

# Aggregation Enabled Alkene Insertion into Carbon–Halogen Bonds

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## Abstract

Molecular aggregation affects the electronic interactions between molecules and has emerged as a powerful tool in material science. Molecular aggregation finds wide applications in the research of new physical effects; however, its value for chemical reaction development has been far less explored. Herein, we report the development of aggregation-enabled alkene insertion into carbon–halogen bonds. The spontaneous cleavage of C–X (X = Cl, Br, or I) bonds generates an intimate ion pair, which can be quickly captured by alkenes in the aggregated state. Additional catalysts or promoters are not necessary under such circumstances, and solvent quenching experiments indicate that the aggregated state is critical for initiating such sequences. The ionic insertion mode and the intimate ion pair mechanism are supported by mechanistic studies, density functional theory calculations, and symmetry-adapted perturbation theory analysis. Results show that the non-aggregated state may quench the transition state and terminate the insertion process.

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## Introduction

Since Tang and co-worker’s seminal work in 2001,<sup>1</sup> aggregate science has emerged as a productive area of molecular science.<sup>2–4</sup> Unlike previous studies that focused on the properties of isolated molecules, the new perspective brings us the novel characteristics enabled by molecular aggregates. Interactions between molecules in aggregates induce unique physical changes, such as aggregation-induced emission<sup>5</sup> and self-assembly-induced crystallization,<sup>6</sup> in the system, finding wide applications in biology and material sciences. Therefore, it is an obvious logical extension that the increased interactions between molecules in aggregates may induce chemical reactions between corresponding molecules. While studying the dissociation of  $\text{HCl}(\text{H}_2\text{O})_4$  at ultracold temperatures, Birer and co-workers<sup>7,8</sup> proposed a mechanism of aggregation-induced dissociation. Although this physical chemistry study is instructive, it falls short of developing synthetically useful chemical processes.

In solvent-free reactions, reactants are in close contact with each other, and such an aggregated state may benefit the reaction. However, while considerable attention has been paid to the green and sustainable features of this type of system,<sup>9–10</sup> its potential to promote reactions has been neglected. Therefore, we recently initiated a project to discover novel synthetic methods guided by the aggregated state concept (Figure 1A).

Owing to the diverse and rich reaction chemistry associated with carbon–halogen (C–X) bonds, organohalides are crucial in synthetic chemistry.<sup>11–15</sup> Moreover, they are prevalent structural subunits in numerous important natural products and pharmaceuticals.<sup>16–19</sup> Although halides can be obtained by numerous methods, efficient, practical, and green methods are currently being developed.<sup>20–24</sup> Carbohalogenative 1,2-difunctionalization of double bonds with organohalides has emerged as an appealing method with excellent atom economy, step economy, and versatility.<sup>25–28</sup> Insertion of double bonds into C–X bonds is among the most direct and efficient methods for generating C–C and C–X bonds simultaneously.

### Figure 1. Insertion of alkene into carbon–halogen bonds.

To initiate the insertion process, a suitable catalyst or promoter for disconnecting C–X bonds has become an essential tool and rendered three viable pathways (Figure 1B). For  $\text{C}(\text{sp}^2)\text{–X}$  bonds, a palladium-<sup>29–36</sup> and nickel-<sup>37–41</sup> catalyzed oxidative addition/migratory insertion/reductive elimination sequence is a successful route (Figure 1B-i). However, extending this method to the insertion of  $\text{C}(\text{sp}^3)\text{–X}$  bonds would be problematic owing to the competition of  $\beta$ -H elimination. A complementary strategy for  $\text{C}(\text{sp}^3)\text{–X}$  insertion is atom transfer radical addition (ATRA) reaction (Figure 1B-ii).<sup>42–45</sup> When initially proposed by Kharasch<sup>46</sup> in the 1940s, this type of reaction was limited to stoichiometric quantities of harmful oxidants, organotin reagents, and organoboron reagents as radical initiators.<sup>47–48</sup> Subsequently, a series of metal-catalyzed<sup>49–50</sup> or photocatalytic<sup>51–55</sup> ATRA reactions employing haloalkanes were reported. Despite considerable advancements, some major limitations and challenges remain in the methods based on the above mechanism; for example, the need for expensive transition catalysts, the strict requirements of the experimental operations, insufficient accommodation of some reactive functional groups, and difficulty associated with the use of alkyl chloride substrates.

