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ICl-Mediated Functional Group Interconversion from Methyl Homopropargyl Ether to α-Iodo-γ-chloroketone

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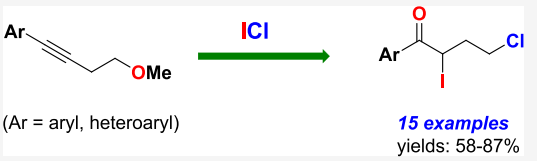
ABSTRACT: An ICl-mediated highly chemo- and regioselective functional group interconversion from methyl homopropargyl ether to α-iodo-γ-chloroketone is reported. Density functional theory (DFT)-calculated reaction coordinate and potential energy surface support the high chemo-selectivity observed for the formation of α-iodo-γ-chloroketone over furan. The five-membered oxonium ring formation−ring opening mechanism is a potential template for the preparation of polyfunctionalized carbonyl compounds.



INTRODUCTION

As a group of versatile synthetic building blocks, halogenated ketones have attracted enormous interest of both organic and medicinal chemists.[1] Among the halogenated ketones explored so far, α-haloketones have received the most attention, which is probably attributed to the ease of keto−enol tautomerization and the high nucleophilicity of the enol species. Numerous synthetic methods have been developed for α-haloketones, including direct α-halogenation of ketones[2] and oxyhalogenation of alkynes[3] or alkenes.[4]

γ-Haloketones have also attracted considerable attention for their significant role as synthetic building blocks in the preparation of pharmaceutical products such as the anti-dopaminergic drug, droperidol,[5] and the antidepressant drug, vilazodone.[6] Hence, quite a few versatile synthetic protocols have been developed for γ-haloketones,[1a] such as ring opening halogenation of cyclobutanols,[7] hydrogen halide mediated ring opening of cyclopropyl ketones,[8] and CuOTf-catalyzed regioselective chlorination at secondary or tertiary γ-C−H bond of ketones.[9]

Alkyl halides are a group of versatile functional groups well-known as facile handles in substitution,[10] elimination,[11] and cross coupling reactions.[12] Synthesis of dihaloalkyl ketones with two halogen groups regioselectively installed at different positions on the alkyl chain is highly attractive due to the fact that it creates both structural diversity and complexity in one simple transformation. However, examples of such regioselective synthesis of dihaloalkyl ketones are still scarce. To date, the known examples are mostly limited to the preparation of chemically more approachable vicinal dihalides such as α,β-dihaloalkyl ketones.[13]

α,γ-Dihalo ketones are a group of high-value synthetic building blocks employed in the synthesis of a variety of bioactive compounds, including those used for the treatment of cancer[14] and osteoporosis,[15] and as nematicides,[16] microbicides, and plant growth regulators.[17] However, only sporadic examples are known for the synthesis of α,γ-dihalo ketones, including two examples prepared by $FeCl_3$-induced direct α-halogenation of γ-haloalkyl-ketones (Scheme 1, eq 1),[2b] four examples prepared by iodobenzene dichloride induced ring-opening 1,3-dichlorination of donor−acceptor cyclopropanes (Scheme 1, eq 2),[18] one example prepared by hydrobromic acid mediated ring-opening of 2-acetyl-2-bromo-4-butanolide (Scheme 1, eq 3),[19] and one example prepared by $HgCl_2/I_2$-mediated ring-opening of cyclopropyl phenyl ketone (Scheme 1, eq 4).[20] More facile and efficient synthetic methods for the preparation of α,γ-dihalo ketones that cover a broader substrate scope are still in high demand.

Developing facile and efficient synthetic methods to transform readily available starting materials into more complex and multifunctional molecules with high chemo- and regioselectivity is one of the ongoing tasks of modern synthetic chemists. Alkynes play a significant role in functional group interconversion due to their ready availability and versatility in conversions to a wide range of valuable chemical functional groups.[21] They are well known as synthetic equivalents of ketones.[22] Although the conversion of alkynes to halo ketones has been widely explored via oxyhalogenation of alkynes,[3,23] the known methods all exclusively led to the formation of α-haloketones. To our best knowledge, the direct transformation from alkyne derivatives to α,γ-dihalo ketones is still unknown. Our interest in iodine-induced electrophilic cyclization of alkynes[24] has led us to the discovery of a facile

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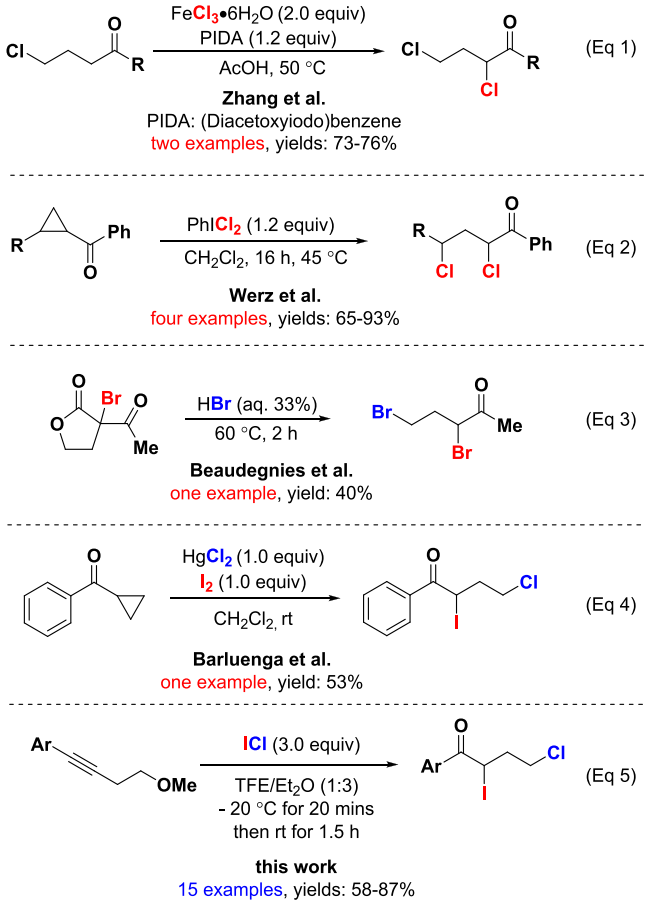
Scheme 1. Literature Methods and Our Approach for the Synthesis of α,γ-Dihalo Ketones

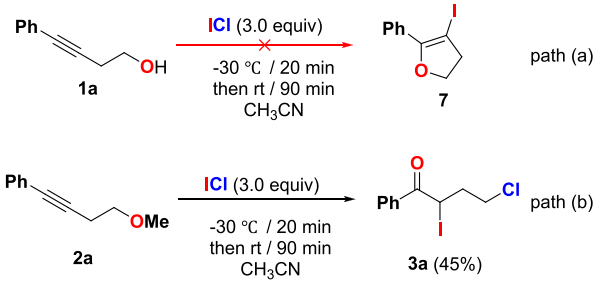


ICl-induced functional group interconversion from readily available methyl homopropargyl ethers to α,γ-dihalo ketones (Scheme 1, eq 5). We herein report the details of the new synthetic approach.

