RĪGAS TEHNISKĀ UNIVERSITĀTE

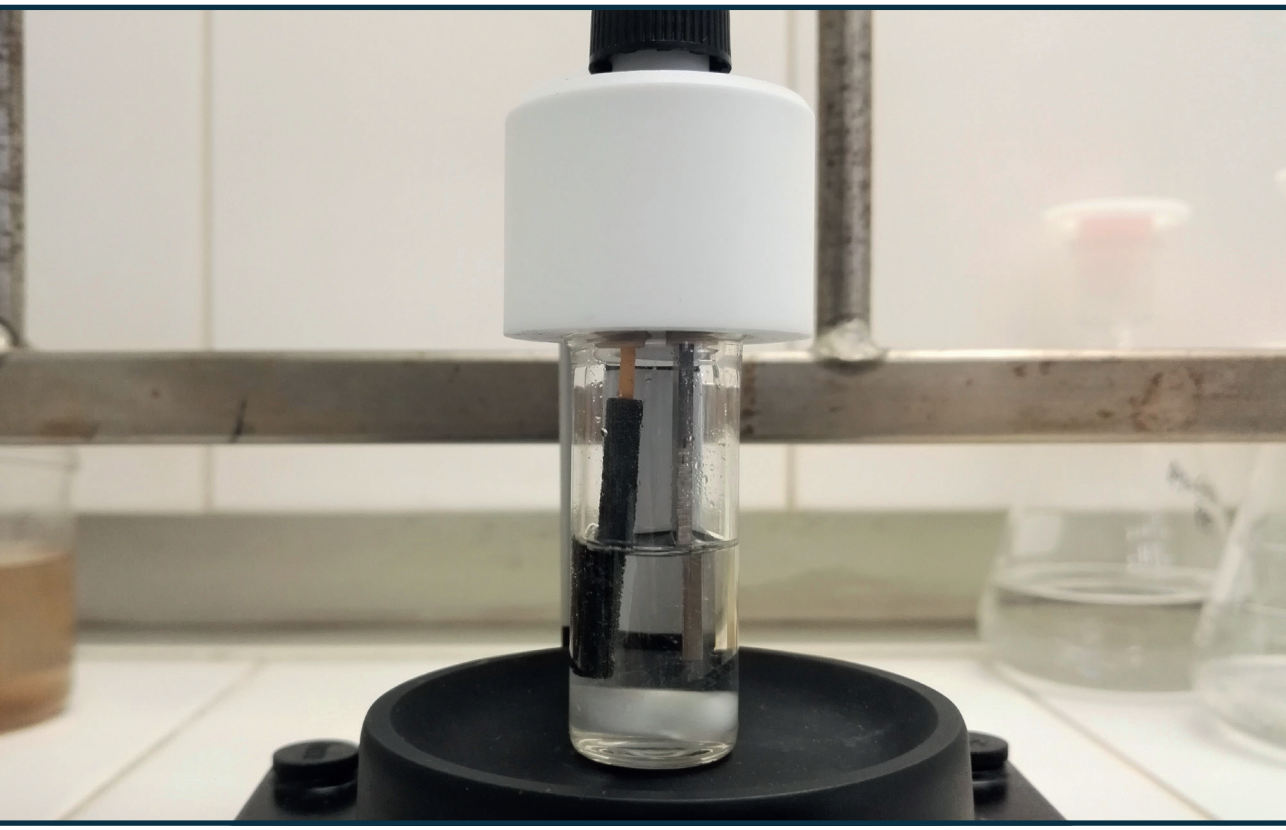
Anna Lielpētere

STANNILMETILĒTERU UN FURĀNA ATVASINĀJUMU ELEKTROĶĪMISKA OKSIDĒŠANA JAUNU SINTĒZES METOŽU IZVEIDEI

Promocijas darbs

DEVELOPMENT OF NEW SYNTHETIC METHODS BASED ON ELECTROCHEMICAL OXIDATION OF STANNYLMETHYLETHERS AND FURAN DERIVATIVES

Doctoral Thesis



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RĪGAS TEHNISKĀ UNIVERSITĀTE
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Scientific supervisor

Profesors *Dr. chem.* AIGARS JIRGENSONS
Professor *Dr. chem.* AIGARS JIRGENSONS

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PROMOCIJAS DARBS IZVIRZĪTS ZINĀTNES DOKTORA GRĀDA IEGŪŠANAI RĪGAS TEHNISKAJĀ UNIVERSITĀTĒ

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APSTIPRINĀJUMS

Apstiprinu, ka esmu izstrādājusi šo promocijas darbu, kas iesniegts izskatīšanai Rīgas Tehniskajā universitātē zinātnes doktora (*Ph. D.*) grāda iegūšanai. Promocijas darbs zinātniskā grāda iegūšanai nav iesniegts nevienā citā universitātē.

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Promocijas darbs ir sagatavots kā tematiski saistītu zinātnisko publikāciju kopa, kas papildināts ar kopsavilkumiem latviešu un angļu valodā. Promocijas darbs apvieno četras zinātniskās publikācijas. Zinātniskās publikācijas ir angļu valodā, to kopējais apjoms ir 79 lappuses, ieskaitot pielikumus.

SATURS

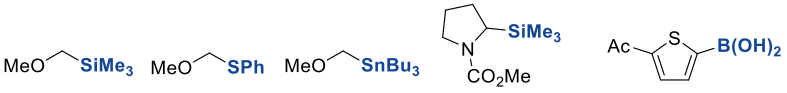
SAĪSINĀJUMI

Ac – acetil-
Alk – alkil-
Ar – aril-
Boc – *terc*-butoksikarbonil-
Bu – butil-
DCM – dihlormetāns
EAux – elektropalīggrupa
Ekviv. – ekvivalenti
E^{ox} – oksidēšanās potenciāls
Et – etil-
HFIP – 1,1,1,3,3,3-heksafluorpropān-2-ols
Ist. t. – istabas temperatūra
KMR – kodolu magnētiskā rezonanse
Me – metil-
MOM – metoksimetil-
PG – aizsarggrupa
Ph – fenil-
Piv – pivaloil-
PPTS – piridīnija *p*-toluosulfonāts
SHE – standarta ūdeņraža elektrods
TBA – tetrabutilamonija jons
TBDMS – *terc*-butildimetilsilil-
THP – tetrahidropirān-2-il-
Tr – tritil-
Ts – tozil-

