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Mangana(III/IV)electro-catalyzed C(sp^3)–H azidation†

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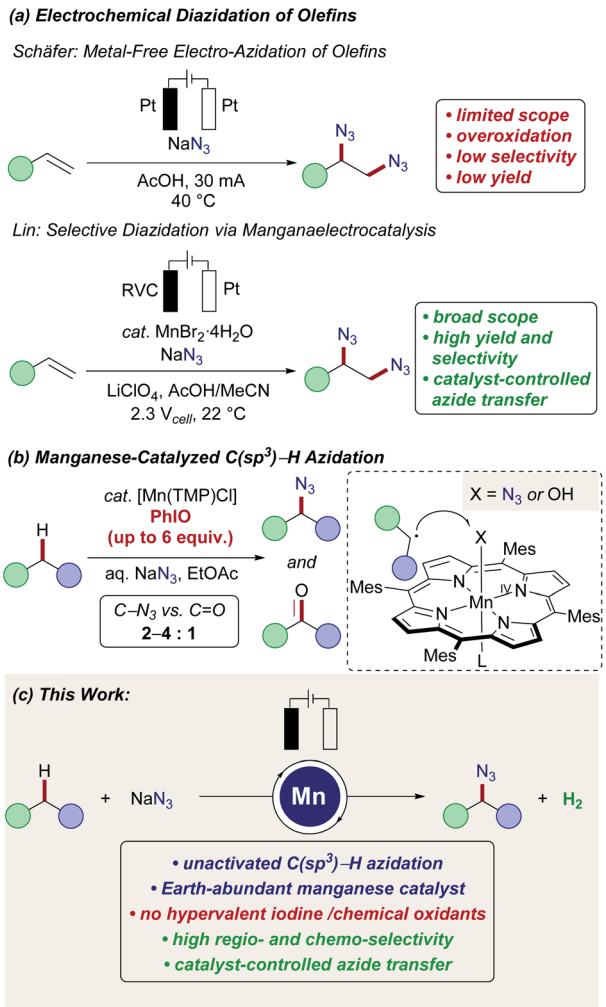
Manganaelectro-catalyzed azidation of otherwise inert C(sp^3)–H bonds was accomplished using most user-friendly sodium azide as the nitrogen-source. The operationally simple, resource-economic C–H azidation strategy was characterized by mild reaction conditions, no directing group, traceless electrons as the sole redox-reagent, Earth-abundant manganese as the catalyst, high functional-group compatibility and high chemoselectivity, setting the stage for late-stage azidation of bioactive compounds. Detailed mechanistic studies by experiment, spectrophotometry and cyclic voltammetry provided strong support for metal-catalyzed aliphatic radical formation, along with subsequent azidyl radical transfer within a manganese(III/IV) manifold.

Introduction

The development of selective, resource-economic methods for the direct conversion of otherwise unreactive C(sp^3)–H bonds is one of the most demanding challenges in molecular sciences.[1] Advances in this field will not only be of direct importance to petrochemical and polymer technologies,[2] but will also enable step-economical syntheses of pharmaceutical relevant compounds[3] by ideally late-stage drug diversification.[4] Within this topical research arena, concepts for direct C(sp^3)–H aminations are particularly prominent.[5] Organic azides[6] are key structural motifs, that are often key-intermediates in numerous molecules of interest to medicinal chemistry,[7] materials sciences,[8] peptide chemistry or molecular biology.[9] Due to this key importance,[10] a plethora of functional group interconversion strategies have been developed, exploiting *inter alia* organic halides, alcohols, epoxides, and aldehydes. However, more step-economical methods that directly install the azido-group into otherwise inert C(sp^3)–H bonds continue to be scarce[11] and generally require stoichiometric amounts of strong indiscriminate chemical oxidants, such as persulfates,[12] *N*-fluorobenzenesulfonimide (NFSI),[13] hypervalent iodine reagents[14] or photochemical[15] irradiation.[16] In previous reports on selective electrochemical vicinal diazidation of olefins, a metal-free approach was introduced by Schäfer in 1970 (Scheme 1a).[17] Subsequently, Lin significantly improved the efficacy and



Scheme 1 Manganaelectro-catalyzed azidation.

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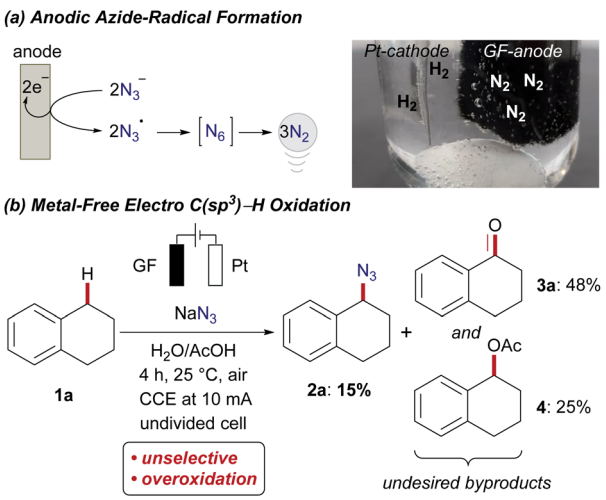
selectivities upon the addition of a metal catalyst, that is able to mediate the transfer of an azidyl radical to the double bond.[18] Here, particularly a manganese(II) pre-catalyst served as an efficient azide transfer reagent *via* a manganese(II/III) manifold.

Despite numerous reports on C(sp^2)–H transformations catalyzed by manganese,[19] reports on manganese-catalyzed C(sp^3)–H functionalization remain underdeveloped.[20] For the direct azidation of unactivated C(sp^3)–H bonds, early reports by Hill and Groves indeed employed manganese complexes derived from porphyrin or a Schiff-base (Scheme 1b).[21] Here, polymeric and potentially explosive iodosylbenzene was however used as the chemical oxidant to generate high-valent manganese(V)-oxo intermediates, which have been reported to undergo hydrogen-abstraction of aliphatic C(sp^3)–H bonds to form the desired alkyl radical.[22] Thereafter, the thus formed aliphatic radical is proposed to be captured by the Mn(IV)–X intermediate to form either azidated or undesired oxygenated products. Unfortunately, depending on the substrate, the reported azide to oxygen incorporation ratio was relatively low (2–4 : 1).[21a]

