was extended. In the cases of 16- and 17-membered ring sizes, the starting alkynyl-phenyldiazoacetate substrates also underwent intramolecular carbene insertion to alkyl C(sp^3)–H bonds (19–35% yields). When more challenging substrates bearing the less nucleophilic benzyl group as the carbene acceptor, no desired carbene insertion to aryl C(sp^2)–H bonds of the benzyl moiety was observed, and only a complex decomposition mixture was generated. However, this kind of substrates could undergo efficient intramolecular Büchner reaction to give cycloheptatriene-embodied macrocyclic alkyne products by using $Rh_2(esp)_2$ as the catalyst at 0 °C. These results are the first example of direct and selective construction of cycloalkyne scaffolds through transition-metal-catalyzed C–H functionalization by carbene insertion and Büchner reaction. $Cu(acac)_2$ was also reported as the catalyst for intramolecular carbene insertion to the aryl C(sp^2)–H bonds of 2-diazo-2-sulfamoylacetamides in refluxing toluene.[291] AgOTf was identified as an effective catalyst for intramolecular carbene insertion to aryl C(sp^2)–H bonds to access 3-alkylideneoxindoles by DFT calculations.[292]



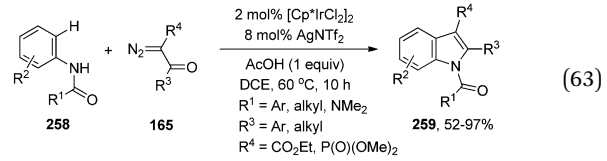
(62)

3.2.3. Iridium and cobalt complex catalysts. For aryl C(sp^2)–H functionalization involving carbene insertion iridium(III) complexes usually behave similarly compared to those Rh(III) complex catalysts. A few Ir(III) complexes have been documented as the efficient catalysts for directed intermolecular aryl C(sp^2)–H functionalization by carbene insertion with diazo compounds. With 2 mol% $[Cp^*IrCl_2]_2$/8 mol% $AgNTf_2$/4 mol% AgOAc as the catalyst system in dichloroethane at 90 °C, *N-tert*-butyl benzamides and their amide or ketone analogs (**256**) reacted with diazomalonates similar to dimethyl diazomalonate (1.2 equiv.) afforded the *ortho*-alkylation products **257** in up to 99% yields (Scheme 80).[293] Increasing the diazo



Scheme 80 Ir(III)-catalyzed aryl C(sp^2)–H functionalization by carbene insertion with diazo compounds.

compound loading to 2.4 equiv. led to double *ortho*-C–H arylation, affording the corresponding double alkylation products **257′** in 51–92% yields. When diazomalonates bearing one or two *tert*-butyl groups were used as the carbene source, the aryl C(sp^2)–H functionalization was followed by decarboxylation to produce the products with a CH_2CO_2Me or CH_2CO_2H moiety at the position *ortho* to the directing group. By using a similar catalytic system with amido as the directing group, acetanilides **258** and other aniline substrates featuring an *N*-substituent such as propenoyl, pivoloyl, and benzoyl, reacted with 2-carbonyl diazoacetates to form *N*-alkanoyl or *N*-aroyl-protected indole derivatives **259** (eqn (63)).[294] With dimethyl (1-diazo-2-oxopropyl)-phosphonate as the carbene source compound 3-indolylphosphonates were accessed in 59–75% yields.



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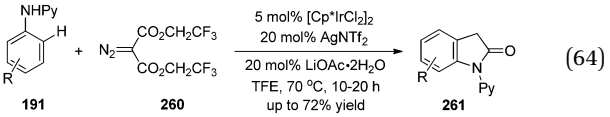

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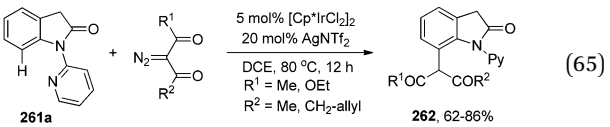

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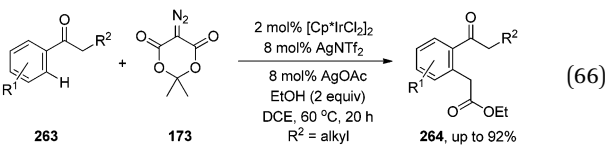
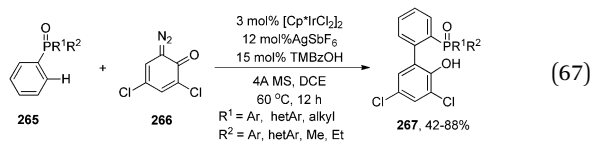


(66)

Other directing groups such as pyridyl,[295] ketone,[296] phosphine oxide,[297] and pyrazolyl[298] were also applied in iridium-catalyzed intermolecular aryl C(sp^2)–H functionalization by carbene insertion with diazo compounds. Under Ir(III) catalysis 2-(arylamino)pyridines (**191**) reacted with acceptor/acceptor diazo compound **260** in the presence of LiOAc in CF_3CH_2OH (TFE) to afford oxindole derivatives **261** in up to 72% yields (eqn (64)).[295] 2-Pyridyl as the directing group enabled the further C–H functionalization at 7-position of oxindole **261a** by switching the reaction conditions (eqn (65)), producing the enol-type products **262**. Aryl alkyl ketones **263** reacted with 2-diazotized Meldrum's acid (**173**) under the conditions similar to those shown in Scheme 80[293] to produce the alkylated ketone products **264** in moderate to excellent yields without occurrence of carbene insertion to the alkyl C(sp^3)–H bonds (eqn (66)).[296] In the presence of 2,4,6-trimethylbenzoic acid (TMBzOH) arylphosphine oxides **265** underwent Ir(III)-catalyzed *ortho*-C–H functionalization by carbene insertion with 2,4-dichloro-6-diazocyclohexa-2,4-dienone (**266**), giving the corresponding biphenyl-based arylphosphine oxide products **267** in 42–88% yields (eqn (67)).[297] The analogs of **266** and 1-diazonaphthoquinones were also applied for the synthesis of multi-functionalized arylphosphine oxides, which are potentially useful MOP-type ligand precursors. It is noteworthy that Ir(I) complex $[Ir(COD)Cl]_2$ could act as an efficient catalyst for *ortho*-C–H functionalization of 1-arylindazolones (**268**) with 2-diazo carbonyl compounds *via* a carbene insertion to aryl C(sp^2)–H bond/[4+2] annulation sequence (eqn (68)).[298] This method features excellent functional group tolerance on 1-arylindazolones.



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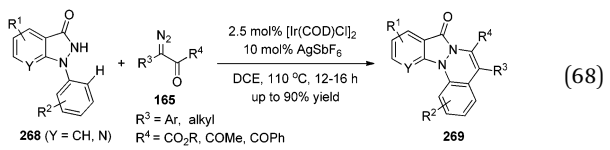

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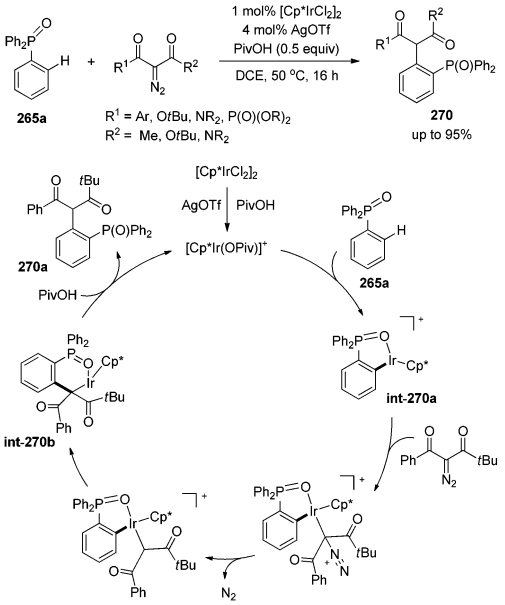
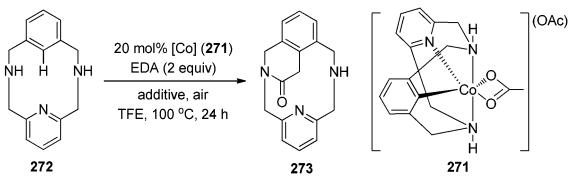
Triarylphosphine oxide moiety can act as an effective directing group in iridium-catalyzed intermolecular carbene insertion to aryl C–H bonds (Scheme 81).[299] With triphenylphosphine oxide (**265a**) and derivatives as the C–H substrates and 2-diazo-4,4,-dimethyl-1-phenylpentane-1,3-dione and analogs as the carbene source, $[Cp^*IrCl_2]_2$ (1.0 mol%)/AgOTf (4.0 mol%) catalyzed the desired C–H functionalization by carbene insertion in the presence of pivalic acid (PivOH). The target products **270** were obtained in up to 95% yields. It is noteworthy that diethyl phosphate functionality could be tolerated in the diazo compounds to give the corresponding bis(phosphate) derivatives. The five- and six-membered iridacycles of types **int-270a** and **int-270b** are the key intermediates to transfer to the target products.

Carboxylate-assisted formation of aryl-Co(III) masked carbenes have been identified in cobalt-catalyzed intermolecular aryl C(sp^2)–H functionalization with diazo ester EDA (Table 11).[300] The stoichiometric reaction of aryl-Co(III) complex **271** with EDA in TFE at 100 °C under air atmosphere gave compound **273** in 91% isolated yield (96% NMR yield). Under the catalytic conditions using 20 mol% **271** as the catalyst, the reaction of compound **272** with EDA formed **273** in 93% yield.



Scheme 81 Ir(III)-catalyzed, triarylphosphine oxide-directed aryl C(sp^2)–H functionalization by carbene insertion with diazo compounds.

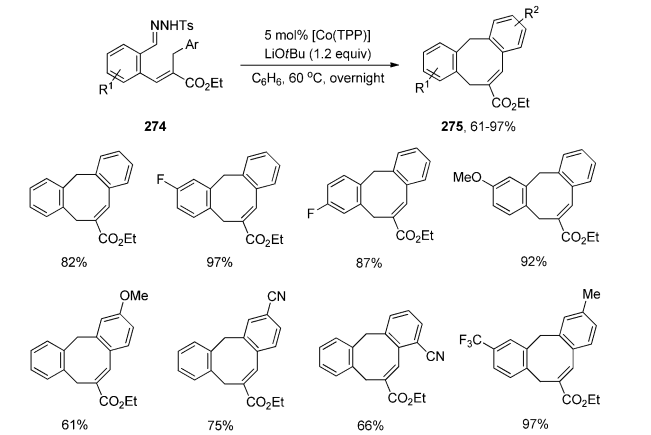
Table 11 Cobalt(III)-catalyzed aryl C(sp^2)–H functionalization by carbene insertion with EDA



[Co]	Additive	Yield[a] (%)
None	H_2O (4)	n.r.
271	H_2O (4)	93 (87)[b]
271[c]	H_2O (4)	95 (84)[b]
$Co(OAc)_2$	H_2O (4)	96 (89)[b]
$Co(OAc)_2$[c]	H_2O (4)	Trace
$Co(OAc)_2$	None	15
$Co(OAc)_2$	LiOTf (1)	96 (88)[b]

[a] ^{1}H NMR yield determined using 1,3,5-trimethoxybenzene as an internal standard. [b] Isolated yield. [c] Under nitrogen.

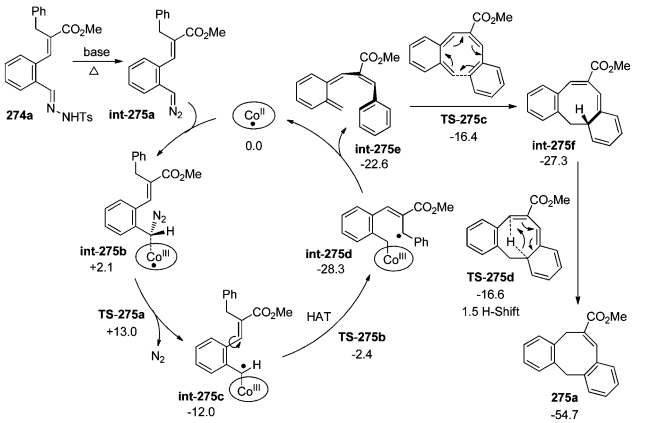
Under a nitrogen atmosphere the isolated yield was slightly decreased. Co(II) also acted as the efficient catalyst for the formation of the target product, but it did not work under a nitrogen atmosphere. Water played a crucial role in enabling the reaction and a Lewis acid additive such as LiOTf promoted the reaction. DFT calculations have revealed that Co(III) mediated intramolecular S_N2-type C–C bond formation (formal carbene insertion to aryl C(sp^2)–H bond) in which the carboxylate moiety acts as a relay. This reaction proceeded *via* a metastable Co(III)- carbene insertion to the aryl C–H bond followed by an annulation. The metalloradical activation of *ortho*-benzallylaryl *N*-tosylhydrazones (**274**) with [Co(TPP)] (TPP = tetraphenylporphyrin) as the catalyst was realized



Scheme 82 Co(III)-catalyzed carbene insertion to aryl C(sp^2)–H bonds.

through an intramolecular Co(III)-carbene radical insertion to the aryl C(sp^2)–H bond/tautomerism sequence, affording unique dibenzocyclooctenes **275** in 61–97% yields (Scheme 82).[301] The single-electron reactivity of the redox non-innocent carbene intermediate was investigated, and the eight-membered-ring products were obtained in good to excellent yields (61–97%) with good tolerance of functional groups. The proposed mechanism suggests that the first step is the formation of diazo compound **int-275a** from the C–H substrate **274a** (Scheme 83).

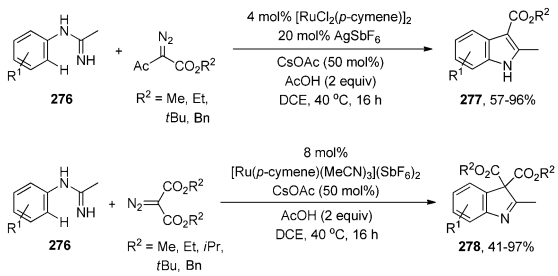
Trapping and activation of the diazo compound by the catalyst results in dinitrogen, generating carbene radical intermediate **int-275c** in an exergonic reaction sequence with a lower barrier. Hydrogen atom transfer (HAT) from the allylic position to the radical-bearing carbene carbon atom forms allyl radical species **int-275d** with a low barrier (+9.6 kcal mol^{-1}). The resultant delocalized allyl radical moiety of **int-275d** is in direct conjugation with the weak Co–C bond, facilitating homolysis with release of *ortho*-quinodimethane (*o*-QDM) intermediate **int-275e** from the metal. Species **int-275e** readily undergoes an 8π cyclization, which exhibits a very low barrier (TS3: +6.2 kcal mol^{-1}) to give the final product **275a** *via* intermediate **int-275f** by a low-barrier 1,5-H shift (TS4: +10.7 kcal mol^{-1}).



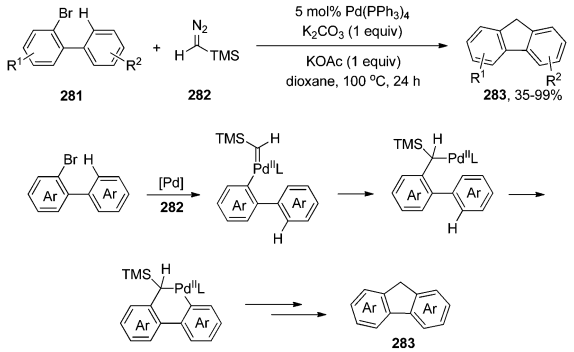
Scheme 83 Proposed mechanism for Co(III)-catalyzed carbene insertion to aryl C(sp^2)–H bonds based on DFT calculations.

3.2.4. Ruthenium and palladium complex catalysts. The strategy using directing groups has also been applied for ruthenium-catalyzed intramolecular aryl C(sp^2)–H functionalization by carbene insertion with diazo compounds as the carbene source. In the presence of 4 mol% $[RuCl_2(p\text{-cymene})]_2$ as the catalyst, and $AgSbF_6$, CsOAc, and acetic acid as the additives in dichloroethane at 40 °C, imidamides (**276**) reacted with acceptor/acceptor diazo compounds to afford *NH*-indoles **277** in 57–96% yields by cleavage of the C(=N_2)–C(acyl) bond with tolerance of various functional groups on the aryl moieties (Scheme 84).[302] However, use of the cationic Ru(II) complex, that is, $[Ru(p\text{-cymene})(MeCN)_3](SbF_6)_2$, as the catalyst, the reaction with 2-diazomalonates formed 3*H*-indoles (**278**) in 41–97% yields through cleavage of the C–N bond. Both the reactions initially proceeded through a carbene insertion to *ortho* aryl C(sp^2)–H bond followed by cyclization under Ru(II) catalysis. In this case, the imino group acted as a traceless directing group. A similar directing group strategy was documented.[303] With a similar Ru(II) catalyst system and in the presence of a phosphoric acid as the additive, the reaction of 2-aryl oxazolines (**279**) underwent intermolecular carbene insertion/ring-opening cyclization with acceptor/acceptor diazo compounds by the assistance of CsOAc as a reactant, giving N-heterocycles **280** (eqn (69)).[304] The oxazolinyl directed the initial carbene insertion to the *ortho* aryl C(sp^2)–H bond in **279**. Other N-heterocyclic motifs were reported as the effective directing groups in Ru(II)-catalyzed carbene insertion to *ortho* aryl C(sp^2)–H bonds by diazo compounds.[305,306] It should be noted that Ru(II) complex catalysts can also be applied for intramolecular carbene insertion to aryl C–H bonds.[307]

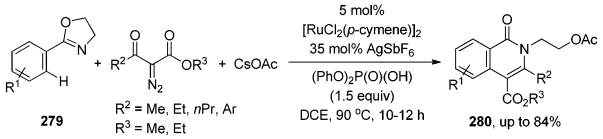
Palladium catalysts have been well investigated in carbene-involved cross-coupling reaction.[7,21] However, only a few reports were disclosed on direct aryl C(sp^2)–H functionalization by carbene insertion with diazo compounds. A Pd(0)-catalyzed C–Br activation/intramolecular carbene insertion to aryl C(sp^2)–H bond sequence was developed to access polycyclic aromatic hydrocarbons (PAHs) (**283**) (Scheme 85).[308] In the presence of 5 mol% $Pd(PPh_3)_4$ as the catalyst, K_2CO_3 as the base, and KOAc as the additive in dioxane at 100 °C, 2-bromo-1,1′-biphenyls (**281**) efficiently reacted with the readily available (trimethylsilyl)diazomethane (**282**), forming PAHs (**283**) and 1*H*-indenes. It was found that *N*-tosylhydrazones and aryldiazoacetates could not be used as the carbene source compounds. Although the reaction was proposed to proceed through C–Br activation by Pd(0) species, and carbene insertion followed by C–H activation, the overall process is a formal carbene insertion to aryl C(sp^2)–H bond/cyclization sequence under palladium catalysis.



Scheme 84 Ru(II)-catalyzed aryl C(sp^2)–H functionalization by carbene insertion with diazo compounds.

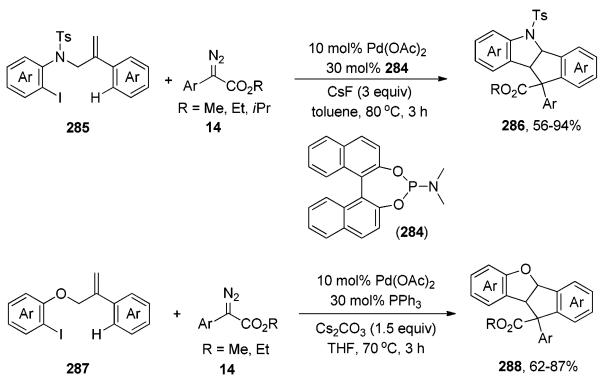


Scheme 85 Palladium-catalyzed aryl C(sp^2)–H functionalization by carbene insertion with diazo compounds.



(69)

By means of 10 mol% $Pd(OAc)_2$ as the catalyst, and in the presence of monophosphoramidite ligand (**284**), alkene-tethered aryl iodides **285** reacted with donor/acceptor diazo compounds **14** to give spirocyclized products **286** (56–94%) (Scheme 86).[309] Use of the *O*-tethered substrates **287** led to the target products **288** (62–87%). The reaction formally proceeded through intramolecular spirocyclization, remote C–H activation, and diazocarbonyl carbene insertion. Notably, palladium catalysts have also been documented to enable intramolecular aryl C(sp^2)–H functionalization by carbene insertion.[310,311] To suppress cyclopropanation as the side reaction the strategy is to diminish coordination of the C=C bond of an arene or alkene substrate to the catalytically active metal center.[4,216,293]



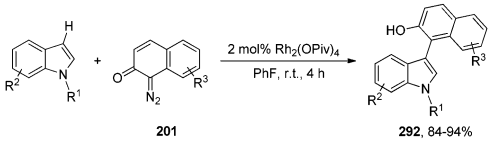
Scheme 86 Palladium-catalyzed ary C(sp^2)–H functionalization by carbene insertion with donor/acceptor diazo compounds.

4. Carbene insertion to heteroaryl C(sp^2)–H bonds

Aromatic heteroarenes play an important role in organic synthesis, materials science, agrochemicals and medicinal chemistry. Considerable efforts have been made to realize their direct functionalization.[13,312–315] Indoles are one of the most important heterocyclic motifs in organic synthesis. However, C–H functionalization of indoles by carbene insertion is challenging due to their multiple reactivities. In general, the electronic or structural properties of indole substrates, the reaction system including catalysts and reaction conditions should be elaborated for such a purpose.

4.1. Carbene insertion to indolyl C(sp^2)–H bonds

Carbene insertion to indolyl C(sp^2)–H bonds was applied for the construction of complex molecules such as the aglycon, that is, staurosporinone (K252c, **291**), and its protected variants (Scheme 87).[316] Multistep procedures are usually required to construct a bisindole-fused benzo-lactam unit. Surprisingly, with the "carbene insertion to C–H bond" strategy such a synthesis was achieved in one single step by using cyclic diazo compound **289** and bisindole **290** under Rh(II) catalysis. With 1 mol% $Rh_2(OAc)_4$ as the catalyst in degassed pinacolone at 120 °C, the reaction of bisindole **290** reacted for 8 h to give the desired product **291** (25%) *via* the enol isomer of the direct carbene insertion intermediate **int-291a**. However, compound **291** could only be obtained in 3% yield in refluxing benzene. It is noted that the desired product from the reaction of indole and **289** in refluxing benzene through carbene insertion to C(3)–H bond of indole was formed in 65% yield. The *N*-protected derivatives of **291** were also obtained in 40–62% yields by reacting the *N*-protected derivatives of **289** with bisindole **290**. This protocol has demonstrated a concise route to indolocarbazoles. A similar strategy was used for arylation of indoles (eqn (70)).[317]



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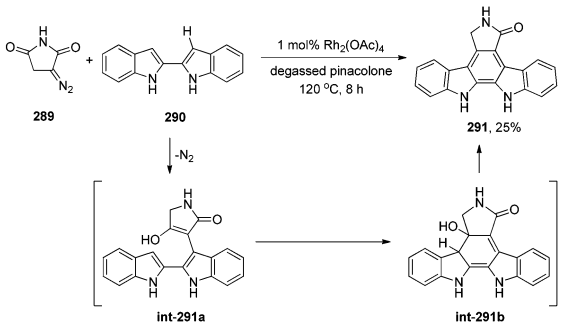
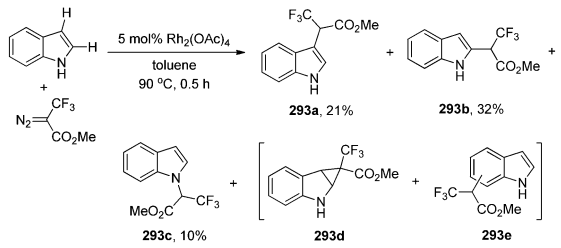


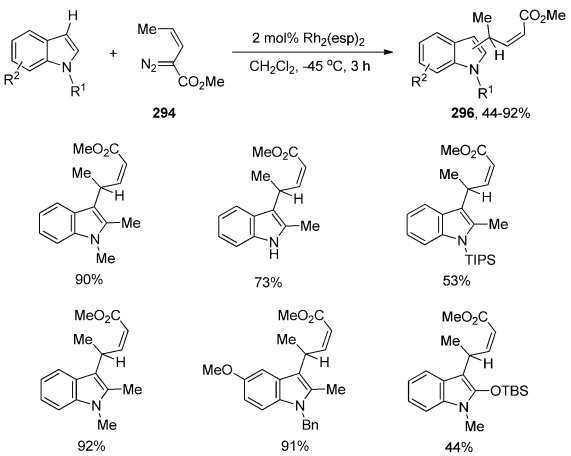
Scheme 87 Rh(II)-catalyzed carbene insertion to inodyl C(sp^2)–H bond.



Scheme 88 Possible products from transition-metal-catalyzed reaction of indole with an acceptor/acceptor diazo compound.

Due to the multiple reactivities of indoles, they usually exhibit diverse chemo- and regioselectivity, depending on the electronic property and steric hindrance of the substrates as well as the catalyst systems. For example, indole reacted with trifluoromethyldiazoacetate to afford both products **293a** (21%) and **293b** (32%) from carbene insertion to the C(3)–H and C(2)–H bonds, and **293c** (10%) from carbene insertion to the N–H bond (Scheme 88).[318] Under certain circumstances, cyclopropanation and carbene insertion to the benzo aryl C–H bond as well as Büchner reaction may occur to form compounds of types **293d** and **293e**.[319,320] Thus, substrate reactivity and catalyst-control strategies have often been employed to directly functionalize indole derivatives by carbene insertion to the N-heterocyclic indolyl C(sp^2)–H bonds.

Rh(II)-catalyzed, steric hindrance-directed C–H functionalization of indoles was achieved with vinyldiazoacetate.[321] With $Rh_2(esp)_2$ as the catalyst at −20 °C, *N*-methylindole reacted with (2)-vinyldiazoacetate (**294**) to give the desired carbene insertion product **295** in 78% yield (eqn (71)). In general, the reaction of vinylcarbenes at the carbene site is very sensitive to steric crowding.[5] Thus, substituted indoles reacted at −45 °C to afford the unexpected products **296** (44–92%) (Scheme 89). Compounds **296** were formed exclusively as the (*Z*)-isomer and they were obviously resulted from attack at the vinylogous

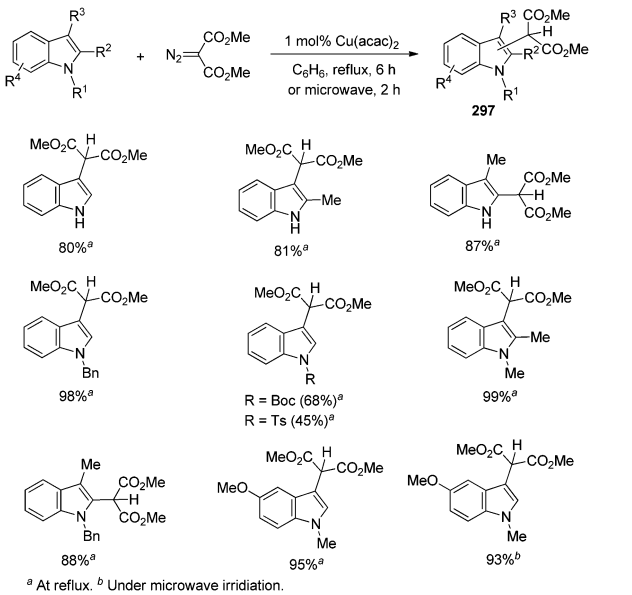


Scheme 89 Steric hindrance directed C–H functionalization of indoles.

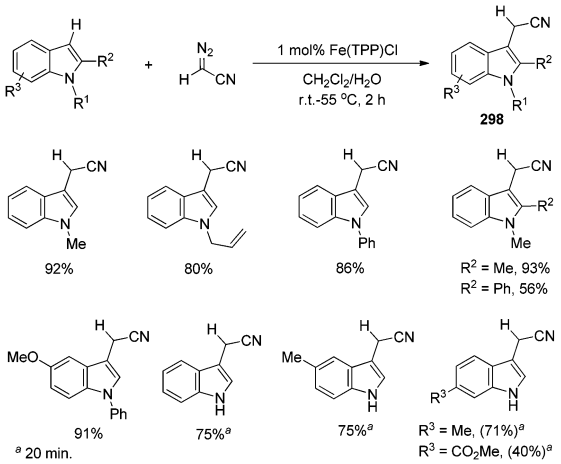
position of the metal vinylcarbene intermediate. This type of reactivity is rare in rhodium-catalyzed reactions of vinylcarbenes with a substituent at the vinyl terminus. The reaction proceeded at −45 °C presumably because of the greater nucleophilicity of *C*-substituted indoles over *N*-methylindole. Typically, substitution at the 2-position is required for the vinylogous reactivity to occur, and introduction of a bulky group at the 4-position of the indole backbone also led to the same type of reaction.

(71)

Cu(II)-catalyzed malonyl carbene insertion to indolyl C–H bonds was efficiently conducted in refluxing benzene or under microwave irradiation (Scheme 90).[322] In the presence of 1 mol% $Cu(acac)_2$ as the catalyst in refluxing benzene, unprotected indole reacted with dimethyl diazomalonate to form the product (**297a**: $R^1 = R^2 = R^3 = H$) with carbene insertion to the $C(sp^2)$–H bond at the 2-position in 80% yield. When the 3-position is substituted, the carbene insertion reaction occurred at the 2-position. It is noted that carbene insertion to the N–H bond (<10%) could be ignored. The indole substrates with *N*-protection by benzyl or methyl facilitated the reaction, while use of Boc and Ts as the protecting groups diminished the reaction efficiency. An electron-withdrawing ester group (CO_2Me) at the 2-position, or nitro and AcO at the 5-position also deteriorated the reaction efficiency (55–79%). However, 1-methyl-7-nitroindole reacted to generate the target product in



Scheme 90 Cu(II)-catalyzed C–H functionalization of indoles by carbene insertion with an acceptor/acceptor diazo compound.

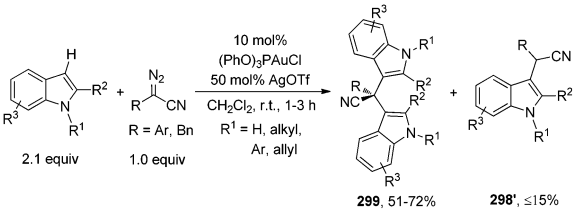


Scheme 91 Fe(III)-catalyzed carbene insertion to indolyl C(3)–H bond with diazoacetonitrile.

94% yield. It is noteworthy that the *N*-protected indoles also efficiently underwent the desired carbene insertion reaction under microwave irridiation conditions, forming the products in comparable yields.

An iron(II) catalyst system consisting of 1 mol% $Fe(ClO_4)_2$, 1.2 mol% TMEDA (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine), and 1.2 mol% $NaBAr'_4$ in dichloroethane at 60 °C was employed for the C(3)–H functionalization of *N*-benzylindoles with donor/acceptor diazo compounds methyl aryldiazoacetates (**14**).[323] Iron(III) porphyrin complex Fe(TPP)Cl was found to be an efficient catalyst to functionalize the C(3)–H bond of indoles by carbene insertion with diazoacetonitrile as the carbene source (Scheme 91).[324] 1*H*-Indole-3-acetonitrile and derivatives (**298**) were accessed, which can be readily reduced to useful tryptamine derivatives, and alkaloid precursors. This method streamlines the classic four-step preparation of tryptamines starting from the Mannich reaction of indole followed by quaternization of the amine, nucleophilic substitution with cyanide, and final reduction (41% yield over four steps).[325] In this study, diazoacetonitrile was generated *in situ* from aminoacetonitrile hydrochloride and $NaNO_2$ in water at 55 °C in continuous flow to minimize the safety hazards associated with this diazo compound. Using *N*-methylindole as the model substrate, the catalysts were screened. $AgNTf_2$, $Rh_2(OAc)_4$, $Rh_2(esp)_2$, Co(salen), Mn(salen), and CuOTf proved to be incompatible, and only in the case of Co(TPP), a 32% yield was obtained. However, use of 1 mol% Fe(TPP)Cl led to 92% yield for *N*-methyl-3-indolyl-acetonitrile (**298a**). *N*-Unprotected indoles underwent the same type of reaction to give the C(3)–H functionalization products, but in a less efficient fashion than those *N*-protected indole substrates. An electron-withdrawing group at the 1-position (*N*-Boc) or on the aryl moiety (6-CO_2Me) resulted in no reaction (for *N*-Boc) or a low product yield (40% for 6-CO_2Me), and a phenyl at α-position also diminished the product yield (56%). It is noteworthy that the C(2)–H bond could not be functionalized

under the stated conditions. The mechanistic studies reveal that the reaction proceeds *via* a radical pathway.

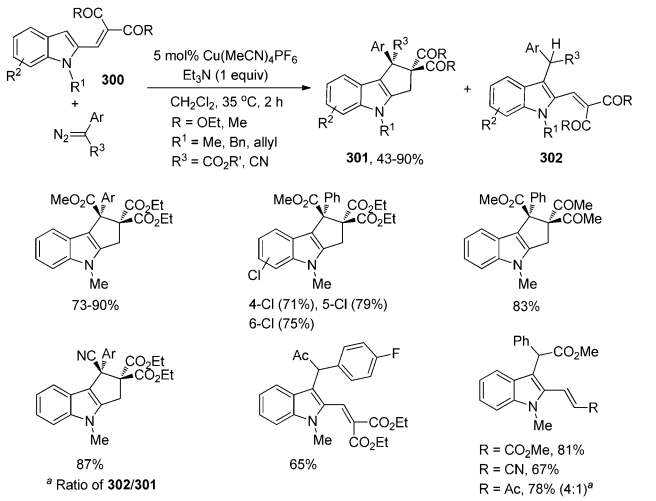


(72)

Usually, diazo compounds are excessively used for the carbene insertion reaction due to their considerable decomposition to dimerize during the reaction. Unexpectedly, under the catalysis by means of an electron-deficient Au(I) complex as the catalyst two indoles could be coupled with one diazo compound in addition to the desired carbene insertion to C(3)–H bond of indole (eqn (72)).[326] By increasing the ratio of indole:diazo to 2.1 : 1 the double indolylation products **299** were formed in decent yields (51–72%) with the carbene insertion (mono-indolylation) products **298′** as the byproducts (≤15%). $(PhO)_3PAuCl$ (10 mol%) acted as the most efficient catalyst with the assistance of 50 mol% AgOTf. Aryl or benzyldiazo cyanides were used as the donor/acceptor carbene precursor. When two different indoles, that is, *N*-aryl-protected indoles were used, the double hetero-indolylation occurred to give the target products **299′** (42–62%) with the carbene insertion products of type **298′** as the byproducts (10–18%). It is proposed that *N*-arylindoles react with the *in situ* generated gold(I) carbene species at the 3-position more rapidly than their *N*-alkyl analogs.