PROMOCIJAS DARBA VISPĀRĒJS RAKSTUROJUMS

Ievads

Pēdējā desmitgadē sintētiskā organiskā elektroķīmija ir guvusi jaunu ievērību, pateicoties tehnoloģiju attīstībai un tās ieguldījumam ilgtspējīgas ķīmijas attīstībā. Elektroķīmiskajām metodēm piemīt daudzas priekšrocības, piemēram, jauni reakciju ceļi, mērogojamība, maigi reakcijas apstākļi un kontrolēta reaģētspējīgu starpproduktu veidošanās.[1–3] Reakcijas laiku iespējams paredzēt un kontrolēt, mainot pievadītās strāvas stiprumu.[4] Elektroķīmija ļauj tiešā ceļā pievadīt molekulai enerģiju, izvairoties no molekulāru enerģijas nesēju izmantošanas.[5] Elektroni tiek tieši pārnesti starp elektroda virsmu un organisko molekulu, radot reaģētspējīgus starpproduktus. Reaģētspējīgo starpproduktu koncentrācija ir atkarīga no strāvas blīvuma, kas raksturo elektronu kustības ātrumu, savukārt elektrodam pieliktais elektriskais potenciāls raksturo redoksprocesa virzītājspēku. Elektroķīmisko reakciju var veikt vai nu kontrolēta potenciāla, vai kontrolēta strāvas stipruma režīmā. Kontrolēta potenciāla elektrolīze ļauj precīzi kontrolēt savienojumu reaģētspēju, jo potenciāls tiek kontrolēts attiecībā pret references elektrodu. Parasti šāda veida reakcijai nepieciešama dalītā elektroķīmiskā šūna, kurā darba elektrods ir atdalīts no palīgelektroda ar membrānu vai filtru, kas sarežģī iekārtu un palielina šūnas pretestību. Kontrolētas strāvas elektrolīzi bieži var veikt nedalītā šūnā. Kontrolētas strāvas elektrolīzes laikā tiek oksidēti savienojumi ar zemāko redokspotenciālu, un ķīmisko selektivitāti var uzlabot, izmantojot elektroķīmiskos mediatorus vai elektropalīggrupas (*electroauxiliary*) – funkcionālās grupas, kas veicina elektronu pārnesi.[3, 6] Zināmas elektropalīggrupas ir sililgrupas[7–9] (piemēram, 1. att. savienojumi **1**,**4**), stannāni[10–12] (piemēram, 1. att. savienojums **3**), ariltioli[13] (piemēram, 1. att. savienojums **2**) un organiskās borskābes[14] (piemēram, 1. att. savienojums **5**), kas ir izmantotas karbamātu[7, 11], alkoksikarbonilsavienojumu[10], ēteru[8, 9, 11–13], alkēnu[15], sulfīdu[15] un arēnu[14] redokspotenciāla pazemināšanai.

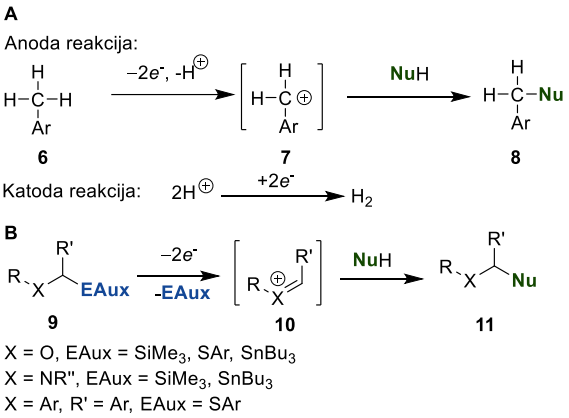


1	**2**	**3**	**4**	**5**
1,60 V	1,40 V	0,91 V	1,23 V	2,5 V 2,1 V F^- klātbūtnē

1. att. Zināmu elektropalīggrupu reprezentatīvi piemēri un attiecīgie savienojumu redokspotenciāli (pret SHE).

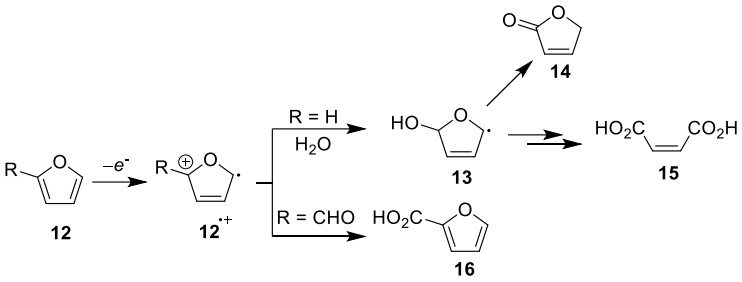
Viens no šajā promocijas darbā īstenotajiem pētījumu virzieniem bija novērtēt elektropalīggrupu izmantošanu karbēnija jonu ģenerēšanai. Anodiskā oksidēšana ļauj ģenerēt karbēnija jonus, piemēram, savienojumu **7** no savienojuma **6** (2. att., A), neizmantojot stehiometriskus oksidētājus, savukārt protonu reducēšana līdz ūdeņradim uz katoda kalpo kā

neitrāla palīgelektroda reakcija (2. att., A). Tomēr tikai daži nukleofīli ir inerti pie substrāta aktivēšanai izmantotā oksidēšanas potenciāla, kas nepieciešams, lai iegūtu savienojumu **8**. Lai paplašinātu izmantojamo nukleofīlu klāstu, Jošidas (*Yoshida*) grupa izstrādāja elektroķīmisku katjonu uzkrāšanas (*cation pool*) metodoloģiju, izmantojot izejmateriālus **9**, kas modificēti ar elektropalīggrupu (EAux) (2. att., B). Šajā metodē katjonus **10** (2. att., B) uzkrāj zemā temperatūrā, kam kā atsevišķs solis seko nukleofīla pievienošana (*ex cell*), lai iegūtu produktus **11** (2. att., B).[6] Lai gan katjonu uzkrāšanas metodei ir daudz izmantošanas iespēju, praktisko lietojumu sarežģī nepieciešamība izmantot dalīto šūnu, zemu temperatūru un lielu daudzumu trifluormetānsulfonskābes katodiskajai reakcijai. Praktiskāka būtu elektrosintēze nedalītā šūnā, kur karbēnija joni veidotos nukleofīlu klātbūtnē. Šim nolūkam substrātu **6** un **9** redokspotenciālam jābūt zemākam par attiecīgā nukleofīla redokspotenciālu. Šajā darbā elektropalīggrupu izmantošana karbēnija jonu ģenerēšanai ļāva paplašināt izmantojamo oglekļa nukleofīlu klāstu.



