# Mechanistic Analysis of the C−H Amination Reaction of Menthol by CuBr2 and Selectfluor

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Ⓢ *Supporting Information*

ABSTRACT: The mechanism of the Ritter-type C−H amination reaction of menthol with acetonitrile using CuBr2, Selectfluor, and Zn(OTf)2, first disclosed by Baran and coworkers in 2012, was studied using a combination of online electrospray ionization mass spectrometry, continuous UV/vis spectrometric monitoring, and density functional theory calculations. In addition to corroborating Baran's original mechanistic proposal, these studies uncovered a second pathway to product formation, which likely only occurs in microdroplets. DFT calculations show that neither pathway has a barrier that is greater than 6.8 kcal/mol, suggesting that both mechanisms are potentially operative under ambient conditions.
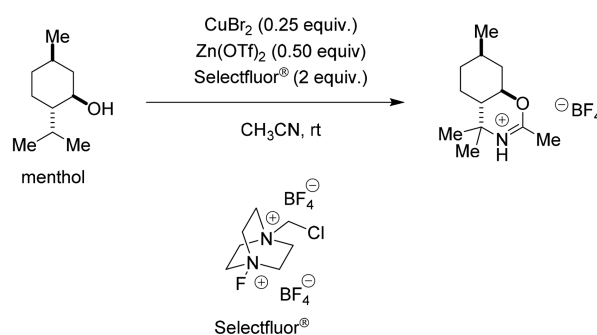

Mechanistic Pathway Elucidated With ESI-MS, UV/vis spectroscopy, and DFT Calculations
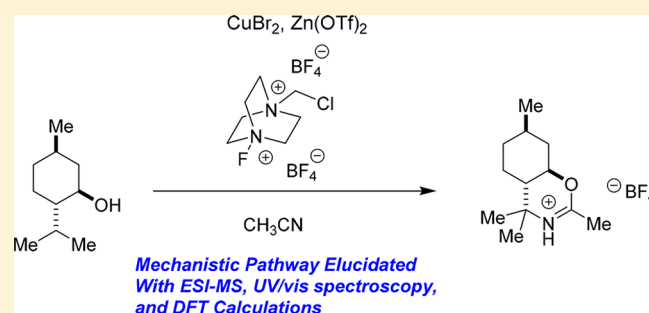
INTRODUCTION

Over the past 15 years, advances in C−H oxidation have allowed the unactivated C−H bond to serve as a viable synthon for the installation of carbon, nitrogen, oxygen, sulfur, and halogen moieties.[1−4] The vast majority of these transformations utilize transition metals in catalytic quantities in conjunction with powerful terminal oxidants in stoichiometric amounts.[5−9] Many of these reactions reach completion within minutes, and their mechanisms are often complex organometallic processes with numerous short-lived intermediates. The capture of such fleeting intermediates poses a significant challenge for the modern physical organic chemist. Our laboratory has a deep interest in studying these reactions using high-resolution mass spectrometry coupled with more conventional physical organic techniques.[10−13] It is our hope that the elucidation of the mechanisms of these fascinating reactions will provide a foundation for the rational design of more efficient C−H functionalization processes.

We were particularly drawn to a C−H amination reaction disclosed in 2012 by Baran and coworkers (Scheme 1).[14] Building upon a seminal disclosure by Banks et al.,[15] these researchers found a much improved protocol for a Ritter-type C−H amination reaction of unactivated secondary and tertiary C−H bonds using CuBr2 (0.25 equiv), Zn(OTf)2 (0.50 equiv), the fluorine oxidant Selectfluor (2 equiv), and acetonitrile. On the basis of kinetic isotope effect (KIE) studies, reaction inhibition with 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO), and isolation of reduced Selectfluor (H-TEDA-BF4), the authors proposed the mechanism outlined in Scheme 2. We were quite interested in the use of Selectfluor not as an electrophilic fluorine transfer agent but as an oxidant for C−H functionalization,[16] and we hoped to conclusively determine the species responsible for the key C−H abstraction event. On

the basis of literature studies using Selectfluor for other applications,[17−26] including radical fluorination and aromatic substitution, we hypothesized that such a species might be an amine radical carbocation.

