How to cite: *Angew. Chem. Int. Ed.* **2024**, *63*, e202410616
doi.org/10.1002/anie.202410616

Decarboxylative Functionalization

Photoinduced Cu(II)-Mediated Decarboxylative Thianthrenation of Aryl and Heteroaryl Carboxylic Acids

*Zhen He and Paweł Dydio**

Abstract: Given that (hetero)aryl carboxylic acids are inexpensive materials available in a great variety from commercial and natural resources or synthesis, the strategies enabling their use as starting materials for preparing fine chemicals are highly sought after. Here we report a photoinduced Cu(II)-mediated protocol converting (hetero)aryl carboxylic acids into (hetero)aryl thianthrenium salts, high value-added building blocks that can undergo various subsequent transformations, creating an attractive two-step pathway for the divergent functionalization of these ubiquitous starting materials. The excellent compatibility of the method is shown by preparing a broad range of sterically and electronically varied (hetero)aryl thianthrenium salts, including derivatives of pharmaceuticals, such as ataluren, celecoxib, flavoxate, probenecid, repaglinide, and tamibarotene. The syntheses of 13 C-labeled probenecid and bioisosteres of ataluren as well as the unconventional modifications of celecoxib and flavoxate, illustrate the synthetic potential of the strategy. Mechanistic studies are in line with a reaction occurring through a photoinduced ligand-to-metal charge transfer (LMCT) of Cu(II)-arylcarboxylates, enabling radical decarboxylative carbometallation to form arylcopper(II) intermediates that in turn react with thianthrene to form the product. Noteworthy, the susceptibility of aryl thianthrenium salts to photodegradation is overcome by a Cu(I)-driven salvage loop, which continuously intercepts the transiently formed radicals and regenerates the products.

Introduction

The use of abundant carboxylic acids as attractive starting materials for fine chemical synthesis has been broadly recognized and sought after.[1–6] Decarboxylative methods leveraging aryl carboxylic acids as an alternative to classic aryl building blocks, such as preformed organometallic reagents, are highly appealing (Figure 1a).[2,7] However,

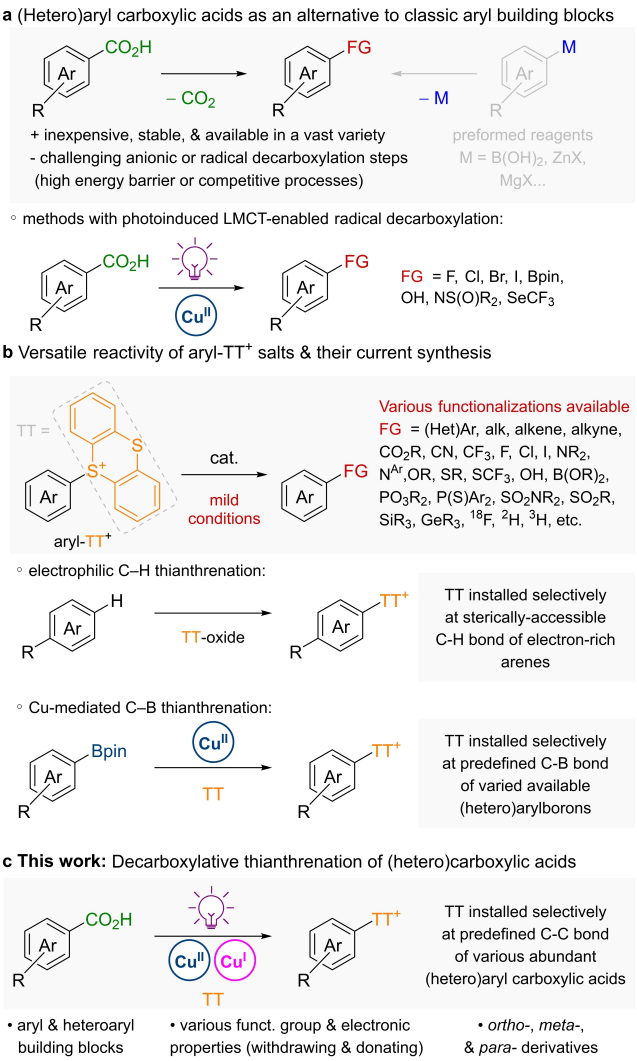


Figure 1. Context of this work. **a**, decarboxylative functionalization of aryl carboxylic acids. **b**, Synthesis & functionalization methods of aryl thianthrenium salts. **c**, Decarboxylative thianthrenation strategy reported here, as well as its main features.

[*] Z. He, P. Dydio
University of Cambridge
Lensfield Road, Cambridge, CB2 1EW, UK
E-mail: pd552@cam.ac.uk
Z. He, P. Dydio
University of Strasbourg, CNRS
ISIS UMR 7006
8 Allée Gaspard Monge, 67000 Strasbourg, France

anionic decarboxylation of aryl carboxylates is typically of a high energy barrier.[3] Therefore, methods involving anionic decarboxylation step require forcing reaction temperatures or are compatible with a limited scope of aryl building blocks.[2] In sharp contrast, decarboxylation of aroyloxyl radicals is substantially faster.[3,8] Nevertheless, aroyloxyl radicals can also enter competitive processes, most significantly facile hydrogen atom transfer (HAT; $k \approx 10^6\ M^{-1}s^{-1}$–$10^7\ M^{-1}s^{-1}$ versus $k \approx 10^6\ s^{-1}$ for radical decarboxylation)[8–11] from solvents or other hydrogen sources. Therefore, successful functionalization of aryl carboxylic acids occurring via radical decarboxylative pathways requires careful optimization of activators and reaction partners.[1,3] In that context, a photoinduced ligand-to-metal charge transfer (LMCT) of copper(II) arylcarboxylates was recently introduced as a practical manifold to generate aroyloxyl radicals that undergo radical decarboxylative carbometallation forming arylcopper(II) species, which can react further to furnish the functionalized product (Figure 1a, bottom).[12] Upon careful optimization of reagents, the strategy proved effective for decarboxylative halogenation, borylation, hydroxylation, sulfoximination, and trifluoromethylselenolation of (hetero)aryl carboxylic acids.[12–20]

