Combinatorial Electrosynthesis in Microtiter Plate Wells with Ionic Liquid Electrolytes

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Introduction: Electrosynthesis of Compound Libraries?

- combinatorial synthesis of compound libraries
  → multiple reactions of similar starting compounds
  → small amount of individual product(s)

- screening: quickly assess some properties of library elements
  → redox behavior ("redox screening")
  → synthesis products ("synthesis screening")
  → mechanisms ("mechanistic screening")
  → reaction channels ("reactivity screening")

- standard method in drug design and catalyst optimization

- electrosynthesis?
earlier approaches:

- Yudin et al.: spatially addressable electrolysis platform – galvanostatic

Introduction: Approaches and Examples

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- Breinbauer et al.: mediated electrolysis with polymer bead support

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Introduction: Approaches and Examples

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- Yudin et al.: spatially addressable electrolysis platform – galvanostatic
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our system:

- combi-SECM instrument
- C–C-bond forming reaction: reductive coupling of $\alpha,\beta$-unsaturated esters and allylbromides
- electrolyte: room temperature ionic liquid
The Experiment: Instrument

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The Experiment: Reaction

cathodic reduction,

allyl bromide (1) + $\alpha,\beta$-unsaturated ester (2)

Combinatorial diversity ($R_1$ – $R_7$)
cathodic reduction,

allylbromide (1) + \( \alpha,\beta \)-unsaturated ester (2)

```
\begin{align*}
&\text{allylbromide (1) + } \alpha,\beta\text{-unsaturated ester (2)} \\
&\text{Combinatorial diversity (R}^1 \text{ – R}^7\text{)} \\
&\text{two reaction pathways (primary reduction of 1 or 2)}
\end{align*}
```
The Experiment: Reaction

cathodic reduction,

allylbromide (1) + \( \alpha,\beta \)-unsaturated ester (2)

combinatorial diversity (\( R^1 - R^7 \))

two reaction pathways (primary reduction of 1 or 2)

isomeric products depending on symmetry of educts
The Experiment: Design of the Experiment


changes:
- galvanostatic $\rightarrow$ potentiostatic (in DMF)
- DMF $\rightarrow$ ionic liquid electrolyte ([BMIM]BF$_4$)
- macro cell $\rightarrow$ miniaturization (200 $\mu$l)
- single reaction $\rightarrow$ combinatorial ($6 \times 8 = 48$ elements)
The Experiment: Components

6 allylbromides

1a
\[ \text{H} - \text{H} - \text{Br} \]

1b
\[ \text{H}_3\text{C} - \text{H} - \text{Br} \]

1c
\[ \text{H}_3\text{C} - \text{H} - \text{Br} \]

1d
\[ \text{H} - \text{CH}_3 - \text{Br} \]

1e
\[ \text{H}_3\text{C} - \text{O} - \text{O} - \text{CH}_3 \]

1f
\[ \text{H}_3\text{C} - \text{O} - \text{O} - \text{Br} \]

8 \( \alpha,\beta \)-unsaturated esters

2a
\[ \text{H}_3\text{C} - \text{O} - \text{H} - \text{O} - \text{CH}_3 \]

2b
\[ \text{H}_3\text{C} - \text{O} - \text{H} - \text{O} - \text{CH}_3 \]

2c
\[ \text{H}_3\text{C} - \text{O} - \text{H} - \text{O} - \text{CH}_3 \]

2d
\[ \text{H}_3\text{C} - \text{O} - \text{O} - \text{O} - \text{CH}_3 \]

2e
\[ \text{H}_3\text{C} - \text{O} - \text{H} - \text{N} - \text{H}_2 \]

2f
\[ \text{H}_2\text{C} - \text{O} - \text{O} - \text{CH}_3 \]

2g
\[ \text{O}^+\text{N}^-\text{O} - \text{H} - \text{O} - \text{CH}_3 \]

2h
\[ \text{H}_3\text{C} - \text{O} - \text{O} - \text{O} - \text{CH}_3 \]
Potentiostatic Reduction in DMF: Allylbromide + Diethyl Fumarate

1a; $c = 1.2$ mM; $v = 0.2$ V s$^{-1}$

2a; $c = 1.2$ mM; $v = 0.2$ V s$^{-1}$
Potentiostatic Reduction in DMF: Allylbromide + Diethyl Fumarate

1a; $c = 1.2 \text{ mM}; \nu = 0.2 \text{ V s}^{-1}$

2a; $c = 1.2 \text{ mM}; \nu = 0.2 \text{ V s}^{-1}$

- co-electrolysis of equimolar amounts (0.4 mmol) in DMF/0.1 M NBu$_4$PF$_6$ at -1.69 V
- 20 h, 139 C, 1.8 F
- extraction with ether
- GC-MS: formation of ethyl-3-(ethoxycarbonyl)-5-hexanoate 4aa
Potentiostatic Reduction in DMF: Allylbromide + Diethyl Fumarate

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GC-MS: formation of ethyl-3-(ethoxycarbonyl)-5-hexanoate 4aa

transfer galvanostatic $\rightarrow$ potentiostatic ok
Miniaturized Potentiostatic Reduction in [BMIM]BF₄: Allylbromide + Diethyl Fumarate

- cyclic voltammetric monitoring before (full) and after (dotted) electrolysis ($v = 0.3$ V s⁻¹)
- $E_p(2a) = -1.45$ V, $E_p(1a) \approx -2$ V
- decrease of negative extension of potential window
- decrease of $i_p(2a)$
Miniaturized Potentiostatic Reduction in [BMIM]BF$_4$: Allylbromide + Diethyl Fumarate