Electrospray ionization mass spectrometry (ESI-MS) is a powerful technique for studying reaction mechanisms as it allows for the detection and structural elucidation of intermediates using high-resolution mass spectrometry and collision induced dissociation (CID).[27−29] Indeed, ESI-MS has been very effective for the analysis of a variety of organic reactions, including cross-couplings, organocatalysis, and metathesis, but has been underutilized in the study of C−H oxidation processes.[30−33] Mass spectrometry is complementary to nuclear magnetic resonance (NMR) spectroscopy in that it

Scheme 1. C−H Amination of Menthol with CuBr2/Selectfluor®

Baran and co-workers, 2012

Scheme 2. Mechanistic Hypothesis Put Forth by Baran and Coworkers
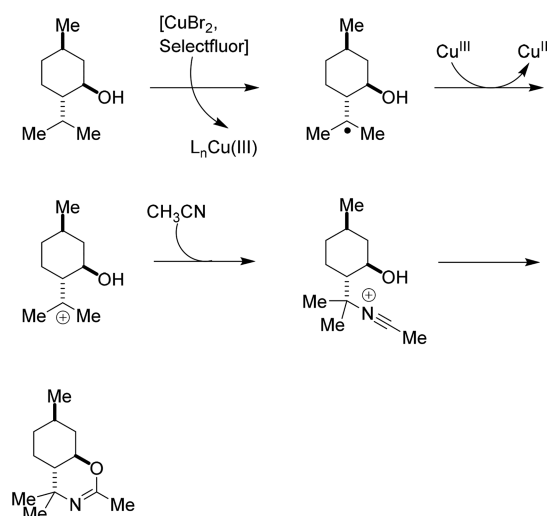
allows for the rapid detection of paramagnetic metal complexes and radical intermediates, both of which often lead to indecipherable line broadening in NMR spectroscopy. Using a pressurized infusion setup allowing for the continuous, direct transfer of a small amount of reaction solution into the mass spectrometric inlet, online ESI-MS (Figure 1) allows for the real time detection of transient intermediates.[34−38]
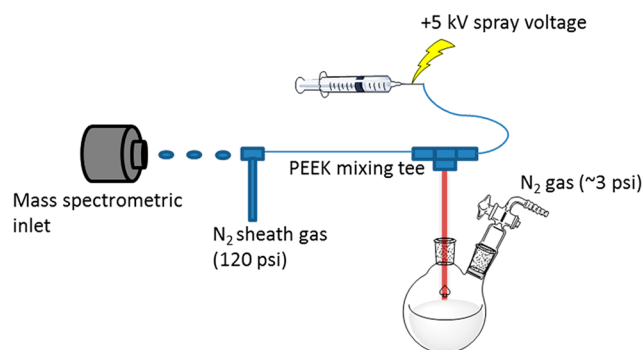

Figure 1. Online ESI-MS allows for real-time reaction monitoring.

■ RESULTS AND DISCUSSION

Using this pressurized infusion setup (Figure 1), online ESI-MS monitoring (+ mode) of the reaction mixture (Scheme 1) allowed for the detection of dehydrated menthol (**9**), several reaction intermediates (**3**, **5**, and **8**), product **6**, and reduced Selectfluor species **4** (Figure 2a). Particularly significant was the detection of carbocation intermediate **3**. CID-MS^2 of this transient intermediate gave several fragments consistent with our structural assignment (Figure 2b). Temporal monitoring shows a clear rise and fall in the relative abundance of carbocation **3** (Figure 3b) concomitant with a continuous decrease of starting material surrogate **9** (Figure 3a). The abundances of both product **6** and reduced Selectfluor species **4** continuously increase (Figures 3c and d). Collectively, these data illuminate a portion of the mechanism of C−H amination where reduction of Selectfluor coincides with formation of carbocation **3**, which ultimately transforms into product **6**.

From this first experiment, despite extensive analysis of the mass spectral data, we were unable to identify the putative amine radical carbocation derived from Selectfluor. We hypothesized that simplifying the reaction mixture by removing menthol would potentially lengthen the lifetime of such a reactive intermediate as there would be an absence of highly reactive secondary and tertiary C−H bonds. Indeed, online ESI-MS monitoring of just CuBr$_2$ and Selectfluor in CH$_3$CN/DMF solvent mixture (Figure 4a) captured species **7**. Such a species most likely arises from the reaction of a DMF radical (**10**) with the amine radical carbocation derived from Selectfluor. CID-MS^2 of this species yielded several fragments supporting this structural assignment (Figure 4b).