Aryl thianthrenium salts, aryl-TT^+, are attractive building blocks that can undergo numerous selective transformations under mild conditions (Figure 1b).[21–25] They can be prepared by electrophilic aromatic C–H thianthrenation reactions,[26,27] occurring selectively at sterically most accessible C–H sites of the most electron-rich aryl rings of the molecules.[28] However, the electrophilic protocols are ineffective for electron-deficient (hetero)aromatic moieties. Alternatively, structurally varied (hetero)aryl thianthrenium salt reagents can be synthesized by Cu(II)-mediated C–B thianthrenation of arylborons,[29] when the corresponding aryl boronic acid derivatives are either commercially available or accessible via C–H borylation protocols.[30] New strategies enabling thianthrenation of other common structural motifs could address the existing limitations in the synthesis of these valuable building blocks and create complementary entry points for arylthianthrenium salt chemistry.

We considered that decarboxylative thianthrenation of (hetero)aryl carboxylic acids forming aryl-TT^+ would be appealing from a synthetic standpoint (Figure 1c). The method would convert readily available starting materials into readily derivable reagents, enabling broad-range decarboxylative functionalization of initial carboxylic acids via two-step protocols. Attractively, the potentially problematic decarboxylation step would be separated from the functionalization step of the aryl-TT^+ intermediate, thereby eliminating the need for careful optimization or reaction parameters in the case of each transformation. The strategy would be desirable when libraries of diverse derivatives of compounds bearing carboxylic acids are needed, for instance, during the structure–activity relationship (SAR) studies.

Results and Discussion

Reaction Design

We considered that merging the photoinduced LMCT-enabled radical decarboxylation of copper(II) (hetero)aryl carboxylates with the capacity of arylcopper(II) species to forge a C–S bond could enable decarboxylative thianthrenation of (hetero)aryl carboxylic acids. Specifically, the in situ formed copper(II) arylcarboxylates could undergo the photoinduced LMCT-driven radical decarboxylative carbometalation to form arylcopper(II) species.[12] In turn, the latter could react with thianthrene and additional copper(II) to form aryl-TT^+, in analogy to the arylcopper(II) species, formed via transmetalation with arylboronic acids, reacting with thianthrene and additional copper(II) to form aryl-TT^+.[29] However, the critical challenge remained regarding the well-established susceptibility of aryl-TT^+ reagents to undergo fragmentation under photoirradiation,[31–33] the conditions intrinsic to the photoinduced LMCT. To overcome this fundamental impediment, we surmised that the decay of the product by the photoinduced fragmentation could be inhibited by copper(I) additives. The latter would capture the prospective aryl radicals generated upon photoinduced product fragmentation, forming arylcopper(II) species,[34,35] which would re-enter the reaction, thereby continuously regenerating the photofragmented product.

Reaction Development

To investigate our design, we examined the reaction between 4-fluorobenzoic acid **1** and thianthrene **2** (Figure 2). Upon exploration of conditions, we found that the model reaction conducted on a 0.1 mmol scale formed aryl-TT^+ **3** in 82 % or 66 % yield when either **2** or **1** was used as the limiting reagent, respectively, in the presence of simple inexpensive Cu(II) and Cu(I) salts ($Cu(OTf)_2$, 3.0 equiv., $Cu(MeCN)_4OTf$, 2.0 equiv.), and a base (NaF, 2.5 equiv.) in acetonitrile (12.5 mM) under purple light (390 nm) irradiation for 90 min. The reaction conducted on a 2 mmol scale at 25 mM concentration with 3 h irradiation, otherwise under standard conditions, delivered 0.58 g (63 % isolated yield) of aryl-TT^+ **3**, illustrating the scale up potential and the synthetic utility of the method. Control experiments confirmed the importance of each element of the reaction design, as summarized in Figure 2 and detailed in the Supporting Information (Tables S1–S7). Notably, the use of poorly soluble NaF as a weak base is essential, presumably allowing to maintain a concentration of the deprotonated carboxylic acid in solution low but sufficient for the reaction. The use a stronger base (e.g., Na_2CO_3) or a more soluable base (e.g., KF, CsF), which favors a high concentration of deprotonated carboxylic acid in solution, resulted in the formation of substantial amounts of side-product **5** from competitive decarboxylative self-coupling of the aryl carboxylic acids.[13] The experiments with electronically varied chalcogen reagents revealed that the target process also occurs quickly and in high yields with dimethoxythianthrene