2. att. A) Tiešā elektroķīmiskā oksidēšana, kurai seko reakcija ar nukleofīlu;
B) elektroķīmiskā oksidēšana, izmantojot elektropalīggrupu.

Papildu priekšrocība elektroķīmijas izmantošanai ir ilgtspējīgas ķīmijas veicināšana, radot metodes biomasas valorizācijai.[2, 16, 17] Furāna atvasinājumi (piemēram, 3. att. savienojums **12**) ir īpaši piemēroti substrāti elektroķīmiskai funkcionalizēšanai, jo furāna gredzena zemais oksidēšanās potenciāls ļauj ģenerēt katjonradikāļus **12**$^{\bullet+}$ tiešā elektroķīmiskā oksidēšanā. Tas paver sintēzes ceļus daudzveidīgu produktu, kā **14**, **15** un **16**, iegūšanai bez elektropalīggrupu izmantošanas (3. att.).



3. att. Furāna atvasinājumu elektrooksidatīvās valorizācijas produkti.[18]

Lai elektroķīmiskās metodes varētu praktiski lietot organiskās sintēzes laboratorijā, ir būtiski, lai tās būtu tehniski viegli īstenojamas, t. i., izmantotu nedalīto šūnu, lētus elektrodu materiālus un vienkāršas iekārtas, piemēram, IKA komerciāli pieejamo potenciostatu *Electrasyn 2.0* vai pat akumulatoru.[1] Arī rūpnieciskos apstākļos ir būtiski, lai elektroķīmiskās metodes būtu drošas, ar augstu selektivitāti, iznākumu un atomekonomiju. Patlaban praktiski rūpniecībā izmanto tādas elektroķīmiskās reakcijas kā adiponitrila sintēzi (*Monsanto*), aizvietota toluola metoksilēšanu (*BASF*), antracēna oksidēšanu par antrahinonu (*ECRC*), maleīnskābes anhidrīda reducēšanu par dzintarskābi (*CERCI*) un 2-metil-2,5-dimetoksifurāna metoksilēšanu kā soli 2-metil-3-merkaptofurāna iegūšanas ceļā (*Tengzhou Tianshui Biological Technology Co.*).[19]

Gan rūpniecībā, gan laboratorijā īpaši pievilcīgas ir metodes, kas paver jaunus reakciju ceļus, ir izmantojamas vēlīnajās sintēzes stadijās augstas funkcionālo grupu tolerances dēļ vai paver vienkāršus veidus, kā veikt pārvērtības, kas tradicionāli izmanto toksiskus vai nestabilus reaģentus.[1] Šo iemeslu dēļ sintētiskās metodes, kas izstrādātas šī promocijas darba gaitā, izmanto nedalīto šūnu, lētus grafīta elektrodus un komerciāli pieejamo *Electrasyn* potenciostatu.

Pētījuma mērķis un uzdevumi

Promocijas darba galvenais mērķis ir izstrādāt jaunas, funkcionāli vienkāršas elektroorganiskās ķīmijas metodes, izmantojot elektroķīmiski ģenerētus karbēnija jonus.

Lai sasniegtu šo mērķi, tika definēti šādi uzdevumi:

1) atrast piemērotu elektropalīggrupu karbēnija jonu ģenerēšanai (iniciējot oksonija jonu fragmentēšanos);
2) izstrādāt jaunu metodi karbēnija jonu alilēšanai, elektroķīmiski aktivējot substrātus, kas modificēti ar elektropalīggrupu;
3) izstrādāt metodi elektroķīmiski ierosinātai Frīdela–Kraftsa alkilēšanai skābes jutīgu substrātu klātbūtnē;

4) izmantot elektroķīmiski ierosinātu iekšmolekulāru Frīdela–Kraftsa alkilēšanas reakciju kondensētu heterociklu sintēzei;
5) izpētīt furāna atvasinājumu valorizāciju, izmantojot elektroķīmiskas katjonradikāļu pārvērtības.

Zinātniskā novitāte un galvenie rezultāti

Promocijas darbā ir izstrādātas praktiski vienkāršas elektroķīmiskās metodes jaunu ķīmisko saišu veidošanai, reaģējot karbēnija joniem. Trialkilstannilmetilgrupa tika izvēlēta kā piemērota elektropalīggrupa karbēnija jonu ģenerēšanai, iniciējot oksonija jona fragmentēšanos, kas ļauj sintezēt karbēnija jonu prekursorus no viegli pieejamiem izejmateriāliem – spirtiem. Trialkilstannilmetilgrupas kā elektropalīggrupas zemais redokspotenciāls ļauj veikt selektīvu elektrooksidēšanu nedalītā šūnā nukleofīlu klātbūtnē. Karbēnija jonu veidošanos papildus veicināja 1,1,1,3,3,3-heksafluorpropān-2-ola (HFIP) kā piedevas izmantošana. Karbēnija jonu elektroķīmiska ģenerēšana no elektropalīggrupu saturošām izejvielām tika lietota alilēšanai, kā nukleofīlus izmantojot aliltrimetilsilānus. Elektroķīmiskā karbēnija jonu ģenerēšanas metode tika tālāk attīstīta, lai veiktu Frīdela–Kraftsa alkilēšanu, izmantojot arēnus kā nukleofīlus. Modificētie elektrolīzes apstākļi, kuros izmantoja piedevu ($NaHCO_3$), ļāva izmantot savienojumus ar skābes jutīgām funkcionālajām grupām, tostarp TBDMS, Boc, Tr, MOM, THP un -$CHPh_2$. Iekšmolekulāra Frīdela–Kraftsa alkilēšana ļāva iegūt jaunus kondensētus heterociklus, saslēdzot sešlocekļu ciklus.

Veicot elektroķīmisku oksidēšanu metanolā, furfurilgrupu saturoši etilēnglikola un aminoetanola atvasinājumi veido spirociklus. Turpinot oksidēšanu, spirociklus var pārveidot par α,β-nepiesātinātiem esteriem ar pilnīgu *Z* selektivitāti. Esteru sintēzi no biomasas izejvielām var veikt vienā vai divās stadijās, iegūstot daudzfunkcionālus būvblokus un funkcionalizētus monomērus polimerizācijai.

