

## Electrocatalysis

## Iodine(III)-Mediated Electrochemical Trifluoroethoxylactonisation: Rational Reaction Optimisation and Prediction of Mediator Activity

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**Abstract:** A new electrochemical iodine(III)-mediated cyclisation reaction for the synthesis of 4-(2,2,2-trifluoroethoxy)isochroman-1-ones is presented. Based on this reaction design of experiments and multivariate linear regression analysis were used to demonstrate their first application in an electrochemical reaction. The broad applicability of these reaction conditions could be shown by a range of substrates and an extensive compatibility test.

Organic electrochemistry has recently drawn much attention due to an increased demand for more environmentally friendly reactions, that is, the substitution of oxidants and reductants by electricity.<sup>[1]</sup> Electrochemical batch reactions are also easy to implement into flow conditions which is an appealing point with regard to industrial applications.<sup>[2]</sup> Although an electrochemical approach often simplifies reactions as oxidants or reductants are avoided and often no inert conditions are required, it brings new challenges especially when it comes to reaction optimisation. In this regard, new reaction parameters, such as electrode material, cell design (e.g., divided, undivided, pseudo-divided), supporting electrolytes and, most importantly, frequently employed mediators are noteworthy. Furthermore, the fact that special cells and power supplies have to be used limits the number of experiments that can be carried out in parallel which aggravates the optimisation process.<sup>[3]</sup>

As optimisation is a fundamental problem, not only for chemical method development, a range of statistical tools are available in order to accelerate, hedge and simplify optimisation processes. One tool which is well-known but nonetheless seldom used in academic research, is design of experiments (DOE). It deals with the challenge of distributing measuring points as efficiently as possible within their experimental space

in order to reduce the number of necessary experiments with at the same time higher statistical significance.<sup>[4]</sup> Another method which has found increasing use in recent years is multivariate linear regression analysis (MLR). This tool deals with the prediction of one or even more variables from multiple descriptor variables. In chemistry it is often combined with theoretical methods like DFT calculations in order to predict outcome variables like yield or enantiomeric excess from computationally accessible predictors.<sup>[5]</sup>

Even though these methods have been used (extensively in case of MLR) for the optimisation of general chemical reactions their application in electrochemistry is rare.<sup>[5]</sup> Two examples for multivariate modelling of electrochemical reactions have been reported by Sigman regarding reaction yield prediction of a TEMPO-mediated oxidation<sup>[6]</sup> and for the prediction of the stability of anolytes.<sup>[7]</sup> The only example for the usage of DOE in an electrochemical reaction has, to our knowledge, been reported recently by us in which we used DOE for the optimisation of an electrochemical iododesilylation reaction.<sup>[8]</sup>


On the basis of the promising results we obtained with DOE in this reaction, we were interested in whether we could expand the use of DOE and furthermore combine it with multivariate modelling to be able to optimise the used mediator in a virtual screening.

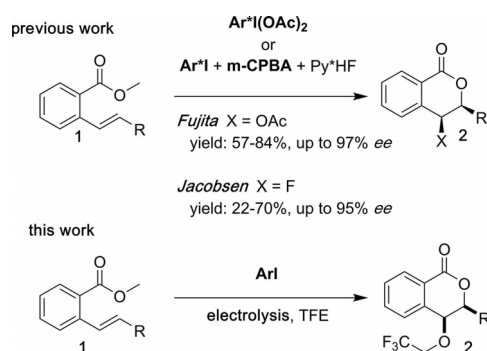
In order to prove the concept, we chose the field of hypercoordinate iodine(III) chemistry. The choice for an iodine(III)-mediated reaction was governed by several reasons; most importantly, the fascinating reactivity of those compounds that show reactivity patterns comparable to that of transition metals.<sup>[9]</sup> Although iodine(III)-mediated reactions depend on a stoichiometric use of oxidants, only a rare number of examples of their application as in-cell mediators in electrochemical reactions has been reported. In addition, these examples cover exclusively simple oxidative fluorination reactions at highly activated substrates (thioacetals, 1,3-dicarbonyls).<sup>[10]</sup> More challenging reactions at unactivated substrates with more complicated reaction mechanisms or efforts towards iodine(III)-mediated enantioselective electrochemical reactions have not been reported.<sup>[10d]</sup>