Results and discussion

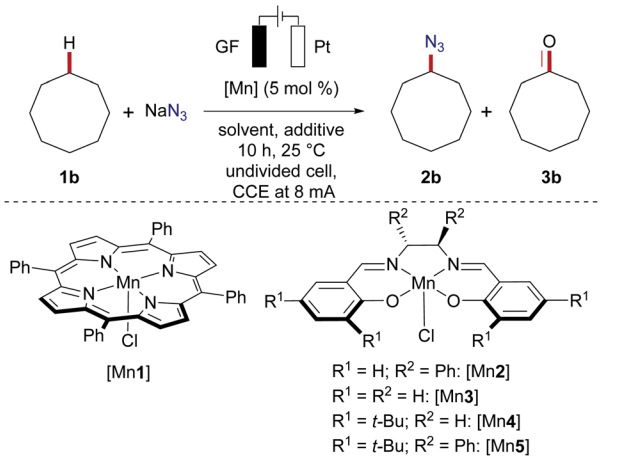
Within our program on sustainable organic electrosynthesis[23] for strong bond activation,[24] we envisioned the direct azidation of activated C(sp^3)–H bonds *via* anodically formed azidyl-radicals in aqueous acidic media (Scheme 2).[23g,25] The generation of transient azidyl-radicals by anodic oxidation was reported earlier,[26] yet, direct electrochemical C(sp^3)–H azidations are thus far unprecedented. The azide anion is thus proposed to be oxidized at the graphite-felt (GF) anode and hence results in nitrogen gas formation, while hydrogen gas is formed on the platinum cathode (Scheme 2a). Unfortunately, the direct oxidation of activated benzylic C(sp^3)–H (BDE C–H = 82.9 ± 1.2 kcal mol^{-1},[27] $E_{p,a}$ = 2.1 V *vs.* SCE[28]) occurred with only poor chemoselectivity, yet with high conversion of **1a** (Scheme 2b). This unsatisfactory outcome, was however very promising since the desired organo-azide **2a** was formed in 15% yield, motivated us to study envisioned electrochemical C(sp^3)–H azidation in further detail.[29]

Herein, we report the manganaelectro-catalyzed C(sp^3)–H azidation of unactivated secondary, tertiary and benzylic C–H bonds. Key features of our findings include (a) C(sp^3)–H azidation *via* synergistic electrosynthesis and an Earth-abundant manganese catalyst, (b) mild and chemical oxidant-free reaction conditions, (c) high regio- and chemoselectivity, (d) and late-stage azidation of bioactive compounds. It is noteworthy that efficient manganese-catalyzed electro-azidation occurred in the absence of photochemical irradiation,[15] with detailed



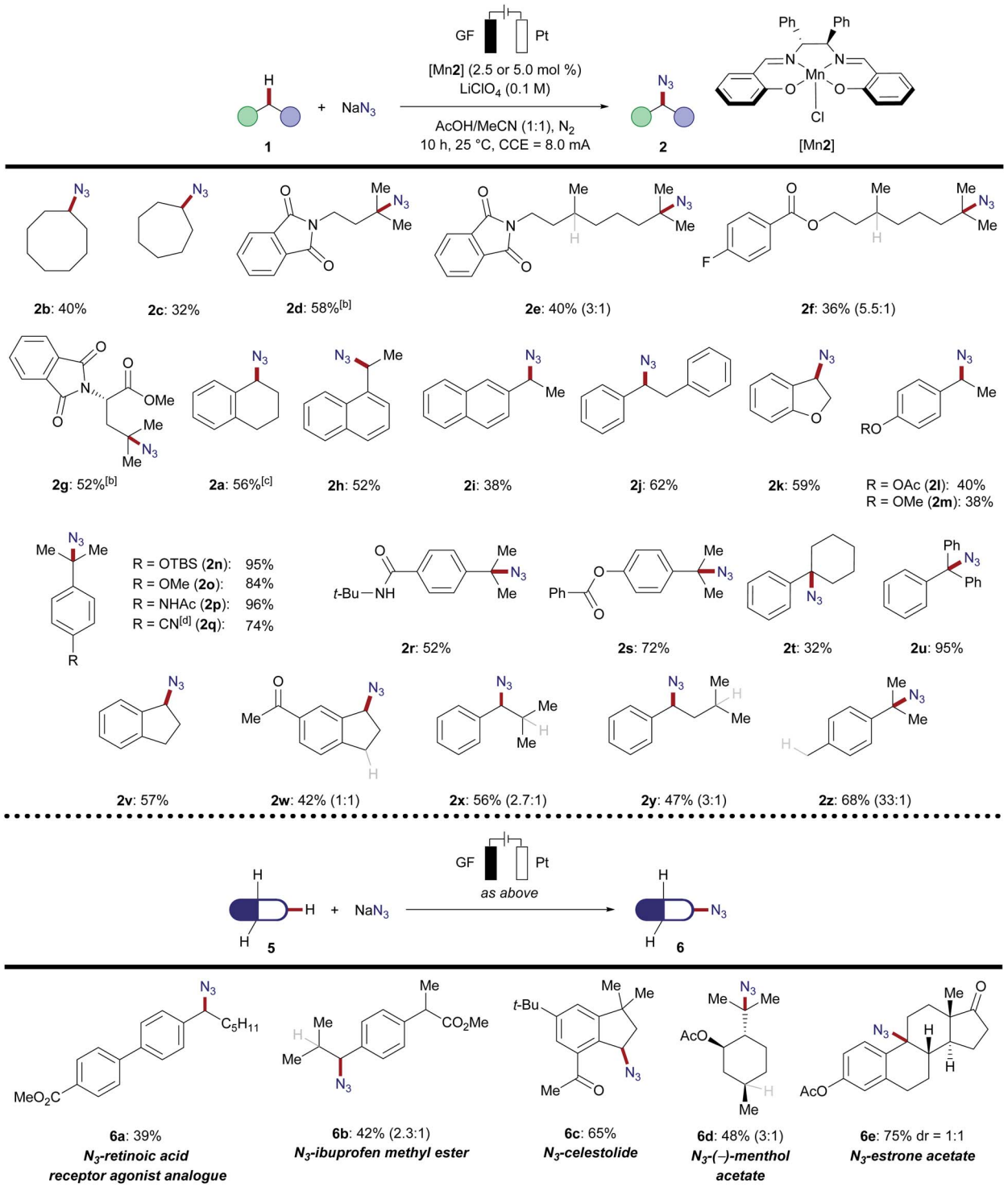
Scheme 2 Proof of concept electro C(sp^3)–H azidation.