We next sought to elucidate the role of the Cu(II) catalyst. Adding Selectfluor to a solution of CuBr$_2$ in acetonitrile led to a dramatic color change from emerald green to dark red followed by rapid bleaching to a yellow-green solution. Continuous ultraviolet−visible (UV/vis) monitoring of this reaction showed a clear disappearance of λ_{max} at 639 nm and the appearance of a new λ_{max} at 889 nm within seconds of oxidant addition (Figure 5). This transient red species rapidly disappeared, resulting in a featureless spectrum. In reactions involving both copper and Selectfluor, several groups have posited the intermediacy of a highly reactive Cu(III) species.[14,39−41] We thus hypothesized that this transient red species may in fact be a short-lived Cu(III) intermediate. Despite extensive evaluation of the online ESI-MS data from both the full reaction (Scheme 1 and Figure 2) and the simplified mixture (Figure 4a), however, we were unable to identify a discrete Cu(III) species. Nevertheless, this does not rule out the possibility that Cu(III) forms in situ. Reduction of Cu (II) to Cu (I) during the electrospray process is a well-documented phenomenon.[42,43] Corroborating this, we too see a prominent signal corresponding to [Cu(CH$_3$CN)$_2$]$^+$ (Figure 2a and Figure 4a). It is highly likely that in the absence of stabilizing ligands,[44,45] Cu(III) is rapidly reduced to Cu(II) and Cu(I) in either an electrochemical process at the tip of the spray source or by free electrons in the electrospray plume. Prominent signals appear for both [Cu(F)(DMF)$_2$]$^+$ and [Cu(F)(DMF)$_3$]$^+$ (Figure 4a). It is possible that these Cu(II)-F species result from the reduction of Cu(III)-F adducts during electrospray. In a seminal study, Xiong et al. identified a Cu(III) species, [Cu(OH)(F)(1,10-phenanthroline)(CH$_3$CN)·2H$_2$O]$^+$ by ESI-MS.[41] Such a species was generated by treatment of CuI with an oxidant closely related to Selectfluor, *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate, in the presence of 1,10-phenanthroline. In their experiment, 1,10-phenanthroline stabilizes Cu (III) sufficiently for detection by ESI-MS.