An unsaturated iminium species may be formed to further react with the *N*-alkylindole to afford the double indolylation product. This protocol provides a direct route to bis(indolyl) methane derivatives. With indole-3-tosylhydrazones as the carbene precursor, unsymmetrical 3,3-bis(indolyl)methanes could be synthesized from the reaction with *N*-unprotected indoles by means of CuI as the catalyst.[327] It should be noted that the indolyl moieties in both the substrates are *N*-unprotected, and the *N*-protected indoles or indole-based *N*-tosylhydrazones did not exhibit any reactivity.

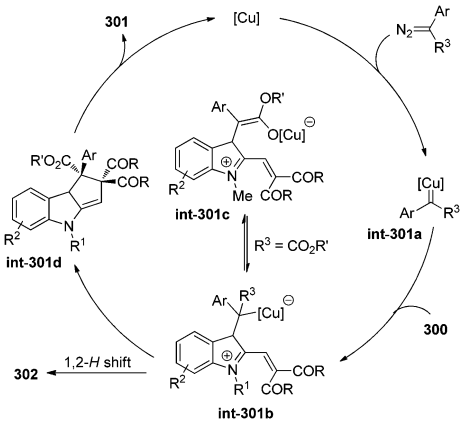
A Cu(I)-catalyzed carbene insertion to indolyl C(3)–H bond/annulation sequence of *N*-alkyl-2-vinylindoles (**300**) and donor/acceptor diazo compounds was developed for the synthesis of dihydrocyclopenta[*b*]indoles (**301**) (Scheme 92).[328] Use of 5 mol% $Cu(MeCN)_4PF_6$ as the catalyst enabled the transformation to occur efficiently, yielding **301** (43–90%), and in most of the cases, the product yields were higher than 80% with the carbene insertion products **302** as the side products. The *N*-benzyl and *N*-allyl-protected 2-vinylindoles produced the corresponding products in 83–89% yields from their reaction with phenyldiazoacetates (**14**) and analogs. It should be noted that no carbene insertion to indolyl C(3)–H bond was observed in these two cases. The diester analog, that is, the diketone variant also underwent the reaction efficiently to afford the product



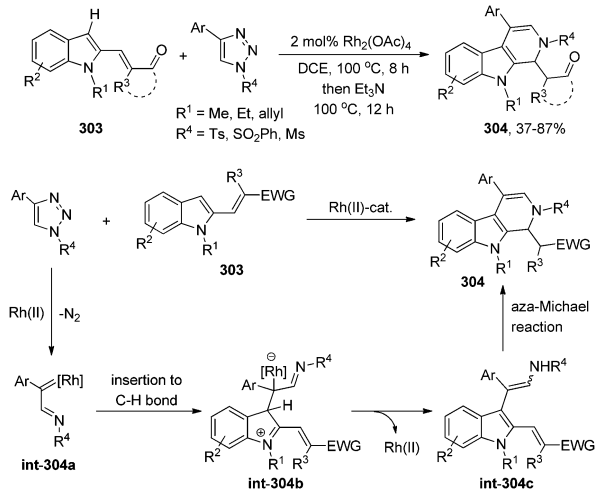
Scheme 92 A Cu(I)-catalyzed carbene insertion/annulation sequence of 2-vinylindoles and diazo compounds.

(83%). However, *N*-Boc-protected 2-vinylindole showed no reactivity. The aryldiazonitrile favored formation of the formal [4+1] annulation product (87%), whereas the aryldiazoketone led to the carbene insertion product of type **302** in 65% yield. Other diazo compounds such as those derived from diaryl ketones, benzaldehyde, dimethyl malonate and isatin failed in both the reactions. In the case of mono-EWG-substituted 2-vinylindoles (EWG = ester, CN, and Ac) the carbene insertion products were formed (67–81%), and only in the case of using the acetyl-substituted substrate, the [4+1] annulation product was generated as a side product. However, the nitrovinyl-substituted substrate exhibited a very low reactivity under the stated conditions. The mechanistic studies have revealed that the annulation products **301** are not formed *via* **302** as the intermediates. Copper(I) carbene **int-301a** is formed to assist carbene insertion to C(3)–H bond of the indole substrates. The zwitterionic and tricyclic intermediates **int-301d** are generated to tautomerize to the final products of type **301**, and 1,2-*H* shift of the zwitterionic species **int-301b**/**int-301c** leads to the carbene insertion product **302** (Scheme 93). A carbene insertion to indolyl C(3)–H bond/base-mediated aza-Michael reaction cascade was applied to access dihydro-β-carbolines (**304**) from α-vinylindoles (**303**) and *N*-sulfonyl-1,2,3-triazoles (Scheme 94).[329] The reaction may proceed *via* the intermediate species **int-304a**–**int-304c**.

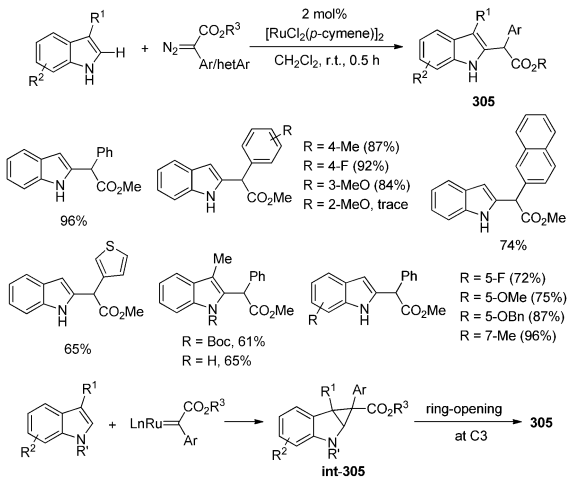
As discussed above,[318,322] regioselective C–H functionalization of 2,3-unsubstituted indoles usually occurs at the 3-position by carbene insertion with diazo compounds, and the relevant C(2)–H functionalization is only possible when the 3-position is substituted. In addition, double carbene insertion to both the C–H bonds at 2- and 3-positions can not happen. For the regioselective C(2)–H functionalization of indoles a directing group strategy or substrate/catalyst-control strategy has been applied.[1–3,7] In 2010, Yu, *et al.* disclosed Ru(II)-catalyzed C(2)-selective functionalization of *N*-unprotected indoles by donor/acceptor diazo compounds, that is, aryldiazoacetates (**14**) (Scheme 95).[330] With 2.5 mol% $[RuCl_2(p\text{-cymene})]_2$ as the



Scheme 93 Proposed mechanism for Cu(I)-catalyzed carbene insertion/[4+1] annulation of 2-vinylindoles with aryldiazo compounds.

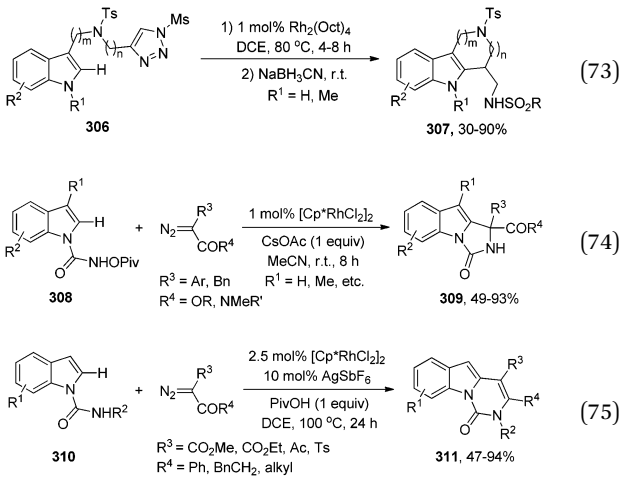


Scheme 94 Rh(II)-catalyzed carbene insertion/[4+3] annulation of 2-vinylindoles with *N*-sulfonyl-1,2,3-triazoles.



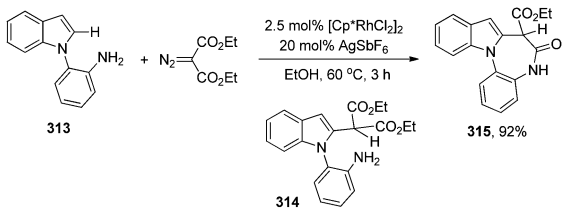
Scheme 95 Ru(II)-catalyzed carbene insertion to C(2)–H bond of indoles with diazo compounds.

catalyst in CH_2Cl_2 at room temperature, unprotected indole reacted with methyl phenyldiazoacetate (**14a**) for half an hour to afford the desired 2-alkylated product **305a** in 96% yield. In a similar fashion, indole efficiently reacted with substituted diazo compounds aryldiazoacetates to produce the target products **305** in good to excellent yields (50–96%). The steric and electronic effects obviously affected the reaction efficiency. 4-Nitro group on the aryl moiety and allyl in the ester group of the diazo compound diminished the product yields to 48% and 50%, respectively. The steric hindrance from 2-MeO on the aryl moiety, and *tert*-butyl in the ester group of the diazo compounds, and 1-naphthyl inhibited the reaction or remarkably reduced the yields to 12–22%. *N*-Boc-3-methylindole participated in the reaction to result in the desired product in 61% yield. 3-Substituents such as methyl and CH_2CO_2Me exhibited negative impacts on the reaction. In the case of methyl, the yield was dropped from 96% to 65%, and 3-CH_2CO_2Me completely inhibited the desired reaction. Various substituents on the aryl moiety of indoles are tolerant. The mechanistic studies suggest a cyclopropylindoline intermediate from the interaction of the indole substrate and ruthenium carbene generated *in situ* from the diazo compound and the Ru(II) catalyst, which undergoes ring-opening at C3 to form the target 2-alkylated product. When the 3-position is substituted, the alkylation occurred at C(2)-position with a lower efficiency (eqn (73)).[331] With 3-indolyl-tethered *N*-sulfonyl-1,2,3-triazoles **306** as the substrates and $Rh_2(Oct)_4$ as the catalyst in dichloroethane at 80 °C the intramolecular carbene insertion reaction afforded the carbene insertion intermediates which were subsequently reduced by $NaBH_3CN$ to the corresponding indole-fused polycyclic compounds **307** (30–90%). When the catalyst was changed to Rh_2(*S*-PTTL)$_4$ pyrrole-fused tetracyclic compounds were obtained through the dearomatization of indolyl N-heterocycles.



Indolyl *N*-tethered directing group strategy has been used for the C(2)–H functionalization of indole derivatives. Rh(III)-catalyzed carbene insertion to C(2)–H bond/cyclization has been reported for indole functionalization by deriving indoles from their *N*-carboxamides (**308**), in which the carboxamide

motif acts as an oxidative bidentate directing group to enable the C–H functionalization of indoles by carbene insertion at the C(2)–H position (eqn (74)).[332] Use of 1 mol% $[Cp^*RhCl_2]_2$ as the catalyst and CsOAc (1 equiv.) as the additive in acetonitrile at room temperature led to 1*H*-imidazol[1,5-*a*]indol-3(2*H*)-one derivatives **309** (49–93%) through a Rh(III)-catalyzed formal carbene insertion to C(2)–H bond/cyclization of the prefunctionalized indoles **308**. With a similar strategy intermolecular indolyl C(2)–H functionalization of **310** by carbene insertion with diazocarbonyls was achieved to give the target products 2*H*-pyrimido[1,6-*a*]indol-1-ones (**311**) in 47–94% yields (eqn (75)).[333]

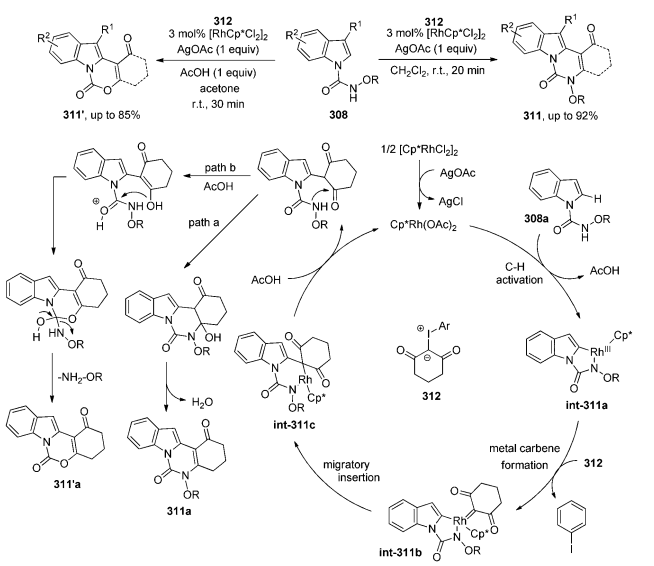


(76)

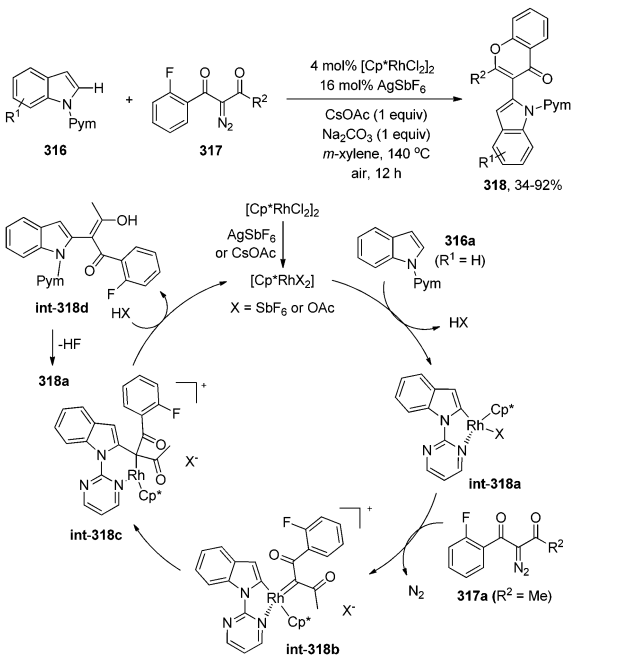
An acid-controlled carbene insertion to the (C(2)–H) bond of indoles of type **308**/annulation sequence was investigated to access indolones of type **311** as well as those of type **311′** from the [3+3] annulation under Rh(III) catalysis by means of iodonium ylides **312** as the carbene source (Scheme 96).[334] In the presence of 3 mol% $[Cp^*RhCl_2]_2$/AgOAc (1 equiv.) in CH_2Cl_2 at room temperature, the reaction of *N*-carboxamide indoles **308** gave the target products **311** in up to 92% yields, while addition of acetic acid (1 equiv.) led to formation of products **311′** in up to 85% yields when the reaction was conducted in acetone. The protocol features good tolerance of a wide range of functional groups and is ready to be scaled up. A Rh-carbene species of type **int-311b** is proposed as the reactive intermediate to result in both the products **311** and **311′**.

o-Aminophenyl was used as a directing group to enable a carbene insertion to C(2)–H bond/cyclization cascade to prepare diazepino[1,7-*a*]indole (**315**) in 92% yield (eqn (76)).[335] The carbene insertion product **314** is considered to be the reactive intermediate which undergoes annulation to give **315** by release of EtOH. *N*-Pyrimidyl is also an effective directing group for C(2)–H functionalization of indoles by carbene insertion. Under Rh(III) catalysis, *N*-pyrimidylindoles **316** reacted with 2-*F*-phenyldiazocarbonyls (**317**) to generate indole-functionalized chromones **318** in 34–92% yields (Scheme 97).[336] The reaction proceeded through a Rh(III)-catalyzed carbene insertion to C(2)–H bond/enolization/dehydrofluorination sequence, giving the target products **318**. It is noted that bioactive catalyst such as myoglobin can be employed for the C(3)–H functionalization of *N*-unprotected indoles by carbene insertion.[337]

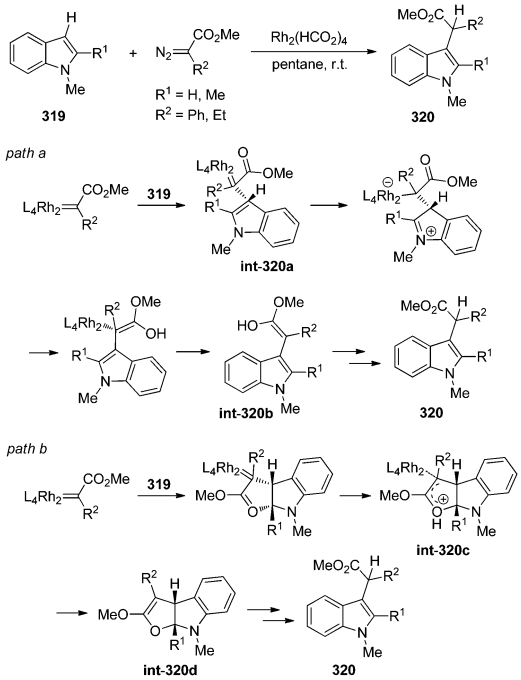
DFT calculations were conducted to elucidate the reaction pathways of indoles with diazo compounds. Taking Rh(II)-catalyzed reaction of *N*-methylindoles **319** with methyl phenyl- or ethyldiazo-acetates as the model reaction, the theoretical results suggest that C(3)–H functionalization of indoles may proceed *via* an enol or oxocarbenium ylide intermediate (Scheme 98).[338] Path a indicates that the reaction proceeds *via* a nucleophilic attack at the carbene carbon first (**int-320a**) to generate a carbonium ylide followed by a 1,4-proton transfer to give a free enol (**int-320b**). The nucleophilic attack may involve the concerted pathway (path b) by concerted formation of both C–O and C–C bonds to provide an oxocarbonium ylide intermediate (**320c**). Subsequent 1,2-*H* shift catalyzed by a molecule of enol is energetically feasible to give the carbene insertion product **320** through intermediate **int-320d**. DFT calculations were performed to probe into the mechanisms of the catalyst-controlled selective reactions of *N*-pyrimidylindoles with



Scheme 96 Rh(III)-catalyzed, acid-controlled chemodivergent annulations between indoles and iodonium carbenes.



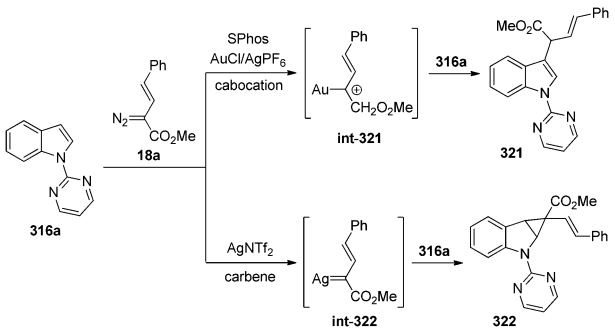
Scheme 97 Rh(III)-catalyzed, pyrimidyl-directed formal carbene insertion to C(2)–H bond of indoles with a diazo compound.



Scheme 98 Reaction pathways of indoles and diazo compounds by DFT calculations.

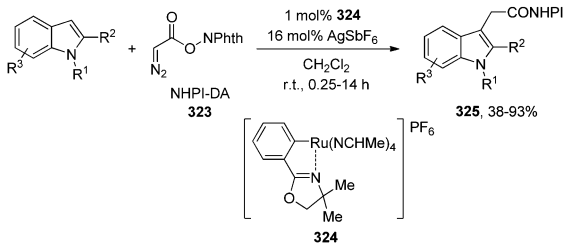
vinyl diazoacetates (Scheme 99).[339] With SPhosAuCl/$AgPF_6$ as the catalyst the key intermediate **int-321** from the interaction of the catalyst with styryl diazoacetate **18a** acts as a carbocation rather than a metal carbene in the reaction with indoles, affording the C(3)–H alkylation product **321.** In the case of using $AgNTf_2$ as the catalyst intermediate **int-322** behaves as a metal carbene more than **int-321**, resulting in the cyclopropanation product **322.** However, the overall result for the C(3)–H alkylation is usually considered as a carbene insertion process.

N-Hdroxyphthalimidyl diazoacetate (NHPI-DA, **323**)[340] was used as a modular methylene linchpin for the C–H alkylation of indoles *via* Ru(II)-catalyzed carbene insertion (eqn (77)).[341] The reaction proceeded under mild conditions with good tolerance of functional groups on the heteroaryl and aromatic rings. When 2,3-unsubstituted indoles were used as the C–H substrates by means of Ru(II) complex **324** as the catalyst, the C(3) regioselectivity was greater than 20 : 1, giving products **325** in



Scheme 99 Mechanisms of catalyst-controlled selective functionalization of indoles with vinyldiazo compounds.

38–93% yields. In the case of using 3-substituted indoles, the C(2)-alkylation efficiently occurred to afford the similar products (60–76%). The target products can undergo Ni-catalyzed decarboxylative borylation with Li[B_2pin_2Me] and are suitable for mild C–C coupling with different types of organometallics and Michael acceptors.

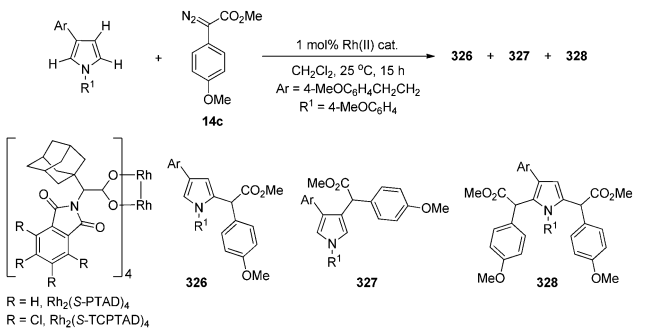


(77)

4.2. Carbene insertion to pyrrolyl C(sp^2)–H bonds

As for the C–H functionalization of other heteroaryl C(sp^2)–H bonds, it often encounters the issues such as regioselectivity, and side reactions including cyclopropanation, ring-opening, and other transformations.[342] A catalyst-controlled regioselective C(sp^2)–H functionalization of pyrroles by carbene insertion was achieved (Table 12).[343] Rh(II) complex catalysts such as $Rh_2(OAc)_4$, Rh_2(*S*-DOSP)$_4$, $Rh_2(esp)_2$, Rh_2(*S*-PTAD)$_4$, Rh_2(*S*-PPTL)$_4$, Rh_2(*S*-BTPCP)$_4$, Rh_2(*S*-TCPPTL)$_4$, and Rh_2(*S*-TCPTAD)$_4$ were screened for the reaction in CH_2Cl_2 at room temperature. It was found that the popularly used Rh(II) complex catalysts

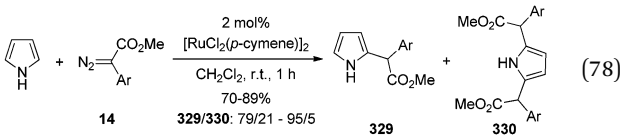
Table 12 Catalyst-controlled C–H functionalization of 3-arylpyrroles[a]



Catalyst	Ratio (**326** : **327** : **328**)	Yield of **326** + **327** (%)	Yield of **328** (%)
$Rh_2(OAc)_4$		<1	
$Rh_2(esp)_2$	76/24/<1	53	
Rh_2(*S*-PTAD)$_4$	55/45/<1	33	
Rh_2(*S*-TCPTAD)$_4$	90/10/<1	36	
Rh_2(*S*-TCPTAD)$_4$[b]	92/8/<1	78	
Rh_2(*S*-TCPTAD)$_4$[c]	<1/7/<93	2	30
Rh_2(*S*-TCPTAD)$_4$[d]	<1/7/<93	2	82

[a] Conditions: pyrrole (0.1 mmol), **14c** (2 equiv.). [b] 0.1 mol% cat., pyrrole (3 mmol), **14c** (1.3 equiv.). [c] 2 mol% cat., pyrrole (0.1 mmol), **14c** (6 equiv.). [d] 2 mol% cat., **14c** (2.5 equiv.). The catalyst and **14c** were added in two portions.

$Rh_2(OAc)_4$ and Rh_2(*S*-DOSP)$_4$ hardly initiated the reaction, $Rh_2(esp)_2$, Rh_2(*S*-PTAD)$_4$, and Rh_2(*S*-PPTL)$_4$ favored formation of products **326** and **327** by carbene insertion to the C(2) and C(3)–H bonds of pyrroles with donor/acceptor vinyldiazo compound **14c**. By changing the ratio of **14c**/pyrrole from 2/1 to 1/2.3 in the presence of 2 mol% Rh_2(*S*-TCPTAD)$_4$ the C(2)–H functionalization product **326** was preferentially formed in 78% yield with a 92/8/<1 ratio for **326**/**327**/**328**. Surprisingly, the double C–H functionalization product **328** was formed in 82% isolated yield (**326**/**327**/**328** = <1/7/<93) by using 2 mol% Rh_2(*S*-TCPTAD)$_4$ as the catalyst through addition of the catalyst and the diazo compound in two portions (Table 12). Such a strategy was applied for the synthesis of fully substituted pyrroles such as dictyodendrins A and F.



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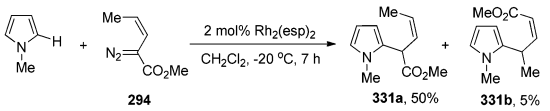
In the presence of $[RuCl_2(p\text{-cymene})]_2$ as the catalyst in CH_2Cl_2 at room temperature, *N*-unprotected indole reacted with aryldiazo compounds to undergo the C(2)–H functionalization by carbene insertion, giving the C(2)-alkylation products **329** in 70–89% yields, but concurrently accompanied by the 2,5-dialkylation products **330** (ratio of **329**/**330** from 79/21 to 95/5) (eqn (78)).[330] The catalyst systems effective for the C–H functionalization of indoles by carbene insertion are usually applicable for the C–H functionalization of pyrrole derivatives in a similar fashion.[317,321,330–333] With $Rh_2(esp)_2$ as the catalyst in CH_2Cl_2 at −20 °C, pyrroles reacted with vinyldiazoacetate (**294**) to give diverse C–H alkylation products **331–333** by carbene insertion (eqn (79)–(81)).[321] Arylation of pyrrole was also achieved by a Rh(II)-catalyzed carbene insertion/tautomerization sequence of pyrrole and diazo compounds **201** (eqn (82)).[317] Pyrrolyl-tethered *N*-sulfonyl-1,2,3-triazoles underwent Rh(II)-catalyzed intramolecular carbene insertion to afford pyrrole-fused polycyclic compounds.[331] With pivaloyloxy-protected pyrroles **335** as the C–H substrates and donor/acceptor diazo compounds as the carbene source, a Rh(III)-catalyzed carbene insertion/cyclization cascade gave the corresponding N-heterocyclic compounds **336** (56–80%) (eqn (83)).[332] 2*H*-Pyrrolo[1,2-*c*]pyrimidin-1-one was also accessed by a similar method.[333]

Highly efficient C(3)–H functionalization of *N*-protected 2,5-dimethylpyrroles by carbene insertion was achieved by means of $Tp^{Br3}Cu(NCMe)$ as the catalyst in CH_2Cl_2 at room temperature or 60 °C (eqn (84)).[344] With EDA as the carbene source the reaction occurred at room temperature, giving the target products (**337**) in 95–98% yields. In the case of using ethylphenyldiazoacetate the reaction was conducted at 60 °C to afford the products in 95–97% yields. When *N*-unprotected pyrrole was reacted with phenyldiazoacetate in CH_2Cl_2 at 60 °C, the C(2)-alkylation product **329b** was obtained in 75% yield (eqn (85)). Altering the ratio of the catalyst/diazo compound/pyrrole substantially changed the product distribution, almost exclusively forming the mono (**329c**) or double (**330c**) alkylation product, respectively (eqn (86)).



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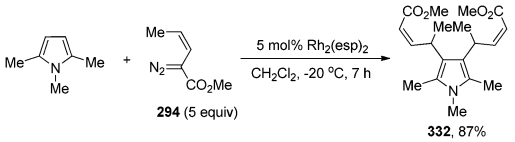

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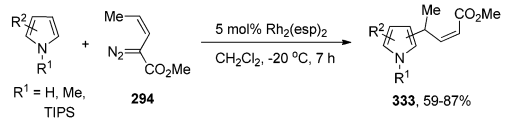

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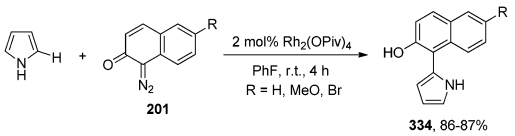

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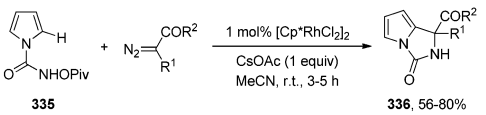
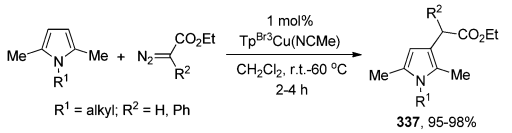


(83)

Blue LED-induced, manganese(I)-catalyzed C(2)–H functionalization of pyrroles was achieved through carbene insertion.[345] With 1 mol% $Mn(CO)_5Br$ as the catalyst, and NaOAc (2 equiv.) as the additive in CH_2Cl_2, the reaction of *N*-unprotected pyrroles and donor/acceptor or acceptor/acceptor diazo compounds proceeded smoothly under blue LED irradiation, affording the C(2)–H functionalization products **338** in 67–82% yields with minor formation of the corresponding dialkylation products (5–8%) when the C5 position was not substituted (Scheme 100). In the case of *N*-protected pyrroles, cyclopropanation occurred as the major reaction to produce the corresponding cyclopropanation products **339** (71–76%). Based on the control experiments, Mn(I)–carbene species **int-338** is proposed as the reactive intermediate.



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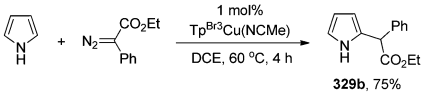

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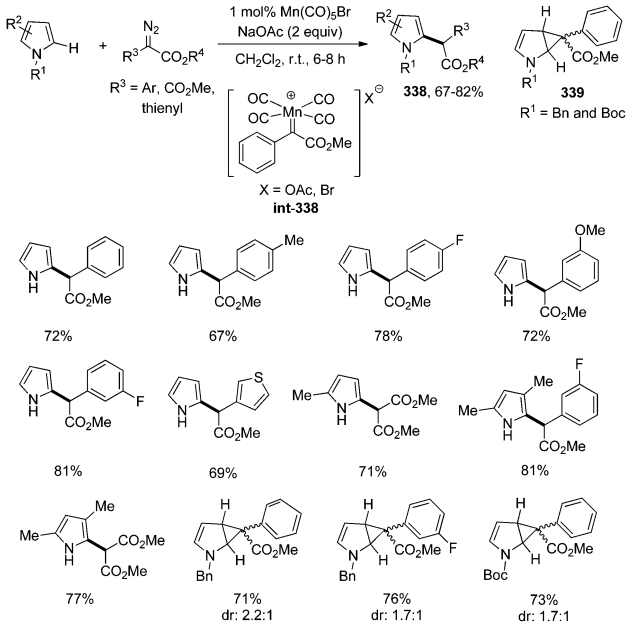
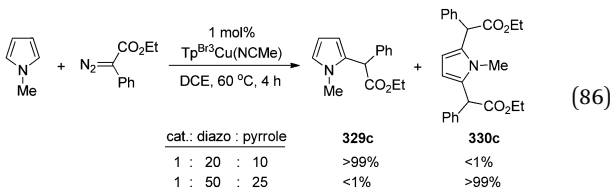


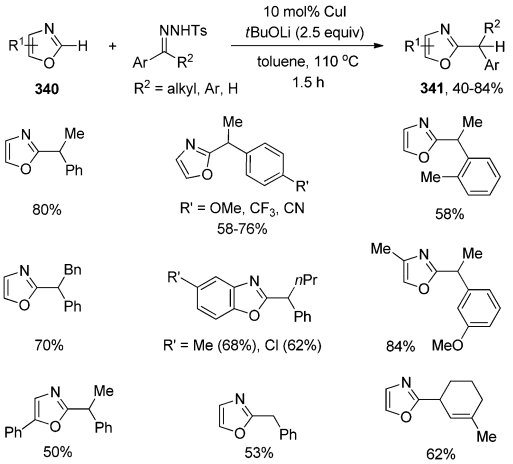
Scheme 100 LED-induced, Mn(I)-catalyzed C(2)–H functionalization of pyrroles *via* carbene insertion.



