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Halodiazoacetates as useful tools for selective halo-functionalization*

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Abstract: The halodiazoacetates are a group of synthetically useful halogenated diazo compounds that can be used in Rh(II)-catalyzed carbenoid reactions. In the reactions between the halodiazoacetates and electron-rich, sterically unhindered alkenes, halocyclopropanes are formed in good to excellent yields. The halodiazoacetates also react well in C–H and Si–H insertion reactions, broadening the synthetic utility of these reactions. The products of the reactions are synthetically useful α-halocarbonyl compounds. Density functional theory (DFT) calculations have given insight into the mechanism of the cyclopropanation and C–H insertion reactions of the halodiazoacetates, and have also shown that the halodiazoacetates have a particularly high kinetic activity.

Keywords: C–H insertion; cyclopropanation; diazo compounds; density functional theory (DFT) calculations; halogens; synthesis.

INTRODUCTION

Halogenated molecules are widely distributed in the biosphere [1–3]. Though once "considered to be rare chemical freaks of nature or artefacts formed during isolation" [1], more than 4500 halogenated natural products are now known [4], many of them chiral. Several halogenated natural products have therapeutic interest [5], and new examples are continuously discovered. The frequent utilization of fluoro- and chloro-substituents in drug design further illustrates the ability of halogens to modulate selectivity, enzymatic stability, and/or affinity of pharmaceutically active compounds [6,7]. The immense importance of alkyl halides in organic synthesis needs no explanation; substitution reactions, coupling chemistry, the list of valuable reactions is long. The desirable biological and chemical properties of halogenated molecules make the development of methods for selective introduction of halogen atoms an important challenge.

We have recently focused our work on selective halo-functionalizations through Rh(II)-catalyzed carbenoid reactions of halodiazoacetates, a group of halogenated diazo compounds [8–12]. Diazo compounds can partake in a wide range of transition-metal-catalyzed carbon–carbon and carbon–heteroatom bond-forming reactions [13–16]. The intermediacy of a carbenoid, less reactive than a free carbene, enables reactions of high chemo-, regio-, and stereoselectivities, while still allowing for high yields and mild conditions. The use of halodiazoacetates in carbenoid reactions represents a useful method for the simultaneous introduction of a halogen and an ester functionality, and gives easy access to a wide array of α-halocarbonyl compounds.

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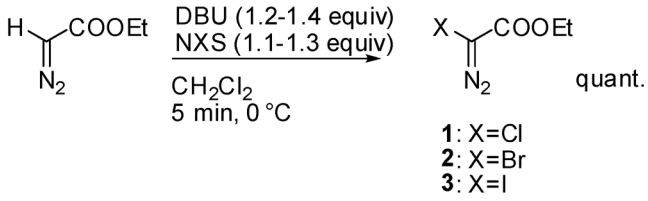
SYNTHESIS OF HALODIAZOACETATES

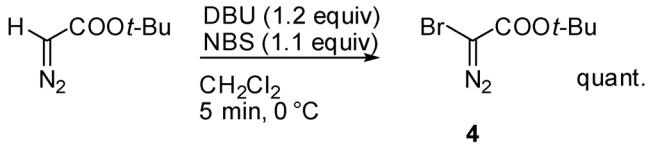
The first syntheses of α-halodiazoacetates were reported around 1970, and relied on the formation of silver or mercury derivatives of ethyl diazoacetate (EDA) as intermediates [17–21]. Treatment with an electrophilic halogenating agent gave the chlorinated, brominated, and iodinated analogues of EDA in yields ranging from 30 to 90 %. Because of the toxicity and environmental hazards associated with mercury chemistry, and the explosive nature of ethyl silverdiazoacetate, we considered it desirable to develop a new, more convenient synthetic method for generating halodiazoacetates.

Our new method for synthesis of halodiazoacetates allows for halogenation of the diazoacetate through treatment with the relatively mild base DBU and an *N*-halosuccinimide [12]. A protocol of stirring EDA with 1.2–1.4 equiv of DBU and 1.1–1.3 equiv of *N*-chloro-, bromo-, or iodosuccinimide in dichloromethane at 0 °C (Scheme 1) gives quantitative conversion of EDA to halodiazoacetates **1**–**3** in only 5 min reaction time.



Scheme 1 Synthesis of ethyl halodiazoacetates.