Table 1 Optimization of the reaction conditions[a]



Entry	[Mn]	Solvent	Additive (equiv.)	Yield [%] (ratio **2b**/**3b**)
1[b]	[Mn**1**]	AcOH/H_2O	PhI (0.2)	25 (2.6 : 1.0)
2[b]	[Mn**2**]	AcOH/H_2O	PhI (0.2)	33 (2.0 : 1.0)
3[b]	[Mn**2**]	AcOH/H_2O	—	30 (2.8 : 1.0)
4[b]	[Mn**2**]	AcOH/MeCN	$LiClO_4$ (1.0)	31 (5.2 : 1.0)
5[c,d]	[Mn**2**]	AcOH/MeCN	$LiClO_4$ (1.0)	40 (12.3 : 1.0)
6[d]	[Mn**2**]	AcOH/MeCN	$LiClO_4$ (1.0)	45 (10.0 : 1.0)
Deviation from entry 6				
7	[Mn**1**] instead of [Mn**2**]			44 (1.6 : 1.0)
8	[Mn**3**] instead of [Mn**2**]			10 (4.0 : 1.0)
9	[Mn**4**] instead of [Mn**2**]			39 (12.0 : 1.0)
10	[Mn**5**] instead of [Mn**2**]			47 (8.4 : 1.0)
11	KN_3 instead of NaN_3			44 (5.3 : 1.0)
12	$TMSN_3$ (4.0 equiv.) instead of NaN_3			30 (8.0 : 1.0)
13	TsN_3 (4.0 equiv.) instead of NaN_3			0
14	No current: under a N_2 or air atmosphere			0
15	No [Mn]			10 (2.0 : 1.0)
16	Light irradiation with blue LEDs			30 (1.0 : 1.0)
17	In the dark			42 (10.0 : 1.0)

[a] Reaction conditions: undivided cell, **1b** (0.5 mmol), [Mn] (5.0 mol%), NaN_3 (8.0 equiv.), an additive (*xx* equiv.), solvent (1 : 1, 5 mL), 25 °C, constant current electrolysis (CCE) at 8 mA, a graphite felt (GF) anode, and a Pt-plate cathode. Yields are determined by GC-FID with *n*-dodecane as the internal standard. [b] 5 h, 6 mA, 2.24 F. [c] 10 h, 6 mA, 4.48 F. [d] Under nitrogen atmosphere.

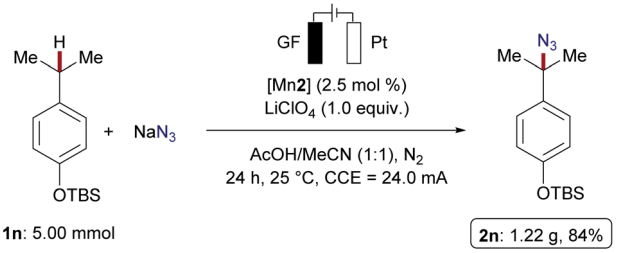


Scheme 3 Reaction scope of manganaelectro-catalyzed C(sp^3)–H azidation. [a] Standard conditions: substrate (0.5 mmol), NaN_3 (4.0 mmol), [Mn**2**] (2.5 or 5.0 mol%), $LiClO_4$ (0.5 mmol), MeCN/AcOH (5 mL, 1 : 1), a nitrogen atmosphere, 10 h, 25 °C, and constant current electrolysis at 8.0 mA in an undivided cell. All yields are isolated products; ratios for site-selectivity are determined by ^{1}H-NMR of the crude mixture. [b] At 50 °C. [c] 3,4-Dihydronaphthalen-1(2*H*)-one **3** was detected in 10% from crude ^{1}H-NMR with 1,3,5-trimethoxy benzene as the internal standard. [d] Standard conditions for 20 h.[32]

mechanistic studies being supportive of a manganaelectro(III/IV) regime. We initiated our studies by probing various reaction parameters for the envisioned manganaelectro-catalyzed C(sp^3)–H azidation of unactivated alkane **1b** (BDE C–H: 95.7 kcal mol^{-1},[30] $E_{ox} \geq 2.5$ V [31]) (Tables 1 and S-2–S-5 in the ESI†).[32]

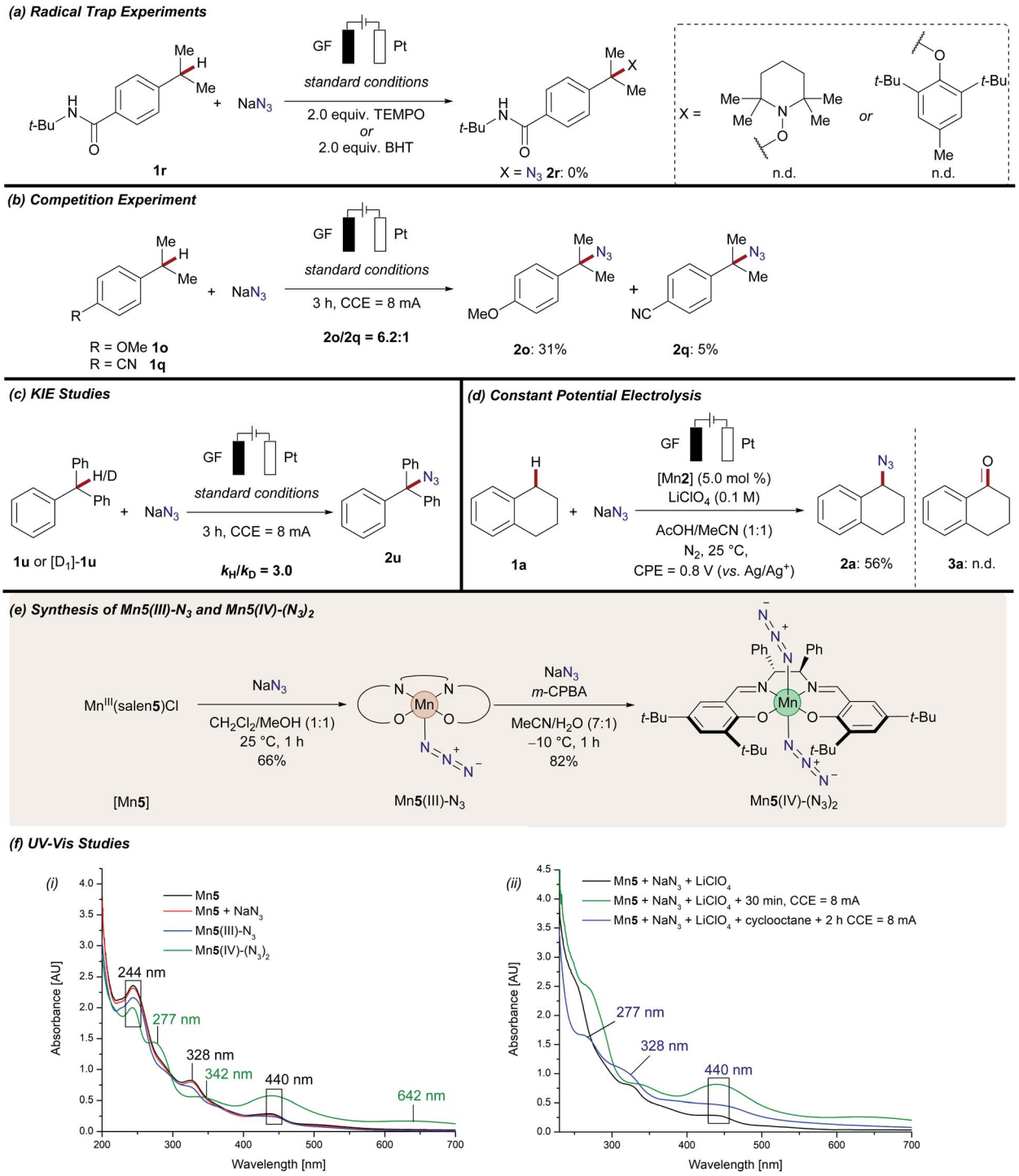
Preliminary optimization demonstrated that C–H azidation to afford **2b** could indeed be achieved with a manganese(III) porphyrin[33] or salen complex at 25 °C in acetic acid/H_2O mixtures, under air, albeit with significant amounts of over-oxidized ketone **3b** as the side product (entries 1–3). After considerable experimentation, we found that the desired electrochemical C–H azidation was accomplished with high chemoselectivity and efficacy (5.97 F per mole **1b**) when a mixture of MeCN/AcOH was used as the reaction medium under a N_2 atmosphere (entries 4–6). Variation of the manganese catalyst did not improve the catalytic performance (entries 7–10). Nucleophilic azide sources proved to be beneficial (entries 11–13). Likewise, control experiments revealed the key role of electricity, as well as the importance of the high surface area of a carbon-based anode material (entry 14).[32] The absence of the manganese catalyst resulted in a major nitrogen gas formation at the anode, translating into significantly reduced yield and chemoselectivity (entry 15). Light irradiation resulted in rather unselective product mixtures and a diminished yield (entry 16). However, the reaction efficacy remained unaffected under dark conditions (17).[32]