A substrate class that has been used before in iodine(III)-mediated lactonisation reactions are vinyl benzoic esters (Scheme 1). Fujita reported a lactonisation using tosylate and acetate as nucleophiles together with stoichiometric amounts of the respective iodine(III) reagent.<sup>[11]</sup> Jacobsen could improve a similar reaction with fluorine as nucleophile by using *meta*-chloroperbenzoic acid as oxidant and thereby facilitating a

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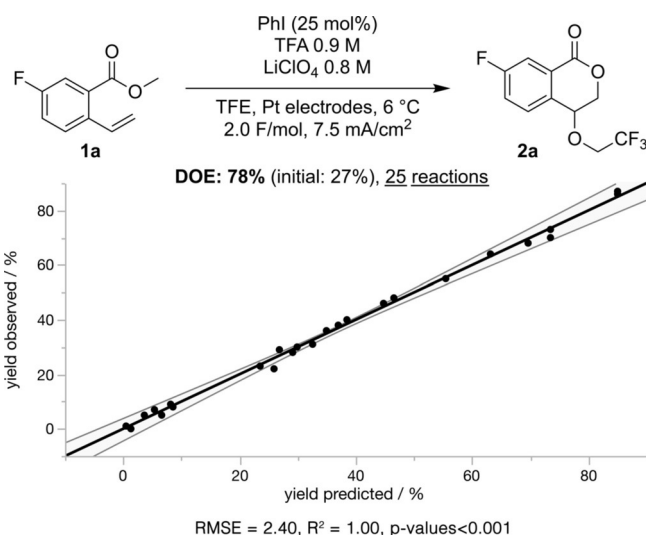


**Scheme 1.** Previous work on iodine(III)-mediated lactonisation by Fujita<sup>[11]</sup> and Jacobsen.<sup>[12]</sup>

sub-stoichiometrically use of the iodine mediator.<sup>[12]</sup> We wanted to expand this type of reaction by using electrochemical conditions in order to circumvent the use of stoichiometric amounts of oxidant or iodine(III) reagent and furthermore by using a different introduced nucleophile. We chose trifluoroethoxylate as it is a challenging anion due to its low nucleophilicity and furthermore due to its potential application in pharmacologically active compounds.<sup>[13]</sup>

We started the optimisation process using a D-optimal screening design consisting of 19 reactions (covering only linear terms and, in case of concentrations, their corresponding acids/electrolytes cross terms) in order to probe as many variables as possible with the lowest possible number of experiments. Investigated factors were: the mediator loading (iodobenzene was chosen as mediator to avoid possible substituent effects on the reaction), an additional acid, as preceding test reactions showed an impact on the yield (acetic acid, trifluoroacetic acid and methanesulfonic acid) and the supporting electrolyte (tetrabutylammonium tetrafluoroborate, lithium perchlorate and lithium hexafluorophosphate), their respective concentrations, the electrodes (graphite and platinum), temperature (6 to 35 °C), the current density (2.5 to 7.5 mA cm<sup>-2</sup>) and the applied charge (1.8 to 2.4 F mol<sup>-1</sup>). The styrene derivative **1a** was chosen as screening substrate in order to be able to follow the reaction progress and determine yields using <sup>19</sup>F NMR spectroscopy.