I_2 can be used as an alternative source of electrophilic iodine under the same conditions, giving quantitative formation of **3**. The protocol can also be employed with other diazoacetates, as exemplified in Scheme 2, where the bromination of *t*-butyl diazoacetate gives quantitative formation of bromodiazoacetate **4**. Halodiazoacetates **1**–**4**, although unstable when neat or at room temperature, can all be conveniently handled in solution at 0 °C.

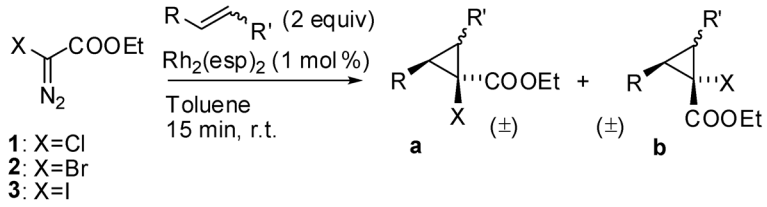


Scheme 2 Synthesis of *tert*-butyl bromodiazoacetate.

Our new method for the synthesis of halodiazoacetates is considerably "greener" than the previous mercury-based syntheses.

CYCLOPROPANATION REACTIONS WITH HALODIAZOACETATES

The cyclopropanation of alkenes with transition-metal carbenoids, most often generated from diazo compounds, has found wide applications in the synthesis of functionalized cyclopropanes [22,23], and is among the most general and best developed cyclopropanation methods available [24]. The use of halodiazoacetates in carbenoid cyclopropanation reactions with alkenes is a convenient way of synthesizing halocyclopropanes. We have developed a quick and facile procedure for these cyclopropanation reactions (Scheme 3) [12].



Scheme 3 Cyclopropanation of alkenes with ethyl halodiazoacetates.

Commercially available bis[rhodium(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)] [25], $Rh_2(esp)_2$, a robust Rh(II) complex with tethered ligands, is dissolved in toluene and added in one portion to a toluene solution of the diazo compound and the alkene, and the reaction mixture is stirred for 15 min at room temperature. The halodiazoacetate is used as the limiting reagent, and 2 equiv of alkene and a catalyst loading of 1 mol % is typically employed. Experiments with styrene as the alkene have shown that the catalyst loading can be lowered to 0.5 mol % without reduction in yield, and that a catalyst loading of 0.1 mol % also works fairly well [12]. The procedure is considerably more practical than many other reported procedures for carbenoid cyclopropanation reactions, in which dropwise addition of the diazo compound to the other reagents is necessary to avoid formation of formal carbene dimers and/or azines.

As illustrated in Table 1, entries 1–3, all three halodiazoacetates **1**–**3** react very well in cyclopropanation reactions with styrene, giving yields of 85–91 % over two steps, starting from EDA. The diastereomeric ratios are quite good, and highest (14:1) in the reaction with ethyl iododiazoacetate (**3**) and lowest (6:1) with the chlorinated analogue **1**.

Table 1 Scope of the cyclopropanation reaction with halodiazoacetates.

