Combinatorial Electrosynthesis in Microtiter Plate Wells with Ionic Liquid Electrolytes

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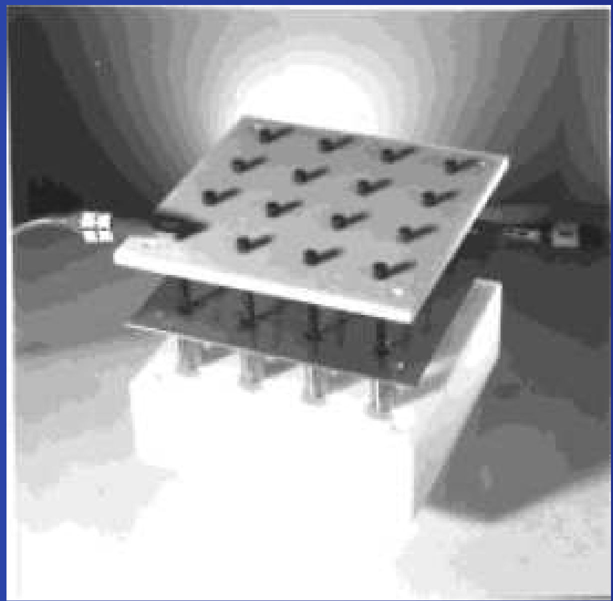
Introduction: Electrosynthesis of Compound Libraries?

- combinatorial synthesis of compound libraries
  $\longrightarrow$ multiple reactions of similar starting compounds
  $\longrightarrow$ small amount of individual product(s)
- screening: quickly assess some properties of library elements
  $\longrightarrow$ redox behavior ("redox screening")
  $\longrightarrow$ synthesis products ("synthesis screening")
  $\longrightarrow$ mechanisms ("mechanistic screening")
  $\longrightarrow$ reaction channels ("reactivity screening")
- standard method in drug design and catalyst optimization
- electrosynthesis?

Introduction: Approaches and Examples

earlier approaches:

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



T. Siu, W. Li, and A.K. Yudin, J. Comb. Chem. *2*, 545 – 549 (2000)

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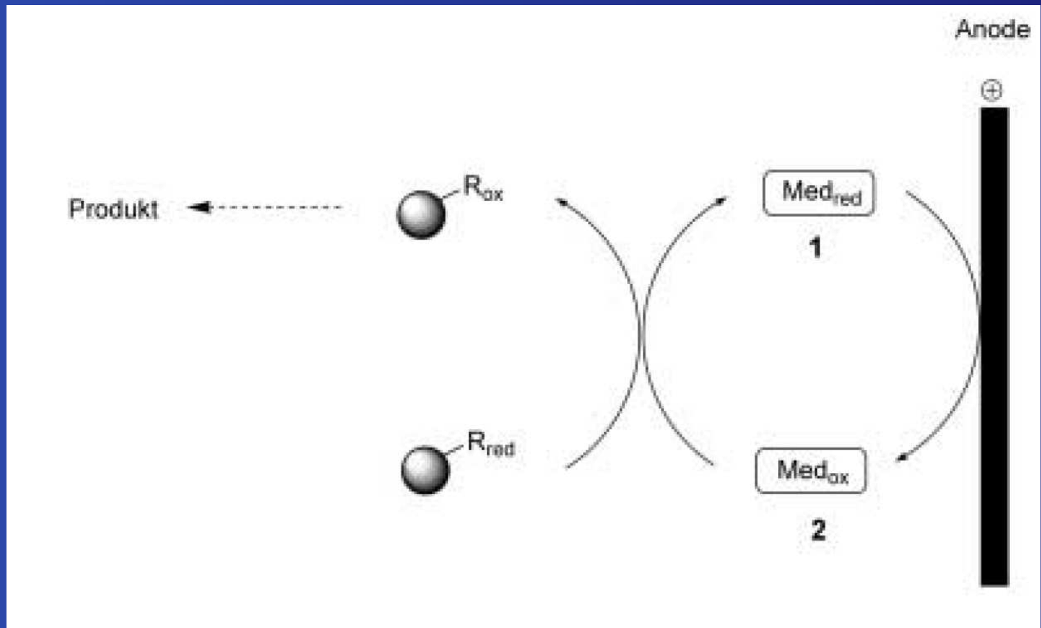

S. Nad and R. Breinbauer, Angew. Chem. *116*, 2347 – 2349 (2004); Angew. Chem. Intl. Ed. *43*, 2297 – 2299 (2004)

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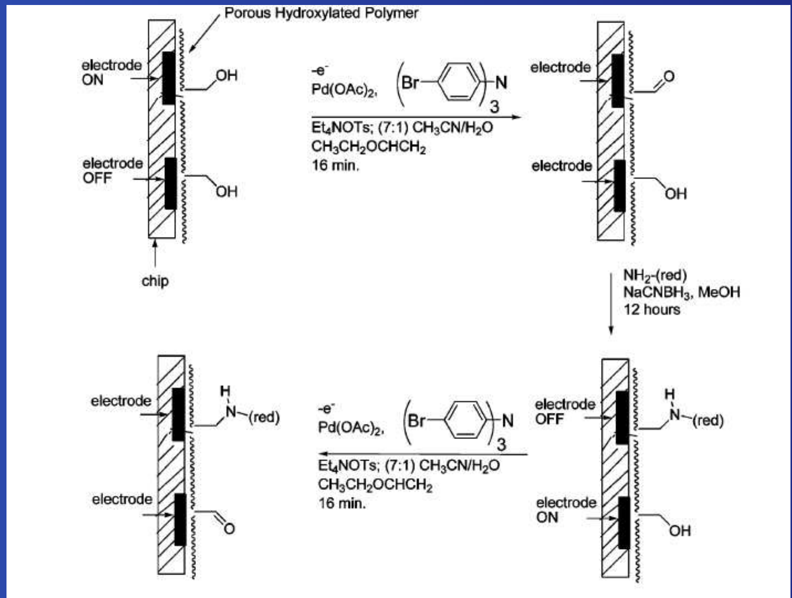

E. Tesfu, K. Maurer, and K.D. Moeller, J. Am. Chem. Soc. *128*, 70 – 71 (2006)

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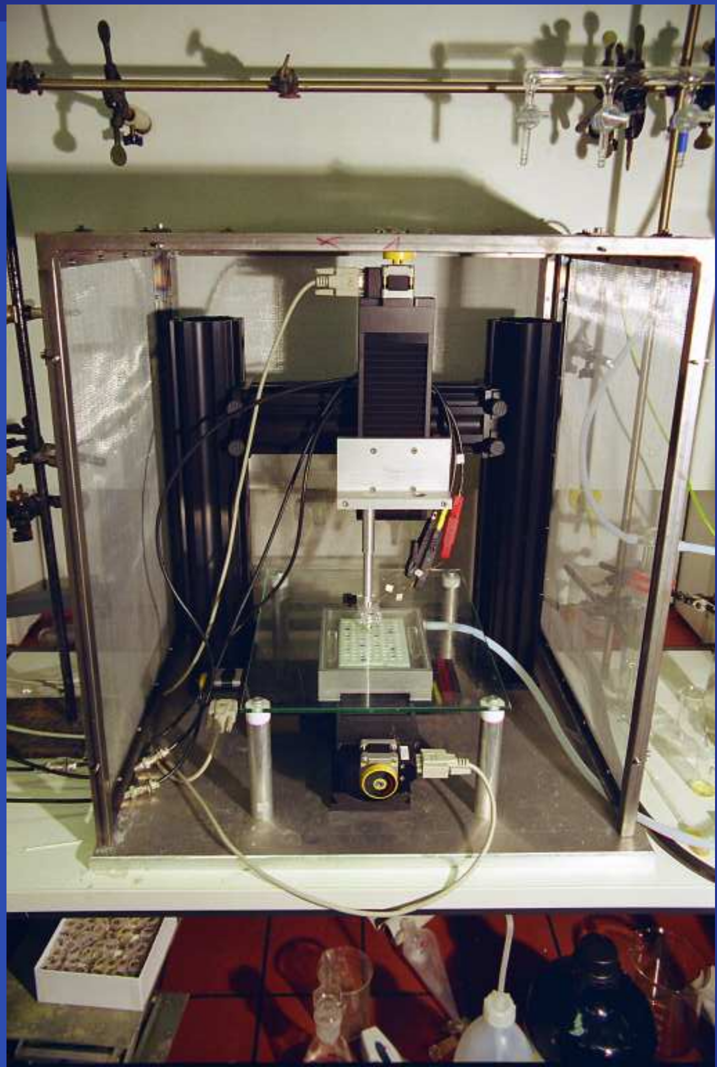
our system:

- combi-SECM instrument
- C–C-bond forming reaction: reductive coupling of α,β-unsaturated esters and allylbromides
- electrolyte: room temperature ionic liquid

The Experiment: Instrument



T. Erichsen, S. Reiter, V. Ryabova, E.M. Bonsen, W. Schuhmann, W. Märkle, C. Tittel, G. Jung, and B. Speiser, Rev. Sci. Instrum. *76*, 062204-1 – 062204-11 (2005)

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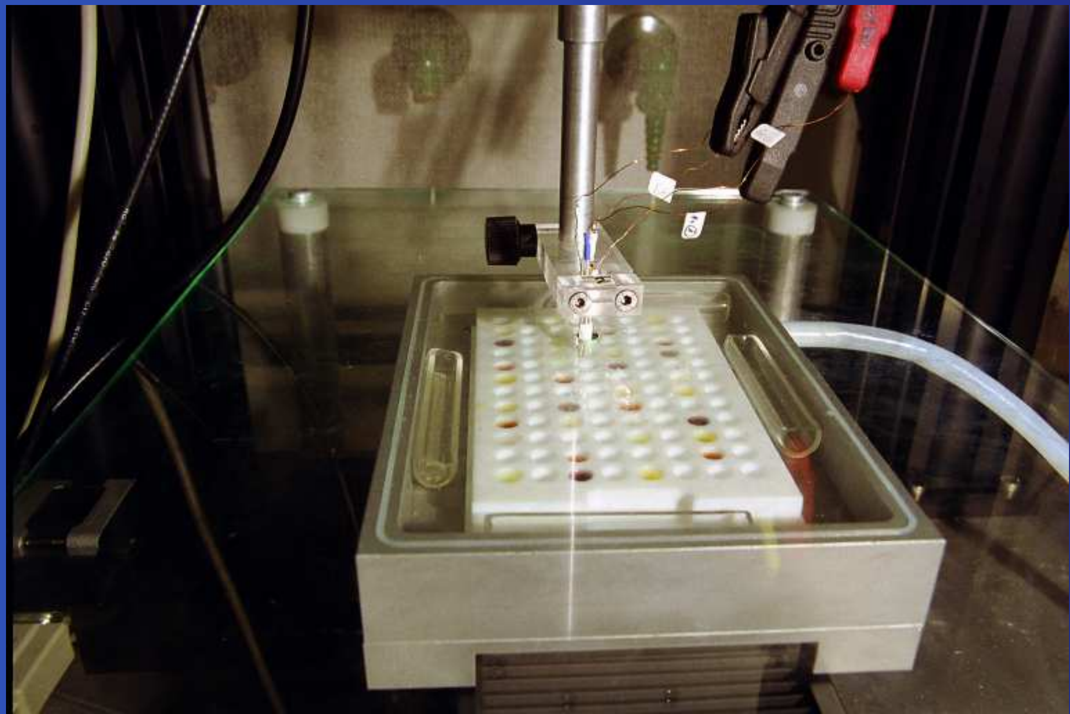

