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Nucleophilic Halogenations of Diazo Compounds, a Complementary Principle for the Synthesis of Halodiazo Compounds: Experimental and Theoretical Studies

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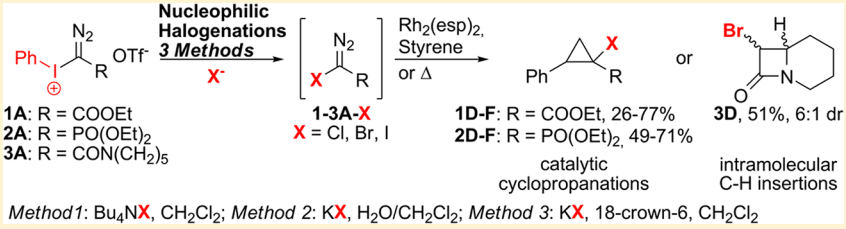
Supporting Information



ABSTRACT: Three new protocols for the nucleophilic halogenations of diazoesters, diazophosphonates, and diazopiperidinylamides as complementary methods to our previously reported electrophilic halogenations are presented for the first time. On the basis of hypervalent α-aryliodonio diazo triflate salts **1A**, **2A**, and **3A**, the corresponding halodiazo compounds are generated via nucleophilic halogenations with tetrabutylammonium halides or potassium halides. The products from subsequent catalytic intermolecular cyclopropanations of the halodiazoesters and halodiazophosphonates and thermal intramolecular C−H insertion of the brominated diazopiperidinylamide are obtained in moderate to good yields after two steps. DFT calculations are presented for the diazoesters to give insight into the mechanism and transition states of the nucleophilic substitutions with the neutral nucleophiles dimethyl sulfide and triethylamine and the bromination with Br^-.

INTRODUCTION

Diazo compounds are valuable organic compounds for several transformations,[1] among which their ability to generate carbenoids in combination with an appropriate transition-metal catalyst has found wide applications.[2] These carbenoids can undergo important reactions[3] such as cyclopropanations,[4] C−H insertions,[5] and ylide transformations,[6] among others. Several methods for the synthesis of diazo compounds are known, and the majority consist of introducing the diazo functionality into a prefunctionalized starting material.[7] The inherent instability of the diazo compounds, however, often is a limitation to the reaction conditions that can be applied. Methods for direct functionalizations of diazo compounds at the diazo carbon under preservation of the diazo group, on the other hand, are scarce and only the electrophilic substitution in which the diazo compound reacts as a nucleophile has been thoroughly explored.[8] We have previously shown that the synthesis of thermally unstable halodiazo compounds can be achieved in a mild and efficient way via a deprotonation−electrophilic halogenation sequence with *N*-halosuccinimides and DBU or NaH as a base.[9] The availability of reagents for the transfer of atoms or groups as electrophiles, however, is limited, especially with regard to the transfer of heteroatoms.

A complementary direct functionalization of diazo compounds was reported by Robert Weiss et al.[10] in 1994 in which a nucleophilic substitution on diazoesters was performed for the first time. The preparation of hypervalent α-aryliodonio diazoester triflate **1A** was followed by nucleophilic substitution with the neutral nucleophiles NEt_3, SMe_2, pyridine, $AsPh_3$, and $SbPh_3$ to generate the corresponding α-onium triflate salts (Scheme 1). This alternative approach to the electrophilic substitution has to the best of our knowledge not found applications for the synthesis of other diazo compounds, but has a great potential given the large amount of nucleophiles available. We wanted to apply this methodology in nucleophilic halogenations[11] on different classes of diazo compounds as an alternative method to the electrophilic halogenations and looked to gain insight into the mechanism of the nucleophilic substitutions by DFT calculations.

RESULTS AND DISCUSSION

α-Onium diazoester triflates **1A**, **1B**, and **1C** were prepared according to the described literature procedure[10] starting from ethyl diazoacetate (EDA) to prepare α-aryliodonio diazoacetate triflate **1A**, followed by nucleophilic substitutions of **1A** with dimethyl sulfide (**1B**) or triethylamine (**1C**), respectively, which occur readily at room temperature (Scheme 2a; the corresponding phosphonates and amides will be discussed later in the paper). The X-ray crystal structure of α-aryliodonio diazoacetate triflate **1A** was reported by Weiss et al.,[10] and we were able to obtain X-ray crystal structures of the α-

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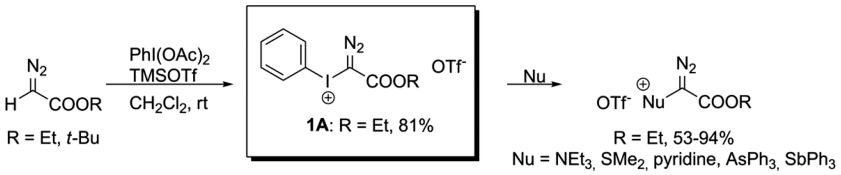
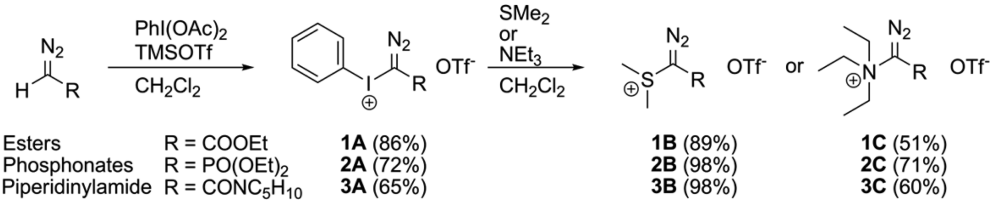
Scheme 1. Nucleophilic Substitution with α-Aryliodonio Diazoester 1A by Weiss et al.[10]



Scheme 2. Preparation of α-Onium Diazoesters 1A–1C, α-Onium Diazophosphonates 2A–2C, and α-Onium Diazopiperidinylamides 3A–3C



dimethylsulfonium diazoacetate triflate **1B** and α-triethylammonium diazoacetate triflate **1C**.[12]

α-Aryliodonio diazoacetate triflate **1A** was chosen as the substrate for the nucleophilic halogenations because iodobenzene is the best and most inert leaving group compared to dimethyl sulfide and triethylamine. Furthermore, dimethyl sulfide and triethylamine could coordinate and deactivate the catalyst in the following cyclopropanation step and could also undergo unwanted side reactions, such as C–H insertions or ylide formations. However, investigation of the reactivities of compounds **1B** and **1C** in catalytic carbenoid reactions are ongoing in our laboratories. Compound **1C** formally contains an amino acid fragment, which makes this compound particularly interesting.

To develop a new route to halogenated diazo compounds, initial nucleophilic halogenation experiments were performed with tetrabutylammonium halides (TBAX, X = I, Br, Cl) as the halide sources (method 1). Addition of TBAX to **1A** in dichloromethane at 0 °C showed rapid conversion to the corresponding bromo- and iododiazoacetates **1A-Br** and **1A-I** and slower conversion to the chlorodiazoacetate **1A-Cl** (monitored by TLC analysis and ^{1}H NMR, Scheme 3a).[13] Fluorination with TBAF was also attempted, but no conversion was detected, probably due to the low nucleophilicity of the fluoride ion.

Having demonstrated the nucleophilic halogenation to be a new method to generate the corresponding halogenated diazoesters, we investigated their dirhodium(II)-catalyzed intermolecular cyclopropanation. Styrene and 2 mol % $Rh_2(esp)_2$[14] in toluene as the solvent was chosen as a test system, since it was most efficient in our previously reported electrophilic halogenations.[9] The corresponding halocyclopropyl esters **1D–1F** were obtained in moderate yields of 50–67% over two steps and good diastereomeric ratios in favor of the *trans* diastereomer (Table 1, method 1). Although the yields of the isolated cyclopropanes were lower compared to those obtained with the electrophilic halogenation, a convenient alternative method for the nucleophilic halogenation of diazo esters was achieved for the first time and opens numerous possibilities for further investigations.

After these initial results we wanted to test alternative procedures for the nucleophilic halogenations. Potassium halides were chosen as halide sources and a biphasic system with water and dichloromethane as the reaction medium.[15] After the biphasic reaction mixture containing KX (X = I, Br, Cl) and **1A** was stirred at 0 °C (10 min for X = I and Br and 30 min for X = Cl), the organic phase was separated and passed through a Celite/$MgSO_4$ plug into a flask containing toluene at 0 °C, and the dichloromethane was removed in vacuo at 0 °C. Following addition of styrene and $Rh_2(esp)_2$ to the residual toluene solution, the catalytic cyclopropanation gave the same yields of 66% for **1D** and **1E** (X = I and Br) and a lower yield of 26% for **1F** (X = Cl) compared to method 1 (Table 1, method 2). The ^{1}H NMR spectra of the crude reaction mixture contained less impurities compared to those for method 1 because the byproducts potassium triflate, iodobenzene, and styrene could be easily removed by phase separation and evaporation in vacuo.