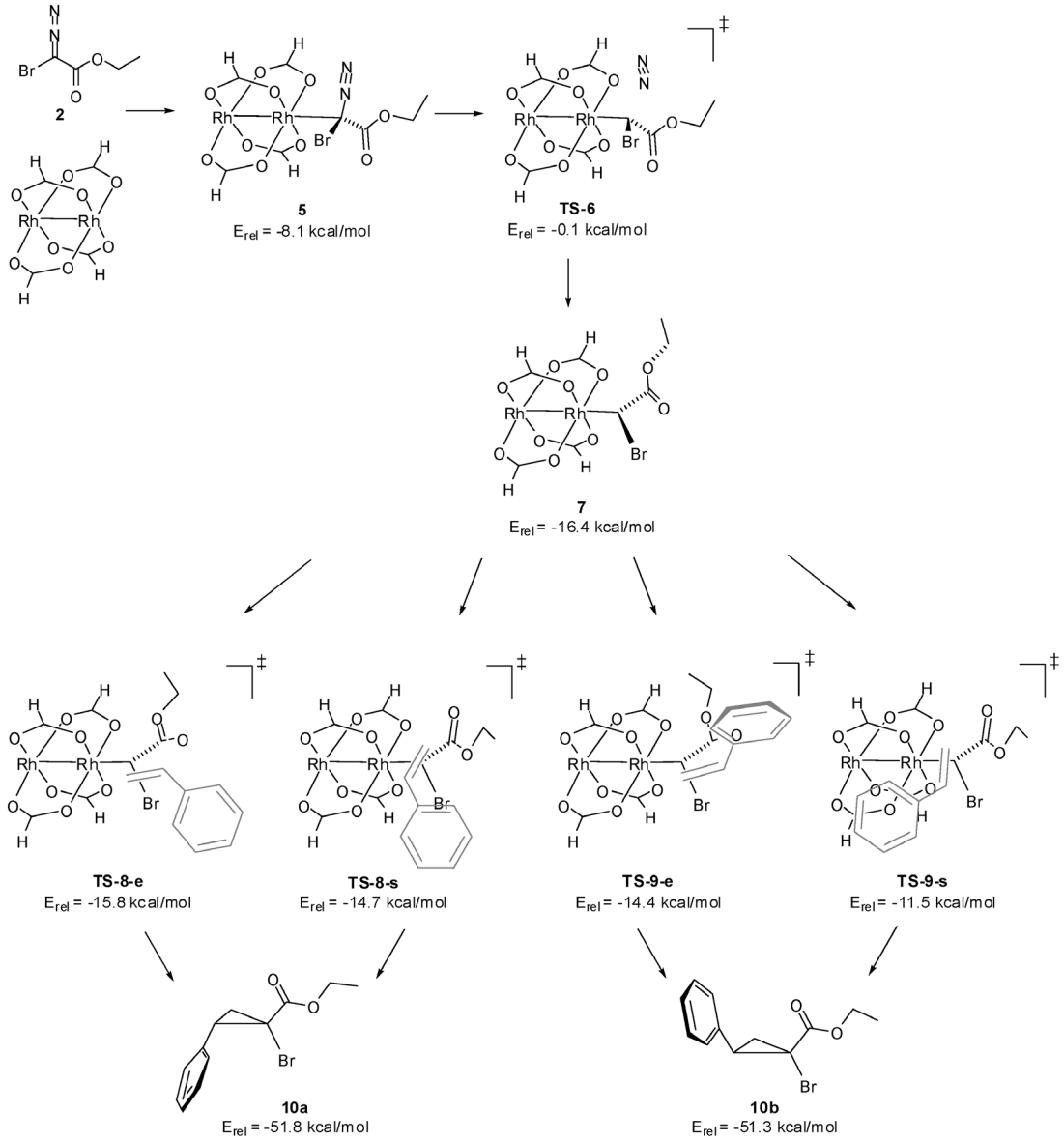
Entry	Diazo compound	Alkene	Yield[a] (%)	d.r.[b] (a:b)
1	**1**	Styrene	87	6:1
2	**2**	Styrene	91	9:1
3	**3**	Styrene	85	14:1
4	**2**	2-Vinylnaphthalene	99	9:1
5	**2**	Indene	99[c]	–
6	**2**	*N*-Vinylphthalimide	90	>20:1
7	**2**	4-MeO-styrene	87	9:1
8	**2**	4-Me-styrene	84	7:1
9	**2**	4-CF_3-styrene	83	6:1
10	**2**	1,1-Diphenylethene	79	–
11	**2**	4-Cl-styrene	77	6:1
12	**2**	*cis*-Stilbene	0	–
13	**2**	*trans*-Stilbene	0	–

[a]Isolated yield after two steps from EDA. Products purified by silica gel chromatography.
[b]Measured by ^{1}H NMR analysis of crude reaction mixture.
[c]Isolated as ethyl 2-naphthoate after 3 steps.

The halodiazoacetate cyclopropanation reaction has been tested on a range of alkenes using **2** as the diazo compound (entries 4–13). The reaction works very well with electron-rich, sterically unencumbered alkenes; yields are good to excellent with all the tested alkenes except the sterically hindered stilbenes (entries 12 and 13). Both 2-vinylnapththalene and indene (entries 4 and 5) react quantitatively.

The diastereomeric ratios of the cyclopropanation products are typically between 6:1 and 9:1, except for in the reaction with *N*-vinylphthalimide, where the diastereomeric ratio is higher than 20:1. In the reaction with indene, the cyclopropane products undergo a further, spontaneous ring expansion reaction resulting in ethyl 2-naphthoate [26,27]. This reaction goes to completion after treatment with K_2CO_3. The other halocyclopropanes are all stable. The only detected by-products are minimal amounts of the formal carbene dimers.