Third is insertion *via* the heterolytic cleavage of C–X bonds (Figure 1B-iii). However, although such ionic reactions have a long history, only alkyl C–Cl bond insertion with limited substrate scope has been presented and literature reports in this regard are sparse.<sup>56–59</sup> Lack of interest might be ascribed to the challenge in controlling carbocation-involved E1 elimination and cationic polymerization.<sup>60–62</sup> Furthermore, insertion into

more reactive C–Br and C–I *via* this approach remains elusive. Therefore, developing creative strategies that can address the limitations to provide new opportunities to this research area is highly desirable.

We envisioned that an aggregated state could enable spontaneous cleavage of alkyl C–X bonds to initiate ionic insertion reactions.<sup>63</sup> If the reaction is performed under an aggregated state, it is possible to capture a transient ion pair through the contact touch with alkenes.<sup>64</sup> Furthermore, the cleavage of the C–X bond may be facilitated by alkenes through the formation of a  $\pi$  complex<sup>65</sup> or the stabilization of the generated cations to onium ions, which is not stable under dilute solution state (Figure 1C-i).<sup>66</sup> This promotes the insertion of the desired alkene without transition metal catalysts. Compared with ionic insertion through Lewis-acid catalysis, the contact nature under an aggregated state may facilitate a fast cascade process, which avoids competitive E1 elimination reactions and cationic polymerization.<sup>67-68</sup>

Herein, we report the development of aggregation-enabled alkene insertion into carbon–halogen bonds (Figure 1C-ii). The insertion into C–Cl, C–Br, and C–I bonds can be realized with the completed atom economy and high step economy under catalyst-free conditions. Specifically, the excellent compatibility of functional groups indicates that this methodology has potential applications in the field of organic synthesis.

## Results

**Reaction Development.** After extensive optimization, the reaction of alkene **1a** and benzyl chloride **2a** afforded the highest yield of 93% at 100°C for 5 h in an aggregated state (Table 1, entry 1). Decreasing the reaction temperature considerably reduced the conversion of **1a** and **2a**, yielding only 7% of **3aa**. The yield did not improve by increasing the temperature (entries 7 and 9) or by adjusting the ratio of **1a** and **2a** (entries 10 and 11). Further, the solvent effect of this process was tested. Thus, no product formation was observed in either polar or nonpolar solvents. We believe that nonpolar solvents such as toluene and *n*-hexane (entries 1 and 2, respectively) increase the free energies of the carbocation transition state, raising the activation energies.<sup>64</sup> Conversely, in polar solvents (entries 3–6), the positive charge of the carbocations would be dispersed by coordination with the solvent, reducing the electrophilicity of benzyl cations<sup>68</sup>. The cage effect of the solvent can also block the reaction by reducing the collision probability of alkenes and benzyl cations.<sup>71</sup> A high yield was maintained during the reaction that proceeded in the dark, indicating a nonphotocatalytic process (entry 13).

**Table 1.** Effect of reaction parameters on the insertion of alkenes into C–Cl bonds.

Entry <sup>a</sup>	Solvent	T (°C)	t (h)	Conversion of <b>1a</b> (%)	Yield of <b>3aa</b> (%)
1	Toluene	100	5	2	n.d.
2	<i>n</i> -hexane	100	5	3	n.d.
3	CH <sub>2</sub> Cl <sub>2</sub>	100	5	13	n.d.
4	DMF	100	5	5	n.d.
5	MeCN	100	5	6	n.d.
6	THF	100	5	9	n.d.
7	none	100	5	100	93
8	none	80	24	13	7
9	none	120	5	100	81
10 <sup>b</sup>	none	100	5	97	73
11 <sup>c</sup>	none	100	5	100	81
12 <sup>d</sup>	none	100	5	100	90
13 <sup>e</sup>	none	100	5	100	91