RESULTS AND DISCUSSION

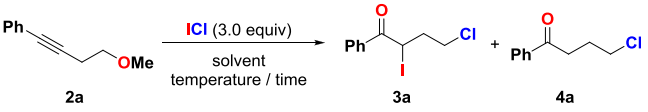
Homopropargyl alcohols are known to undergo iodine-induced intramolecular cyclization, leading to furans.[25] When we first examined the possibility of preparing 4-iodo-5-phenyl-2,3-dihydrofuran (**7**) by an iodine monochloride (ICl)-induced cyclization of 4-phenylbut-3-yn-1-ol (**1a**), we however obtained an unidentifiable mixture (Scheme 2, path a). We subsequently explored the ICl-induced intramolecular cyclization of (4-methoxybut-1-yn-1-yl)benzene (**2a**), which led to an unprecedented functional group interconversion, forming 4-chloro-2-iodo-1-phenylbutan-1-one (Scheme 2, path b) instead of the desired furan product. Considering the high synthetic value of α,γ-dihalo ketones and the excellent chemo- and regioselectivity observed in this novel chemical transformation, we decided to explore the reaction in more detail.

Scheme 2. Our Early-Stage Study of the ICl-Induced Functional Group Interconversion of Homopropargyl Alcohol (1a) and Methyl Homopropargyl Ether (2a)



The ICl induced conversion of (4-methoxybut-1-yn-1-yl)benzene (**2a**) was first tested in the presence of 3 equiv of ICl in acetonitrile (CH_3CN). The reaction mixture was stirred at −30 °C for 20 min and then at room temperature for 90 min until thin-layer chromatography showed that all starting materials (**2a**) were consumed (Table 1, entry 1). 4-Chloro-2-iodo-1-phenylbutan-1-one (**3a**) was obtained in a 45% yield after column chromatography. We inspected the temperature effect by first stirring the reaction mixtures for 20 min at −45, −20, and −10 °C, respectively (Table 1, entries 2−4). The best yield obtained was 46% when the reaction was first stirred at −20 °C for 20 min (Table 1, entry 3). We also carried out the reaction in the presence of two and four equivalents of ICl (Table 1, entries 5 and 6), but neither condition afforded a better yield. We further examined the reaction in different solvents other than CH_3CN, including 1,2-dichloroethane (DCE), dichloromethane (DCM), 2,2,2-trifluoroethanol (TFE), and diethyl ether (Et_2O), which resulted in 51%, 38%, 44%, and 61% yield, respectively (Table 1, entries 7−10). We subsequently examined a combination solvent of TFE and Et_2O (volume ratio as 1:3), and obtained **3a** in a 73% yield (Table 1, entry 11). It is worth

Table 1. Reaction Condition Optimization[a]



entry	temp./time	solvent	yield 3a[b]	yield 4a[b]
1	−30 °C/20 min, then rt/90 min	CH_3CN	45%	trace
2	−45 °C/20 min, then rt/90 min	CH_3CN	26%	trace
3	−20 °C/20 min, then rt/90 min	CH_3CN	46%	trace
4	−10 °C/20 min, then rt/90 min	CH_3CN	40%	trace
5[c]	−20 °C/20 min, then rt/90 min	CH_3CN	42%	trace
6[d]	−20 °C/20 min, then rt/90 min	CH_3CN	40%	trace
7	−20 °C/20 min, then rt/90 min	DCE	51%	4%
8	−20 °C/20 min, then rt/90 min	DCM	38%	8%
10	−20 °C/20 min, then rt/90 min	Et_2O	61%	4%
11	−20 °C/20 min, then rt/90 min	TFE/Et_2O (1/3)	73%	9%
12[e]	−20 °C/20 min, then rt/90 min	TFE/Et_2O (1/3)	83%	4%
13[e]	rt/2 h	TFE/Et_2O (1/3)	71%	5%

[a]General procedure: **2a** (80.1 mg, 0.5 mmol, 1.0 equiv) and solvent (4 mL) were added to a 25 mL round-bottom flask sealed with a rubber septum. The reaction mixture was cooled to the designated temperature. ICl (3.0 equiv) was added dropwise to the reaction mixture. The reaction mixture was stirred at the designated temperature for 20 min. The cooling bath was removed, and the mixture was stirred at room temperature for 90 min. [b]Isolated yields after column chromatography. [c]4 equiv of ICl was added into the reaction. [d]2 equiv of ICl was added into the reaction. [e]The glassware was flame-dried and both TFE and Et_2O were dried over activated 4 Å molecular sieves for 2 days before use.

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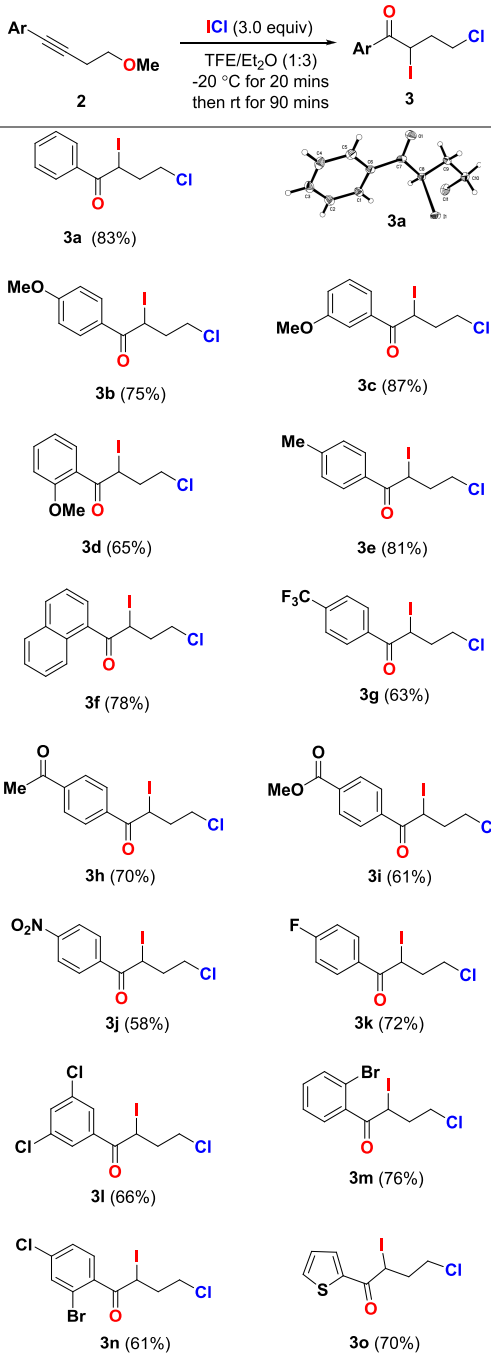
noting that 4-chloro-1-phenylbutan-1-one (**4a**) was observed as a side product during our investigation of the current ICl-induced functional group interconversion. In the combination solvent of TFE and Et_2O (1:3), **4a** was obtained in a 9% yield (Table 1, entry 11). We subsequently carried out the reaction in anhydrous solvents and were able to further raise the yield of **3a** to 83% and meanwhile to reduce the formation of **4a** to a 4% yield. When the reaction was completely carried out at room temperature, the chemical yield of **3a** dropped to 71% and **4a** was obtained in a 5% yield (Table 1, entry 13).

After determining the optimal conditions, we examined the substrate scope by employing a variety of methyl arylhomopropargyl ethers bearing diverse functional groups. Both electron-donating groups such as methoxy (Table 2, **3b**–**d**) and methyl (**3e**) and electron-withdrawing groups such as trifluoromethyl (**3g**), ketone (**3h**), ester (**3i**), nitro (**3j**), and halogens (**3k**–**n**) are well tolerated in the reaction. However, lower chemical yields were obtained when a strong electron-withdrawing group is present at the *para*-position of the phenyl ring, such as trifluoromethyl (**3g**), ketone (**3h**), ester (**3i**), and nitro (**3j**). About 10% to 15% of a mixture of regioisomers generated from the direct addition of ICl to an alkyne triple bond was observed in these cases. Steric hindrance was detrimental to the reaction yield. A lower chemical yield was obtained when a steric hindered substituent is present at the *ortho*-position of the phenyl group (**3d** and **3n**). In addition, naphthalene (**3f**) and thienyl groups (**3o**) were both well accommodated, affording good yields of the corresponding α-iodo-γ-chloro-ketones. 4-Chloro-1-aryllbutan-1-ones, analogues of **4a**, were observed in the reactions of most substrates investigated. However, these side products in general were obtained in less than 10% yield and were not fully characterized. In order to unambiguously prove the observed functional group interconversion, we developed a single crystal of compound **3a**. The X-ray crystallographic analysis confirmed its proposed chemical structure (see the Supporting Information for the details).

