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Electrochemical oxidative Z-selective C(sp²)-H chlorination of acrylamides†‡

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An electrochemical method for the oxidative Z-selective C(sp²)-H chlorination of acrylamides has been developed. This catalyst and organic oxidant free method is applicable across various substituted tertiary acrylamides, and provides access to a broad range of synthetically useful Z-β-chloroacrylamides in good yields (22 examples, 73% average yield). The orthogonal derivatization of the products was demonstrated through chemoselective transformations and the electrochemical process was performed on gram scale in flow.

A diverse array of important compounds contain chlorine atoms, including pharmaceuticals, natural products, agrochemicals, and polymers.¹ Furthermore, Z-chloroacrylic acid derivatives serve as useful building blocks to selectively access ubiquitous Z-configured olefins.² Existing synthetic methods to access Z-β-chloroacrylic acid derivatives include Vilsmeier-Haack,³ Wittig,⁴ and chloropalladation/Heck approaches,⁵ in addition to hydrochlorination⁶ and carbochlorination⁷ of alkynes, which somewhat limits the accessible substitution patterns and some of these methods can exhibit poor E/Z selectivity. As such, the development of new synthetic methods that enable the direct and selective access to Z-chloroacrylic acid derivatives is an important and timely goal in organic synthesis. Recently, Besset and co-workers reported the Pd-catalyzed Z-selective chlorination of secondary acrylamides bearing an 8-aminoquinoline directing group (Scheme 1A),

employing N-chlorosuccinimide as the chlorinating agent, representing a state-of-the-art approach.⁸

Organic electrochemistry presents vast opportunities for the development of efficient and selective synthetic methods.⁹ A variety of electrochemical methods have been developed for the chlorination of organic compounds, including alkene dichlorination,¹⁰ chlorofunctionalization of alkenes¹¹ and alkynes,¹² aromatic chlorination,¹³ α-chlorination of 1,3-dicarbonyl compounds,¹⁴ and deconstructive chlorination of cycloalkanols.¹⁵ As such, we envisaged the development of an electrochemical oxidative Z-selective C(sp²)-H chlorination of acrylamides to generate valuable Z-β-chloroacrylamides (Scheme 1B), and herein we report the successful realization of this approach.

To commence our studies, N-methyl-N-tosylacrylamide **1** was selected as the model substrate (Table 1).¹⁶ It was found that an electrochemical system composed of MgCl₂ (5 equiv.) as both chloride source and electrolyte in MeCN:AcOH (7 : 1, [1] = 0.05 M) using galvanostatic conditions (*i* = 10 mA, *j*_{anode} = 7.8 mA cm⁻², *Q* = 2.5 F mol⁻¹), a graphite anode and a platinum cathode at 25 °C for 2 h under N₂, enabled the oxidative C(sp²)-H chlorination of **1**, with Z-β-chloroacrylamide **2** formed in 97% NMR yield as a single stereoisomer (>95 : <5 Z : E) (entry 1).¹⁷ No conversion occurs in the absence of electricity (entry 2).

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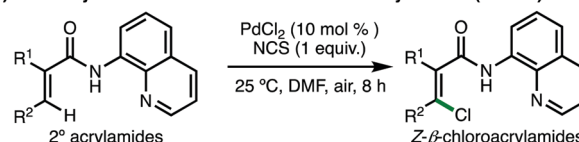
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† Information about the data that underpins the results presented in this article, including how to access them, can be found in the Cardiff University data catalogue at <http://doi.org/10.17035/d.2021.0143191217>.

‡ Electronic supplementary information (ESI) available: Optimization data, experimental procedures, characterization of new compounds and spectral data. CCDC 2104458. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1cc05824j

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A) Pd-catalyzed Z-selective chlorination of 2° acrylamides (Besset)



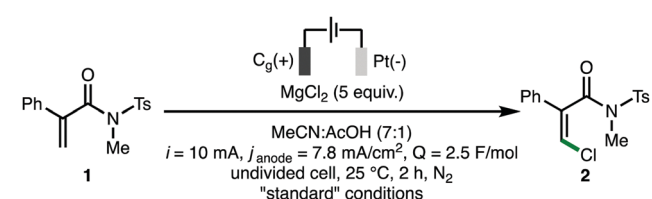
B) Electrochemical Z-selective chlorination of 3° acrylamides (this work)



Scheme 1 State-of-the-art and outline of the electrochemical strategy.



Table 1 Reaction optimization^a

		
Entry	Variation from "standard" conditions	Yield ^b (%)
1	None	97 (92)
2	No electricity	< 2
3	$E_{\text{cell}} = 3.75 \text{ V}$	91
4	$i = 15 \text{ mA}, j_{\text{anode}} = 11.7 \text{ mA cm}^{-2}$	91
5	$i = 5 \text{ mA}, j_{\text{anode}} = 3.9 \text{ mA cm}^{-2}$	85
6	Graphite cathode instead of Pt foil	83
7	LiCl instead of MgCl_2	83
8	NaCl instead of MgCl_2	25
9	MeCN:MeOH (3.5:1)	67
10	MgCl_2 (3 equiv.)	68
11	MgCl_2 (3 equiv.) + LiClO_4 (2 equiv.)	78
12 ^c	$Q = 2 \text{ F mol}^{-1}$	85

^a Reactions performed using 0.3 mmol of acrylamide **1** using the ElectraSyn 2.0 batch electrochemical reactor. [**1**] = 0.05 M. ^b Yield after 2 h as determined by ¹H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Formed as a single stereoisomer (>95: <5 Z:E). Isolated yield given in parentheses. ^c 96 minutes reaction time.