Entry <sup>a</sup>	Solvent	T (°C)	t (h)	Conversion of <b>1a</b> (%)	Yield of <b>3aa</b> (%)
<sup>a</sup> Reaction conditions: <b>1a</b> (0.3 mmol) and <b>2a</b> (0.9 mmol) at 100 °C for 5 h under air. Corrected GC yields using <i>n</i> -dodecane as an internal standard were reported. n.d. = not detected.	<sup>a</sup> Reaction conditions: <b>1a</b> (0.3 mmol) and <b>2a</b> (0.9 mmol) at 100 °C for 5 h under air. Corrected GC yields using <i>n</i> -dodecane as an internal standard were reported. n.d. = not detected.	<sup>a</sup> Reaction conditions: <b>1a</b> (0.3 mmol) and <b>2a</b> (0.9 mmol) at 100 °C for 5 h under air. Corrected GC yields using <i>n</i> -dodecane as an internal standard were reported. n.d. = not detected.	<sup>a</sup> Reaction conditions: <b>1a</b> (0.3 mmol) and <b>2a</b> (0.9 mmol) at 100 °C for 5 h under air. Corrected GC yields using <i>n</i> -dodecane as an internal standard were reported. n.d. = not detected.	<sup>a</sup> Reaction conditions: <b>1a</b> (0.3 mmol) and <b>2a</b> (0.9 mmol) at 100 °C for 5 h under air. Corrected GC yields using <i>n</i> -dodecane as an internal standard were reported. n.d. = not detected.	<sup>a</sup> Reaction conditions: <b>1a</b> (0.3 mmol) and <b>2a</b> (0.9 mmol) at 100 °C for 5 h under air. Corrected GC yields using <i>n</i> -dodecane as an internal standard were reported. n.d. = not detected.
<sup>b</sup> <b>1a/2a</b> = 1:1.					
<sup>c</sup> <b>1a/2a</b> = 1:2.					
<sup>d</sup> Under argon.					
<sup>e</sup> In dark.					

**Substrate Scope.** The scope of the reaction under optimized conditions was investigated. Various aryl ethylenes were tested as nucleophiles, and the corresponding ionic insertion products delivered moderate to excellent reaction yields (Figure 2A). For substrates with substitutions on the *para* position, electron-deficient substrates usually gave higher reaction yields, which were primarily ascribed to their relatively low reactivity toward the newly generated benzyl chloride. Further, excellent functional-group tolerance was observed (**3ac**–**3ae**). For example, the reaction with substrates bearing –OCF<sub>3</sub> and –SCF<sub>3</sub> substitutions, often embedded in pharmaceutical and agrochemical products, afforded the corresponding products in excellent yields (**3af** and **3ag**). The –Br (**3ae**), –I (**3ap**), alkyne (**3aj**), and boronate (**3an** and **3ao**) substitutions, which may have been incompatible in previous transition-metal catalyzed processes, were all well tolerated, thereby providing handles for further derivation. Some reactive functional groups in conventional synthetic methods, including aryl esters, aldehydes, carboxyl, and benzyl chloride groups, were well accommodated (**3ak**–**3am** and **3aq**). Furthermore, functional groups at *meta* or *ortho* positions of the phenyl ring were acceptable (**3ar**–**3av**) and showed a similar electronic preference compared with the *para* substitutions.

Subsequently, the feasibilities of benzyl chlorides **2** were explored, beginning with the examination of the electronic effects of the substituents (Figure 2B). After comparing **3ba** and **3be**, we found that the electron-donating substituents at the *para* position increased the reaction yield. The electron-donating conjugation effect on the aromatic ring decreased the activation energy of the heterolytic cleavage of the C–Cl bond. The substrates featuring halogen atom, such as –F, –Cl, –Br, and –I, at the phenyl ring (**3ba**–**3bd**), reacted with styrene to afford products in good yields.

Further, steric effect was analyzed by changing the position of the methyl group. This showed that the steric effect of an aryl ring has a slight influence on the proposed reaction. The *ortho*-methyl-substituted substrate provided the product in 92% yield (**3bg**). In addition, long alkyl chains provided products (**3bi** and **3bj**) in moderate yields.

**Figure 2.** Insertion of alkenes into C–Cl bonds. <sup>a</sup>Reaction conditions: **1** (0.6 mmol) and **2** (1.8 mmol) at 80 °C–120 °C for 1–5 h under air. R<sup>1</sup> = 1-phenylethyl, R<sup>2</sup> = benzhydryl, Ar<sup>1</sup> = Ph, Ar<sup>2</sup> = 4-CF<sub>3</sub>-Ph, and Ar<sup>3</sup>

= 4-MeO-Ph. SI provides the detailed conditions for each substrate.<sup>b</sup>A gram scale reaction was performed under air using **1** (10.0 mmol).

Diphenylmethane has highly important applications in the synthesis of bioactive compounds;<sup>72</sup> thus, a series of diarylmethyl chlorides as substrates were investigated. Owing to the stability of a carbocation, excellent compatibility of these substrates was observed for the proposed reaction. Both electron-withdrawing (**3bl**) and electron-donating (**3br**) substituents underwent insertion reactions with good yields. A heteroaromatic thienyl group (**3bq**) was also well tolerated in the reaction. In addition to benzyl chlorides, primary and secondary allyl chlorides were verified as suitable coupling partners (**3bs** and **3bt**). Furthermore, the scalability of the proposed reaction was evaluated by performing a reaction with 10.0 mmol of **1b**. An improved yield of 95% was obtained compared with small-scale trials.