As a third method, a one-phase system with 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6) solubilized potassium halides in dichloromethane was tested. The yield of the bromocyclopropyl ester **1E** increased to 77%, whereas the yield for iodocyclopropyl ester **1D** decreased to 49%. Unfortunately, no chlorinated diazo compound was obtained due to insolubility of the potassium chloride in dichloromethane with 18-crown-6 (Table 1, method 3).

Among the three protocols developed for the nucleophilic halogenations, the highest yields for the iodocyclopropyl ester **1D** were achieved with methods 1 and 2 (65% and 66%), for the bromocyclopropyl ester **1E** with method 3 (77%), and for the chlorocyclopropyl ester **1F** with method 1 (50%). The diastereoselectivity was >7:1 in favor of the *trans* diastereomer for all products. Thus, three new protocols for the nucleophilic halogenations of diazoesters were developed for the first time and added as alternative methods to the generation of halodiazoacetates.

Having demonstrated that the nucleophilic halogenation of diazoesters is a complementary synthetic method to the electrophilic halogenation, we performed DFT calculations to understand the mechanism and describe the transition states of the nucleophilic substitutions with dimethyl sulfide, triethylamine, and bromide and to support our experimental observations.

Calculations were performed on the Gaussian 09 program package[16] using the hybrid density functional B3LYP.[17] All atoms except iodine were described by the 6-31+g(d,p) basis set.[18] Iodine was described by the LanL2DZ basis set.[19] All calculations were performed using the continuum solvation

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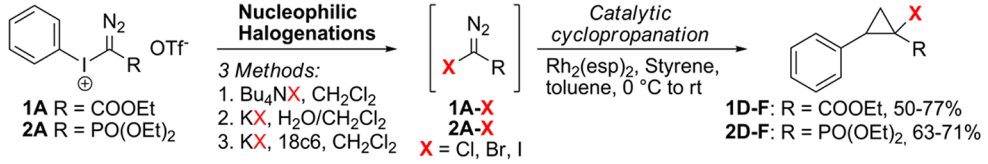
Scheme 3. Nucleophilic Halogenations of α-Aryliodonio Diazoacetate 1A and α-Aryliodonio Diazophosphonate 2A with Methods 1−3 and the Following Catalytic Intermolecular Cyclopropanation[a]



[a]The phosphonates will be discussed later in the paper.

Table 1. Isolated Yields of Halocyclopropyl Esters 1D−1F from 1A with Methods 1−3

			yield[a] (%) (dr (*trans*:*cis*))[b]			
entry	X, **1A**	product	method 1[c]	method 2[d]	method 3[e]	electrophilic[9b−d]
1	I	**1D**	65 (8:1)	66 (8:1)	49 (9:1)	85 (9:1)
2	Br	**1E**	67 (8:1)	66 (8:1)	77 (7:1)	91 (9:1)
3	Cl	**1F**	50 (7:1)	26 (7:1)		87 (7:1)

[a]Isolated yields of both diastereomers after two steps after column chromatography. [b]Estimated by ^{1}H NMR spectra of the crude product mixture. [c]Reagents and conditions: **1A** (0.1−0.2 mmol) dissolved in dry CH_2Cl_2 (1−2 mL), 0 °C, TBAX (1.5 equiv) added, 1 h at 0 °C, SiO_2 plug optional, CH_2Cl_2 exchange with dry toluene (0 °C, 2 mL), styrene (5 equiv), 2 mol % $Rh_2(esp)_2$ (1 mL of dry toluene), 0 °C to rt. [d]Reagents and conditions: **1A** (0.1−0.2 mmol) dissolved in dry CH_2Cl_2 (1 mL), 0 °C, KX (1.5 equiv) in H_2O (1 mL) added, 0 °C for 10−30 min, $MgSO_4$/Celite plug (CH_2Cl_2, −30 °C), CH_2Cl_2 exchange with dry toluene (0 °C, 2 mL), styrene (5 equiv), 2 mol % $Rh_2(esp)_2$ (1 mL of dry toluene), 0 °C to rt. [e]Reagents and conditions: KX (1.5 equiv) and 18-crown-6 (2 equiv) dissolved in dry CH_2Cl_2 (1 mL), 0 °C, **1A** (0.1−0.2 mmol) added, 0 °C for 1 h, CH_2Cl_2 exchange with dry toluene (2 mL), styrene (5 equiv), 2 mol % $Rh_2(esp)_2$ (1 mL of dry toluene), 0 °C to rt.

model CPCM with dichloromethane as the solvent.[20] All structures were fully optimized without any geometry or symmetry constraints. Each stationary point was identified as either a minimum or a saddle point by analytical calculation of the frequencies. The connectivity between different structures was verified by following the intrinsic reaction coordinates (IRCs) from each saddle point.

The nucleophilic substitutions of α-aryliodonio diazoacetate triflate **1A** with SMe_2 to the α-dimethylsulfonium diazoacetate triflate **1B** and with NEt_3 to the α-triethylammonium diazoacetate triflate **1C** proceed via calculated energy-minimized transition states **TS-1B**‡ and **TS-1C**‡ (Figure 1) at room temperature. The energy of transition state **TS-1B**‡ is calculated to be 19.4 kcal mol^{-1} and the energy for **TS-1C**‡ 18.9 kcal mol^{-1}, and the relative energies of the products are −32.2 kcal mol^{-1} for **1B** and −39.3 kcal mol^{-1} for **1C**, which explains the high driving force for the reaction. The substitution of α-dimethylsulfonium diazoacetate triflate **1B** with triethylamine, however, would proceed via transition state **TS-1BC**‡ with an energy barrier of 39.3 kcal mol^{-1} relative to **1B**, which is twice as high as for the two other transition states and confirmed the experimental result that no reaction of **1B** with NEt_3 was observed at room temperature.

For the bromination of **1A** with TBAB an ion exchange from triflate to bromide prior to the nucleophilic substitution step is assumed (**1ABr**). An energy gain of 5.9 kcal mol^{-1} for **1ABr** results, and the transition state **TS-1A-Br**‡ is calculated to have an energy barrier of 29.3 kcal mol^{-1} relative to **1ABr**. The α-bromodiazoacetate **1A-Br** is 25.7 kcal mol^{-1} lower in energy relative to **1ABr** and 31.6 kcal mol^{-1} in relation to the triflate salt **1A** (Figure 2).

In the case of the α-dimethylsulfonium diazoacetate triflate **1B** an energy barrier of 35.7 kcal mol^{-1} for the nucleophilic bromination results in an impractical reaction rate at room temperature. Furthermore, the energy difference of **1BBr** and product **1A-Br** would be positive, 2.1 kcal mol^{-1} (energy profile shown in the Supporting Information). The barrier for the nucleophilic bromination of α-triethylammonium diazoacetate triflate **1C** would be even higher, 43.3 kcal mol^{-1}, and the product **1A-Br** 8.6 kcal mol^{-1} higher in energy compared to **1CBr**. Both theoretical results correspond to the experimental observation that no bromination with **1B** and **1C** occurred.

The geometries of the energy-minimized calculated transition states **TS-1B**‡, **TS-1C**‡, and **TS-1A-Br**‡ are depicted in Figure 3. The bond distances of the nucleophile−carbon bond (Nu−C, Nu = SMe_2, NEt_3, Br^-) and leaving group−carbon bond (LG−C, LG = IPh) are displayed. In all transition states the bond distances of the developing Nu−C bond and the breaking LG−C bond are lengthened compared to those of the starting material **1A** and the corresponding products.[21] In **TS-1B**‡ the LG−C bond difference is $\Delta(LG-C)_{1B}$ = 0.45 Å (21%) compared to the starting material **1A** (2.10 Å in **1A** compared to 2.55 Å in **TS-1B**‡) and the Nu−C bond difference is $\Delta(Nu-C)_{1B}$ = 1.03 Å (59%) (Nu = SMe_2) compared to the product **1B** (2.79 Å in **TS-1B**‡ compared to 1.76 Å in **1B**). For **TS-1C**‡ the $\Delta(LG-C)_{1C}$ of 0.44 Å (21%) is similar to that in **TS-1B**‡, but the $\Delta(Nu-C)_{1C}$ (Nu = NEt_3) of 1.22 Å (82%) is significantly higher compared to that of **TS-1B**‡. In the case of the bromination, the bond difference $\Delta(LG-C)_{1A\text{-}Br}$ in **TS-1A-Br**‡ is 0.36 Å (17%) compared to **1ABr** and $\Delta(Nu-C)_{1A\text{-}Br}$ = 0.75 Å (40%) compared to the bromodiazoacetate **1A-Br** (2.64 Å compared to 1.89 Å in **1A-Br**). The differences Δ(Nu−C) in all transition states are significantly larger than the differences for the LG−C bonds, Δ(LG−C), compared to the corresponding starting materials and products. This indicates asynchronous, reactant-like transition states, which is in accordance with the Hammond postulate[22] for an exergonic reaction.