Collectively, these experiments allowed us to propose a more complete mechanism for the Ritter-type C−H amination of menthol (Schemes 3a and b). Oxidation of Cu(II) to Cu(III) occurs with concomitant cleavage of the N−F bond of Selectfluor to form a radical carbocation intermediate. This intermediate abstracts the tertiary C−H bond of menthol, which subsequently loses its unpaired electron to Cu(III), regenerating Cu(II) and forming carbocation intermediate **3**. This carbocation is then trapped by acetonitrile, followed by attack of the alcohol to form heterocyclic product **6**. We refer to this in Scheme 3 as pathway 1, which was previously proposed by Baran and coworkers.[14] A second pathway (Scheme 3b) is attack of the alcohol onto a protonated molecule of acetonitrile, forming imine intermediate **5**, which was also detected in our online ESI-MS experiments. In bulk
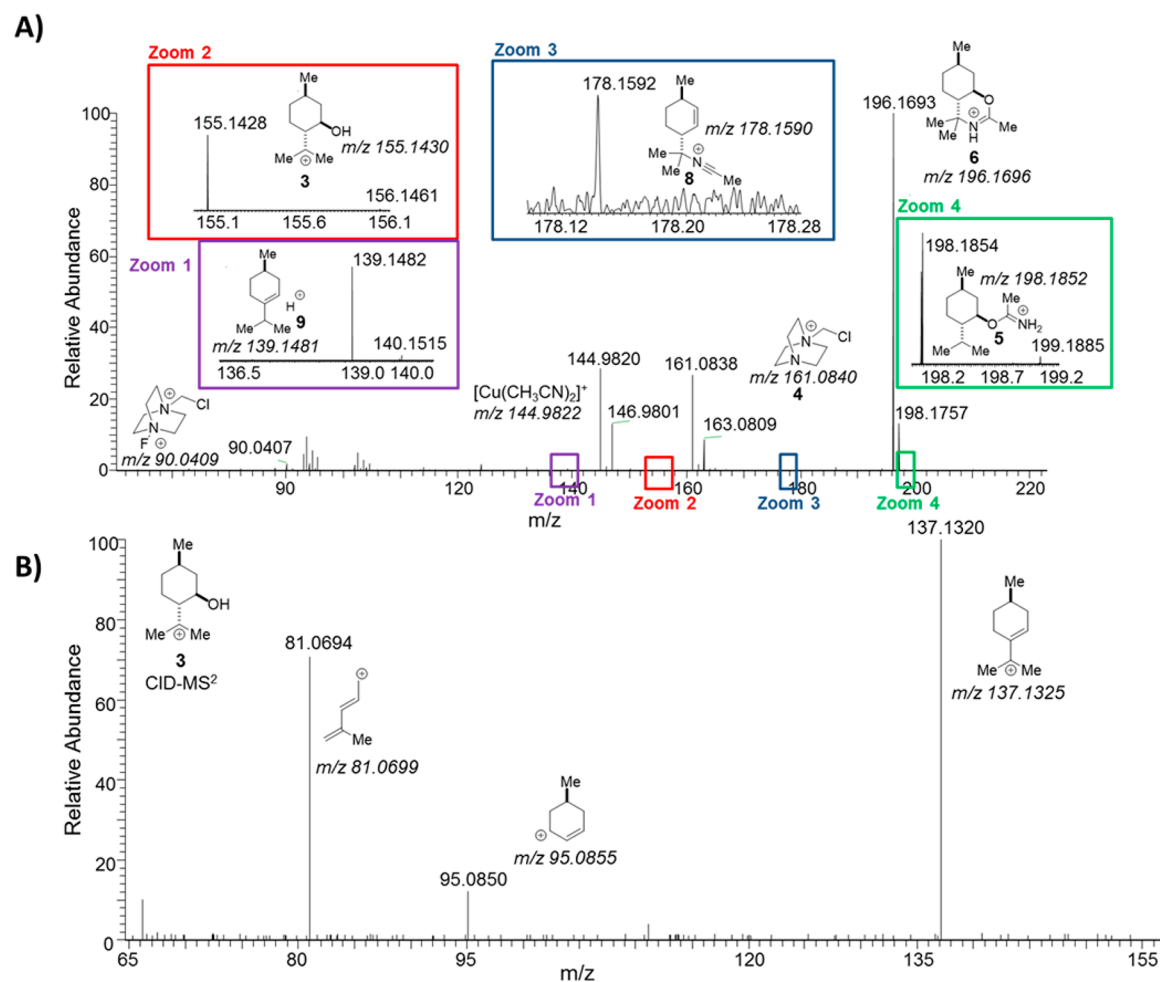
Figure 2. (a) Online ESI-MS monitoring (+ mode) of the C–H amination of menthol with CuBr$_2$/Selectfluor (Scheme 1) in CH$_3$CN. (b) CID-MS^2 of carbocation intermediate **3**. See Table S1 for the part per million (ppm) accuracy of the *m/z* measurement. Please note that the italicized *m/z* values are theoretical and are provided so that comparisons can be made to those that have been experimentally found.
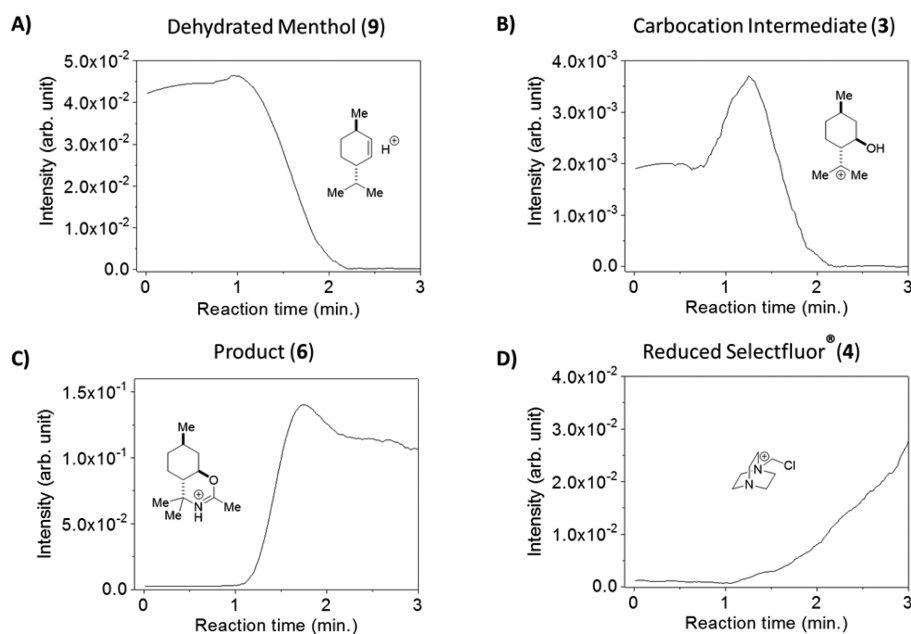