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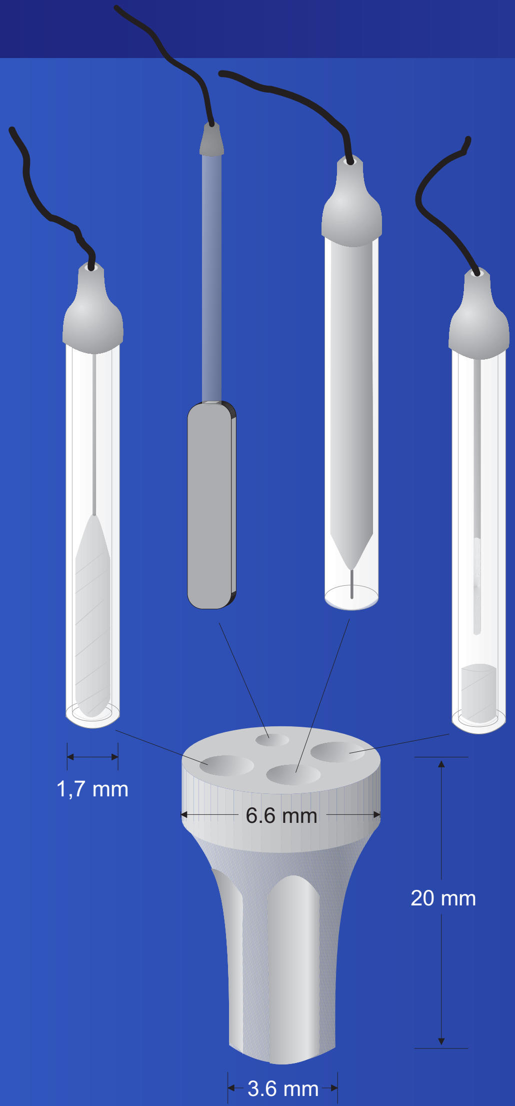

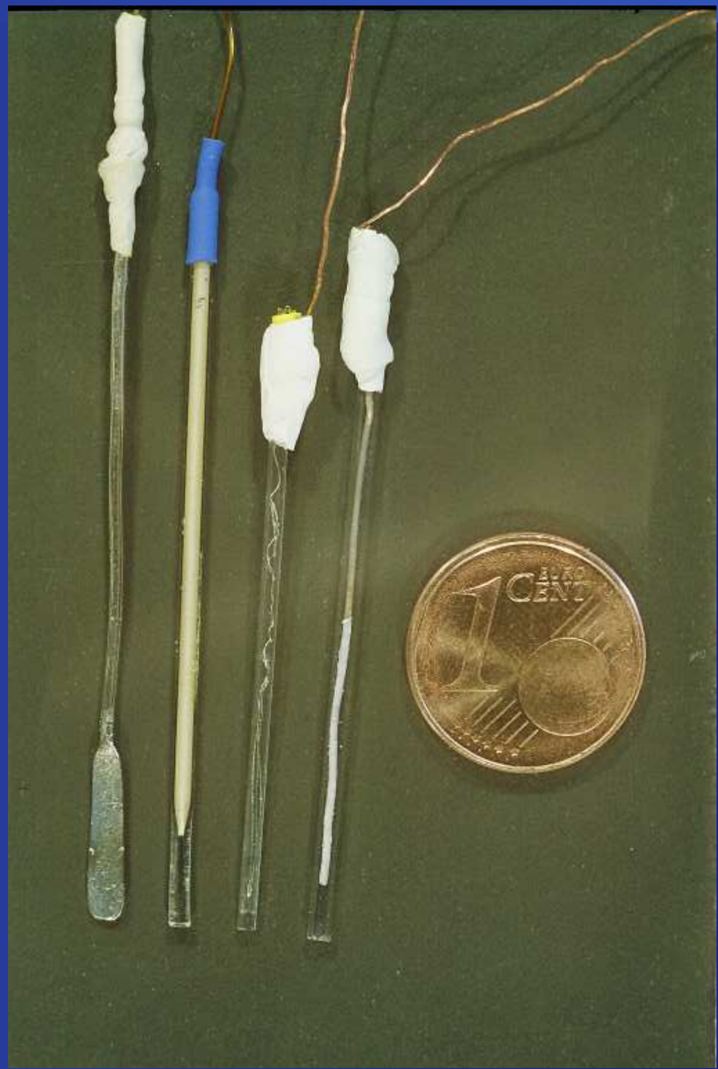

W. Märkle, B. Speiser, C. Tittel, and M. Vollmer, Electrochim. Acta *50*, 2753 – 2762 (2005)

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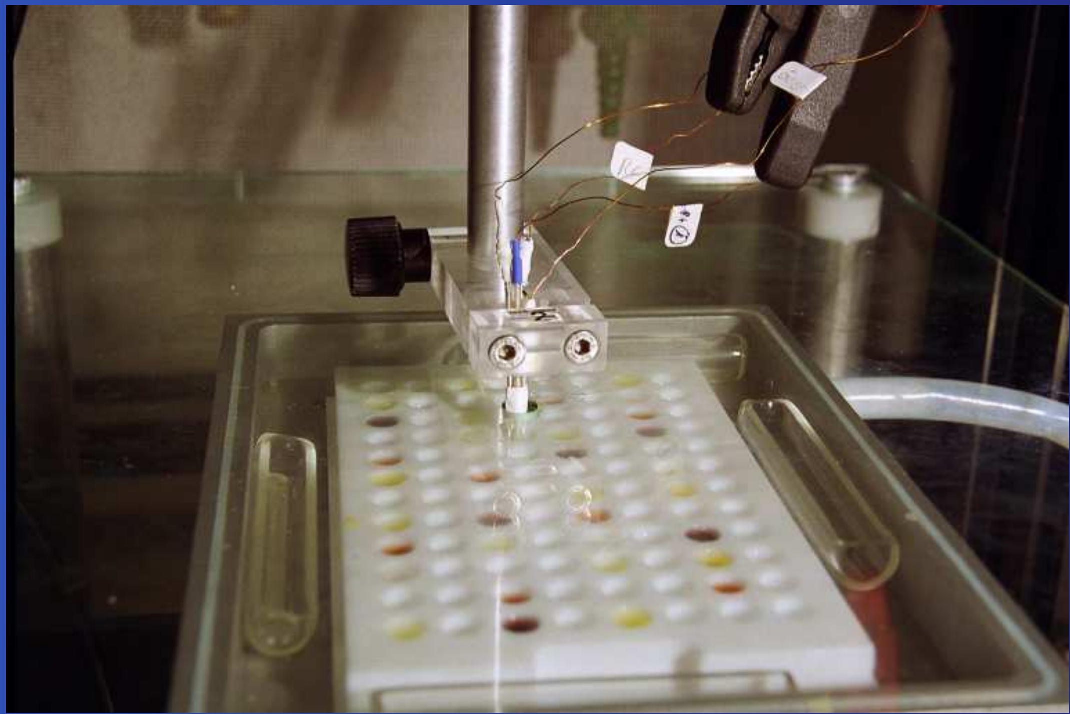
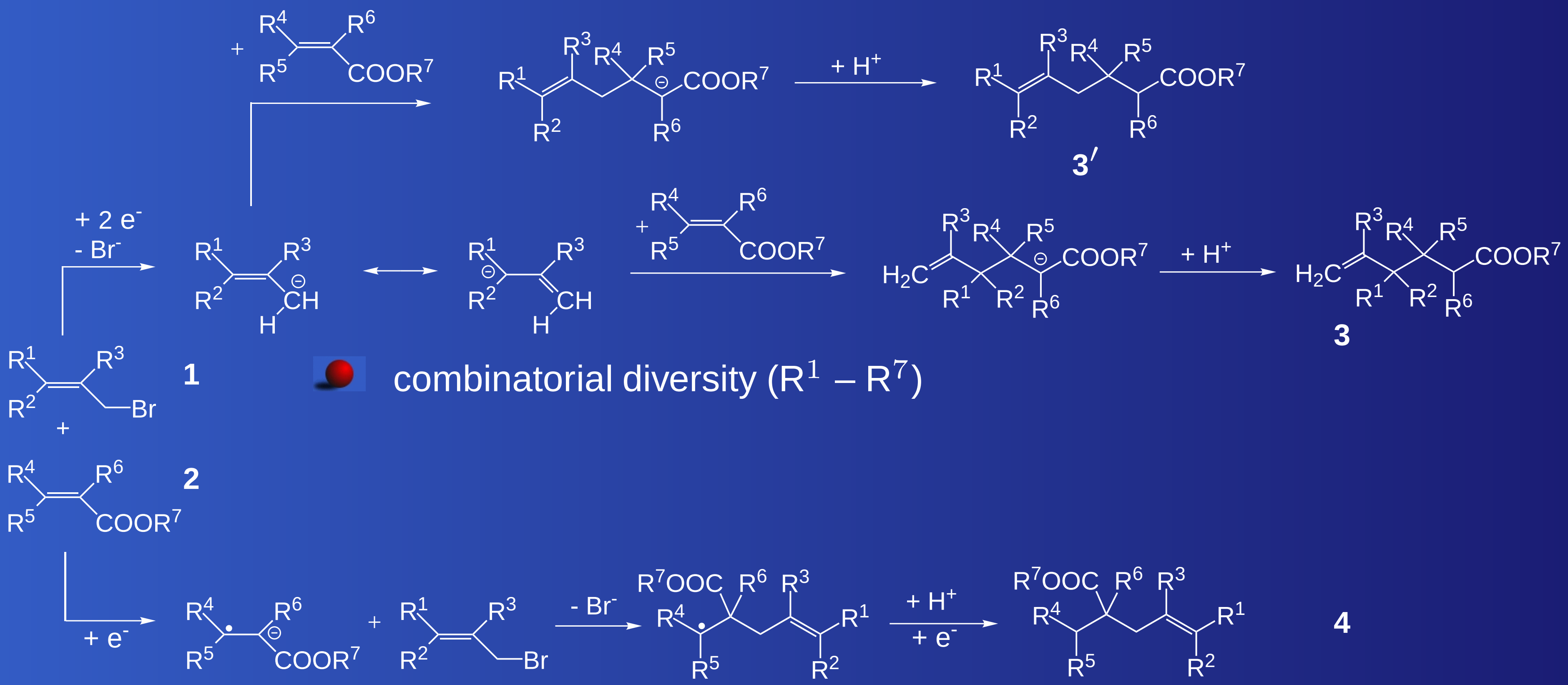


The Experiment: Reaction

cathodic reduction,

allylbromide (**1**) + α,β-unsaturated ester (**2**)



- combinatorial diversity (R^1 – R^7)

