Highly efficient formation of halodiazoacetates and their use in stereoselective synthesis of halocyclopropanes†

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Halogenated analogues of ethyl diazoacetate are synthesised by a novel and highly efficient procedure and give halocyclopropanes in good to excellent yields when exposed to a Rh(II) catalyst in the presence of alkenes.

Halogenated molecules are widely distributed in the biosphere;[1,2] more than 4500 halogenated natural products are currently known, many of them chiral. Several halogenated natural products have therapeutic interest,[3] and new examples are continuously discovered. The frequent utilisation of chlorine and fluorine substituents in drug design further illustrates the ability of halogens to modulate selectivity, enzymatic stability and/or affinity of pharmaceutically active compounds. Within the field of organic chemistry, halogenation reactions are not only among the most historically significant reactions, but also of great practical importance. Alkyl halides can serve as precursors in numerous useful reactions, including the synthesis of carbon–carbon bonds and introduction of a wide range of functional groups. The desirable biological as well as chemical properties of halogenated molecules have spurred renewed effort in the synthetic community to develop methodologies that will allow selective introduction of halogen atoms. The most recent noticeable advances have been made in the area of α-halogenation,[4] a current example being the asymmetric, organocatalytic introduction of F, Cl and Br in the α-position to aldehydes and ketones.[5]

Diazo compounds undergo a variety of useful synthetic transformations, such as cyclopropanation and C–H insertion reactions.[6] We started looking into the synthesis of α-halodiazoacetates for utilisation in the selective formation of α-halocyclopropanecarboxylates, as a complementary approach to the already developed methodologies for selective introduction of halogens. The first syntheses of α-halodiazoacetates were reported in the literature around 1970.[7–12] These syntheses were based on mercury or silver chemistry. Diethyl mercurybisdiazoacetate was generated from ethyl diazoacetate (EDA) by treatment with mercury oxide, whereas ethyl silverdiazoacetate was synthesised by treatment of EDA with silver(I) oxide. Either of these were then treated with an electrophilic halogen source to give the desired halodiazoacetates. Decomposition, thermally or by irradiation, gave low to moderate yields and poor stereocontrol in cyclopropanation and C–H insertion reactions.

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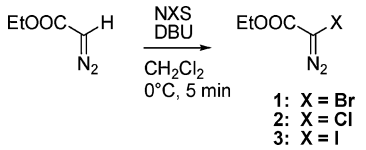
The introduction of rhodium(II) catalysts has since the mid 1970's allowed tremendous progress within the field of carbene chemistry, greatly improving the synthetic use of carbene reactions through increased chemo-, regio- and stereoselectivity. The new advances in both carbene chemistry and the synthesis of diazo compounds prompted us to go back and revisit the synthesis of halodiazoacetates and explore their reactivity in metal catalysed cyclopropanation reactions.

Because of the toxicity and environmental hazards associated with mercury chemistry, and the explosive nature of ethyl silverdiazoaceate,[7] we wanted to pursue a new way of synthesising α-halodiazoacetates. We started our investigations by searching for a mild base that would be strong enough to deprotonate EDA, as the use of strong bases such as LDA and *n*-BuLi typically requires low reaction temperatures. DBU, recently used to promote aldol and Mannich reactions with EDA,[13] proved to be a good choice. *N*-Halosuccinimides were selected as electrophilic halogenation reagents. In our first attempt to synthesise ethyl diazobromoacetate (**1**) from EDA we used DBU and NBS in dichloromethane at 0 °C (Scheme 1).



Scheme 1 Formation of halogenated EDA-analogues.

These reaction conditions gave quantitative conversion of EDA to **1** in less than 5 min. After some screening, we were able to obtain quantitative yields of **1**, **2** and **3** using 1.4–1.6 equiv. of DBU and 1.3–1.5 equiv. of NBS, NCS, NIS or I_2. Triethylamine could also be used as a base, but the reaction was much slower, and it was difficult to reach full conversion of EDA.