We have used density functional theory (DFT) calculations to study cyclopropanation reactions of the halodiazoacetates [8,10]. A full computational study of cyclopropanation reactions of **1**–**3** using model catalyst $Rh_2(O_2CH)_4$ has been performed [10], along with a more limited study using $Rh_2(esp)_2$ as the catalyst [8], which confirms the results from the full study. Scheme 4 shows the mechanism of



Scheme 4 Mechanism of the $Rh_2(O_2CH)_4$-catalyzed cyclopropanation of styrene with ethyl bromodiazoacetate.

cyclopropanation of styrene with ethyl bromodiazoacetate (**2**), catalyzed by $Rh_2(O_2CH)_4$. The structures of the reaction course for the chlorinated and iodinated **1** and **3** are very similar to those in the reaction with **2**. The structures in the reaction with **3** are slightly higher in relative energy compared to the corresponding starting materials, and with **1** slightly lower, than **2**.

The catalytic cycle is instigated by the interaction between the diazo compound and $Rh_2(O_2CH)_4$, resulting in an intermediate complex in which the diazo compound is coordinated to the catalyst through the diazo carbon (**5**). This is followed by nitrogen extrusion to give a Rh(II) carbenoid (**7**), which reacts with the substrate alkene to yield the cyclopropane.

In the reaction with **2**, the nitrogen extrusion represents a predicted barrier of 8.0 kcal/mol, making this the rate-limiting barrier of the reaction. When other complexes than **5**, bystanders to the catalytic cycle but still affecting the reaction rate, are taken into account, the barrier increases slightly to 12.7 kcal/mol. The analogous barriers with **1** and **3** are similarly low. The barriers for other studied Rh(II) catalyzed cyclopropanation reactions of diazo compounds are substantially higher [10,28], meaning that the halodiazoacetates are particularly kinetically active. Their high activity has been confirmed experimentally [10], and is reflected in their short reaction times of only 15 min in the cyclopropanation reactions.

The carbenoids formed from halodiazoacetates **1**–**3** are all considerably more stable than their respective starting materials (the diazo compound and the catalyst). Their formation is quite exothermic, and can be considered irreversible. Positive NBO charges on the carbene moieties [29,30], and a large contribution of the 2p orbital of the carbenoid carbon in the lowest unoccupied molecular orbital (LUMO) of the carbenoids, show that the carbenoids are electrophilic. Furthermore, a computational study of a range of Rh(II) carbenoids shows that the carbenoids formed from the halodiazoacetates belong to a group of relatively stable Rh(II) carbenoids [31]. The carbenoids have relatively high carbon–halogen bond orders of 1.3, indicative of a stabilizing π-interaction between the halogen and the carbenoid carbon.

For the cyclopropanation step, we found both end-on (**TS-8-e** and **TS-9-e**) and side-on trajectory (**TS-8-s** and **TS-9-s**) transition states [8,10]. The trajectory of the alkene toward the carbenoid in the transition states for cyclopropanation is a subject that has been debated. Previously, the prevalent belief was that the alkene approaches the carbenoid in a side-on manner, with the alkene perpendicular to the Rh–C axis [15], but lately, theoretical calculations have supported an end-on, or parallel, approach in which steric interactions between the carbenoid ester group and substituents on the alkene are minimized [28,32,33]. Our results show that both trajectories can be important; in the studied reactions low-energy side-on as well as end-on trajectory transition states were identified. Furthermore, we have demonstrated that both the carbenoid substituents and the substrate alkene can influence the relative energies of the trajectories of the alkene toward the carbenoid. The existence of low-energy side-on trajectory transition states has consequences for the use of models to rationalize the stereochemical outcome of carbenoid cyclopropanation reactions. Even though the end-on model satisfactorily explains the origin of the observed diastereoselectivity in certain carbenoid cyclopropanations with styrene [28], our results show that this model cannot be used exclusively in all instances, as side-on trajectory transition states also can be important. The prospect that other factors, such as the choice of catalyst, also may have an influence, cannot be ruled out. Consequently, the possible existence of more than one favored type of transition state should be taken into consideration when using models to explain or predict diastereo- and enantioselectivity in carbenoid cyclopropanation reactions.