Darba struktūra un apjoms

Promocijas darbs ir tematiski saistītu zinātnisko publikāciju kopa par jaunu elektroķīmisko metožu izstrādi karbēnija jonu iegūšanai un izmantošanai reakcijās. Promocijas darbā apkopoti rezultāti no četriem oriģināliem zinātniskajiem rakstiem, kas indeksēti *Scopus* un *Web of Science*.

Publikācijas un promocijas darba aprobācija

Promocijas darba rezultāti ir publicēti četrās zinātniskajās publikācijās. Rezultāti ir prezentēti astoņās zinātniskajās konferencēs.

Publikācijas

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Dalība konferencēs

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3. **Lielpētere, A.** Electrochemical Generation of Carbenium Ions via Electroauxiliary and Their Reactions with Nucleophiles. *50t^{h} Heyrovský Discussion on Molecular Electrochemistry in Organic and Organometallic Research.* Třešť, Czech Republic, June 18–22, **2017**.
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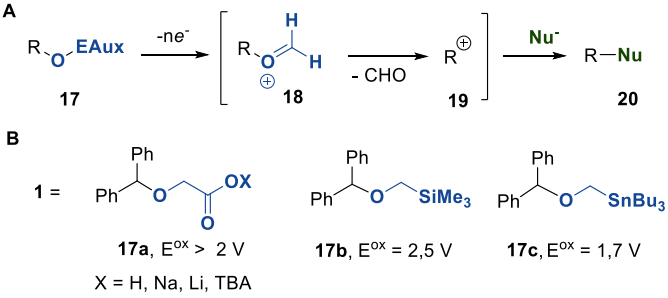
PROMOCIJAS DARBA GALVENIE REZULTĀTI

1. Elektroķīmiska karbēnija jonu ģenerēšana, izmantojot elektropalīggrupas, un to reakcijas ar nukleofīliem

Karbēnija jonu elektroķīmiskā ģenerēšana tika paredzēta divās stadijās – vispirms, elektroķīmiski aktivējot elektropalīggrupu izejvielā **17**, tiktu ģenerēts oksonija jons **18**, kas *in situ* fragmentētos līdz karbēnija jonam **19** (4. att., A). Divu stadiju process ļautu ģenerēt substrātus no viegli pieejamiem izejmateriāliem – spirtiem.

Kā potenciālās elektropalīggrupas tika izmēģinātas oksietiķskābes (**17a**), sililmetilētera (**17b**) un stanilmetilētera (**17c**) funkcionālās grupas (4. att., B). No tām zemākais redokspotenciāls tika noteikts stannilmetilēterim – 1,7 V (pret SHE) savienojumā **17c**.



4. att. A) Karbēnija jonu veidošanās no oksonija jonu fragmentēšanās;
B) izmēģinātās elektropalīggrupas un to oksidēšanās potenciāli (pret SHE).

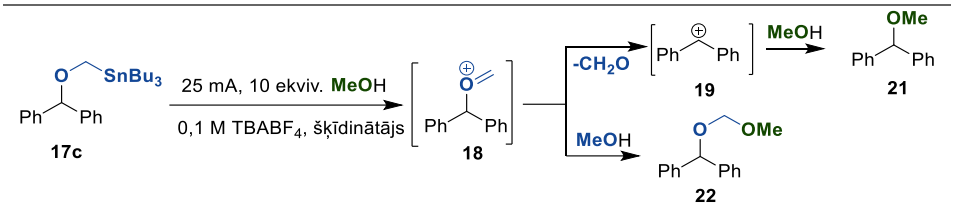
Balstoties cikliskās voltampetrometrijas rezultātos, par elektropalīggrupu karbēnija jonu ģenerēšanai, inicējot oksonija jonu fragmentēšanos, tika izvēlēta stannilmetilētera grupa. Substrāti tika sintezēti vienā solī no attiecīgajiem spirtiem. Reakcijai starp spirtu un tributil(jodmetil)stannānu bija nepieciešama spēcīga bāze – kālija hidrīds.

Karbēnija jonu ģenerēšanai no tributilstannilmetilēteriem bija nepieciešama ne tikai *C–Sn* saites šķelšana, bet arī efektīva oksonija jona fragmentēšanās elektrolīzes apstākļos. Fragmentēšanās efektivitāti pētīja ar elektroķīmisku metanolizēšanu dažādos apstākļos (1. tab.). Metanols kalpoja kā protonu donors katodiskajai reakcijai, savukārt reakcijas gaitā ģenerētais metoksīds reaģēja kā nukleofīls ar elektroķīmiski ģenerētajām elektrofīlajām daļiņām **18** un **19**. Pakļaujot ((benzhidriloksi)metil)tributilstannānu (**17c**) kontrolētas strāvas elektrolīzei metanolā vai acetonitrilā, oksonija jona **18** un karbēnija jona **19** produkti **21** un **22** veidojās ekvimolārā attiecībā ar vidēju iznākumu (1. tab., 1. un 2. aile). Ievērojamu selektivitātes un karbēnija jona produkta **21** iznākuma uzlabojumu novēroja, izmantojot HFIP kā reakcijas šķīdinātāju (1. tab., 4. aile). Ir zināms, ka HFIP stabilizē katjonu un katjonradikāļu starpprodukts, pateicoties tā spējai būt par ūdeņraža saites donoru, zemajai nukleofilitātei un

spējai veidot ambivalentas polaritātes mikrostruktūru.[20] Neliela produktu veidošanās tika novērota arī bez elektriskās strāvas HFIP veicinātas izejvielas jonizācijas dēļ, tomēr elektroķīmiskā procesa izmantošana bija izšķiroša, lai produktus iegūtu ar augstu iznākumu.

1. tabula

Substrāta **17c** elektroķīmiskā aktivēšana MeOH klātbūtnē



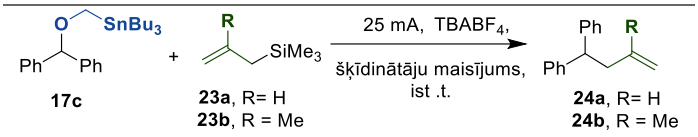
Nr.	Šķīdinātājs	**21** : **22** attiecība	**21** un **22** kopējais iznākums (%)[a]
1	MeOH	1 : 1.1	50
2	MeCN	1,3 : 1	50
3	DCM	7,5 : 1	85
4	**HFIP**	**> 99 : 1**	**73**

[a] Kopējais produktu **21** un **22** ^{1}H-KMR iznākums, izmantojot 1,4-bis-trihlormetilbenzolu kā iekšējo standartu.

