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Electrochemical alkene azidocyanation via 1,4-nitrile migration†

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An electrochemical method for the azidocyanation of alkenes via 1,4-nitrile migration has been developed. This organic oxidant free method is applicable across various alkene containing cyanohydrins, and provides access to a broad range of synthetically useful 1,2-azidonitriles (28 examples). This methodology was extended to an electrochemical alkene sulfonylcyanation procedure, as well as to access a trifunctionalized hexanenitrile from a malononitrile starting material. The orthogonal derivatization of the products was also demonstrated through chemoselective transformations.

Organic azides¹ are highly sought after within biological and medicinal chemistry,² and materials science,³ both as compounds of interest and as key intermediates due to their ease of conversion into a wide range of functional groups. As such, the development of new synthetic methods to incorporate the azide functionality into organic compounds is an important and timely goal in organic synthesis.

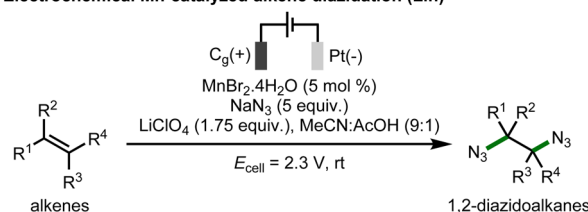
Organic electrochemistry, which allows for the development of efficient and selective synthetic methods,⁴ has been established as a tool to incorporate azides into organic compounds. In 1970, Schäfer and co-workers developed a metal-free electrochemical alkene 1,2-diazidation protocol.⁵ This methodology was improved in terms of efficacy and selectivity by Lin and co-workers (Scheme 1A) by the introduction of $\text{MnBr}_2 \cdot 4\text{H}_2\text{O}$ (5 mol%) that served as a transfer reagent to deliver the azide to the alkene.⁶ Subsequently, Ackermann and co-workers developed a manganese-catalyzed $\text{C}(\text{sp}^3)\text{-H}$ azidation protocol under electrochemical conditions.⁷

In recent years, functional group migration has developed into a useful strategy for the difunctionalisation of unactivated alkenes.⁸ Through this manifold, intramolecular nitrile,⁹ carbonyl,¹⁰ alkynyl,^{10b,11} and heteroaryl^{9d,10b,12} migration methodologies have

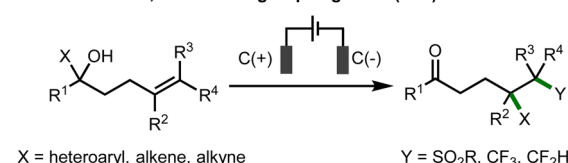
been developed using stoichiometric oxidants. For example, Zhu and co-workers reported an alkene azidocyanation protocol using PIDA,^{9a} a high molecular weight oxidant which generates stoichiometric organic waste that requires separation from the desired product. To overcome the necessity for chemical oxidants, electrochemistry has been employed within this strategy to generate radical intermediates.¹³ Recently, Pan and co-workers reported electrochemical 1,4-migration of heteroaromatics, alkenes, and alkynes with alkene sulfonylation and fluoro-alkylation (Scheme 1B).^{13a,c}

As such, following our research programme into the development of new electrochemical methodologies in organic synthesis, using manganese(II) salts,¹⁴ and on alkene functionalization,¹⁵ we envisaged the development of an electrochemical

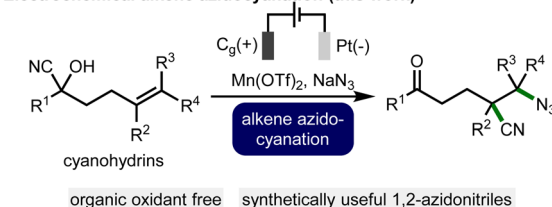
A) Electrochemical Mn-catalyzed alkene diazidation (Lin)



B) Electrochemical 1,4-functional group migration (Pan)



C) Electrochemical alkene azidocyanation (this work)



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

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azidocyanation of alkenes *via* addition of an azide radical followed by 1,4-nitrile migration to generate a range of valuable products (Scheme 1C), and herein we report the successful realization of this approach.