A plausible mechanism is proposed and illustrated in Scheme 3, employing compound **2a** as a sample substrate. The reaction presumably takes place from an ICl-induced 5-*endo-dig* cyclization of the methyl homopropargyl ether (**2a**) forming a five-membered oxonium ring intermediate (**5**). A nucleophilic attack of a chloride anion at the methylene carbon next to the oxonium ion leading to a ring-opening intermediate (**6**) (Scheme 3, path a). The latter undergoes protonation, demethylation by either a chloride or 2,2,2-trifluoroethoxide anion, and subsequent enol–keto tautomerization, leading to the corresponding α-iodo-γ-chloro-ketone (**3a**).

It is worth noting that the ICl-induced 5-*endo-dig* cyclization of the methyl homopropargyl ether led to the formation of an intimate ion pair between the oxonium ion and chloride. The subsequent S_Ni (substitution nucleophilic intramolecular) reaction with a chloride anion may take place via two probable pathways as shown in the schematic reaction coordinate (Figure 1) calculated at the SMD (solvent = diethylether)//ωB97XD/LANL2DZ level of theory. Due to the interaction between the oxonium cation and chloride anion, the chloride ion selectively attacks the sp^3-hybridized carbons from the same side of the oxonium ion in both reaction pathways.[26] Pathway (a): the chloride anion attacks the α-methylene carbon of the oxonium intermediate via a transition state **TS5-6**, leading to a ring-opening intermediate **6**; and pathway (b): the chloride anion attacks the methyl group on the oxonium intermediate via a transition state **TS5-7**, forming a furan (**7**) and CH_3Cl. A more comprehensive view of the two S_Ni pathways is provided by a 2D relaxed potential energy surface (PES, Figure 2) which was scanned along the reaction

Table 2. Synthesis of α-Iodo-γ-chloro-ketones from Methyl Homopropargyl Ethers[a,b]



[a]General procedure: Methyl homopropargyl ether **2** (1.0 mmol, 1.0 equiv) and 2,2,2-trifluoroethanol/diethyl ether (2 mL/5 mL) were added to a 25 mL flame-dried round-bottom flask sealed with a rubber septum. The reaction mixture was cooled to −20 °C. ICl (3 equiv, dissolved in 1 mL of Et_2O) was added dropwise to the reaction mixture via a syringe. The resulting mixture was stirred at −20 °C for 20 min and then at room temperature for 90 min. [b]Isolated yields after column chromatography.

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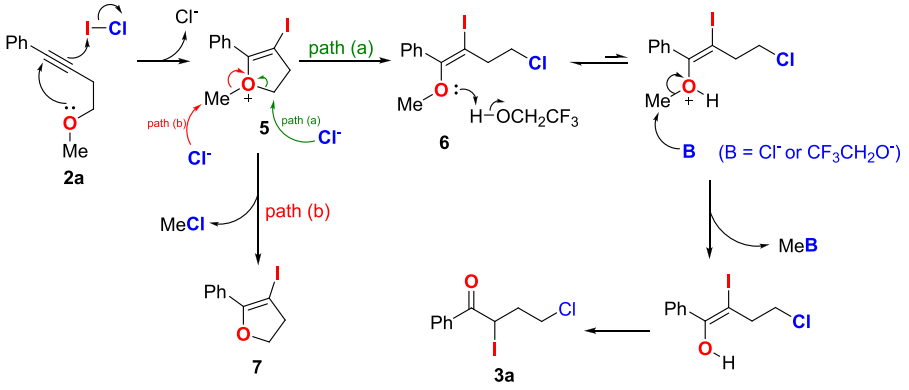
Scheme 3. Proposed Mechanism for the ICl-Induced Functional Group Interconversion



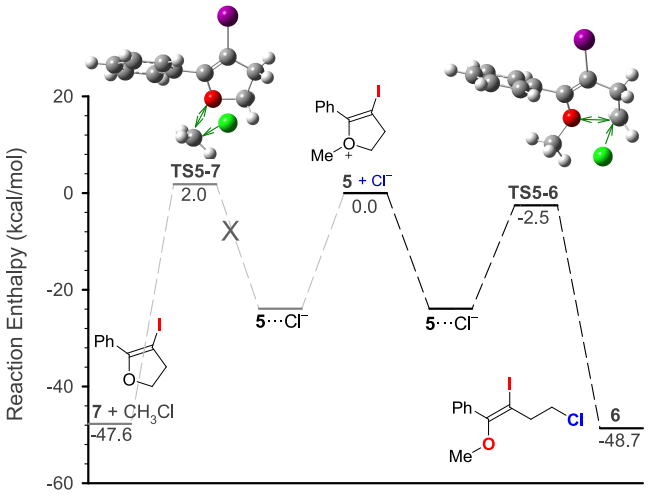


Figure 1. Two probable S_Ni reaction pathways of the intermediate **5** with Cl^- in diethylether, calculated at the ωB97XD/LANL2DZ level of theory. Reaction enthalpies are relative to the sum of **5** + Cl^- and include thermal corrections to 298 K. Diethylether solvation effects were calculated using the SMD model. For TSs, vibrational modes corresponding to imaginary frequencies/transition vectors are indicated by displacement vectors.

coordinates R(Cl−CH_2) and R(Cl−CH_3) in an ion−molecule complex of **5**···Cl^-. R(Cl−CH_2) is the distance between the chloride and the α-methylene carbon, which describes the formation of **6**. R(Cl−CH_3) is the distance between the chloride and the methyl carbon, which follows the reaction trajectory leading to **7** + $CHCl_3$. The PES scanned R(Cl−CH_2) from 4.0 to 1.6 Å and R(Cl−CH_3) from 3.6 to 1.6 Å continuously, with a step size of 0.1 Å for each. All of the other bond lengths and bond angles in the conversion of **5 to 5**···Cl^- were fully optimized at each step using the aforementioned SMD//DFT methods with the solvent parameters that were consistent with the experiment. The computational results may be interpreted in the context of the Arrhenius rate constant equation $k = Ae^{-E_a^{\#}/RT}$, where $E_a^{\#}$ designates the reaction activation energy, R is the gas constant, T represents the reaction temperature, and the pre-exponential factor A represents reaction degeneracy, collision probability, reaction bottleneck, and other kinetics factors. The major findings from the calculated reaction coordinate and PES are the following: (1) the activation energy of **TS5-6** was calculated to be 2.5 kcal/mol below **5**···Cl^-; whereas that of **TS5-7** was calculated to be 2 kcal/mol above **5**···Cl^-. The energy difference in the two transition states accounts for a factor of 10^3 difference in the rate constants leading to **6** vs **7**; (2) the reaction 2D PES shows that the pathway leading from **5**···Cl^- to **6** crosses a strip of high-energy but wide plateau (labeled **TS5-6**, with R(Cl−CH_2) = 2.6 Å and R(Cl−CH_3) in the range of 2.6−3.6 Å), which indicates that **TS5-6** is a loose transition state and is restricted mostly by the R(Cl−CH_2) bond length. In contrary, the pathway leading from **5**···Cl^- to **7** has to pass through a saddle point, which is located exactly at R(Cl−CH_2) = 3.0 and R(Cl−CH_3) = 2.4 Å (indicated by * in the PES). The implication is that this pathway bears a very tight bottleneck imposed by the R(Cl−CH_2) and R(Cl−CH_3) bond lengths. The distinctively different landscapes in the PES for the two reaction pathways lead to different dynamics, which should be factored into the pre-exponential factor A in the Arrhenius equation. On the basis of the DFT calculations, the formation of **6** is both thermodynamically more feasible (i.e., the product **6** produces more reaction exothermicity than that of **7** + CH_3Cl) and kinetically more favorable (i.e., the relatively low-energy and loose **TS5-6** vs the high-energy and tight bottleneck of **TS5-7**).