(86)

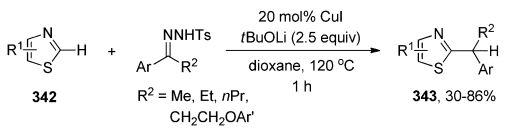
4.3. Carbene insertion to other heteroaryl C(sp^2)–H bonds

Although direct C(sp^3)–H and heteroaryl C(sp^2)–H functionalization has recently been extensively explored, direct methods to functionalize aromatic heterocycles other than indoles and pyrroles have been underdeveloped. In 2011, Wang, *et al.* developed Cu(I)-catalyzed direct benzylation and allylation of 1,3-azoles by carbene insertion to their heteroaryl C(sp^2)–H bonds with *N*-tosylhydrazones as the carbene source (Scheme 101).[346] By using 10 mol% CuI as the catalyst benzo[*b*]oxazole (**340a**) reacted with the *in situ* generated copper carbene from the *N*-tosylhydrazone of acetophenone to give the desired C(2)-alkylation product **341a** in 80% yield. The analogs of **340a** reacted well under the stated conditions to afford the target products in up to 84% yields. 5-Phenylazole also underwent the reaction, exhibiting a lower reactivity (40–50% yields) compared to its benzo[*b*]oxazole analogs. *N*-Tosylhydrazone of benzaldehyde and those of allyl, alkyl, and diaryl ketones participated in the reaction to produce the target products (38–66%). In a similar fashion, benzylation of thiazoles (**342**) was achieved by enhancing the catalyst loading to 20 mol% CuI at 120 °C, giving the target products **343** in 30–86% yields (eqn (87)).[346] Mechanistically, compounds **341** and **343** were



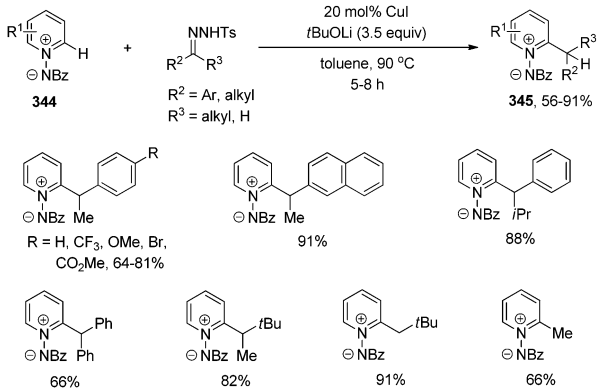
Scheme 101 Cu(I)-catalyzed C–H functionalization of 1,3-azoles by carbene insertion.

formed by a formal carbene insertion to heteroaryl C–H process. It is noteworthy that other aromatic heterocycles with similar acidic C–H bonds underwent the reaction well. However, direct benzylation of benzofuran, benzo[*b*]thiophene, and benzo[*d*]imidazole with *N*-tosylhydrazones under similar conditions did not proceed well. With the same catalyst system and bis(trimethylsilyl)diazomethane as the carbene source, 1,1-bis(trimethylsilyl)methyl group was efficiently installed at the 2-position of benzoxazoles and oxazoles.[347] It should be noted that Miura, *et al.* reported a catalyst system consisting of $NiBr_2$ and 1,10-phen for C–H functionalization of benzoxazoles, and $CoBr_2$/1,10-phen for that of azoles, and benzothiazole, with *N*-tosylhydrazones bearing unactivated alkyl groups as the carbene precursor.[348] In the case of benzoxazoles, $NiBr_2$/1,10-phen was used as the catalyst at 100 °C to promote formation of the target products (34–86%), while the reaction of azoles and benzothiazole with *N*-tosylhydrazones should be conducted at an elevated temperature (120 °C) for 7 h to reach 31–81% yields. Ferrocenyl-based *N*-tosylhydrazones were used for the same purpose.[349]

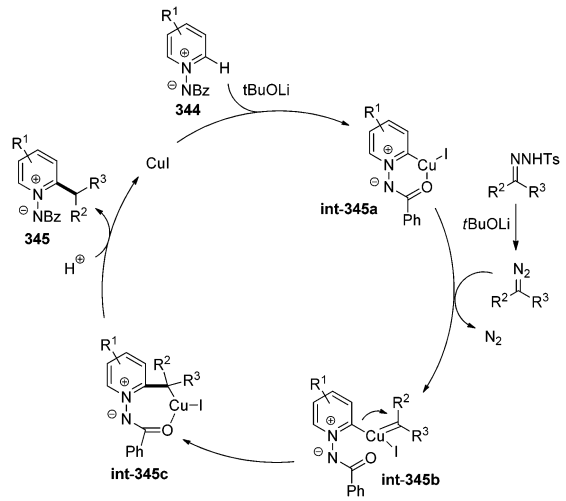


(87)

In the presence of 20 mol% CuI catalyst in toluene at 90 °C, regioselective C–H functionalization of pyridine derivatives, that is, *N*-iminopyridinium ylides (**344**) was efficiently conducted, giving the corresponding C(2)–H alkylation products (**345**) in 56–91% yields (Schemes 102 and 103).[350] It was found that excess of the base is necessary for the transformation. Copper carbene **int-345b** is considered to be the reactive intermediate to transfer to the target product based on DFT calculations. Without the *t*BuOLi base diphenyldiazo-methane did not undergo the desired carbene insertion reaction. Diverse functional groups were tolerant in the *N*-tosylhydrazone substrates, and both aromatic and aliphatic ketone and aldehyde



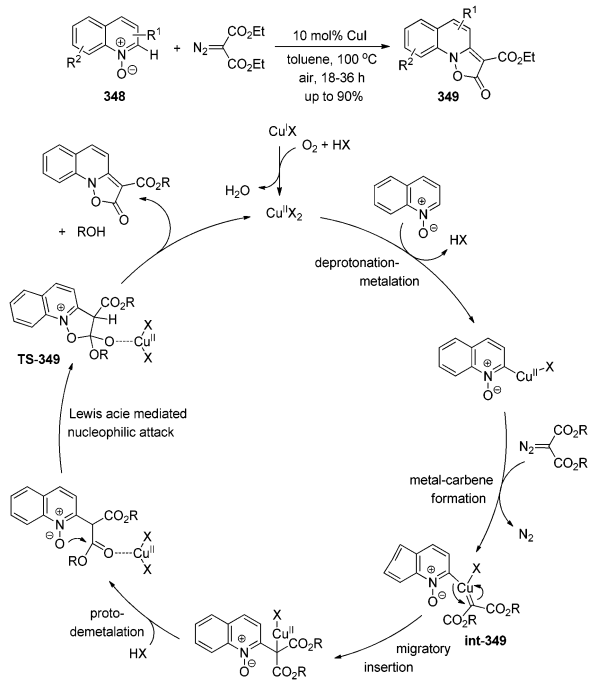
Scheme 102 Cu(I)-catalyzed carbene insertion to C(2)–H bond of *N*-iminopyridinium ylides.



Scheme 103 Proposed mechanism for Cu(I)-catalyzed carbene insertion to C(2)–H bond of *N*-iminopyridinium ylides.

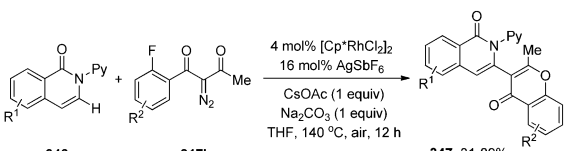
N-tosylhydrazones were employed in the reaction. Under Rh(III) catalysis *N*-pyridyl-substituted isoquinolinones (**346**) could be functionalized by 2-pyridyl-directed carbene insertion to the *ortho*-C(sp^2)–H bond by diazo compounds **317'** followed by tautomerization (eqn (88)).[336]

Direct alkylation of quinoline *N*-oxides by carbene insertion was achieved with different transition-metal catalysts and carbene source compounds. Gold(I)-catalyzed α-furanylation of 8-alkylquinoline *N*-oxides using vinyldiazocarbonyls as the carbene source was realized.[351] The C(8)–H alkylation of quinoline *N*-oxides by carbene insertion with acceptor/acceptor diazodiesters was also conducted under rhodium catalysis.[352] With *N*-tosylhydrazones as the carbene source under CuI catalysis and microwave irradiation, *ortho*-benzylation of quinoline *N*-oxides was performed to give 2-benzylated quinoline *N*-oxides.[353] In the presence of 10 mol% CuI as the catalyst in toluene at 100 °C under an air atmosphere, quinoline *N*-oxides (**348**) reacted with acceptor/acceptor diazo compounds to form N,O-heterocyclic compounds (**349**) in up to 90% yields (Scheme 104).[354] The reaction proceeded by carbene insertion to the C(2)–H bond of



Scheme 104 Cu(I)-catalyzed C(2)–H functionalization of quinoline *N*-oxides *via* carbene insertion.

the heteroarene substrate followed by intramolecular cyclocondensation to remove one molecule of ethanol. The overall reaction sequence is a Cu(I)-catalyzed carbene insertion to C(sp^2)–H bond/cyclization cascade. The Cu(II) carbene species **int-349** is considered as the reactive intermediate. The Lewis acid mediated nucleophilic attack occurs through the transition state **TS-349**. Under air conditions, the Cu(I) precatalyst is oxidized to the catalytically active Cu(II) species to initiate the reaction sequence. However, when ethyl 2-diazo-2-(phenylsulfonyl)acetate (**350**) was used, no cyclocondensation occurred and the reaction only produced the carbene insertion product **351** in 72% yield (eqn (89)).



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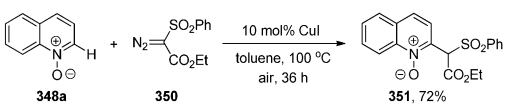
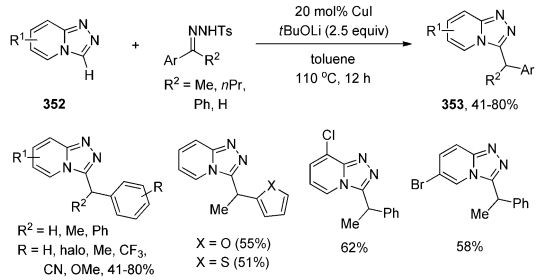
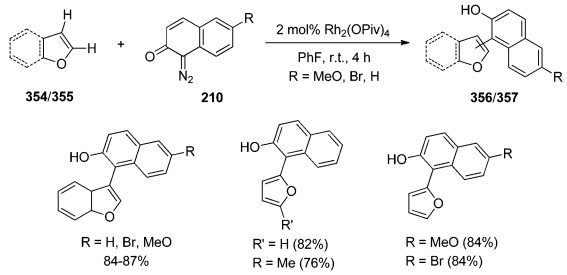


(89)

Nitrogen-containing fused N-heterocycles such as triazolopyridines **352** were selectively functionalized the triazolyl moiety by Cu(I)-catalyzed carbene insertion to the C(2)–H bond with *N*-tosylhydrazones (Scheme 105).[355] 20 mol% CuI was used as the catalyst in refluxing toluene, and the target benzylated triazolopyridines (**353**) were obtained in 41–80% yields. Tolerance of various functional groups such as alkyl, aryl, halogen, methoxy, cyano, CF_3, and heteroaryl may enable their diverse application in organic synthesis.



Scheme 105 Cu(I)-catalyzed C–H functionalization of trizolopyridines by carbene insertion.

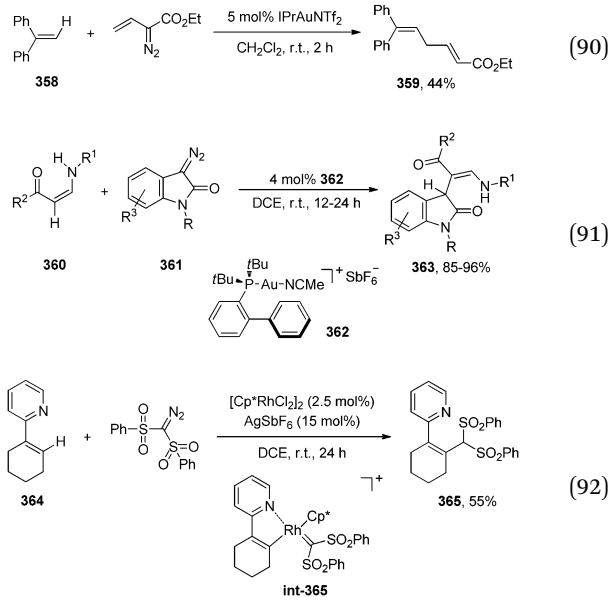


Scheme 106 Rh(II)-catalyzed carbene insertion to C(sp^2)–H bonds of benzofuran and furans.

Transition-metal-catalyzed carbene insertion to the C(sp^2)–H bonds of furan motif is often accompanied by unexpected reactions such as cyclopropanation, ring-opening, and other transformations. It is usually difficult to enable carbene insertion to furyl C–H bond(s) as the major reaction.[342,356] By means of Rh(II) complex $Rh_2(OPiv)_4$ as the catalyst in fluorobenzene at room temperature, benzofuran (**354**) and substituted furans (**355**) reacted with diazo compounds **201** to undergo the Rh(II)-catalyzed carbene insertion reaction, furnishing 3-arylated benzofurans (**356**) and 2-arylated furans (**357**) in 76–87% yields, respectively (Scheme 106).[320] This protocol provides a direct route to 3- or 2-naphthyl (or 2-naphthol) substituted *O*-heteroarenes. It is notable that transition-metal-free photochemical carbene insertion,[357] and metal-free conditions by using Lewis acids such as $BF_3{\cdot}OEt$[358] or borane $B(C_6F_5)_3$[359] have been documented for heteroaromatic C(sp^2)–H functionalization of indoles and pyrroles.

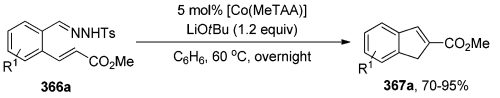
5. Carbene insertion to alkenyl C(sp^2)–H bonds

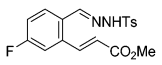
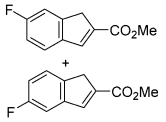
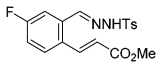
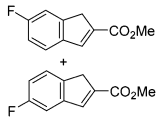
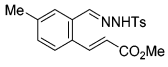
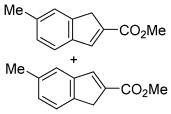
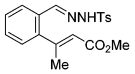
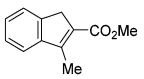
Although C–H functionalization has been developed rapidly, reports on direct alkenyl C–H functionalization are very limited due to the multiple reactivities of the alkenyl moiety under diverse reaction conditions.[227,360,361] Complex (IPr)$AuNTf_2$ was found to be an effective catalyst for the alkenyl C–H bond functionalization of 1,1-diphenylethylene (**358**) with vinyl diazoacetate in CH_2Cl_2 at room temperature, giving skipped diene **359** (eqn (90)).[268] The proposed mechanism suggests that interaction of the alkenyl diazo compound with the gold complex catalyst initially forms a gold carbene species, which can be described as an allyl gold cation intermediate.[362] Regioselective nucleophilic attack of the alkene substrate at the C3 position of the allyl cation generates the most stable carbocation intermediate. Subsequent deprotonation/demetalation leads to the target products **359**. Under Au(I) catalysis chem- and diastereoselective C(sp^2)–H functionalization of enaminones (**360**) was achieved by donor/acceptor diazo compounds **361**, affording functionalized enaminones **363** (eqn (91)), which can be efficiently transformed to the corresponding pyrrolo[3,4-*c*]quinolin-1-one derivatives in the presence of *p*-TsOH.[363] Au(I) complex catalyst **362** was found to be crucial to enable such a C–H functionalization process. Rh(III)-catalyzed, 2-pyridyl-directed alkenyl C–H functionalization occurred *via* carbene insertion with bis(phenylsulfonyl)diazomethane as the carbene source (eqn (92)).[244] Thus, the reaction of 2-pyridyl-substituted cyclohexene (**364**) gave the corresponding alkylation product **365** in 55% yield. A Rh(III)-carbene species **int-365** is considered to be the reactive intermediate leading to the target product.



The readily available Co(II) complex [Co(MeTAA)] (MeTAA = tetramethyltetraaza[14]annulene) proved to be an efficient catalyst enabling intramolecular carbene insertion to alkenyl C–H bond in *o*-cinnamyl *N*-tosylhydrazones (**366**).[364] The reaction proceeded *via* a Co(III)-carbene radical pathway to afford functionalized 1*H*-indene derivatives (**367**). Various functional groups such as ester groups CO_2Me (86%), CO_2Et (78%), CO_2nBu (80%), CO_2tBu (76%), and CO_2Ph (82%), amide $CONMe_2$ (98%), cyano (52%), and phenyl (85%) were introduced onto the vinylic double bond, affording the target products in good to excellent yields (eqn (93)). However, the substituents on the aromatic ring had no obvious impact on the reactivity (Table 13). Substituents (F, Cl, NO_2, CF_3, Me) at the 5- or 6-position did not obviously affect the product yields (82–88%). A naphthalene-based substrate led to the product in a better yield (93%), while a methoxy group diminished the yield to 72%. In the case of using the substrate with a methyl

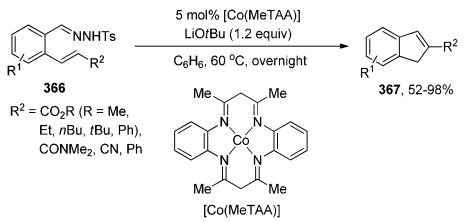
Table 13 Co(II)-catalyzed intermolecular carbene insertion to alkenyl C–H bonds



Substrate	Products	Yield (%)
		87[a]
		85[a]
		88[a]
		94

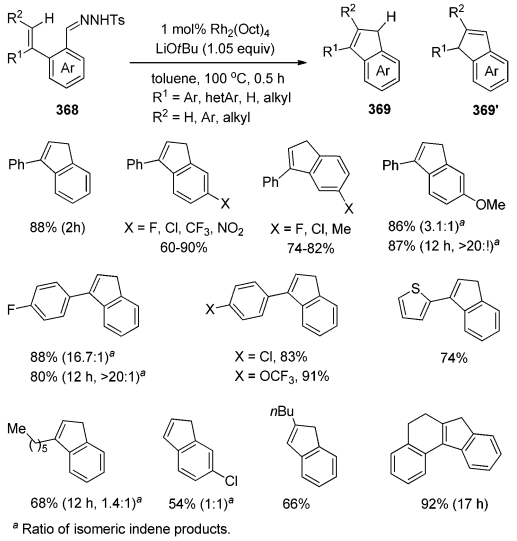
[a] Nearly 1 : 1 ratio of both isomers were formed.

substituent on the vinylic C=C bond, the indene product was regioselectively formed (94%). It is noted that use of the unsymmetrically substrates usually resulted in a mixture of two regio-isomeric products, suggesting that allylic/benzylic double bond isomerization occurred under the reaction conditions. The mechanistic studies reveal that the transformation proceeds *via* a Co(III)-carbene radical process. Under photo irradiation a Co(I) complex, that is, cobalester (a natural non-toxic vitamin B12 derivative) catalyzed the intermolecular alkenyl C–H functionalization of terminal alkenes by carbene insertion with diazo compounds.[365]



(93)

Rhodium complexes have been widely used to facilitate C–H functionalization reactions. Rh(II) complex $Rh_2(Oct)_4$ was documented to catalyze the intramolecular alkenyl C–H functionalization by carbene insertion (Scheme 107).[366] With 1mol% $Rh_2(Oct)_4$ as the catalyst in the presence of LiO*t*Bu base in toluene at 100 °C, *ortho*-vinyl *N*-tosylhydrazones (**368**) reacted to afford 1*H*-indene products **369** in 33–92% yields. In most of the cases, the target products were obtained in >80% yields. In some of the cases involving the vinyl-attached aryl groups bearing a 2- or 4-substituent, the isomeric products **369′** could be formed with a ratio of **369**/**369′** from 3 : 1 to 16.7 : 1 within 0.5 h, while formation of **369′** was remarkably diminished by extending the

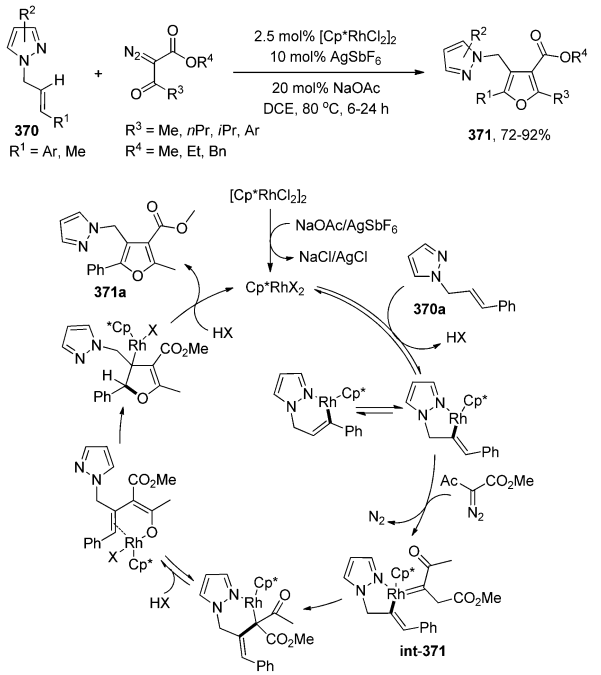


Scheme 107 Rh(II)-catalyzed intermolecular carbene insertion to alkenyl C–H bonds.

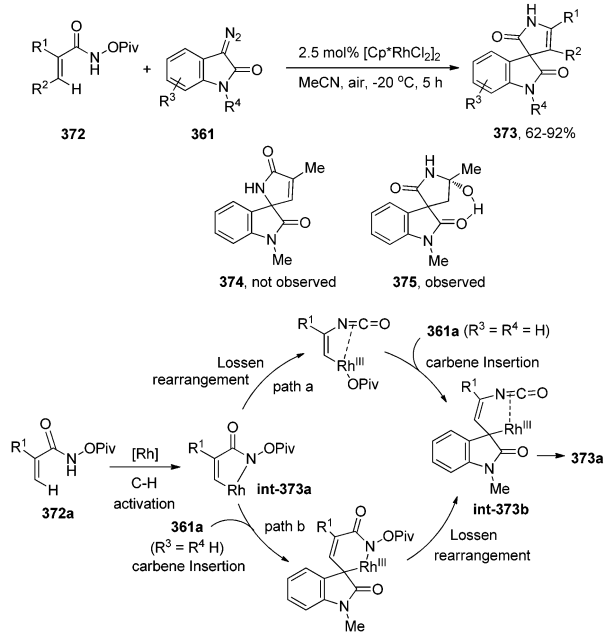
reaction time to reach a ratio of 20 : 1 or >20 : 1. Non-substituted vinyl led to a 1 : 1 ratio for **369**/**369′**. These results are contrary to those by means of the [Co(MeTAA)] catalyst (Table 13) in which a 1 : 1 mixture of isomeric products were usually obtained.[364] The present protocol features a wide substrate scope, excellent tolerance of functional groups, and high efficiency, providing a direct route to 1*H*-indene derivatives.

Rh(III) complexes have also been documented to catalyze alkenyl C–H functionalization by carbene insertion. A Rh(III)-catalyzed, *N*-heteroaryl-directed intermolecular alkenyl C–H functionalization was achieved by carbene insertion with acceptor/acceptor diazo compounds as the carbene source.[367] In the presence of 2.5 mol% $[Cp^*RhCl_2]_2$ as the catalyst, $AgSbF_6$ and NaOAc as the additives in dichloroethane at 80 °C, 1-cinnamyl-1*H*-pyrrazole (**370a**) and its analogs reacted with methyl 2-diazo-3-oxobutanoate or other acceptor/acceptor diazo compounds to give the corresponding furan derivatives **371** in 72–92% yields (Scheme 108). Various substituents on the diazodicarbonyl moiety and the aryl groups led to furan products bearing different functionalities. Rhodium carbene complex **int-371** is proposed to be the reactive intermediate to render the catalytic transformation. Cyclic diazodicarbonyls were used to access cyclohexanone and quinolinone-fused furan derivatives.

Rh(III)-catalyzed domino annulation of simple alkenes with diazo oxindoles afforded spirooxindole pyrrolone products.[368] In the presence of 2.5 mol% $[Cp^*RhCl_2]_2$ in acetonitrile at −20 °C in air, *N*-pivaloyloxy methacrylamide (**372a**) and its analogs reacted with diazooxindoles (**361**) to give products **373** in 62–92% yields (Scheme 109). However, the desired products of type **374** were not observed. A Rh(III)-catalyzed C–H activation/carbene insertion/Lossen rearrangement sequence was proposed for the reaction. Five-membered rhodacycle **int-373a** and Rh(III)-isocyanate complex **int-373b** are considered as the reactive intermediates to enable the carbene insertion process. Both compounds **373** and **375** are the arrangement



Scheme 108 Rh(III)-catalyzed formal intermolecular carbene insertion to alkenyl C–H bonds.

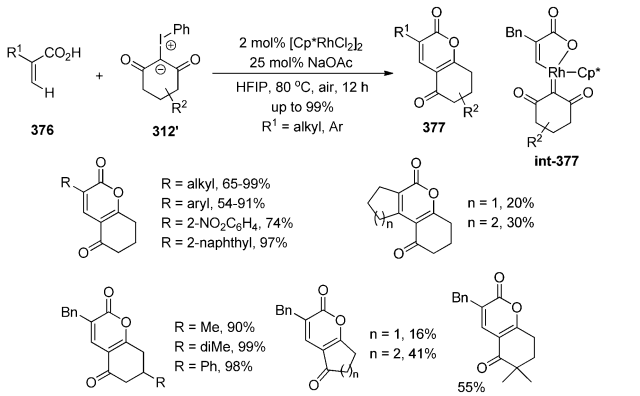


Scheme 109 Rh(III)-catalyzed formal carbene insertion to alkenyl C–H bonds *via* Lossen rearrangement.

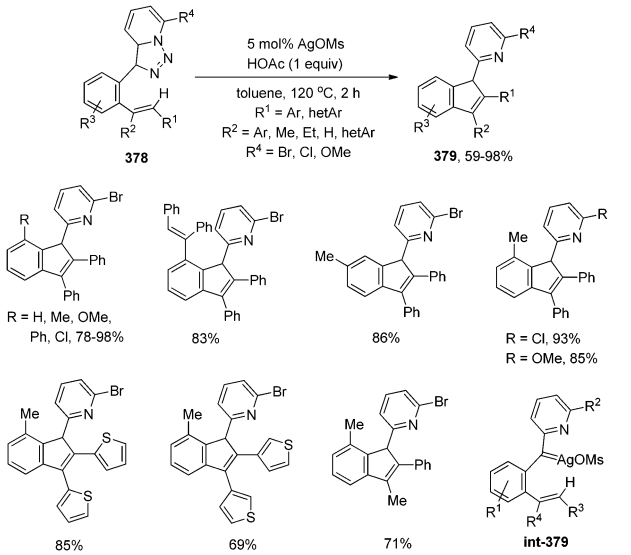
products, and formation of **375** was nearly completely inhibited at a low temperature such as −20 °C. This reaction can be formally considered as a process of carbene insertion to alkenyl C–H bond followed by rearrangement and annulation. Such a protocol is potentially useful for the late-stage diversification of drug molecules. The proposed mechanism suggests that path a is more favorable based on the control experiments although two possible reaction pathways exist. Cleavage of the alkenyl C–H bond with the Rh^{III} species followed by carbene insertion with the diazo compound gives a new alkyl rhodium species, which undergoes a formal Lossen rearrangement to generate isocyanate **int-373b**. Subsequent intramolecular nucleophilic attack at the isocyanate functionality affords product **373**.

Iodonium ylides (**312′**) were reported as the carbene source for Rh(III)-catalyzed intermolecular alkenyl C–H functionalization by carbene insertion (Scheme 110).[369] By means of 2 mol% $[Cp^*RhCl_2]_2$ as the catalyst in the presence of 25 mol% NaOAc in HFIP at 80 °C, acrylic acids **376** reacted with **312′** to give lactone products **377** in up to 99% yields. The 2-substituents in acrylic acids could be alkyl and aryl groups. Cyclic acrylic acids reacted much less efficiently to form the corresponding products in 20–30% yields. For the scope of iodonium ylides, different substituted cyclohexane-1,3-diones generally afforded the target products in good to excellent yields, but the acyclic iodonium ylides failed to undergo the desired reaction under the stated conditions. Based on these results rhodium carbene complex **int-377** is considered as the reactive intermediate for the formal carbene insertion to alkenyl C–H bond. It is noted that a Ru(II) complex, that is, $[Ru(p\text{-cymene})Cl_2]_2$, can facilitate the alkenyl C–H functionalization of α-oxo ketene dithioacetals, a class of polarized internal alkenes, with acceptor/acceptor diazo compounds.[370]

A silver(I) catalyst was recently reported to promote the intramolecular alkenyl C–H functionalization by azavinyl carbene insertion (Scheme 111).[371] The reaction was conducted under the conditions using 5 mol% AgOMs as the catalyst, and HOAc (1 equiv.) as the additive in toluene at 120 °C. Treatment of *ortho*-styryl-functionalized triazoles (**378**) under the stated conditions for 2 h gave 2-pyridyl-substituted 1*H*-indenes (**379**) in good to excellent yields (59–98%). In most of the cases, the yields were higher than 80%. DFT calculations have suggested that a Ag(I) carbene (**int-379**) is the reactive intermediate to furnish the C–H functionalization process. This method features high efficiency and excellent functional group tolerance. The experimental and computational studies suggest that water involvement favors the reaction.



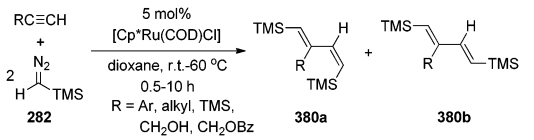
Scheme 110 Rh(III)-catalyzed formal carbene insertion to alkenyl C–H bonds with iodonium ylides.



Scheme 111 Ag(I)-catalyzed intermolecular carbene insertion to alkenyl C–H bonds.

6. Carbene insertion to alkynyl C(sp)–H bonds

Transition-metal-catalyzed cross-coupling of terminal alkynes with different coupling partners can provide versatile alkynes and allenes. Carbene insertion to terminal C(sp)–H bond offers a direct route to functionalized alkynes and derivatives as well as diverse possibilities for the development of cascade or multi-component reactions.[372] The reaction of diazo compound $N_2CHSiMe_3$ (TMSC(H) = N_2, **282**) with terminal alkynes was conducted in the presence of 5 mol% [Cp*Ru(COD)Cl] in dioxane at 60 °C, affording functionalized conjugate dienes (**380**) in up to 80% yields (eqn (94)).[373] This reaction constructed two carbon–carbon double bonds in a single step under mild conditions, and ratio of the isomeric products was dependent on the steric hindrance of the alkyne substrates. (*Z*)-Stereoselectivity is favorable for the less hindered double bond, while disubstituted alkynes favor (*E*)-configuration for the same double bond. The reaction also occurred with EDA and PhCH=N_2. Such a transformation can be understood by addition of two carbene units to a triple bond involving formal carbene insertion to the alkynyl C(sp)–H bond. Ruthenium carbene Ru=CHTMS is considered as the reactive intermediate capable of coordinating a second carbene unit to generate the conjugated dienes.

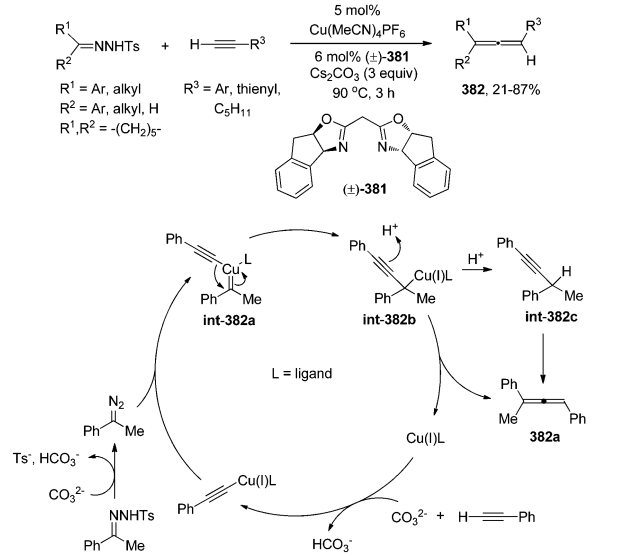


(94)

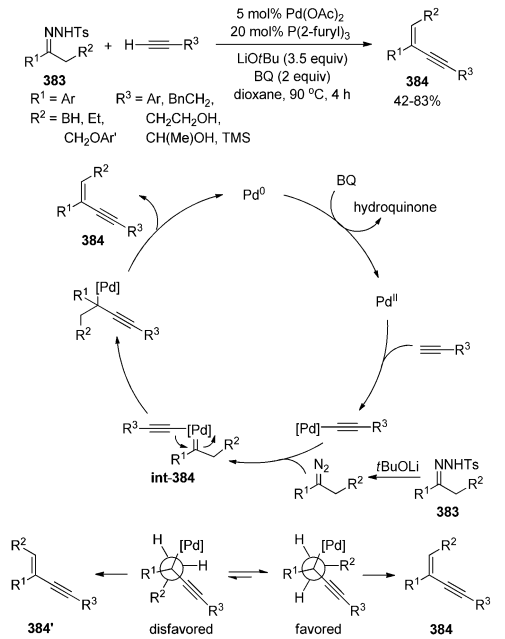
Cu(I)-catalyzed synthesis of trisubstituted allenes from terminal alkynes and *N*-tosylhydrazones was achieved in the presence of 5 mol% $Cu(MeCN)_4PF_6$ catalyst, bis(oxazoline) ligand (±)-**381**, and Cs_2CO_3 base in dioxane at 90 °C (Scheme 112).[374] Use of the *N*-tosylhydrazones of acetophenones as the donor/donor carbene source usually led to >50% yields, while the *N*-tosylhydrazones of benzophenone and dialkyl ketones, and cyclic *N*-tosylhydrazones resulted in the target products in 21–40% yields. Aryl, heteroaryl, and alkyl-based alkynes worked well for the reaction. Notably, formation of Cu(I) carbene complex **int-382a** is crucial to enable the carbene insertion transformation. The proposed mechanism suggests that the formal carbene insertion product **int-382c** isomerizes to afford the corresponding final allene product **382**.

Palladium-catalyzed oxidative cross-coupling of *N*-tosylhydrazones or diazoesters with terminal alkynes was conducted to prepare 1,3-enynes.[375] By means of the *N*-tosylhydrazones of aryl alkyl ketones as the carbene precursor under oxidative cross-coupling conditions, that is, 5 mol% $Pd(OAc)_2$ as the catalyst, 20 mol% P(2-furyl)$_3$ as the ligand, and BQ (benzoquinone) as the oxidant in dioxane at 90 °C, *N*-tosylhydrazones **383** reacted with terminal alkynes in the presence of LiO*t*Bu to give the desired conjugate enynes **384** in 42–83% yields (Scheme 113). Various substituents such as methyl, chloro, methoxy, and nitro were tolerated on the aryl moiety, and diverse terminal alkynes also worked well in the desired reaction. In general, (*Z*)-1,3-enynes were obtained. When donor/acceptor diazoesters **383a** were used as the carbene source, the reaction proceeded in a similar fashion to give the target products **385** (27–75%) (eqn (95)). Palladium carbene complexes of type **int-384** are considered as the reactive intermediates to enable the present formal carbene insertion reaction. Under Cu(I) catalysis, trifluoromethyl *N*-tosylhydrazones were reacted with terminal alkynes to give difluorinated conjugate enynes through a β-fluoride elimination process.[376]

During the investigation of Cu(I)-catalyzed synthesis of allenes from the reaction of *N*-tosylhydrazones and terminal alkynes,[374] Wang, *et al.* found that use of trimethylsilylethyne

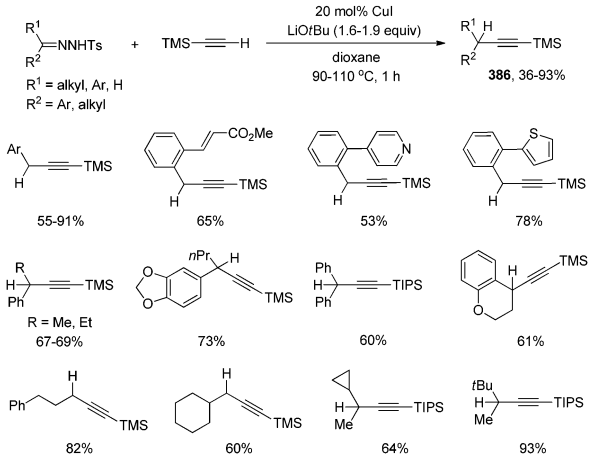


Scheme 112 Cu(I)-catalyzed formal carbene insertion to alkynyl C(sp)–H bond to form allenes.



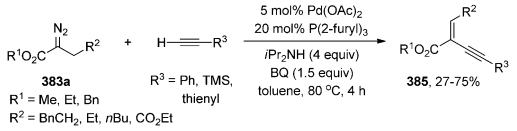
Scheme 113 Palladium-catalyzed oxidative cross-coupling of terminal alkynes with *N*-tosylhydrazones.

as the cross-coupling partner led to the ethynylation products through carbene insertion to alkynyl C(sp)–H bond.[377] With 20 mol% CuI as the catalyst in the presence of LiO*t*Bu base in dioxane, *N*-tosylhydrazones of benzaldehydes reacted at 90 °C to produce the target products **386** in 53–91% yields (Scheme 114). Various functional groups are tolerant on the aryl moiety of the *N*-tosylhydrazones. The reaction of the *N*-tosylhydrazones of diaryl or aryl alkyl ketones should be conducted at a higher temperature (110 °C) to reach 44–73% yields. In a similar fashion, *N*-tosylhydrazones of aliphatic aldehydes and dialkyl ketones also efficiently reacted with trimethylsilylethyne at 110 °C to form the products in 40–93% yields. It is noted that triisoproplsilylethyne (HC≡C-TIPS) also reacted well under the stated conditions. As discussed in



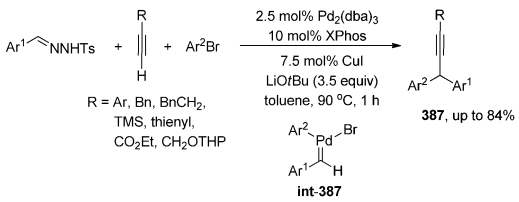
Scheme 114 Cu(I)-catalyzed carbene insertion to alkynyl C(sp)–H bond of trimethylsilylethynes.