With the optimized manganese catalyst in hand, we evaluated manganaelectro-catalyzed C(sp^3)–H azidation for benzylic, secondary and tertiary C–H bonds (Scheme 3). Azidation occurred in moderate to excellent yields with high selectivity for tertiary over secondary or primary C–H bonds. We also observed an unprecedented chemoselectivity for manganese-catalyzed C(sp^3)–H azidation in terms of the azidation to oxygenation ratio. Functional groups including silyloxy, amides, ethers, esters, enolizable ketones and nitriles, were well tolerated, while the mass balance accounted for unreacted substrates **1**. Cyclic, secondary hydrocarbons provided the organic azide in moderate yields **2b** and **2c** (32–40%). When multiple reactive sites were present, C–H azidation inherently took place at the tertiary C–H bond over secondary or primary C–H scission. Amide **1d** and dihydrocitronellol derivatives **1e** and **1f** afforded the desired azidated products **2d–2f** likewise, with good selectivity for the tertiary C–H bond. Leucine derivative **1g** reacted efficiently under exceedingly mild reaction conditions. Similar to aliphatic substrates, the manganaelectro-catalyzed C(sp^3)–H azidation of benzylic substrates preferentially selected tertiary over primary or secondary C–H bonds. Generally, electron-donating substituents facilitated C–H azidation; however, longer reaction times proved viable to convert electron-deficient substrates. Isobutylbenzene **1x** and isopentylbenzene **1y** containing both secondary benzylic and tertiary C–H bonds were next selected to examine site selectivity. Here, a preference for the benzylic C–H bond was detected, with a benzylic to tertiary ratio of about 3 : 1. The reaction of *p*-cymene **1z** almost exclusively delivered azidation of tertiary C–H, highlighting the strong influence of C–H bond dissociation energies (BDE) over steric effects (**2x–2z**). Subsequently, we probed the manganaelectro-catalyzed C–H azidation of complex molecules and for late-stage functionalization of pharmaceutically active molecules **5**.[14a] Biaryl **5a**, an analogue of a retinoic acid receptor agonist[34] was effectively converted into the corresponding azide **6a**. Ibuprofen methyl ester **5b** preferentially reacted at the secondary benzylic position (2.3 : 1, 42% yield), surprisingly without azidation of the tertiary C–H bond adjacent to the ester group. Azidation of celestolide **5c** proceeded efficiently and afforded **6c** in high yield (65%). Functionalization of acetyl(−)-menthol **5d**, containing four tertiary C(sp^3)–H bonds, afforded azide **6d**, favoring the sterically more accessible isopropyl sidechain. Estrone acetate **5e** was transformed into the desired azide **6e** in 75% yield as a diastereomeric mixture. This result is supportive of a radical pathway, compared to previous reports where the proposed formation of benzylic carbocation resulted in different diastereomeric ratios.[14a] The user-friendly nature of our manganaelectro-catalyzed C(sp^3)–H azidation was further illustrated by a gram-scale preparation of azidated product **2n** with similar levels of efficiency (Scheme 4).



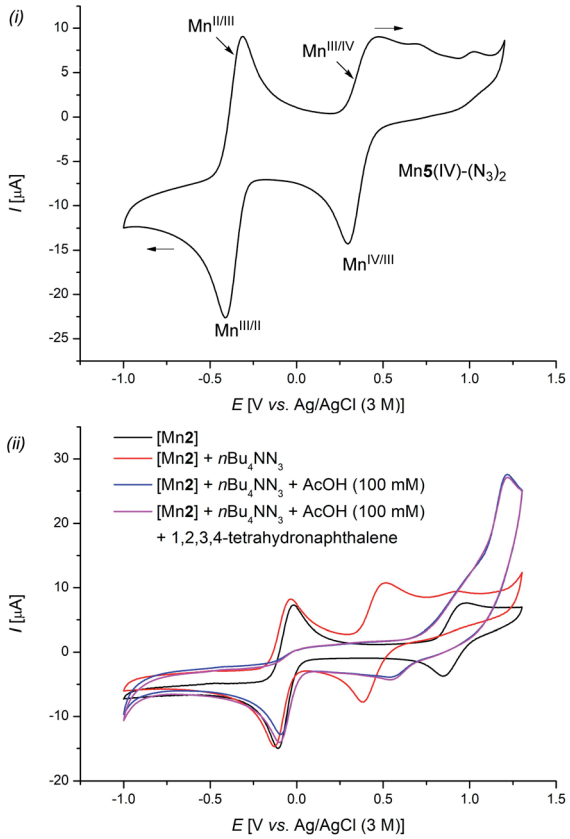
Scheme 4 Gram-scale manganaelectro-catalyzed C–H azidation (4.30 F).