**Figure 3.** Insertion into C–Br and C–I bonds.<sup>a</sup>Ar<sup>2</sup> = 4-CF<sub>3</sub>-Ph. SI provides the detailed conditions for each substrate.

We extended the reaction scope of benzyl bromides and iodides (Figure 3). The insertion reaction was explored using styrene as the nucleophile. Alkyl bromide **5aa** was successfully obtained with a satisfactory yield under standard reaction conditions. Introduction of an electron-withdrawing substituent decreased the reaction yield (**5ab**), which can be attributed to an increased difficulty for the heterolytic cleavage of the C–Br bond. The replacement of methyl with ethyl provided **5ac** but with a slight reduction in yield. When bromodiphenylmethane was used as the electrophile, the yield (**5ad**) was improved because C–Br bonds are easier to cleave owing to the conjugation effect. Halogens on the alkyl chains were well tolerated (**5ae** and **5af**), and their insertion into unactivated carbon–halogen bonds was not observed. Further, benzyl iodides were suitable substrates in the insertion reaction (**5ag**), for which the insertion process was difficult.<sup>73</sup>

**One-pot Reaction.** To demonstrate the practical application of the proposed reaction, a series of one-pot transformation sequences was investigated (Figure 4). The C–C, C–O, C–S, C–N, and C–B difunctionalizations of alkenes were realized through this reaction (**6aa–6af**). Reductive coupling (**6ag**) and deprotonation (**6ah**) products were obtained after treating **3bk** with a reductant and base, respectively.

**Figure 4.** Carbohalogenative 1,2-difunctionalization of double bonds.

**Mechanistic Investigations.** To shed light on the reaction mechanism, some control experiments were conducted. The reactions of **1b** and **2k** were performed in the presence of a radical inhibitor, 2,6-bis(1,1-dimethylethyl)-4-methylphenol (BHT). The insertion product was obtained in 86% yield, indicating that the proposed reaction is unlikely to proceed *via* a radical pathway (Figure 5A). The increased yield (compared with Figure 2B) may be explained by the inhibition of the radical polymerization of alkene by BHT. Subsequently, a cation-exchange experiment was designed (Figure 5B), where benzhydrol was introduced as a cation donor. As expected, the normal insertion product **3ab** was obtained in 21% yield, and **3bk** that was generated using benzhydrol as the benzhydryl cation donor was obtained in 55% yield. The formation of these products implied that the proposed reaction proceeded through an ionic mode.<sup>74</sup> In addition, the intermolecular competition between styrene **1b** and its dideuterated analog *d*<sub>8</sub>-**1b** showed a kinetic isotope effect  $k_H/k_D = 1.00$  (Figure 5C); however, a secondary isotope effect was not observed, suggesting that C–C and C–Cl bond formations were not involved in the rate-determining step.<sup>75</sup> In addition, solvent quenching experiments were designed to elaborate the influence of the aggregated states on such ionic insertion processes. As shown in Figure 5D, while a trace amount (three equivalents) of commonly used solvent was introduced into the reaction system, the desired transformation could be interrupted, which may be ascribed to the disconnection of the aggregated state of reactants by the solvent molecules. Notably, even nonpolar, weak coordinating solvents such as mesitylene were competent blockers. Possibly, there are three reasons why the solvent prevents the above reaction. First, the cage effect of the solvent can reduce effective collision between substrates and increase the activation energy of the insertion process (restricted intermolecular collision, RIC). Next, induction and coordination effects will reduce the transient effective charge produced by the system, which is not conducive to the reaction (charge dispersion, CD). Finally, the solvent effect may quench the intermediates or transition states produced by the reaction, inhibiting the reaction (intermediate

quenching or transition state quenching, IQ or TSQ). To confirm the above speculation, density functional theory (DFT) calculations and symmetry-adapted perturbation theory (SAPT) analysis were conducted.