Employing a constant cell potential ($E_{\text{cell}} = 3.75 \text{ V}$) or variation of the current ($i = 15 \text{ mA}$ or 5 mA) lowered the NMR yield of

2 (entries 3–5), as did substituting the platinum foil cathode for graphite (entry 6). Employing LiCl or NaCl as the chloride source was detrimental to conversion, presumably due to the decreased solubility in MeCN:AcOH (entries 7 and 8). Using MeCN:MeOH (3.5:1) as solvent resulted in reduced conversion to **2**. Lowering the quantity of MgCl_2 to 3 equivalents reduced the NMR yield of **2** to 68%, which increased to 78% upon the addition of LiClO_4 (2 equiv.) as a supporting electrolyte. A faradaic efficiency of 85% was obtained when 2 F mol^{-1} of charged was passed (entry 12), which indicated that most of the electricity passing through the cell is utilized productively. Replacing MgCl_2 with MgBr_2 resulted in recovery of **1** (>90%).

With optimized reaction conditions in hand (Table 1, entry 1), the full scope and limitations of the electrochemical method with respect to the acrylamide starting materials was evaluated (Scheme 2). Unless otherwise stated, only the Z-alkene isomer was observed for all substrates. Employing N-methyl-N-tosylacrylamide starting materials (Scheme 2A), it was found that various substituents could be incorporated into the C(2)-aromatic unit, including electron-releasing (e.g., 4-OMe), electron-withdrawing (e.g., 4- CF_3) and halogen substituents, with the corresponding Z-β-chloroacrylamides products accessed in good yields (products 3–13). Introducing sterically demanding groups into the acrylamide starting materials did not negatively impact upon product formation, with products **8** and **9** formed in 74% and 83% isolated yields, respectively.



Scheme 2 Scope and limitations. Reactions performed using 0.3 mmol of starting material. All yields are isolated yields after chromatographic purification unless noted otherwise. ^a Isolated as a mixture of isomers. ^b 3.5 F mol⁻¹. ^c As determined by ¹H NMR analysis of the crude reaction mixture.



The introduction of a C(3)-methyl substituent afforded tetra-substituted *Z*- β -chloroacrylamide **14** in 75% isolated yield,¹⁸ whereas the C(2)-aryl group could be replaced with a C(2)-methyl substituent to access **15** as the major regioisomer (86:14 r.r.). Further variation of the acrylamide starting material revealed that a selection of *N*-alkyl, *N*-phenyl, and *N*-sulfonyl substituents could be incorporated to access products **16–20** in high isolated yields (Scheme 2B). Employing a Weinreb acrylamide substrate produced the corresponding vinyl chloride **21** as a 2:1 mixture of *Z*:*E* alkene isomers, which was isolated in a combined 61% yield. This lower observed selectivity may be attributed to increased C–N partial double-bond character within the Weinreb amide functionality, resulting in a greater steric effect, in comparison to the twisted amide (*c.f.*, substrate **1**).¹⁹ *N,N*-Dialkylacrylamides could be employed as substrates, with *Z*- β -chloroacrylamides **22** and **23** isolated in 61% and 73% isolated yields, respectively. When *N,N*-diphenylacrylamide **24** was subjected to the optimized reaction conditions, oxindole **25** was accessed as the sole product (Scheme 2C), which can be formed *via* intramolecular trapping of a *C*-centered radical intermediate with a *N*-phenyl substituent.²⁰ Substituted methyl acrylate **26** produced a mixture of *Z*- β -chloroacrylate **27** and dichloro ester **28** in 44% and 32% NMR yields, respectively. The formation of **28** may indicate that it is an intermediate on route to the formation of **27**, or that the operative reaction mechanism for methyl acrylate substrate **26** is distinct to the tertiary acrylamide substrates predominantly employed. Secondary acrylamide **29** produced a complex reaction mixture whereas acrylamides **30** and **31** were found to be unreactive, presumably due to radical instability and steric encumbrance, respectively.