Figure 3. Online ESI-MS monitoring of the reaction mixture allows for real-time tracking of (a) starting material surrogate **9**, (b) carbocation intermediate **3**, (c) product **6**, and (d) reduced Selectfluor derivative **4**. Please note that all intensities were normalized to the total ion current and thus are presented in arbitrary units.
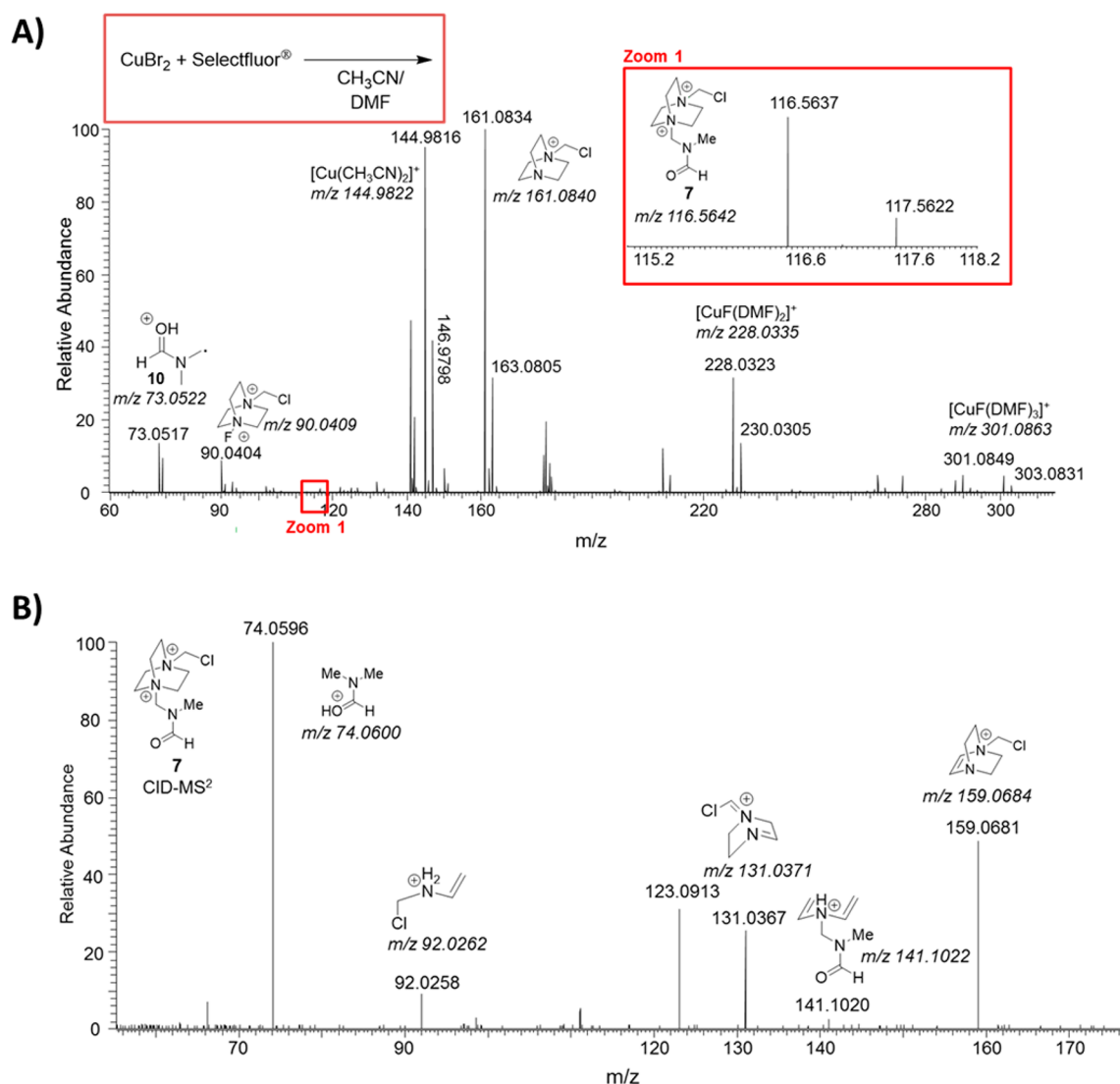
Figure 4. (a) Online ESI-MS monitoring (+ mode) of the reaction of CuBr$_2$ with Selectfluor. (b) CID-MS^2 of DMF radical adduct 7. See Table S1 for the ppm accuracy of the m/z measurement. Please note that the italicized m/z values are theoretical and are provided so that comparisons can be made to those that have been experimentally found.
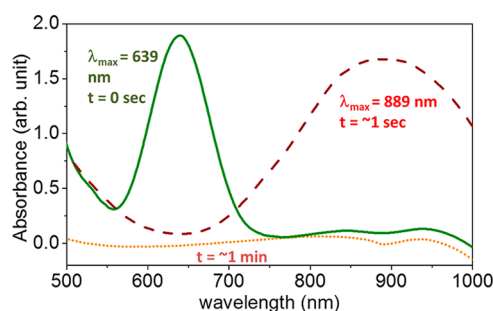