Given the versatility of manganaelectro-catalyzed C–H azidation, we became attracted to probe its mode of action (Scheme 5). Upon the addition of persistent radical sources, such as TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) or BHT (2,6-di-*tert*-butyl-4-methylphenol) the reaction was completely inhibited and no desired product **2r** could be detected (Scheme 5a). Intermolecular competition reactions of **1o** and **1q** confirmed the general trend that electron-rich substrates reacted preferentially (Scheme 5b). Independent rate measurements revealed a significant kinetic isotope effect (KIE) of $k_H/k_D = 3.0$ (Scheme 5c). To unambiguously identify the involvement of a *trans*-diazidomanganese(IV) complex as the active catalyst for manganaelectro-catalyzed C–H azidation, the novel complexes Mn**5**(III)–N_3 and Mn**5**(IV)–$(N_3)_2$ were prepared and fully characterized.[32] Initially, Mn**5**(III)–N_3 was synthesized by treating the corresponding chloride complex [Mn**5**] with sodium azide. Subsequently, the thus derived manganese(III) complex was oxidized to manganese(IV) in the presence of an excess of sodium azide to afford Mn**5**(IV)–$(N_3)_2$ (Scheme 5e). With the well-defined complexes in hand, spectrophotometric and electroanalytic studies were performed (Schemes 5f, 6 and Fig. S-2–S-17†).[32] UV-vis spectroscopy of [Mn**5**], a mixture of [Mn**5**] and sodium azide, and the well-defined Mn**5**(III)–N_3 complex resulted in similar spectra with characteristic absorption maxima at 244, 328, and 440 nm (Scheme 5f(i)). In comparison, Mn**5**(IV)–$(N_3)_2$ revealed significantly different absorption properties with maxima at 277, 342, 442, and 642 nm. The strong increased absorption at 442 nm can be assigned to the charge transfer bands from coordinating azide to the manganese(IV) metal center.[35]



Scheme 5 Mechanistic investigation of manganaelectro-catalyzed azidation of unactivated C(sp^3)–H bonds. (a) Radical trap experiments. (b) Competition experiment. (c) Kinetic experiments. (d) Chronoamperometric studies at 0.8 V *vs.* Ag/Ag^+. (e) Stoichiometric synthesis of well-defined manganese(III) azide and manganese(IV) diazide complexes. (f) UV-vis spectroscopic studies: (i) MeCN (0.04 mM) was used as the solvent at 25 °C. (ii) MeCN/AcOH (1 : 1, 0.05 mM) was used as the solvent at 25 °C.

Similar absorption maxima were detected when a mixture of [Mn5], NaN_3, and $LiClO_4$ in a MeCN/AcOH mixture was anodically oxidized for 30 min at 8 mA (Scheme 5f(ii), green line). However, when the crude reaction mixture was analyzed, mixed absorption maxima of both species, manganese(III) (328 nm) and manganese(IV) (277, and 440 nm), were detected, giving strong support for the catalytic formation and consumption of Mn5(IV)–$(N_3)_2$ (Scheme 5f(ii), blue line). These results were further supported by detailed cyclic voltammetric (CV) studies (Scheme 6). The well-defined complex Mn5(IV)–



Scheme 6 Cyclic voltammetry: MeCN (0.3 mm) and $LiClO_4$ (0.1 m) was used as the electrolyte and Ag/AgCl (3 M) as the reference electrode, at 25 °C and a scanning rate of 100 mV s^{-1}.

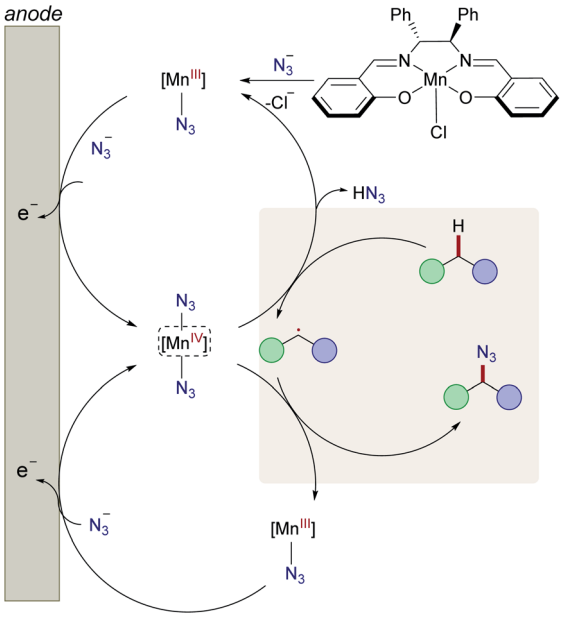


Fig. 1 Proposed mechanism for manganaelectro-catalyzed C(sp^3)–H azidation.

$(N_3)_2$ showed two characteristic redox-events at $E_{1/2} = -0.37$ V (*vs.* Ag/AgCl), which can be assigned to the Mn(II/III) redox couple and $E_{1/2} = +0.37$ V (*vs.* Ag/AgCl) for the formal Mn(III/IV) oxidation (Scheme 6(i)).[36] Complex **Mn5**(III)–N_3 showed similar values (Fig. S-5–S-7†).[32] In stark contrast, a solution of the azide anion in MeCN showed irreversible oxidation at $E_{p,a} = +0.89$ V (*vs.* Ag/AgCl), which shifted to $E_{p,a} = +1.45$ V (*vs.* Ag/AgCl) when AcOH was added (Fig. S-3†). This was likely due to a protonation, which was substantially higher in potential, compared to the manganese-complexes. Mixtures of the manganese chloride complex with tetra-*n*-butylammonium azide showed comparable redox properties with the well-defined manganese azide complexes (Scheme 6(ii)).[32] Finally, chronoamperometric experiments revealed selective product formations of tetralin **1a** to the corresponding azide product **2a**, at potentials as low as 0.8 V *vs.* Ag/Ag^+, without the formation of oxygenated side-products **3a** (Scheme 5d). This gives strong support that the manganese catalyst is involved in both steps of the reaction.

Based on our mechanistic studies, we propose the catalytic cycle to be initiated by facile ligand-exchange to form the active Mn(III)–N_3 complex, followed by anodic oxidation to generate the manganese(IV) diazide complex (Fig. 1). The high-valent d^3 manganese(IV) complex is prone[35b] to undergo hydrogen-atom-transfer (HAT)[37] with the substrate, thus generating the aliphatic radical. Subsequently, the key C–N_3 bond is formed *via* manganese-catalyzed azide radical transfer, yet alternative azide transfer scenarios, such as radical-polar crossover, can at this point not be fully ruled out.