The Nu−C−LG angle of attack in **TS-1B**‡ (Nu = SMe_2) is almost linear at 161.2°, and the angle of attack on the diazo carbon (Nu−C−N) is 89.4°. The Nu−C−LG angle in **TS-1C**‡ (Nu = NEt_3) of 163.1° is similar to that in **TS-1B**‡; the angle of attack on the C═N bond, however, is smaller, only 83.5°. In **TS-1A-Br**‡, for the bromination, the Nu−C−LG (Nu = Br^-) angle of 83.2° is significantly smaller compared to those in **TS-1B**‡ and **TS-1C**‡, which could result from stronger Coulomb

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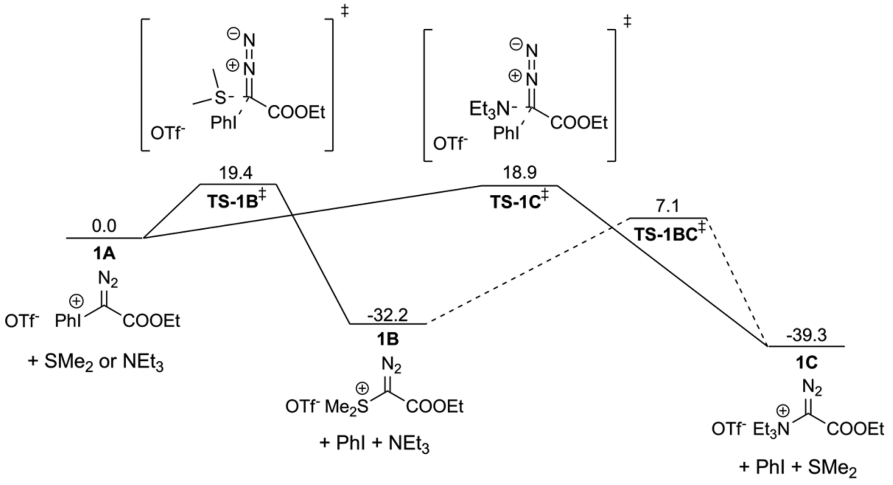

Figure 1. Energy profile for the nucleophilic substitutions of **1A** with SMe_2 and NEt_3 to **1B** and **1C** at room temperature. The energies are relative energies with **1A** as the zero point and are reported in kilocalories per mole.

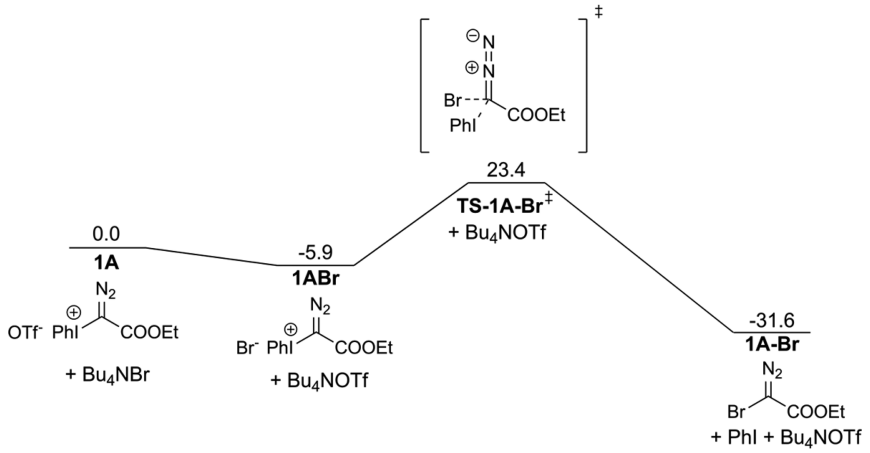

Figure 2. Energy profile for the nucleophilic bromination of **1A** with TBAB at room temperature. Energies are reported in kilocalories per mole.

interactions between the bromide and the partially positively charged iodine atom. The Nu−C−N angle of attack of the bromide on the C═N bond of 102° is significantly larger than the angles of the incoming SMe_2 and NEt_3. For the nucleophilic substitutions of **1A** with Me_2S and Et_3N the transition states resemble an S_N2-type mechanism, whereas for the bromination a tetrahedral-like transition state indicates a carbonyl-like addition−elimination reaction mechanism.

The obtained computational results are in agreement with the experimental observations and give insight into the mechanism of the nucleophilic substitutions of the prepared α-onium diazoester **1A** as concerted, asynchronous, and dependent on the leaving group and nucleophile.

Having shown the possibility of nucleophilic halogenations of diazoesters, we wanted to extend and apply this methodology to other classes of diazo compounds. Diazophosphonates[23] are another widely used class of diazo compounds, and we recently reported their electrophilic halogenations.[9a] The phosphonate analogues **2A**, **2B**, and **2C** were prepared in a manner similar to that of the esters **1A**−**1C** in good to excellent yields (Scheme 2b). α-Aryliodonio diazophosphonate triflate **2A**, however, is thermally less stable than the corresponding ester **1A** and had to be kept below 5 °C to avoid thermal decomposition by loss of iodobenzene.[24] Compound **2A** is a yellow solid, whereas the α-dimethylsulfonium diazophosphonate triflate **2B** and the α-triethylammonium diazophosphonate triflate **2C** are oils which were thermally more stable than **2A**. With these new compounds in hand, we investigated the nucleophilic halogenations of **2A** followed by cyclopropanation of **2A-X** in analogy to the ester **1A** (Scheme 3b).

The cyclopropanations with the halogenated diazophosphonates **2A-X** via the tetrabutylammonium halides (method 1) gave medium yields of the corresponding halocyclopropylphosphonates **2D**−**2F**, with the brominated product **2E** formed in the highest yield of 71%. The chlorinated cyclopropane **2F** was obtained in 63% yield and the iodocyclopropylphosphonate **2D** in 66% yield (Table 2, method 1).

Changing to the biphasic method 2 increased the yield of the iodocyclopropylphosphonate **2D** slightly to 70% with a decrease in yield for the brominated analogue **2E** to 55%. The chlorocyclopropylphosphonate **2F**, as in the case of the diazoester, was only obtained in a low yield.

Method 3 gave a yield of 66% of **2E** and a lower yield of 49% for **2D**. As for the ester **1A**, no chlorination with KCl could be achieved with this method.

The isolated yields of the halocyclopropylphosphonate **2D**−**2F** via the nucleophilic halogenation were approximately 10% lower than the yields obtained with our previously reported electrophilic halogenations. However, we have demonstrated for the first time that the nucleophilic halogenation can be

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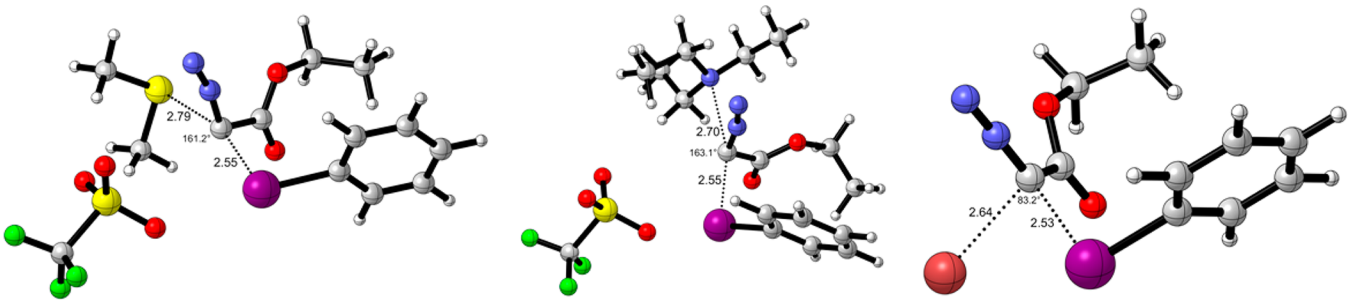

Figure 3. Geometries of calculated transition states **TS-1B**‡ (left), **TS-1C**‡ (middle), and **TS-1A-Br**‡ (right) and relevant bond lengths in angstroms and angles (Nu = SMe_2, NEt_3, Br^-, LG = IPh).