Figure 5. UV/vis monitoring shows the appearance of a transient copper species immediately upon addition of Selectfluor.

solution, it is unlikely that this intermediate forms because of the absence of strong acid in the reaction mixture. However, it is also known that microdroplets can promote acid-catalyzed reactions[46] due to the accumulation of H$^+$ to the surface. Formation of a carbocation in a manner similar to that outlined above followed by trapping of the pendant imine forms product 6. We presented the two pathways in Scheme 3 because DFT

calculations showed that they had comparable barrier heights (Supporting Information).

To recapitulate, a variety of online ESI-MS experiments coupled with continuous UV/vis reaction monitoring allowed us to unravel two pathways for the Ritter-type C−H amination reaction mediated by CuBr$_2$ and Selectfluor. We detected and elucidated the structures of a variety of substrate and oxidant derived reaction intermediates. Continuous UV/vis reaction monitoring shows the appearance of a highly transient species, which we posit to be a reactive Cu(III) intermediate. We hope the elucidation of this reaction mechanism will serve for the advancement of C−H oxidation technology.

■ EXPERIMENTAL SECTION

General. Electrospray ionization mass spectrometric (ESI-MS) studies were performed on a high-resolution mass spectrometer (Thermo Scientific LTQ Orbitrap XL Hybrid Ion Trap-Orbitrap mass spectrometer) with a home-built source. Nitrogen (120 psi) was used as the nebulizing sheath gas. Electrospray of the reaction solution was performed in positive ion mode with a spray voltage of +5 kV. The heated capillary (mass spectrometric inlet) temperature and voltage were maintained at 275 °C and 44 V, respectively. Helium was used as

Scheme 3. ESI-MS and UV/Vis Analysis Allows for the Proposal of Two Pathways for the C−H Amination of Menthol, One Expected to Dominate in Bulk and the Other Likely Occurring in Microdroplets
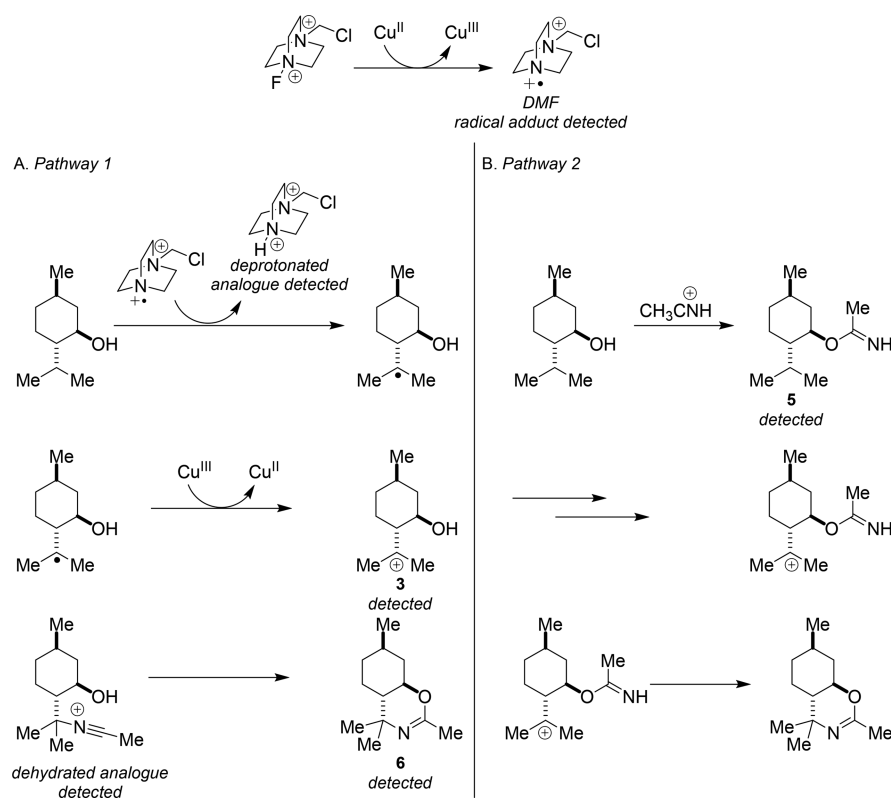
the collision gas in the collision induced dissociation cell (CID cell; an ion trap). CID spectra (MS/MS) were acquired using an isolation width of 1.0 m/z unit with activation Q and activation time set to 0.25 and 30 ms, respectively. The normalized collision energy was varied between 20 and 40% as needed. Mass spectra were recorded in full scan mode in ESI(+) using a range of m/z 50 to 1000. The ion optics were tuned to get the maximum ion count. Data acquisition and subsequent analyses were performed using XCalibur software (Thermo Fisher Scientific).