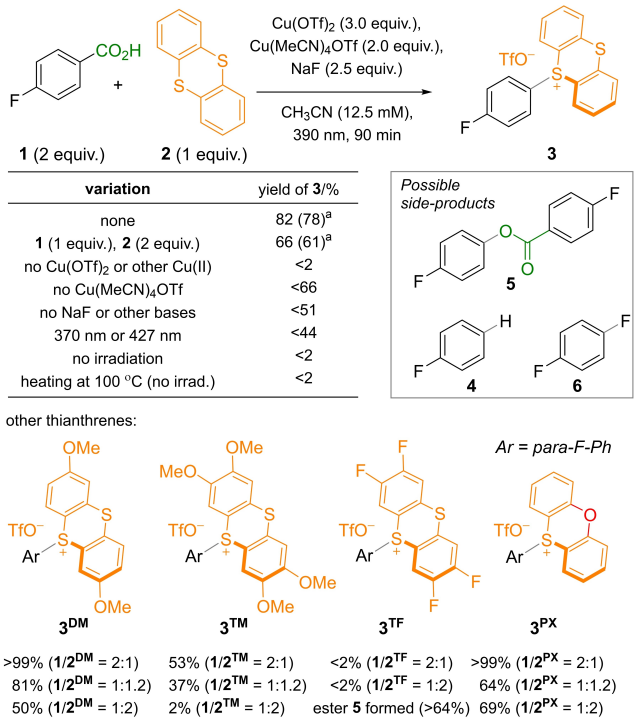


Figure 2. Reaction development. [a] Yield of isolated material.

2^{DM} and phenoxathiine **2^{PX}**. In turn, the reactions with either strongly electron-rich tetramethoxythianthrene **2^{TM}** or electron-deficient tetrafluorothianthrene **2^{TF}** were slow or unproductive. In the case of tetramethoxythianthrene **2^{TM}**, the reactions were selective toward the formation of **3^{TM}** but sluggish, especially when excess **2^{TM}** was used. In contrast, for **2^{TF}**, the reaction resulted in the formation of ester **5** as the primary product (>64 % yields by the ^{19}F NMR analysis) in a competitive process.[13]

Substrate Scope

We found that a broad range of structurally diversified (hetero)aryl thianthrenium salts **7**–**45** bearing an array of functional groups of varied electronic influence and steric demand can be prepared under the developed conditions underscoring the generality of the strategy (Figure 3). For instance, electron-deficient products, such as nitro **10^{DM}**, nitrile **11^{DM}**, and sulfone **12^{DM}**, as well as electron-rich derivatives, including acetoxy **14**, methoxy **15**, and amine **26^{DM}**, were all successfully prepared under standard conditions. Also, radical-prone or redox-sensitive moieties, such as benzyl bromide **27^{DM}** and aldehyde **28**, were amenable. In addition, different substitution patterns were tolerated, including *para*-, *meta*-, *ortho*-substituted, and most congested 2,6-bissubstituted derivatives, such as **33^{DM}**, albeit in a lower (unoptimized) yield. Further, the reactions for a range of heteroaryl carboxylic acids furnished target thianthrenation products **34**–**44**.

In general, for electron-deficient (hetero)aryl carboxylic acids, we observed that the reactions with **2^{DM}** or **2^{PX}** typically formed the aryl-TT$^+$ products in higher yields than those with **2**. Besides, when the reactions under the purple light (390 nm) yielded the products inefficiently, the reactions under blue light irradiation (427 nm) typically formed the products in higher yields. For instance, the reaction of 2,4-bis(trifluoromethyl)benzoic acid formed a trace of **32** under the purple light but furnished the product in 78 % under the blue light, under otherwise standard conditions. The control experiments showed that **32** is unstable and undergoes fast decomposition under reaction conditions with purple light irradiation.

Synthetic Application

Bolstered by these results, we investigated the functionalization of bioactive molecules that contain either carboxylic acid or carboxylic-acid derivable functional group (Figure 4). We showed that carboxylic acid-containing drug molecules, such as probenecid used in the treatment of gout and hyperuricemia, ataluren for treating Duchenne muscular dystrophy, tamibarotene used against acute promyelocytic leukaemia, and repaglinide treating diabetes mellitus type 2, were all converted into their aryl thianthrenium salts **46**, **47**, **55**, and **56**. The latter could be readily transformed into the ^{13}C-labeled carboxylic acids,[36] as exemplified with probenecid derivative ^{13}C-**48**. Such a facile two-step isotope labelling procedure is attractive for the isotope tracing metabolomics of complex bioactive carboxylic acids.[37] Furthermore, the easy access to carboxylic acid bioisosteres is valuable for drug design,[38] especially when the carboxylic acid moiety is an essential constituent of a pharmacophore but carries significant drawbacks, such as metabolic instability or limited passive diffusion across biological membranes. Attractively, thianthrenium salts of carboxylic acid drug molecules can be readily converted to their (caged) bioisosteres, as exemplified here by preparing derivatives of ataluren, namely caged boronic acid ester[26] **49** and sulfonamide[39] **50**. In turn, flavoxate, an anticholinergic drug bearing a carboxylate ester motif, was converted into its phosphate ester derivative **52** in a three-step sequence of hydrolysis, thianthrenation, and functionalization.[26] Similarly, celecoxib, a non-steroidal anti-inflammatory drug containing an arylalkyl moiety, was precisely modified at its alkyl site. Upon chemoselective oxidation of its methyl group to the carboxylic acid function,[40] followed by thianthrenation and Negishi-type coupling,[41] derivative **54**, the isobutyl homolog of celecoxib was attained.