Table 2. Isolated Yields of Halocyclopropylphosphonate 2D−2F with Methods 1−3

			yield[a] (%) (dr (*trans*:*cis*))[b]			
entry	X, **2A**	product	method 1[c]	method 2[d]	method 3[e]	electrophilic[9a]
1	I	**2D**	66 (12:1)	70 (12:1)	49 (13:1)	77 (16:1)
2	Br	**2E**	71 (12:1)	55 (12:1)	66 (11:1)	82 (12:1)
3	Cl	**2F**	63 (12:1)	<10		77 (12:1)

[a]Isolated yields of both diastereomers after two steps after column chromatography. [b]Measured by ^{1}H NMR spectra of the crude product mixture. [c]Reagents and conditions: **2A** (0.1−0.2 mmol) dissolved in dry CH_2Cl_2 (2 mL) at 0 °C, TBAX (1.5 equiv) added, 1 h at 0 °C, CH_2Cl_2 exchange with dry toluene (0 °C, 2 mL), styrene (5 equiv), 2 mol % $Rh_2(esp)_2$ (1 mL of dry toluene), 0 °C to rt. [d]Reagents and conditions: **2A** (0.1−0.2 mmol) dissolved in dry CH_2Cl_2 (1 mL), 0 °C, KX (1.5 equiv) in H_2O (1 mL) added, 0 °C for 30 min to 1 h, $MgSO_4$/Celite plug (CH_2Cl_2, −30 °C), CH_2Cl_2 exchange with dry toluene (0 °C, 2 mL), styrene (5 equiv), 2 mol % $Rh_2(esp)_2$ (1 mL of dry toluene), 0 °C to rt. [e]Reagents and conditions: KX (1.5 equiv) and 18-crown-6 (2 equiv) dissolved in dry CH_2Cl_2 (1 mL), 0 °C, **2A** (0.1−0.2 mmol) added, 0 °C for 1 h, CH_2Cl_2 exchange with dry toluene (2 mL), styrene (5 equiv), 2 mol % $Rh_2(esp)_2$ (1 mL of dry toluene), 0 °C to rt.

applied and extended to the diazophosphonates in addition to the diazoesters.

As a third class of diazo compounds, we prepared the diazopiperidinylamide triflates **3A−3C** in good to high yields (Scheme 2c). The synthesis of the α-aryliodonium diazopiperidinylamide triflate **3A** had to be done at −40 °C to avoid decomposition by loss of iodobenzene. Compound **3A** is the thermally least stable of all synthesized diazo compounds **1A−1C**, **2A−2C**, and **3A−3C** and had to be kept and stored below −30 °C.[25] α-Dimethylsulfonium and α-triethylammonium diazopiperidinylamide triflates **3B** and **3C** are significantly more stable than **3A** and can be kept at room temperature for several hours without decomposition. The bromodiazopiperidinylamide **3A-Br** gave a high yield (84%) of the α-bromo-β-lactam **3D** in a thermal intramolecular C−H insertion via the electrophilic bromination and was therefore chosen as the substrate.[9e]

Nucleophilic brominations of **3A** with methods 1−3 led to rapid extrusion of iodobenzene and a color change to red at temperatures at or below 0 °C (see the Supporting Information for kinetic measurements). Upon being warmed to room temperature, the red reaction mixture decolorized, and the corresponding α-bromo-β-lactam **3D** was obtained in a maximum 51% yield (method 3), along with byproducts from di- and tribromination and dimerization (**3E**, **3F**, and **3G**, Scheme 4). Unfortunately, it was difficult to obtain reproducible high yields of lactam **3D**, and the product distributions varied with the conditions (Table 3). A low concentration of the reaction mixture with respect to **3A** (0.02−0.04 M) and dropwise addition of 1.0−1.1 equiv of a solution of the bromide source instead of bulk addition decreased overbromination reactions, but formation of byproducts **3E−3G** could never be completely avoided.[26] An average of 18% dibrominated byproduct **3E** was obtained via the nucleophilic bromination, but only 3% via the electrophilic bromination in relation to *cis*/*trans*-**3D**. The highest isolated yield of 51% for **3D** was achieved with method 3 by dropwise addition of a solution of KBr and 18-crown-6 in dichloromethane to **3A** at −30 °C. While the reaction temperature for methods 1 and 3 had to be kept at or below −30 °C to avoid decomposition of **3A**, the biphasic procedure had to be done at 0 °C due to the aqueous phase. This may have caused some decomposition of **3A** prior to addition of the potassium bromide in H_2O, although it was done immediately after **3A** was dissolved. In contrast to the diazoester **1A** and diazophosphonate **2A**, the organic phase did not have to be separated and dried before the second step because no catalyst was involved in the thermal intramolecular C−H insertion.

Interestingly, only traces of overhalogenated products were detected for the diazoester **1A** and diazophosphonate **2A**, which showed greater tolerance to the concentration and halide equivalents. Also, elemental iodine was formed in the attempted iodinations with all methods, and its formation could not be avoided.

Having demonstrated that the nucleophilic halogenation can be applied to three major classes of diazo compounds, we wanted to study and compare the experimental properties and reactivities of the prepared diazo triflate salts **1A−C**, **2A−C**, and **3A−C**.[27] Nucleophilic substitutions of α-aryliodonio diazo triflates **1A−3A** with dimethyl sulfide and triethylamine proceeded readily at room temperature to the corresponding substituted α-onium diazo triflate salts **1B−3B** and **1C−3C**. A ^{1}H NMR experiment of **1A** (0.05 M in $CDCl_3$) with 2 equiv of SMe_2 at room temperature showed full conversion to **1B** after 20 min. The substitution of the analogous diazophosphonate **2A** with SMe_2 gave **2B** quantitatively after 3 min, and the diazopiperidinylamide **3A** reacted instantaneously to the corresponding α-dimethylsulfonium diazopiperidinylamide tri-

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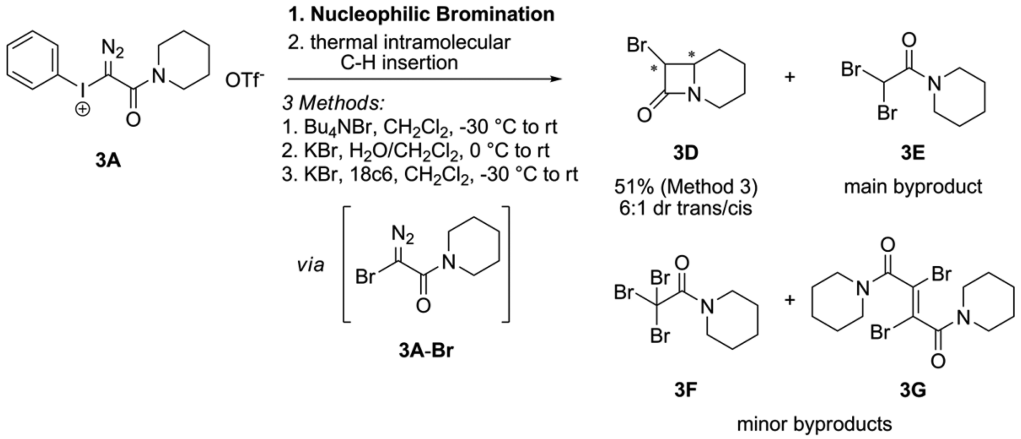
Scheme 4. Nucleophilic Bromination of α-Aryliodonio Diazopiperidinylamide Triflate 3A and the Following Thermal Intramolecular C−H Insertion to α-Bromo-β-lactam 3D with Formation of Byproducts 3E, 3F, and 3G



flate **3B**. Nucleophilic halogenations with the tetrabutylammonium halides showed quantitative loss of iodobenzene for **1A** after 35 min with chloride, for the bromination after 14 min, and for the iodination after 1 min, which indicates a direct dependence on the nucleophile. In the case of the bromination and iodination, the corresponding halodiazoesters **1A-Br** and **1A-I** could be detected in the ^{1}H NMR spectra, whereas for the chlorination, overlapping signals, probably from dimerizations, resulted. Thus, iodobenzene was chosen as a reliable indicator to compare the nucleophilic substitution rates.