By this means, we could exclude the current density and the applied charge as impact factors. In case of the categorical factors, we constricted the design to the top scorers meaning lithium perchlorate as electrolyte and trifluoroacetic acid as supporting acid. The remaining design was expanded by only six reactions in order to cover quadratic terms as well as the cross interactions of the acid and the electrolyte concentration. The resulting model consists of nine factors with a very good R<sup>2</sup> of >0.99, *p*-values <0.01 and a very good lack of fit of 0.31. The most important factor was found to be the applied electrolyte together with its respective concentration. The single quadratic term which is relevant is the acid concentration. The thereby derived optimal conditions are shown in Figure 1. Not surprisingly, the mediator loading showed an equally small positive effect but was set to 25 mol% in all following investigations to obtain catalytic conditions. Using those optimised conditions,

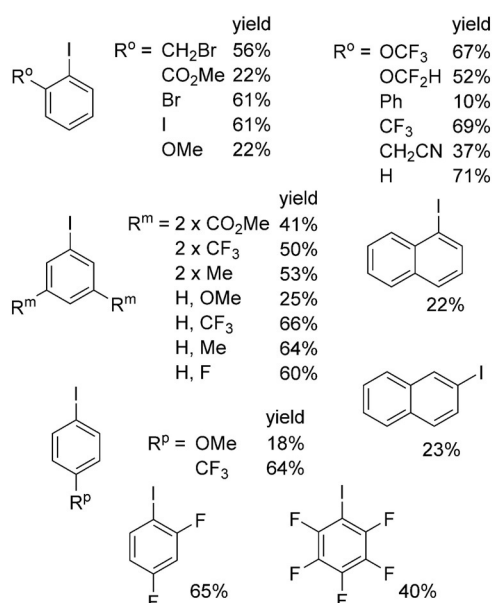


**Figure 1.** DOE optimised reaction conditions and plot of measured versus predicted yields. Reactions were performed on a 0.5 mmol scale. Yields were determined by <sup>19</sup>F NMR analysis using C<sub>6</sub>F<sub>6</sub> as internal standard (for detailed information see the Supporting Information).

we were able to increase the yield dramatically from 27 to 78% carrying out only 25 reactions.

With these optimised reaction conditions in hand, the next variable to optimise was the mediator. By screening a set of commercially available aryl iodides and subsequent multilinear regression with theoretically obtained values, a model for the prediction of the yield was to be generated. The second step should be a virtual screening of potentially chiral mediators to reduce the effort invested in the synthesis of those synthetically challenging mediators dramatically. An often-occurring problem when screening new systems is an asymmetrical distribution of the predictor and connected with this of the target values. To minimize this problem, we generated a descriptor set for a large set of 46 mediators. Only commercially available mediators were considered to ensure an as efficient and rapid screening as possible. From this set we selected 18 mediators as fitting and 6 mediators as validation set using a D-optimal design ensuring an even distribution of the predictors and thereby hopefully a uniform yield distribution. The selected mediators span a broad range of electron-rich as well as electron-poor arenes with *ortho*-, *meta*- and *para*-substitution (Figure 2) confirming the DOE approach. Each mediator was used in triplicate to ensure good reproducibility applying the optimised reaction conditions (the reaction temperature was set to 25 °C in ease of preparational simple conditions).

For the generation of the descriptor set, we calculated three distinctive structures: the iodobenzene derivative, its dication, and the respective hypercoordinate iodine(III) structure with two trifluoroacetoxy ligands.<sup>[14]</sup> The calculated predictors were: the free oxidation enthalpy  $\Delta G_{ox}$ , the free binding enthalpy of the trifluoroacetoxy ligands  $\Delta G_{bond,TFA}$  and for each structure, respectively, the NBO charge on the iodine, HOMO and LUMO energies. Furthermore, an IR deformation vibration in **III** and in order to cover steric effects, various *Sterimol* parameters and finally the distance L<sub>O-O</sub> between the two oxygen atoms in struc-



**Figure 2.** Screened iodoarene mediators for MLR. All reactions were carried out three times (for determination of the standard deviation) on a 0.5 mmol scale. Yields were determined by GC-FID analysis using mesitylene as internal standard at room temperature.

ture III (for more information see Scheme 2 and the Supporting Information).