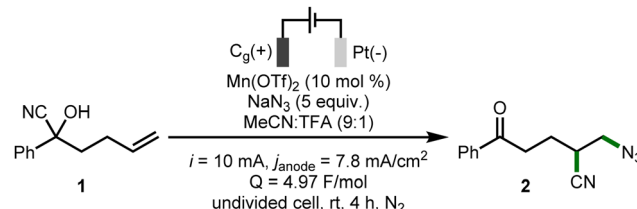
To commence our studies, cyanohydrin **1** was selected as the model substrate (Table 1).¹⁶ It was found that an electrochemical system composed of Mn(OTf)₂ (10 mol%), and NaN₃ (5 equiv.) as both azide source and electrolyte in MeCN:TFA (9:1, [1] = 0.05 M) using galvanostatic conditions (*i* = 10 mA, *j*_{anode} = 7.8 mA cm⁻², *Q* = 4.97 F mol⁻¹), a graphite anode and a platinum cathode at r.t. for 4 h under N₂, enabled the azidocyanation of **1**, with ketone **2** formed in a 55% NMR yield (entry 1). No conversion occurs in the absence of electricity (entry 2), and the yield of **2** was significantly reduced in the absence of Mn(OTf)₂ (entry 3). Employing a constant cell potential (*E*_{cell} = 2.4 V) saw **2** obtained in a 55% yield, albeit in a significantly increased reaction time (entry 4). Alterations in the current applied (*i* = 12.5 mA or 7.5 mA) lowered the yield of **2** (entries 5 and 6), as did adding LiClO₄ (1.75 equiv.) as a supporting electrolyte (entry 7) and substituting the platinum foil cathode for graphite or Ni plate (entries 8 and 9). Employing MnBr₂·4H₂O or Mn(OAc)₂·4H₂O in place of Mn(OTf)₂ was also detrimental to conversion (entries 10 and 11). Substituting TFA for AcOH as the proton source resulted in a reduced conversion to **2** (entry 12), presumably due to the decreased solubility of NaN₃ in the MeCN:AcOH solvent system. It was found that lowering the quantity of NaN₃ to 2.5 equivalents

reduced the NMR yield of **2** to 19% (entry 13), but reducing the loading of Mn(OTf)₂ to 5 mol% had a negligible impact on the yield obtained (entry 14). Extending the reaction time to 5 h saw a decreased NMR yield of **2** to 42% (entry 15), suggesting that the product may be somewhat unstable under the reaction conditions. Evidence supporting this claim was obtained when **2** was subjected to the “standard” reaction conditions, where only 64% was returned by ¹H NMR analysis of the crude reaction mixture.

With optimized reaction conditions in hand (Table 1, entry 1), the full scope of the electrochemical method with respect to the cyanohydrin starting materials was evaluated (Scheme 2). Upon increasing the reaction scale to 1.0 mmol, product **2** was obtained in a 64% isolated yield. Employing cyanohydrin starting materials, it was found that steric hinderance around the aromatic ring did not impact the reaction in an appreciable manner, with 4-, 3-, and 2-Me substitution providing access to the corresponding products (products 3–5) in comparable yields. Various substituents could be incorporated into the aromatic ring, including aryl (*e.g.*, 4-Ph), and electron-withdrawing groups (*e.g.*, 4-CN), with the corresponding azido-nitrile products accessed in moderate to good yields (products 6–8). Halogens could be tolerated in the *para* position, as could pinacol-borane (products 9–13), giving the potential for further derivatization of the products obtained. The electrochemical method exhibits good functional group tolerance, demonstrated by the presence of carboxylic acid, methyl ester, primary amide, tertiary amide, and ketal in the 4-position (products 14–18). Methyl ester **16** was obtained in a 75% isolated yield, suggesting that this electron-withdrawing substituent may stabilise intermediates in this reaction, disfavours non-productive pathways that may occur under the electrochemical conditions. Extension of the aromatic system was tolerated, with 1-naphthyl product **19** obtained in a 38% NMR yield. Alkyl cyanohydrins were also evaluated under the reaction conditions (*e.g.*, Bn), which provided the products **20–24** in moderate yields. Substitution on the olefin was then evaluated, allowing for the formation of secondary azides **25** and **26** (as a single diastereoisomer), as well as quaternary nitrile **27**. Substitution on the alkyl chain allowed for the formation of tetralone **28** in a 51% NMR yield. Substrates with decreased and increased distances between the cyanohydrin and alkene resulted in no observable product formation. Alternative transformations were also evaluated under this electrochemical manifold, with sulfone **29** formed from **1** by substituting the NaN₃ for NaSO₂Ph, demonstrating the ability to initiate the nitrile migration *via* addition of sulfonyl radicals to the alkene. Malononitrile **30** was also successfully converted to trifunctionalized hexanenitrile **31** in a 42% NMR yield when subjected to the “standard” reaction conditions (Table 1, entry 1).