### Figure 5. Preliminary mechanistic experiments.

DFT calculations provide mechanistic insights into the abovementioned insertion reactions of alkenes to C–X bonds. For C–Cl bond insertion (Figure 6A), the benzyl chloride substrate **2k** heterolytically dissociated to carbocation and chloride anion before styrene attacked the so-generated carbocation *via* a chloride anion bound transition state (TS). Such an S<sub>N</sub>1-like reaction pathway was exergonic (3.5 kcal/mol) with an overall free-energy barrier of 26.2 kcal/mol. Consistent with the mechanistic studies, the radical mechanism was ruled out because the homolysis of the C–Cl bond in **2k** seemed unfavorable as it required higher energy (by >20 kcal/mol) than that in the heterolysis of the C–Cl bond (Figure S4). Moreover, the S<sub>N</sub>2 mechanism in which a styrene directly attacks the C(sp<sup>3</sup>) atom of **2k** to release a chloride anion was ruled out because it encounters a 5 kcal/mol higher energy barrier than that in the S<sub>N</sub>1-like mechanism.

### Figure 6. DFT calculations and SAPT analysis.

SAPT analysis evaluates the intermolecular interaction energy between the fragments of the obtained TS in the C–Cl bond insertion reaction (Figure 6B). The results from this energy decomposition calculation clearly show a strong electrostatic stabilization interaction of ~77.2 kcal/mol between the chloride anion and its bounded benzylic counterpart. Interestingly, almost half of the electrostatic stabilization (i.e., ~35.6 kcal/mol) was found between styrene and the remaining fragments in the TS. Furthermore, second-order perturbation analysis based on natural bond orbital calculations showed that a strong orbital interaction existed between the pz orbital of the carbocation and p bonding orbital of the olefin fragment of styrene. The calculated second-order perturbation energy was 108.2 kcal/mol. Therefore, the temporary anchorage of the chloride anion provided a channel for the nucleophilic attack of an olefin and facilitated its subsequent combination with a newly generated carbocation, providing an almost synergetic reaction mode while suppressing the possible side reactions associated with the carbocation. Therefore, the insertion reaction of alkenes into C–X bonds was controlled by intrinsic factors such as strong orbital interactions and electrostatic stabilizations between the fragments involved in the reactions. However, if the reaction is performed under a non-aggregated state, the abovementioned TSs or intermediates would be excluded owing to their inevitable and much stronger interactions with solvent.

## Discussion

In summary, a new strategy relying on aggregated state has enabled the catalyst-free insertion of alkenes into C–X bonds. The difunctionalization of alkene can be realized without using any transition metal catalysts in the aggregated state. Practically, alkenes were inserted into C–X (X = Cl, Br, and I) bonds *via* ionic mode. The method exhibits excellent atom and step economy and environmental sustainability. Moreover, its practicality is highlighted by a broad substrate scope, excellent functional-group tolerance, and extremely simple operation. The method tolerates active functional groups such as CHO, B(OH)<sub>2</sub>, CO<sub>2</sub>H, Me<sub>2</sub>SiH, alkynes, and CO<sub>2</sub>Me, which are often incompatible in transition-metal catalyzed or Lewis-acid catalyzed reactions. This work is the first attempt to apply aggregate science to the field of synthetic chemistry, which further expands the application reaction of aggregation strategy as well as provides a new idea for designing new reactions in organic chemistry.

## Materials and Methods

General procedure for probing the scope of insertion of alkenes into carbon-halogen bonds. To an oven-dried, 10 mL Teflon-lined screw-capped Pyrex test tube was added aryl ethylenes (0.6 mmol) and benzyl halides (1.8 mmol) without argon protection. A magnetic stir bar were added to the tube carefully and the mixture was stirred slowly for 5 min at room temperature. Then increase the temperature to 100 degC and continue to stir for extra 5 h. After being cooled down to room temperature, it was purified by flash chromatography on silica gel to afford pure product. DFT calculations were performed using the ORCA program and SAPT analysis was performed using the PSI4 code at the SAPT2+/aug-cc-pVDZ level.

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## Conflict of Interests

The authors declare no conflict of interests.

## Supporting Information

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Molecular aggregation affects the electronic interactions between molecules and has emerged as a powerful tool in material science. In this study, aggregation strategy was applied to synthetic chemistry, ionic insertion of alkene into carbon-halogen bond can occur smoothly in aggregated state without any catalysts. Results show that the non-aggregated state may quench the transition state and terminate the insertion process.

**Keywords** aggregation enabled alkene insertion, solvent-free and catalyst-free, atom-and step-economy

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**Title** Aggregation-enabled Alkene Insertion into Carbon-Halogen Bonds

ToC figure