CONCLUSIONS

In summary, an efficient, benign, and straightforward ICl-mediated functional group interconversion from methyl homopropargyl ethers to α-iodo-γ-chloro-ketones has been developed. The new synthetic method employs readily available starting materials and well accommodates diverse conventional functional groups, leading to α,γ-dihalo ketones in a regiospecific manner with advanced molecular complexity. The reaction protocol involves iodo-induced intramolecular cyclization via oxyiodination to form a favorable five-membered oxonium ring intermediate, which undergoes ring-opening via a chloride anion-induced nucleophilic substitution. Our DFT calculation shows that the high chemoselectivity results from the kinetically favored nucleophilic substitution pathway on the methylene group inside the five-membered oxonium ring intermediate. Our future study will focus on applying the five-membered oxonium ring formation−ring opening mechanism template in the preparation of poly-functionalized carbonyl compounds. The corresponding results will be reported in due course.

EXPERIMENTAL SECTION

General Information. All commercially available chemicals were used as received without further purification, unless otherwise noted. Diethyl ether and 2,2,2-trifluoroethanol were dried by 4 Å molecular

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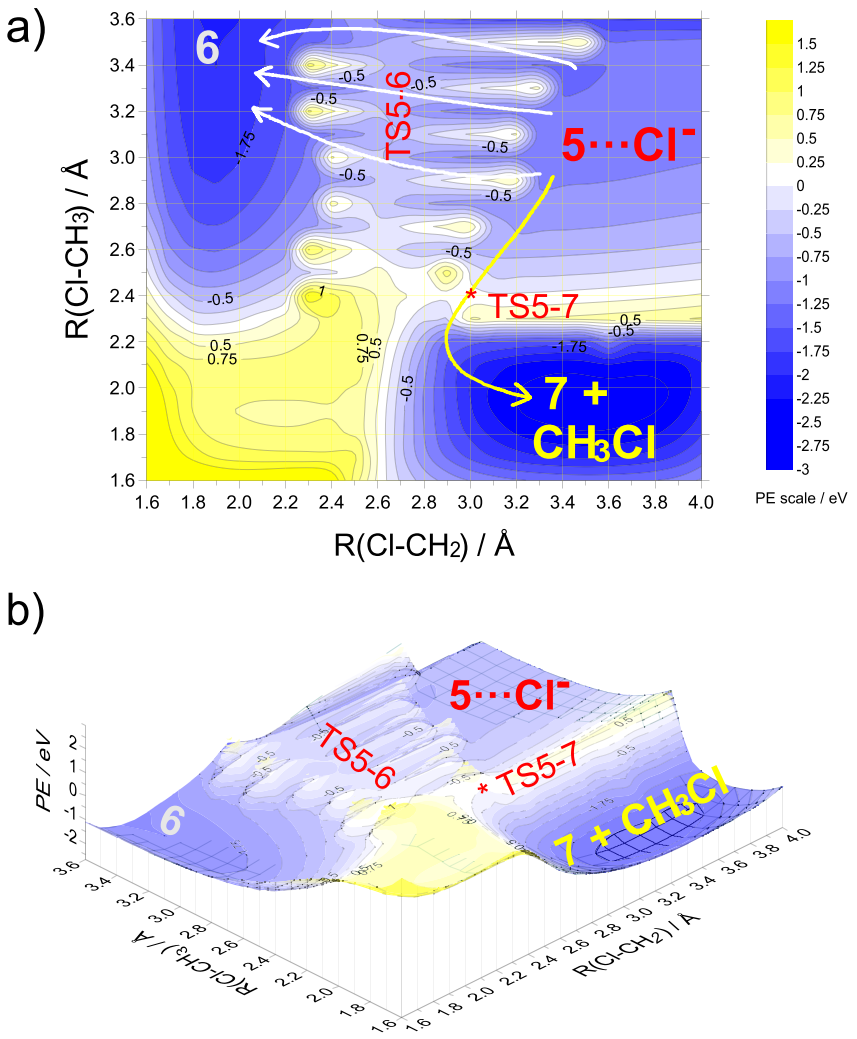

Figure 2. (a) Contour map and (b) 3D surface for a relaxed 2D-PES scan along the R(Cl−CH_2) and R(Cl−CH_3) bond lengths in an ion−molecule complex of **5**···Cl^-. Numbers in the contour map are the electronic potential energies (with respect to the sum of **5** + Cl^-) calculated at the ωB97XD/LANL2DZ level of theory. Diethylether solvation effects were calculated using the SMD model.

sieves overnight before use. Molecular sieves (4 Å) were activated at 200 °C at 0.5 mmHg for a week before use. All ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded at either 400 or 500 MHz and 100 or 125 MHz, respectively, using $CDCl_3$ as the solvent. The chemical shifts of all ^{1}H and ^{13}C{1H} NMR spectra are referenced to the residual signal of $CDCl_3$ (δ 7.26 ppm for the ^{1}H NMR spectra and δ 77.23 ppm for the ^{13}C{^{1}H} NMR spectra). ^{19}F NMR spectra were recorded at 376 MHz with fluorobenzene as the internal standard and $CDCl_3$ as the solvent. The chemical shifts of the ^{19}F NMR spectra are referenced to fluorobenzene (δ −113.15 ppm). The high-resolution mass analysis was carried out on high-resolution mass spectrometers using either electrospray ionization (ESI) or a heated electrospray ionization (HESI) method. Samples were dissolved in methylene chloride and methanol or methylene chloride and acetonitrile and analyzed via flow injection into the mass spectrometer at a flow rate of 200 μL/min. The mobile phase was 90:10 methanol:water, with 0.1% formic acid, or 90:10 acetonitrile:water, with 0.1% formic acid. The melting points are uncorrected.