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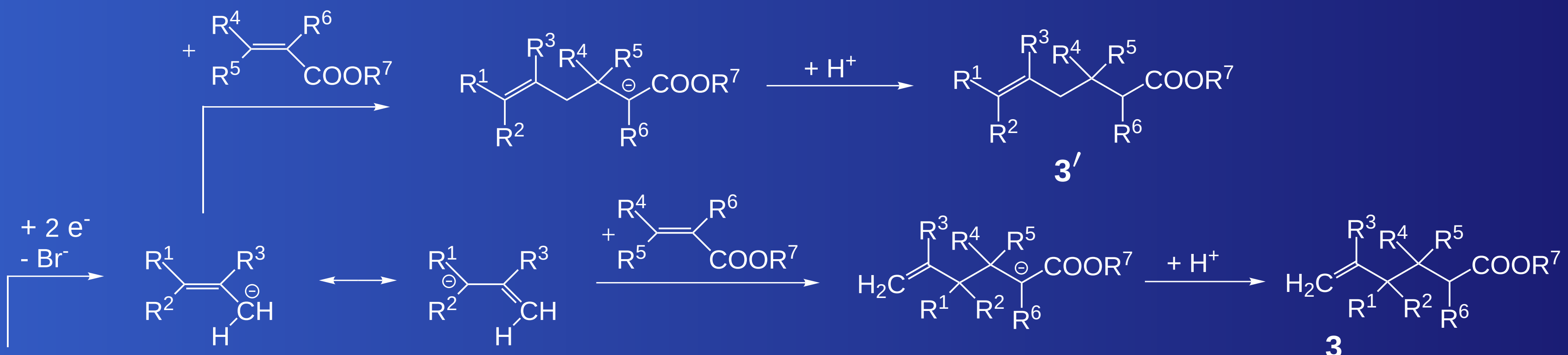
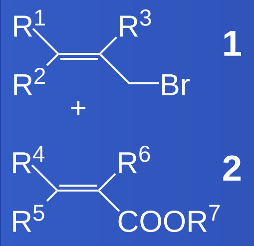
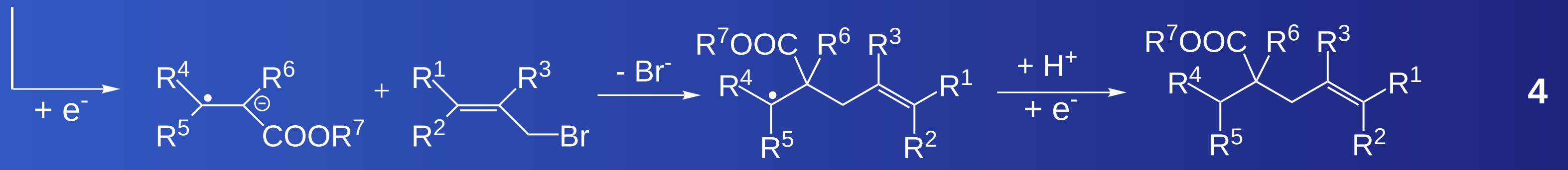




- combinatorial diversity (R^1 – R^7)
- two reaction pathways (primary reduction of **1** or **2**)



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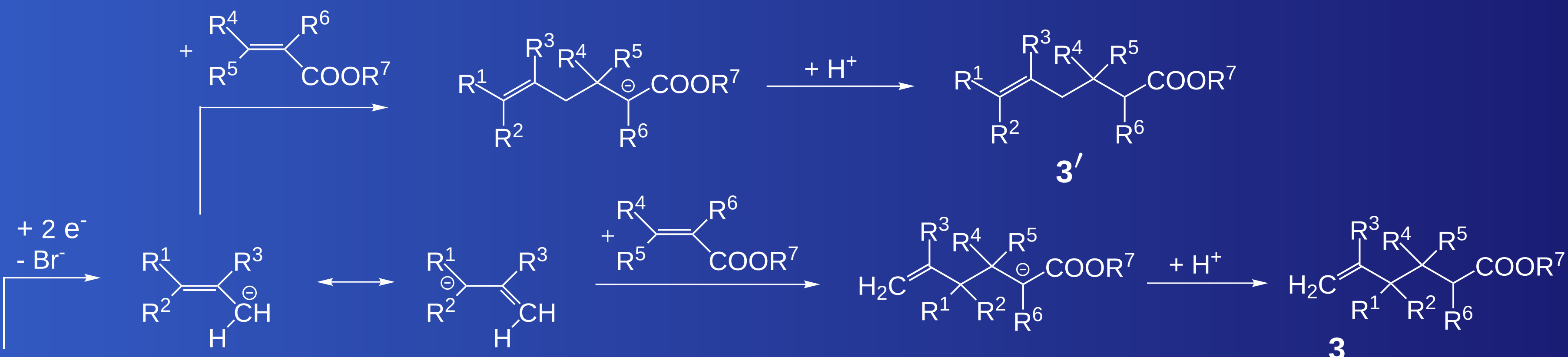
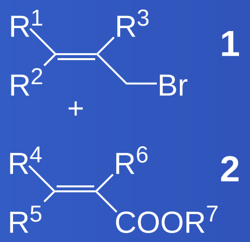
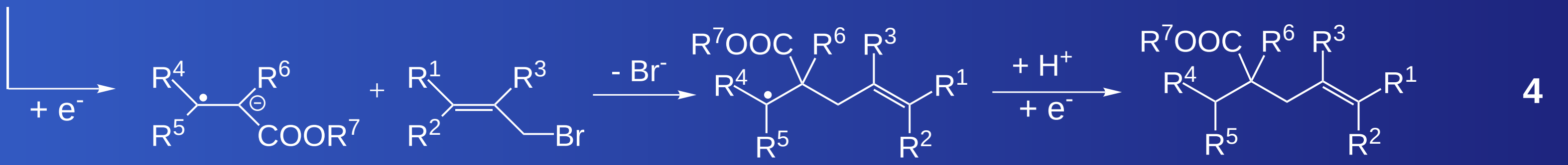




- combinatorial diversity ($R^1 – R^7$)
- two reaction pathways (primary reduction of **1** or **2**)
- isomeric products depending on symmetry of educts



The Experiment: Design of the Experiment

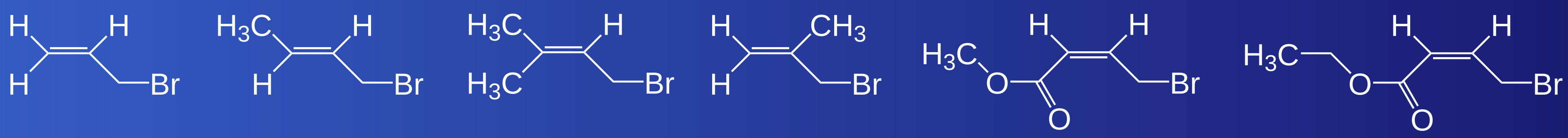
galvanostatic reduction of allylbromides and α,β-unsaturated esters:
S. Satoh et al., Bull. Chem. Soc. Jpn. *54*, 3456 – 3459 (1981)

changes:

- galvanostatic $\longrightarrow$ potentiostatic (in DMF)
- DMF $\longrightarrow$ ionic liquid electrolyte ([BMIM]BF_4)
- macro cell $\longrightarrow$ miniaturization (200 μl)
- single reaction $\longrightarrow$ combinatorial ($6 \times 8 = 48$ elements)