Table 3. Obtained Product Distributions and Yields of the Thermal Intramolecular C−H Insertions with α-Bromodiazopiperidinylamide 3A-Br

	yield[a] of **3D** (*cis* + *trans*) (%)	nucleophilic *cis*-**3D**:*trans*-**3D**:**3E**[b]	electrophilic[9e] *cis*-**3D**:*trans*-**3D**:**3E**[b]
method 1[c]	45	1:6:1.5	84%, 1:6:0.2
method 2[d]	40	1:5:1	
method 3[e]	51	1:6.3:1.3	

[a]Isolated yields of both diastereomers after two steps after column chromatography. [b]Determined by ^{1}H NMR of crude reaction mixture. [c]Reagents and conditions: **3A** (0.1−0.2 mmol) dissolved in dry CH_2Cl_2 (3−5 mL) at −30 °C, TBAB (1.05 equiv) in dry CH_2Cl_2 (3−5 mL) added dropwise over 15 min, −30 °C for 15 min, −30 °C to rt. [d]Reagents and conditions: **3A** (0.1−0.2 mmol) dissolved in dry CH_2Cl_2 (3−5 mL), 0 °C, KBr (1.0−1.1 equiv) in H_2O (1−2 mL) added, 0 °C for 15 min, 0 °C to rt. [e]Reagents and conditions: KBr (1.0−1.1 equiv) and 18-crown-6 (1.5−2.0 equiv) dissolved in dry CH_2Cl_2 (5 mL) at rt, added dropwise to a solution of **3A** (0.1−0.2 mmol) in dry CH_2Cl_2 (5 mL) at −30 °C, 15 min at −30 °C, −30 °C to rt.

Decomposition experiments of **1A**, **2A**, and **3A** in $CDCl_3$ at room temperature showed quantitative loss of iodobenzene within 75 min for the diazopiperidinylamide **3A** and after 4 days for the diazophosphonate **2A**. The diazoester **1A** showed no decomposition even after several days. This indicates a direct influence of the electron-withdrawing group on the leaving group activity of iodobenzene. The ester, being the strongest electron-withdrawing group, deactivates, whereas the less electron-withdrawing amide has a less stabilizing effect on the leaving group iodobenzene. The triethylammonium diazo triflates **1C−3C** could only be synthesized from the α-aryliodonio diazo compounds **1A−3A** at room temperature; no nucleophilic substitution was achieved with the dimethylsulfonium diazo triflates **1B−3B** and triethylamine, which was confirmed by the computational calculations. Furthermore, nucleophilic halogenations were achieved only with the α-aryliodonio diazo triflates **1A−3A**; no halogenations were observed with the α-dimethylsulfonium and α-triethylammonium analogues **1B−3B** and **1C−3C**.

CONCLUSION

We have shown that the nucleophilic halogenation of α-aryliodonio diazoacetate triflate, as well as the corresponding α-aryliodonio diazophosphonate and α-aryliodonio diazopiperidinylamide, is an alternative method to the electrophilic halogenation for the synthesis of halodiazo compounds. Three different methods for the nucleophilic halogenations are presented employing different halide sources. Subsequent dirhodium(II)-catalyzed intermolecular cyclopropanation of the halodiazoester and halodiazophosphonate and thermal intramolecular C−H insertion of the bromodiazopiperidinylamide gave the halocyclopropylesters and halocyclopropylphosphonates and the α-bromo-β-lactam in medium to good yields. DFT calculations have been performed, the experimental results were confirmed, and the geometries of the transition states could be obtained.

EXPERIMENTAL SECTION

General Procedures. ^{1}H NMR spectra were recorded at 500, 400, and 200 MHz, decoupled ^{13}C NMR spectra at 125 and 100 MHz, and decoupled ^{31}P NMR spectra at 162 MHz at the given temperatures. Chemical shifts (δ) are reported in parts per million and referenced to the residual solvent peak, and *J* values are given in hertz. Assignments of protons and carbon atoms have been performed according to COSY45SW as well as DEPT135 and HMQC NMR spectra. HRMS-ESI spectra were measured with a QTOF instrument. Flash chromatography was performed with silica gel (60 Å, 35−70 μm). Ethyl acetate (EtOAc), diethyl ether (Et_2O), and distilled *n*-hexane were used as eluents. X-ray diffraction crystallography was performed at room temperature. Structures have been deposited in the Cambridge Crystallographic Data Base. Melting points (°C) for all thermally stable new solid compounds are reported or, if measurable, decomposition temperatures. Physical data of known compounds were in agreement with previously published data, and ^{1}H NMR data are given. For new compounds synthetic procedures and full characterizations are reported. (See the Supporting Information for spectra and graphical plots.)

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Preparation and Characterization of Diazo Compounds 1A–3C. Compounds **1A**, **1B**, and **1C** have been prepared according to the literature procedure by Weiss et al.[10]

(1-Diazo-2-ethoxy-2-oxoethyl)(phenyl)iodonium Triflate (1A). Yellow crystalline solid. Yield: 10.45 g (22.4 mmol, 86%). Decomposition temperature: 80 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 8.08 (d, J = 8.0 Hz, 2H, ArH), 7.65 (t, J = 7.3 Hz, 1H, ArH), 7.49 (t, J = 7.6 Hz, 2H, ArH), 4.32 (q, J = 7.0 Hz, 2H, CH_2), 1.30 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, CD_2Cl_2, −50 °C): δ = 161.8 (CO), 135.4 (CHAr), 133.2 (CHAr), 131.9 (CHAr), 119.6 (q, ^1J(C,F) = 320 Hz, CF_3), 116.8 (C), 64.3 (CH_2), 41.7 (CN_2), 14.1 (CH_3). IR (solution, DCM, cm^{-1}): $\tilde{\nu}$ = 2110, 1706, 1280, 1024, 637. MS (ESI): m/z (rel intens) 317.0 (100) [M$^+$]. HRMS (ESI): m/z calcd for $C_{10}H_{10}IN_2O_2^+$ 316.9787 [M$^+$], found 316.9793 (1.9 ppm).

(1-Diazo-2-ethoxy-2-oxoethyl)dimethylsulfonium Triflate (1B). White crystalline solid. Yield: 1.269 g (3.9 mmol, 89%). Mp: 76 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 4.35 (q, J = 7.1 Hz, 2H, CH_2), 3.32 (s, 6H, CH_3), 1.34 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, CD_2Cl_2, −50 °C): δ = 160.4 (CO), 120.3 (q, ^1J(C,F) = 320 Hz, CF_3), 63.4 (CH_2), 26.6 (CH_3), 14.00 (CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 23 °C): δ = 55.2 (CN_2). IR (solution, DCM, cm^{-1}): $\tilde{\nu}$ = 2151, 1710, 1282, 1032, 751, 640. MS (ESI): m/z (rel intens) 175.0 (100) [M$^+$]. HRMS (ESI): m/z calcd for $C_6H_{11}N_2O_2S^+$ 175.0541, found 175.0546 (2.9 ppm). Assignment and structure elucidation are supported by an X-ray crystallographic structure.

1-Diazo-2-ethoxy-*N*,*N*,*N*-triethyl-2-oxoethanaminium Triflate (1C). Light yellow crystalline solid. Yield: 0.361 g (0.99 mmol, 51%). Mp: 88 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 4.35 (q, J = 7.1 Hz, 2H, CH_2), 3.86 (q, J = 7.1 Hz, 6H, CH_2), 1.44 (t, J = 7.1 Hz, 9H, CH_3), 1.34 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 23 °C): δ = 160.0 (CO), 120.9 (q, ^1J(C,F) = 320 Hz, CF_3), 63.5 (CH_2), 56.4 (CH_2), 14.3 (CH_3), 8.49 (CH_3), CN_2 could not be detected. IR (solution, DCM, cm^{-1}): $\tilde{\nu}$ = 2103, 1713, 1255, 1031, 639. MS (ESI): m/z (rel intens) 214.2 (100) [M$^+$]. HRMS (ESI): m/z calcd for $C_{10}H_{20}N_3O_2^+$ 214.1556, found 214.1558 (0.9 ppm). Assignment and structure elucidation are supported by an X-ray crystallographic structure.