To demonstrate product utility, the orthogonal functionalization of azido-nitrile **2** was investigated (Scheme 3). It was found that the azide could be converted to the corresponding 1,4-disubstituted 1,2,3-triazole **32** in a 47% isolated yield *via* a CuAAC reaction with phenylacetylene.¹⁷ Furthermore, the

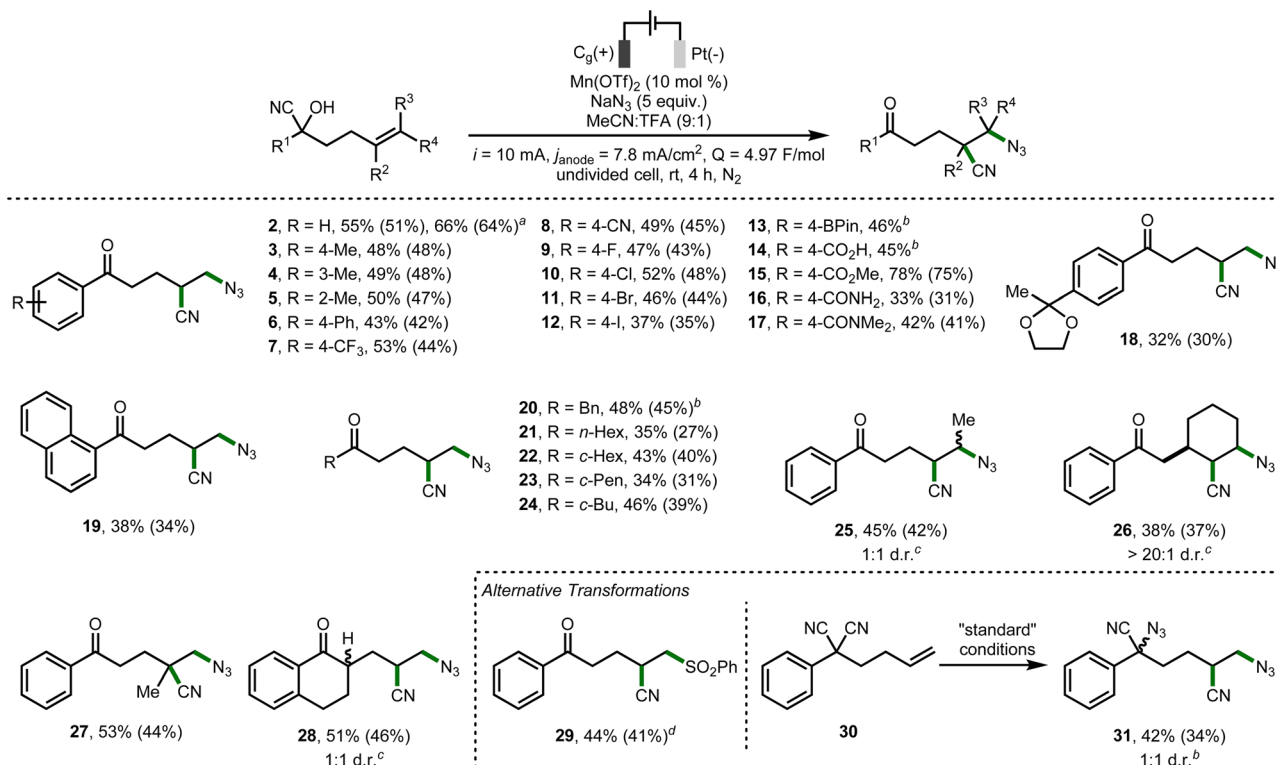
Table 1 Reaction optimization^a



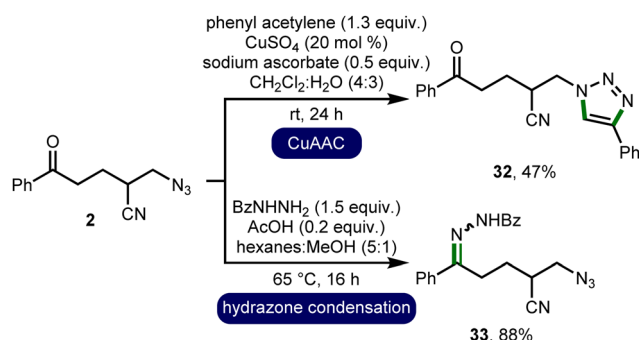
Entry	Variation from “standard” conditions	1 ^b (%)	2 ^b (%)
1	None	<2	55 (51)
2	No electricity	94	<2
3	No Mn(OTf) ₂	34	23
4	<i>E</i> _{cell} = 2.4 V	<2	55
5 ^c	<i>i</i> = 12.5 mA, <i>j</i> _{anode} = 9.8 mA cm ⁻²	4	32
6 ^d	<i>i</i> = 7.5 mA, <i>j</i> _{anode} = 5.9 mA cm ⁻²	<2	42
7	LiClO ₄ (1.75 equiv.) as electrolyte	20	38
8	Graphite cathode instead of Pt foil	6	23
9	Ni plate cathode instead of Pt foil	10	43
10	MnBr ₂ ·4H ₂ O instead of Mn(OTf) ₂	<2	34
11	Mn(OAc) ₂ ·4H ₂ O instead of Mn(OTf) ₂	<2	48