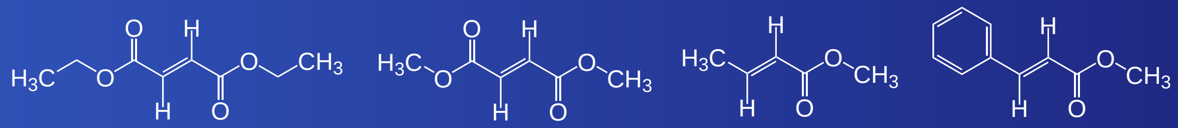
The Experiment: Components

6 allylbromides

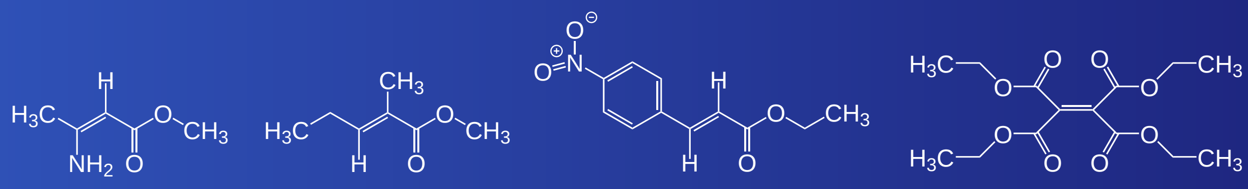


1a **1b** **1c** **1d** **1e** **1f**

8 α,β-unsaturated esters

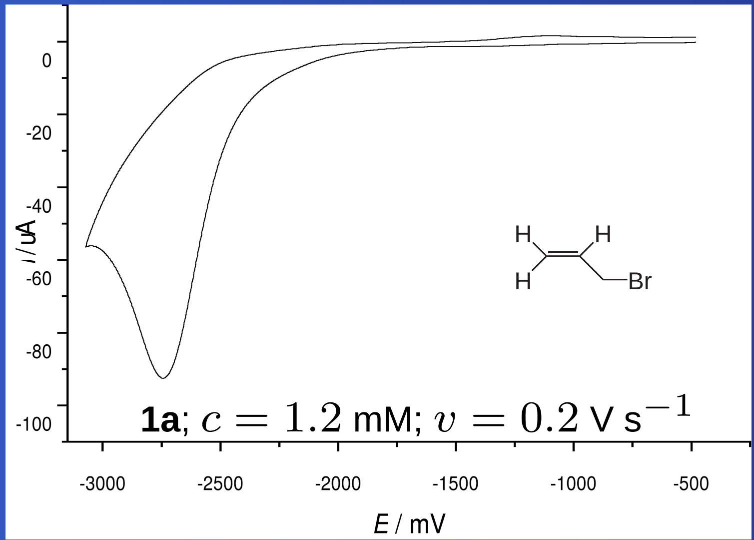


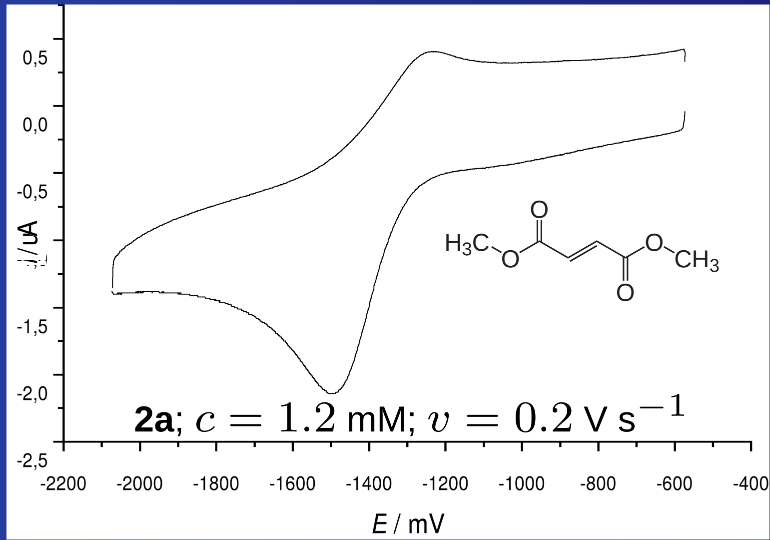
2a **2b** **2c** **2d**



2e **2f** **2g** **2h**

Potentiostatic Reduction in DMF: Allylbromide + Diethyl Fumarate





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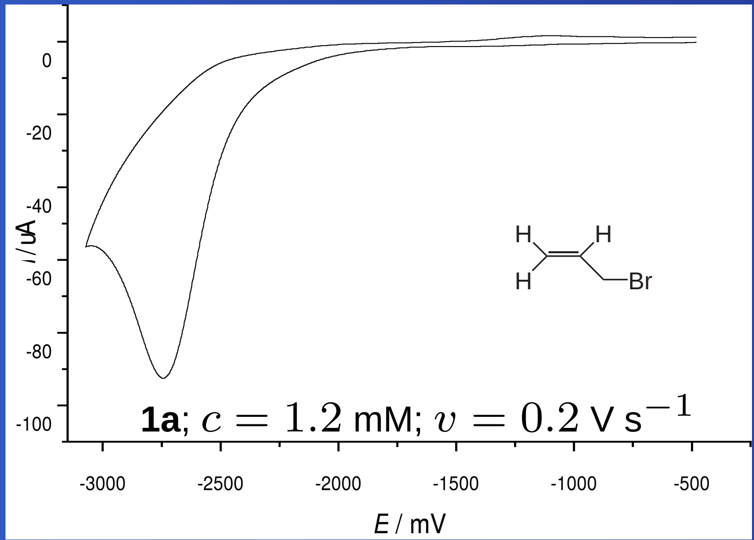
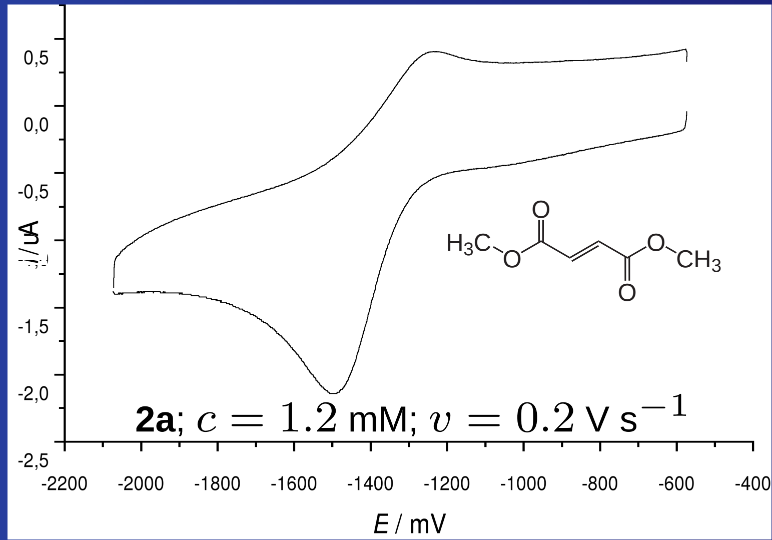
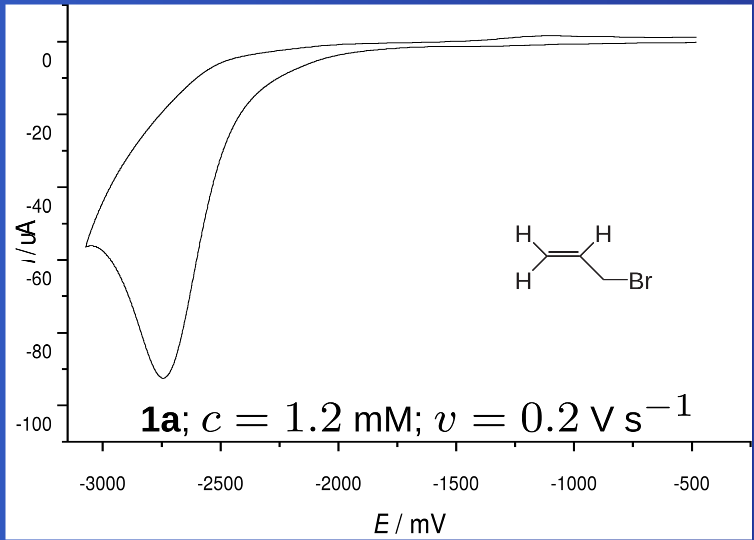
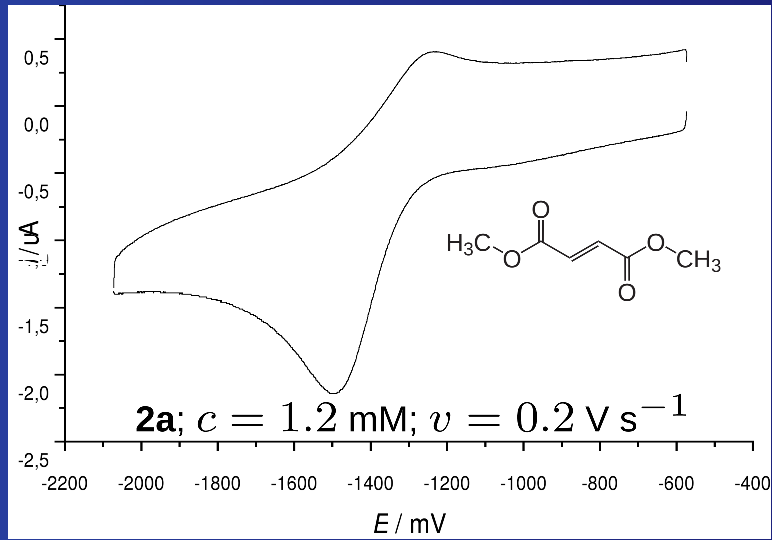




- co-electrolysis of equimolar amounts (0.4 mmol) in DMF/0.1 M NBu_4PF_6 at -1.69 V
- 20 h, 139 C, 1.8 F
- extraction with ether
- GC-MS: formation of ethyl-3-(ethoxycarbonyl)-5-hexanoate **4aa**

Potentiostatic Reduction in DMF: Allylbromide + Diethyl Fumarate





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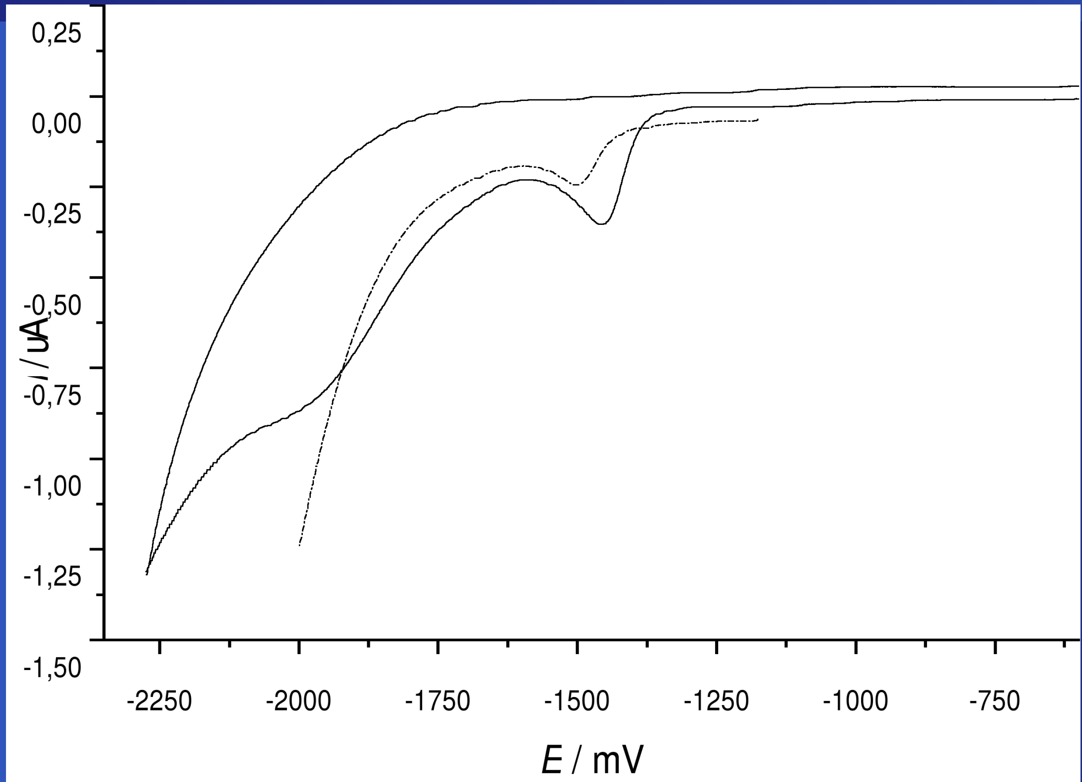
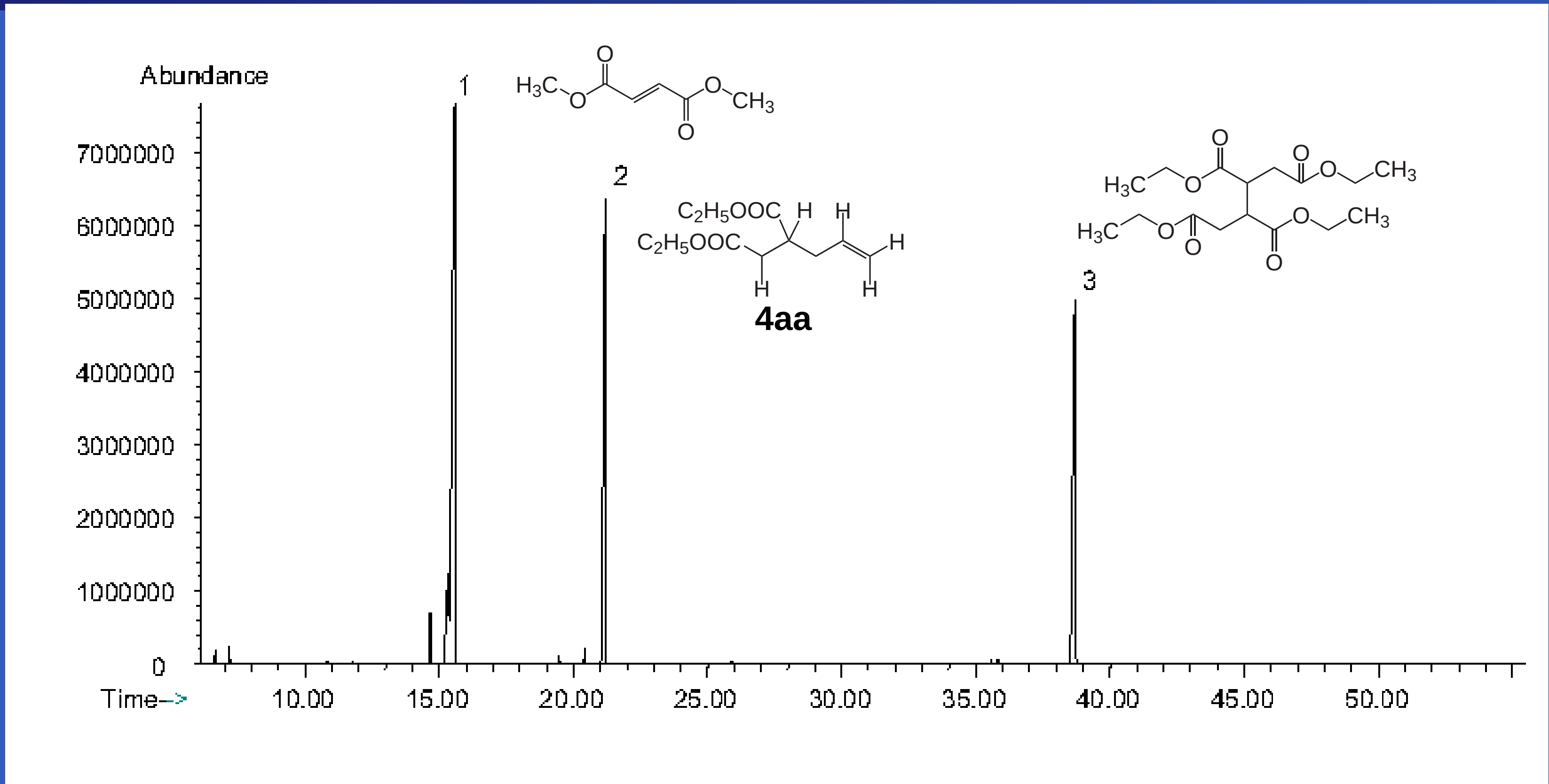
transfer galvanostatic $\longrightarrow$ potentiostatic ok

Miniaturized Potentiostatic Reduction in [BMIM]BF_4: Allylbromide + Diethyl Fumarate