Scheme 112, copper(I) carbene species of type **int-382** are considered as the key reactive intermediates for such a carbene insertion to C(sp)–H process.



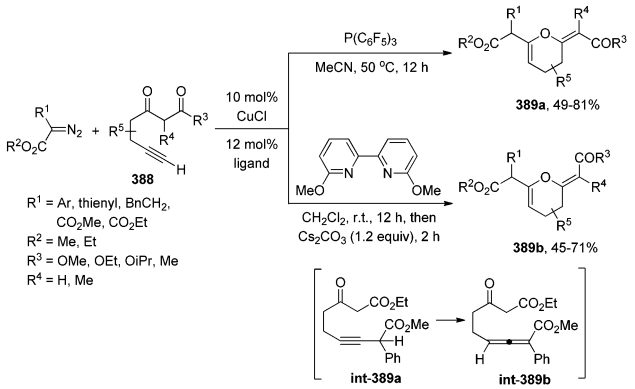
(95)

Interestingly, a palladium-catalyzed three-component coupling of *N*-tosylhydrazones, terminal alkynes, and aryl halides was carried out to access internal alkynes through a palladium-catalyzed carbene insertion to alkynyl C(sp)–H bond/transmetalation/reductive elimination sequence, which leads to formation of two new C–C bonds (eqn (96)).[378] Use of the palladium catalyst (2.5 mol% $Pd_2(dba)_3$/10 mol% XPhos) to reach the cross-coupling with aryl bromides, and the copper catalyst (7.5 mol% CuI) for alkynyl transfer furnished the three-component transformation to generate internal alkynes **387**. Stereodivergent synthesis of N-heterocycles by catalyst-controlled, activity-directed tandem annulation of diazo compounds with terminal amino-alkynes was also achieved.[379] In the presence of 10 mol% CuCl in MeCN or $CHCl_3$ at 60 °C, homopropargyl sulfonamides or *N*-benzylamino alkynes reacted with aryldiazoacetates to give five-membered N-heterocycles such as 2,3-dihydropyrroles (52–87%) or 2-methylene pyrrolidines (69–87%) involving formal carbene insertion to the alkynyl C–H bond. However, the reaction of *N*-benzyl amino alkynes and diazodicarbonyls under $Rh_2(esp)_2$ catalysis in the presence of $ZnCl_2$ gave 3-methylene pyrrolidines through a carbene insertion to N–H bond/Conia-ene cyclization sequence. The asymmetric versions of carbene insertion to alkynyl C–H bonds by using *N*-tosylhydrazones as the carbene precursor or other relevant tandem reactions have also been documented.[312]



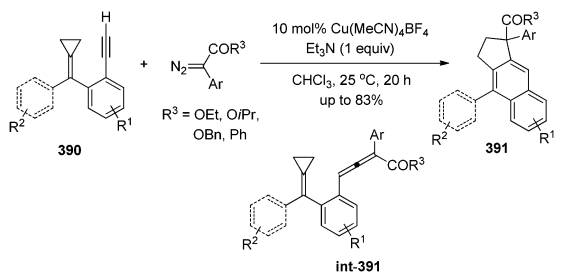
(96)

A Cu(I)-catalyzed carbene insertion to alkynyl C–H bond/cyclization sequence of dicarbonyl-functionalized terminal alkynes (**388**) was developed to access multifunctionalized dihydropyran derivatives **389** (Scheme 115).[380] The configurations of the target products were controlled by $P(C_6F_5)_3$ and 2,2′-bipyridine ligands, respectively, exhibiting opposite exocyclic double bonds in a controlled manner. The Cu(I)-catalyzed carbene insertion products of types **int-389a** and **int-389b** are proposed as the reactive intermediates for such a process. The donor/acceptor diazo compounds aryldiazoacetates were the effective carbene precursor. Terminal alkynes **390** bearing an alkylidenecyclopropane moiety were used to react with donor/acceptor diazo compounds under Cu(I) catalysis, giving tricyclic



Scheme 115 Cu(I)-catalyzed formal carbene insertion to alkynyl C(sp)–H bond to access dihydropyrans.

cyclopenta[*b*]naphthalene derivatives **391** (eqn (97)).[381] The reaction proceeded smoothly in the presence of 10 mol% $Cu(MeCN)_4BF_4$ and Et_3N (1 equiv.) in $CHCl_3$ at room temperature, forming **391** in up to 83% yields. The allene species of type **int-391** generated *in situ* from the Cu(I)-catalyzed carbene insertion to alkynyl C–H bond is considered as the reactive intermediate to facilitate the tandem reaction sequence. This reaction underwent *via* allene species **int-391** to furnish a domino cycloisomerization of a 6π-electrocyclization and cyclopropane ring-opening rearrangement, resulting in the target products in moderate to excellent yields. It is noteworthy that donor/donor carbenes from electron-rich aryl/aryl diazo compounds can be efficiently inserted to alkynyl C–H bonds under mild condoitions.[382] However, the desired reaction did not occur in the presence of Rh(II) or Cu(I) catalysts, only leading to decomposition of the diazo compounds.



(97)

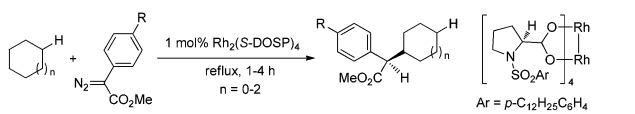
7. Enantioselective carbene insertion to C–H bonds

Enantioselective direct C–H functionalization has become more and more attractive in organic synthesis. In this context, catalytic enantioselective carbene insertion to aliphatic $C(sp^3)$–H and heteroaryl $C(sp^2)$–H bonds for direct construction of chiral carbon centers has been paid considerable attention due to the protocol applicability to modify complex molecules and/or enable site-selective C–H functionalization by means of chiral transition-metal complex catalysts, chiral ligands, and/or chiral substrates.[24,39,81–84,314,383,384] Catalyst- and substrate-control strategies are usually applied for regioselective and stereoselective C–H functionalization by carbene insertion with diverse carbene source compounds. This section will summarize the advance in transition-metal-catalyzed enantioselective direct C–H functionalization through carbene insertion by the categories of C–H bonds.

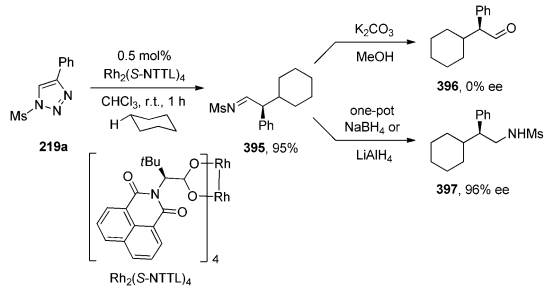
7.1. Enantioselective carbene insertion to alkane $C(sp^3)$–H bonds

In 1997, Davies, *et al.* reported the first example of Rh(II)-catalyzed enantioselective intermolecular carbene insertion to aliphatic C–H bonds with donor/acceptor diazo compounds.[108] In the presence of Rh_2(*S*-DOSP)$_4$ catalyst and cycloalkanes as both the reactants and solvents, the reaction of cycloalkanes with aryldiazoacetates gave the corresponding benzylation products (*R*)-**392** in 55–96% yields with 60–93% ee (Table 14). The product yields were found to be much higher when the reaction was conducted under refluxing conditions. It was noticed that electron-donating substituents on the aryl moiety of the diazo compounds diminished the product yields, while the electron-withdrawing groups enhanced both the yields and enantioselectivities. However, the apparent trend toward increased enantioselectivity could not be extended to *p*-nitrophenyldiazoacetate due to its insolubility in the hydrocarbon solvent. The reaction efficiency is very dependent on the used diazo compounds. Use of acceptor diazo compound EDA did not result in a stereogenic center with significant formation of the dimerization side product from the diazo compound in the reaction with cyclohexane (eqn (98)). It is noted that no dimeric carbene products were observed in the reaction of aryldiazoacetates described in Table 14. With the acceptor/acceptor diazo compound, the desired product **393** was formed in 51% yield with only 3% ee (eqn (99)). However, in the case of using donor/acceptor vinyldiazo compound **18a** the target product **394** was obtained in 83% ee (eqn (100)). Such an efficiency of the diazo compounds is consistent with that observed in the enantioselective cyclopropanation by Rh_2(*S*-DOSP)$_4$, in which a high asymmetric induction occurred only with donor/acceptor vinyl or aryldiazoacelates.[385] In the present

Table 14 Rh(II)-catalyzed enantioselective carbene insertion to cycloalkane $C(sp^3)$–H bonds

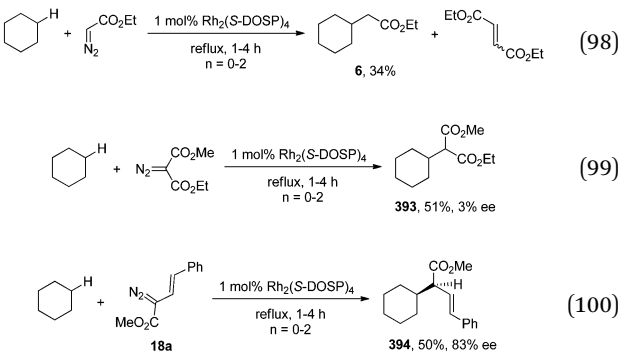


R	*n*	Temp. (°C)	Yield (%)	ee (%)
OMe	1	50	55	83
H	1	50	84	87
Cl	1	50	78	89
Cl	2	81	91	86
Cl	2	25	53	93
OMe	3	118	78	60
H	3	118	84	70
Cl	3	118	96	81

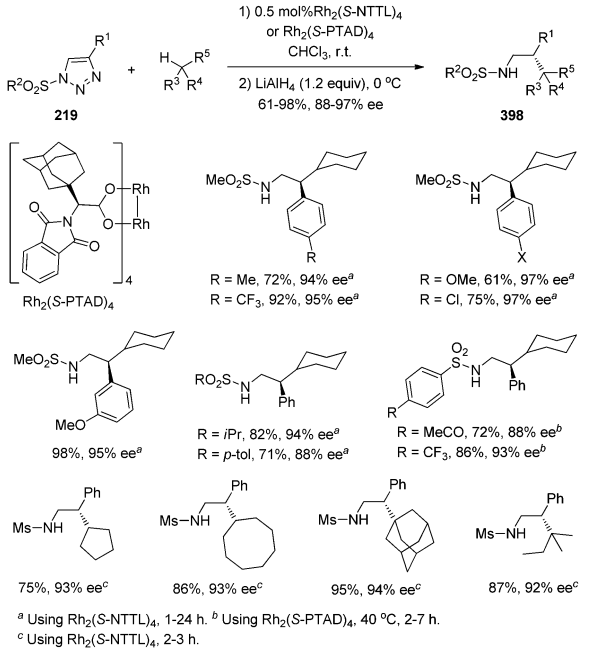


Scheme 116 Rh(II)-catalyzed enantioselective azavinyl carbene insertion to cyclohexane C–H bond.

case, one of the key requirements for high stereoselectivity in this Rh(II) prolinate catalyzed reaction is the presence of both the acceptor (ester) and donor (vinyl or phenyl) groups on the *in situ* generated Rh(II) carbene. The C–H substrate approaches the metal carbene center in a side-on manner to result in such a high enantioselectivity. These results have shown the promising potential for enantioselective C–C bond formation through intermolecular direct C–H functionalization by carbene insertion.



Azavinylcarbene sources were reported for direct enantioselective C–H functionalization of non-activated alkanes by intermolecular carbene insertion. Enantioselective functionalization of the secondary C–H bonds of cyclohexane using 1-(methanesulfonyl)-substituted 1,2,3-triazole (**219a**) in the presence of 0.5 mol% Rh_2(*S*-NTTL)$_4$ as the catalyst was achieved (Schemes 116 and 117).[386] The desired imine product **395** was formed in 95% yield at ambient temperature by means of a 1 : 1 (v/v) mixture of the alkane and chloroform. Hydrolysis of **395** using K_2CO_3 in wet methanol gave the corresponding carbaldehyde **396** as a racemic mixture, while one-pot treatment of the imine intermediate with sodium borohydride or lithium aluminum hydride led to quantitative reduction of **395** to afford mesyl-protected chiral amine **397** with 96% ee. This one-pot protocol was then applied for the direct functionalization of cyclohexane and other non-activated alkanes with other triazole compounds **219** in the presence of Rh_2(*S*-NTTL)$_4$ or Rh_2(*S*-PTAD)$_4$ catalyst (Scheme 117). It was found that 1-mesyl-substituted triazoles with both election-donating and electron-withdrawing aryl groups at C4 position underwent the reaction to give the target amine products with excellent

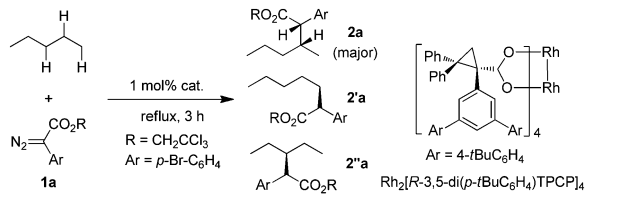


Scheme 117 Rh(II)-catalyzed enantioselective direct C–H functionalization of non-activated alkanes.

enantioselectivity. The triazole bearing a *p*-methoxyphenyl at C4 position gave 61% yield and 97% ee, while the *m*-methoxyphenyl-substituted triazole at the C4 position yielded the target product in 98% yield with 95% ee. Various substituents such as isopropyl, 2-(trimethylsilyl)ethyl, and aryls were tolerated in the sulfonyl moiety, leading to both lower yields and enantioselectivity compared to the mesyl-based triazole **219a**. Non-activated cycloalkanes, that is, cyclopentane and cyclooctane, also efficiently underwent the secondary C–H functionalization with **219a** to afford the desired products in 75–86% yields with 93% ee, while adamantane underwent the tertiary C–H functionalization, efficiently affording the target product (95% yield, 94% ee). Both 2-methylbutane and 2-methylpentane underwent the carbene insertion reaction with **219a** at the tertiary C–H bonds to form the corresponding products in 87% (92% ee) and 63% (91% ee) yields, respectively. These results have demonstrated that azavinyl carbenes derived from *N*-sulfonyl-1,2,3-triazoles can be efficiently applied for highly enantioselective C–H functionalization of simple non-activated alkanes.

Transition-metal-catalyzed C–H functionalization provides direct routes to C–C and C-heteroatom bonds. However, modification of a C–H bond at will has been a great challenge in modern organic synthesis. To make a C–H functionalization method be useful, effective strategies for site-selective C–H functionalization need to be developed. The directing group strategy and modification of the electronic and steric properties of the substrates have been well used to achieve regioselective reactivity for specific reactions. In principle, it is possible for a potentially general method using a catalyst/substrate-control strategy to enable the site-selective C–H

Table 15 Bulky Rh(II)-catalyzed enantioselective site-selective secondary C–H functionalization of *n*-pentane by carbene insertion

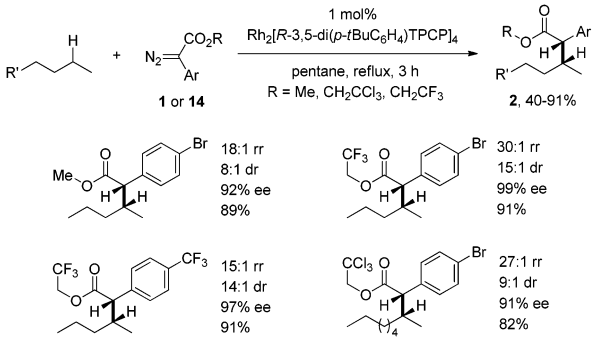


Site selectivity (**2a** : **2′a** : **2″a**)	Diastereoselectivity (dr for **2a**)	Enantioselectivity (% ee for **2a**)	Combined yield (%)
25 : 1 : N.D.	20 : 1	99	99
29 : N.D. : 1[a]	3 : 1	82	98

[a] Using Rh_2(*S*-DOSP)$_4$ as the catalyst.

functionalization of non-activated alkanes by carbene insertion.

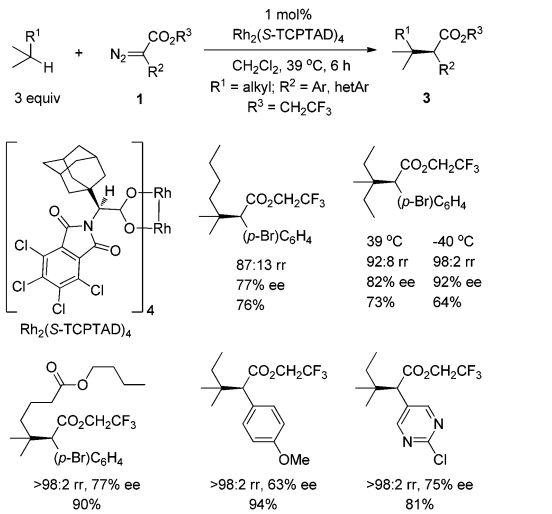
In 2016, a breakthroughing catalyst-control strategy was developed in this area by Davies, *et al.* for the site-selective and stereoselective C–H functionalization of non-activated simple linear alkanes (Table 15).[81] On one hand, carbene-induced C–H functionalization is usually initiated by a hydride transfer process that the reaction is favored at sites of stabilizing a build-up of positive charge and thus tertiary C–H bonds are electronically preferred to be inserted by a carbene species.[64] On the other hand, the dirhodium–carbene complexes are sterically demanding that primary C–H bonds are preferred to be inserted by the carbene species. With 1 mol% of the bulky dirhodium(II) triarylcyclopropanecarboxylate complex Rh_2[*R*-3,5-di(*p*-*t*BuC_6H_4)TPCP]$_4$ as the catalyst, simple *n*-alkanes underwent highly regio-, diastereo- and enantioselective C–H functionalization at the unactivated C(2) position of the *n*-alkanes or terminally substituted *n*-alkyl compounds. This Rh(II) complex was found to be the most efficient catalyst for the secondary C–H functionalization of pentane at its C(2) position with donor/acceptor diazo compound, that is, 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**1a**) as the carbene precursor under refluxing conditions, giving highly regio-, diastereo-, and enantioselective C–H functionalization product **2a**. The reaction formed both products **2a** and **2′a** in 99% yield and a 25 : 1 site selectivity with 20 : 1 dr and 99% enantioselectivity for **2a**. The C–H functionalization at the C(3) position did not occur to form **2″a**. In the case of using Rh_2(*S*-DOSP)$_4$ as the catalyst, the reaction only gave products **2a** and **2″a** with a lower enantioselectivity for **2a** (82% ee). In general, the C(3) position secondary C–H functionalization of *n*-pentane did not occur for the screened dirhodium complex catalysts of the same type, and carbene insertion to the primary C–H bond at C1 position always concurrently occurred as the side reaction. The ester group in the diazo compounds could be modified by using methyl, CH_2CBr_3 or CH_2CF_3 to replace the CH_2CCl_3 group (Scheme 118). The aryl group substituted by 4-CF_3 or 4-*t*Bu did not obviously affect the reaction efficiency, and 3-(2-chloropyridyl)diazoacetate also efficiently participated in the reaction to afford the desired product in 87% yield with 28 : 1 rr,



Scheme 118 Bulky Rh(II)-catalyzed enantioselective site-selective secondary C–H functionalization of linear non-activated alkanes.

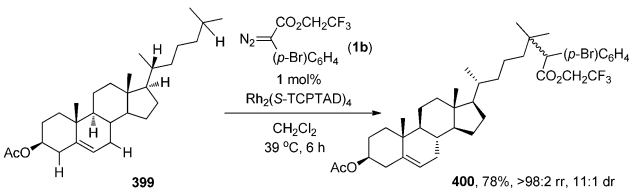
55 : 1 dr, and 91% ee. Octane and terminally substituted *n*-hexanes by F, Cl, Br, and TMS underwent the reaction in lower yields (84–85%). The site selectivity for the C–H functionalization of terminally halo, TMS, and *t*Bu-substituted *n*-alkanes and octane catalyzed by dirhodium tetrakis(triarylcyclopropanecarboxylate) complexes was comparatively investigated.[387]

In the above mentioned work,[81] the bulky dirhodium(II) complex catalyst Rh_2[*R*-3,5-di(*p*-*t*BuC_6H_4)TPCP]$_4$ was successfully employed for the functionalization of the most accessible non-activated, that is, not next to a functional group, secondary C–H bonds by carbene insertion with donor/acceptor diazo compounds as the carbene precursor. By modulating the electronic and steric properties of the dirhodium complexes, complex Rh_2(*S*-TCPTAD)$_4$ was developed to enable the precise site-selective functionalization of the most accessible tertiary C–H bonds in non-activated alkanes and related compounds (Scheme 119).[82] During the screening of reaction conditions for the reaction of 2-methylpentane and an aryldiazoacetate, it was found that Rh_2(*S*-DOSP)$_4$ preferentially reacted at the tertiary C–H bond but with considerable secondary C–H functionalization. Complex Rh_2[*R*-3,5-di(*p*-*t*BuC_6H_4)TPCP]$_4$ favored the



Scheme 119 Rh(II)-catalyzed enantioselective site-selective tertiary C–H functionalization of non-activated alkanes by carbene insertion.

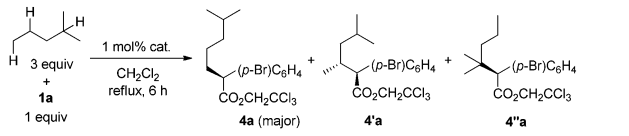
reaction at the methylene site, but with a low enantioselectivity, presumably because the methylene sites are sterically compromised by being too close to the isopropyl group. With the trifluoroethyl diazo compound (**1b**) the highest site-selectivity was achieved. Lowering the temperature to −40 °C, the regio- and enantioselectivities were enhanced with decrease of the product yield. In refluxing CH_2Cl_2, the reaction is compatible with various non-activated alkane substrates and terminally ester-substituted alkanes, aryl and heteroaryldiazo compounds, affording the target products **3** in up to 94% yields, >98 : 2 rr, and 92% ee. Notably, the present protocol can be used to functionalize natural products such as steroid compound cholesteryl acetate (**399**) in a precise way (eqn (101)). The reaction was conducted by using 1 : 1 molar ratio of the C–H substrate and diazo compound **1b** (R^2 = *p*-BrC_6H_4, R^3 = CH_2CF_3) in the presence of 1 mol% Rh_2(*S*-TCPTAD)$_4$ as the catalyst in CH_2Cl_2 at 39 °C. The reaction proceeded clearly to give the C–H functionalization product (*S*)-**400** (78%, >98 : 2 rr, and 11 : 1 dr) from the reaction at the most accessible tertiary C–H bond. By means of Rh_2(*R*-TCPTAD)$_4$ as the catalyst the product yield of (*R*)-**400** was increased to 86%, and the dr value could be increased to 16 : 1 with a 60% yield when the reaction was conducted at 0 °C.[82] Vitamin E acetate, phytyl pivatate, and cholesteryl perlargonate were also successfully functionalized in a similar manner. This work may inspire the design of more complex catalysts to enable catalyst-controlled precise C–H functionalization in a practical way.

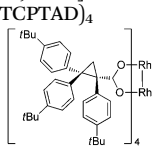


(101)

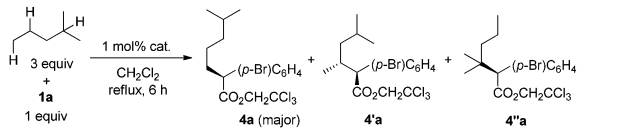
The catalyst-control strategy was further developed for the site-selective and enantioselective primary C–H functionalization of non-activated alkanes and relevant substituted alkanes by Davies, *et al.*[83] In this case, modification of the substrates by introduction of functional groups or directing group is not necessary. In Davies' previous work, [Rh_2(R-3),5-di(*p*-*t*BuC_6H_4)TPCP]$_4$,[81] Rh_2(*S*-TCPTAD)$_4$, and Rh_2(*R*-TCPTAD)$_4$[82] were successfully used for the site-selective and enantioselective C–H functionalization of non-activated secondary and tertiary C–H bonds by carbene insertion, respectively. Their present work disclosed a powerful dirhodium catalyst, that is, Rh_2[(*R*-tris(*p*-*t*BuC_6H_4)TPCP)]$_4$, for the highly effective functionalization of non-activated primary C–H bonds in alkanes and relevant substituted molecules (Table 16).[83] The donor/acceptor diazo compound **1a**[81] was the most effective carbene precursor. In the presence of the widely used Rh_2(*R*-DOSP)$_4$ catalyst for C–H functionalization, no primary C–H bond functionalization of 2-methylpentane occurred and the catalyst only exhibited a low catalytic activity. As expected, catalyst Rh_2[*R*-3,5-di(*p*-*t*BuC_6H_4)TPCP]$_4$ favored the secondary C–H functionalization

Table 16 Rh(II)-catalyzed enantioselective site-selective primary C–H functionalization of non-activated alkane by carbene insertion



Catalyst	rr (**4a** : **4′a** : **4″a**)	ee for **4a**	Yield (%) (**4a** + **4′a**)
Rh_2(*S*-DOSP)$_4$	N.D. : 19 : 81	—	10
[Rh_2(*R*-3),5-di(*p*-*t*BuC_6H_4)TPCP]$_4$	7 : 75 : 18	81	75
Rh_2(*S*-TCPTAD)$_4$	N.D. : 11 : 89	—	10
			
Rh_2[(*R*-tris(*p*-*t*BuC_6H_4)TPCP)]$_4$	84 : 16 : N.D.	98	90

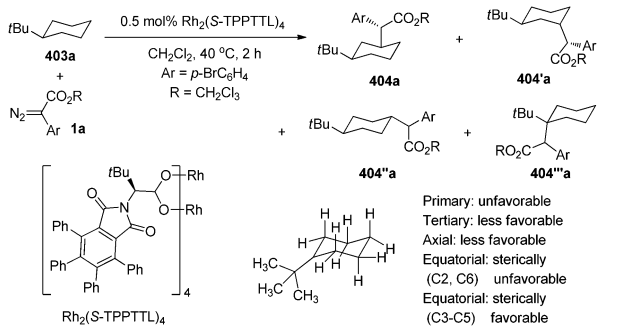
at the C2 position, and complex Rh_2(*S*-TCPTAD)$_4$ facilitated the tertiary C–H functionalization with a low catalytic activity. Gratifyingly, complex Rh_2[(*R*-tris(*p*-*t*BuC_6H_4)TPCP)]$_4$ enabled the most accessible primary C–H bond functionalization of the C–H substrate, and the more crowded secondary and tertiary sites were no longer functionalized. For other non-activated alkane substrates and chiral substrates containing other primary, secondary, and tertiary C–H bonds and functional groups, such as bromide and silyl ether, the same type of reaction also efficiently occurred. Notably, the present protocol is applicable for the functionalization of complex molecules. Catalyst Rh_2[(*R*-tris(*p*-*t*BuC_6H_4)TPCP)]$_4$ exhibited a low catalytic activity for the functionalization of stingmasteryl acetate (**401**) with **1c**, but Rh_2[(*S*-tris(*p*-*t*BuC_6H_4)TPCP)]$_4$ enabled the transformation to give the most accessible primary C–H functionalization product **402** in 88% yield with 96 : 4 rr and >100 : 1 dr (eqn (102)).[83]



(102)

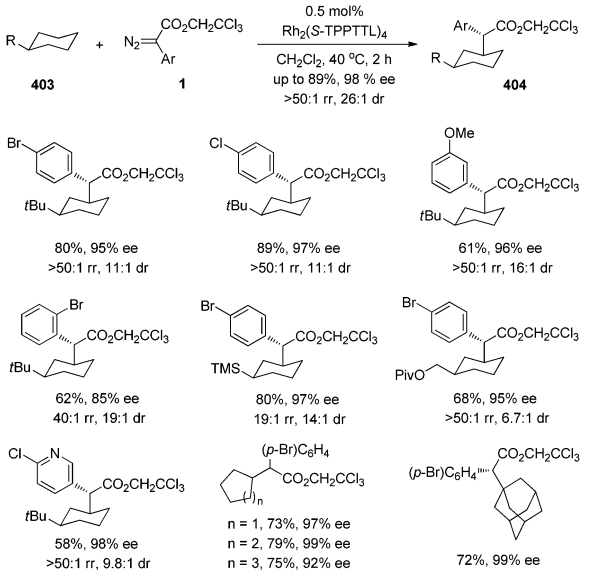
Davies' catalyst control strategy can enable the site- and enantioselective primary, secondary, and tertiary C–H functionalization of non-activated *n*-alkanes and related molecules by carbene insertion.[81–83,387] A dirhodium complex structurally related to Rh_2(*S*-TCPTAD)$_4$, that is, Rh_2(*S*-TPPTTL)$_4$ was successfully used for the site- and enantioselective C–H functionalization of cyclohexanes.[388] It has been known that Rh_2(*S*-DOSP)$_4$ can enable the enantioselective C–H functionalization of cyclohexane with methyl phenyldiazoacetate (**14a**) in 74% yield with 92% ee.[109] Using Rh_2(*S*-TPPTTL)$_4$ as the catalyst, the reaction of mono-substituted cyclohexanes could establish three stereocenters in one step from the achiral substrates.

Table 17 Desymmetrization of *tert*-butylcyclohexane by carbene insertion with **1a**



	Product ratio			
Rh(II) catalyst	**404a**	**404′a**	**404″a**	**404‴a**
Rh_2(*S*-DOSP)$_4$	60.8	9.7	24.1	5.3
Rh_2(*S*-TPPTTL)$_4$	91.3	8.7	N.D.	N.D.

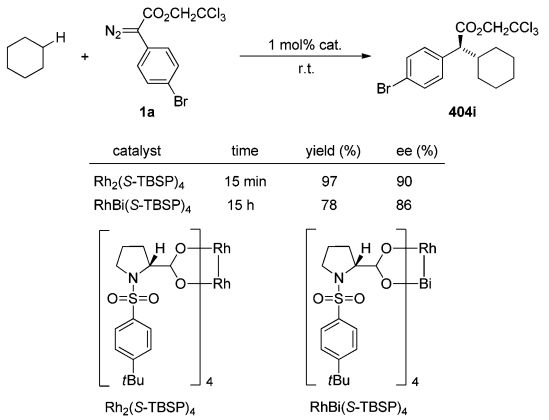
This catalyst not only differentiates between C3 and C4, but also between C3 and C5, resulting in desymmetrization of cyclohexanes and formation of the products with high diastereo- and enantioselectivities. In the reaction of *tert*-butylcyclohexane (**403a**) with diazo compound **1a**, use of Rh_2(*S*-DOSP)$_4$ as the catalyst led to a mixture of three methylene-insertion products **404a**, **404′a**, and **404″a** (60.8 : 9.7 : 24.1), with a small amount of the C1 methine-insertion product **404‴a** (Table 17).[388] However, among the screened dirhodium complexes, only Rh_2(*S*-TPPTTL)$_4$ gave a very clean reaction, favoring predominately a single methylene C–H functionalization product **404a** with high site-selectivity (>50 : 1 rr) and asymmetric induction (95% ee). It is noteworthy that product **404″a** derived from C4 insertion was not observed in the reaction by this catalyst. The products **404a** and **404′a** are diastereomers and were formed through a desymmetrization. This catalyst can therefore effectively distinguish between C3 and C4, and between the enantiotopic equatorial hydrogens at C3 and C5, such a phenomenon was first reported in this work for any C–H functionalization of alkyl cyclohexanes. Such a protocol was efficiently applied to functionalize other mono-substituted cyclohexanes and unsubstituted cycloalkanes (Scheme 120). A series of alkyl-substituted cyclohexanes were tested in the reaction with **1a**, and all the substrates underwent functionalization at C3 position with very high site selectivity (12.5 : 1 to >50 : 1 rr) with ≥90% ee. As the alkyl size increased, the site-selectivity was enhanced to >50 : 1. Replacement of *t*Bu with TMS group only resulted in a minimal change in the reaction outcome. Cyclohexanes bearing various ester groups also efficiently underwent the reaction with good regio- and stereocontrol. It is notable that the level of asymmetric induction is sensitive to the steric hindrance of the *para*-substituent on the aryl group, and a *t*Bu or Ph led to 75% and 79% ee, respectively. Heteroaryldiazo compounds of type **1** were also the effective carbene precursor for this reaction. For other cycloalkanes such as cyclopentane, cyclohexane, cycloheptane, and adamantane, their reaction with **1a** afforded the desired products of type **404**



Scheme 120 Rh(II)-catalyzed site- and enantioselective C–H functionalization of non-activated cycloalkanes by carbene insertion.

in 72–79% yields with 90–99% ee. The present catalyst also worked well for disubstituted cyclohexanes. The potentially useful *cis*-1,2-dimethylcyclohexane and *trans*-1,3-dimethylcyclohexane reacted with **1a** to give the corresponding products with moderate to high levels of asymmetric induction (98% and 59% ee) in 62–70% yields. However, the diastereoselectivity was quite low (2.7–3.7 : 1 dr), indicating that the reaction occurred with both enantiomeric chair forms as the substrate. *trans*-1,2-Dimethylcydohexane is chiral and was reacted as the racemic mixture to form the desired product in 75% yield with 85% ee, >50 : 1 rr, and 25 : 1 dr. *trans*- and *cis*-1,4-Dimethylcyclohexane reacted with **1a** to generate the products in 77% (94% ee, 48 : 1 rr, >50 : 1 dr) and 80% (91% ee, >50 rr, >50 : 1 dr) yields, respectively. These results have further demonstrated the potential application of the catalyst-control strategy for diverse production of fine chemicals through site- and enantioselective C–H functionalization of non-activated alkanes by carbene insertion.