12	AcOH instead of TFA	20	30
13	NaN ₃ (2.5 equiv.)	29	19
14	Mn(OTf) ₂ (5 mol%)	8	50
15 ^e	<i>Q</i> = 6.22 F mol ⁻¹	<2	42

^a Reactions performed using 0.3 mmol of cyanohydrin **1** using the ElectraSyn 2.0 batch electrochemical reactor. [1] = 0.05 M. ^b Yield after 4 h as determined by ¹H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses. ^c 192 minutes reaction time. ^d 320 minutes reaction time. ^e 300 minutes reaction time.





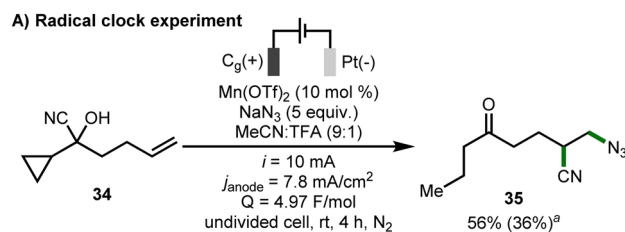
Scheme 2 Scope. Reactions performed using 0.3 mmol of starting material using the ElectraSyn 2.0 batch electrochemical reactor. [Substrate] = 0.05 M. All yields are as determined by ¹H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield after chromatographic purification given in parentheses. ^a1.0 mmol, *t* = 13 h 20 min. ^b5 h (6.22 F mol⁻¹). ^cAs determined by ¹H NMR analysis of the crude reaction mixture. ^dNaSO₂Ph (5 equiv.) instead of NaN₃.