Tālāk tika pētīta citu nukleofīlu izmantošana reakcijā ar elektroķīmiski ģenerētajiem karbēnija joniem. Optimālajos reakcijas apstākļos kā šķīdinātājs tika izmantots dihlormetāns (DCM) ar HFIP piedevu, lai veicinātu katodisko reakciju un oksonija jona fragmentēšanos (2. tab., 2. un 3. aile). Elektrolīzi veica nedalītā šūnā istabas temperatūrā bez inertas atmosfēras, izmantojot grafīta elektrodus. Tika konstatēts, ka alilsilāni **23a** un **23b** ir saderīgi ar elektrolīzes apstākļiem un reakcijā ar ģenerētajiem karbēnija joniem veidojas jauna *C–C* saite.

2. tabula

Substrāta **17c** elektroķīmiskā aktivēšana alilsilānu klātbūtnē



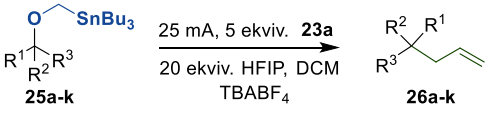
Nr.	**23**, šķīdinātāju maisījums	**24**, iznākums (%)
1	**23a**, HFIP	**24a**, 40 (KMR)[a]
2	**23a**, DCM, 20 ekviv. HFIP	**24a**, 87 (izdalīts)
3	**23b**, DCM, 20 ekviv. HFIP	**24b**, 64 (izdalīts)

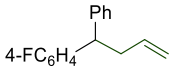
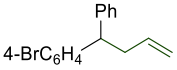
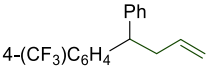
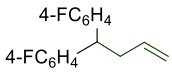
[a] ^{1}H-KMR iznākums, izmantojot 1,4-bis-trihlormetilbenzolu kā iekšējo standartu.

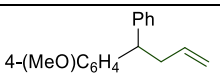
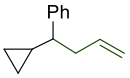
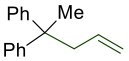
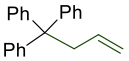
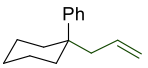
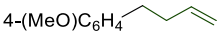
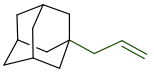
Elektrolīzē izmantojamais stannilmetilēteru klāsts (3. tab.) ietvēra substrātus, kas iegūti no difenilmetanoliem ar elektronakceptoriem (produkti **26a–d**) un elektrondonoriem (**26e**) aizvietotājiem. Arī fenilciklopropilmetil- un fenilcikloheksilkarbēnija joni ļāva iegūt attiecīgos alilēšanas produktus **26f** un **26i**. Trešējie karbēnija joni reaģēja ar alilsilānu, dodot produktus **26g**,**h** ar vidēji zemu iznākumu. Mazāk stabili karbēnija joni veidojās neefektīvi – metoksibenzilēteris deva produktu **26j** ar zemu iznākumu.

3. tabula

Elektroķīmiskās alilēšanas substrātu klāsts



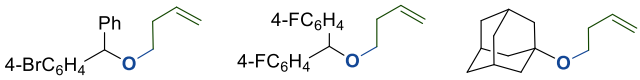
Nr.	Produkts	**26**, iznākums (%)
1		**26a**, 74
2		**26b**, 79
3		**26c**, 76
4		**26d**, 81

5		**26e**, 72
6		**26f**, 91
7		**26g**, 26[a]
8		**26h**, 42[b]
9		**26i**, 75
10		**26j**, 14
11		**26k**, 0

[a] 1,1-Difeniletilēns (20 %) tika izdalīts kā blakusprodukts.

[b] ^{1}H-KMR iznākums, izmantojot 1,4-bis-trihlormetilbenzolu kā iekšējo standartu; iegūts kā nedalāms maisījums ar trifenilmetānu.

Reakcijās, kurās tika ģenerēti nestabili karbēnija joni, varēja izdalīt oksonija jonu alilēšanas produktus (5. att.). Adamantilētera gadījumā oksonija jona pievienošanās produkts **29** tika iegūts kā galvenais produkts.



27, 6 % **28**, 6 % **29**, 44 %

5. att. Izdalītie oksonija jonu alilēšanas produkti.

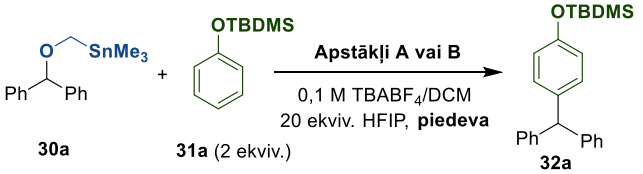
Apskatītie rezultāti ir publicēti 1. pielikumā pievienotajā dokumentā.

Pēc veiksmīgas karbēnija jonu ģenerēšanas metodes izstrādes, kurā izmanto elektroķīmisku stannilmetilētera oksidēšanu un oksonija jona fragmentēšanos, tika pētīta citu nukleofīlu izmantošana *C–C* saites veidošanai. Elektroķīmiskās metodes ļauj karbēnija jonus ģenerēt vidē, kas nesatur skābi, kamēr lielākajai daļai karbēnija jonu ģenerēšanas metožu nepieciešama Luisa vai Brensteda skābes klātbūtne. Nozīmīga karbēnija jonu reakcija ir Frīdela–Kraftsa alkilēšana. Lai papildinātu pieejamo klāstu ar elektroķīmiskajām arēnu funkcionalizēšanas reakcijām, tika izpētīta iespēja veikt elektroķīmisku Frīdela–Kraftsa reakciju, izmantojot stannilmetilēterus kā elektroķīmiski aktivējamus karbēnija jonu prekursorus.