Mechanistic Studies

Mechanistic investigations support our initial reaction design, including the conceived copper(I)- and unexpected copper(II)-driven stabilization of the aryl-TT$^+$ products in the reaction mixture under photoirradiation (Figures 5–6). First, the stability of the aryl-TT$^+$ products under the standard reaction conditions was confirmed in a control experiment, in which **3** was recovered in >90 % NMR yield

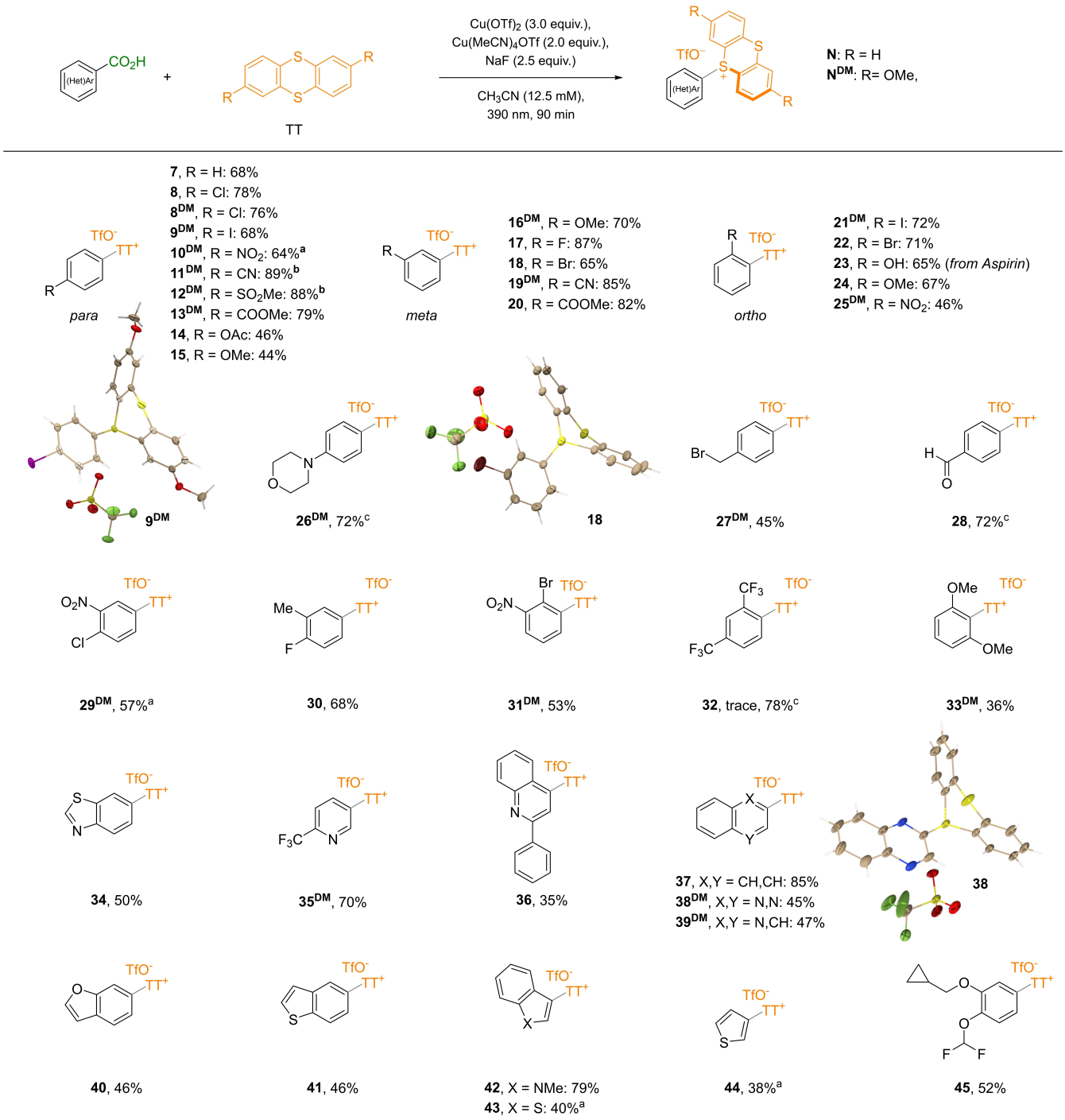


Figure 3. Substrate scope. [a] 3 h, [b] 2 h, [c] 427 nm light; for further details and additional examples, see the SI.

when present as an additive in a thianthrenation of benzoic acid **57** with **2** (Figure 5a). We also observed that aryl-TT$^+$ **3** remained stable under purple light irradiation in solution on its own (Figure 5b, entry 1). However, aryl-TT$^+$ **3** did decompose when irradiated in the presence of thianthrenes. For instance, upon 30 min irradiation in solution with **2** or **2**^{DM}, respectively, 18 % or 64 % of initial **3** decomposed, forming fluorobenzene **4**, in 18 % or 51 % (along with 12 % of **3**^{DM} in the latter experiment; entries 2–3, Figure 5b). The data indicate that the photodegradation of **3**, in that case, most likely involves the photoactivation of the electron donor-acceptor (EDA) complexes of aryl-TT$^+$ and thianthrenes,[32,33,42] rather than the previously reported direct photoinduced homolytic cleavage of the C–S bond.[43] In agreement, the UV/Vis absorption spectroscopy (Figure 6a) and the NMR data (Figure S5) show that aryl-TT$^+$ salts associate with thianthrenes, forming photoactive EDA complexes.[32,33,42] Most importantly, in the presence of the