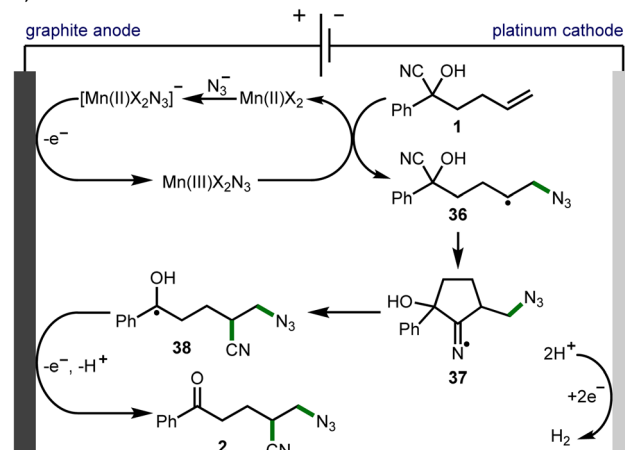
Scheme 3 Product utility.

ketone was converted to hydrazone **33** via condensation with benzhydrazide in an 88% isolated yield.¹⁸

To obtain insight into the reaction mechanism, cyanohydrin **34** was subjected to the optimized electrochemical reaction conditions as a radical clock mechanistic probe (Scheme 4A). It was found that ring-opened azido-nitrile **35** was obtained as the sole product in a 56% NMR yield, signifying the presence of radical intermediates in the reaction mechanism. Cyclic voltammetry was employed to gain further insight into the mechanism of this electrochemical process.¹⁶ In accordance with the literature,^{6,14} $Mn(OTf)_2$ displays no redox events between 0 and



B) Plausible reaction mechanism



Scheme 4 Reaction mechanism. ^aAs determined by ¹H NMR analysis of the crude reaction mixture. Isolated yield in parentheses.

1.6 V vs. Fc/Fc^+ , and TBAN_3 exhibits an irreversible oxidation event at ~ 0.97 V vs. Fc/Fc^+ , indicating the formation of azide radicals, which can themselves induce the desired reactivity (Table 1, entry 3). However, the combination of $\text{Mn}(\text{OTf})_2$ with TBAN_3 produced a new irreversible oxidation event at ~ 0.50 V vs. Fc/Fc^+ , providing evidence for the generation of a $\text{Mn}(\text{III})\text{X}_2\text{N}_3$ species from $[\text{Mn}(\text{II})\text{X}_2\text{N}_3]^-$.

With these observations, as well as literature precedent from previous related investigations,^{6,9a} a plausible reaction mechanism would initiate with the formation of $[\text{Mn}(\text{II})\text{X}_2\text{N}_3]^-$ from $\text{Mn}(\text{II})\text{X}_2$ and NaN_3 , which is oxidized at the anode to form $\text{Mn}(\text{III})\text{X}_2\text{N}_3$ (Scheme 4B). This intermediate delivers an azide radical to cyanohydrin **1**, giving secondary alkyl radical intermediate **36**. Intramolecular interception of this secondary alkyl radical by the nitrile affords cyclic iminyl radical **37**, which can then undergo β -scission to afford α -hydroxy alkyl radical **38**. A second oxidation at the anode, followed by proton loss affords product **2**. Hydrogen gas is evolved *via* proton reduction at the cathode.

In conclusion, we have developed a new electrochemical method for the azidocyanation of alkenes. The method is applicable across various alkene containing cyanohydrins, providing access to a broad range of synthetically useful 1,2-azidonitriles (28 examples). The methodology was also extended to an electrochemical sulfonylcyanation procedure, as well as to a malononitrile starting material, giving access to a trifunctionalized hexanenitrile product. The orthogonal derivatization of the products was also demonstrated through chemoselective transformations.

The data that support the findings of this study are openly available in the Cardiff University data catalogue at <http://doi.org/10.17035/d.2022.0214744028>.

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Conflicts of interest

There are no conflicts to declare.

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