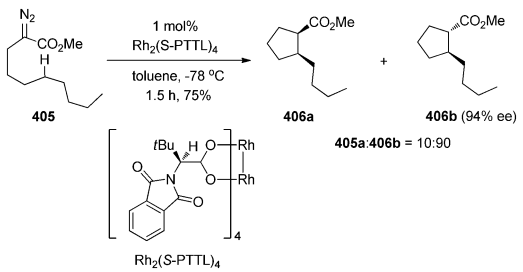
Chiral ligand (*S*)-*tert*-butylsulphonylprolinate (*S*)-TBSP was employed to construct dirhodium complex Rh_2(*S*-TBSP)$_4$ and heterobimetallic complex RhBi(*S*-TBSP)$_4$ from its reaction with Rh_2(OAc)$_4$ and RhBi(TFA)$_4$,[389] respectively. These complexes were comparatively investigated as the catalysts for the reaction of cyclohexane with donor/acceptor diazo compound **1a** (Scheme 121). Even though replacement of a Rh atom with a Bi atom changed the electronic properties of the complex, the RhBi complex still exhibited several similarities to the corresponding Rh_2 catalyst, with regard to their catalytic behaviors in the carbene insertion reaction. The asymmetric induction with RhBi(*S*-TBSP)$_4$ is very similar to that of Rh_2(*S*-TBSP)$_4$. The difference between them is that the reaction proceeded faster in the presence of the Rh_2 complex catalyst than by means of the RhBi complex as the catalyst.



Scheme 121 Comparison of reactivity and enantioselectivity between chiral bimetallic complex catalysts.

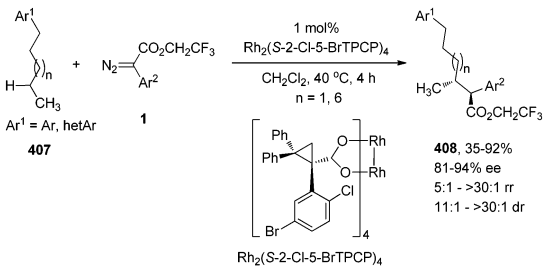
7.2. Enantioselective carbene insertion to non-activated alkyl C(sp^3)–H bonds

This section is focused on transition-metal-catalyzed enantioselective functionalization of alkyl C(sp^3)–H bonds which are not next to a functional group or heteroatom in non-alkane compounds, and such aliphatic C–H bonds are referred as non-activated alkyl C(sp^3)–H bonds. Because enantioselective C–H functionalization by carbene insertion has usually been applied to transform functionalized compounds to carbo- or heterocycle scaffolds or specific structural motifs, only a limited number of reports have been disclosed for non-activated alkyl C(sp^3)–H functionalization by carbene insertion. In 2005, Hashimoto, *et al.* reported the intramolecular C–H functionalization of methyl *n*-octyldiazoacetate (**405**) through carbene insertion by means of dirhodium(II) tetrakis(*N*-phthaloyl)-(*S*)-*tert*-butyl-leucinate (Rh_2(*S*-PTTL)$_4$) (eqn (103)).[390] The reaction was conducted in the presence of 1 mol% Rh_2(*S*-PTTL)$_4$ in toluene at −78 °C, giving a 10 : 90 mixture of *cis*- and *trans*-cyclopentane products **406a** and **406b** in 75% yield. The isomer **406b** was determined to be (1*S*, 2*S*) with 94% ee. In a similar fashion, this catalyst system effected the intramolecular benzylic C–H functionalization by carbene insertion, producing *cis*-2-arylcyclopentane-1-carboxylates in up to 99% yields and 95% ee.



(103)

Intermolecular non-activated secondary C–H functionalization by carbene insertion was also realized by using the catalyst-control strategy. In 2018, Davies, *et al.* used chiral dirhodium complex Rh_2(*S*-2-Cl-5-BrTPCP)$_4$ as the catalyst for the reaction of 1-bromo-5-pentylbenzene and derivatives (**407**) with donor/acceptor diazo compounds of type 1 (eqn (104)).[391] Although other methylene sites are present in the C–H substrates, the terminal methylene is more sterically accessible than the internal methylene sites. In this case, only the benzylic and terminal methylene sites would be the competing sites. Screening of the catalysts revealed that complex Rh_2(*S*-2-Cl-5-BrTPCP)$_4$ was the most suitable catalyst for the C–H functionalization at the terminal methylene site, remarkably compressing the benzylic C–H reaction with 20 : 1 rr (regioselectivity for terminal secondary C–H/benzylic C–H) at 40 °C to form the target products in 84–87% yields depending on the CH_2CX_3 group (X = Cl, Br, and F) in the *p*-Br-phenyldiazoacetates **1**. Use of the CH_2CF_3 diazo compounds led to the highest level of enantioselectivity. Thus, various products of type **408** (35–92%) were obtained in moderate to excellent yields with 81–94% ee, 5 : 1–>30 : 1 rr, and 11 : 1–>30 : 1 dr. Extending the alkyl chain (n = 6) led to the desired product in 92% yield with 94% ee, >30 : 1 rr and 23 : 1 dr (Ar′ = Ar = *p*-BrC_6H_4). Interestingly, this protocol was successfully applied for the synthesis of cylindrocyclophane class of natural products. By means of Rh_2(*R*-2-Cl-5-BrTPCP)$_4$ as the catalyst, a double carbene insertion to the sterically most accessible non-activated secondary C–H bond sequence was developed for the synthesis of cylindrocyclophane **412** (Scheme 122). It should be noted that every type of carbenes is capable of intermolecular C–H functionalization, but only the donor/acceptor carbenes enable highly site-selective, diastereoselective, and enantioselective C–H functionalization with a wide range of substrates.



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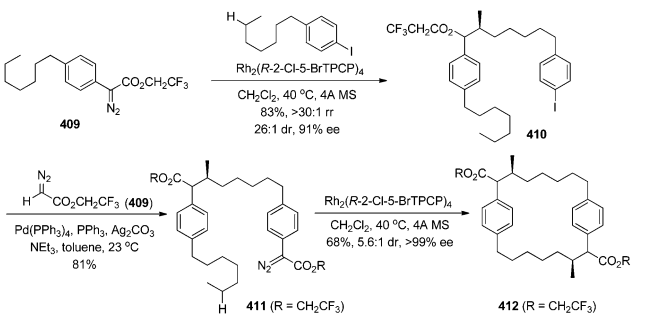
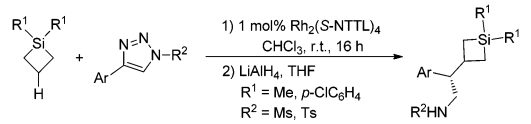
A β-silicon effect was applied to enable the regio- and stereoselective Rh(II)-catalyzed C–H functionalization by the donor/acceptor carbene derived from *N*-sulfonyl-1,2,3-triazoles



Scheme 122 Cylindrocyclophane synthesis *via* Rh(II)-catalyzed sequential enantioselective carbene insertion to aliphatic C–H bonds.

(eqn (105)).[392] Four dirhodium(II) complex catalysts, that is, Rh_2(*S*-PTTL)$_4$, Rh_2(*R*-PTAD)$_4$, Rh_2(*S*-TCPTAD)$_4$, and Rh_2(*S*-NTTL)$_4$ were screened for the reaction of silacyclobutane (**413a**) with 4-phenyl-1-(methanesulfonyl)-1,2,3-triazole (**219a**), and Rh_2(*S*-NTTL)$_4$ was found to be the most efficient catalyst for the exclusive carbene insertion to the C–H bond at the β-position to silicon. Larger silacycles such as six-membered silacyclohexanes[393] and five-membered silacyclopentanes (eqn (106))[394] underwent the β-C–H functionalization by acceptor carbene insertion with $Rh_2(OAc)_4$ as the catalyst or by donor/acceptor carbene insertion in the presence of Rh_2(*S*-TPPTTL)$_4$ as the catalyst, respectively. This protocol can generate diverse stereofined substituted silaalkanes.



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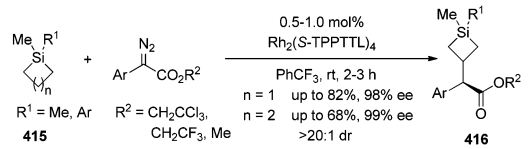
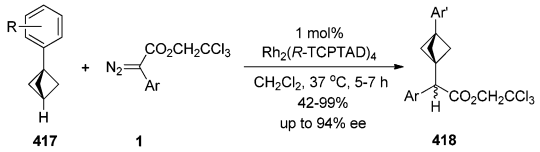


(106)

Highly strained carbocycles have been paid considerable attention due to their unique structures. Although many efforts have been devoted to their synthesis and functionalization, access of their derivatives has been a challenge. Upon success of the catalyst-control strategy in non-activated C(sp^3)–H bond functionalization by carbene insertion, Davies, *et al.* performed the direct enantioselective C–H functionalization of bicyclo[1.1.1]pentanes (BCPs, **417**) by carbene insertion with donor/acceptor diazo compounds **1** as the carbene precursor in the presence of dirhodium(II) complex catalyst Rh_2(*R*-TCPTAD)$_4$ (eqn (107)).[395] In the presence of 5 mol% catalyst and the CH_2CCl_3 diazo compound (2 equiv.) in CH_2Cl_2 at 37 °C, the reaction of BCPs (**417**) gave the desired products **418** in 42–99% yields with up to 94% ee. Rh_2(*S*-TCPTAD)$_4$ was also effective for this transformation, but resulting in a less efficient result. It is notable that the reaction preferentially occurred at the tertiary position of BCPs. Various substituents were tolerated in both the aryl groups in BCPs and the diazo compounds. This work has demonstrated that highly strained molecules can undergo direct C–H functionalization without loss of the integrity of their carbocyclic framework. The same catalyst system could render the tertiary C–H functionalization of the less strained monoarylated cyclobutanes **419**, and the desired products **420** were obtained in moderate to excellent yields with high level of stereocontrol (88–99% ee) (eqn (108)).[396] In some cases, Rh_2(*S*-TCPTAD)$_4$ exhibited a much better selectivity control. However, in the case of using Rh_2(*S*-2-Cl-5-Br-TPCP)$_4$ as the catalyst under the same conditions, the carbene insertion reaction preferentially occurred at the sterically most accessible secondary C–H bond of the arylcyclobutane substrates (eqn (109)). The reaction at tertiary C1 position concurrently occurred as the side reaction. Up to 92% yields were obtained with up to 94% ee, *cis* : *trans* > 95 : 1, and C3 : C1 > 95 : 1 regioselectivity.



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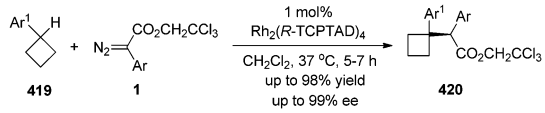

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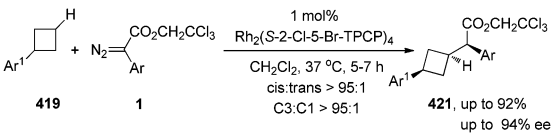
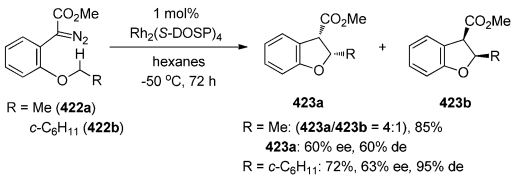


(109)

7.3. Enantioselective carbene insertion to C(sp^3)–H bonds adjacent to an oxygen atom

Aliphatic C–H bonds next to an oxygen atom are activated by this heteroatom to some extent and can be functionalized by enantioselective carbene insertion under transition-metal catalysis. For such a transformation, it seems much easier to achieve the stereocontrol in an intramolecular manner. In 2001, Davies, *et al.* reported Rh(II)-catalyzed construction of chiral dihydrofuran motifs by using *ortho*-alkoxy-substituted aryldiazoacetate (**422**) as the C–H substrates in the presence of 1 mol% Rh_2(*S*-DOSP)$_4$ as the catalyst in hexanes at −50 °C (eqn (110) and (111)).[397] The carbene insertion reaction occurred at the secondary C–H bond next to the oxygen atom. In the case of **422a** (R = Me), the carbene insertion products dihydrobenzofurans **423a** and **423b** were formed in 85% yield as a 4 : 1 mixture of *cis* and *trans* isomers, and the major *cis* isomer was obtained in 60% ee. When **422b** (R = cyclohexyl) was reacted under the same conditions, the *cis* isomer **423a** was formed in 63% ee and 95% de. When a methine group was adjacent to an oxygen atom, highly stereoselective carbene insertion to the tertiary C–H bond occurred in substrate 424, affording the corresponding product **425** in 98% yield with 94% ee (eqn (111)). This work has suggested that effective enantioselective intramolecular carbene insertion to C(sp^3)–H bonds is possible with donor/acceptor diazo compounds, and the level of asymmetric induction strongly depends on the site of the C–H bond as well as the catalyst.



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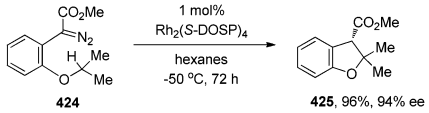
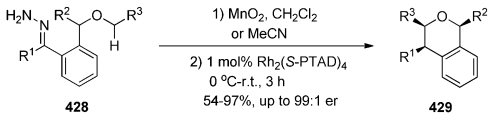


(111)

Donor/donor diazo precursors, that is, *N*-tosylhydrazones or hydrazones of diaryl and aryl alkyl ketones were applied for the construction of chiral 2,3-dihydrobenzofurans under Rh(II) catalysis.[398–400] In 2014, Shaw, *et al.* reported enantioselective Rh(II)-catalyzed intramolecular carbene insertion to C(sp^3)–H bonds adjacent to a phenolic oxygen atom (Scheme 123).[399] The hydrazones of diaryl ketones were used as the diazo precursor. In the presence of 1 mol% Rh_2(*R*-PTAD)$_4$ as the catalyst, and MnO_2 (8 equiv.) as the oxidant to *in situ* access the diazo species in CH_3CN at 0 °C – room temperature, diaryl hydrazones **426** reacted to give the corresponding *syn* diastereomers of dihydrobenzofurans **427** in up to 99% yields with >99 : 1 dr and >99 : 1 er. The products were usually obtained in >77% yields with ≥92 : 8 dr and ≥92 : 8 er. This protocol was successfully applied for the first enantioselective synthesis of an oligoresveratrol natural product (*E*-δ-viniferin). Rh_2(*S*-PTTL)$_4$, Rh_2(*S*-TCPTTL)$_4$, and other Rh(II) complex catalysts were also used for the same purpose.[400]

Rh_2(TPA)$_4$ enabled intramolecular azavinyl carbene insertion to the C(sp^3)–H bond adjacent to an oxygen atom, affording chiral tetrahydrofurans **65** (Scheme 31).[170] The hydrazone/MnO_2/Rh(II) catalyst system shown in Scheme 123399 was also effective for the construction of a six-membered O-heterocycle motif (eqn (112)).[401] By installing an oxygen atom at the 5-position, Rh(II)-catalyzed enantioselective intramolecular 1,6-carbene insertion underwent in hydrazones **428** to give chiral isochromans **429**. The product yields were >80% with ≥95 : 5 er in most of the cases. Use of a chiral iridium(III) complex catalyst of the D_4-symmetric Halterman porphyrin ligand [Ir((+)-D_4-Por)Me] enabled the enantioselective intramolecular carbene insertion to the benzylic C(sp^3)–H bond next to an oxygen atom in 2-diazoesters **430**, yielding chiral *cis*-β-lactones **431** in up to 87% yields and 78% ee (eqn (113)).[402]



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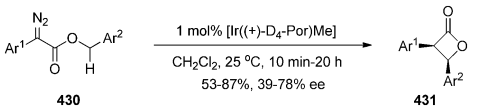
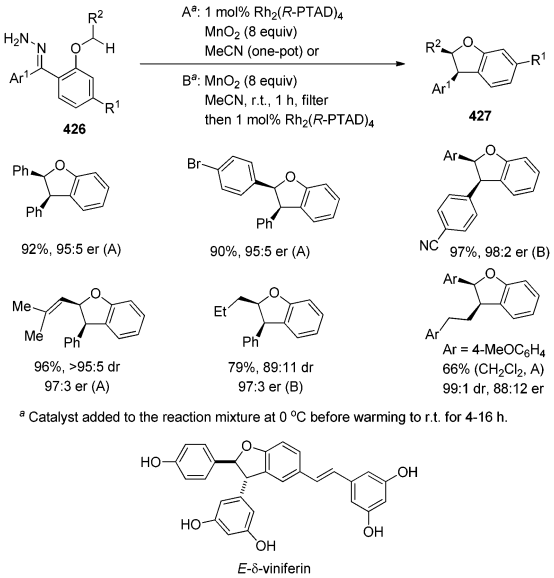
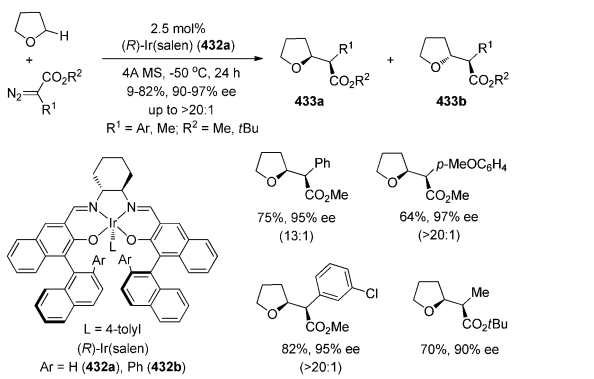


(113)

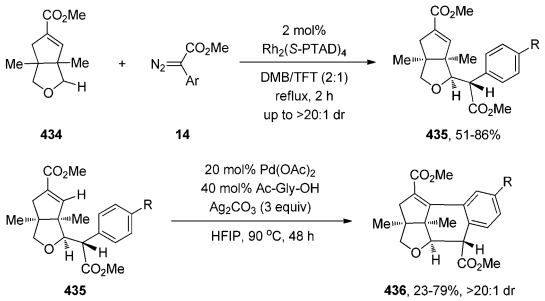
Immobilized box-Cu(OTf)$_2$ complexes have been documented to effect the enantioselective intermolecular carbene insertion to the oxygen-adjacent secondary C–H bonds of tetrahydrofuran with methyl phenyldiazoacetate (**14a**), reaching up to 88% ee, 78 : 22 dr, and moderate to good yields.[403] Ir(III) complex (*R*)-Ir(salen) (**432a**) was found to be a very efficient catalyst for such a reaction (Scheme 124).[404] In the presence of 2.5 mol% (*R*)-Ir(salen) catalyst in THF at −50 °C, the donor/acceptor diazo compounds decomposed to react with the oxygen-adjacent C–H bond of THF to give 2-benzylated tetrahydrofurans of type **433a** as the major products in 64–82% yields with 93–97% ee and up to >20 : 1 ratio of **433a**/**433b**. *ortho*-Methyl on the aryl group of the diazo compound remarkably diminished the product yield to 9%, exhibiting an obvious negative steric effect. 2-Naphthyl diazoacetate also efficiently underwent the reaction to result in the target product (80% yield, 98% ee). It is noteworthy that *tert*-butyl α-diazopropionate reacted to achieve 70% yield for the desired product with 90% ee and 13 : 1 ratio for the two product isomers, demonstrating the first example of enantioselective intermolecular carbene insertion to C–H bonds using an α-alkyl-substituted α-diazoacetate. These results have been shown a promising potential for developing new catalyst systems enabling the challenging enantioselective intermolecular carbene insertion to C–H bonds.



Scheme 123 Rh(II)-catalyzed enantioselective intramolecular carbene insertion to C(sp^3)–H bonds adjacent to an oxygen atom.



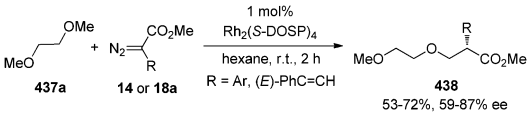
Scheme 124 Ir(III)-catalyzed enantioselective intermolecular carbene insertion to oxygen-adjacent C(sp^3)–H bond in THF.



Scheme 125 Rh(II)-catalyzed asymmetric intermolecular carbene insertion to oxygen-adjacent C(sp^3)–H bonds of THF derivatives.

The oxygen-adjacent C(sp^3)–H functionalization protocol of THF by intermolecular carbene insertion was utilized to build the tricyclic core architecture of the indoxamycin family of secondary metabolites (Scheme 125).[405] With 2 mol% Rh_2(*S*-PTAD)$_4$ catalyst in a mixed solvent of 2,2-dimethylbutane (DMB) and 2,2,2-trifluorotoluene (TFT) (DMB/TFT = 2 : 1, v/v), a tetrahydrofuran derivative, that is, rigid bicyclo[3.3.0]octane (**434**), reacted with methyl aryldiazoacetates **14** under refluxing conditions to give the carbene insertion products **435** in 51–86% yields with 9 : 1–>20 : 1 dr. Substituents such as F, Cl, Br, I, OTf, Bpin, CF_3, and CO_2Me were tolerated at the 4-position of the aryl moiety in the diazo compounds. Only in the cases of using Bpin and CO_2Me-substituted diazo compounds, the products were obtained in 9 : 1 and 17 : 1 dr, respectively, and in other cases the desired products were formed with high levels of enantioselectivity (>20 : 1 dr). Palladium-catalyzed oxidative intramolecular C–H/C–H coupling of **435** formed the tetracyclic products **436** in 23–79% yields with >20 : 1 dr. It is noteworthy that no reaction occurred when the substituents were I and Bpin. In the case of OTf a low yield (5%) was detected. Ir(III)-bis(imidazolinyl)-phenyl complex catalysts were documented for similar carbene insertion to C(sp^3)–H bonds of dihydrofuran derivatives with EDA.[406]

By means of a substrate-control strategy enantioselective primary C(sp^3)–H bond functionalization can be *site*-selectively achieved in dialkyl ethers. Rh_2(*S*-DOSP)$_4$ catalyzed the reaction of 1,2-dimethoxyethane (**437a**) and methyl *tert*-butyl ether (**437b**) with methyl aryldiazoacetates (**14**) or styryldiazoacetate (**18a**), to give the corresponding 2-aryl- or 2-styryl-substituted propanoates of type **438** or methyl tropinate (Ar = Ph) and its aryl derivatives **439** in 53–72% (59–87% ee) and 21–39% (76–95% ee) yields after acid-induced removal of the *tert*-buty group, respectively (eqn (114) and (115)).[407] With Rh_2(*R*-BPCP)$_4$ as the catalyst and TCE (2,2,2-trichloroethyl) diazoesters as the carbene precursor, methyl ethers **437c** were regio- and enantioselectively functionalized to form **440** by carbene insertion to the primary C–H bond at the methyl group (eqn (116)).[408] Up to 95% yields and 98% ee were obtained with tolerance of various functional groups in the C–H substrates. It is noteworthy that the TCE diazo ester result in a more robust carbene compared to the corresponding methyl diazoester. Methyl 4-fluorophenyl ether reacted with the methyl diazoester (by replacing TCE with a methyl in **1a**) to give the desired product in 15% yield without any enantioselectivity. However, use of **1a** (Ar = *p*-BrC_6H_4) led to the target product in 65% yield with 97% ee.



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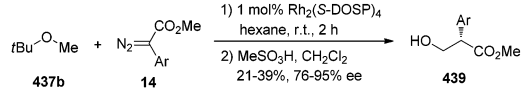

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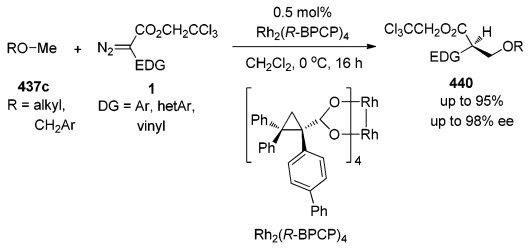

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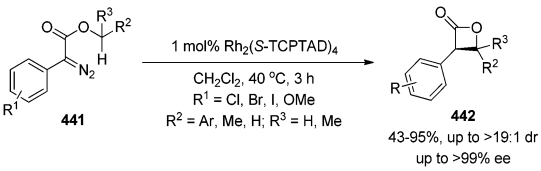
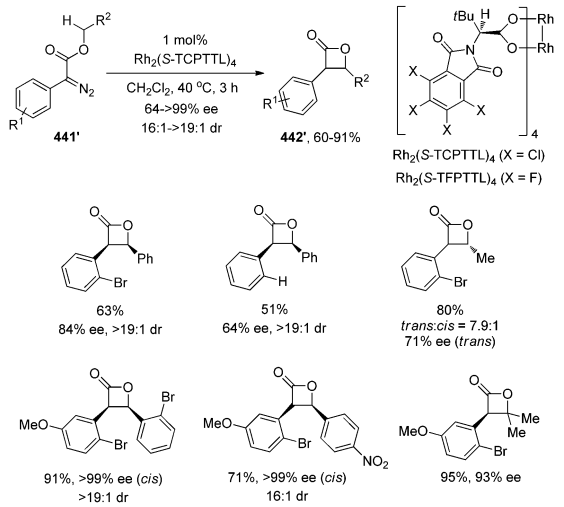


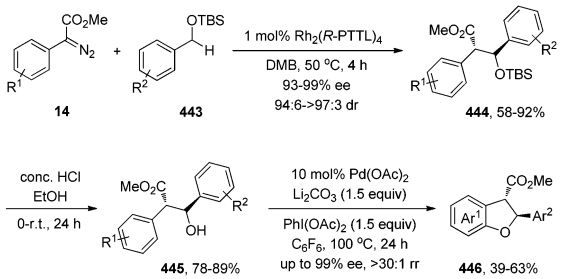
(117)

In the presence of 1 mol% Rh_2(*S*-TCPTAD)$_4$ as the catalyst in refluxing CH_2Cl_2, enantioselective carbene insertion to oxygen-adjacent methyl C–H bond was achieved to establish β-lactones **442** in moderate to excellent yields with up to 99% ee (eqn (117)).[409] In a similar fashion, use of Rh_2(*S*-TCPTTL)$_4$ enabled the oxygen-adjacent alkyl C–H bond to be efficiently functionalized by carbene insertion, reaching 60–91% yields, up to 99% ee, and up to >19 : 1 dr (Scheme 126). It should be noted that the substituents, especially the *ortho* substituents, on the aryl moiety of the alkyl aryldiazoacetates (**441′**) are crucial for a high level of enantioselectivity, and Rh_2(*S*-DOSP)$_4$ could only achieve a low asymmetric induction.

Transition-metal-catalyzed enantioselective carbene insertion to oxygen-adjacent C(sp^3)–H bond can be considered as a surrogate to aldol reaction. Davies, *et al.* developed Rh(II)-catalyzed enantioselective intermolecular carbene insertion to trialkylsiloxyl-adjacent C(sp^3)–H bonds in silyl alkyl/allyl/benzyl ethers **443**.[410–412] After removal of the silyl group by acid-promoted hydrolysis, the corresponding chiral products were obtained. Such a strategy was applied for the synthesis of highly functionalized chiral 2,3-dihydrobenzofurans **406** through a three-step sequence, that is, Rh(II)-catalyzed carbene insertion/acid-promoted desilylation/Pd(II)-catalyzed oxidative cyclization (Scheme 127).[412] Rh_2(*R*-PTTL)$_4$ acted as the most efficient catalyst for the carbene insertion process, generating the desired products **444** in 58–92% yields with 93–99% ee and 94 : 6–>97 : 3 dr. These resultant silyl ethers were efficiently



Scheme 126 Rh(II)-catalyzed enantioselective intramolecular carbene insertion to oxygen-adjacent alkyl C–H bonds.

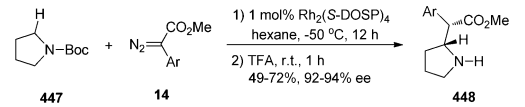


Scheme 127 Rh(II)-catalyzed enantioselective intramolecular carbene insertion to silyloxy-adjacent C(sp^3)–H bonds.

deprotected to afford the corresponding chiral alcohols **445** (78–89%). Subsequent Pd(II)-catalyzed oxidative cyclization gave the chiral dihydrobenzofuran products **446** in moderate to good yields with a high level of asymmetric induction (93–99% ee). Rh_2(*S*-PTTL)$_4$ was also efficient as the catalyst for the synthesis of TBS ethers of type **444**.[413]

7.4. Enantioselective carbene insertion to C(sp^3)–H bonds adjacent to a nitrogen atom

A combination of a transition-metal compound with a chiral ligand and chiral transition-metal complexes have been known well to enable enantioselective functionalization of C(sp^3)–H bonds adjacent to a nitrogen atom by both intramolecular[414] and intermolecular[415,416] carbene insertions. Intramolecular carbene insertion to such a C(sp^3)–H bond seems to be much easier to achieve the stereocontrol than an intermolecular process. With 1 mol% Rh_2(*S*-DOSP)$_4$ as the catalyst in hexane at −50 °C, *N*-Boc-pyrrolidine (**447**) and analogs underwent nitrogen-adjacent C(sp^3)–H functionalization by carbene insertion with methyl aryldiazoacetates (**14**) as the carbene precursor, forming the desired products **448** and derivatives in 49–72% yields with 92–94% ee (eqn (118)).[415] When *N*-Boc-piperidine was reacted with **14** in 2,3-dimethylbutane (DMB) as the solvent at 25 °C, and followed by treatment with trifluoroacetic acid, a mixture of *threo*- and *erthro*-methylphenidate was obtained in 49–86% yields with a ratio ranging from 43 : 57 to 71 : 29, and up to 86% ee for the threo-isomers, and 81% ee for the erthro-isomers by modifying the reaction conditions. In the case of *N*-Boc-tetrahydropyridine, a mixture of product enantiomers was also formed in an overall yield up to 63% and 80% ee for the major isomer (18 : 22 ratio). Use of excess of the diazo compound (6 equiv.), double carbene insertions occurred to **447**, yielding the C_2-symmetric amines **449** (eqn (119)).[415,417] Using both the catalyst- and substrate-control strategies piperidine and *N*-protected piperidine derivatives **450** were effectively functionalized by carbene insertion to the nitrogen-adjacent C(sp^3)–H bond with TCE aryldiazoacetates (**1**) as the carbene precursor under Rh_2(*R*-TCPTAD)$_4$, and the target products **451** were obtained in good to excellent yields (54–89%) with low to good levels of asymmetric induction (29–74% ee) (eqn (120)).[418] Notably, with Rh_2(*S*-2-Cl-5-Br-TPCP)$_4$ as the catalyst, the carbene insertion reaction occurred at the C(4)-position of **450**.



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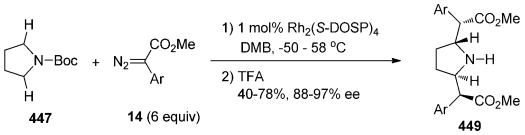

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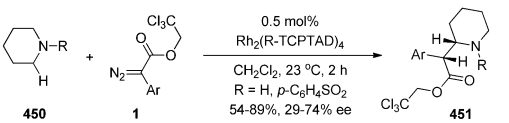
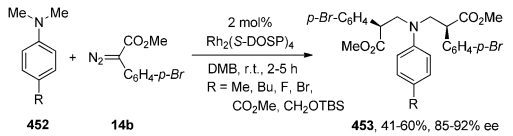


(120)

Double carbene insertion to methyl C(sp^3)–H bonds next to a nitrogen atom was successfully applied for the synthesis of C_2-symmetric anilines (eqn (121)).[419] From the reaction of *N*,*N*-dimethylainilines (**452**) and the donor/acceptor carbene precursor compound methyl 4-bromophenyldiazoacetate (**14a**) in DMB the chiral double benzylation products **453** were obtained with 85–92% ee. In a similar fashion, chiral β-amino esters **455** were synthesized from bis-silyl methylamine (**454**) (eqn (122)).[420] Using this method, the enantiomers of the antidepressant Venlafaxine were synthesized in three simple steps with high enantioselectivity. Engineered cytochrome P450s[421] and P411-C10 variants[422] were also effective for enantioselective nitrogen-adjacent C–H functionalization by carbene insertion to build contiguous chiral centers, giving the target products **457** bearing two contiguous chiral centers with a TTN up to 4000, up to 99% ee, and up to 99 : 1 dr (eqn (123)).[422]



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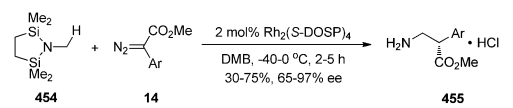

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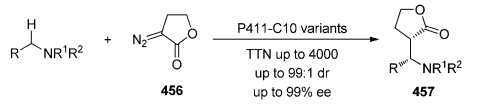
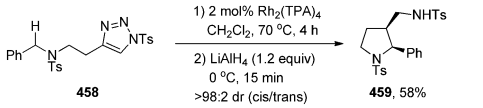


(123)

With (*N*-benzyl)ethyl-substituted *N*-sulfonyl-1,2,3-triazole 458 as the C–H substrate, 2 mol% $Rh_2(TPA)_4$ catalyzed the enantioselective intramolecular carbene insertion to nitrogen-adjacent benzylic C–H bond to form the piperidine-type product **459** (58%) with excellent diastereoselectivity, and the *cis*/*trans* product isomer ratio reached >98 : 2 (eqn (124)).[170] In the presence of 2 mol% Rh_2(*S*-PTTL)$_4$ as the catalyst in DMB at 0 °C, *N*-*tert*-butyl-*N*-(*p*-methoxybenzyl)-enoldiazoacetamide (**460a**) and analogs under-went enantioselective intramolecular carbene insertion to nitrogen-adjacent benzylic C–H bond to produce *cis*-β-lactams (**461**) in 80–92% yields with 77–99% ee for the products bearing 4- and/or 3-substituent(s) (eqn (125)).[423] The steric effect was remarkable from 1-naphthyl, 2-methoxyphenyl, and *N*,*N*-diisopropyl, which led to 24% ee, 25% ee, and 67% ee, respectively. Control experiments have revealed that donor/acceptor cyclopropanes of type **462** are the reactive intermediates for both the carbene insertion to the C(sp^3)–H bond and Büchner reaction to form β-lactams and cycloheptatrienes (Scheme 128). This protocol features exclusive *cis*-diastereoselectivity, providing an efficient method to access *cis*-β-lactams.



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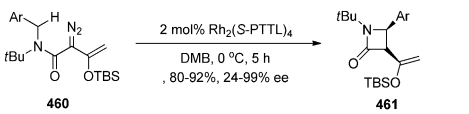
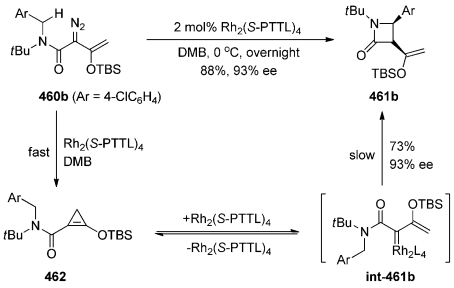


(125)

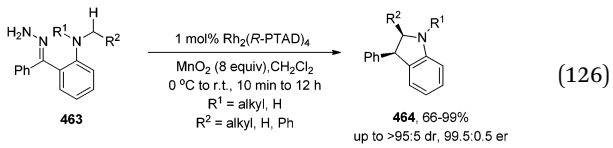
The donor/donor metal carbenes derived from the hydrazones of diaryl ketones and Rh_2(*R*-PTAD)$_4$ catalyst were used for the enantioselective intramolecular nitrogen-adjacent C(sp^3)–H functionalization by carbene insertion (eqn (126)).[424] In a one-pot manner, hydrazones **463** were treated with MnO_2 in CH_2Cl_2 at 0 °C-r.t. to afford indoline derivatives **464** in 66–99% yields with up to >95 : 5 dr and 95.5 : 0.5 er. Fused indolines were accessed in good to excellent yields, dr, and er values from cyclic anilines. Changing from a methyl to an ethyl substituent on the dialkyl amino moiety had a drastic effect on the enantioselectivity, and the product from the substrate bearing



Scheme 128 Donor/acceptor cyclopropenes as the reactive intermediates for carbene insertion.