C–H AND Si–H INSERTION REACTIONS WITH HALODIAZOACETATES

C–H insertion reactions

Carbenoid C–H insertions through Rh(II)-catalyzed reactions of diazo compounds represent an attractive method for C–H functionalization, combining selectivity with mild conditions [15,34–38]. The

field of intramolecular carbenoid C–H insertions of diazo acetates is well established [15], with a range of diazoesters reacting well, but the choice of diazo compounds for use in intermolecular C–H insertions has been limited to aryl- or vinyl-substituted diazoacetates [37,39,40]. There are few examples of C–H insertions with other classes of diazo compounds [36,41], and the need for specialized, noncommercial catalysts or inconvenient reaction procedures significantly reduces their synthetic utility.

The halodiazoacetates are a novel class of diazo compounds that can be used in intermolecular C–H insertion reactions [11]. Contrasting the often quite time-consuming reaction procedures necessary for intermolecular C–H insertion reactions with other diazo compounds, we have found that the procedure that gives the best yields for the C–H insertion reactions with halodiazoacetates is the same, practical procedure that is used for the cyclopropanation reactions.

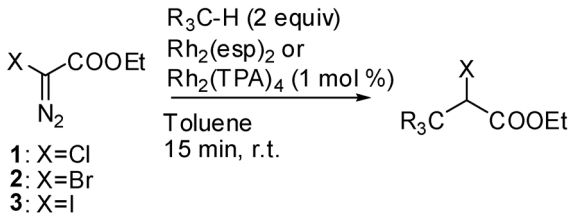
In C–H insertion reactions with 1,4-cyclohexadiene, catalyzed by dirhodium tetra(triphenylactetate), $Rh_2(TPA)_4$, diazo compounds **1**–**3** give yields of 53, 68, and 45 %, respectively, over two steps from EDA. No cyclopropanes are formed. The lower isolated yields in the reactions with **1** and **3** than with **2** may in part be explained by product instability. This is especially clear in the case of **3**, where rapid formation of free iodine is observed both during purification and storage of the C–H insertion product.

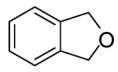
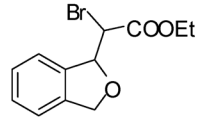
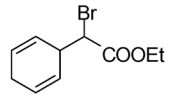
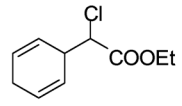
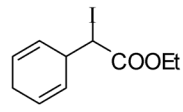
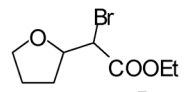
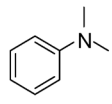
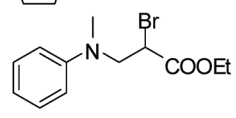
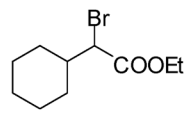
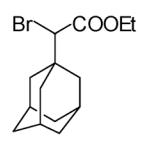
The reaction has been tested on a range of substrates, using standard halodiazoacetate **2**. All the tested substrates undergo C–H insertion reactions, with yields varying from 82 % with phthalan (entry 1) to 2 % with adamantane (entry 8). The only observed by-products are the formal carbene dimers. The regioselectivity is high and predictable in all cases, with only the most electron-rich C–H bonds reacting.

DFT calculations have given new insights into the mechanism of the C–H insertion reactions of the halodiazoacetates [9]. Using model catalyst $Rh_2(O_2CH)_4$, we have studied the reaction between **2** and the substrates methane, 1,4-cyclohexadiene and tetrahydrofuran (THF). Insertion into the simple model substrate methane was found to follow a concerted mechanism with the methane C–H bond breaking and the new C–H and C–C bonds forming in a single event, in accordance with the commonly accepted theory [38] and other computational studies [32,42,43]. The reaction is predicted to be highly exothermic. The C–H insertion step, which represents a barrier of 22.9 kcal/mol, is the rate-limiting step.