Procedure for the Preparation of 4-Phenylbut-3-yn-1-ol (1a). An oven-dried 100 mL round-bottom flask was charged with $PdCl_2(PPh_3)_2$ (42.1 mg, 0.06 mmol, 2 mol %), CuI (5.7 mg, 0.03 mmol, 1 mol %), iodobenzene (612.0 mg, 3.0 mmol, 1.0 equiv), 3-butyn-1-ol (252.4 mg, 3.6 mmol, 1.2 equiv), and triethylamine (30 mL). The flask was flushed with nitrogen and sealed with a rubber septum. The reaction mixture was stirred at room temperature overnight until the disappearance of the starting material monitored by thin-layer chromatography. The reaction mixture was diluted with diethyl ether (40 mL) and washed with brine (40 mL). The aqueous phase was then extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated using a rotary evaporator at 45 °C under reduced pressure (20 mmHg). The resulting residue was purified by flash column chromatography on silica gel (eluent: 3/1 hexanes/ethyl acetate). This product was obtained as a light-yellow oil (429.8 mg, 98% yield): R_f = 0.26 (1:3 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.42 (m, 2H), 7.27−7.30 (m, 3H), 3.82 (t, J = 6.4 Hz, 2H), 2.70 (t, J = 6.3 Hz, 2H), 1.91 (s, 1H). The ^{1}H NMR spectral data are in good agreement with the literature data.[27]

General Procedure for the Preparation of Methyl Homopropargyl Ethers (2). An oven-dried 100 mL round-bottom flask was charged with $PdCl_2(PPh_3)_2$ (42.1 mg, 0.06 mmol, 2 mol %), CuI (5.7 mg, 0.03 mmol, 1 mol %), aryl iodide (3.0 mmol, 1.0 equiv), 4-methoxybut-1-yne (302.8 mg, 3.6 mmol, 1.2 equiv), and triethylamine (30 mL). The flask was flushed with nitrogen and sealed with a rubber septum. The reaction mixture was stirred at room temperature overnight until the disappearance of the starting material monitored by thin-layer chromatography. The reaction mixture was diluted with diethyl ether (40 mL) and washed with brine (40 mL). The aqueous phase was then extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated using a rotary evaporator at 45 °C under reduced

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pressure (20 mmHg). The resulting residue was purified by flash column chromatography on silica gel.

*(4-Methoxybut-1-yn-1-yl)benzene (**2a**).* This product was obtained as a light-yellow oil (456.6 mg, 95% yield). Flash column chromatography eluent: 1/10 ethyl acetate/hexanes, R_f = 0.77 (1:10 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.42 (m, 2H), 7.27−7.29 (m, 3H), 3.60 (t, J = 7.0 Hz, 2H), 3.41 (s, 3H), 2.70 (t, J = 7.0 Hz, 2H). The ^{1}H NMR spectral data are in good agreement with the literature data.[28]

*1-Methoxy-4-(4-methoxybut-1-yn-1-yl)benzene (**2b**).* This product was obtained as a colorless oil (519.2 mg, 91% yield). Flash column chromatography eluent: 1/10 ethyl acetate/hexanes, R_f = 0.57 (1:10 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 3.79 (s, 3H), 3.58 (t, J = 7.2 Hz, 2H), 3.41 (s, 3H), 2.67 (t, J = 7.1 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.3, 133.1, 115.9, 113.9, 85.2, 81.3, 71.2, 58.8, 55.3, 20.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{15}O_2$ 191.1067; Found 191.1065.

*1-Methoxy-3-(4-methoxybut-1-yn-1-yl)benzene (**2c**).* This product was obtained as a yellow oil (524.9 mg, 92% yield). Flash column chromatography eluent: hexanes, R_f = 0.33 (hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, J = 7.6 Hz, 1H), 7.00 (d, J = 7.3 Hz, 1H), 6.94 (s, 1H), 6.81 (d, J = 8.4 Hz, 1H), 3.74 (s, 3H), 3.56 (t, J = 6.9 Hz, 2H), 3.37 (s, 3H), 2.66 (t, J = 6.9 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.3, 129.3, 124.7, 124.2, 116.6, 114.3, 86.7, 81.4, 70.8, 58.7, 55.1, 20.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{15}O_2$ 191.1067; Found 191.1065.

*1-Methoxy-2-(4-methoxybut-1-yn-1-yl)benzene (**2d**).* This product was obtained as a yellow oil (507.8 mg, 89% yield). Flash column chromatography eluent: 1/3 ethyl acetate/hexanes, R_f = 0.69 (1:3 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (dd, J = 7.8, 1.9 Hz, 1H), 7.23−7.26 (m, 1H), 6.82−6.88 (m, 2H), 3.85 (s, 3H), 3.61 (t, J = 7.3 Hz, 2H), 3.39 (s, 3H), 2.75 (t, J = 7.2 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 160.0, 133.9, 129.3, 120.5, 112.7, 110.6, 90.9, 77.7, 71.1, 58.8, 55.9, 21.1; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{14}O_2Na$ 213.0886; Found 213.0884.

*1-(4-Methoxybut-1-yn-1-yl)-4-methylbenzene (**2e**).* This product was obtained as a light-yellow oil (480.8 mg, 92% yield). Flash column chromatography eluent: hexanes, R_f = 0.33 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J = 7.3 Hz, 2H), 7.09 (d, J = 7.3 Hz, 2H), 3.59 (t, J = 6.9 Hz, 2H), 3.41 (s, 3H), 2.69 (t, J = 6.6 Hz, 2H), 2.33 (s, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[29]

*1-(4-Methoxybut-1-yn-1-yl)naphthalene (**2f**).* This product was obtained as a light-yellow oil (523.6 mg, 83% yield). Flash column chromatography eluent: 1/10 ethyl acetate/hexanes, R_f = 0.55 (1:10 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, J = 8.3 Hz, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.79 (d, J = 8.3 Hz, 1H), 7.63 (dd, J = 7.1, 0.8 Hz, 1H), 7.54−7.56 (m, 1H), 7.48−7.52 (m, 1H), 7.40 (dd, J = 8.2, 7.1 Hz, 1H), 3.71 (t, J = 7.0 Hz, 2H), 3.46 (s, 3H), 2.86 (t, J = 6.9 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 133.7, 133.4, 130.4, 128.4, 126.8, 126.5, 125.4, 121.5, 91.9, 79.7, 71.2, 59.0, 21.2 (missing two aromatic carbon peaks due to signal overlap); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{15}O$ 211.1117; Found 211.1112.

*1-(4-Methoxybut-1-yn-1-yl)-4-(trifluoromethyl)benzene (**2g**).* This product was obtained as a light-yellow oil (527.1 mg, 77% yield). Flash column chromatography eluent: 1/10 ethyl acetate/hexanes, R_f = 0.55 (1:10 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49−7.54 (m, 4H), 3.60 (t, J = 6.7 Hz, 2H), 3.42 (s, 3H), 2.71 (t, J = 6.8 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 132.1, 129.7 (q, J_{C-F}= 33.9 Hz), 127.7, 125.3 (q, J_{C-F} = 3.7 Hz), 123.6 (q, J_{C-F} = 270.9 Hz), 89.8, 80.5, 70.8, 58.9, 20.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.90 (s, 3F); HRMS (HESI-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{12}H_{12}F_3O$ 229.0835; Found 229.0835.

*1-(4-(4-Methoxybut-1-yn-1-yl)phenyl)ethan-1-one (**2h**).* This product was obtained as a light-yellow oil (570.5 mg, 94% yield). Flash column chromatography eluent: 1/10 ethyl acetate/hexanes, R_f = 0.38 (1:10 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, J = 8.6 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 3.61 (t, J = 6.9 Hz, 2H), 3.42 (s, 3H), 2.73 (t, J = 6.9 Hz, 2H), 2.59 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 197.3, 135.8, 131.7, 128.6, 128.1, 90.7, 80.9, 70.5, 58.7, 26.5, 20.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{15}O_2$ 203.1067; Found 203.1064.

*Methyl-4-(4-methoxybut-1-yn-1-yl)benzoate (**2i**).* This product was obtained as a colorless oil (563.2 mg, 86% yield). Flash column chromatography eluent: 1/10 ethyl acetate/hexanes, R_f = 0.28 (1:10 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H), 3.89 (s, 3H), 3.59 (t, J = 6.8 Hz, 2H), 3.40 (s, 3H), 2.70 (t, J = 6.8 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.8, 131.8, 129.6, 129.3, 128.6, 90.4, 81.1, 70.8, 59.0, 52.4, 20.9; HRMS (HESI-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{13}H_{15}O_3$ 219.1016; Found 219.1015.