(Diazo(diethoxyphosphoryl)methyl)(phenyl)iodonium Triflate (2A). Diacetoxyiodobenzene (1.496 g, 4.64 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (30 mL) at room temperature. To this solution was added trimethylsilyl trifluoromethanesulfonate, (TMS)OTf (0.9 mL, 4.64 mmol, 1.0 equiv), in one portion, followed by dropwise addition of diethyl diazomethanephosphonate, EDP (0.827 g, 4.64 mmol, 1.0 equiv), dissolved in dry CH_2Cl_2 (2 mL). The mixture became orange, and some gas evolution occurred. The orange solution was stirred at room temperature for 15 min, and then Et_2O was added until the mixture became cloudy and precipitation occurred. The mixture was cooled to 0 °C with an ice bath and stirred for 30 min to complete precipitation. The solid was filtered off with suction and washed with cold Et_2O to afford 1.755 g (3.3 mmol, 72%) of **2A** as a yellow amorphous solid. The product has to be kept below 5 °C to avoid thermal decomposition. ^{1}H NMR (500 MHz, CD_2Cl_2, −50 °C): δ = 8.10 (d, J = 7.8 Hz, 2H, ArH), 7.69 (t, J = 7.5 Hz, 1H, ArH), 7.51 (t, J = 7.8 Hz, 2H, ArH), 4.01–3.86 (m, 2H, CH_2), 3.86–3.69 (m, 2H, CH_2), 1.11 (t, J = 7.1 Hz, 6H, CH_3). ^{13}C NMR (125 MHz, CD_2Cl_2, −50 °C): δ = 135.4 (CHAr), 133.3 (CHAr), 131.9 (CHAr), 119.7 (q, ^1J(C,F) = 320 Hz, CF_3), 117.1 (C), 64.3 (d, ^2J(C,P) = 5.0 Hz, CH_2), 25.3 (d, ^1J(C,P) = 217 Hz, CN_2), 15.8 (d, ^3J(C,P) = 7.9 Hz, CH_3). ^{31}P NMR (162 MHz, $CDCl_3$, 23 °C): δ = 9.61. IR (solution, DCM, cm^{-1}): $\tilde{\nu}$ = 2090, 1261, 1023, 638. MS (ESI): m/z (rel intens) 381.0 (100) [M$^+$]. HRMS (ESI): m/z calcd for $C_{11}H_{15}IN_2O_3P^+$ 380.9865, found 380.9878 (3.4 ppm).

(Diazo(diethoxyphosphoryl)methyl)dimethylsulfonium Triflate (2B). **2A** (0.621 g, 1.17 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (15 mL) at 0 °C. To this solution was added dimethyl sulfide (0.215 mL, 0.182 g, 2.93 mmol, 2.5 equiv) with stirring. The mixture decolorized and was stirred at 0 °C for 1 h and then concentrated in vacuo at 20 °C. The residue was dried in high vacuum to afford 0.445 g (1.146 mmol, 98%) of **2B** as a colorless oil. The product was kept in the refrigerator below 5 °C without decomposition. ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 4.26 (dq, J = 14.3 Hz, 7.1 Hz, 4H, CH_2), 3.32 (s, 6H, CH_3), 1.41 (t, J = 7.1 Hz, 6H, CH_3). ^{13}C NMR (125 MHz, CD_2Cl_2, −50 °C): δ = 120.3 (q, ^1J(C,F) = 320 Hz, CF_3), 64.4 (d, ^2J(C,P) = 4.8 Hz, CH_2), 42.0 (d, ^1J(C,P) = 213 Hz, CN_2), 28.9 (CH_3), 15.9 (d, ^3J(C,P) = 7.9 Hz, CH_3). ^{31}P NMR (162 MHz, $CDCl_3$, 23 °C): δ = 7.87. IR (solution, DCM, cm^{-1}): $\tilde{\nu}$ = 2130, 1286, 1028, 751, 640, 595. MS (ESI): m/z (rel intens) 239.1 (100) [M$^+$]. HRMS (ESI): m/z calcd for $C_7H_{16}N_2O_3PS^+$ 239.0619, found 239.0615 (1.7 ppm).

***N*-(Diazo(diethoxyphosphoryl)methyl)-*N*,*N*-diethylethanaminium Triflate (2C).** **2A** (0.487 g, 0.91 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (15 mL) at 0 °C. To this solution was added triethylamine (0.134 mL, 0.097 g, 1.05 mmol, 1.05 equiv). The mixture was stirred at 0 °C for 1 h and then concentrated in vacuo at 20 °C. The residue was dried in high vacuum to afford 0.275 g (0.646 mmol, 71%) of **2C** as a yellow oil. The product was kept in the refrigerator below 5 °C without decomposition. ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 4.36–4.23 (m, 4H, CH_2), 3.75 (q, J = 7.1 Hz, 4H, CH_2), 3.17 (qd, J = 7.3 Hz, 5.0 Hz, 2H, CH_2), 1.48 (t, J = 7.1 Hz, 6H, CH_3), 1.45–1.34 (m, 9H, CH_3); the three CH_2 groups and the CH_3 groups of the NEt_3 unit are unequal and split into two signals of four and two protons and three and six protons, respectively (identified by COSY). ^{13}C NMR (100 MHz, $CDCl_3$, 23 °C): δ = 120.8 (q, ^1J(C,F) = 320 Hz, CF_3), 65.6 (d, ^2J(C,P) = 6.4 Hz, CH_2), 57.2 (CH_2), 47.0 (CH_2), 16.3 (d, ^3J(C,P) = 6.4 Hz, CH_2), 8.8 (CH_3), 8.4 (CH_3). ^{31}P NMR (162 MHz, $CDCl_3$, 23 °C): δ = 7.20. IR (solution, DCM, cm^{-1}): $\tilde{\nu}$ = 2085, 1285, 1027, 640. MS (ESI): m/z (rel intens) 278.2 (100) [M$^+$]. HRMS (ESI): m/z calcd for $C_{11}H_{25}N_3O_3P^+$ 278.1634, found 278.1630 (1.4 ppm).

(1-Diazo-2-oxo-2-(piperidin-1-yl)ethyl)(phenyl)iodonium Triflate (3A). Diacetoxyiodobenzene (0.603 g, 1.87 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (10 mL) and the solution cooled to −40 °C. To this solution was added (TMS)OTf (0.361 mL, 1.87 mmol, 1.0 equiv) in one portion, followed by dropwise addition of 2-diazo-1-(piperidin-1-yl)ethanone (0.287 g,1.87 mmol, 1.0 equiv) dissolved in dry CH_2Cl_2 (5 mL). The mixture turned red, and some gas evolution occurred. The red solution was stirred at −40 °C for 15 min. Et_2O was added until the mixture became cloudy. At this point the temperature was raised to 0 °C, and more Et_2O was added in small portions until precipitation occurred. The mixture was stirred at 0 °C for 15 min and then cooled again to −40 °C to complete precipitation. The solid was filtered off quickly with suction and washed with −40 °C cooled Et_2O to afford 0.611 g (1.21 mmol, 65%) of **3A** as an orange solid. The product has to be kept below −20 °C to avoid thermal decomposition. ^{1}H NMR (500 MHz, CD_2Cl_2, −18 °C): δ = 8.18–8.10 (m, 2H, ArH), 7.71–7.65 (m, 1H, ArH), 7.54–7.48 (m, 2H, ArH), 3.40–3.35 (m, 4H, CH_2), 1.65–1.56 (m, 2H, CH_2), 1.56–1.46 (m, 4H, CH_2). ^{13}C NMR (125 MHz, CD_2Cl_2, −50 °C): δ = 159.2 (CO), 135.8 (CHAr), 133.2 (CHAr), 131.8 (CHAr), 119.8 (q, ^1J(C,F) = 320 Hz, CF_3), 115.9 (C), 46.7 (CN_2), 25.4 (CH_2), 24.0 (CH_2). ^{13}C NMR (125 MHz, CD_2Cl_2, −18 °C): δ = 47.6 (CH_2). IR (solution, DCM, cm^{-1}): $\tilde{\nu}$ = 2075, 1642, 1023, 638. MS (ESI): m/z (rel intens) 356.0 (18) [M$^+$], 328 (100) [M$^+$ − N_2], 245 (95), 201 (32). HRMS (ESI): m/z calcd for $C_{13}H_{15}IN_3O^+$ 356.0260, found 356.0267 (2.0 ppm).

(1-Diazo-2-oxo-2-(piperidin-1-yl)ethyl)dimethylsulfonium Triflate (3B). **3A** (0.046 g, 0.092 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (2.5 mL) at −30 °C. To this solution was added dimethyl sulfide (8.1 μL, 6.9 mg, 0.111 mmol, 1.2 equiv) with stirring in one portion. The mixture changed from orange to light yellow and was stirred at −30 °C for 1 h and then concentrated in vacuo at 0 °C. The residue was dried in high vacuum to afford 32.9 mg (0.090 mmol, 98%) of **3B** as a light yellow amorphous solid. The product was kept in the freezer below −20 °C without decomposition. Mp: 63 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 3.50–3.39 (m, 4H, CH_2), 3.34 (s, 6H, CH_3), 1.72–1.64 (m, 2H, CH_2), 1.64–1.55 (m, 4H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, 23 °C): δ = 159.2 (CO), 120.7 (q, ^1J(C,F) = 320 Hz, CF_3), 54.1 (CH_2), 46.8 (CN_2), 28.2 (CH_3), 25.8 (CH_2), 24.3 (CH_2). IR (solution, DCM, cm^{-1}): $\tilde{\nu}$ = 2115, 1638, 1165, 1031, 751, 639. MS (ESI): m/z (rel intens) 214.1 (100) [M$^+$], 186 (33) [M$^+$ −

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N_2]. HRMS (ESI): m/z calcd for $C_9H_{16}N_3OS^+$: 214.1014, found 214.1018 (1.9 ppm).