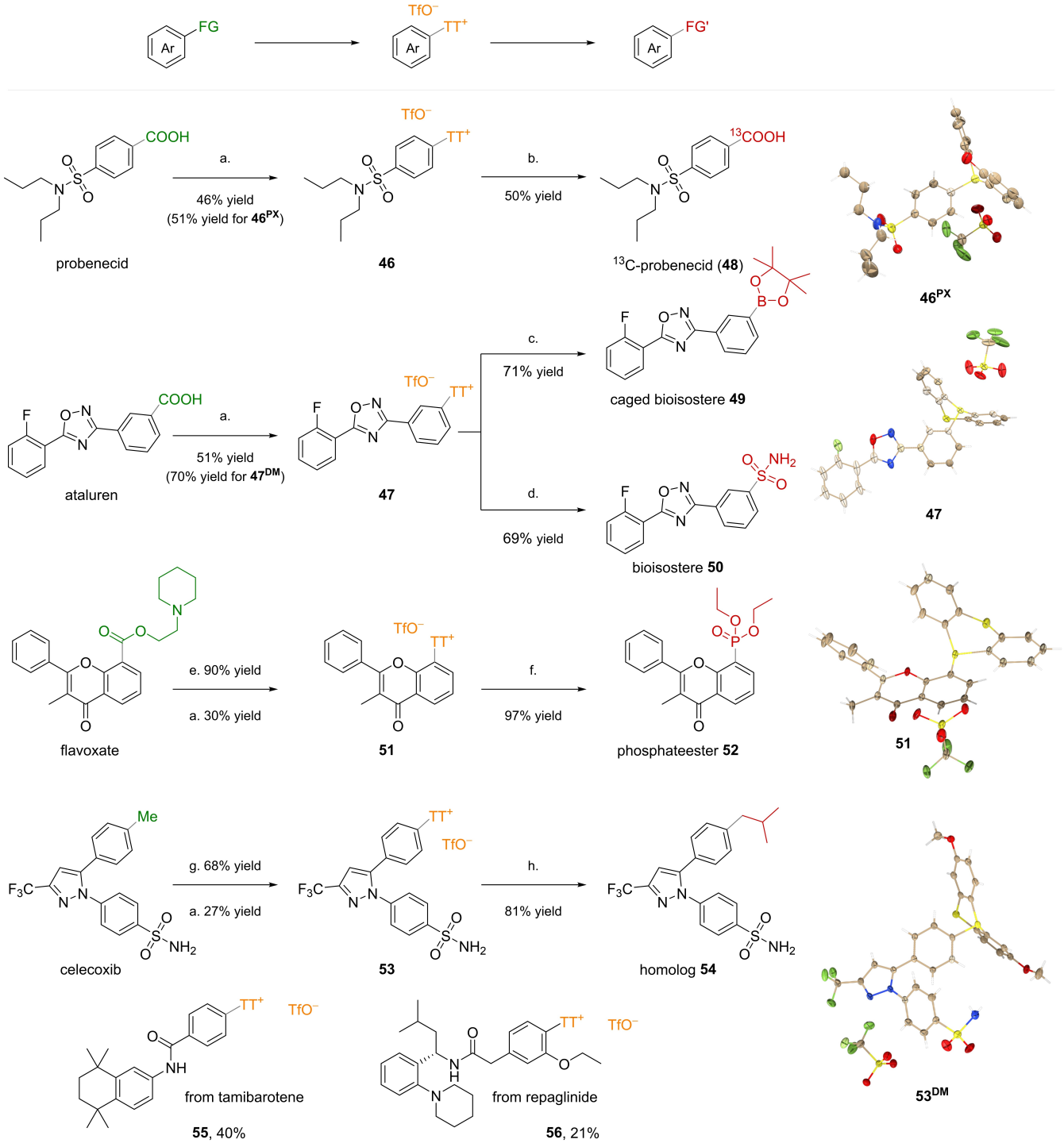
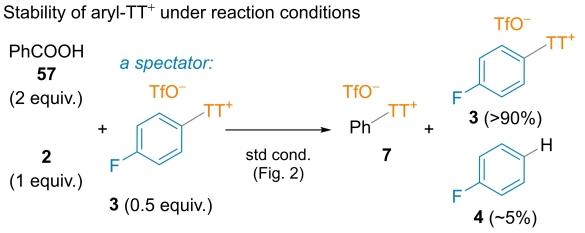


Figure 4. Modifications of pharmaceuticals through decarboxylative thianthrenation. Reaction conditions: a. acid (2.0 equiv.), **2** (1.0 equiv.), $Cu(OTf)_2$ (3.0 equiv.), $Cu(MeCN)_4OTf$ (2.0 equiv.), NaF (2.5 equiv.), CH_3CN, 390 nm, 90 min; b. i: $^{13}CO_2$, $ZnEt_2$ (5.0 equiv.), CuCl (10 mol%), $(BnNHCO)_2CH_2$ (20 mol%), dmf, rt, 12 h, ii: HCl (4.0 M in dioxane); c. B_2pin_2 (2.5 equiv.), pyridine (5.0 equiv.), $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ (1 mol%), MeCN, 456 nm, 6 h; d. i: Rongalite (1.5 equiv.), $Pd(dppf)Cl_2$ (5 mol%), iPrOH, 60 °C, 12 h, ii: HOSA (4.0 equiv.), NaOAc (7.0 equiv.), 0–25 °C, 1 h; e. LiOH (10 equiv.), thf, MeOH, H_2O, rt, 2 h; f. $P(OEt)_3$ (5.0 equiv.), pyridine (5.0 equiv.), NaI (20 mol%), $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ (1 mol%), MeCN, 456 nm, 3 h; g. $KMnO_4$ (2.0 equiv.), H_2O, reflux, 6 h; h. iBuI, Zn (3.0 equiv.), pyridine (0.5 equiv.), $PdCl_2$ (10 mol%), APhos (30 mol%), DMF (0.1 M), 60 °C, 1 h.