With the theoretical as well as experimental data in hand, multivariate linear regression analysis was applied. To cope with the high number of descriptors we applied various techniques. To initially reduce the number of relevant descriptors, we used principal component analysis and the partial least squares method implemented in JMP 13.<sup>[16]</sup> Ensuing, the stepwise algorithm implemented in JMP 13 using fivefold internal cross validation—taking quadratic and two-way cross interactions into account—was used (for further information see the Supporting Information). The final model consists of seven descriptors. It shows a high predictive power with a RMSE of 5.59 in the validation set. The model is dominated by two terms,

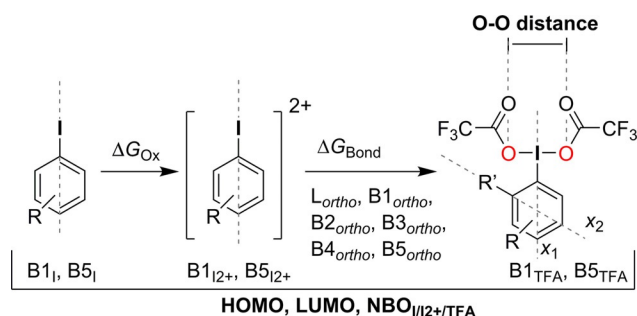
the **HOMO<sub>I</sub>** and the **HOMO<sub>I2+</sub>** energy. Less important are the **B5<sub>I2+</sub>**, **L<sub>O-O</sub>**, **NBO<sub>I</sub>**, and **LUMO<sub>I</sub>**. Using cyclic voltammetry, some of those terms could be attributed to two different factors that determine the performance of the mediator (see the Supporting Information). **HOMO<sub>I</sub>** and **HOMO<sub>I2+</sub>** as the most important terms could be connected to their oxidation potential which most likely reflects their stability towards oxidative degradation processes. **LUMO<sub>I</sub>**, **L<sub>O-O</sub>** and **NBO<sub>I</sub>** correlate with the peak current ratios *j*, depicting the reactivity of the mediator towards the substrate.

As we found the optimal achiral mediator to be iodobenzene (it possesses nearly ideal descriptor values, thus further virtual screening is not promising) we drew our attention to chiral mediators. This field is much more challenging as all tested chiral mediators, commonly used in literature, decomposed under the reaction conditions (yields are plotted in Figure 3 as test set, see the Supporting Information for a complete list with their respective structures). According to the model, this can be mainly attributed to their low oxidation potential. That is why we calculated in a virtual screening a large set of chiral mediators in order to find a new potential chiral mediator that is stable under the reaction conditions. One of the top scorers **3g** which could be obtained by directed optimisation of a literature known mediator, is shown in Figure 3. It shows a promising yield of 56% (compared to 71% for iodobenzene) and perfectly illustrates the time saving benefits in synthesis due to a virtual screening. Current investigations on the enantiomeric excess of this and other high yielding chiral mediators are under way and will be reported soon.

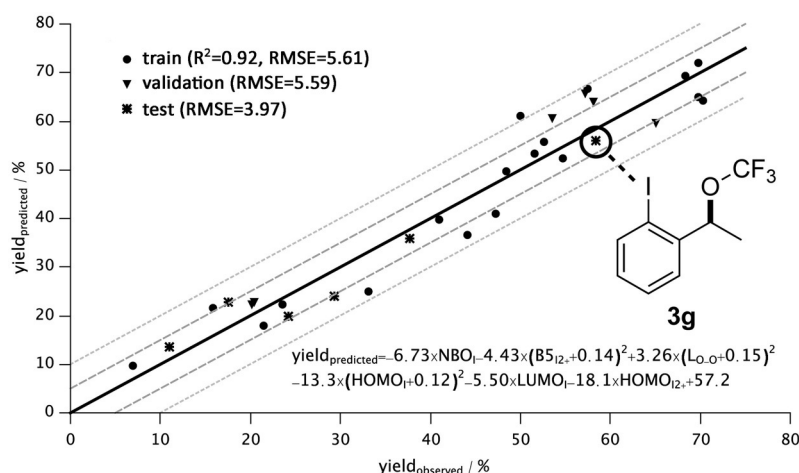
In a last step, the performance of iodobenzene as mediator under the optimised reaction conditions should be evaluated. Once again, we wanted to reduce the experimental expenditure by refraining from testing a large range of substrates. Only a small number of substrates were subjected to the reaction in order to check for electronic and steric effects. Electronic effects were examined by modifying the aromatic core. For electron-neutral or electron-deficient substrates no distinct dependency could be observed (Figure 4).