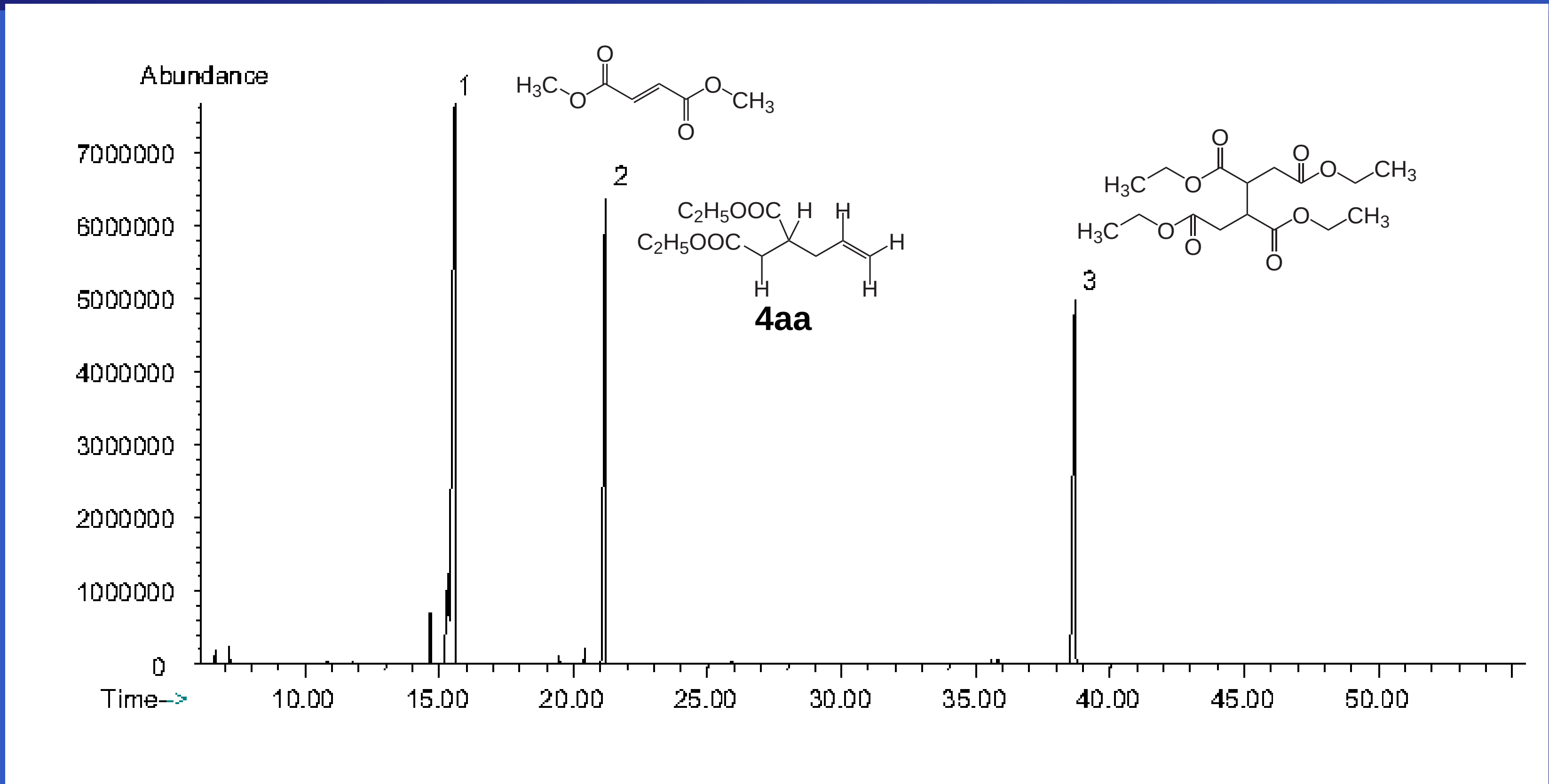
- cyclic voltammetric monitoring before (full) and after (dotted) electrolysis ($v = 0.3$ V s^{-1})
- E_p(**2a**) $= -1.45$ V, E_p(**1a**) ≈ -2 V
- decrease of negative extension of potential window
- decrease of i_p(**2a**)

Miniaturized Potentiostatic Reduction in $[BMIM]BF_4$: Allylbromide + Diethyl Fumarate



- $c(\textbf{1a}) = c(\textbf{2a}) = 0.2$ 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 $\longrightarrow$ $[BMIM]BF_4$ ok
miniaturization ok