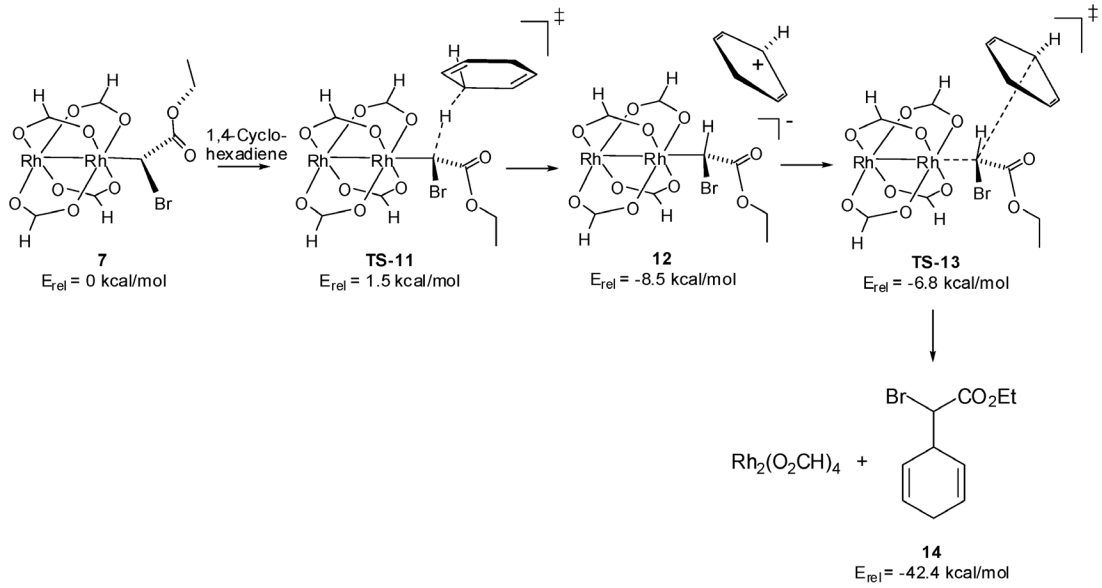
Interestingly, the reactions with 1,4-cyclohexadiene and THF, two substrates that have been tested experimentally (Table 2) [11], were found to follow two-step mechanisms. No concerted pathways could be located. The structures of the reaction course for $Rh_2(O_2CH)_4$ catalyzed C–H insertion reaction between **2** and 1,4-cyclohexadiene, from carbenoid **7** and onwards, are depicted in Scheme 5. The first step of the insertion is hydride transfer from 1,4-cyclohexadiene to carbenoid **7**, leading to a zwitterionic complex with the hydride completely transferred from 1,4-cyclohexadiene. This is then followed by C–C bond formation to give the product. The two steps represent barriers of 1.5 and 1.7 kcal/mol, respectively, meaning that the rate-determining step of the reaction is the nitrogen extrusion to form carbenoid **7** (**TS-6**).

Table 2 C–H insertion reactions with halodiazoacetates.



Entry	Diazo compound	Substrate	Product	Yield[a] (%)	d.r.[b]
1	2			82[c]	1.2:1
2	2			68[d]	–
3	1			53[d]	–
4	3			45[d]	–
5	2			63[c]	2.5:1
6	2			40[d]	–
7	2			12[d,e]	–
8	2			2[c]	–

[a]Yield over two steps from EDA, isolated after silica gel chromatography.
[b]Measured by internal standard (2-naphthaldehyde) in ^{1}H NMR analysis of crude reaction mixture.
[c]Catalyst: $Rh_2(esp)_2$.
[d]Catalyst: $Rh_2(TPA)_4$.
[e]Cyclohexane was used both as reactant and solvent.



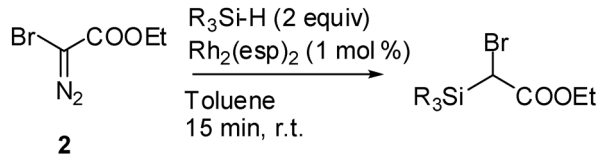
Scheme 5 Mechanism of the $Rh_2(O_2CH)_4$-catalyzed C-H insertion reaction between 1,4-cyclohexadiene and ethyl bromodiazoacetate.

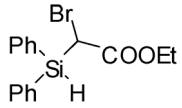
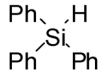
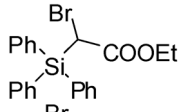
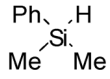
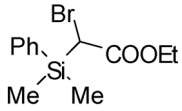
The reaction with THF follows a similar two-step mechanism with complete hydride transfer preceding C–C bond formation, and nitrogen extrusion as the rate-determining step. Both 1,4-cyclohexadiene and THF are compounds with a good ability to stabilize a positive charge on carbon in a C–H insertion reaction, which may explain why these substrates follow two-step rather than concerted mechanisms. The studied C–H insertion reactions between **2** and 1,4-cyclohexadiene or THF are the first reported examples of intermolecular Rh(II) catalyzed C–H insertion reactions in which hydride transfer precedes C–C bond formation.

Si–H insertion reactions

Halodiazoacetates can also partake in Si–H insertion reactions [11], another well-established, synthetically useful class of carbenoid reaction [15,44–46] (Table 3).