Tika konstatēts, ka trimetilstannilmetilēteri ir tikpat efektīvi elektroķīmiskai karbēnija jonu ģenerēšanā kā tributilstannilmetilēteri, uzrādot zemāku redokspotenciālu nekā arēniem. Elektroķīmiski ierosināta modeļreakcija starp stannilmetilēteri **30a** un *O*–TBDMS aizsargātu fenolu HFIP klātbūtnē noritēja ar labu iznākumu un augstu *para*-selektivitāti (4. tab., 1. aile). Ņemot vērā, ka HFIP piemīt vājas skābes īpašības, karbēnija jonu veidošanos HFIP izraisītas solvolīzes rezultātā novēroja pat bez elektriskās strāvas, ja izmantoja lielāku šīs piedevas daudzumu (4. tab., 2. aile). Šī iemesla dēļ tika izpētītas dažādas bāzes, lai reakcijas apstākļi būtu savietojami ar skābes jutīgām funkcionālajām grupām (4. tab., 3.–6. aile). $NaHCO_3$ pievienošana pilnībā novērsa izejvielas solvolīzi, vienlaikus nodrošinot labu produkta iznākumu (4. tab., 6. aile).

4. tabula

Reakcijas apstākļi selektīvai substrāta **30a** elektroķīmiskai aktivēšanai



30a **31a** (2 ekviv.) **32a**

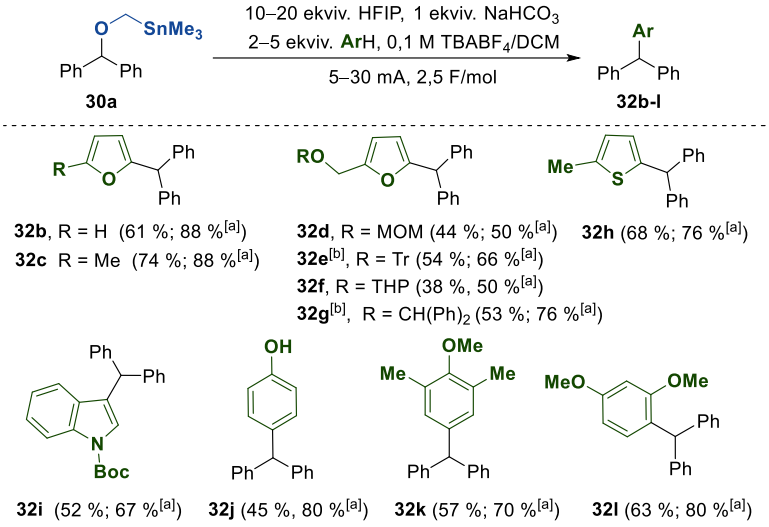
Apstākļi A: I = 2,5 F/mol, 20 mA, grafīta elektrodi, ist. t., 40 min
Apstākļi B: bez strāvas, ist. t., 18 h

Nr.	Piedevas	Apstākļi A **32a** iznākums[a] (%)	Apstākļi B **32a** iznākums[a] (%)
1	nav	63	9
2	papildu HFIP[b]	56	74
3	1 ekviv. 2,6-lutidīns	0	0
4	1 ekviv. PivONa	38	0
5	1 ekviv. $PhCO_2Li$	51	0
6	1 ekviv. $NaHCO_3$	64 (55[c])	0

[a] ^{1}H-KMR iznākums, izmantojot EtOAc kā iekšējo standartu.
[b] Šķīdinātājs: HFIP: DCM 1 : 1.
[c] Izdalītais iznākums.

Kad optimālie elektrolīzes apstākļi bija atrasti, tika izpētīts arēnu klāsts, kas piemērots elektroķīmiskajai Frīdela–Kraftsa reakcijai (6. att.). Furāns un metilfurāns reaģēja ar elektroķīmiski ģenerētu karbēnija jonu, dodot produktus **32b** un **32c** ar labiem iznākumiem. Optimizētie reakcijas apstākļi bija saderīgi ar *O*-aizsargātiem furfurilspirtiem (produkti **32d–g**), kas liecināja par pirmo Frīdela–Kraftsa alkilēšanas piemēru, kas veikts ar skābes jutīgiem (MOM, Tr, THP un -$CHPh_2$) *O*–aizsargātiem substrātiem. Alkilēšanas reakcijai bija piemēroti arī citi heterocikli, piemēram, tiofēns un *N*–aizsargāts indols (produkti **32h**,**i**). Ar elektroniem

bagāti fenola un anizola atvasinājumi bija saderīgi ar elektrolīzes apstākļiem, neraugoties uz to zemajiem redokspotenciāliem. Neaizsargāts fenols, dimetilanizols un 1,3-dimetoksibenzols elektrolīzē deva produktus **32j–l** ar labiem iznākumiem.