1-Diazo-*N*,*N*,*N*-triethyl-2-oxo-2-(piperidin-1-yl)ethanaminium Triflate (3C). **3A** (0.1135 g, 0.224 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (5 mL) at 0 °C. To this solution was added triethylamine (31.2 μL, 22.7 mg, 0.224 mmol, 1.0 equiv). The solution changed from orange to yellow and was strirred at 0 °C for 30 min. Et_2O was added until the mixture became cloudy, and then the mixture was warmed to room temperature until the solution became clear again. Et_2O was added until the mixture became cloudy again, and precipitation occurred upon cooling to 0 °C. The mixture was stirred at that temperature for 30 min. The obtained solid was filtered with suction to afford **3C** as a yellow, amorphous, sticky solid. The solid product was collected from the filter paper, with the remaining solid dissolved in CH_2Cl_2 and concentrated in vacuo at room temperature to afford a second batch of a yellow oil of **3C** with an overall yield of 54.0 mg (0.134 mmol, 60%). **3C** was stored in the freezer below −20 °C but can also be handled at higher temperatures without decomposition. ^{1}H NMR (500 MHz, CD_2Cl_2, −50 °C): δ = 3.76 (q, J = 7.2 Hz, 6H, CH_2), 3.44−3.33 (m, 4H, CH_2), 1.70−1.60 (m, 2H, CH_2), 1.60−1.46 (m, 4H, CH_2), 1.37 (t, J = 7.2 Hz, 9H, CH_3). ^{13}C NMR (125 MHz, CD_2Cl_2, −10 °C): δ = 158.7 (CO), 121.0 (q, ^1J(C,F) = 320 Hz, CF_3), 77.1 (CN_2), 56.1 (CH_2), 46.9 (CH_2), 25.7 (CH_2), 24.4 (CH_2), 8.5 (CH_3). IR (solution, DCM, cm^{-1}): $\tilde{\nu}$ = 2077,1639, 1257, 1032, 761, 707, 639. MS (ESI): m/z (rel intens) 253.3 (33) [M^+], 225.3 (100) [$M^+ - N_2$], 142 (18). HRMS (ESI): m/z calcd for $C_{13}H_{25}N_4O^+$ 253.2028, found 253.2021 (2.8 ppm).

General Procedure for the Intermolecular Cyclopropanations of Halogenated 1A and 2A: Method 1. α-Aryliodonium diazoacetate triflate **1A** or phosphonate **2A** (0.1−0.2 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (1−2 mL) at 0 °C. Tetrabutylammonium halide, TBAX (X = I, Br, Cl, 1.5 equiv), was added in one portion. The mixture was stirred for 1 h at 0 °C, and then dry toluene (2 mL) was added and the CH_2Cl_2 removed in vacuo at 0 °C. To the residue was added styrene (5 equiv) at 0 °C followed by a solution of $Rh_2(esp)_2$ (2 mol %) in dry toluene (1 mL). The mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was concentrated in vacuo and the product purified by flash column chromatography with *n*-hexane/EtOAc (100:0 to 5:1) for the esters and *n*-hexane/EtOAc (100:0 to 2:1) for the phosphonates to afford the halocyclopropyl esters **1D**−**1F** in 50−67% isolated yields and the halocyclopropanephosphonates **2D**−**2F** in 63−71% isolated yields as a mixture of both diastereomers.

General Procedure for the Intermolecular Cyclopropanations of Halogenated 1A and 2A: Method 2. α-Aryliodonium diazoacetate triflate **1A** or phosphonate **2A** (0.1−0.2 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (1 mL) at 0 °C. A solution of potassium halide, KX (X = I, Br, Cl, 1.5 equiv), in distilled H_2O (1 mL) was added in one portion. The biphasic mixture was stirred at 0 °C for 10 min for X = I and Br and 30 min for X = Cl. The organic phase was then separated and passed through a $MgSO_4$/Celite plug with −30 °C cooled CH_2Cl_2 as the eluent into a flask containing dry toluene (2 mL) at −30 °C. The remaining aqueous residue was extracted twice with 0 °C cooled CH_2Cl_2, and the organic phases were also passed through the $MgSO_4$/Celite plug. The CH_2Cl_2 was removed in vacuo at 0 °C, and to the residual reaction mixture was added styrene (5 equiv) followed by a solution of $Rh_2(esp)_2$ (2 mol %) in dry toluene (1 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was concentrated in vacuo and the product purified by flash column chromatography with *n*-hexane/EtOAc (100:0 to 5:1) for the esters and *n*-hexane/EtOAc (100:0 to 2:1) for the phosphonates to afford the halocyclopropyl esters **1D**−**1F** in 26−66% isolated yields and the halocyclopropanephosphonates **2D** and **2E** in 55−70% isolated yields as a mixture of both diastereomers.

General Procedure for the Intermolecular Cyclopropanations of Halogenated 1A and 2A: Method 3. Potassium halide (KBr or KI, 1.5 equiv) and 18-crown-6 (2.0 equiv) were stirred in dry CH_2Cl_2 (1 mL) at 0 °C until fully dissolved (approximately 20−30 min). α-Aryliodonium diazoacetate triflate **1A** or phosphonate **2A** (0.1−0.2 mmol, 1.0 equiv) was added and the mixture stirred at 0 °C for 1 h. Dry toluene (2 mL) was added and the CH_2Cl_2 removed in vacuo at 0 °C. The residual was redissolved by addition of a minimum amount of dry CH_2Cl_2 at 0 °C, and styrene (5 equiv), followed by a solution of $Rh_2(esp)_2$ (2 mol %) in dry toluene (1 mL), was added. The mixture was allowed to warm to room temperature, stirred for 1 h, and then concentrated in vacuo. The product was purified by flash column chromatography with *n*-hexane/EtOAc (100:0 to 5:1) for the esters and *n*-hexane/EtOAc (100:0 to 2:1) for the phosphonates to afford the halocyclopropylesters **1D** and **1E** in 49−77% isolated yields and the halocyclopropanephosphonates **2D** and **2E** in 49−66% isolated yields as a mixture of both diastereomers.

General Procedure for the Thermal Intramolecular C−H Insertion of Brominated 3A: Method 1. **3A** (0.1−0.2 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (3−5 mL) at −30 °C. To this solution was added dropwise tetrabutylammonium bromide (1.05 equiv) in dry CH_2Cl_2 (3−5 mL) over 15 min. The red solution was stirred at −30 °C for a further 15 min, then allowed to warm to room temperature, and left with or without stirring until full decolorization (30−60 min). The reaction mixture was left at room temperature for an additional 1 h and then concentrated in vacuo. The product was purified by flash column chromatography with *n*-hexane/Et_2O (95:5 to 1:1 to 0:100) to afford 45% α-bromo-β-lactam **3D** as a mixture of both diastereomers.

General Procedure for the Thermal Intramolecular C−H Insertion of Brominated 3A: Method 2. **3A** (0.1−0.2 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (3−5 mL) at 0 °C. A solution of KBr (1.0−1.1 equiv) in distilled H_2O (1−2 mL) was added in one portion immediately thereafter with stirring. The organic phase turned red immediately, and the biphasic solution was stirred at 0 °C for 15 min and then allowed to warm to room temperature. Decolorization of the organic phase occurred within ca. 30 min, and the mixture was stirred for another 30 min at room temperature. The organic phase was then separated and the aqueous phase diluted with H_2O (2 mL) and extracted with dry CH_2Cl_2 (3 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. The remaining crude oil was purified by flash column chromatography with *n*-hexane/Et_2O (95:5 to 1:1 to 0:100) to afford 40% α-bromo-β-lactam **3D** as a mixture of both diastereomers.