Conclusions

In conclusion, we have reported the unprecedented manganese-electrocatalyzed C–H azidation of otherwise inert C(sp^3)–H bonds devoid of chemical oxidants, hypervalent iodine reagents or photochemical irradiation. Detailed mechanistic studies by experiment, spectrophotometry and cyclic voltammetry are supportive of an unique manganese(III/IV) electrocatalysis, thus avoiding overoxidation to the carbocation, while minimizing undesired side-reactions to oxygenated products. The robustness and utility of the most user-friendly method was highlighted by azidation of bioactive and pharmaceutically-relevant compounds by late-stage diversification.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (*a*) S. M. Khake and N. Chatani, *Trends Chem.*, 2019, **1**, 524; (*b*) P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz and L. Ackermann, *Chem. Rev.*, 2019, **119**, 2192; (*c*) J. C. K. Chu and T. Rovis, *Angew. Chem., Int. Ed.*, 2018, **57**, 62; (*d*) J. He, M. Wasa, K. S. L. Chan, Q. Shao and J.-Q. Yu, *Chem. Rev.*, 2017, **117**, 8754; (*e*) J. F. Hartwig and M. A. Larsen, *ACS Cent. Sci.*, 2016, **2**, 281; (*f*) M. C. White, *Science*, 2012, **335**, 807; (*g*) T. Brückl, R. D. Baxter, Y. Ishihara and P. S. Baran, *Acc. Chem. Res.*, 2012, **45**, 826; (*h*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (*i*) T. Satoh and M. Miura, *Chem.–Eur. J.*, 2010, **16**, 11212; (*j*) R. G. Bergman, *Nature*, 2007, **446**, 391; (*k*) J. A. Labinger and J. E. Bercaw, *Nature*, 2002, **417**, 507.

2 (*a*) G. Laudadio, Y. Deng, K. van der Wal, D. Ravelli, M. Nuño, M. Fagnoni, D. Guthrie, Y. Sun and T. Noël, *Science*, 2020, **369**, 92; (*b*) A. Bunescu, S. Lee, Q. Li and J. F. Hartwig, *ACS Cent. Sci.*, 2017, **3**, 895; (*c*) J.-R. Pouliot, F. Grenier, J. T. Blaskovits, S. Beaupré and M. Leclerc, *Chem. Rev.*, 2016, **116**, 14225; (*d*) D. J. Schipper and K. Fagnou, *Chem. Mater.*, 2011, **23**, 1594.

3 (*a*) O. Baudoin, *Angew. Chem., Int. Ed.*, 2020, **59**, 17798; (*b*) R. Hili and A. K. Yudin, *Nat. Chem. Biol.*, 2006, **2**, 284.

4 (*a*) J. Börgel and T. Ritter, *Chem*, 2020, **6**, 1877; (*b*) F. Wu, J. Zhang, F. Song, S. Wang, H. Guo, Q. Wei, H. Dai, X. Chen, X. Xia, X. Liu, L. Zhang, J.-Q. Yu and X. Lei, *ACS Cent. Sci.*, 2020, **6**, 928; (*c*) W. Wang, M. M. Lorion, J. Shah, A. R. Kapdi and L. Ackermann, *Angew. Chem., Int. Ed.*, 2018, **57**, 14700; (*d*) T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal and S. W. Krska, *Chem. Soc. Rev.*, 2016, **45**, 546; (*e*) A. F. M. Noisier and M. A. Brimble, *Chem. Rev.*, 2014, **114**, 8775.

5 For selected examples, see: (*a*) R. Singh and A. Mukherjee, *ACS Catal.*, 2019, **9**, 3604; (*b*) J. R. Clark, K. Feng, A. Sookezian and M. C. White, *Nat. Chem.*, 2018, **10**, 583; (*c*) S. M. Paradine, J. R. Griffin, J. Zhao, A. L. Petronico, S. M. Miller and M. Christina White, *Nat. Chem.*, 2015, **7**, 987; (*d*) A. McNally, B. Haffemayer, B. S. L. Collins and M. J. Gaunt, *Nature*, 2014, **510**, 129; (*e*) J. L. Jeffrey and R. Sarpong, *Chem. Sci.*, 2013, **4**, 4092; (*f*) J. L. Roizen, M. E. Harvey and J. Du Bois, *Acc. Chem. Res.*, 2012, **45**, 911; (*g*) F. Collet, R. H. Dodd and P. Dauban, *Chem. Commun.*, 2009, 5061; (*h*) H. M. L. Davies and M. S. Long, *Angew. Chem., Int. Ed.*, 2005, **44**, 3518; (*i*) X.-Q. Yu, J.-S. Huang, X.-G. Zhou and C.-M. Che, *Org. Lett.*, 2000, **2**, 2233.

6 For reviews, see: (*a*) M. Goswami and B. de Bruin, *Eur. J. Org. Chem.*, 2017, 1152; (*b*) W. Song, S. I. Kozhushkov and L. Ackermann, *Angew. Chem., Int. Ed.*, 2013, **52**, 6576; (*c*) S. Chiba, *Synlett*, 2012, **2012**, 21; (*d*) N. Jung and S. Bräse, *Angew. Chem., Int. Ed.*, 2012, **51**, 12169; (*e*) S. Bräse, C. Gil, K. Knepper and V. Zimmermann, *Angew. Chem., Int. Ed.*, 2005, **44**, 5188; (*f*) M. Köhn and R. Breinbauer, *Angew. Chem., Int. Ed.*, 2004, **43**, 3106.

7 (*a*) P. P. Geurink, W. A. van der Linden, A. C. Mirabella, N. Gallastegui, G. de Bruin, A. E. M. Blom, M. J. Voges, E. D. Mock, B. I. Florea, G. A. van der Marel, C. Driessen, M. van der Stelt, M. Groll, H. S. Overkleeft and A. F. Kisselev, *J. Med. Chem.*, 2013, **56**, 1262; (*b*) D. B. Smith, G. Kalayanov, C. Sund, A. Winqvist, T. Maltseva, V. J. P. Leveque, S. Rajyaguru, S. L. Pogam, I. Najera, K. Benkestock, X.-X. Zhou, A. C. Kaiser, H. Maag, N. Cammack, J. A. Martin, S. Swallow, N. G. Johansson, K. Klumpp and M. Smith, *J. Med. Chem.*, 2009, **52**, 2971; (*c*) G. C. Tron, T. Pirali, R. A. Billington, P. L. Canonico, G. Sorba and A. A. Genazzani, *Med. Res. Rev.*, 2008, **28**, 278; (*d*) A. G. Habeeb, P. N. Praveen Rao and E. E. Knaus, *J. Med. Chem.*, 2001, **44**, 3039.