R^1 = Me and R^2 = H was formed as one enantiomer (99% yield, 82 : 18 er), while the other product from the substrate bearing R^1 = Et and R^2 = Me was produced in 85% yield with >95 : 5 dr and 99.5 : 0.5 er. An indoline derived from an *N*-tosyl protected aniline was also obtained (66%), allowing for further modification after deprotection. By means of the same catalyst system, tetrahydroisoquinolines **466** were also synthesized (eqn (127)).[401]

Due to the propensity of the highly nucleophilic sulfur atom to attack the carbene carbon to form an ylide, carbene insertion-involved benzodihydrothiophene synthesis has seldom been reported.[425] However, in a fashion similar to the synthesis of indolines **464** benzodihydrothiophenes **468** were efficiently obtained from the hydrazones of alkylthio-substituted diaryl ketones **467** (eqn (128)). A benzylic alcohol moiety was tolerated in the substrate without carbene insertion to the O–H bond. The desired products were formed in good to excellent yields (67–97%) with up to >95 : 5 dr and 99 : 1 er. These results have demonstrated a rare example of Rh(II)-catalyzed intramolecular carbene insertion to sulfur-adjacent C(sp^3)–H bonds.



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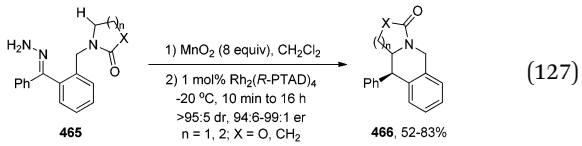
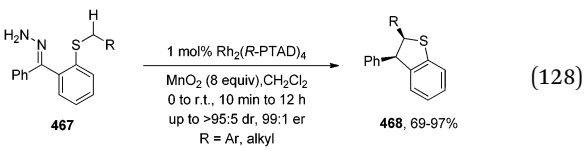


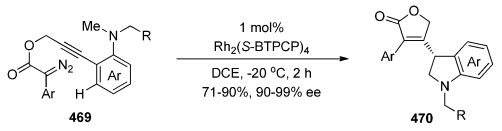
(127)

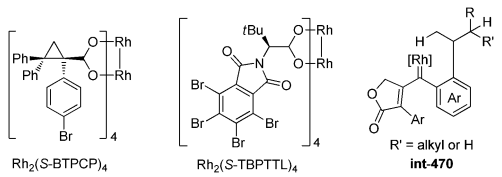


(128)

A Rh(II)-catalyzed carbene insertion to nitrogen-adjacent C(sp^3)–H bonds/alkyne metathesis sequence was developed to synthesize 2,3-dihydroindoles through catalyst-controlled intramolecular carbene insertion to primary, secondary, and tertiary C–H bonds (eqn (129)–(131)).[426] With 1 mol% Rh_2(*S*-BTPCP)$_4$ as

the catalyst in dichloroethane at −20 °C, alkyne-tethered diazo compounds **469** underwent selective carbene insertion to the primary methyl C–H bond by the *in situ* generated rhodium(II) carbene of type **int-470**, giving dihydroindole derivatives **470** in 71–90% yields with 90–99% ee (eqn (129)). Use of Rh_2(*S*-TBPTTL)$_4$ as the catalyst in chlorobenzene preferentially resulted in intramolecular carbene insertion to the secondary C–H bond adjacent to the nitrogen atom, forming the desired products **471** in 77–91% yields with up to 99% ee and >95 : 5 dr (eqn (130)). Under the same conditions, carbene insertion to the tertiary C–H bond in **472** preferentially occurred over the primary methyl C–H bond concurrently attached to the nitrogen atom (eqn (131)), efficiently forming the target products **473** (81–92%) with a high level of asymmetric induction (93–97% ee). In this work, the chiral dirhodium(II) catalysts not only promote the *in situ* generation of the donor/donor carbene intermediates, but also are responsible for the high-level asymmetric induction.





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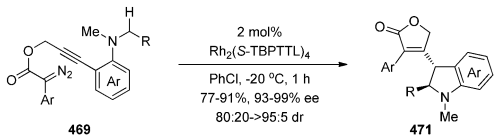
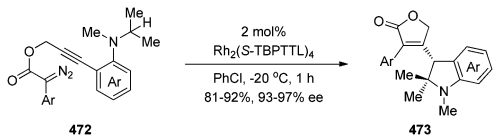
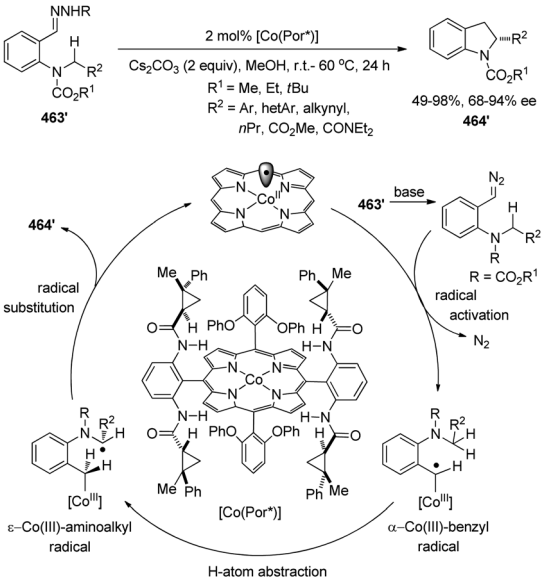


(130)



(131)

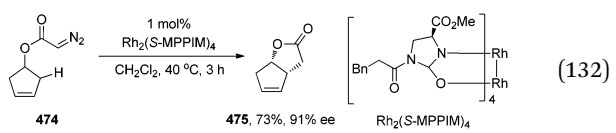
Chiral indolines can also be synthesized by metallo-radical alkylation of diverse C(sp^3)–H bonds adjacent to a nitrogen atom in the presence of a Co(II)-prophorin complex catalyst (Scheme 129).[427] With 2 mol% [Co(Por*)] (Por* = 2,6-DiPhO-QingPhyrin) as the catalyst in methanol at room temperature, the reaction of **463′** smoothly proceeded to afford the target products **464′** in 49–98% yields with 68–94% ee. In most of the cases, the product yields are greater than 90% with ≥90% ee. In addition to the excellent chemo- and regioselectivity, this Co(II)-catalyzed alkylation features a good tolerance to functional groups and compatibility with heteroaromatic C–H substrates. The mechanistic studies have suggested that the reaction occurs *via* a stepwise radical pathway. It should be noted that carbene insertion to nitrogen-adjacent C(sp^3)–H bonds needs to be compressed as a side reaction in some cases.[428]



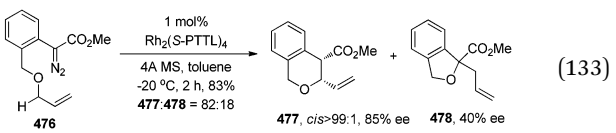
Scheme 129 Construction of 2-substituted indolines by intramolecular carbene insertion to C(sp^3)–H bond *via* Co(II)-metalloradical catalysis (Co(II)-MRC).

7.5. Enantioselective carbene insertion to allylic C(sp^3)–H bonds

Allylic C(sp^3)–H bonds are activated by the α-vinyl moiety to some extent that they can take part in diverse synthetic reactions. In the area of transition-metal-catalyzed enantioselective allylic C–H functionalization by carbene insertion, the major efforts have been devoted to the intermolecular reaction of allylic C–H substrates with diazo compounds as the carbene precursor, because it is usually difficult to achieve a high level of stereocontrol as well as the side reaction such as cyclopropanation in an intramolecular carbene insertion process by means of a functionalized allyl-based diazo compound. Diazoacetate **474** was subject to the catalytic conditions by using Rh_2(*S*-MPPIM)$_4$ as the catalyst to give the desired product, that is, chiral lactone **475** in 73% yield with 91% ee (eqn (132)).[429] With 1 mol% Rh_2(*S*-PTTL)$_4$ as the catalyst donor/acceptor aryldiazoacetate **476** reacted to afford a mixture of the desired carbene insertion product **477** (>99 : 1 *cis* selectivity, 85% ee) and the ylide formation/rearrangement product **478** (40% ee) in 83% yield with a 82 : 18 ratio of **477**/**478** (eqn (133)).[430]



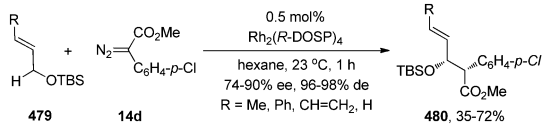
(132)

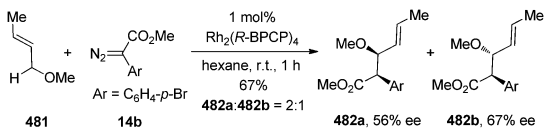


(133)

For allylic C–H functionalization by intermolecular carbene insertion there are two types of allylic C–H bonds, that is, those in the acyclic and cyclic systems, which can be transformed

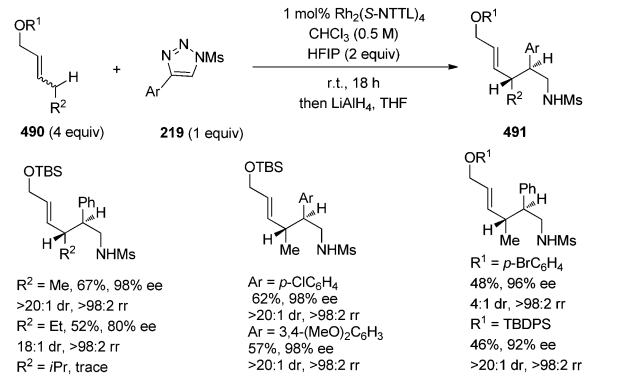
under carbene insertion conditions. In general, the allylic C–H bonds in a cyclic system can be functionalized by intermolecular carbene insertion with a higher level of asymmetric induction. In 1999, Davies, *et al.* reported Rh(II)-catalyzed intermolecular carbene insertion to silyloxy-adjacent allylic C–H bond under Rh_2(*R*-DOSP)$_4$ catalysis (eqn (134)).[431] At room temperature treatment of substituted silyl allyl ethers (**479**) with the donor/acceptor diazo compound, that is, methyl (4-chlorophenyl)diazoacetate (**14d**), led to the *syn*-aldol products **480** in 35–72% yield with 74–90% ee and 96–98% de. After acid-promoted deprotection, the corresponding chiral allyl alcohols were obtained. This protocol can be considered as an alternative to aldol reaction featuring reasonably high levels of asymmetric induction in the presence of a low loading of the catalyst. Under the same conditions in the presence of 1 mol% Rh_2(*R*-DOSP)$_4$ crotyl methyl ether **481** reacted with methyl (4-bromophenyl)diazo-acetate (**14b**) to form a 2 : 1 mixture of diastereomers **482a** and **482b** in 67% yield, in which the major diastereomer **482a** was formed in 56% ee and the minor one was formed in 67% ee (eqn (135)).[407] No carbene insertion to the methyl group in **479a** (R = Me) was observed, suggesting that the allylic methylene is highly activated towards the carbene insertion. The relatively low diastereoselectivity is presumably attributed to the size differentiation between the crotyl and methoxy groups, which is not sufficient to induce high diastereoselectivity. In some cases, cyclopropanation occurred as the major side reaction,[432] diminishing the reaction efficiency of carbene insertion to the allylic C(sp^3)–H bonds.





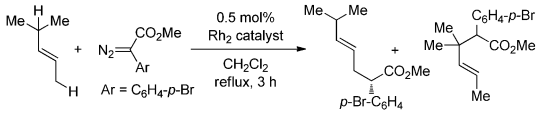
In order to achieve a high level of asymmetric induction, the catalyst-control strategy was applied to play the crucial role. The catalytic activity of complexes Rh_2(*R*-DOSP)$_4$ and Rh_2(*R*-BPCP)$_4$ was compared in the reaction of (*E*)-4-methylpent-2-ene (**483**) and (*E*)-2-hexene (**484**) with methyl (4-bromophenyl)diazoacetate (**14a**) in refluxing CH_2Cl_2 (eqn (136) and (137)), demonstrating the catalyst-control effect on the asymmetric induction.[433] The Rh_2(*R*-DOSP)$_4$-catalyzed reaction of **483** with the diazo compound produced a 1 : 7 mixture of C–H functionalization products **485a** and **485b**, favouring carbene insertion to the tertiary allylic C–H bond with a poor enantioselectivity (48% ee), while Rh_2(*R*-BPCP)$_4$ switched the selectivity toward carbene insertion to the primary allylic C–H bond, forming **485a** as the major product in 60% yield (94% ee) with a 17 : 1 ratio of **485a: 485b** (eqn (136)). The same trend of selectivity was observed with 2-hexene (**484**) (eqn (137)). The Rh_2(*R*-BPCP)$_4$-catalyzed reaction of (*E*)-2-hexene preferentially occurred to give the carbene insertion products at the primary allylic C–H site (**486a**) instead of the secondary allylic C–H site (**486b**). With donor/acceptor TCE diazo compounds **1a** electron-deficient primary allylic C–H bonds were efficiently functionalized by carbene insertion under Rh_2(*R*-BPCP)$_4$ catalysis.[434] Various functional groups such as CF_3, *t*Bu, CO_2Me, Br, and Cl were tolerated on the aryl moiety of **1**, leading to the target products **488**/**489** in 60–87% yields with 88–>99% ee (eqn (138)). In the case of using 4-Cl-2-pyridyl to replace the aryl group, the desired product from **1a** and **487** was obtained in 48% yield with 92% ee. These results have demonstrated that both catalyst-control and substrate-control play a combined role in reaching a decent asymmetric induction and reaction efficiency.

N-Sulfonyl-1,2,3-triazoles are another class of carbene precursor compounds for enantioselective intermolecular C–H functionalization of allylic C–H bonds by means of Rh_2(*S*-NTTL)$_4$ or Rh_2(*S*-TPPTTL)$_4$ as the catalyst.[435–437] In the presence of 1 mol% Rh_2(*S*-NTTL)$_4$ as the catalyst, (*E*)-allyl silyl ether **490a** (R^1 = TBS, R^2 = Me) reacted with phenyl-*N*-(methane-sulfonyl)-1,2,3-triazole (**219a**) in HFIP solvent at room temperature, almost exclusively giving a 3 : 1 mixture of diastereomers **491a**/**491b** in 81% yield with 96% ee for the major diastereomer **491a** and 85% ee for the minor diastereomer **491b**.[437] Although two types of allylic C–H bonds exist in the C–H substrate, the C–H functionalization by carbene insertion preferentially occurred at the distal allylic site, reaching a 98 : 2 rr. The (*Z*)-substrates could result in a much higher level of asymmetric induction under the same reaction conditions (Scheme 130). In the case of (*Z*)-allyl silyl ether **490b** (R^1 = TBS, R^2 = Me) the target product **491b** was obtained in 67% yield with 98% ee and >20 : 1 dr and >98 : 2 rr. Inspired by this excellent result in the formation of **491b**, other (*Z*)-allyl silyl ethers were examined, and the impact of substitution at the distal position was investigated. It was found that increasing the steric hindrance of R^2 group led to remarkable decrease of the C–H substrate reactivity and enantioselectivity of the target products. In the case of R^1 = TBS and R^2 = iPr, the reaction hardly occurred. Other aryl-substituted triazoles underwent the reaction to afford the desired products in moderate yields (48–62%) with excellent levels of diastereo-, enantio-, and regioselectivity (>98 : 2 dr, 93–98% ee, and >98 : 2 rr). Substituted benzyl



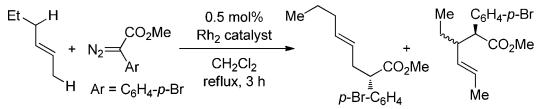
Scheme 130 Rh(II)-catalyzed enantioselective intermolecular carbene insertion to allylic C–H bonds.

and TMS groups in the silyl ether moiety inhibited the reaction, and presence of *p*-BrC_6H_4 or TBDPS diminished the reaction efficiency. It is noteworthy that (*Z*)-allyl silyl ether (**490b**) could also be functionalized at the distal position by carbene insertion with aryldiazoacetates as the carbene precursor in the presence of Rh_2(*S*-TPPTTL)$_4$ catalyst in CH_2Cl_2 at −20 °C, reaching up to 88% yields, 99% ee, 19 : 1 dr, and >98 : 2 rr. These results have revealed that by using a suitable rhodium carbene system, regioselectivity can be completely switched from the electronically most preferred allylic C–H bond to the less preferred C(sp^3)–H bond.



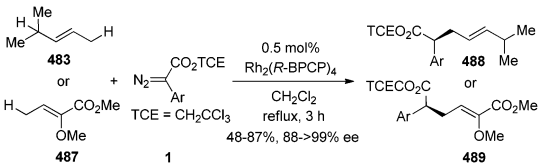
483 14a 485a 485b (136)

Rh_2 catalyst	485a:485b	yield	ee of 485a
Rh_2(*R*-DOSP)$_4$	1:7	81%	-
Rh_2(*R*-BPCP)$_4$	17:1	60%	94%



484 14a 486a 486b (137)

Rh_2 catalyst	486a:486b	yield	ee of 486a
Rh_2(*R*-DOSP)$_4$	1:9	75%	-
Rh_2(*R*-BPCP)$_4$	8:1	80%	95%



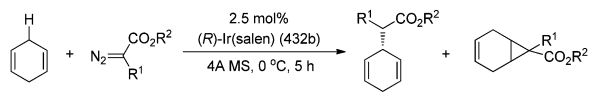
483 or 487 1 488 or 489 (138)

In the presence of 2.5 mol% (*R*)-Ir(salen) catalyst (**432b**) and 4A MS in neat 1,4-cyclohexadiene (**492**) at 0 °C, carbene insertion to 3-methylene (allylic C–H bond at 3-position) with donor/acceptor aryldiazoacetates efficiently proceeded to give the desired chiral benzylation products **493** in 54–95% yields with 94–99% ee, and the undesired cyclopropanation was not observed with >20 : 1 rr of **493** : **494** (Table 18).[404] The electron-donating substituents on the aryl moiety exhibited an obvious impact on the reaction efficiency. *Para*-Methoxyphenyldiazoacetate only produced the desired product in 39% yield with 90% ee, and the *ortho*-methoxyphenyldiazoacetate gave the product in 54% yield with 97% ee, while the *meta*-methoxyphenyl-substituted diazo compound led to the desired product in 95% yield with 96% ee. The electron-withdrawing groups facilitated the reaction, and the 3,4-dichlorophenyldiazoacetate reacted to afford the product in 95% yield with the highest level of enantioselectivity (99% ee). 3-Thienyl and alkyl-substituted diazoacetates also underwent the reaction to reach good yields and good to excellent enantioselectivity. It is noted that in the case of using the alkyldiazoacetates less bulky complex catalyst **432a** was used.

With iridium(III) phebox complex **495** as the catalyst in $PhCF_3$ at room temperature diene **492** could be functionalized by carbene insertion with methyl phenyldiazoacetate (**14a**) as the carbene precursor, reaching 60% yield and 96% ee for the desired product.[438] In a similar fashion, this catalyst enabled the allylic C–H functionalization of cycloheptatriene (**496**), leading to chiral benzylated cycloheptatriene (**497**) in 51% yield with 86% ee (eqn (139)). With DDQ (DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone) as the oxidant, a two-step process was developed to access chiral benzylated arene products **499** from dienes **498** (52–98%) yields with 88–99% ee through the desired carbene insertion to allylic C–H bond intermediate **int-499** (eqn (140)). Rh(II) complex catalysts Rh_2(*S*-PTAD)$_4$,[439] Rh_2(*S*-PTTL)$_4$, and Rh_2(*S*-TFPTTL)$_4$,[440] Rh_2(*S*-TBSP)$_4$, and RhB(*S*-TBSP)$_4$,[388] were also effective for the same reaction systems involving diene **492** and the donor/acceptor diazo carbene precursor. It is noteworthy that the Rh_2 complex Rh_2(*S*-TBSP)$_4$ exhibited a better catalytic activity than the corresponding RhBi heterobimetallic complex RhBi(*S*-TBSP)$_4$ for the same purpose.

Double allylic C–H functionalization of cyclooctadiene (1,5-COD) (**500**) by carbene insertion with donor/acceptor diazo compounds **1** or **14** was conducted with 1 mol% Rh_2(*R*-2-Cl-5-Br-TPCP)$_4$ as the catalyst (eqn (141)).[441] In the presence of excessive aryldiazoacetates the reaction proceeded smoothly in refluxing CH_2Cl_2, giving 3,7-dibenzylated-1,5-COD derivatives **501** in 53–84% yields with up to >99% ee and 7.9 : 1 dr. The substituents on the aryl moiety of the diazo compounds could be Br, I, OMe, CF_3 or *t*Bu at 4-position, and methyl, CH_2CCl_3 (TCE), and CH_2CF_3 (TFE) aryldiazoacetates of type **1** were also used as the effective carbene precursor. By adjusting the ratio of COD/diazo compound to 2.5 : 1, the reaction at 0 °C gave the corresponding mono-functionalized products in 64–85% yields with 63–95% ee and up to >30 : 1 dr. It was found that 1*E*,5*E*,9*E*-cyclododecatriene (**502**) also underwent the monobenzylation reaction under the same conditions (eqn (142)), forming a 1.0 : 0.9 mixture of two diastereomers with high levels of asymmetric induction for both the products. However, in the case of cyclohexene the reaction gave a 2.9 : 1.0

Table 18 Rh(II)-catalyzed enantioselective intermolecular carbene insertion to allylic C(sp^3)–H bonds

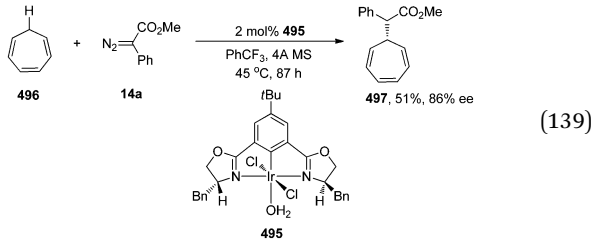


492 493 494

R^1	R^2	493 : 494	Yield[a] (%)	% ee
Ph	Me	>20 : 1	91	94
p-ClC_6H_4	Me	>20 : 1	79	95
m-$MeOC_6H_4$	Me	>20 : 1	95	96
o-$MeOC_6H_4$	Me	>20 : 1	54	97
3,4-$Cl_2C_6H_3$	Me	>20 : 1	95	99
3-Thienyl	C_2H_4Cl	>20 : 1	67	97
Me	Et	>20 : 1	68[b]	83
Me	*t*Bu	>20 : 1	84[b]	>99

[a] Using 1 mol% (*R*)-Ir(salen) (**432b**). [b] Using 1 mol% (*R*)-Ir(salen) (**432a**) at −50 °C.

mixture of cyclopropanation and carbene insertion to allylic C–H bond, and *cis*-cyclooctene only gave the cyclopropanation product (79% yield, >20 : 1 dr). Unexpectedly, 1,3-cyclohexadiene (**504**) reacted with vinyldiazoacetates under $Rh_2(S\text{-DOSP})_4$ catalysis to form the product of type **505** through a formal carbene insertion to allylic C–H bond/Cope rearrangement (eqn (143)).[442]



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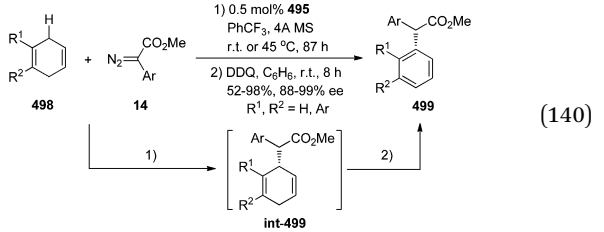

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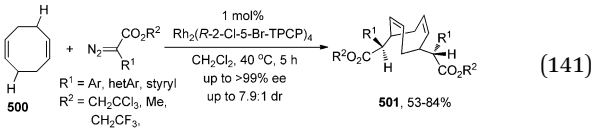
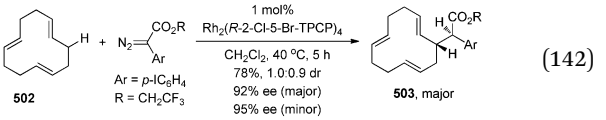
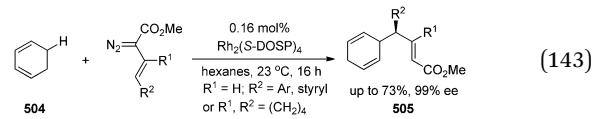


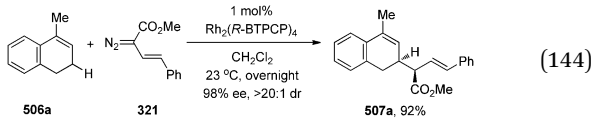
(141)



(142)

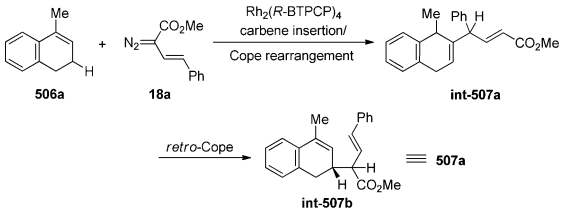


(143)



(144)

With 1 mol% $Rh_2(S\text{-BTPCP})_4$ as the catalyst in CH_2Cl_2 at room temperature, dihydronaphthalene (**506a**) underwent a formal intermolecular carbene insertion to the allylic C–H bond with methyl styryldiazoacetate (**18a**) to form product **507a** in 92% yield as a single diastereomer with 98% ee and >20 : 1 dr (eqn (144)).[443] This reaction is proposed to proceed through a sequence involving a combined C–H functionalization/Cope rearrangement followed by a reverse Cope rearrangement (Scheme 131).[444] However, when $Rh_2(S\text{-DOSP})_4$ was used as the catalyst, methoxy-substituted dihydronaphthalene (**506b**) reacted with methyl 3-pentenyldiazoacetate in 2,3-dimethylbutane at room temperature to form 1,4-disubstituted product **508** which was rearranged to the formal

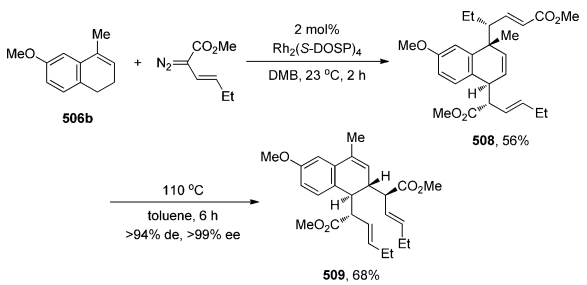


Scheme 131 Rh(II)-catalyzed formal enantioselective intermolecular carbene insertion to allylic C(sp^3)–H bond.

double carbene insertion product **509** in refluxing toluene in 68% yield with >94% de and 99% ee (Scheme 132).[444] This result has demonstrated a sequence of asymmetric double formal intramolecular carbene insertion to allylic and benzylic C–H bonds.

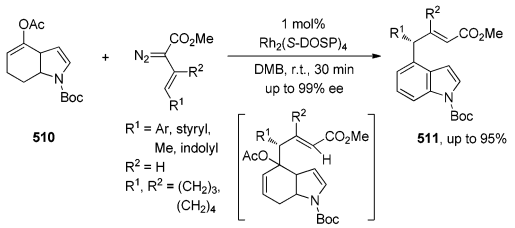
In a similar fashion with the same catalyst system, 4-acetoxy-6,7-dihydroindole (**510**) could be transformed to chiral 4-allylindoles **511** in up to 95% yield with 99% ee (eqn (145)).[445] Species **int-511** is considered as the reactive intermediate. This catalyst was also effective for the carbene insertion to allylic C–H bond occurring between 4-substituted 6,7-dihydrobenzothiophene (**512**) and methyl styryldiazoacetate (**18a**) (eqn (146)). The reaction proceeded smoothly to give 4-substituted benzothiophene **513** in a high yield (89%) with an excellent level of asymmetric induction (99% ee). These results have offered an alternative route to 4-substituted indoles and benzothiophenes. The reaction proceeds *via* a combined carbene insertion to allylic C–H/Cope rearrangement-elimination mechanism, resulting in good yields and very high asymmetric induction.

By means of a chiral diene, that is, bicyclo[2.2.2]octadiene (**514**), as the ligand, a Rh(II) catalyst system was established for the enantioselective allylic C–H functionalization of 1,4-cyclohexadienes of type **515** by carbene insertion with aryldiazoacetates (**14** or **1**).[446] The reaction could smoothly undergo under mild conditions in the presence of $[Rh(\mathbf{514})Cl]_2$ as the catalyst, affording the target products in 61–90% yields with 83–99% ee (eqn (147)). In most of the cases, the product yields are >90% with ≥95% ee. The reaction was well tolerated with 1,4-cyclohexadienes bearing substituents at the alkenyl moiety. Subsequent oxidation of the products by DDQ afforded the *gem*-diarylacetates (**516**) in 53–95% yields with 85–96% ee. Such a



Scheme 132 Rh(II)-catalyzed enantioselective intermolecular double carbene insertion to allylic and benzylic C(sp^3)–H bonds.

carbene insertion only occurred at the less sterically hindered allylic positions.



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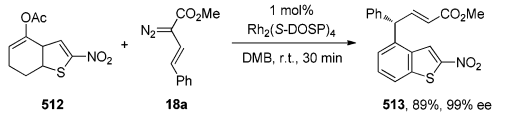
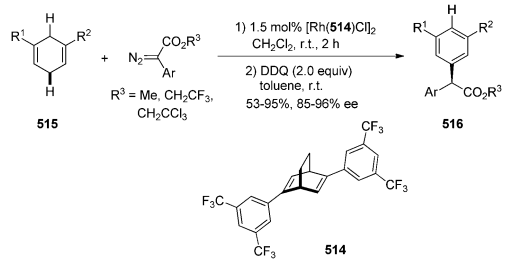


(146)

Engineered cytochrome P450 enzyme such as cytochrome P411 in which the native cysteine axial ligand was substituted for serine, and fully genetically encoded and produced in bacteria can facilitate enantioselective carbene insertion to acyclic allylic C–H bonds. The carbene insertion reaction was performed using *E. coli* expressing cytochrome P411-CHF (OD_{600} = 30) with 10 mM C–H substrate and 10 mM ethyl diazoacetate at room temperature under anaerobic conditions for 18 h (eqn (148)).[447] In a similar fashion, propargylic C–H bond was functionalized, achieving 190 TTN. This process usually occurs *via* an iron(III)-catalyzed C(sp^3)–H functionalization pathway. These results have suggested that diverse haem proteins could serve as potential catalysts for this abiological transformation.



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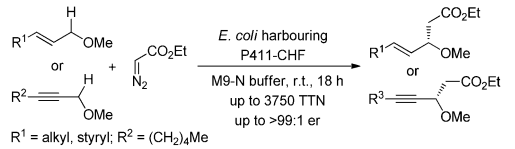
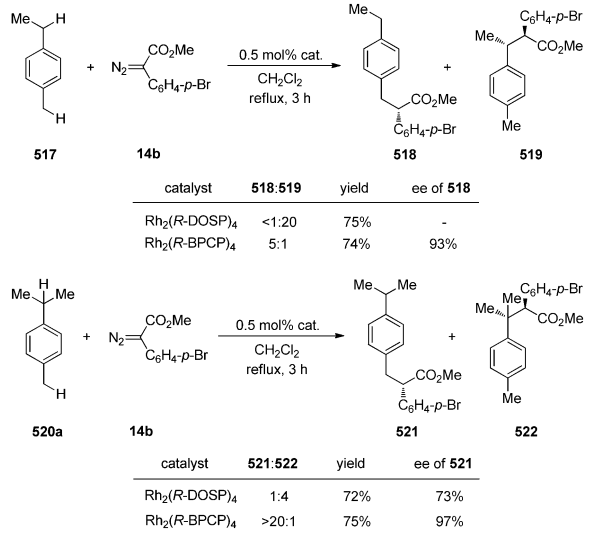


(148)

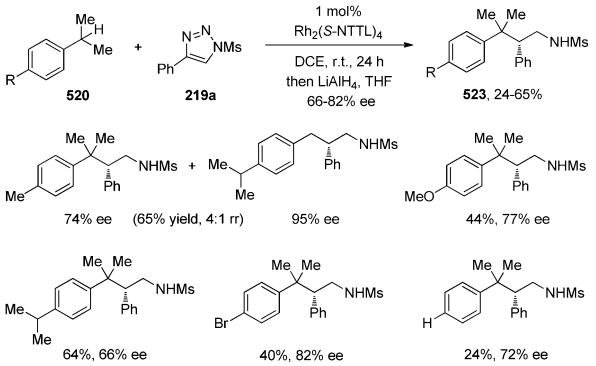
7.6. Enantioselective carbene insertion to benzylic C(sp^3)–H bonds

Benzylic C(sp^3)–H bonds are relatively activated by the adjacent aryl group and widely exist in aryl-containing compounds. Transition-metal-catalyzed enantioselective carbene insertion to benzylic C–H bonds can provide a direct route to functionalized benzylated compounds.[448] However, competing carbene insertions always occur due to the coexistence of various C–H bonds in a functionalized C–H molecule. The catalyst-control strategy as well as the substrate-control method may play a crucial role in enabling highly selective carbene insertion at the desired benzylic C–H site.[428] By means of the catalyst-control strategy benzylic C–H bonds in 4-ethyltotuene and 4-isopropyltoluene were regioselectively functionalized by carbene insertion with the donor/acceptor diazo compounds under various Rh(II) catalysis (Scheme 133).[433] The Rh_2(*R*-DOSP)$_4$-catalyzed reaction of 4-ethyltoluene (**517**) selectively occurred at the secondary benzylic site (**518 : 519** < 1 : 20),[449] while the Rh_2(*R*-BPCP)$_4$-catalyzed reaction preferentially occurred at the primary benzylic site (**518 : 519** = 5 : 1) in a combined yield of 74%, with **518** formed in 92% ee. For the challenging isopropyltoluene (**520a**) as the C–H substrate, the Rh_2(*R*-DOSP)$_4$-catalyzed reaction gave a mixture of primary and tertiary C–H functionalization[448] (**521 : 522** = 1 : 4). However, the Rh_2(*R*-BPCP)$_4$-catalyzed reaction selectively afforded the primary benzylic C–H functionalization product **521** by carbene insertion (**521 : 522** > 20 : 1) in 75% yield with 97% ee. The protocol using Rh_2(*R*-BPCP)$_4$ as the catalyst was efficiently applied for the primary benzylic C–H (activated primary C–H bond) functionalization of various toluenes substituted at 4-position by alkyls, alkoxys, alkynyl, and ester, reaching 38–88% yields with 90–96% ee. It is noteworthy that electron-deficient primary benzylic C–H bonds were also functionalized by carbene insertion with TCE aryldiazoacetate (**1a**) in 77–89% yields with high levels of asymmetric induction (96–98% ee) by means of Rh_2(*R*-BPCP)$_4$ as the catalyst.[434]



Scheme 133 Rh(II)-catalyzed enantioselective benzylic C(sp^3)–H functionalization of ethyltoluene and isopropyltoluene by carbene insertion.