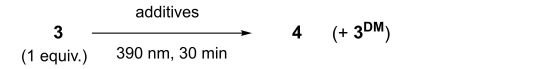
Cu(I) or Cu(II) additives, the aryl-TT^+ salts in the solution with thianthrenes were stabilized against photodegradation (entries 4–6, Figure 5b). As initially proposed, the Cu(I) salts can capture the aryl radicals and regenerate the aryl-TT^+ salts, as indicated by the formation of cross-exchange $\mathbf{3}^{DM}$ in 37 % in the reaction of $\mathbf{2}^{DM}$ and **3**. Cu(II) did also

a Stability of aryl-TT$^+$ under reaction conditions



*Most of **3** present as a spectator remained intact, indicating the stability of aryl-TT$^+$ salts under reaction conditions*

b Stability of aryl-TT$^+$ with additives under irradiation



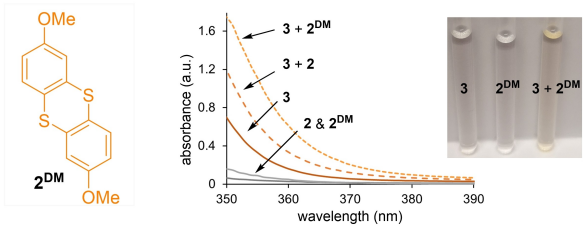
entry	additives	remaining **3**/%	yields of **4**/% & $\mathbf{3}^{DM}$/%
1	no additives	>95	<2
2	**2** (1.5 equiv.)	83	18
3	$\mathbf{2}^{DM}$ (1.5 equiv.)	36	51 12
4	$\mathbf{2}^{DM}$ (1.5 equiv.) + Cu(I) (2 equiv.)	36	6 37
5	$\mathbf{2}^{DM}$ (1.5 equiv.) + Cu(II) (3 equiv.)	>95	<2 <2
6	$\mathbf{2}^{DM}$ (4 equiv.) + Cu(II) (1.5 equiv.)	74 (58)*	<2 (2)* 8 (19)*

* 90 min

- Aryl-TT$^+$ salts remain intact under 390 nm irradiation in the absence of thianthrenes but readily decay in their presence
- Photodegradation is slowed down in the presence of Cu(I) & Cu(II) salts that, respectively, mediate the regeneration of aryl-TT$^+$ salts & prevent their photoactivation

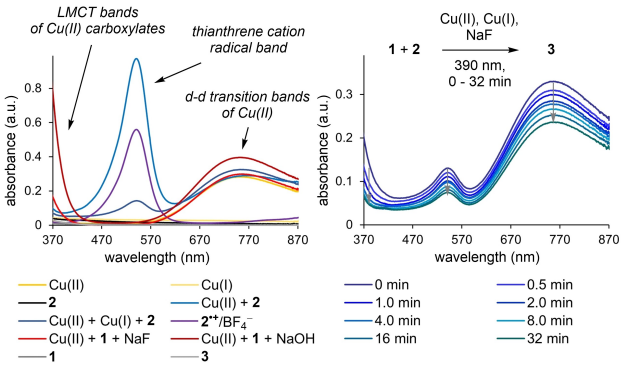
Figure 5. Stability of aryl-TT$^+$ salts under reaction conditions & the influence of different components of the reaction mixture.

a UV-Vis absorption spectra of aryl-TT$^+$ salt in the presence of thianthrenes

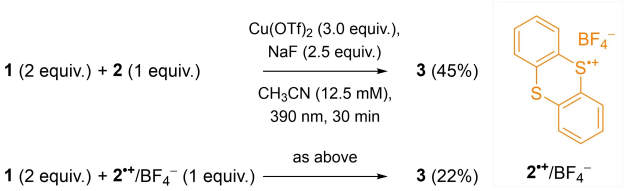


*Aryl-TT$^+$ & thianthrenes associate to form photoactive electron donor-acceptor complexes, according to the UV-Vis spectra, i.e., bathochromic shifts of the band of **3** in the presence of **2** or $\mathbf{2}^{DM}$, and the NMR titration data (Fig. S5)*

b UV-Vis absorption spectra of reaction components & model reaction mixture



c Control reactions with thianthrene cation radical vs thianthrene



d Radical trapping experiments

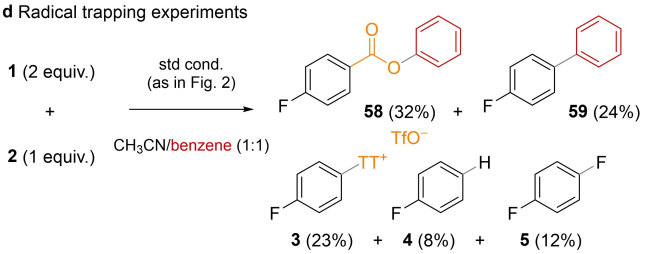


Figure 6. Spectroscopic studies & control experiments.

stabilize the aryl-TT$^+$ salts, albeit most likely via a different mechanism than Cu(I). Neither $\mathbf{3}^{DM}$ nor **4** were formed when irradiating the solution of $\mathbf{2}^{DM}$ and **3** in the presence of excess Cu(II) ($\mathbf{2}^{DM}$/**3**/Cu(II) ratio of 1.5:1:3). However, both $\mathbf{3}^{DM}$ and **4** were formed slowly when excess thianthrene was present ($\mathbf{2}^{DM}$/**3**/Cu(II) ratio of 4:1:1.5). The data suggest that Cu(II) can effectively prevent thianthrenes from forming the EDA complexes with aryl-TT$^+$, thereby inhibiting the photodegradation of the latter.