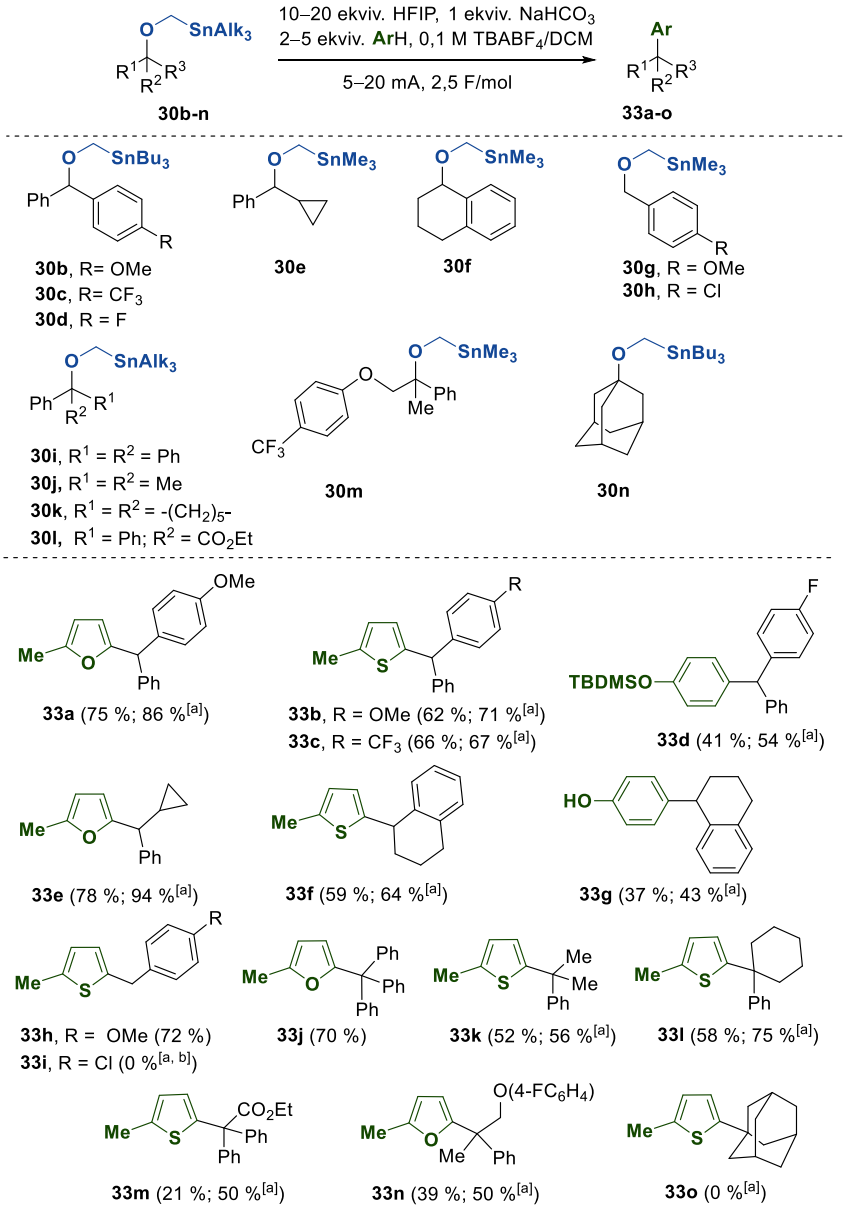


[a] ^{1}H-KMR iznākums, izmantojot EtOAc kā iekšējo standartu [b] 10 ekviv. HFIP

6. att. Elektroķīmiski ierosinātas Frīdela–Kraftsa reakcijas substrātu klāsts.

Stannilmetilēteru klāsts ietvēra substrātus, kas iegūti no difenilmetanola ar dažādiem aizvietotājiem benzola gredzena 4. pozīcijā (7. att.). Diarilmetilkatjoni ar elektrondodošām (izejviela **30b**) un elektronatvelkošām (izejviela **30c**) grupām deva 2-metilfurāna un 2-metiltiofēna alkilēšanas produktus **33a–c** ar labiem iznākumiem. Fluoru saturošs diarilmetilkatjons (no **30d**) reaģēja ar *O*–TBDMS aizsargātu fenolu, dodot nedaudz zemāku produkta **33d** iznākumu, salīdzinot ar nefluorētu analogu (produkts **32a**). Reakcija notika ar benzilkatjona prekursoriem, kas saturēja karbēnija jonu stabilizējošo metoksigrupu (**30g**), savukārt no 4-hlorbenzilsubstrāta **30h** neizdevās iegūt vēlamo produktu **33i**. Trešējā karbēnija jona prekursori deva produktus ar vidēju iznākumu, izņemot adamantilkatjona prekursoru **30n,** kas nedeva gaidīto alkilēšanas produktu **33o**.

Apspriestie rezultāti ir publicēti 2. pielikumā pievienotajā dokumentā.



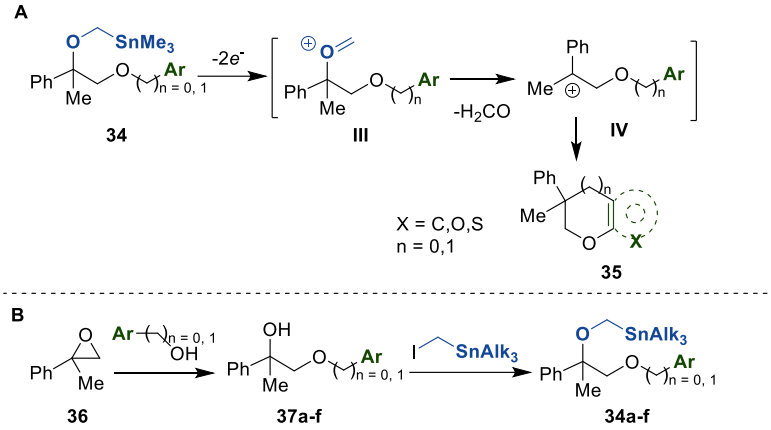
[a] ^{1}H-KMR iznākums, izmantojot EtOAc kā iekšējo standartu, [b] oksonija jonu arilēšanas produkts 35 % pēc KMR.

7. att. Stannilmetilēteru klāsts elektroķīmiski ierosinātai Frīdela–Kraftsa reakcijai.

Tika izstrādāta arī iekšmolekulāra Frīdela–Kraftsa alkilēšana, lai iegūtu kondensētus heterociklus kā reakcijas produktus. Šim nolūkam tika izstrādāti substrāti **34**, kuros iekšējais

(hetero)aromātiskais nukleofīls tika pievienots reakcijas centram ar piemērota garuma savienotājposmu, lai pēc iekšmolekulārās ciklizēšanās veidotos pieclocekļu vai sešlocekļu cikls (8. att., A).

Substrātu sintēzi sāka no epoksīda **36**, ko uzšķēla ar aromātiskiem spirtiem, lai iegūtu iekšmolekulāru nukleofīlu saturošus spirtus **37a–f,** kas pēc tam tika modificēti ar trialkilstannilmetiljodīdu, lai iegūtu izejvielas **34a–f** (8. att., B).

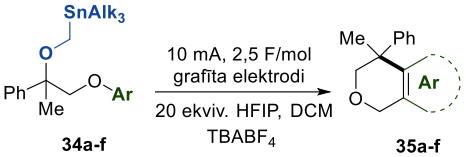


8. att. A) Iekšmolekulāra Frīdela–Kraftsa reakcija;
B) sintēzes ceļš iekšmolekulārās Frīdela–Kraftsa reakcijas izejvielu iegūšanai.

Elektrolīze ar substrātiem, kas satur 3-metoksifenil (**34a**), 3-furfuril (**34b**), 3-benzofurfuril- (**34d**) un 3-tienilgrupu (**34e**) kā iekšējo nukleofīlu, deva attiecīgos kondensētus sešlocekļu heterociklus **35a**,**b**,**d**,**e** ar vidēju līdz zemu iznākumu (5. tab.). Elektrolīzes apstākļos netika novērota kondensēta pieclocekļu cikla **35f** veidošanās, kā arī savienojums **34c** nedeva vēlamo ciklizēšanas produktu, jo elektroķīmiskās reakcijas laikā tika nošķelta 2-furfurilgrupa.