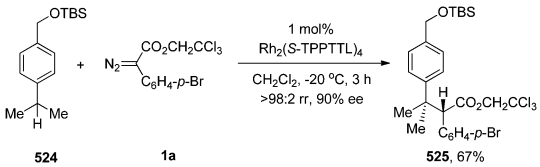
In the presence of 1 mol% Rh_2(*S*-NTTL)$_4$ catalyst and *N*-sulfonyl-1,2,3-triazoles as the carbene precursor, the tertiary benzylic C–H functionalization by carbene insertion was achieved in moderate to good yields with good enantioselectivity (Scheme 134).[435] The *para*-substitution by an electron-donating group is crucial for the reaction to proceed smoothly. In the case of isopropyl-substituted benzyl TBS ether ($iPrC_6H_4$-OTBS), Rh_2(*S*-NTTL)$_4$ catalyzed its C–H functionalization at the distal primary benzylic C–H bond with the same triazole in a



Scheme 134 Rh(II)-catalyzed enantioselective tertiary benzylic C–H functionalization by carbene insertion with triazoles.

mixed solvent of $CHCl_3$ and HFIP, giving the desired product in 72% yield with 74% ee and 98 : 2 rr.[437] These results have shown that efficient enantioselective selective functionalization of tertiary benzylic C–H bonds by carbene insertion is quite challenging. Gratifyingly, use of the TCE aryldiazoacetate (**1a**) as the carbene precursor and Rh_2(*S*-TPPTTL)$_4$ as the catalyst, the desired product was obtained in a good yield (67%) with a much better level of asymmetric induction (90% ee) (eqn (149)).[437]

When benzylic and other aliphatic C–H bonds coexist in a C–H substrate, a compatible combination of catalyst-control and substrate-control can switch the C–H functionalization selectivity (Table 19).[391] With Rh_2(*S*-TCPTAD)$_4$ as the catalyst in refluxing CH_2Cl_2, 4-bromo-*n*-butylbenzene (**526a**) reacted with donor/acceptor aryldiazoacetate **1c** (X = Br) afforded benzylic C–H functionalization product **527a** as the major product in 82% yield with 94% ee, 25 : 1 rr, and 14 : 1 dr, while use of Rh_2(*S*-2-Cl-5-Br-TPCP)$_4$ as the catalyst and **1b** (X = F) as the carbene precursor led to dominant formation of the unactivated secondary C–H functionalization product **528a** in 90% yield with 93% ee, 1 : 5 rr, and 16 : 1 dr. When the substituent on the aryl moiety is an ester group (CO_2Me), product **528b** was exclusively formed, while a methoxy substituent combined with the use of Rh_2(*S*-TCPTAD)$_4$ as the catalyst and **1c** as the carbene source completely switched the reaction selectivity to give the benzylic C–H functionalization product **527d** in 91% yield with 87% ee, >30 : 1 rr, and 13 : 1 dr. It is noted that vinyldiazo compounds can also be used for benzylic C–H functionalization by carbene insertion,[444] and Rh(I) complex catalysts can enable the benzylic C–H functionalization by intermolecular carbene insertion with aryldiazoacetates.[450]



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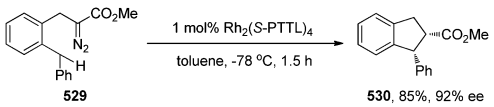
Intramolecular carbene insertion to benzylic C–H bonds can be applied for the synthesis of chiral indene derivatives or cyclopentanes.[390] By means of 1 mol% Rh_2(*S*-PTTL)$_4$ catalyst in toluene at −78 °C, α-diazoester **529** bearing a benzene ring on the tether reacted to give methyl *cis*-2,3-dihydro-1-phenyl-1*H*-indene-2-carboxylate (**530**) in 85% yield with 92% ee (eqn (150)). Under similar conditions, diazo compound **531** reacted to exclusively form the *cis* product **582** in 85% yield with 95% ee (eqn (151)). When other dirhodium(II) catalysts were used the *trans* product might be formed.



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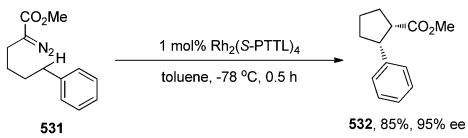
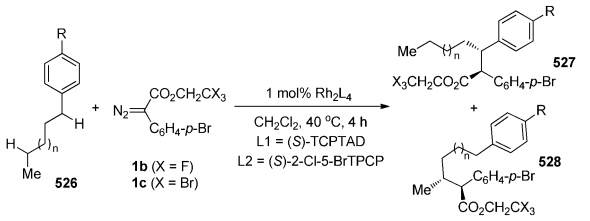


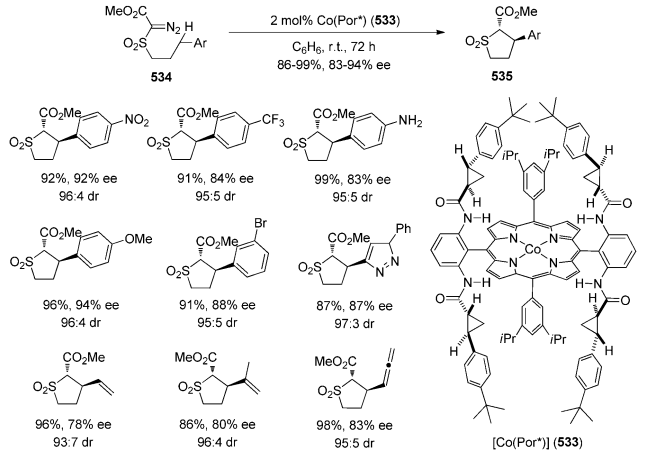
(151)

A Co(II)-based metalloradical system was established for the enantioselective radical C–H functionalization by carbene insertion with acceptor/acceptor diazo compounds.[451] In the presence of 2 mol% Co(Por*) (Por* = 3,5-DiiPr-(4′-*t*Bu)Xu-Phyrin) (**533**) as the catalyst in benzene at room temperature, α-methoxy carbonyl-α-diazosulfones (**534**) containing different types of C–H bonds with varied electronic properties and substituents reacted to give *trans*-sulfolane derivatives **535** in excellent yields (86–99%) with 83–94% ee for the benzylic C–H functionalization products and 78–87% ee for other heteroarylmethylene, allylic, and allenic C–H functionation products (Scheme 135). The benzylic C–H functionalization products were efficiently obtained with excellent levels of efficiency and asymmetric induction. Hydroxy and amino groups could be tolerated on the aryl moiety, and both of these two groups did not participate in the carbene insertion reaction, giving the desired products in 98–99% yields with 83–91% ee and 95 : 5–96 : 4 dr. Triazolyl-methylene, allylic, and allenic C–H bonds

Table 19 Catalyst and substrate-control-directed enantioselective benzylic C–H functionalization by carbene insertion



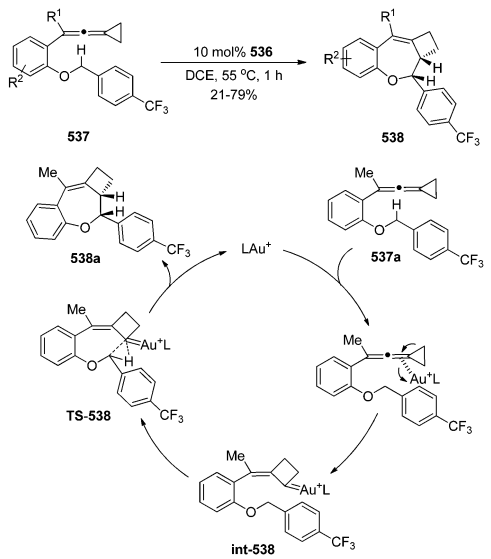
						Major product		
L	R	*n*	X	Yield (%)	rr (**527** : **528**)	dr	ee (%)	
L1	Br	0	Br	82	25 : 1	14 : 1	94	(**527a**)
L2	Br	0	F	90	1 : 5	16 : 1	93	(**528a**)
L1	CO_2Me	1	Br	42	3 : 1	20 : 1	92	(**527b**)
L2	CO_2Me	1	F	90	<1 : 30	29 : 1	94	(**528b**)
L1	OAc	1	Br	83	17 : 1	18 : 1	94	(**527c**)
L2	OAc	1	F	89	1 : 18	30 : 1	93	(**528c**)
L1	OMe	1	Br	91	>30 : 1	13 : 1	87	(**527d**)
L2	OMe	1	F	54	1 : 1.1	28 : 1	93	(**528d**)



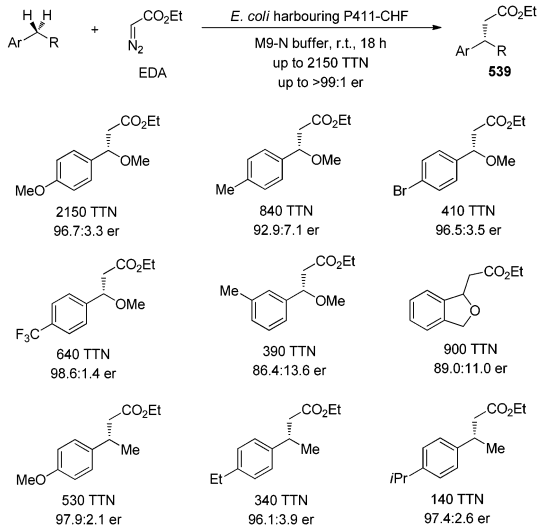
Scheme 135 Co(II)-catalyzed enantioselective intramolecular carbene insertion to benzylic C–H bonds.

could also be efficiently functionalized under the same conditions. These compounds were potentially useful for further transformations.

In situ generation of metal carbenes is another strategy for C–H functionalization by carbene insertion. In the presence of complex (Me_4*t*BuXPhos)Au(MeCN)NTf_2 (**536**) (Me_4*t*BuXPhos = 2-*di-tert*-butylphosphino-3,4,5,6-tetramethyl-2′,4′,6′-triisopropyl-biphenyl) as the catalyst in dichloroethane at 55 °C, gold carbene was generated *in situ* from vinylidenecyclopropanes (**537**) to render the intramolecular carbene insertion reaction at the benzylic C–H site (Scheme 136).[452] The desired products *syn*-benzoxepines **538** were obtained in moderate to good yields (27–79%) under mild conditions. The KIE studies suggest that the carbene insertion process might be the rate-determining step. The *in situ* generated gold carbene **int-538**



Scheme 136 Au(I)-catalyzed enantioselective intramolecular carbene insertion to benzylic C–H bonds.



Scheme 137 Enzymatic carbene insertion to benzylic C–H bonds.

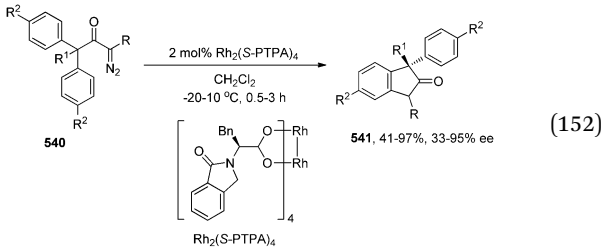
is proposed to be the reactive intermediate which transforms to the target product *via* transition state **TS-538**. These results have demonstrated the first example of the asymmetric variant of gold carbene insertion to C(sp^3)-H bonds.

Enzymatic benzylic C–H functionalization was achieved by means of *E. coli* expressing cytochrome P411-CHF as shown in eqn (148), with 10 mM C–H substrate and 10 mM ethyl diazoacetate at room temperature under anaerobic conditions for 18 h. A wide range of benzylic substrates were applied in the reaction with good tolerance of electron-rich and -deficient functionalities on the aromatic ring (Scheme 137).[447] Cyclic C–H substrates were also suitable for the reaction. The functionalization of alkyl benzenes at secondary benzylic C–H bonds was successful, but showing a lower reactivity than the benzylic C–H bonds adjacent to an oxygen atom. Up to 2150 TTN (TTN = total turnover number) with up to >99 : 1 er was reached. P411-CHF preferentially functionalized the secondary position despite its higher dissociation energy. When 4-methoxy-substituted allylbenzene was used as the C–H substrate, the reaction occurred at the benzylic C–H bond, achieved 100 TTN and >99 : 1 er.

7.7. Enantioselective carbene insertion to aryl C(sp^2)–H bonds

Functionalization of aromatic C–H bonds is generally considered to occur through formation of a zwitterionic intermediate from the electrophilic addition of a metal carbene to the aromatic ring followed by a rapid 1,2-H transfer. This stepwise mechanism makes it very challenging to achieve a high level of enantioselectivity with chiral transition-metal complex catalysts. Due to the poor site-selectivity, prefunctionalization of arene substrates by installation of a directing group, unexpected side reactions such as cyclopropanation and Büchner reaction occurring at the aryl moiety with the carbene source compounds under transition-metal catalysis, and difficult asymmetric stereocontrol, enantioselective aryl C(sp^2)–H

functionalization by carbene insertion has not been shown a promising potential in enantioselective organic synthesis. In addition, the well-developed chiral Rh(II) complex catalysts preferentially facilitate the enantioselective aliphatic C–H functionalization in aryl-bearing C–H substrates. Within this context, only a few reports have been documented so far[40] although non-enantioselective functionalization of aryl C(sp^2)–H bonds has been developed to some extent.



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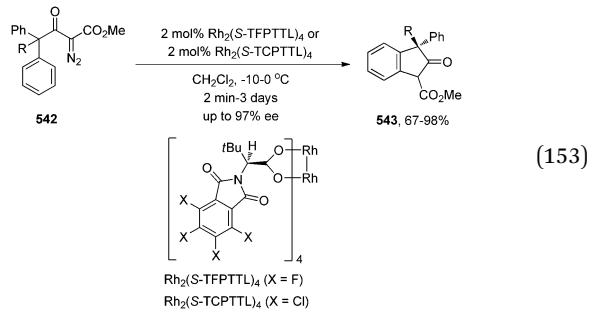

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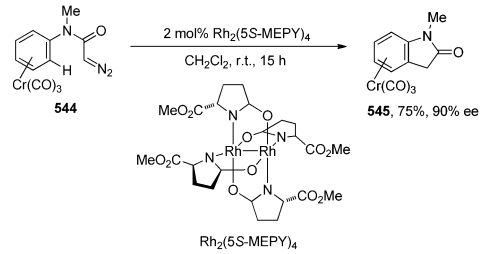
In 1995, Hashimoto, *et al.* reported Rh(II)-catalyzed enantio-selective functionalization of aryl C(sp^2)–H bonds through intramolecular carbene insertion (eqn (152)).[453] In the presence of 2 mol% Rh_2(*S*-PTPA)$_4$ as the catalyst in CH_2Cl_2 at −20 to −10 °C, α-diazo ketones **540** underwent intramolecular carbene insertion to aromatic C–H to afford chiral indanone derivatives **541** in moderate to excellent yields (41–97%) with 33–95% ee. Usually, a moderate to good level of enantioselectivity (41–77% ee) was achieved, and only in the case of R^1 = Et, R^2 = R = H, the desired product was obtained in 86% yield with the highest enantioselectivity. However, this work has demonstrated a potential for enantioselective aromatic C(sp^2)–H functionalization by carbene insertion under transition-metal catalysis. With Rh_2(*S*-PTTL)$_4$ as the catalyst, better enantioselectivity (88–98% ee) was obtained.[454] This methodology was successfully used for the first enantioselective synthesis of FR115427 ((*S*)-(+)-1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline hydrochloride), a non-competitive *N*-methyl-D-aspartate receptor antagonist. This result has suggested that increase of the bulkiness of a chiral complex catalyst can enhance the enantioselectivity of the carbene insertion to aromatic C–H bonds. The same catalyst also enabled intramolecular carbene insertion to the aromatic C–H bonds in acceptor/acceptor diazo compounds **542** (eqn (153)).[455] However, dirhodium(II) complex Rh_2(*S*-TFPTTL)$_4$ exhibited a much better catalytic activity than Rh_2(*S*-PTTL)$_4$ and Rh_2(*S*-TCPTTL)$_4$, and in the reaction of **542a** (R = Me) a 98% yield with 97% ee was reached for the target product **543a** (R = Me) in the presence of 0.01 mol% Rh_2(*S*-TFPTTL)$_4$ as the catalyst.



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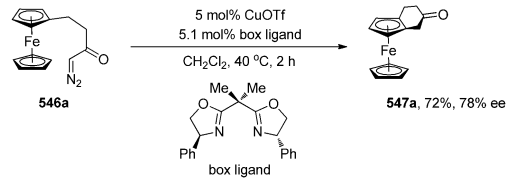

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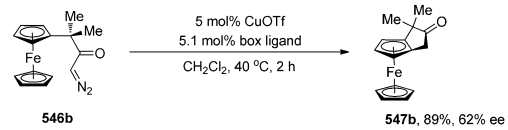


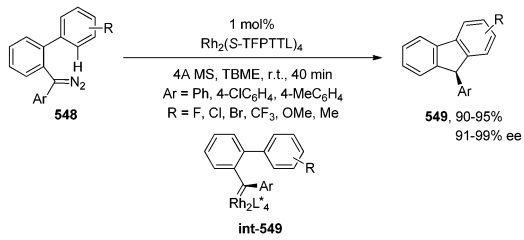
(156)

(η^6-Arene)tricarbonylchromium complexes were reported to undergo Rh(II)-catalyzed enantioselective aromatic C–H functionalization by carbene insertion. In the presence of 2 mol% Doyle's Rh_2(5*S*-MEPY)$_4$ carboxamide catalyst in CH_2Cl_2 diazo complex **544** reacted to afford the corresponding chiral indolinone complex product **545** in 75% yield with 90% ee (eqn (154)).[456] In a similar fashion, $Rh_2(OAc)_4$ catalyzed the intramolecular carbene insertion reaction of *N*-aryldiazoamides to give 2(3*H*)-indolinones in moderate to excellent yields (67–98%), and in most cases the yields were >85%.[457]

A combination of 5 mol% CuOTf and 5.1 mol% chiral bis(oxazole) (box ligand) was employed to realize the ferrocenyl C–H functionalization by intramolecular carbene insertion.[458] Ferrocenyl-based diazoketone **546a** underwent the reaction in refluxing CH_2Cl_2 by means of the *in situ* generated catalyst, giving the cyclization product **547a** derived from carbene insertion to the aromatic ferrocenyl C(sp^2)–H bond in 72% yield with 78% ee (eqn (155)). In a similar fashion, chiral product **547b** was obtained from the reaction of diazo compound **546b** in 89% yield and 62% ee (eqn (156)). It is noteworthy that Rh(II) complexes $Rh_2(OAc)_4$ and $Rh_2(TFA)_4$, and copper complexes Cu(hfacac) and Cu(hfacac)$_2$ exhibited much lower catalytic activity than such a combination of CuOTf and the box ligand. This protocol provides an alternative route to chiral ferrocene derivatives.

With a transient-axial-chirality-control strategy, Xu and Yu, *et al.* achieved aryl C(sp^2)–H functionalization by intramolecular carbene insertion, accessing diverse chiral fluorenes.[459] In the presence of 1 mol% Rh_2(*S*-TFPTTL)$_4$ as the catalyst in *tert*-butyl methyl ether (TBME) at room temperature, donor/donor diaryl diazo compounds **548** underwent the intramolecular carbene insertion reaction to form

chiral fluorenes **549** in 90–95% yields with 91–99% ee (eqn (157)).



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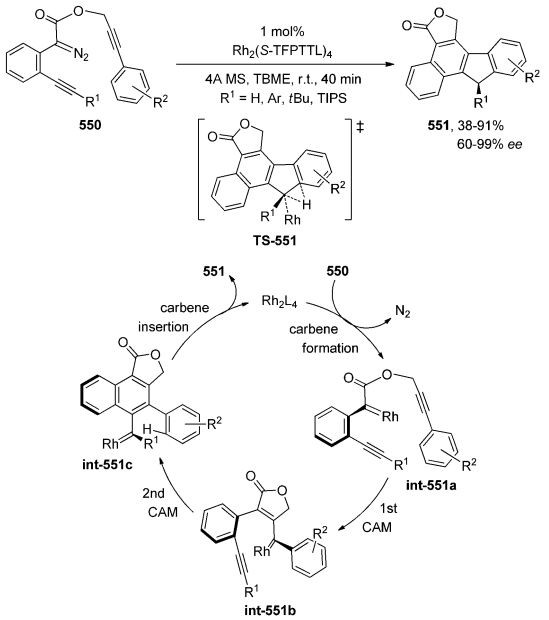
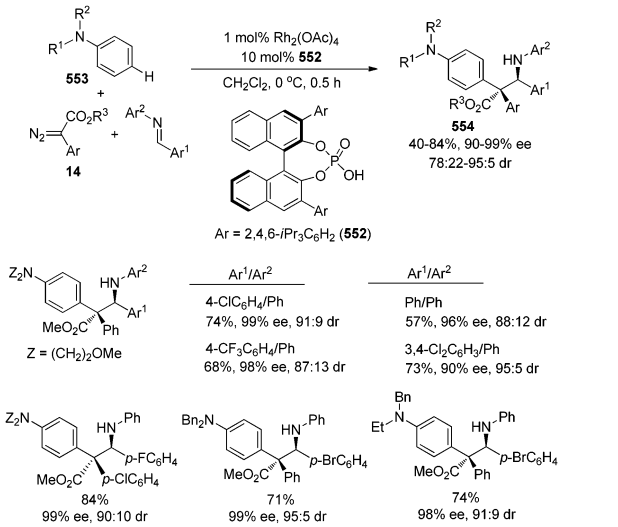
Slow addition of the catalyst solution in the same solvent was crucial to reach the high level of enantioselectivity. The substrate scope of **548** is quite limited because one of the aryl groups in the biaryl moiety should be substituted by F, Cl, Br, CF_3, Me, or OMe at 4-position or by 3-F, and in most of the cases the aryl group is phenyl. This transformation is considered to proceed *via* Rh(II) carbene intermediate **int-549** under mild conditions. To overcome the limited accessibility and inherent instability of the donor/donor carbene precursor compounds of type **548**, the carbene/alkyne metathesis (CAM) reaction was used to generate similar carbene species *in situ* for the same transformation (Scheme 138). Electron-neutral, -deficient, and -rich substituents F, Cl, Br, CF_3, Me, and OMe were tolerated on the aryl group in the arylalkynyl moiety, and a naphthylalkynyl in **550** was also effective for the desired reaction. 38–91% yields were obtained with 60–99% ee for products **551**. For the formation of **551** a double carbene/alkyne metathesis pathway is proposed, and the transition state **TS-551** is rationalized by DFT calculations.

Hu, *et al.* used a trapping-carbene strategy to achieve the enantioselectivity control in a three-component reaction of *N*,*N*-disubstituted anilines, donor/acceptor diazo compounds,



Scheme 138 Enantioselective Rh(II)-catalyzed carbene insertion to aryl C(sp^2)–H bond *via* double carbene/alkyne metathesis (CAM).

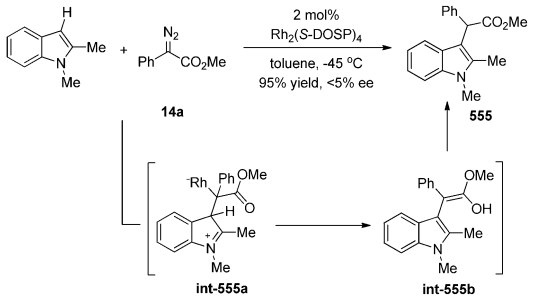


Scheme 139 Enantioselective Rh(II)-catalyzed carbene insertion to aryl C(sp^2)–H bonds in a three-component reaction.

and benzaldehyde imines under Rh(II) catalysis (Scheme 139).[260] With 1 mol% $Rh_2(OAc)_4$/10 mol% chiral phosphoric acid (*R*)-3,3′-bis(2,4,6-triisopropylphenyl)binol phosphoric acid (**552**) as the catalyst in CH_2Cl_2 at 0 °C, *p*-*N*,*N*-disubstituted anilines (**553**) efficiently reacted with aryldiazoacetates (**14**) and imines to give the three-component reaction products **554** in 40–84% yields with 90–99% ee and up to 95 : 5 dr. In most of the cases, the yields are >67% with ≥96% ee, demonstrating a high level of enantioselectivity for the desired products. An intermolecular kinetic isotope effect (KIE) experiment with deuterated *N*,*N*-dibenzylaniline and methyl phenyldiazoacetate (**14a**) under the stated conditions revealed a $k_{H/D}$ of 1.0, suggesting that the aryl C–H bond cleavage is not involved in the rate-determining step of the catalytic cycle. The observed stereochemistry for this aromatic C–H transformation may be rationalized by the zwitterionic intermediate mode proposed by Simón and Goodman.[460] The chiral phosphoric acid **552** initially interacts with the imine substrate through hydrogen bonding between the catalyst proton and the nitrogen atom of the imine. In addition, a weak hydrogen bond between the Lewis basic phosphoryl oxygen atom and the acidic C–H proton is also established. Such hydrogen interactions render the *N*-substituent of the imine to be oriented toward the empty side of the catalyst pocket to avoid steric hindrance with the bulky substituents on the chiral phosphoric acid. Followed by a proton transfer process, efficient chiral induction is achieved.

7.8. Enantioselective carbene insertion to heteroaryl C(sp^2)–H bonds

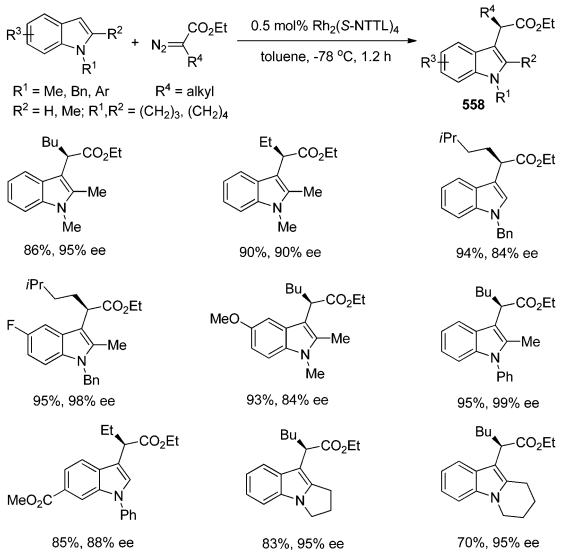
Transition-metal-catalyzed carbene insertion to heteroaryl C(sp^2)–H bonds is challenging because unexpected side reactions such as cyclopropanation and ring-opening always concurrently occur.[314,342,356] It was found that the reaction of 1,2-dimethylindole with methyl phenyldiazoacetate (**14a**) in toluene at 45 °C only reached a negligible level of asymmetric



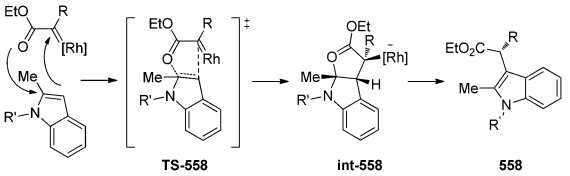
Scheme 140 Rh(II)-catalyzed carbene insertion to indolyl C(sp^2)–H bonds.

induction (<5% ee) in the presence of 2 mol% Rh_2(*S*-DOSP)$_4$ as the catalyst (Scheme 140).[461] The lack of asymmetric induction is presumably attributed to the rapid proton transfer of the zwitterionic intermediate **int-555a** to generate the achiral enol **int-555b**, which then tautomerizes to the observed product **555**. Unexpectedly, methyl styryldiazoacetate (**18a**) reacted with indoles exclusively gave the [3+2] annulation products under similar conditions. However, with Rh_2(*S*-biTISP)$_2$ as the catalyst, formal carbene insertion to the C–H bonds occurred at the 3-position of substituted indoles (eqn (158)) and pyrroles (eqn (159)) with the vinylcarbene precursor (*E*)-**294**.[462] This bridged dirhodium catalyst not only selectively enabled the reaction to occur at the vinylogous position of the metal carbene but also reached high levels of asymmetric induction. The Rh(II) carbenes in *S-trans* configurations (conformers **int-556a** and **int-556b**) are proposed to be more likely to display vinylogous reactivity than the carbenes in (*S*)-*cis* configurations (conformers **int-556c** and **int-556d**).

In 2011, Fox, *et al.* realized rhodium(II)-catalyzed enantioselective C–H functionalization of indoles by means of Rh_2(*S*-

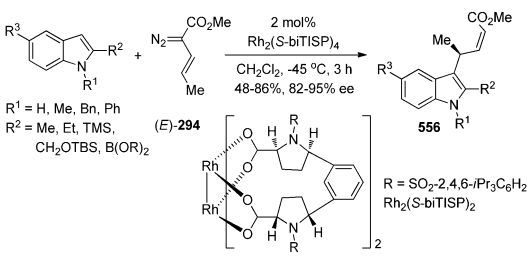


Scheme 141 Rh(II)-catalyzed enantioselective carbene insertion to indolyl C(sp^2)–H bonds.



Scheme 142 A proposed mechanism for enantioselective carbene insertion to indolyl C(sp^2)–H bonds.[442]

NTTL)$_4$ catalyst and the donor/acceptor carbene precursor in toluene at −78 °C (Scheme 141).[463] In the presence of 0.5 mol% Rh_2(*S*-NTTL)$_4$ catalyst, *N*-protected indoles reacted with ethyl alkyldiazoacetates to afford the target chiral 3-alkylated indole derivatives **558** in 82–96% yields with good to excellent levels of asymmetric induction (79–99% ee). 1,2-Fused indoles also underwent the reaction efficiently (70–83% yields and 95% ee). A mechanism is proposed as shown in Scheme 142 based on the DFT calculations of the reaction pathway between 2-methylindole and Et(EtO$_2$C)C = Rh_2(O$_2$CH)$_4$. Intermediate **int-558** is a stabilized oxocarbenium ion generated from transition state **TS-558**. Relative to a pre-reaction complex between the carbene and indole, **TS-558** has a barrier of $\Delta E(\mathrm{ZPE})^{\neq}$ = 8.8 kcal mol^{-1}, and formation of ylide **int-558** is exothermic by *E*(ZPE) = 16.0 kcal mol^{-1}. **TS-558** is formed by end-on approach of indole to the carbene ceneter. The conversion of **int-558** to **558** is proposed to proceed stepwise. The DFT calculations have suggested that an intramolecular 1,2-hydride shift for the conversion of **int-558** to **558** is impossible ($\Delta E(\mathrm{ZPE})^{\neq}$ = 30.2 kcal mol^{-1}) at −78 °C. A possible explanation is that asymmetry is induced *via* dynamic kinetic resolution of the Rh-enolate intermediates that are not configurationally stable. With 0.5 mol% Rh_2(*S*-PTTL)$_4$ catalyst the reaction of 1-phenyl-4-methylindole and ethyl ethyldiazoacetate gave the carbene insertion product at 3-position in 43% yield with 64% ee, while use of Rh_2(*S*-NTTL)$_4$ only resulted in a negligible amount of the desired product (5% yield, 40% ee).[464] However, complex Rh_2(*S*-PTTL)$_3$(TPA) enabled formation of the desired product in 80% yield with 81% ee.



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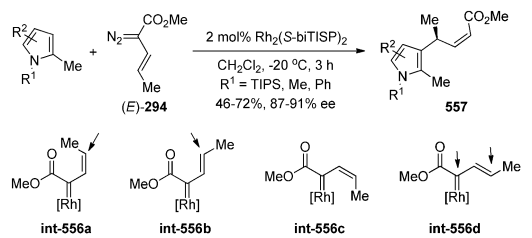

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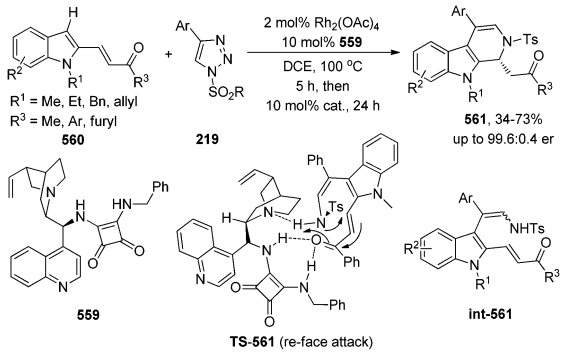
Tandem Rh(II) and chiral squaramide (**559**) relay catalysis was employed for the enantioselective synthesis of dihydro-β-carbolines **561** *via* carbene insertion to indolyl C–H at 3-position and an aza-Michael reaction (eqn (160)).[465] The reaction was conducted in the presence of 2 mol% $Rh_2(OAc)_4$ catalyst and 10 mol% chiral squaramide **559** as the cocatalyst in dichloroethane at 100 °C. Interaction of 2-vinylindoles **560** with aryl-substituted *N*-sulfonyl-1,2,3-triazoles (**219**) initially generates the desired carbene insertion product at 3-position of the indole substrate, which then tautomerizes to the more stable enamide intermediate **int-561**. Subsequent aza-Michael cyclization affords the dihydro-β-carboline product **561** in moderate to good yields (34–73% yield) with up to 99.6 : 0.4 er. The potential of the present synthetic strategy was demonstrated by the ready conversion to potent tetrahydro-β-carolines and the tetracyclic alkaloid core structure. The potential interaction of **int-561a** (R^1 = Me, R^2 = H, R^3 = Ph) and the cocatalyst **559** was investigated by analysis of the equimolar mixture of both in DCE with ESI-MS technology. The peak at 1011.4266 was observed, which corres-ponds to the cocatalyst + substrate adduct (**559** + **int-561a** + H). This result suggests a strong interaction between the cocatalyst and **int-561a**. A plausible transition state is thus proposed as shown in **TS-561**. The enantioselective aza-Michael addtition process may undergo through a re-face attack pathway.