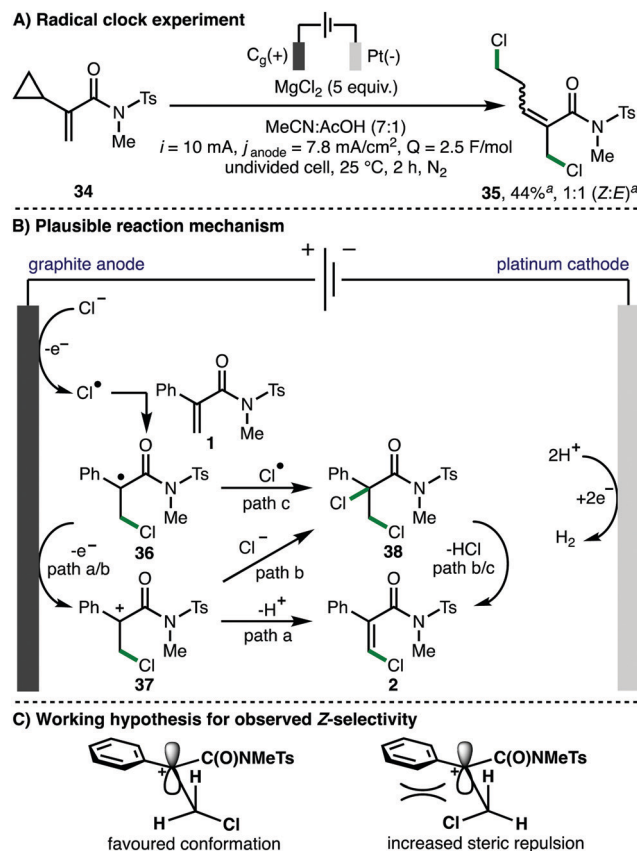
To demonstrate product utility, the orthogonal functionalization of *Z*- β -chloroacrylamide **2** was investigated (Scheme 3A). It was found that the C(sp²)-Cl functionality could serve as a coupling partner in a palladium-catalyzed Suzuki cross-coupling with 4-methoxyphenylboronic acid to access arylated

alkene **32** in 49% isolated yield. Furthermore, the *N*-sulfonyl activated twisted amide functionality within **2** was hydrolyzed to give the corresponding carboxylic acid derivative **33** in 72% isolated yield, which can serve as a useful building block for further synthetic elaboration. To demonstrate scalability, the batch process was translated to a flow electrochemical setup (Scheme 3B).²¹ Employing a syringe pump in combination with commercially available Ammonite8 flow electroreactor (volume = 1 mL, *i* = 370 mA),²² 4.4 mmol of acrylamide **1** was converted to *Z*- β -chloroacrylamide **2** in 91% isolated yield (1.40 g) in a single-pass.

To obtain insight into the reaction mechanism, acrylamide **34**, containing a C(2)-cyclopropyl substituent, was synthesized and subjected to the optimized electrochemical reaction conditions as a radical clock mechanistic probe (Scheme 4A). It was found that ring-opened dichlorinated acrylamide **35** was obtained as a 1:1 mixture of *Z*:*E* alkene isomers in 44% NMR yield, signifying the likelihood of radical intermediates within the operative reaction mechanism. Cyclic voltammetry studies indicated that chloride ions ($E_{\text{ox}} = 1.10$ V vs. Fc/Fc⁺) should undergo preferential oxidation in the presence of electron-deficient acrylamide **1** ($E_{\text{ox}} = 1.31$ V vs. Fc/Fc⁺). It was also found that replacing MgCl₂ with *N*-chlorosuccinimide in the absence of electricity resulted in quantitative recovery of **1**. In line with these observations, and previous related



Scheme 3 Product utility and reaction scale up in flow.



Scheme 4 Reaction mechanism. ^a As determined by ¹H NMR analysis of the crude reaction mixture.

investigations,²³ a plausible reaction mechanism would initiate with anodic chloride oxidation to form a chlorine radical,^{11d,12b,13c,13d} which undergoes regioselective addition to the electron-deficient acrylamide **1** to furnish tertiary C-centered radical **36**. Further anodic oxidation would form carbocation **37**, with subsequent deprotonation providing access to the observed Z-β-chloroacrylamide **2** (path a). Substitution at C(2) is crucial for reactivity (*c.f.* Scheme 2C, starting material **30**), presumably due to the requirement to stabilize intermediates **36** and **37**. Deprotonation of carbocation **37** proceeds *via* the conformation that minimizes steric repulsion between the chlorine atom and the phenyl ring to afford the Z-isomer as the major product stereoisomer (Scheme 4c). Alternatively, carbocation **37** or radical **36** could be intercepted by a chloride anion (path b) or a chlorine radical (path c), respectively, to form dichlorinated compound **38**, which could subsequently generate **2** *via* loss of HCl. Dichlorinated species such as **38** have not been directly observed using acrylamide substrates, however, we cannot unambiguously rule out their intermediacy. Hydrogen gas is generated *via* proton reduction at the cathode.

In conclusion, we have developed a new electrochemical method for the oxidative Z-selective C(sp²)-H chlorination of acrylamides. The method is applicable across various substituted tertiary acrylamides, accessing a broad range of synthetically useful Z-β-chloroacrylamides (22 examples). The orthogonal derivatization of the products was demonstrated through chemoselective transformations, and the electrochemical process was performed on gram scale in flow.

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Conflicts of interest

There are no conflicts to declare.

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- See the ESI† for full experimental details.
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- Only the Z isomer of product **14** was observed upon varying the acrylamide substrate *E*:*Z* ratio from 10:1 to 1:1.
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