$c(1a) = c(2a) = 0.2$ mM, reaction volume $= 1$ ml

potentiostatic electrolysis at $-1.725$ V

13.5 h, 2.31 C, 1.2 F

extraction with hexane, GC-MS
Miniaturized Potentiostatic Reduction in [BMIM]BF$_4$: Allylbromide + Diethyl Fumarate

Transfer DMF $\rightarrow$ [BMIM]BF$_4$ ok
miniaturization ok
Miniaturized Potentiostatic Reduction in [BMIM]BF<sub>4</sub>: A Small Collection

<table>
<thead>
<tr>
<th>1a/2a</th>
<th>1c/2a</th>
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<tr>
<td>1a/2c</td>
<td>1c/2c</td>
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</table>
Miniaturized Potentiostatic Reduction in [BMIM]BF₄: A Small Collection

- Ester more easy to reduce
- Coupling product identified by molecular ion and main fragments
- Identity of 4aa assigned based on ester radical anion attack on allylbromide
- MS does not allow to differentiate between isomers easily
Miniaturized Potentiostatic Reduction in [BMIM]BF$_4$: A Small Collection

1a/2a

ester more easy to reduce

coupling product identified by molecular ion and main fragments

4ca is main product

isomeric side product, tentatively assigned as 3ca

1c/2a

1c/2c
Miniaturized Potentiostatic Reduction in [BMIM]BF$_4$: A Small Collection

- allylbromide more easy to reduce
- coupling product identified by M$^+$ and main fragments (very low yield)
- identity of 3ac assigned based on attack of allyl anion on ester
Miniaturized Potentiostatic Reduction in [BMIM]BF₄: A Small Collection

allylbromide more easy to reduce
no products identified
Miniaturized Potentiostatic Reduction in [BMIM]BF$_4$: A Small Collection

Electrolysis with subsequent GC-MS provides screening technique.
Interpretation of Mass Spectra: The Example of 4aa

- small molecular ion peak $M^+$
Interpretation of Mass Spectra: The Example of 4aa

- small molecular ion peak $M^+$
- $\alpha$-cleavage of ester group $\rightarrow F1$
Interpretation of Mass Spectra: The Example of 4aa

- small molecular ion peak $M^+$
- $\alpha$-cleavage of ester group $\rightarrow F1$
- hydrogen loss $\rightarrow F2$
Interpretation of Mass Spectra: The Example of 4aa

- small molecular ion peak $M^+$
- $\alpha$-cleavage of ester group $\rightarrow F1$
- hydrogen loss $\rightarrow F2$
- cleavage of CO $\rightarrow F3$ or $F4$
## The Combinatorial Experiment: A Collection of 48 Electrolyses – Microtiter Plate Loading

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<th>D</th>
<th>E</th>
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<tr>
<td>1</td>
<td>WW</td>
<td>1a/2a</td>
<td>1b/2a</td>
<td>1c/2a</td>
<td>1d/2a</td>
<td>1e/2a</td>
<td>1f/2a</td>
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<td>WW</td>
<td>1a/2b</td>
<td>1b/2b</td>
<td>1c/2b</td>
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<td>1c/2e</td>
<td>1d/2e</td>
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<td>1f/2e</td>
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<td>6</td>
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<td>1a/2f</td>
<td>1b/2f</td>
<td>1c/2f</td>
<td>1d/2f</td>
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<td>1d/2g</td>
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<td>8</td>
<td>WW</td>
<td>1a/2h</td>
<td>1b/2h</td>
<td>1c/2h</td>
<td>1d/2h</td>
<td>1e/2h</td>
<td>1f/2h</td>
<td>WW</td>
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</table>

- **WW** = wash well
- 48 combinations of allylbromides and esters
- sequential electrolysis (30 min) in wells (volume: 200 µl) – mixing – washing
### The Combinatorial Experiment: A Collection of 48 Electrolyses – Screening for Fragments in MS

#### after 30 min:

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<td>F1/F2/F3/F4</td>
<td>M⁺/F1/F2/F3/F4</td>
<td>M⁺/F1/F3/F4</td>
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The Combinatorial Experiment: A Collection of 48 Electrolyses – Screening for Fragments in MS

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esters 2c, 2e, 2f, and 2g do not react at all to expected products (rows 3, 5, 6, 7)
allylbromides 1e and 1f do only react with 2h to expected products (columns F, G)
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*esters 2c, 2e, 2f, and 2g do not react at all to expected products (rows 3, 5, 6, 7)*

*allylbromides 1e and 1f do only react with 2h to expected products (columns F, G)*

**how can this pattern be explained?**
The Mechanistic Pattern: Esters with Electron-Donating Substituents are Not Reactive

Very negative reduction potential $\rightarrow$ allylbromide is reduced

Allyl anion attacks

Electron-donating substituents $R^4$ or $R^5$ decrease positive charge density

Esters become less reactive
The Mechanistic Pattern: Nitrophenyl Substituted Ester is Not Reactive

- two reduction waves – characteristic for NO$_2$ reduction
- radical anion of 2g stabilized and unreactive
The Mechanistic Pattern: Allylbromides with Electron-Withdrawing Substituents are Not Reactive

- Relatively positive reduction potential → allylbromides are reduced
- Electron-withdrawing substituents decrease charge density in allyl anions
- Allyl anions become less reactive
- Exception: reaction with ester 2h – even less negative potential and ester reduction mechanism prevails
Conclusions

- C–C-bond forming reaction
- Transfer from classical galvanostatic electrolysis conditions in DMF to miniaturized potentiostatic reaction in an ionic liquid
- Combi-SECM approach with GC-MS allows synthesis screening: which combinations do react as intended?
- Explanations through mechanism
- Differentiation between reaction channels (isomers) difficult: instead of MS use NMR (coupling with HPLC, GC)?
Acknowledgements

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- Wolfgang Schuhmann, Bochum, for cooperation
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