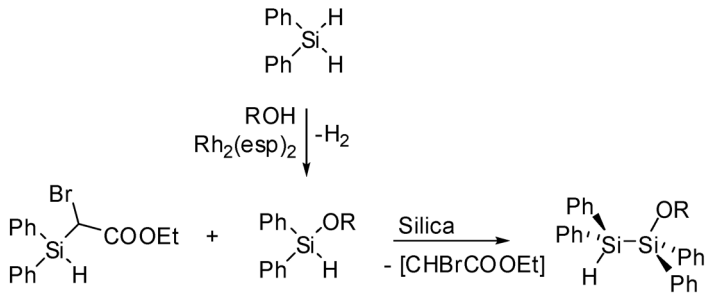
Table 3 Si–H insertion reactions with ethyl bromodiazoacetate (**2**).



Entry	Substrate	Product	Yield (%)
1			80[a]
2			51[b]
3			25[b]

[a]Yield over two steps from EDA, measured by internal standard (1,3,5-trimethoxybenzene) in ^{1}H NMR analysis of crude reaction mixture, as product decomposed on silica and alumina gel.
[b]Isolated yield after silica gel chromatography.

Si–H insertion reactions between **2** and triphenylsilane (entry 2) and dimethylphenylsilane (entry 3) give the desired products in isolated yields of 51 and 25 %, respectively. The yield of the desired product from the reaction with diphenylsilane (entry 1) has been measured to 80 % by internal standard in ^{1}H NMR. However, attempts at purifying the crude product by flash chromatography—using silica, neutral alumina, or basic alumina—result in decomposition of the product and formation of 1,1,2,2-tetraphenyldisilanol (Scheme 6). If ethanol is added to the crude reaction mixture before flash chromatography, 1-ethoxy-1,1,2,2-tetraphenyldisilane is formed instead.



Scheme 6 Plausible further transformations of the product from a Si–H insertion reaction.

These are the first examples of generation of disilanes from carbenoid Si–H-insertion products. A plausible reaction sequence for the observed transformations is outlined in Scheme 6. It is known that Rh(II) complexes, including $Rh_2(OAc)_4$, can catalyze alcoholysis of silanes [47–49]. Thus, the first step

may be $Rh_2(esp)_2$-catalyzed alcoholysis of diphenylsilane. The next step, in which the Si–H insertion product loses [CHBrCOOEt] and is coupled to the presumed silanol, has yet to be explained.

SUMMARY

Halodiazoacetates, which are precursors for a new group of halogen-substituted Rh(II) carbenoids, can be synthesized from readily available diazoacetates in a quick and facile manner. The reaction gives quantitative yields of iodo-, bromo-, and chlorodiazoacetates in only 5 min reaction time.

Rh(II)-catalyzed carbenoid reactions of the halodiazoacetates represent a new method for selective halo-functionalization. The use of the halodiazoacetates in cyclopropanation reactions gives easy access to highly substituted cyclopropanes. The halodiazoacetates give good to excellent yields and good diastereoselectivities in the cyclopropanation of electron-rich, sterically unencumbered alkenes. They are also a new class of diazo compounds that can be used in intermolecular carbenoid C–H insertion reactions, thus broadening the synthetic utility of these reactions. They also partake in Si–H insertion reactions. The products from the reactions of the halodiazoacetates are α-halocarbonyl compounds that are useful substrates for a range of further transformations.

Ethyl iodo-, bromo-, and chlorodiazoacetates have a high kinetic activity; they are very rapidly decomposed by Rh(II) catalysts. This high activity is explained by a relatively low energy barrier for nitrogen extrusion in the formation of Rh(II) carbenoids from the halodiazoacetates, as shown by DFT calculations. DFT calculations have also been used to study the mechanisms for cyclopropanation and C–H insertion reactions with the halodiazoacetates. The computational study of the cyclopropanation reaction has revealed that both end-on and side-on trajectory transition states can be of importance, and that the relative energies of these depend on both the alkene and the carbenoid substituents. These findings contrast popular belief, and should be taken into account when using models to explain or predict the stereochemical outcome of Rh(II) carbenoid cyclopropanation reactions. The study of the C–H insertion reaction has showed that the mechanism of the C–H insertion is dependent on the substrate. The insertion can follow either a concerted mechanism or a two-step path in which hydride transfer precedes C–C bond formation.

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