*1-(4-Methoxybut-1-yn-1-yl)-4-nitrobenzene (**2j**).* This product was obtained as an orange solid (498.6 mg, 81% yield). m.p. = 43.1−44.5 °C; flash column chromatography eluent: 1/5 ethyl acetate/hexanes, R_f = 0.53 (1:5 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13−8.15 (m, 2H), 7.51−7.54 (m, 2H), 3.60 (t, J = 7.8 Hz, 2H), 3.41 (s, 3H), 2.73 (t, J = 6.5 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 146.7, 132.4, 130.8, 123.5, 93.2, 80.0, 70.4, 58.8, 20.9; HRMS (HESI-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{11}H_{12}NO_3$ 206.0812; Found 206.0812.

*1-Fluoro-4-(4-methoxybut-1-yn-1-yl)benzene (**2k**).* This product was obtained as a colorless oil (384.9 mg, 72% yield). Flash column chromatography eluent: 1/10 ethyl acetate/hexanes, R_f = 0.65 (1:10 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.39 (m, 2H), 6.94−6.98 (m, 2H), 3.57 (t, J = 7.1 Hz, 2H), 3.39 (s, 3H), 2.66 (t, J = 6.9 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 162.3 (d, J_{C-F} = 246.3 Hz), 133.6 (d, J_{C-F} = 8.5 Hz), 119.8 (d, J_{C-F} = 2.8 Hz), 115.5 (d, J_{C-F} = 22.1 Hz), 86.5 (d, J_{C-F} = 1.7 Hz), 80.5, 71.0, 58.9, 20.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.08 − −112.00 (m, 1F); HRMS (HESI-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{11}H_{12}FO$ 179.0867; Found 179.0867.

*1,3-Dichloro-5-(4-methoxybut-1-yn-1-yl)benzene (**2l**).* This product was obtained as a colorless oil (522.3 mg, 76% yield). Flash column chromatography eluent: hexanes, R_f = 0.33 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25−7.26 (m, 3H), 3.56 (t, J = 6.9 Hz, 2H), 3.39 (s, 3H), 2.67 (t, J = 6.7 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 134.8, 130.0, 128.2, 126.6, 89.9, 79.2, 70.6, 58.9, 20.7; HRMS (HESI-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{11}H_{11}Cl_2O$ 229.0181; Found 229.0182.

*1-Bromo-2-(4-methoxybut-1-yn-1-yl)benzene (**2m**).* This product was obtained as a light-yellow oil (631.2 mg, 88% yield). Flash column chromatography eluent: 1/10 ethyl acetate/hexanes, R_f = 0.55 (1:10 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (dd, J = 8.0, 1.3 Hz, 1H), 7.44 (dd, J = 7.6, 1.7 Hz, 1H), 7.20 (td, J = 7.5, 1.3 Hz, 1H), 7.10 (td, J = 7.9, 1.6 Hz, 1H), 3.62 (t, J = 6.9 Hz, 2H), 3.40 (s, 3H), 2.75 (t, J = 6.6 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 133.5, 132.4, 129.0, 127.0, 125.8, 125.6, 92.0, 80.3, 70.8, 58.9, 21.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{12}BrO$ 239.0066; Found 239.0066.

*2-Bromo-4-chloro-1-(4-methoxybut-1-yn-1-yl)benzene (**2n**).* This product was obtained as a light-yellow oil (771.6 mg, 94% yield). Flash column chromatography eluent: hexanes, R_f = 0.51 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 2.1 Hz, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.19 (dd, J = 8.5, 2.1 Hz, 1H), 3.62 (t, J = 6.8 Hz, 2H), 3.41 (s, 3H), 2.75 (t, J = 7.0 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 133.88, 133.85, 132.0, 127.3, 125.9, 124.3, 93.0, 79.3, 70.5, 58.7, 20.9; HRMS (HESI-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{11}H_{11}BrClO$ 272.9676; Found 272.9676.

*2-(4-Methoxybut-1-yn-1-yl)thiophene (**2o**).* This product was obtained as a light-yellow oil (463.7 mg, 93% yield). Flash column chromatography eluent: 1/10 ethyl acetate/hexanes, R_f = 0.72 (1:10 ethyl acetate:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (dd, J = 5.2, 1.2 Hz, 1H), 7.14−7.15 (m, 1H), 6.93 (dd, J = 5.0, 3.6 Hz, 1H), 3.59 (t, J = 6.7 Hz, 2H), 3.40 (s, 3H), 2.71 (t, J = 6.8 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 131.6, 127.0, 126.4, 123.9, 91.0, 74.8, 70.8, 59.0, 21.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_9H_{11}OS$ 167.0525; Found 167.0524.

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General Procedure for the Preparation of α-Iodo-γ-chloroketones (3). A flame-dried 25 mL round-bottom flask was charged with methyl homopropargyl ether (**2**, 1.0 mmol, 1.0 equiv) and 2,2,2-trifluoroehtanol/diethyl ether (2 mL/5 mL). The reaction mixture was cooled to −20 °C, and an iodine monochloride diethyl ether solution (ICl, 487.1 mg, 3.0 mmol, 3.0 equiv, dissolved in 1 mL of diethyl ether) was added dropwise to the reaction solution. The resulting reaction mixture was stirred at −20 °C for 20 min and then at room temperature for 1.5 h until the thin-layer chromatography showed that all methyl homopropargyl ether was consumed. The reaction mixture was diluted with 20 mL of diethyl ether and washed with saturated sodium thiosulfate (30 mL). The aqueous phase was extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated using a rotary evaporator at room temperature under reduced pressure (20 mmHg). The subsequent residue was purified by flash column chromatography on silica gel to afford the corresponding product.

*4-Chloro-2-iodo-1-phenylbutan-1-one (**3a**).* This product was obtained as a light-yellow solid (256.1 mg, 83% yield). m.p. = 36.2−37.5 °C; flash column chromatography eluent: hexanes, R_f = 0.45 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01−8.03 (m, 2H), 7.59−7.62 (m, 1H), 7.48−7.52 (m, 2H), 5.69 (dd, *J* = 8.1, 6.1 Hz, 1H), 3.70−3.77 (m, 2H), 2.58−2.65 (m, 1H), 2.46−2.52 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 194.1, 134.0, 133.9, 129.1, 128.9, 44.4, 37.2, 22.2; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{10}H_{11}ClIO$ 308.9538; Found 308.9526; FT-IR ($\tilde{\nu}$ = cm^{-1}): 1674(s), 1595(m), 1580(m), 1447(m), 1321(m), 1306(m), 1288(m), 1249(m), 1184(m), 1168(m), 1075(m), 1001(m), 971(m), 844(m), 791(m), 700(s).

*4-Chloro-2-iodo-1-(4-methoxyphenyl)butan-1-one (**3b**).* This product was obtained as a light-yellow oil (254.0 mg, 75% yield). Flash column chromatography eluent: 1/10 ethyl acetate/hexanes, R_f = 0.49 (1:10 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 9.0 Hz, 2H), 6.96 (d, *J* = 9.0 Hz, 2H), 5.64 (dd, *J* = 7.9, 6.1 Hz, 1H), 3.88 (s, 3H), 3.70−3.74 (m, 2H), 2.56−2.63 (m, 1H), 2.43−2.50 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 192.7, 164.2, 131.3, 126.5, 114.3, 55.8, 44.5, 37.3, 22.0; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{11}H_{13}ClIO_2$ 338.9643; Found 338.9644; FT-IR ($\tilde{\nu}$ = cm^{-1}): 1675(m), 1597(s), 1574(m), 1510(m), 1253(s), 1167(s), 1106(m), 1025(s), 842(m), 772(m).