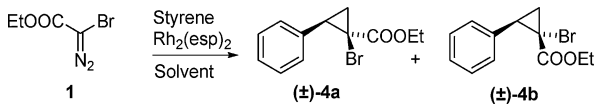
One potential problem with diazo compounds is their thermal instability and decomposition when exposed to heat and light. Commercially available EDA itself is relatively stable when neat and can be stored in the fridge for months. The halogenated EDA-analogues are less stable, and decompose within hours at room temperature, both as neat compounds and in solution. However, all three halogenated EDA-analogues can be conveniently handled in solution at 0 °C.[9]

After having established an efficient procedure for the synthesis of the halogenated EDA-analogues, we turned to the use of these diazo compounds in the cyclopropanation of alkenes. Styrene was selected as the alkene in our initial attempts to make 1-bromocyclopropanecarboxylates **4** (Scheme 2). Selected results from experiments with different reaction conditions are shown in

Table 1 Cyclopropanation of styrene with **1**. Screening of reaction conditions

Entry	Catalyst loading (mol%)	Solvent	Additive	Yield of **4** (%)[a]	Diastereomeric ratio (**4a** : **4b**)[f]
1	5	CH_2Cl_2[c]	—	17	6 : 1
2	1	CH_2Cl_2[c]	15 mol% $Na_2S_2O_3$	11	6 : 1
3	1	CH_2Cl_2[c]	15 mol% Cu	25	7 : 1
4	1	CH_2Cl_2[c]	1 equiv. Cu	24	6 : 1
5	1	CH_2Cl_2[d]	15 mol% Cu	33	6 : 1
6	1	CH_2Cl_2[e]	15 mol% Cu	20	ND
7	1	Dry CH_2Cl_2[d]	15 mol% Cu	58	7 : 1
8	1	Dry toluene[d]	15 mol% Cu	86[b]	9 : 1
9	1	Dry toluene[d]	—	91[b]	9 : 1
10	0.5	Dry toluene[d]	—	90	7 : 1
11	0.1	Dry toluene[d]	—	81	7 : 1

[a] Measured by internal standard (2-naphthaldehyde) in ^{1}H NMR analysis of crude reaction mixture. [b] Isolated yield. [c] Dropwise addition of dilute solution of **1** to styrene and Rh_2esp_2 in DCM over 3 h at rt; total reaction volume *ca.* 50 mL; stirring for additional 15 min. [d] Bulk addition of solution of $Rh_2(esp)_2$ to dissolved **1** and styrene at rt; stirring for 15 min. [e] Bulk addition of solution of $Rh_2(esp)_2$ to dissolved **1** and styrene at 0 °C, stirring for 15 min. [f] Measured by ^{1}H NMR analysis of crude reaction mixture.



Scheme 2 Synthesis of ethyl 1-bromo-2-phenylcyclopropanecarboxylate.

Table 1. Freshly prepared **1** was used in all the experiments since formation of **1** from EDA was quantitative within 5 min reaction time. The dichloromethane solution of **1** was washed with aq. $Na_2S_2O_3$ and passed quickly through a plug of silica gel before the cyclopropanation reaction was initiated. Our earlier positive experiences[14,15] with commercially available $Rh_2(esp)_2$,[16] a robust Rh(II) catalyst with bidentate ligands, made this catalyst a natural choice.

Our starting point was the common procedure for cyclopropanation with EDA and many other diazo compounds,[6] dropwise addition (3 h) of a cold, diluted dichloromethane solution of the diazo compound to alkene and catalyst (entry 1). We were delighted to find that formation of **4** had taken place. However, the yield was low, and products from carbene dimerisation abundant. Copper powder or $Na_2S_2O_3$, both additives known to stabilise alkyl halides, were added to the reaction mixture in attempts to prevent any undesired decomposition of the diazo compound (entries 2–8). Whereas $Na_2S_2O_3$ gave a slight reduction in yield, the copper powder had a minor positive effect. The main reason for doing a dropwise addition of the diazo compound to the catalyst solution is to prevent dimer formation. In a simplification of the experimental procedure, the time consuming dropwise addition of the diazo compound was proved unnecessary. Addition of the dissolved catalyst to a solution of diazo compound and styrene, followed by stirring for 15 minutes at room temperature, was just as effective. Addition of the catalyst at room temperature (entry 5) was more advantageous than addition at 0 °C (entry 6). The yields were not significantly improved, however, demonstrating that the main competing reaction, the carbene dimerisation, happened quickly in the reaction mixture and not in the dichloromethane solution of **1** during the slow addition.

Performing the reaction under dry conditions drastically improved yields (entry 7). As Kim *et al.* have noted,[17] the efficiency of $Rh_2(esp)_2$ may in certain cases be improved by the use of toluene as solvent. This solvent effect was observed in our case as well; switching from dichloromethane to toluene gave another large improvement in yield (entry 8). Only traces of the carbene dimerisation products could be detected. Eliminating the copper additive took the yield of **4** from 86% to 91% (entry 9), and it was also shown that lower catalyst loadings could be used with satisfactory results (entries 10 and 11).