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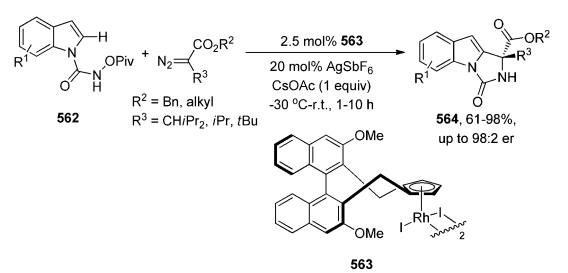
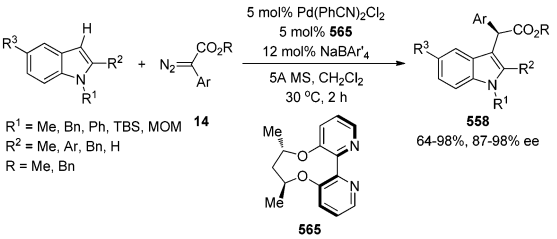
With the assistance of an amide directing group at 1-position of indoles **562**, a formal carbene insertion to indolyl C–H at 2-position/annulation sequence was developed to access 1,2-dihydro-3*H*-imidazo[1,5-*a*]indol-3-ones by means of a chiral Rh(III) complex catalyst (eqn (161)).[466] Products **564** feature a quaternary carbon stereocenter and were obtained in high yields with excellent enantioselectivity (up to 98 : 2 er). It is crucial to enable such a transformation by using the chiral half-sandwich rhodium(III) complex **563** as the catalyst and *O*-pivaloyl 1-indolehydroxamic acids as the C–H substrates.



(161)

Other transition-metal complex catalysts have also been documented for the enantioselective carbene insertion to heteroaryl C(sp^2)–H bonds. However, a combination of 5 mol% $Fe(ClO_4)_2$ and Zhou's chiral spiro bisoxazoline ligands only enabled carbene insertion to indolyl C–H bond at 3-position with good levels of asymmetric induction.[323] In 2015, Zhou, *et al.* disclosed a palladium catalyst system for the same purpose (eqn (162)).[467] In the presence of 5 mol% $Pd(PhCN)_2Cl_2$ as the precatalyst, chiral bipyridine **565** as the ligand, and $NaBAr'_4$ as the additive, substituted indoles reacted with aryldiazoacetates **14** to give the target chiral 3-alkylated indole derivatives **558** in 64–98% yields with high levels of asymmetric induction (87–98% ee) when 1,2-disubstituted indoles were used. In most of the cases, the yields are ≥80% and the enantioselectivity is ≥93% ee.



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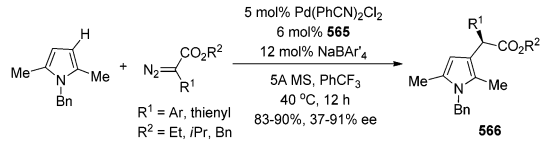
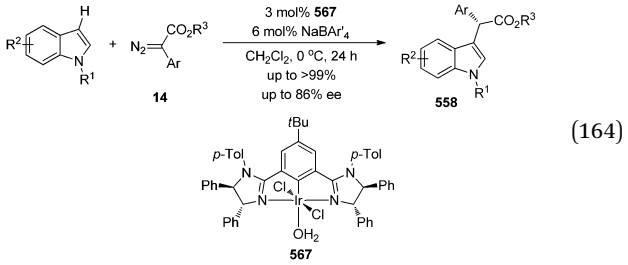


(163)

When 2-unsubstituted indoles were used as the C–H substrates, the asymmetric induction was remarkably dropped to 12–58% ee. In the case of benzyl methyldiazoacetate as the carbene precursor, its reaction with 1,2-dimethylindole gave the desired product in 34% yield with a moderate level of asymmetric induction (42% ee). In a similar fashion, this catalyst system effected for C–H functionalization of 1,2,5-trisubstituted pyrroles by carbene insertion (eqn (163)).[468] A combination of CuCl and ligand **565** behaved the same for the enantioselective C(3)–H functionalization of *N*-substituted indoles by carbene insertion with aryldiazoacetates.[469]

A chiral pincer iridium(III)–NCN complex **567** bearing a 1,3-bis (2′-imidazolinyl)phenyl ligand was found to be an effective catalyst for the C(3)–H functionalization of the *N*-protected indoles (eqn (164)).[470] In the presence of 3 mol% **567** catalyst with the assistance of $NaBAr'_4$, *N*-protected indoles reacted with aryldiazoacetates **14** to result in the carbene insertion products **558** functionalized at 3-position of the indolyl moiety in low to excellent yields (21–99%) with moderate to good levels of asymmetric induction (37–86% ee). These results have demonstrated the catalyst diversity for enantioselective indolyl C–H functionalization of indoles by carbene insertion, and more work can be done to develop efficient catalyst systems for this purpose.

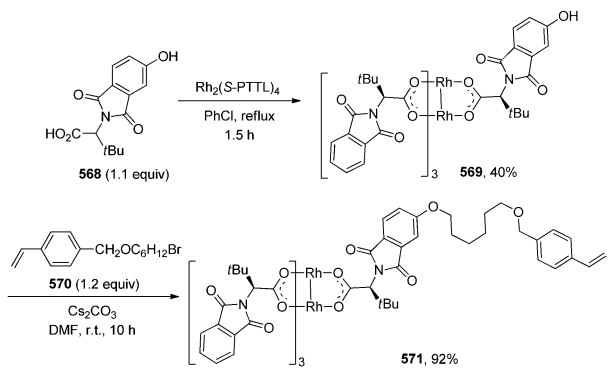


(164)

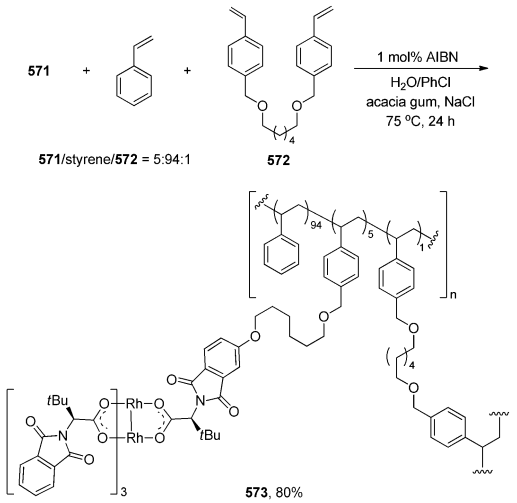
7.9. Supported complex catalysts for enantioselective carbene insertion to C–H bonds

Two issues are usually encountered in order to realize an efficient C–H functionalization process *via* carbene insertion with diazo compounds as the carbene precursor: catalyst cost and safety to handle the carbene precursor compounds. In this area, expensive rhodium complexes are found to be the most efficient catalysts in most cases.[471] On one hand, lowering the catalyst cost is often required. On the other hand, special efforts have to be made to avoid the explosion danger from the diazo compounds or intermediates. In principle, two measures can be considered in practice. Recycling the expensive transition-metal catalysts by supporting them on heterogenous materials may be achieved to reduce the catalyst cost. Use of a specific reactor such as a microflow reactor by reducing the reaction scale or slow addition of the potentially explosive diazo compounds is another possible method to diminish the explosion danger during the reaction.

In 2010, Hashimoto, *et al.* reported a polymer-supported chiral dirhodium(II) complex which acted as a highly durable and recyclable catalyst for enantioselective C–H functionalization by carbene insertion.[472] With *N*-4-hydroxyphthaloyl-(*S*)-*tert*-butylleucine (**568**) as a replaceable ligand to react with Rh_2(*S*-PTTL)$_4$, the mixed dirhodium(II) tetracarboxylate complex **569** was obtained in 40% yield. *O*-Alkylation of complex **569** with 6-(4-vinylbenzyloxy)bromohexane (**570**) gave monomer **571** in 92% yield (Scheme 143). The polymer-supported chiral dirhodium(II) catalyst **573** was then prepared by suspension copolymerization of monomer **571** with styrene and 1,6-bis(4-vinylbenzyloxy)-hexane (**572**) as a cross-linker (Scheme 144).



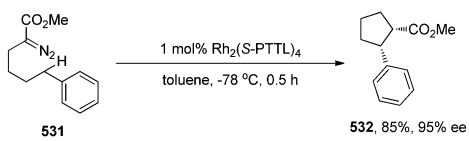
Scheme 143 Preparation of a Rh(II)-catalyst-containing monomer.



Scheme 144 Preparation of a polymer-supported chiral Rh(II) complex.

Elemental analysis indicated incorporation of 0.27 mmol dirhodium(II) complex per gram of the resultant complex, corresponding to the composition of the monomer feed. The polymer-supported complex **573** was examined for its catalytic performance in the enantioselective intramolecular C–H functionalization of α-alkyl-α-diazo ester, aryldiazoacetate, and α-diazo-β-ketoester by comparison with complex catalyst Rh_2(*S*-PTTL)$_4$. In the case of α-alkyl-α-diazo ester **531**, its reaction with 2 mol% of the immobilized catalyst **573** proceeded at −70 °C to give methyl *cis*-2-phenylcyclopentane-1-carboxylate (**532**) as the sole product in 85% yield with 94% ee, and no *trans* isomer or β-hydride elimination product (alkene) was observed although **573** exhibited a lower catalytic activity than Rh_2(*S*-PTTL)$_4$. After the immobilized catalyst was reused for 20 times, only a small decrease in the catalytic activity was observed without an impact on the enantioselectivity (Table 20), suggesting that the present immobilization method only resulted in a negligible effect on the chiral environment of the immobilized catalyst. Similar results were obtained in the intramolecular C–H functionalization of aryldiazoacetate **422c**, and the catalyst was recycled for 15 times with no obvious loss of catalytic activity and enantioselectivity (Table 21). This immobilized

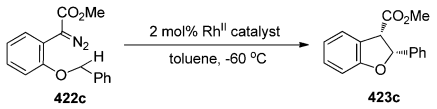
Table 20 Immobilized chiral Rh(II)-catalyzed intramolecular C–H functionalization of alkyl α-diazo ester



Rh^{II} cat.	Cyclo no.[a]	*t* (h)	Yield	ee
Rh_2(*S*-PTTL)$_4$	—	0.5	85%	95%
573	1	4	85%	94%
573	10	4	83%	95%
573	20	4	81%	94%

[a] Using 1 mol% Rh_2(*S*-PTTL)$_4$.

Table 21 Immobilized chiral Rh(II)-catalyzed intramolecular C–H functionalization of aryldiazoacetate



Rh^{II} cat.	Cyclo no.[a]	t (h)	Yield	ee
Rh_2(*S*-PTTL)$_4$	—	0.5	87%	90%
573	1	2	83%	91%
573	10	2	84%	91%
573	15	2	80%	91%

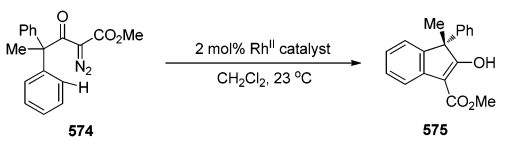
[a] Using 1 mol% Rh_2(*S*-PTTL)$_4$.

catalyst was also applicable for the intramolecular aryl C–H functionalization by carbene insertion. It could be recycled for 100 times in the case of diazo compound **574**, and still kept the same catalytic activity and reached the same asymmetric induction (Table 22). These results have demonstrated an efficient protocol to immobilize Rh_2(*S*-PTTL)$_4$ complex catalyst, and also provide the first example of a chiral mixed dirhodium(II) tetracarboxylate complex catalyst (**571**). A similar method may prove to be beneficial for the immobilization of homogeneous catalysts bearing various chiral ligands.

The efficiency of chiral bis(oxazoline)- and azabis(oxazoline)-copper complexes in the carbene insertion to C(sp^3)–H bonds of cyclic ethers in homogeneous phase strongly depends on the structure of the C–H substrates. However, immobilization of these Cu(II) complexes by LAPONITE® clay through electrostatic interactions not only allows recovery and reuse of the heterogenized catalysts, but in some cases also improves the enantioselectivity and overall chemoselectivity, making possible reactions that do not occur or lead to low yields, even with the widely used Rh_2(*S*-DOSP)$_4$ catalyst.[473] The same heterogenized catalyst systems can also be applied for benzylic C–H functionalization by carbene insertion.[474]

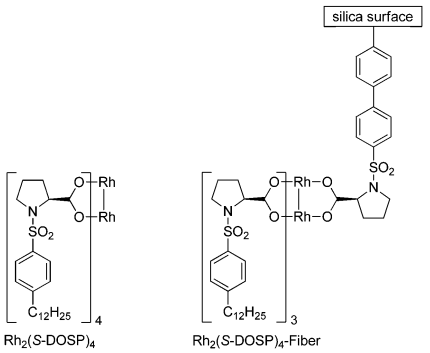
Flexible composite polymer/oxide hollow fibers were used as the flow reactors for carbene insertion to C–H bond and other processes. The fiber synthesis allowed for a variety of supported catalysts to be embedded in the walls of the fibers, leading to various reactions that can be catalyzed in flow. In addition, the

Table 22 Immobilized chiral Rh(II)-catalyzed intramolecular C–H functionalization of α-diazo-β-ketoester



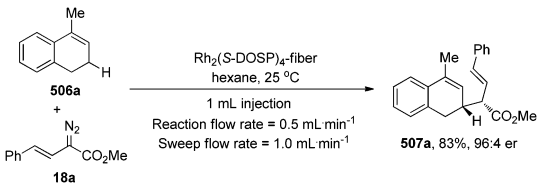
Rh^{II} cat.	Cyclo no.[a]	t (min)	Yield	ee
Rh_2(*S*-PTTL)$_4$	—	5	89%	91%
573	1	20	86%	91%
573	10	20	90%	90%
573	50	20	90%	91%
573	100	20	88%	92%

[a] Using argonaut quest-210 synthesizer.



Scheme 145 Homogeneous Rh_2(*S*-DOSP)$_4$ and its immobilized analog on silica.

fiber synthesis is scalable and they might be used for large-scale production of organic compounds. The polymer/oxide hollow fibers used in this research were comprised of cellulose, an aluminosilicate zeolite (ZSM-5), or commercially available porous amorphous silica on which molecular catalysts were tethered as shown in Scheme 145.[475] In a similar fashion as reported,[476] a Rh_2(*S*-DOSP)$_4$ derivative containing a styryl group on a prolinate ligand was tethered to styryl-functionalized silica in the fiber wall through a radical coupling initiated by ABIN. The fiber-supported catalyst was successfully used for the enantioselective allylic C–H functionalization/Cope rearrangement/retro-Cope rearrangement of 1-methyl-3,4-dihydronaphthalene (**506a**)[443] by intermolecular carbene insertion with styryldiazoacetate **18a** (eqn (165)). The target product **507a** was obtained in 83% yield with 94 : 6 er, which are slightly lower than those obtained by using Rh_2(*S*-DOSP)$_4$ in batch (94% yield, >99 : 1 er). This Rh(II)-hollow fiber reactor system was also applicable for the enantioselective cyclopropanation of alkenes with diazo compounds at room temperature. These results have demonstrated a promising potential for the synthesis of natural products and other organic compounds using hollow fibers.



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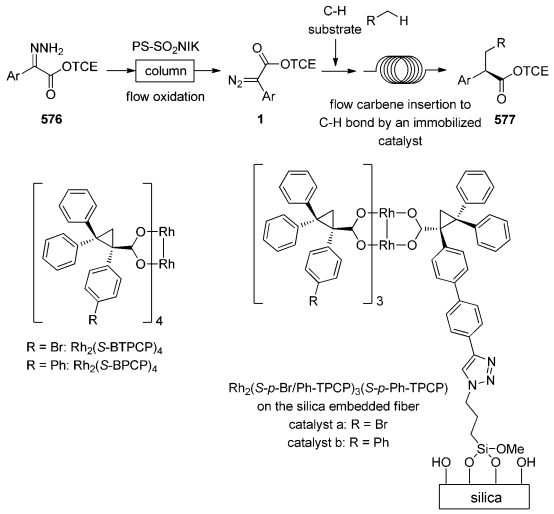
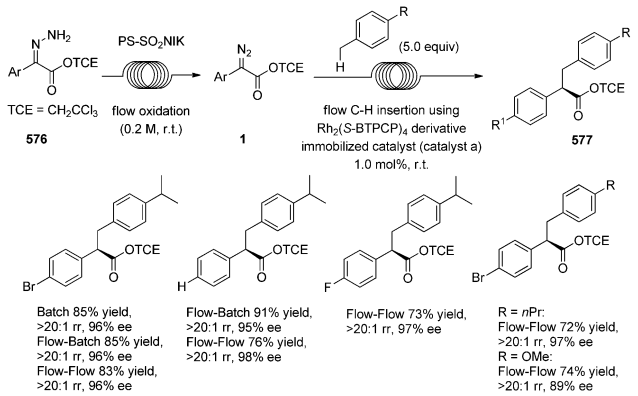
A cascade reaction strategy was developed by using a microfluidic flow reactor system containing immobilized dirhodium complex catalyst in conjunction with the flow synthesis of diazo compounds from α-ketoesters at room temperature (Scheme 146).[477] In the reactor system, the first column is filled with poly(styrene)-supported NIK resin (PS-SO_2NIK), where relatively stable hydrazones were converted to the corresponding diazo compounds. A pre-mixed stream of the diazo compound and C–H substrate solutions was then introduced to a hollow fiber flow reactor containing supported chiral dirhodium catalysts, where the products of C–H functionalization by



Scheme 146 The hollow fiber reactor strategy for chiral Rh(II)-catalyzed carbene insertion to C(sp^3)–H bonds with diazo compounds.

carbene insertion were formed and collected at the end of the fiber reactor. The fiber reactor was wrapped with non-permeable PTFE tubing, allowing the fiber to be used as axial flow reactor. Embedded within the porous polymer matrix were commercially available silica particles, on which the dirhodium catalysts were grafted. With immobilized Rh_2(*S*-BTPCP)$_4$ as the catalyst (1 mol% at room temperature), benzylic, etheric primary methyl, and allylic C–H bonds were efficiently functionalized by carbene insertion with similar levels of efficiency and asymmetric induction compared to the batch-reaction systems (Scheme 147).

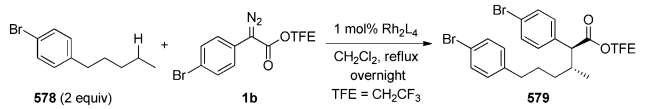
The immobilization strategy has recently been further optimized for dirhodium(II) carboxylate catalysts for C–H functionalization by Davies and Jones, *et al.*[84] The new dirhodium complex Rh_2(*S*-2-Cl-5-CF_3TPCP)$_4$ was synthesized and exhibited a better catalytic activity for the secondary C–H functionalization of 4-bromopentylbenzene (**578**) with trifluoroethyl 4-bromophenyldiazoacetate (**1b**) compared to Rh(II) complex catalysts Rh_2(*S*-*o*-ClTPCP)$_4$ and Rh_2(*S*-2-Cl-5-BrTPCP)$_4$.[84] There



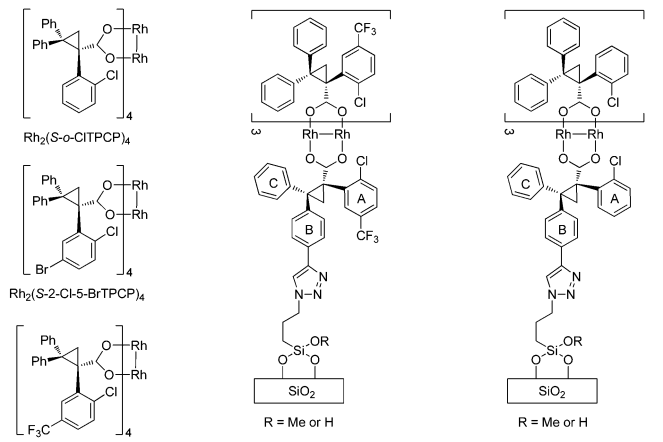
Scheme 147 Chiral Rh(II)-catalyzed flow carbene insertion to C(sp^3)–H bonds with diazo compounds in a hollow fiber reactor.

are two possible C–H bonds that can be functionalized in **578**: the electronically favored benzylic C–H bond and the sterically favored terminal methylene (C2)C–H bond. The effect of the substituents on the aryl moieties was obvious on the aligment of ligand in the dirhodium tetrakis(1,2,2-triarylcyclopropanecarboxylate) catalysts of type Rh_2(TPCP)$_4$ and their catalytic activity for C–H functionalization by carbene insertion.[478] Because of the sterically limited active site constructed by the four bulky aryl rings in the catalyst, carbene insertion to the C(2)–H bonds with the less steric bulkiness is preferred. Thus, a 82% yield was obtained with 96 : 4 rr (C2 : benzylic), 95 : 5 dr (C2), and 93% ee by means of complex Rh_2(*S*-2-Cl-5-CF_3TPCP)$_4$ which was shown the highest asymmetric induction (Table 23). It was then immobilizedon platelet SBA-15 which backbone is composed of silica *via* one of its equatorial phenyl ring of the complex, and implemented in the packed bed flow reactor for the functionalization of non-activated secondary C–H bonds of type **578**. The resultant immobilized catalyst Rh_2(*S*-2-Cl-5-CF_3TPCP)$_3$(platelet SBA-15@B) enabled highly regio- and stereoselective functionalization of those non-activated secondary C–H bonds, which is comparable to that using its homogeneous parent complex Rh_2(*S*-2-Cl-5-CF_3TPCP)$_4$, and better than the silica-supported Rh_2(*S*-*o*-ClTPCP)$_3$(SiO_2@B) complex. Notably, its performance was almost maintained over ten reaction cycles (Table 24). Such a strategy may be applied to other Rh_2(TPCP)$_4$-derived catalysts and achieve high productivity by scaling up this system. All these results have demonstrated that the catalyst cost and manipulation safety for a C–H

Table 23 Comparison of catalytic activity and selectivity between Rh_2(*S*-*o*-ClTPCP)$_4$, Rh_2(*S*-2-Cl-5-BrTPCP)$_4$, and Rh_2(*S*-2-Cl-5-CF_3TPCP)$_4$

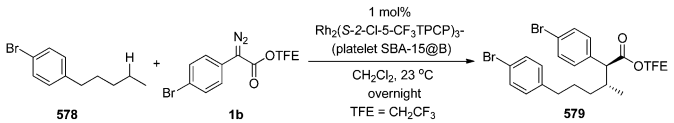


Rh(II) catalyst	Yield[a] (%)	rr[b]	dr (C2)	ee (%)
Rh_2(*S*-*o*-ClTPCP)$_4$	87	91 : 9	96 : 4	77
Rh_2(*S*-2-Cl-5-BrTPCP)$_4$	86	96 : 4	96 : 4	91
Rh_2(*S*-2-Cl-5-CF_3TPCP)$_4$	82	96 : 4	95 : 5	93



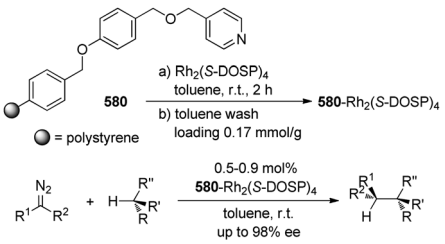
[a] Isolated yield. [b] rr (C2:benzylic).

Table 24 Recyclability of the immobolized Rh_2(*S*-2-Cl-5-CF_3TPCP)$_3$(platelet SBA-15@B) catalyst for C–H functionalization by carbene insertion with diazo compounds in a in a packed bed flow reactior



Recycle no.[a]	1	2	3	4	5	6	7	8	9	10
Yield (%)	75	76	76	75	78	73	71	70	68	67
ee (%)	94	90	90	90	89	90	89	90	90	89

[a] rr = 97 : −96 : 4; dr 96 : 4.



Scheme 148 Polystyrene-pyridine-immobilized chiral Rh(II)-catalyzed carbene insertion to C(sp^3)–H bonds with diazo compounds.

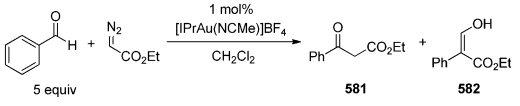
functionalization process by carbine insertion with diazo compounds may be controlled by means of supported heterogenized dirhodium(II) catalysts and flow reactors.

Although the above-discussed supported dirhodium(II) tetracarboxylate complexes have demonstrated powerful catalytic activities for C–H functionalization by carbene insertion with diazo compounds, polystyrene–pyridine-based resins can also be applied to immobilize such dirhodium(II) tetracarboxylates and related complexes through coordination of the pyridyl nitrogen atom to the rhodium metal center(s).[24,479–482] For example, the highly cross-linked polystyrene (Argopore) resin with a benzyloxymethyl–pyridine linker has proved to be an effective system to immobilize dirhodium(II) complexes to enable enantioselective carbene insertion to aliphatic and aromatic C–H bonds (Scheme 148).[480,481]

8. Miscellaneous carbene insertion to C–H bonds

C–H Functionalization by carbene insertion can be performed under various conditions. This review is focused on transition-metal-catalyzed C–H functionalization reactions *via* carbene insertion. Although a considerable number of transition-metal-free, metal-free, and visible light-driven carbene insertion to C–H reactions as well as stoichiometric reactions of carbenes with C–H substrates have been documented, only a few selected examples are given in this section.

Scattered examples of carbene insertion to other types of C–H bonds have been documented.[47,483,484] For example, Au(I) catalyzed the formyl C–H functionalization of benzaldehyde with EDA at −80 °C to 80 °C, affording a mixture of β-ketoester and enol (eqn (166)).[483] At −80 °C, the enol product **582** was preferentially formed from a carbene insertion to C–C bond/enolization process (**581**/**582** = 15 : 85), while the reaction gave **581** as the major product (**581**/**582** = 52 : 48) at 80 °C. In all the cases, >99% conversion was reached. When 1 mol% $[PPh_3Au(NCMe)]BF_4$ was used as the catalyst in the presence of 2 equiv. of benzaldehyde, the **581**/**582** ratio was increased to 57 : 43. A Rh(III)-catalyzed formal carbene insertion to formyl C(sp^2)–H bond was achieved to establish O-heterocycles **584** from substituted salicylaldehydes and diazo compounds **583** (eqn (167)).[484] The same catalyst system was applied for the directed acyl C–H functionalization of 2-aminobenzaldehydes (**585**) by carbine insertion with enynones **586** as the carbene precursor in DCE (Scheme 149).[485] α-Furyl ketone derivatives **587** were obtained in moderate to excellent yields with good functional group tolerance. Rh(III)–carbene migratory insertion *via* the *in situ* generated carbene intermediate **int-587b** is proposed as the key step in this transformation.



temp	time	581:582
-80 °C	7 h	15:85
r.t.	10 min	30:70
0 °C	10 min	33:67
80 °C	10 min	52:48

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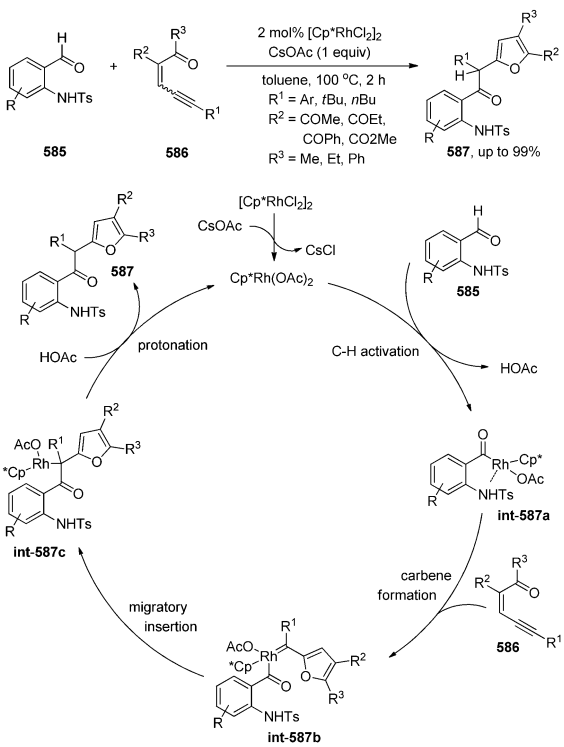
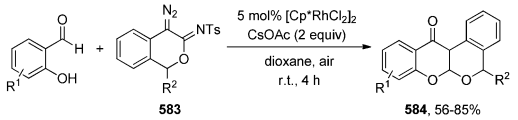


Scheme 149 Rh(III)-catalyzed acyl C–H functionalization by carbene insertion using enynones as the carbene precursor.



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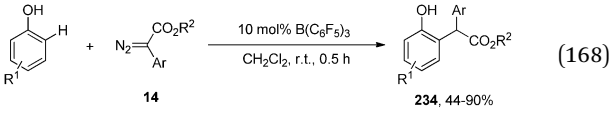
The sodium salts derived from bicyclo[2.2.2]oct-5-en-2-one underwent pyrolysis to give the corresponding intramolecular carbene insertion products *via* 1,3-hydrogen transfer as well as the β-hydride elimination as the side reaction.[486] The DFT calculations are in qualitative agreement with the ease of 1,3-hydrogen migration in these strained carbo-rings. By means of 10 mol% $B(C_6F_5)_3$ as the catalyst, phenols underwent chemo- and *ortho*-selective substitution by carbene insertion to the aromatic C–H bond with the donor/acceptor diazo compounds, that is, aryldiazoacetates (**14**), affording the desired products **234** in 44–90% yields with (eqn (168)).[487] This protocol features a wide substrate scope, mild conditions, high efficiency, and can be readily scaled up. Using the same type of carbene precursor, cyclopentane, cyclohexane, cycloheptane, and cyclooctane were functionalized in moderate to good yields at 80 °C under neat conditions.[488] Main group complexes $Tp^xZn(II)$ were also known to effect the C–H functionalization of unactivated alkanes.[489]

O-Tosylhydrazones **588** derived from diaryl ketones underwent intramolecular carbene insertion to the aromatic C–H bond in the presence of NaH which promoted generation of the diazo intermediates from the corresponding hydrazones, producing functionalized fluorene derivatives **589** in 45–99% yields (eqn (169)).[490] The reaction of α-diazo ketones with lithiated trimethylsilydiazo-methane formed 1,2,3-triazines *via* intramolecular carbene insertion to C–H bond *via* a 3-azidocyclopropene intermediate.[491] *tert*-Butyl hydroperoxide (TBHP) enabled the aryl C–H functionalization of **590** by intramolecular carbene insertion to aromatic C–H bond in the presence of $PhSO_2Na$ and KI, giving polycyclic N-heterocycles **591** (eqn (170)).[492]

Photo irradiation is an alternative strategy to render C–H functionalization by carbene insertion. Bis-diazirines **592** were used as the effective carbene precursor for the cross-linking of cyclohexane by carbene insertion under both photochemical and thermal activation conditions. Both long-wave ultraviolet (UV) irradiation (350 nm) and heating (110 °C or 140 °C) were effective in activating all the three bis-diazirines (eqn (171)).[493] Over a period of 2–7 h, 7.0–9.5% yields were obtained for **593**. This protocol was successfully applied to build the cross-linker of aliphatic polymers containing $C(sp^3)$–H bonds, which increases the mechanical strength and improves corrosion resistance of such polymers. Regioselective aryl C–H alkylation by carbene insertion with EDA was achieved by means of organic photoredox catalysis, furnishing $C(sp^2)$–$C(sp^3)$ coupled products with moderate to good regioselectivity.[494] The photo-driven protocol was also applicable for C(3)–H functionalization of indoles by carbene insertion.[357]



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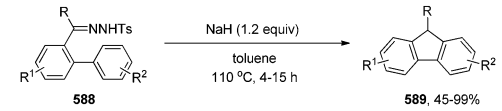

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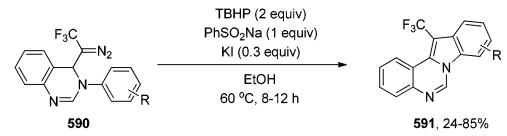
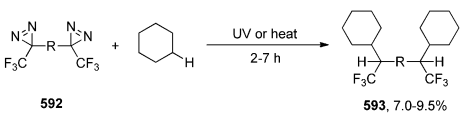


(170)

Stoichiometric reactions of carbenes with C–H substrates have been paid considerable attention.[148,491,495,496] Stable iron porphyrins bearing non-heteroatom-stabilized carbene underwent the stoichio-metric reaction with cyclohexene, tetrahydrofuran, and *tert*-butylbenzene, giving the corresponding aliphatic C–H functiona-lization products in decent yields *via* intermolecular carbene insertion to the $C(sp^3)$–H bonds.[148] Gold carbene $[Au(CH_2)]^+$ efficiently reacted with methane to form $[Au(C_2H_4)]^+$ in 84% yield.[495] *In situ* generated carbenes have also been reported to undergo intramolecular C–H functionalization. A deoxygenative insertion of carbonyl carbon to a $C(sp^3)$–H bond in **594** was achieved to access indoles and indolines **595** *via* a formal intramolecular carbene insertion to C–H process (eqn (172)).[496] The Mo/quinone complex efficiently deoxygenated carbonyl compounds bearing a neighboring dialkylamino group and effected intramolecular cyclization with insertion of a deoxygenated carbonyl carbon into a $C(sp^3)$–H bond, in which the carbonyl carbon acted as a carbene equivalent. In this case, Mo carbene **int-595** is proposed as the reactive intermediate.



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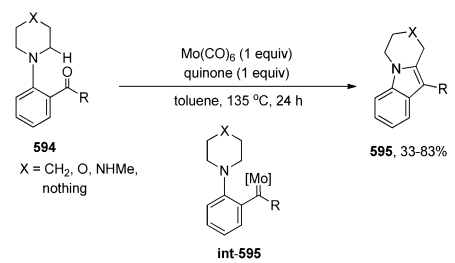

(172)

9. Perspective and outlook

C–H functionalization reactions have been paid more and more attention. In this area, those by means of transition-metal-catalyzed carbene insertion to C–H bonds can enable diverse C–H transformations in chemo- and/or stereoselective manners. The C–H bonds in non-activated alkanes, aliphatic C(sp^3)–H bonds, aryl and heteroaryl C(sp^2)–H bonds, vinyl C(sp^2)–H and alkynyl C(sp)–H bonds can be functionalized by the carbene insertion protocols. However, obvious limits still exist, such as the relatively low catalyst efficiency in the cases of handling challenging substrates such as non-activated alkanes or aliphatic C–H bonds, the poor selectivity for intermolecular functionalization of aromatic C–H bonds, functionalization of simple alkenes, as well as the low selectivity/efficiency in functionalizing complex molecules. In addition, in order to achieve decent yields and selectivity, dirhodium(II) complexes bearing big-size carboxylate ligands have been used in most cases, which pushes up the process cost. How to scale up the C–H functionalization reactions is another issue in this area. For the future work, the following aspects may be paid more attention: (1) more general catalyst- and substrate-control strategies; (2) simple and cheap catalyst systems; (3) site-selective C–H functionalization of non-activated alkanes and alkyl moieties; (4) intermolecular carbene insertion to aryl C–H bonds; (5) carbene insertion to alkenyl C–H bonds; (6) scale-up methods of C–H functionalization with diazo compounds as the carbene precursor and the related safety issue; (7) application of such strategies and methods in the modification of complex molecules. It can be expected that C–H functionalization by carbene insertion will be broadened its applicability in organic synthesis.

10. Conclusion

This review summarizes the advance in transition-metal-catalyzed C–H functionalization by carbene insertion, providing promising synthetic methods to access functionalized organic compounds and modify challenging complex compounds. The present methodologies open an alternative route to direct functionalization of simple and complex, non-activated and activated C–H molecules.

Conflicts of interest

The authors declare no conflict of interest.

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