*4-Chloro-2-iodo-1-(3-methoxyphenyl)butan-1-one (**3c**).* This product was obtained as a light-yellow oil (294.6 mg, 87% yield). Flash column chromatography eluent: hexanes, R_f = 0.38 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58−7.59 (m, 1H), 7.54−7.55 (m, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.12−7.15 (m, 1H), 5.66 (dd, *J* = 8.1, 6.2 Hz, 1H), 3.87 (s, 3H), 3.70−3.74 (m, 2H), 2.57−2.63 (m, 1H), 2.45−2.52 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 193.8, 160.1, 135.1, 129.9, 121.2, 120.4, 113.3, 55.6, 44.4, 37.1, 22.2; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{11}H_{13}ClIO_2$ 338.9643; Found 338.9632; FT-IR ($\tilde{\nu}$ = cm^{-1}): 1667(s), 1594(m), 1464(m), 1443(m), 1362(m), 1289(m), 1263(m), 1230(m), 1077(m), 1002(m), 993(m), 939(m), 876(m), 815(m), 800(m).

*4-Chloro-2-iodo-1-(2-methoxyphenyl)butan-1-one (**3d**).* This product was obtained as a light-yellow oil (220.1 mg, 65% yield). Flash column chromatography eluent: 1/10 ethyl acetate/hexanes, R_f = 0.48 (1:10 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.45−7.49 (m, 1H), 7.02 (td, *J* = 7.6, 0.9 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 5.94 (t, *J* = 7.0 Hz, 1H), 3.92 (s, 3H), 3.71−3.76 (m, 1H), 3.65−3.71 (m, 1H), 2.49−2.53 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 196.6, 158.2, 134.3, 132.1, 125.3, 121.2, 111.8, 55.9, 44.5, 37.2, 29.9; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{11}H_{13}ClIO_2$ 338.9643; Found 338.9642; FT-IR ($\tilde{\nu}$ = cm^{-1}): 1678(m), 1581(m), 1485(m), 1463(m), 1435(m), 1284(m), 1243(s), 1180(m), 1162(m), 1114(m), 1048(m), 1020(m), 752(s).

*4-Chloro-2-iodo-1-(p-tolyl)butan-1-one (**3e**).* This product was obtained as a white solid (261.3 mg, 81% yield). m.p. 63.3−64.1 °C. Flash column chromatography eluent: hexanes, R_f = 0.32 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 5.66 (dd, *J* = 8.2 , 6.2 Hz, 1H), 3.67−3.75 (m, 2H), 2.56−2.63 (m, 1H), 2.45−2.51 (m, 1H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 193.6, 145.0, 131.2, 129.7, 129.0, 44.5, 37.1, 22.2, 21.9; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{11}H_{13}ClIO$ 322.9694; Found 322.9691; FT-IR ($\tilde{\nu}$ = cm^{-1}): 1673(s), 1321(m), 1287(s), 1255(m), 1182(m), 1166(m), 852(m), 826(m), 753(s).

*4-Chloro-2-iodo-1-(naphthalen-1-yl)butan-1-one (**3f**).* This product was obtained as a light-red oil (279.7 mg, 78% yield). Flash column chromatography eluent: 1/10 ethyl acetate/hexanes, R_f = 0.62 (1:10 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (dd, *J* = 8.4, 0.4 Hz, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.89 (d, *J* = 7.9 Hz, 1H), 7.85 (dd, *J* = 7.2, 1.0 Hz, 1H), 7.63−7.67 (m, 1H), 7.56−7.59 (m, 1H), 7.50 (dd, *J* = 8.1, 7.2 Hz, 1H), 5.81 (t, *J* = 7.3 Hz, 1H), 3.78−3.83 (m, 1H), 3.72−3.77 (m, 1H), 2.65−2.70 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 196.6, 134.04, 134.02, 133.4, 131.3, 128.6, 128.3, 127.0, 126.1, 125.7, 124.4, 44.8, 37.2, 27.4; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{14}H_{13}ClIO$ 358.9694; Found 358.9682; FT-IR ($\tilde{\nu}$ = cm^{-1}): 1673(m), 1507(m), 1288(m), 1239(m), 797(m), 774(s), 727(m).

*4-Chloro-2-iodo-1-(4-(trifluoromethyl)phenyl)butan-1-one (**3g**).* This product was obtained as a light-red oil (237.2 mg, 63% yield). Flash column chromatography eluent: 1/10 ethyl acetate/hexanes, R_f = 0.73 (1:10 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.3 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H), 5.67 (dd, *J* = 7.8, 6.2 Hz, 1H), 3.70−3.78 (m, 2H), 2.59−2.66 (m, 1H), 2.48−2.54 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 193.0, 136.7, 135.1 (q, J_{C-F} = 33.0 Hz), 129.3, 126.1 (q, J_{C-F} = 3.7 Hz), 123.6 (q, J_{C-F} = 275.0 Hz), 44.3, 36.9, 22.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.30 (s, 3F); HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{11}H_{10}ClF_3IO$ 376.9411; Found 376.9410; FT-IR ($\tilde{\nu}$ = cm^{-1}): 1713(s), 1241(s), 1096(s), 1044(m), 872(m), 863(m), 723(s).

*1-(4-Acetylphenyl)-4-chloro-2-iodobutan-1-one (**3h**).* This product was obtained as a light-brown oil (245.4 mg, 70% yield). Flash column chromatography eluent: 1/10 ethyl acetate/hexanes, R_f = 0.47 (1:10 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05−8.10 (m, 4H), 5.68 (dd, *J* = 8.1, 6.0 Hz, 1H), 3.70−3.79 (m, 2H), 2.66 (s, 3H), 2.59−2.65 (m, 1H), 2.47−2.54 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 197.5, 193.4, 140.8, 137.2, 129.1, 128.8, 44.3, 36.9, 27.1, 22.3; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{12}H_{13}ClIO_2$ 350.9643; Found 350.9644; FT-IR ($\tilde{\nu}$ = cm^{-1}): 1717(m), 1676(s), 1244(s), 1119(m), 1098(m), 1075(m), 1015(m), 958(m), 857(m), 725(s).

*Methyl-4-(4-chloro-2-iodobutanoyl)benzoate (**3i**).* This product was obtained as a white solid (223.6 mg, 61% yield). m.p. = 62.2−62.6 °C; flash column chromatography eluent: 1/10 ethyl acetate/hexanes, R_f = 0.47 (1:10 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12−8.14 (m, 2H), 8.03−8.05 (m, 2H), 5.66 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.94 (S, 3H), 3.68−3.79 (m, 2H), 2.57−2.63 (m, 1H), 2.45−2.52 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 193.4, 166.1, 137.2, 134.6, 130.1, 128.8, 52.7, 44.3, 36.9, 22.4; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{12}H_{13}ClIO_3$ 366.9592; Found 366.9593; FT-IR ($\tilde{\nu}$ = cm^{-1}): 1717(s), 1673(m), 1279(s), 1244(s), 1104(s), 1073(m), 1014(m), 868(m), 716(s).