The diastereomeric ratio of the products from the cyclopropanation reaction was persistently in the area 6 : 1–9 : 1, which is consistent with cyclopropanation reactions with diazo compounds bearing two electron withdrawing groups.[6] The major diastereomer, mirroring the results of cyclopropanation with EDA, was the diastereomer with the phenyl group and the ester function in a *trans* relationship (**4a**).

Cyclopropanation of styrene with the chlorinated and iodinated EDA-analogues **2** and **3** also worked very well, giving cyclopropanes analogous to **4**, with yields and diastereomeric ratios comparable to the results observed in the reactions with **1**. Table 2 shows the results from cyclopropanation using the conditions described in Table 1, entry 9.

The scope of the cyclopropanation reaction was examined by reaction between **1** and a range of alkenes with varying electronic and steric properties, using the same reaction conditions (Table 3).

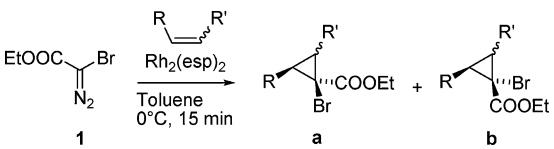


Table 2 Cyclopropanation of styrene with compounds **1–3**

Entry	Diazo compound	Yield (%)[a]	Dr (**a** : **b**)[b]
1	Ethyl diazobromoacetate (**1**)	91	9 : 1
2	Ethyl diazochloroacetate (**2**)	87	7 : 1
3	Ethyl diazoiodoacetate (**3**)	85	9 : 1

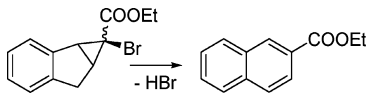
[a] Isolated yield after silica gel chromatography. [b] Measured by ^{1}H NMR analysis of crude reaction mixture.

Table 3 Scope of cyclopropanation reaction with **1**

Entry	Alkene	Yield (%)[a]	Dr (**a** : **b**)[b]
1	Styrene	91	9 : 1
2	2-Vinylnaphthalene	99	9 : 1
3	Indene	99[c]	—
4	*N*-Vinylphthalimide	90	> 20 : 1
5	4-MeO-styrene	87	9 : 1
6	4-Me-styrene	84	7 : 1
7	4-CF_3-styrene	83	6 : 1
8	1,1-Diphenylethene	79	—
9	4-Cl-styrene	77	6 : 1
10	*cis*-Stilbene	0	—
11	*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 alkenes of entries 1–9 gave good to excellent yields, with both 2-vinylnapththalene and indene reacting quantitatively. For indene, the cyclopropane products underwent a further, spontaneous reaction (Scheme 3), resulting in ethyl 2-naphthoate.[18] The reaction went to completion after treatment with K_2CO_3.



Scheme 3 Further reaction of products formed in cyclopropanation reaction with indene.

Five different styrene derivatives with electron-donating or electron-withdrawing substituents in the 4-position were screened (entries 5–7, 9). There seemed to be a slight correlation between the electronic effects of the substituents and the yields, the styrenes with electron-donating substituents giving somewhat higher yields than the styrenes with electron-withdrawing substituents. 1,1-Diphenylethene was a relatively good substrate in the reaction, but *cis*-stilbene and *trans*-stilbene (entries 10 and 11) were completely unreactive towards cyclopropanation, perhaps due to the more sterically encumbered double bonds of the latter. The diastereomeric ratios (dr) of the cyclopropanation products from all the reactions were between 6 : 1 and 9 : 1, except for the case of *N*-vinylphthalimide (entry 4), where the dr was higher than 20 : 1.

The relative stereochemistry of the major diastereomer of **4** was determined by NOESY experiments. We probed the possibility for an asymmetric version of this cyclopropanation reaction by using two chiral Rh(II) catalysts, Rh_2(DOSP)$_4$ and Rh_2(PTTL)$_4$.[19] Both catalysts gave good yields of **4**, but the asymmetric induction was below 10% ee.

In summary, we have developed a novel procedure for the synthesis of halogenated analogues of EDA, employing EDA, DBU and a mild halogenating agent. Ethyl diazobromoacetate (**1**), -chloroacetate (**2**) and -iodoacetate (**3**) are generated quantitatively from EDA in only 5 minutes. The halogenated diazo compounds have been used in Rh(II) catalysed cyclopropanation of a range of olefins. The experimental procedure for the cyclopropanation is quick and simple, with no need for dropwise addition of the diazo compound, and the reaction gives good to excellent yields and a diastereomeric ratio of up to 20 : 1 with electron-rich, sterically unencumbered alkenes. This new synthesis of 1-halocyclopropanecarboxylates represents a novel method for stereoselective introduction of halogens and broadens the range of easily accessible α-halo carbonyl compounds.

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