Online ESI-MS Studies. Online ESI-MS experiments for real-time reaction monitoring was performed using the pressurized infusion method pioneered by McIndoe and coworkers.[47] A photograph of the setup used in these studies is shown in Figure S1. Briefly, a given reaction is run in a Schlenk flask, sealed with a rubber septum, and pressurized with N$_2$ (~3.5 psi). Fused silica capillary (inner diameter 50 μm) was threaded through the septum into the reaction solution, allowing small amounts of the reaction mixture to continuously enter into a PEEK three-way mixing tee, where it is diluted with pure acetonitrile (flow rate 10 μL/min). This diluted mixture is propelled into the ESI ion source, allowing for real-time reaction monitoring and capture of transient intermediates.

Online ESI-MS Monitoring of the Full Reaction Mixture (Menthol, CuBr$_2$, Selectfluor, and Zn(OTf)$_2$ in CH$_3$CN). To a Schlenk flask was added menthol (40.0 mg, 0.256 mmol, 1.00 equiv), CuBr$_2$ (20.0 mg 0.090 mmol, 0.35 equiv), and Zn(OTf)$_2$ (60.0 mg, 0.165 mmol, 0.64 equiv) followed by CH$_3$CN (15.0 mL). Once parameters were optimized for online ESI-MS monitoring, the septum was briefly removed, and Selectfluor (190 mg, 0.536 mmol, 2.00 equiv) was added in one portion. Continuous mass spectra were acquired as described above.

Online ESI-MS Monitoring of the Simplified Reaction Mixture (CuBr$_2$ and Selectfluor in CH$_3$CN/DMF). To a Schlenk flask was added CuBr$_2$ (60.0 mg, 0.270 mmol, 1.00 equiv) and CH$_3$CN (15.0 mL). Continuous mass spectra of this dark green solution were acquired for ~1 min prior to the addition of Selectfluor (96.0 mg,

0.270 mmol, 1.00 equiv) in 4 mL of 3:1 v/v CH$_3$CN/DMF. Reaction monitoring was performed as described above.

Continuous UV/Vis Monitoring of the Simplified Reaction Mixture (CuBr$_2$ and Selectfluor in CH$_3$CN). To a custom-designed sample cell was added a dark green solution of CuBr$_2$ (25.0 mg, 0.112 mmol, 1.00 equiv) in 5 mL of CH$_3$CN. Continuous UV/vis reaction monitoring (Figure 5) was performed using Varian Cary 50 Scan spectrophotometer with fiber-optic leads to a custom-designed quartz immersion probe (Hellma) of 0.1 cm optical path length in a custom-designed sample cell (ChemGlass). Spectra were recorded in intervals of 0.1 s. After approximately 1 min of data acquisition, Selectfluor (40.0 mg, 0.112 mmol, 1.00 equiv) in CH$_3$CN (1 mL) was added in one portion. The solution briefly turned dark red followed by bleaching to a yellow-green. UV/vis spectra were recorded until a reaction time of approximately 5 min.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b00690.

Picture of online ESI-MS study, mass accuracy of detected species, and DFT computational details (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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