Miniaturized Potentiostatic Reduction in $[BMIM]BF_4$: A Small Collection

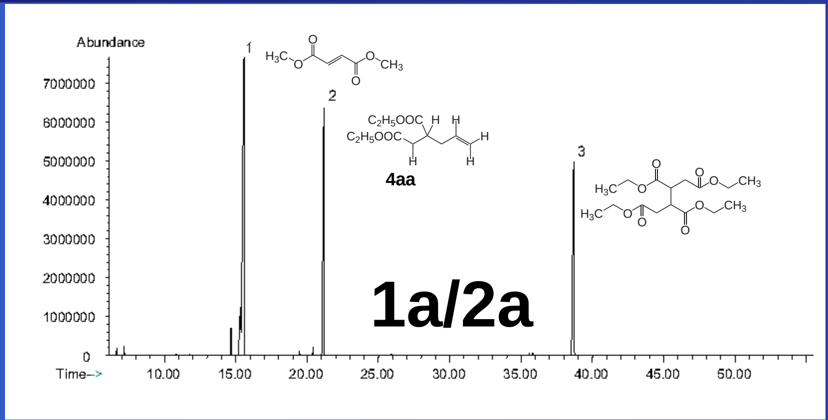
1a/2a

1c/2a

1a/2c

1c/2c

Miniaturized Potentiostatic Reduction in [BMIM]BF_4: A Small Collection



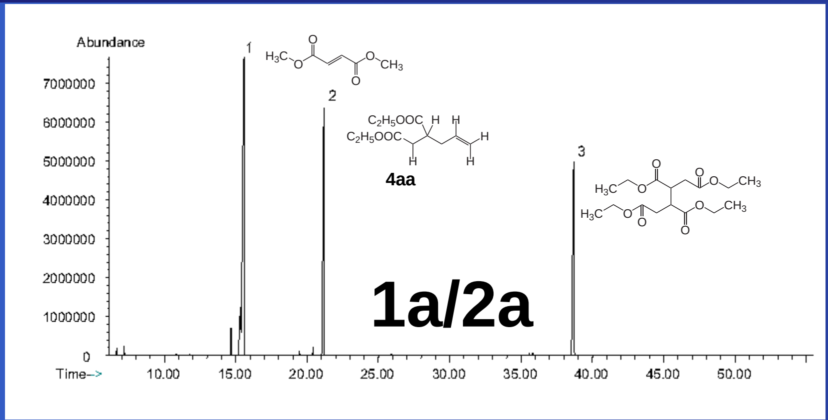
1c/2a

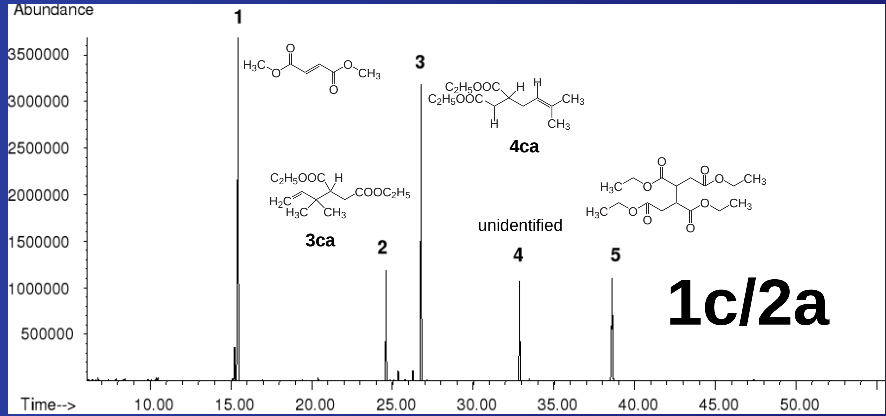
1a/2c

1c/2c

- 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



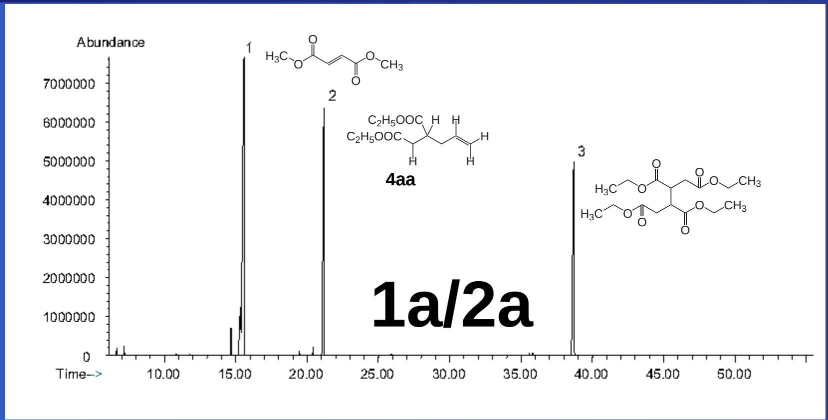


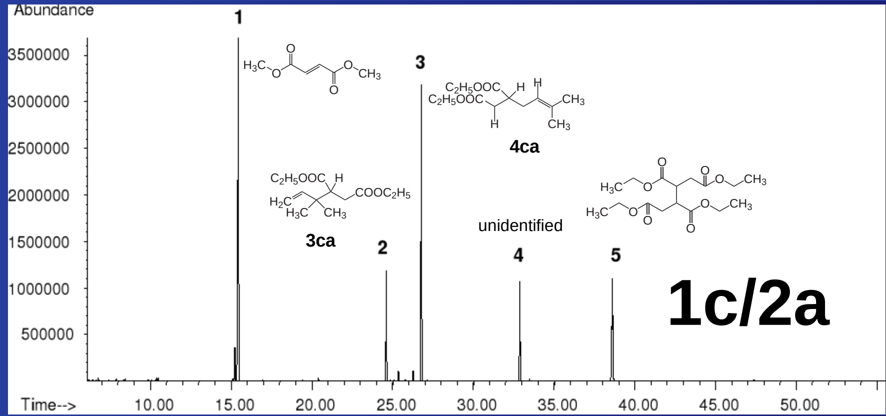
1a/2c

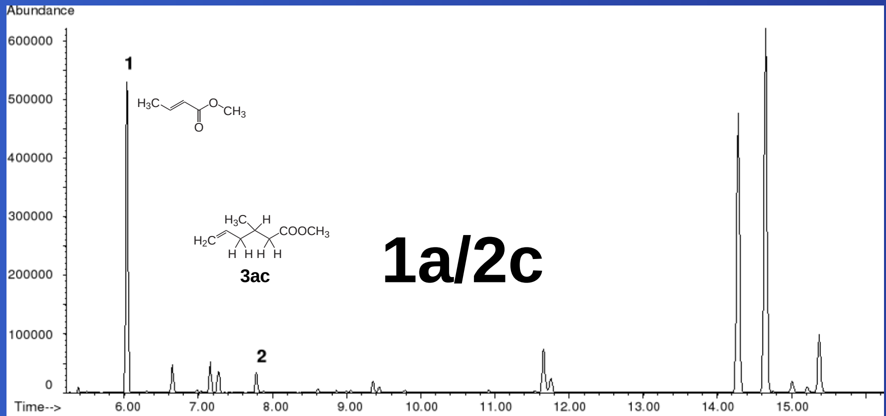
1c/2c

- 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**

Miniaturized Potentiostatic Reduction in [BMIM]BF_4: A Small Collection



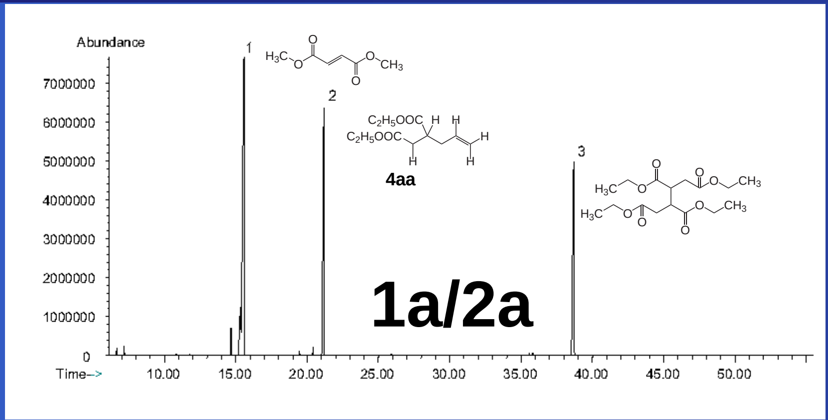


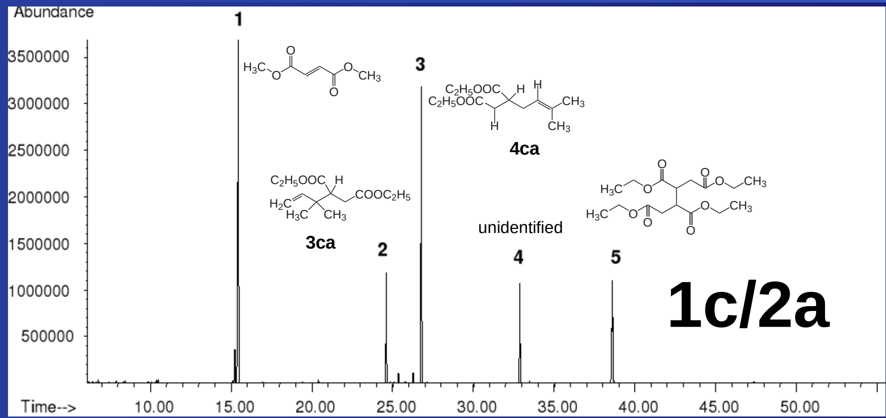


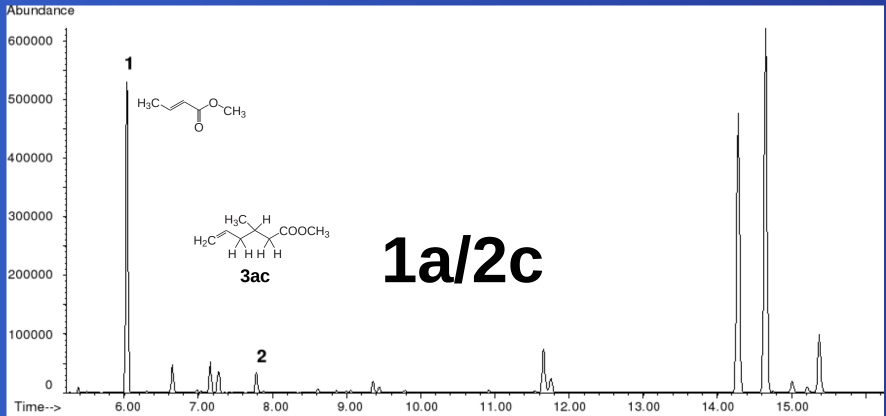
1c/2c

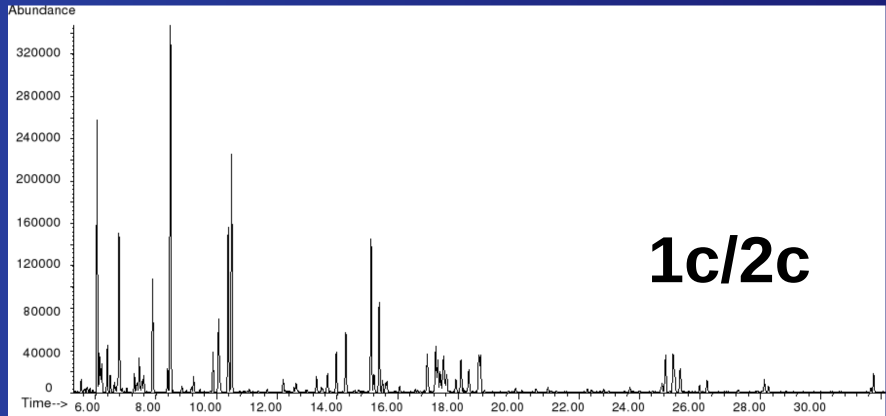
- allylbromide more easy to reduce
- coupling product identified by M^+ and main fragments (very low yield)
- identity of **3ac** assigned based on attack of allyl anion on ester

Miniaturized Potentiostatic Reduction in [BMIM]BF_4: A Small Collection



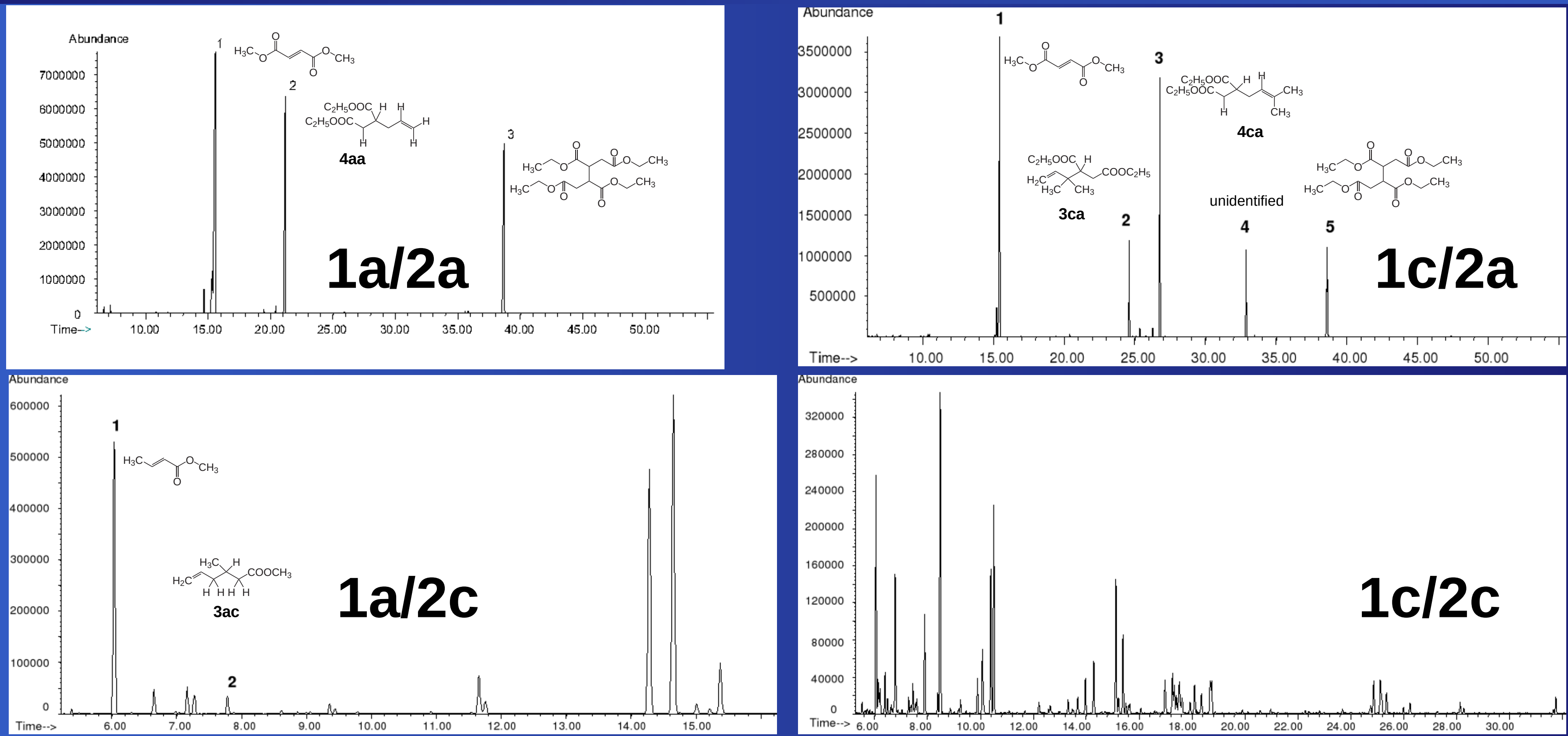






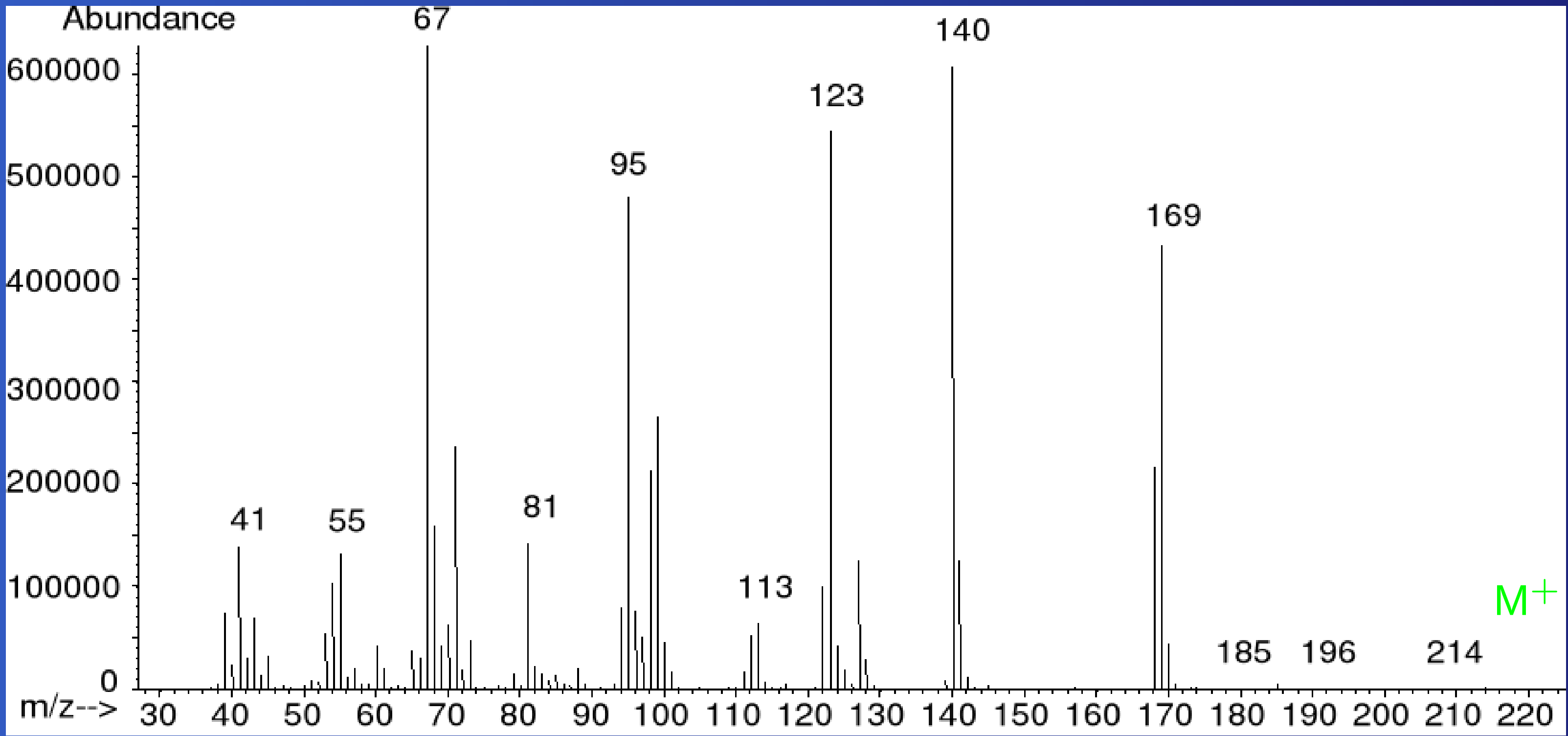
- allylbromide more easy to reduce
- no products identified