The additional spectrophotometric and radical trapping studies are in agreement with the LMCT-enabled radical mechanism (Figure 6b-d). The UV/Vis spectra of the reaction mixture confirmed the presence of the characteristic bands of LMCT of Cu(II) carboxylates and d-d transitions of Cu(II),[12] present also in the mixture of acid **1**, Cu(II), and the bases (Figure 6b). Both bands declined in the course of the reaction, in line with the reduction of Cu(II) to Cu(I) and the conversion of carboxylates. Besides, the UV/Vis spectra of a mixture of **2** and Cu(II), in the presence or absence of Cu(I), indicated that Cu(II) oxidizes a small portion of **2** to the thianthrene cation radical ($\mathbf{2}^{\bullet+}$) of a characteristic purple colour (absorption at 540 nm),[26] which is also present in the model reaction mixture. The characteristic purple colour of the mixture is also present without light irradiation, indicating that the oxidation is independent of light. Based on the molar absorption coefficient of an independently prepared tetrafluoroborate salt of $\mathbf{2}^{\bullet+}$,[44] ~0.3 % of **2** was oxidized into $\mathbf{2}^{\bullet+}$ in the initial reaction mixture, which is in line with the redox potentials ($E_{1/2}^{red}$[Cu(II)/Cu(I)] = +0.96 V[45,46] and $E_{1/2}^{red}$[$\mathbf{2}^{\bullet+}$/**2**] = +1.26 V,[47] both in acetonitrile versus SCE). Control side-by-side reactions of **1** with either **2** or $\mathbf{2}^{\bullet+}$, in the absence of reducing Cu(I) additives, furnished **3** in 45 % or 22 % yield, respectively (Figure 6c). Given the lower yield of **3** in the reaction with $\mathbf{2}^{\bullet+}$ than that with **2**, and the gradual reduction of $\mathbf{2}^{\bullet+}$ to **2** occurring in solution, **2** is most likely involved directly in the product formation, rather than $\mathbf{2}^{\bullet+}$. Lastly, in agreement with the intermediacy of aroyloxyl and aryl radicals, the experiment with benzene as a radical trapping additive resulted in the formation of phenyl ester **58** and fluorobiphenyl **59** (Figure 6d).[12]

Conclusion

Overall, the work presented here reveals that a broad range of electronically and sterically varied (hetero)aryl thianthrenium salts can be prepared from (hetero)aryl carboxylic acids in the operationally simple protocol using inexpensive reagents and light. Given the excellent availability of various carboxylic acids and the versatile reactivity of thianthrenium salts, the methodology can facilitate the synthesis of existing fine chemicals and accelerate the discovery of new functional molecules. For instance, the strategy could be particularly appealing when the synthesis of libraries of derivatives of compounds bearing carboxylic acid or carboxylic acid-derivable functional groups is required.

Acknowledgements

We acknowledge funding from the European Research Council (grant ERC StG 804106), the Fondation Jean-Marie Lehn, and the Morrell Fund, Yusuf Hamied Department of Chemistry, University of Cambridge. We thank L. Karmazin (University of Strasbourg) and C. Bailly (University of Strasbourg) for x-ray crystallography, P. Holban (University of Strasbourg) and J. McNamara (University of Cambridge) for checking the experimental procedures, and T. Ritter (Max-Planck-Institut Kohlenforschung) for comments on the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: (hetero)aryl carboxylic acids · decarboxylative functionalization · (hetero)aryl thianthrenium salt · thianthrenation · photoinduced LMCT