General Procedure for the Thermal Intramolecular C−H Insertion of Brominated 3A: Method 3. KBr (1.0−1.1 equiv) and 18-crown-6 (1.5−2.0 equiv) were stirred in dry CH_2Cl_2 (5 mL) at room temperature until fully dissolved. This mixture was then added dropwise over 15 min to a solution of **3A** (0.1−0.2 mmol) in dry CH_2Cl_2 (5 mL) at −30 °C. The deep red mixture was stirred for an additional 15 min at −30 °C and then allowed to warm to room temperature. Full decolorization occurred after 30 min, and the mixture was then concentrated in vacuo at 20 °C. The remaining solid was treated with a 1:3 mixture of Et_2O/*n*-hexane (3 mL) and CH_2Cl_2 (0.5 mL) and the undissolved solid (18-crown-6) filtered off. The remaining solution was purified by flash column chromatography with *n*-hexane/Et_2O (95:5 to 1:1 to 0:100) to afford 51% α-bromo-β-lactam **3D** as a mixture of both diastereomers.

Characterization of *trans*-Cyclopropanes 1D−1F and 2D−2F, *trans*-α-Bromo-β-lactam 3D, and Byproducts 3E and 3F. Halocyclopropyl esters **1D**−**1F**[9d] and halocyclopropanephosphonates **2D**−**2F**[9a] have been fully characterized before; thus, only ^{1}H NMR data are given. ^{1}H NMR data of *trans*-α-bromo-β-lactam **3D** correspond to the reported data in the literature.[28]

***trans*-Ethyl 1-Iodo-2-phenylcyclopropanecarboxylate (1D).** Yield: 54.5 mg (0.17 mmol, 66%, with method 2). ^{1}H NMR (200 MHz, $CDCl_3$, 23 °C): δ = 7.38−7.29 (m, 3H, ArH), 7.23−7.15 (m, 2H, ArH), 4.23 (q, J = 7.1 Hz, 2H, CH_2), 2.64−2.50 (m, 1H, CH), 2.29 (dd, J = 9.9 Hz, 5.8 Hz, 1H, CH_2), 1.74 (dd, J = 8.2 Hz, 5.8 Hz, 1H, CH_2), 1.32 (t, J = 7.1 Hz, 3H, CH_3).

***trans*-Ethyl 1-Bromo-2-phenylcyclopropanecarboxylate (1E).** Yield: 40.3 mg (0.15 mmol, 77%, with method 3). ^{1}H NMR (200 MHz, $CDCl_3$, 23 °C): δ = 7.39−7.30 (m, 3H, ArH), 7.29−7.21 (m, 2H, ArH), 4.28 (q, J = 7.1 Hz, 2H, CH_2), 3.03−2.89 (m, 1H, CH), 2.22 (dd, J = 10.1 Hz, 6.0 Hz, 1H, CH_2), 1.81 (dd, J = 8.5 Hz, 6.0 Hz, 1H, CH_2), 1.35 (t, J = 7.1 Hz, 3H, CH_3).

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***trans*-Ethyl 1-Chloro-2-phenylcyclopropanecarboxylate (1F).** Yield: 21.8 mg (0.097 mmol, 50%, with method 1). ^{1}H NMR (200 MHz, $CDCl_3$, 23 °C): δ = 7.42−7.33 (m, 3H, ArH), 7.33−7.25 (m, 2H, ArH), 4.33 (q, J = 7.1 Hz, 2H, CH_2), 3.21−3.05 (m, 1H, CH), 2.20 (dd, J = 10.1 Hz, 6.0 Hz, 1H, CH_2), 1.80 (dd, J = 8.5 Hz, 6.0 Hz, 1H, CH_2), 1.39 (t, J = 7.1 Hz, 3H, CH_3).

***trans*-Diethyl 1-Iodo-2-phenylcyclopropanephosphonate (2D).** Yield: 42.3 mg (0.11 mmol, 70%, with method 2). R_f = 0.14 (50% EtOAc/*n*-hexane). ^{1}H NMR (200 MHz, $CDCl_3$, 23 °C): δ = 7.38−7.29 (m, 3H, ArH), 7.23−7.08 (m, 2H, ArH), 4.32−4.14 (m, 4H, CH_2), 2.48 (ddd, J = 13.8 Hz, 10.2 Hz, 7.6 Hz; 1H, CH), 2.22−2.06 (m, 1H, CH_2), 1.61 (ddd, J = 10.2 Hz, 7.6 Hz, 6.2 Hz, 2H, CH_2), 1.47−1.33 (m, 6H, CH_3).

***trans*-Diethyl 1-Bromo-2-phenylcyclopropanephosphonate (2E).** Yield: 38.2 mg (0.11 mmol, 71%, with method 1). R_f = 0.18 (50% EtOAc/*n*-hexane). ^{1}H NMR (200 MHz, $CDCl_3$, 23 °C): δ = 7.38−7.28 (m, 3H, ArH), 7.25−7.17 (m, 2H, ArH), 4.34−4.18 (m, 4H, CH_2), 2.87 (ddd, J = 12.8 Hz, 10.0 Hz, 8.2 Hz, 1H, CH), 2.05 (ddd, J = 13.7 Hz, 10.0 Hz, 6.5 Hz, 1H, CH_2), 1.68 (td, J = 8.2 Hz, 6.5 Hz, 1H, CH_2), 1.40 (td, J = 6.7 Hz, 1.9 Hz, 6H, CH_3).

***trans*-Diethyl 1-Chloro-2-phenylcyclopropanephosphonate (2F).** Yield: 19.2 mg (0.066 mmol, 63%, with method 1). R_f = 0.2 (50% EtOAc/*n*-hexane). ^{1}H NMR (200 MHz, $CDCl_3$, 23 °C): δ = 7.45−7.32 (m, 3H, ArH), 7.32−7.19 (m, 2H, ArH), 4.39−4.20 (m, 4H, CH_2), 3.14−2.92 (m, 1H, CH), 2.03 (ddd, J = 13.0 Hz, 10.1 Hz, 6.1 Hz, 1H, CH_2), 1.67 (dd, J = 14.4 Hz, 7.7 Hz, 1H, CH_2), 1.44 (d, J = 7.1 Hz, 6H, CH_3).

***trans*-7-Bromo-1-azabicyclo[4.2.0]octan-8-one (3D).** Yield: 13.4 mg (0.067 mmol, 51%, with method 3). ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 4.42 (d, J = 1.3 Hz, 1H, CH), 3.87 (dd, J = 13.3 Hz, 4.5 Hz, 1H, CH_2), 3.55 (dd, J = 10.8 Hz, 4.4 Hz, 1H, CH), 2.84−2.75 (m, 1H, CH_2), 2.21−2.12 (m, 1H, CH_2), 1.96−1.89 (m, 1H, CH_2), 1.74−1.66 (m, 1H, CH_2), 1.46−1.38 (m, 2H, CH_2), 1.31−1.19 (m, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, 23 °C): δ = 161.8 (CO), 59.3 (CH), 48.5 (CH), 39.8 (CH_2), 29.6 (CH_2), 24.6 (CH_2), 22.1 (CH_2). MS (EI): m/z (rel intens) 203/205 (3/3) [M^+], 134 (12), 132 (12), 124 (100), 81 (13), 41 (16). HRMS (EI): m/z calcd for $C_7H_{10}BrNO$: 202.9946, found 202.9944 (1.0 ppm).

2,2-Dibromo-1-(piperidin-1-yl)ethanone (3E). ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 6.14 (s, 1H, CH), 3.68−3.55 (m, 4H, CH_2), 1.69 (s, 4H, CH_2), 1.61 (s, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, 23 °C): δ = 48.4 (CH_2), 44.7 (CH_2), 35.7 (CH), 25.9 (CH_2), 25.6 (CH_2), 24.3 (CH_2). MS (EI): m/z (rel intens) 283/285/287 (2/5/2) [M^+], 204/206 (36/36), 112 (100), 84 (12), 69 (41), 55 (11), 41 (23).

2,2,2-Tribromo-1-(piperidin-1-yl)ethanone (3F). ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 3.79 (s, 4H, CH_2), 1.69 (s, 6H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, 23 °C): δ = 158.9 (CO), 37.0 (C), 31.1 (CH_2), 25.7 (CH_2), 24.1 (CH_2). MS (EI): m/z (rel intens) 361/363/365/367 (1/2/2/1) [M^+], 282/284/286 (3/6/3), 112 (100), 84 (7), 69 (38), 55 (12), 41 (29).

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra for all relevant compounds, kinetic plots, and computational and crystallographic (CIF) data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(25) ^1H NMR experiments of **3A** in $CDCl_3$ showed quantitative loss of iodobenzene and decolorization after 75 min at room temperature, whereas **1A** and **2A** were stable for several hours.
(26) The overbrominated byproducts **3E** and **3F** could formally result from insertion of the carbene of the brominated **3A-Br** or nonbrominated diazopiperidinylamide **3A** into elemental bromine, which may have been formed in small amounts during the reaction. Attempts to suppress formation of elemental bromine, however, did not change the ratio of product to byproducts.
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