Miniaturized Potentiostatic Reduction in [BMIM]BF_4: A Small Collection



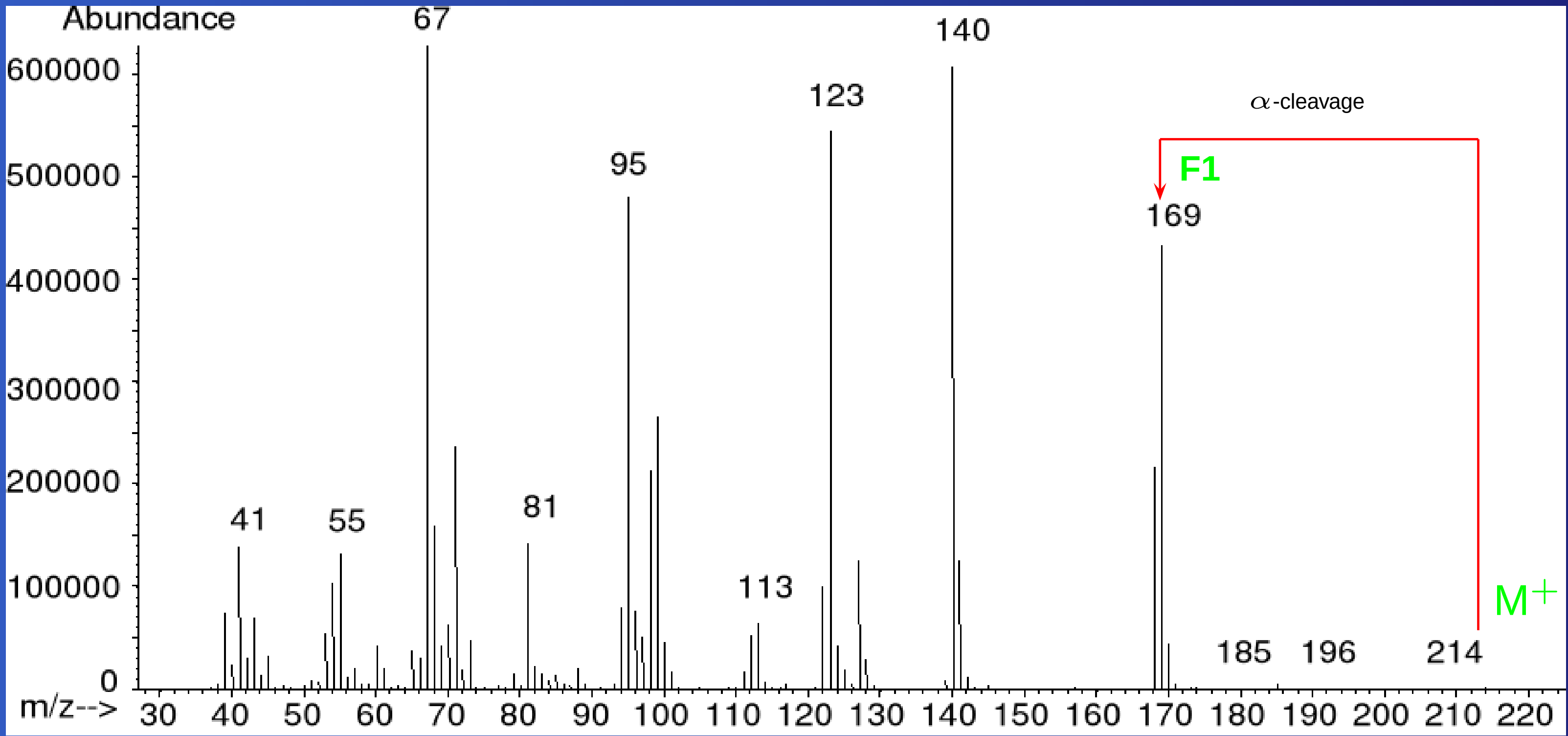
electrolysis with subsequent GC-MS provides screening technique

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^+
- α-cleavage of ester group $\longrightarrow$ F1

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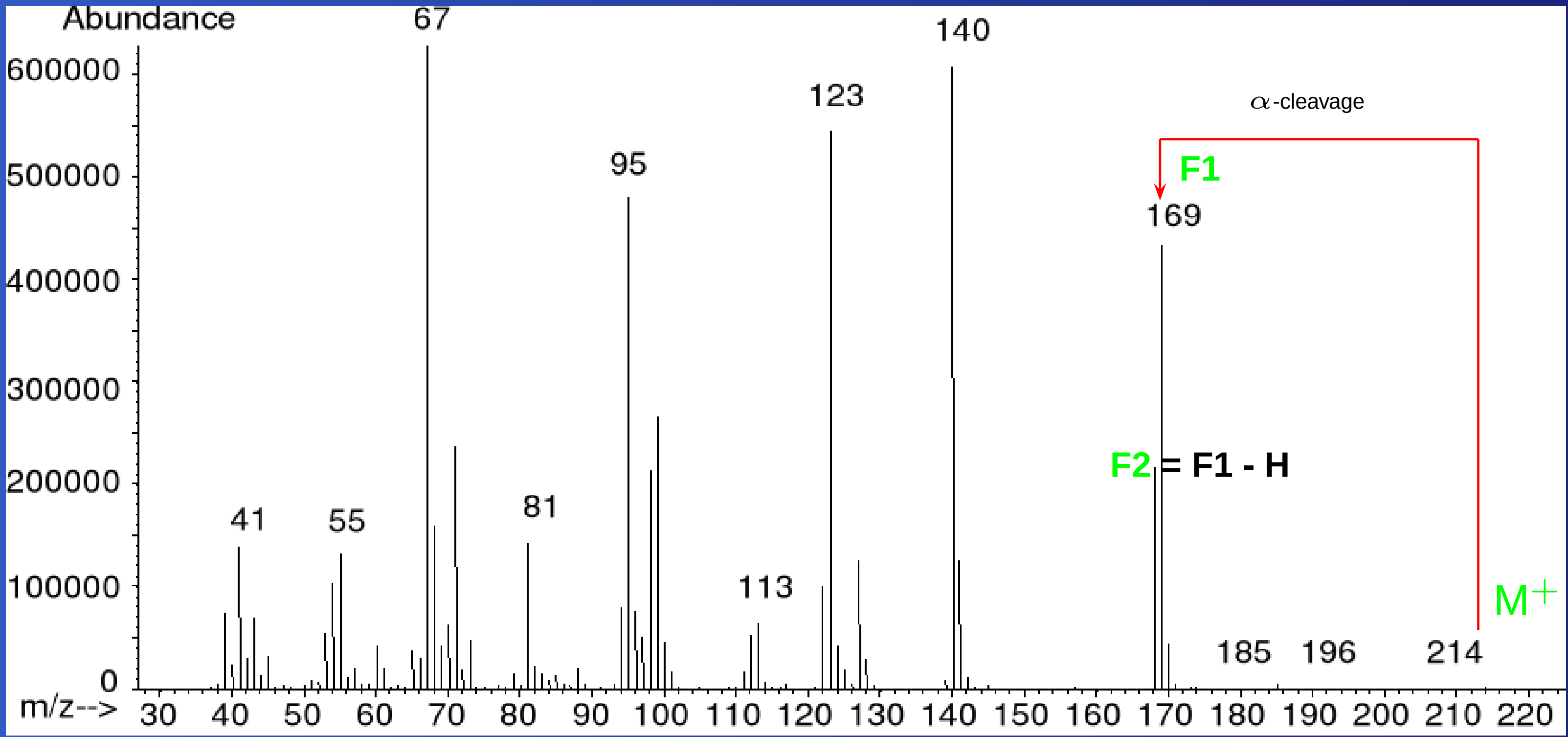

- small molecular ion peak M^+
- α-cleavage of ester group $\longrightarrow$ F1
- hydrogen loss $\longrightarrow$ F2

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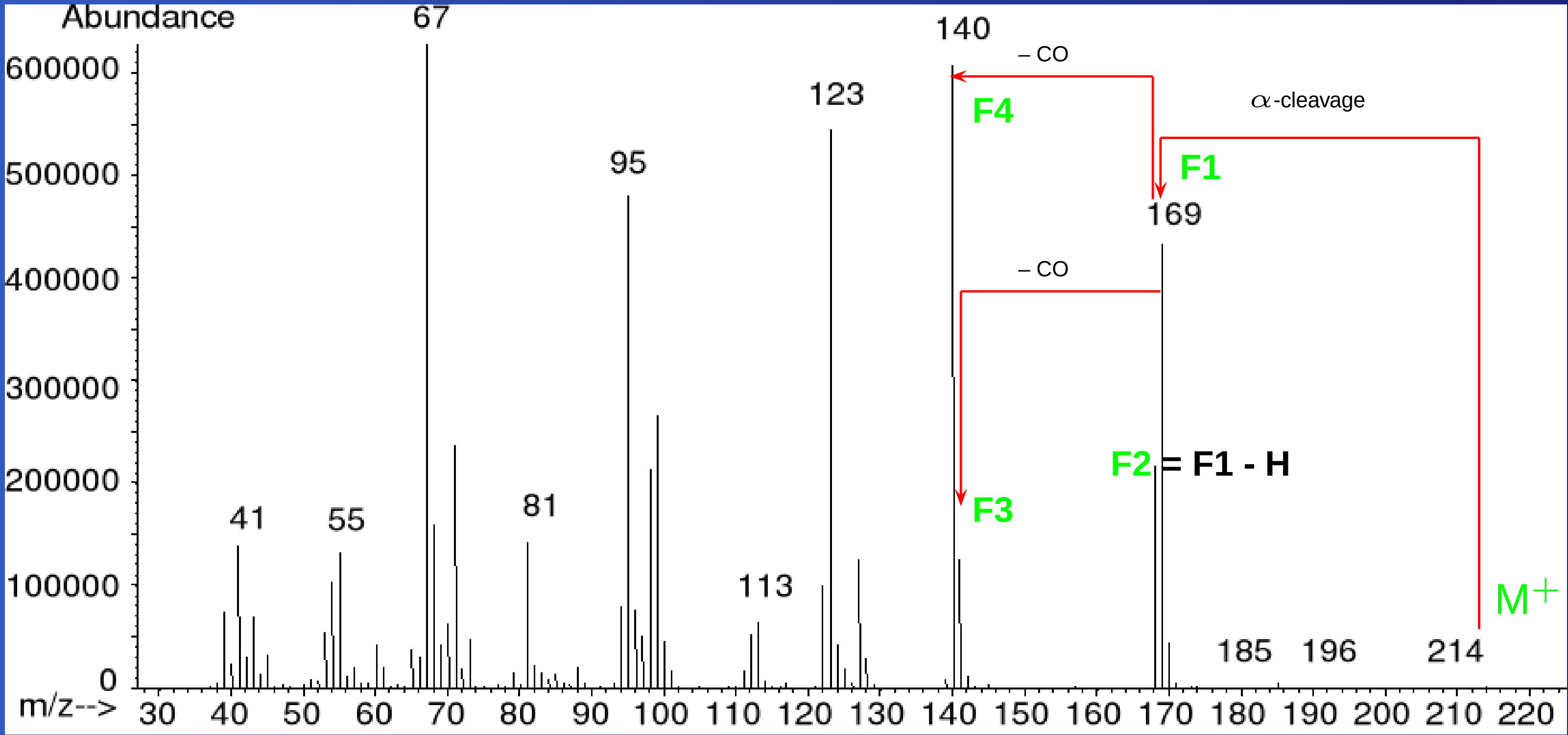