[1] S. B. Beil, T. Q. Chen, N. E. Intermaggio, D. W. C. MacMillan, *Acc. Chem. Res.* **2022**, *55*, 3481–3494.
[2] N. Rodríguez, L. J. Goossen, *Chem. Soc. Rev.* **2011**, *40*, 5030.
[3] J. Schwarz, B. König, *Green Chem.* **2018**, *20*, 323–361.
[4] J. Xuan, Z. Zhang, W. Xiao, *Angew. Chem. Int. Ed.* **2015**, *54*, 15632–15641.
[5] Y. Wei, P. Hu, M. Zhang, W. Su, *Chem. Rev.* **2017**, *117*, 8864–8907.
[6] L. J. Gooßen, N. Rodríguez, K. Gooßen, *Angew. Chem. Int. Ed.* **2008**, *47*, 3100–3120.
[7] L. J. Gooßen, G. Deng, L. M. Levy, *Science* **2006**, *313*, 662–664.
[8] X.-Q. Hu, Z.-K. Liu, Y.-X. Hou, Y. Gao, *iScience* **2020**, *23*, 101266.
[9] J. Chateauneuf, J. Lusztyk, K. U. Ingold, *J. Am. Chem. Soc.* **1988**, *110*, 2886–2893.
[10] J. Chateauneuf, J. Lusztyk, K. U. Ingold, *J. Am. Chem. Soc.* **1988**, *110*, 2877–2885.
[11] L. Candish, M. Freitag, T. Gensch, F. Glorius, *Chem. Sci.* **2017**, *8*, 3618–3622.
[12] P. Xu, P. López-Rojas, T. Ritter, *J. Am. Chem. Soc.* **2021**, *143*, 5349–5354.
[13] W. Su, P. Xu, T. Ritter, *Angew. Chem. Int. Ed.* **2021**, *60*, 24012–24017.
[14] P. Xu, W. Su, T. Ritter, *Chem. Sci.* **2022**, *13*, 13611–13616.
[15] N. W. Dow, P. S. Pedersen, T. Q. Chen, D. C. Blakemore, A.-M. Dechert-Schmitt, T. Knauber, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2022**, *144*, 6163–6172.
[16] T. Q. Chen, P. S. Pedersen, N. W. Dow, R. Fayad, C. E. Hauke, M. C. Rosko, E. O. Danilov, D. C. Blakemore, A.-M. Dechert-Schmitt, T. Knauber, F. N. Castellano, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2022**, *144*, 8296–8305.
[17] L. Liu, Y.-C. Gu, C.-P. Zhang, *J. Org. Chem.* **2023**, *88*, 9372–9380.
[18] Q. Y. Li, S. N. Gockel, G. A. Lutovsky, K. S. DeGlopper, N. J. Baldwin, M. W. Bundesmann, J. W. Tucker, S. W. Bagley, T. P. Yoon, *Nat. Chem.* **2022**, *14*, 94–99.
[19] S. Gavelle, M. Innocent, T. Aubineau, A. Guérinot, *Adv. Synth. Catal.* **2022**, *364*, 4189–4230.
[20] F. Juliá, *ChemCatChem* **2022**, *14*, e202200916.
[21] E. M. Ferreira, *Nature* **2019**, *567*, 184–185.
[22] Á. Péter, G. J. P. Perry, D. J. Procter, *Adv. Synth. Catal.* **2020**, *362*, 2135–2142.
[23] H. Meng, M.-S. Liu, W. Shu, *Chem. Sci.* **2022**, *13*, 13690–13707.
[24] F. Berger, T. Ritter, *Synlett* **2022**, *33*, 339–345.
[25] X.-Y. Chen, Y. Wu, P. Wang, *Synthesis* **2022**, *54*, 3928–3940.
[26] F. Berger, M. B. Plutschack, J. Riegger, W. Yu, S. Speicher, M. Ho, N. Frank, T. Ritter, *Nature* **2019**, *567*, 223–228.
[27] J. Wu, Z. Wang, X.-Y. Chen, Y. Wu, D. Wang, Q. Peng, P. Wang, *Sci. China Chem.* **2020**, *63*, 336–340.
[28] F. Juliá, Q. Shao, M. Duan, M. B. Plutschack, F. Berger, J. Mateos, C. Lu, X.-S. Xue, K. N. Houk, T. Ritter, *J. Am. Chem. Soc.* **2021**, *143*, 16041–16054.
[29] X.-Y. Chen, Y.-N. Li, Y. Wu, J. Bai, Y. Guo, P. Wang, *J. Am. Chem. Soc.* **2023**, *145*, 10431–10440.
[30] I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890–931.
[31] J. Li, J. Chen, R. Sang, W.-S. Ham, M. B. Plutschack, F. Berger, S. Chabbra, A. Schnegg, C. Genicot, T. Ritter, *Nat. Chem.* **2020**, *12*, 56–62.
[32] L. Van Dalsen, R. E. Brown, J. A. Rossi-Ashton, D. J. Procter, *Angew. Chem. Int. Ed.* **2023**, e202303104.
[33] A. Dewanji, L. Van Dalsen, J. A. Rossi-Ashton, E. Gasson, G. E. M. Crisenza, D. J. Procter, *Nat. Chem.* **2023**, *15*, 43–52.
[34] S. E. Creutz, K. J. Lotito, G. C. Fu, J. C. Peters, *Science* **2012**, *338*, 647–651.
[35] M. W. Johnson, K. I. Hannoun, Y. Tan, G. C. Fu, J. C. Peters, *Chem. Sci.* **2016**, *7*, 4091–4100.
[36] S. Tang, X. Zhao, L. Yang, B. Li, B. Wang, *Angew. Chem. Int. Ed.* **2022**, *61*, e202212975.
[37] C. Jang, L. Chen, J. D. Rabinowitz, *Cell* **2018**, *173*, 822–837.
[38] C. Ballatore, D. M. Huryn, A. B. Smith, *ChemMedChem* **2013**, *8*, 385–395.
[39] E. M. Alvarez, M. B. Plutschack, F. Berger, T. Ritter, *Org. Lett.* **2020**, *22*, 4593–4596.
[40] A. Lill, K. Scholich, H. Stark, *Tetrahedron Lett.* **2013**, *54*, 6682–6686.
[41] B. Lansbergen, P. Granatino, T. Ritter, *J. Am. Chem. Soc.* **2021**, *143*, 7909–7914.
[42] H. Zhao, V. D. Cuomo, J. A. Rossi-Ashton, D. J. Procter, *Chem* **2024**, *10*, 1240–1251.
[43] X. Chen, X. Kuang, Y. Wu, J. Zhou, P. Wang, *Chin. J. Chem.* **2023**, *41*, 1979–1986.

[44] B. Boduszek, H. J. Shine, *J. Org. Chem.* **1988**, *53*, 5142–5143.
[45] Byron. Kratochvil, D. A. Zatko, Richard. Markuszewski, *Anal. Chem.* **1966**, *38*, 770–772.
[46] The Cu(II)/Cu(I) redox potential in acetonitrile of +0.96 V refers to the salts bearing weakly coordinating perchlorate. Note that the Cu(II)/Cu(I) redox potential in acetonitrile was reported to depend on the interactions with the anions and additives, and as such the Cu(II)/Cu(I) redox potential in the reaction mixture is modified by the presence and concentrations of triflate, carboxylates, fluoride, and thianthrene. See: H. C. Mruthyunjaya, A. R. Vasudeva Murthy, *J. Electroanal. Chem. Interf. Electrochem.* **1968**, *18*, 200–204.
[47] O. Hammerich, V. D. Parker, *Electrochim. Acta* **1973**, *18*, 537–541.
[48] Deposition numbers 2327788 (for $\mathbf{9^{DM}}$), 2327788 (for **18**), 2327791–2327795 (for **38**, $\mathbf{46^{PX}}$, **47**, **51**, and $\mathbf{53^{DM}}$) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

Manuscript received: June 5, 2024
Accepted manuscript online: July 16, 2024
Version of record online: September 5, 2024