The electron-rich substrate **2f** decomposed and only product traces could be found. Steric effects were studied at three positions: at the aromatic core and at the two *ortho*-positions using the respective methyl derivatives **2h** and **2i** but no significant effect could be observed. The vinylic position was the third position to be modified in order to check for effects on the yield and potential diastereomers. Unfortunately, we observed a negative correlation. For sterically demanding groups, such as cyclohexyl **2l**, satisfying diastereomer ratios of up to 90:10 could be observed but accompanied with low yields. For sterically less demanding substrates like *n*-propyl **2j**, good yields were obtained but the diastereomer ratio was lower.

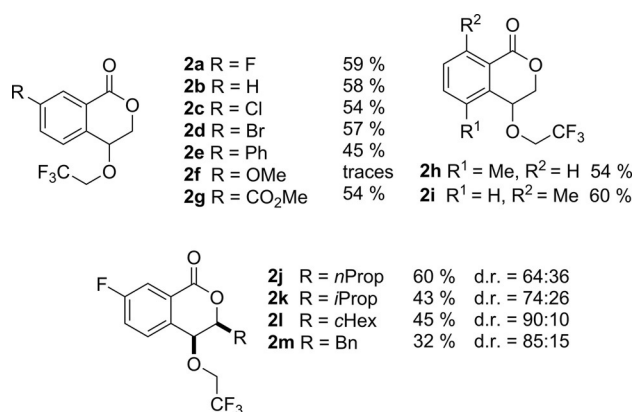
To further reduce the synthetic effort in the determination of the functional group tolerance, a compatibility test was carried out which is based on the addition of additives containing one specific functional group to a screening reaction in order to measure the product and the additive yield and thereby determine the stability or influence on the reaction of the respective functional group.<sup>[17]</sup> A selection of results is shown in



**Scheme 2.** Calculated molecular descriptors for multivariate linear regression modelling. Respective *Sterimol* parameters B1 and B5 were determined along *x<sub>1</sub>*-axis, B1<sub>ortho</sub>, B2<sub>ortho</sub>, B3<sub>ortho</sub>, B4<sub>ortho</sub>, B5<sub>ortho</sub> and L<sub>ortho</sub> along the *x<sub>2</sub>*-axis. Distance L<sub>O-O</sub> was measured along the O–O bond axis. IR<sub>TFA</sub> ring deformation vibration in *x<sub>1</sub>* direction was measured in III. All structures and electronic parameters (ΔG<sub>ox</sub>: free oxidation enthalpy, ΔG<sub>bond</sub>: binding free enthalpy, NBO, HOMO and LUMO values) were determined on the M06-2X/def2-TZVP-D3 level (for computational details, see the Supporting Information).



**Figure 3.** Normalised multivariate linear regression model for the yield of aryl iodide mediators and structure of potentially chiral mediator **3g** (for structures of remaining test set see the Supporting Information).



**Figure 4.** Results of the electrochemical lactonisation reaction using 25 mol% iodobenzene as mediator. All reactions were carried out on a 1.0 mmol scale using the reported optimised reaction conditions. Diastereomer ratios were determined by GC/MS prior to chromatographic purification. For further information see Experimental Section.

Table 1. In general, functional groups that are labile towards oxidative conditions or groups that show intrinsic reactivity towards iodine(III) species show low additive and/or product yields.<sup>[18]</sup> This is the case for alkenes, alkynes or some heterocycles like furanes or indoles. Nevertheless, a broad range of functional groups is stable. Noteworthy are electron-deficient heterocycles such as quinoline or pyridine, Boc-protected amides but oxidative labile groups like aliphatic amines or aldehydes are stable as well (for complete list, see the Supporting Information).