- small molecular ion peak M^+
- α-cleavage of ester group ⟶ F1
- hydrogen loss ⟶ F2
- cleavage of CO ⟶ F3 or F4

The Combinatorial Experiment: A Collection of 48 Electrolyses – Microtiter Plate Loading

	A	B	C	D	E	F	G	H
1	WW	1a/2a	1b/2a	1c/2a	1d/2a	1e/2a	1f/2a	WW
2	WW	1a/2b	1b/2b	1c/2b	1d/2b	1e/2b	1f/2b	WW
3	WW	1a/2c	1b/2c	1c/2c	1d/2c	1e/2c	1f/2c	WW
4	WW	1a/2d	1b/2d	1c/2d	1d/2d	1e/2d	1f/2d	WW
5	WW	1a/2e	1b/2e	1c/2e	1d/2e	1e/2e	1f/2e	WW
6	WW	1a/2f	1b/2f	1c/2f	1d/2f	1e/2f	1f/2f	WW
7	WW	1a/2g	1b/2g	1c/2g	1d/2g	1e/2g	1f/2g	WW
8	WW	1a/2h	1b/2h	1c/2h	1d/2h	1e/2h	1f/2h	WW

- 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:

	A	B	C	D	E	F	G	H
1	WW	F1/F2/F3/F4	M^+/F1/F2/F3/F4	M^+/F1/F3/F4	F1/F2/F3/F4	—	—	WW
2	WW	F1/F2/F4	F1/F2/F3/F4	M^+/F1/F2/F4	F1/F2/F4	—	—	WW
3	WW	—	—	—	—	—	—	WW
4	WW	M^+/F1/F4	—	F1/F3	F1/F4	—	—	WW
5	WW	—	—	—	—	—	—	WW
6	WW	—	—	—	—	—	—	WW
7	WW	—	—	—	—	—	—	WW
8	WW	F1/F3/F4	F1/F4	—	F4	F1/F4	F1	WW

The Combinatorial Experiment: A Collection of 48 Electrolyses – Screening for Fragments in MS

after 30 min:

	A	B	C	D	E	F	G	H
1	WW	F1/F2/F3/F4	M^+/F1/F2/F3/F4	M^+/F1/F3/F4	F1/F2/F3/F4	—	—	WW
2	WW	F1/F2/F4	F1/F2/F3/F4	M^+/F1/F2/F4	F1/F2/F4	—	—	WW
3	WW	—	—	—	—	—	—	WW
4	WW	M^+/F1/F4	—	F1/F3	F1/F4	—	—	WW
5	WW	—	—	—	—	—	—	WW
6	WW	—	—	—	—	—	—	WW
7	WW	—	—	—	—	—	—	WW
8	WW	F1/F3/F4	F1/F4	—	F4	F1/F4	F1	WW

- 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)

The Combinatorial Experiment: A Collection of 48 Electrolyses – Screening for Fragments in MS

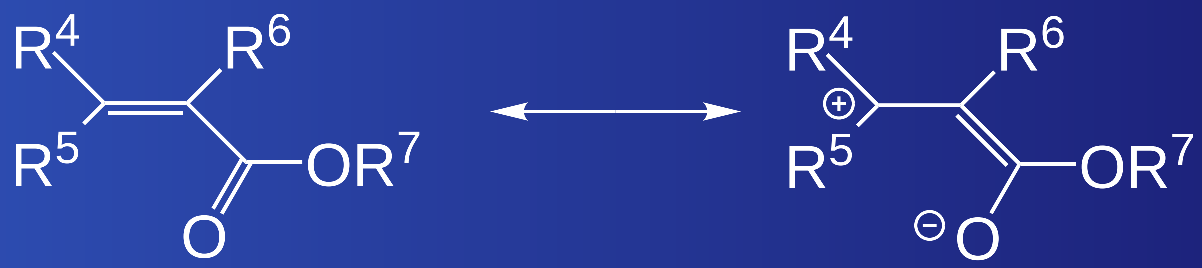
after 30 min:

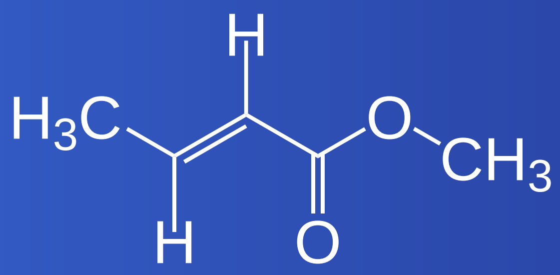
	A	B	C	D	E	F	G	H
1	WW	F1/F2/F3/F4	M^+/F1/F2/F3/F4	M^+/F1/F3/F4	F1/F2/F3/F4	—	—	WW
2	WW	F1/F2/F4	F1/F2/F3/F4	M^+/F1/F2/F4	F1/F2/F4	—	—	WW
3	WW	—	—	—	—	—	—	WW
4	WW	M^+/F1/F4	—	F1/F3	F1/F4	—	—	WW
5	WW	—	—	—	—	—	—	WW
6	WW	—	—	—	—	—	—	WW
7	WW	—	—	—	—	—	—	WW
8	WW	F1/F3/F4	F1/F4	—	F4	F1/F4	F1	WW

- 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?

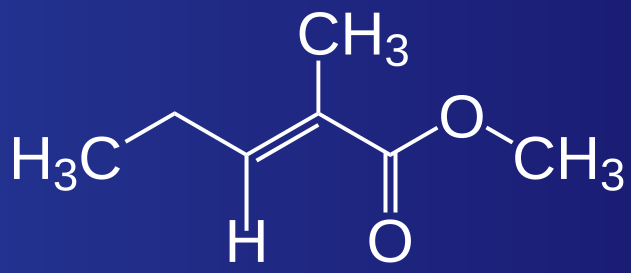
The Mechanistic Pattern: Esters with Electron-Donating Substituents are Not Reactive





2c

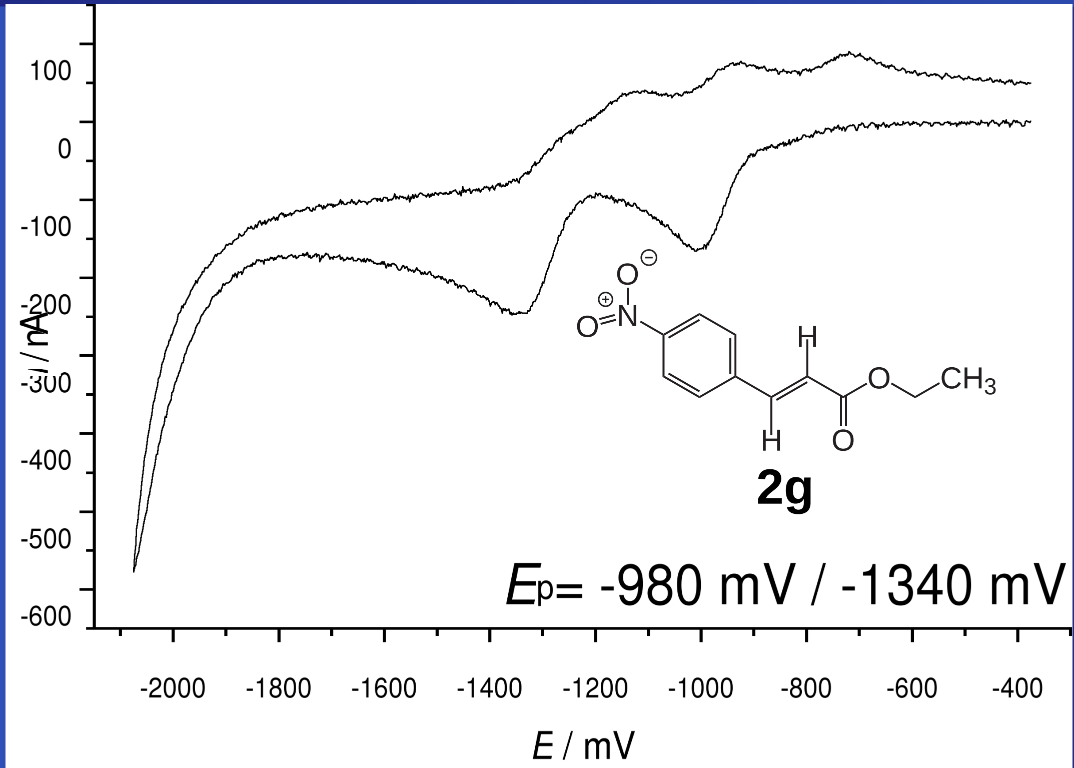
2e



2f

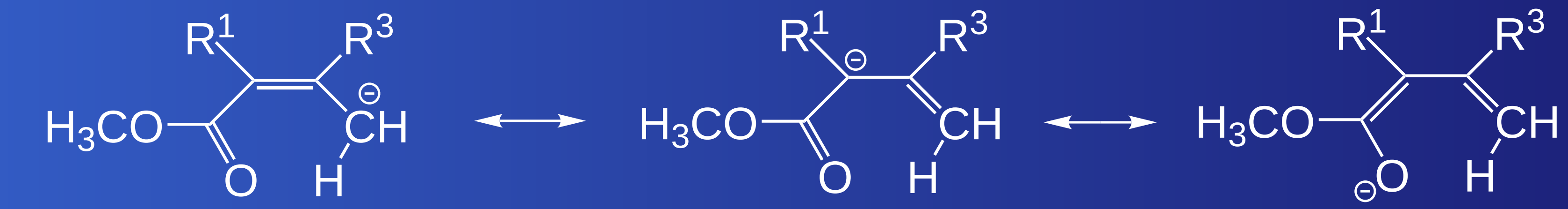
- very negative reduction potential $\longrightarrow$ allylbromide is reduced
- allyl anion attacks
- electron-donating substituents R^4 or R^5 decrease positive charge density
- esters become less reactive

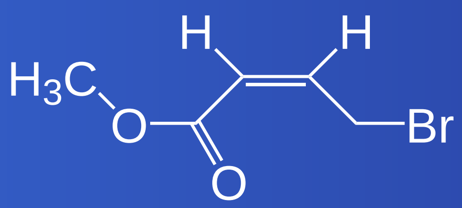
The Mechanistic Pattern: Nitrophenyl Substituted Ester is Not Reactive



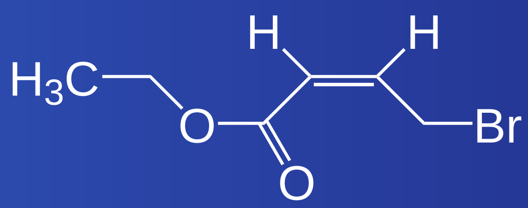
- two reduction waves – characteristic for NO_2 reduction
- radical anion of **2g** stabilized and unreactive

The Mechanistic Pattern: Allylbromides with Electron-Withdrawing Substituents are Not Reactive

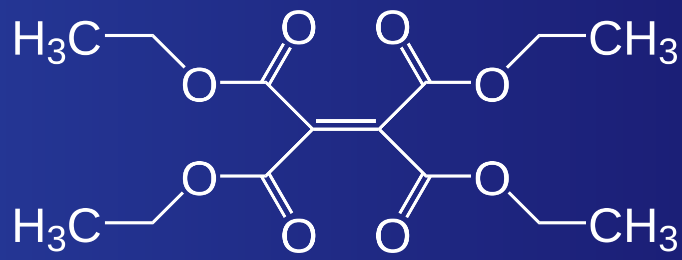




1e



1f



2h

- relatively positive reduction potential $\longrightarrow$ 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)?

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