8 (*a*) W. Xi, T. F. Scott, C. J. Kloxin and C. N. Bowman, *Adv. Funct. Mater.*, 2014, **24**, 2572; (*b*) R. Kluger, *J. Am. Chem. Soc.*, 2010, **132**, 6611.

9 (*a*) P. Thirumurugan, D. Matosiuk and K. Jozwiak, *Chem. Rev.*, 2013, **113**, 4905; (*b*) L. A. Canalle, D. W. P. M. Löwik and J. C. M. van Hest, *Chem. Soc. Rev.*, 2010, **39**, 329; (*c*) M. D. Best, *Biochemistry*, 2009, **48**, 6571; (*d*) D. M. Huryn and M. Okabe, *Chem. Rev.*, 1992, **92**, 1745.

10 H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004.

11 For reviews, see: (*a*) L. Ge, M.-F. Chiou, Y. Li and H. Bao, *Green Synthesis and Catalysis*, 2020, **1**, 86; (*b*) P.-G. Ding, X.-S. Hu, F. Zhou and J. Zhou, *Org. Chem. Front.*, 2018, **5**, 1542; (*c*) X. Huang and J. T. Groves, *ACS Catal.*, 2016, **6**, 751.

12 X. Zhang, H. Yang and P. Tang, *Org. Lett.*, 2015, **17**, 5828.

13 S.-E. Suh, S.-J. Chen, M. Mandal, I. A. Guzei, C. J. Cramer and S. S. Stahl, *J. Am. Chem. Soc.*, 2020, **142**, 11388.

14 (*a*) R. R. Karimov, A. Sharma and J. F. Hartwig, *ACS Cent. Sci.*, 2016, **2**, 715; (*b*) P. T. G. Rabet, G. Fumagalli, S. Boyd and M. F. Greaney, *Org. Lett.*, 2016, **18**, 1646; (*c*) A. Sharma and J. F. Hartwig, *Nature*, 2015, **517**, 600; (*d*) C. Viuf and M. Bols, *Angew. Chem., Int. Ed.*, 2001, **40**, 623; (*e*) V. V. Zhdankin, A. P. Krasutsky, C. J. Kuehl, A. J. Simonsen, J. K. Woodward, B. Mismash and J. T. Bolz, *J. Am. Chem. Soc.*, 1996, **118**, 5192; (*f*) P. Magnus, J. Lacour, P. A. Evans, M. B. Roe and C. Hulme, *J. Am. Chem. Soc.*, 1996, **118**, 3406; (*g*) Y. Kita, H. Tohma, T. Takada, S. Mitoh, S. Fujita and M. Gyoten, *Synlett*, 1994, **1994**, 427; (*h*) P. Magnus, J. Lacour and W. Weber, *J. Am. Chem. Soc.*, 1993, **115**, 9347.

15 L. Niu, C. Jiang, Y. Liang, D. Liu, F. Bu, R. Shi, H. Chen, A. D. Chowdhury and A. Lei, *J. Am. Chem. Soc.*, 2020, **142**, 17693.

16 (*a*) K. A. Margrey, W. L. Czaplyski, D. A. Nicewicz and E. J. Alexanian, *J. Am. Chem. Soc.*, 2018, **140**, 4213; (*b*) S. Kamijo, M. Watanabe, K. Kamijo, K. Tao and T. Murafuji, *Synthesis*, 2016, **48**, 115; (*c*) Y. Wang, G.-X. Li, G. Yang, G. He and G. Chen, *Chem. Sci.*, 2016, **7**, 2679.

17 H. Schäfer, *Angew. Chem., Int. Ed. Engl.*, 1970, **9**, 158.

18 (*a*) J. C. Siu, J. B. Parry and S. Lin, *J. Am. Chem. Soc.*, 2019, **141**, 2825; (*b*) N. Fu, G. S. Sauer and S. Lin, *Nat. Protoc.*, 2018, **13**, 1725; (*c*) J. C. Siu, G. S. Sauer, A. Saha, R. L. Macey, N. Fu, T. Chauviré, K. M. Lancaster and S. Lin, *J. Am. Chem. Soc.*, 2018, **140**, 12511; (*d*) N. Fu, G. S. Sauer, A. Saha, A. Loo and S. Lin, *Science*, 2017, **357**, 575.

19 For reviews, see: (*a*) Y. Hu, B. Zhou and C. Wang, *Acc. Chem. Res.*, 2018, **51**, 816; (*b*) W. Liu and L. Ackermann, *ACS Catal.*, 2016, **6**, 3743; for selected examples, see: (*c*) N. Kaplaneris, T. Rogge, R. Yin, H. Wang, G. Sirvinskaite and L. Ackermann, *Angew. Chem., Int. Ed.*, 2019, **58**, 3476; (*d*) C. Wang, A. Wang and M. Rueping, *Angew. Chem., Int. Ed.*, 2017, **56**, 9935; (*e*) B. Zhou, Y. Hu and C. Wang, *Angew. Chem., Int. Ed.*, 2015, **54**, 13659; (*f*) W. Liu, D. Zell, M. John and L. Ackermann, *Angew. Chem., Int. Ed.*, 2015, **54**, 4092; (*g*) Y. Kuninobu, Y. Nishina, T. Takeuchi and K. Takai, *Angew. Chem., Int. Ed.*, 2007, **46**, 6518.

20 For selected examples, see: (*a*) K. Feng, R. E. Quevedo, J. T. Kohrt, M. S. Oderinde, U. Reilly and M. C. White, *Nature*, 2020, **580**, 621; (*b*) J. Zhao, T. Nanjo, E. C. de Lucca and M. C. White, *Nat. Chem.*, 2019, **11**, 213; (*c*) M. Milan, M. Salamone, M. Costas and M. Bietti, *Acc. Chem. Res.*, 2018, **51**, 1984.

21 (*a*) X. Huang, T. M. Bergsten and J. T. Groves, *J. Am. Chem. Soc.*, 2015, **137**, 5300; (*b*) C. L. Hill, J. A. Smegal and T. J. Henly, *J. Org. Chem.*, 1983, **48**, 3277; (*c*) C. L. Hill and B. C. Schardt, *J. Am. Chem. Soc.*, 1980, **102**, 6374.