*4-Chloro-2-iodo-1-(4-nitrophenyl)butan-1-one (**3j**).* This product was obtained as an orange oil (205.0 mg, 58% yield). Flash column chromatography eluent: 1/10 ethyl acetate/hexanes, R_f = 0.33 (1:10 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33−8.36 (m, 2H), 8.15−8.18 (m, 2H), 5.67 (dd, *J* = 8.3, 6.1 Hz, 1H), 3.70−3.80 (m, 2H), 2.60−2.66 (m, 1H), 2.49−2.55 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 192.4, 150.8, 138.7, 130.0, 124.2, 44.2, 36.8, 22.2; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{10}H_{10}ClINO_3$ 353.9388; Found 353.9384; FT-IR ($\tilde{\nu}$ = cm^{-1}): 1682(m), 1521(s), 1344(s), 1317(m), 1288(m), 1243(m), 1221(m), 1011(m), 867(m), 856(m), 836(m), 710(s).

*4-Chloro-1-(4-fluorophenyl)-2-iodobutan-1-one (**3k**).* This product was obtained as a light-yellow oil (235.1 mg, 72% yield). Flash column chromatography eluent: 1/10 ethyl acetate/hexanes, R_f = 0.77 (1:10 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03−8.07 (m, 2H), 7.14−7.18 (m, 2H), 5.62 (dd, *J* = 7.9, 6.1 Hz, 1H), 3.68−3.76 (m, 2H), 2.56−2.63 (m, 1H), 2.43−2.50 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 192.5, 166.2 (d, J_{C-F} = 256.3

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Hz), 131.6 (d, J_{C-F}= 9.5 Hz), 130.1 (d, J_{C-F} = 3.0 Hz), 116.2 (d, J_{C-F} = 22.0 Hz), 44.4, 37.1, 21.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.70 − −103.63 (m, 1F); HRMS (HESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{10}ClFIO$ 326.9443; Found 326.9444; FT-IR ($\tilde{\nu}$ = cm^{-1}): 1691(s), 1578(s), 1289(m), 1235(m), 1100(m), 1049(m), 970(m), 851(m), 822(m), 788(m), 743(m).

4-Chloro-1-(3,5-dichlorophenyl)-2-iodobutan-1-one (**3l**). This product was obtained as a light-yellow oil (249.1 mg, 66% yield). Flash column chromatography eluent: 1/10 ethyl acetate/hexanes, R_f = 0.45 (1:10 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 1.9 Hz, 2H), 7.57 (t, *J* = 1.9 Hz, 1H), 5.54 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.68−3.76 (m, 2H), 2.56−2.63 (m, 1H), 2.45−2.51 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 191.6, 136.4, 136.1, 133.6, 127.2, 44.2, 36.9, 21.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_9Cl_3IO$ 376.8758; Found 376.8753; FT-IR ($\tilde{\nu}$ = cm^{-1}): 1678(s), 1565(s), 1420(m), 1403(m), 1283(m), 1248(s), 1236(s), 1192(m), 1165(m), 1099(m), 870(m), 800(s), 768(m), 740(m), 700(m).

1-(2-Bromophenyl)-4-chloro-2-iodobutan-1-one (**3m**). This product obtained as a light-yellow oil (294.4 mg, 76% yield). Flash column chromatography eluent: 1/10 ethyl acetate/hexanes, R_f = 0.75 (1:10 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.55 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.39 (td, *J* = 7.6, 1.2 Hz, 1H), 7.33 (td, *J* = 7.7, 1.8 Hz, 1H), 5.64 (dd, *J* = 8.3, 5.8 Hz, 1H), 3.80−3.84 (m, 1H), 3.68−3.73 (m, 1H), 2.53−2.59 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 197.4, 139.1, 133.7, 132.4, 130.7, 127.6, 119.3, 44.2, 36.5, 28.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{10}BrClIO$ 386.8643; Found 386.8639; FT-IR ($\tilde{\nu}$ = cm^{-1}): 1683(m), 1429(m), 1307(m), 1278(m), 1265(m), 1118(m), 1027(m), 904(m), 741(s).

1-(2-Bromo-4-chlorophenyl)-4-chloro-2-iodobutan-1-one (**3n**). This product obtained as a light-yellow oil (257.4 mg, 61% yield). Flash column chromatography eluent: hexanes, R_f = 0.82 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 1.9 Hz, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.38 (dd, *J* = 8.2, 1.9 Hz, 1H), 5.61 (dd, *J* = 8.3, 5.9 Hz, 1H), 3.78−3.82 (m, 1H), 3.67−3.72 (m, 1H), 2.49−2.59 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 196.3, 137.9, 137.3, 133.5, 131.4, 128.0, 120.1, 44.2, 36.4, 27.6; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_9BrCl_2IO$ 420.8253; Found 420.8249; FT-IR ($\tilde{\nu}$ = cm^{-1}): 1691(s), 1578(s), 1366(m), 1289(m), 1235(m), 1100(m), 1049(m), 970(m), 869(m), 851(m), 822(s), 786(m), 763(m), 743(m).

4-Chloro-2-iodo-1-(thiophen-2-yl)butan-1-one (**3o**). This product was obtained as an orange oil (220.2 mg, 70% yield). Flash column chromatography eluent: 1/10 ethyl acetate/hexanes, R_f = 0.50 (1:10 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 3.8, 1.0 Hz, 1H), 7.69 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.16 (dd, *J* = 5.0, 4.0 Hz, 1H), 5.53 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.65−3.74 (m, 2H), 2.53−2.59 (m, 1H), 2.42−2.48 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 187.5, 140.6, 135.3, 133.1, 128.6, 44.3, 37.2, 22.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for C_8H_9ClIOS 314.9102; Found 314.9101; FT-IR ($\tilde{\nu}$ = cm^{-1}): 1651(s), 1410(s), 1290(m), 1097(m), 1058(m), 820(m), 721(s).

Procedure for the Preparation of 4-Chloro-1-phenylbutan-1-one (4a). A 25 mL round-bottom flask was charged with (4-methoxybut-1-yn-1-yl)benzene (**2a**, 160.2 mg, 1.0 mmol, 1.0 equiv) and 2,2,2-trifluoroehtanol/diethyl ether (2 mL/5 mL) (note: the solvents were not dried by molecular sieves). The reaction mixture was cooled to −20 °C, and an iodine monochloride diethyl ether solution (ICl, 487.1 mg, 3.0 mmol, 3.0 equiv, dissolved in 1 mL of diethyl ether) was added dropwise to the reaction solution. The resulting reaction mixture was stirred at −20 °C for 20 min and then at room temperature for 1.5 h until thin-layer chromatography showed that all methyl homopropargyl ether was consumed. The reaction mixture was diluted with 20 mL of diethyl ether and washed with saturated sodium thiosulfate (30 mL). The aqueous phase was extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated using a rotary evaporator at room temperature under reduced pressure (20 mmHg). The subsequent residue was purified by flash column chromatography on silica gel to afford both **3a** (major product) and **4a** (byproduct). Byproduct **4a** was obtained as a colorless oil (16.4 mg, 9% yield). Flash column chromatography eluent: hexanes, R_f = 0.23 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97−7.99 (m, 2H), 7.56−7.59 (m, 1H), 7.46−7.49 (m, 2H), 3.68 (t, *J* = 6.3 Hz, 2H), 3.19 (t, *J* = 6.9 Hz, 2H), 2.21−2.26 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 199.2, 136.9, 133.4, 128.8, 128.2, 44.9, 35.5, 26.9; HRMS (HESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{12}ClO$ 183.0571; Found 183.0568.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c01638.

X-ray crystallographic data for **3a**; experimental procedures, spectral data, and copies of ^{1}H, ^{13}C and ^{19}F NMR spectra for the new compounds and DFT calculations (PDF)

Accession Codes

CCDC 2179135 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

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