All reactions were carried out on a 0.5 mmol scale using the reported optimised reaction conditions. Additive yields were determined by GC-FID analysis using mesitylene as the internal standard. For more examples see the Supporting Information.

In conclusion, we have developed a new electrochemical iodine(III)-mediated lactonisation leading to trifluoroethoxy-substituted isochromanones. To our knowledge, this is the first example of an electrocatalytically mediated iodine(III) reaction in which two new bonds are formed and the hypercoordinate

iodine species not solely serves as an oxidant. Functional group tolerance could be demonstrated using a compatibility test and furthermore, steric and electronic effects were investigated using a range of substrates. Based on this new reaction we could demonstrate several methods that simplify and simultaneously render reaction optimisation more valid and robust. Using design of experiments theory considering seven parameters of which three are categorical, we could reduce

**Table 1.** Functional group tolerance test using 25 mol% iodobenzene as mediator with screening substrate **1a**.<sup>[a]</sup>

Additive	Yield starting material [%]	Yield product [%]	Yield additive [%]
–	0	71	–
1-dodecylamine	0	75	100
benzaldehyde	0	58	77
butanol	0	68	100
1- <i>N</i> -Boc-2-piperidone	0	53	69
2,6-lutidine	0	53	64
2-chlorochinoline	0	67	75
2-butylfuran	2	43	0
1-dodecyne	0	40	7
1-octene	0	33	0
2-methylanisole	86	0	0
<i>N</i> -methyl indole	19	10	34
sulfolane	0	68	90
benzothiazole	0	45	94
1-chlorooctane	0	71	92
chlorobenzene	0	67	87
carbazole	9	51	42
dibutyl ether	0	49	100
heptyl cyanide	0	55	100
2-butylfuran	2	43	0
nitrobenzene	0	64	100
4-(TMS)toluene	10	19	0
valerophenone	0	59	82
methyl benzoate	0	69	88

[a] All reactions were carried out on a 0.5 mmol scale using the reported optimised reaction conditions. Additive yields were determined by GC-FID analysis using mesitylene as the internal standard. For more examples see the Supporting Information.



the number of experiments needed for a statistically significant result dramatically to 25 reactions. Using multivariate linear regression, we could build up a model by which we can predict yields for theoretically calculated mediators. This allowed us to carry out a virtual screen yielding *inter alia* one potentially chiral mediator with a promising yield of 56% doubling the yield of literature known mediators. As far as we know, this is the first reported example for the combination of these methods and we hope that it will be a kick-off for other groups to use design of experiment in combination with multivariate modelling in order to speed up the reaction and mediator optimisation process with simultaneously higher significance of the results.

## Experimental Section

In an H-type cell, both chambers were loaded with 10 mL of an 0.9 M trifluoroacetic acid solution in trifluoroethanol and lithium perchlorate (851 mg, 0.8 M). Iodobenzene (0.125 mmol, 25 mol%) and the respective vinyl benzoate (1.00 equiv, 0.5 mmol) were added to the anode compartment. The cell was equipped with platinum electrodes and the solutions were stirred until all solids were dissolved. The reaction was electrolysed under constant current density ( $7.5 \text{ mA cm}^{-2}$ ) at RT until complete conversion (GC/MS monitoring) could be detected (normally  $2 \text{ F mol}^{-1}$ ). The anode compartment solution was taken up with a syringe and filtered through a pad of neutral aluminium oxide which was rinsed thoroughly with ethyl acetate. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using neutral aluminium oxide as stationary phase.

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** electrochemistry • hypercoordinate iodine • iodine(III) • iodoarenes • multivariate linear regression

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- [18] In a rough MLR analysis, we were able to correlate additive yields with their HOMO energies and an NBO charge, which shows that mainly oxidative degradation processes are important for substrate stability (for more information see the Supporting Information).

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