22 (*a*) M. Guo, T. Corona, K. Ray and W. Nam, *ACS Cent. Sci.*, 2019, **5**, 13; (*b*) M. Guo, M. S. Seo, Y.-M. Lee, S. Fukuzumi and W. Nam, *J. Am. Chem. Soc.*, 2019, **141**, 12187; (*c*) X. Huang and J. T. Groves, *Chem. Rev.*, 2018, **118**, 2491; (*d*) W. Liu and J. T. Groves, *Acc. Chem. Res.*, 2015, **48**, 1727; (*e*) W. Liu, X. Huang, M.-J. Cheng, R. J. Nielsen, W. A. Goddard and J. T. Groves, *Science*, 2012, **337**, 1322; (*f*) V. Lyaskovskyy, A. I. O. Suarez, H. Lu, H. Jiang, X. P. Zhang and B. de Bruin, *J. Am. Chem. Soc.*, 2011, **133**, 12264; (*g*) M. Costas, *Coord. Chem. Rev.*, 2011, **255**, 2912; (*h*) J. E. Lyons, P. E. Ellis and S. N. Shaikh, *Inorg. Chim. Acta*, 1998, **270**, 162; (*i*) P. Battioni, J. P. Renaud, J. F. Bartoli, M. Reina-Artiles, M. Fort and D. Mansuy, *J. Am. Chem. Soc.*, 1988, **110**, 8462; (*j*) J. T. Groves, W. J. Kruper and R. C. Haushalter, *J. Am. Chem. Soc.*, 1980, **102**, 6375.

23 (*a*) R. D. Little, *J. Org. Chem.*, 2020, **85**, 13375; (*b*) K.-J. Jiao, Y.-K. Xing, Q.-L. Yang, H. Qiu and T.-S. Mei, *Acc. Chem. Res.*, 2020, **53**, 300; (*c*) F. Wang and S. S. Stahl, *Acc. Chem. Res.*, 2020, **53**, 561; (*d*) J. C. Siu, N. Fu and S. Lin, *Acc. Chem. Res.*, 2020, **53**, 547; (*e*) J. Liu, L. Lu, D. Wood and S. Lin, *ACS Cent. Sci.*, 2020, **6**, 1317; (*f*) P. Xiong and H.-C. Xu, *Acc. Chem. Res.*, 2019, **52**, 3339; (*g*) Y. Yuan and A. Lei, *Acc. Chem. Res.*, 2019, **52**, 3309; (*h*) J.-i. Yoshida, A. Shimizu and R. Hayashi, *Chem. Rev.*, 2018, **118**, 4702; (*i*) M. D. Kärkäs, *Chem. Soc. Rev.*, 2018, **47**, 5786; (*j*) A. Wiebe, T. Gieshoff, S. Möhle, E. Rodrigo, M. Zirbes and S. R. Waldvogel, *Angew. Chem., Int. Ed.*, 2018, **57**, 5594; (*k*) M. Yan, Y. Kawamata and P. S. Baran, *Chem. Rev.*, 2017, **117**, 13230; (*l*) R. Feng, J. A. Smith and K. D. Moeller, *Acc. Chem. Res.*, 2017, **50**, 2346; (*m*) R. Francke and R. D. Little, *Chem. Soc. Rev.*, 2014, **43**, 2492.

24 (*a*) L. Ackermann, *Acc. Chem. Res.*, 2020, **53**, 84; (*b*) T. H. Meyer, I. Choi, C. Tian and L. Ackermann, *Chem*, 2020, **6**, 2484; (*c*) T. H. Meyer, L. H. Finger, P. Gandeepan and L. Ackermann, *Trends Chem.*, 2019, **1**, 63; (*d*) N. Sauermann, T. H. Meyer, Y. Qiu and L. Ackermann, *ACS Catal.*, 2018, **8**, 7086.

25 V. Plzak and H. Wendt, *Ber. Bunsen-Ges. Phys. Chem.*, 1979, **83**, 481.

26 G. A. Ward and C. M. Wright, *J. Electroanal. Chem.*, 1964, **8**, 302.

27 X.-S. Xue, P. Ji, B. Zhou and J.-P. Cheng, *Chem. Rev.*, 2017, **117**, 8622.

28 M. Zhang, Z.-F. Lu, Y. Liu, G. Grampp, H.-W. Hu and J.-H. Xu, *Tetrahedron*, 2006, **62**, 5663.

29 (*a*) S. Herold, D. Bafaluy and K. Muñiz, *Green Chem.*, 2018, **20**, 3191; (*b*) Y. Kawamata, M. Yan, Z. Liu, D.-H. Bao, J. Chen, J. T. Starr and P. S. Baran, *J. Am. Chem. Soc.*, 2017, **139**, 7448; (*c*) G. Balavoine, D. H. R. Barton, J. Boivin, A. Gref, N. Ozbalik and H. Rivière, *Tetrahedron Lett.*, 1986, **27**, 2849.

30 A. Mukherjee, M. Martinho, E. L. Bominaar, E. Münck and L. Que Jr, *Angew. Chem., Int. Ed.*, 2009, **48**, 1780.

31 H. J. Schäfer, Electrochemical Conversion of Alkanes, in *Alkanes and Cycloalkanes*, ed. S. Patai and Z. Rappoport, Wiley & Sons, New York, 1992, pp. 781–808.

32 For detailed information see the ESI.†

33 (*a*) L. Gaillon, F. Bedioui, P. Battioni and J. Devynck, *J. Mol. Catal.*, 1993, **78**, L23; (*b*) P. Leduc, P. Battioni, J. F. Bartoli and D. Mansuy, *Tetrahedron Lett.*, 1988, **29**, 205; (*c*) J. C. Lennox and R. W. Murray, *J. Am. Chem. Soc.*, 1978, **100**, 3710.

34 B. W. Lund, F. Piu, N. K. Gauthier, A. Eeg, E. Currier, V. Sherbukhin, M. R. Brann, U. Hacksell and R. Olsson, *J. Med. Chem.*, 2005, **48**, 7517.

35 (*a*) T. Kurahashi, M. Hada and H. Fujii, *J. Am. Chem. Soc.*, 2009, **131**, 12394; (*b*) T. Kurahashi and H. Fujii, *Inorg. Chem.*, 2008, **47**, 7556.

36 T. Kurahashi and H. Fujii, *J. Am. Chem. Soc.*, 2011, **133**, 8307.

37 For reviews, see: (*a*) L. Capaldo and D. Ravelli, *Eur. J. Org. Chem.*, 2017, **2017**, 2056; (*b*) J. M. Mayer, *Acc. Chem. Res.*, 2011, **44**, 36.