5. tabula

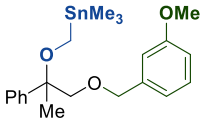
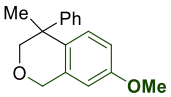
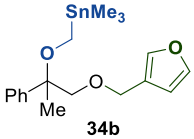
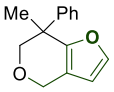
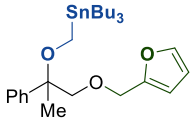
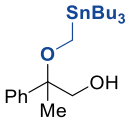
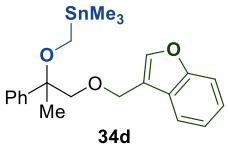
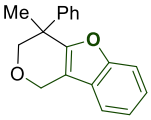
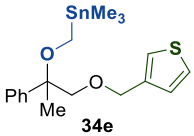
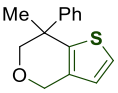
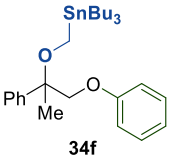
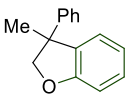
Iekšmolekulārās Frīdela–Kraftsa alkilēšanas produktu klāsts



34a-f

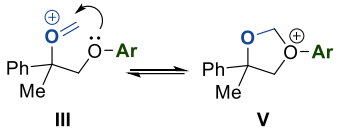
Alk = Me, Bu

35a-f

Nr.	Izejviela **34**	Produkts **35**	Produkts, iznākums (KMR iznākums), %
1	 **34a**	 **35a**	46 (60[a])
2	 **34b**	 **35b**	30 (31[a])
3	 **34c**	 **38**	22
4	 **34d**	 **35d**	32 (39[a])
5	 **34e**	 **35e**	17 (32[a])
6	 **34f**	 **35f**	0

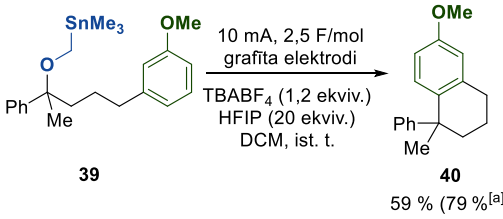
[a] ^{1}H-KMR iznākums, izmantojot EtOAc kā iekšējo standartu.

Iekšmolekulārās Frīdela–Kraftsa reakcijas samazinātos iznākumus, salīdzinot ar starpmolekulāro Frīdela–Kraftsa reakciju, varētu izskaidrot ar oksonija jona **III** vājo fragmentāciju tā stabilizācijas dēļ, veidojoties cikliskai sistēmai **V**, kas ir līdzsvarā ar **III** (9. att.).



9. att. Oksonija jona stabilizācija ar blakus esošā skābekļa nedalīto elektronu pāri.

Izejvielu elektroķīmiskā metanolizēšana norādīja, ka metanola pievienošanās oksonija jonam ir galvenais reakcijas ceļš, un metoksimetilētais starpprodukta **III** (8. att., A) pievienošanās produkts tika iegūts ar augstāku iznākumu nekā metoksilētā starpprodukta **IV** (8. att., A) pievienošanās produkts. Papildus tika sintezēts izejvielas **34a** analogs **39**, kas nesatur papildu skābekļa atomu, tāpēc nav iespējama oksonija jona stabilizācija. Savienojums tika pakļauts elektrolīzes standartapstākļiem, kuros tika iegūts produkts **40** (10. att.).



[a] ^{1}H-KMR iznākums, izmantojot EtOAc kā iekšējo standartu

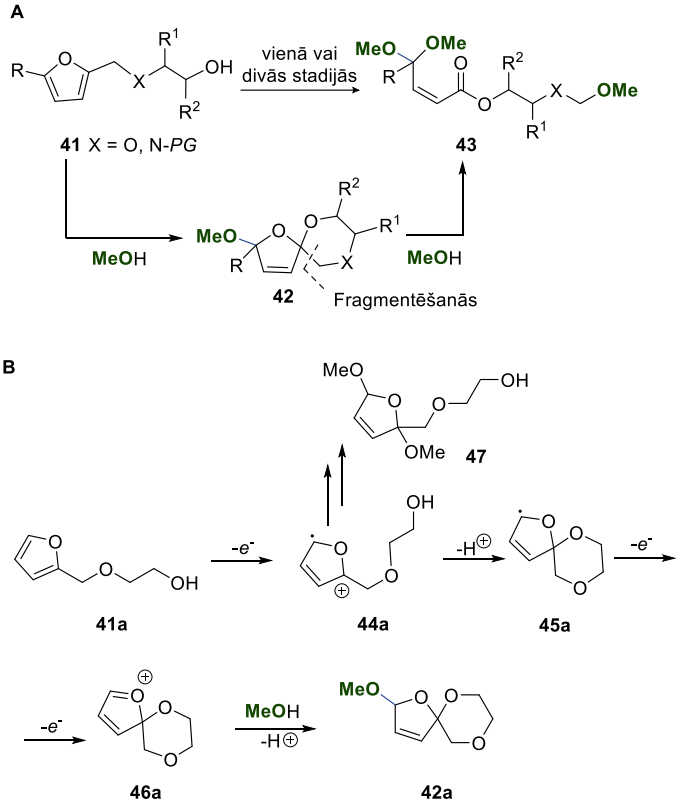
10. att. Karbocikla **40** iegūšana iekšmolekulāras Frīdela-Kraftsa reakcijas ceļā.

Attiecīgais karbocikls **40** veidojās ar paaugstinātu iznākumu, salīdzinot ar ētera saiti saturošo substrātu **34a**, kas apstiprina oksonija jonu stabilizācijas nozīmi, kavējot kondensētu heterociklu veidošanos.
Apspriestie rezultāti ir publicēti 3. pielikumā pievienotajā dokumentā.

2. Furfurilētu etilēnglikolu Torija tipa elektroķīmiskā oksidēšana

Elektroķīmiskā sintēze ir noderīgs rīks ne tikai paaugstinātas pievienotās vērtības reaģentu/izejvielu iegūšanai, bet arī biomasas valorizācijai. Furāna atvasinājumi ir īpaši piemēroti substrāti elektroķīmiskai funkcionalizēšanai, jo furāna gredzenam piemīt zems oksidēšanās potenciāls, kas ļauj veikt elektroķīmiskas pārvērtības, neizmantojot elektropalīggrupas. Šī darba daļa tika veltīta Torija (*Torii*) tipa elektroķīmiskās oksidēšanas izpētei furānmetilatvasinājumos **41**, kuros hidroksilgrupa kalpo kā iekšējais nukleofīls.

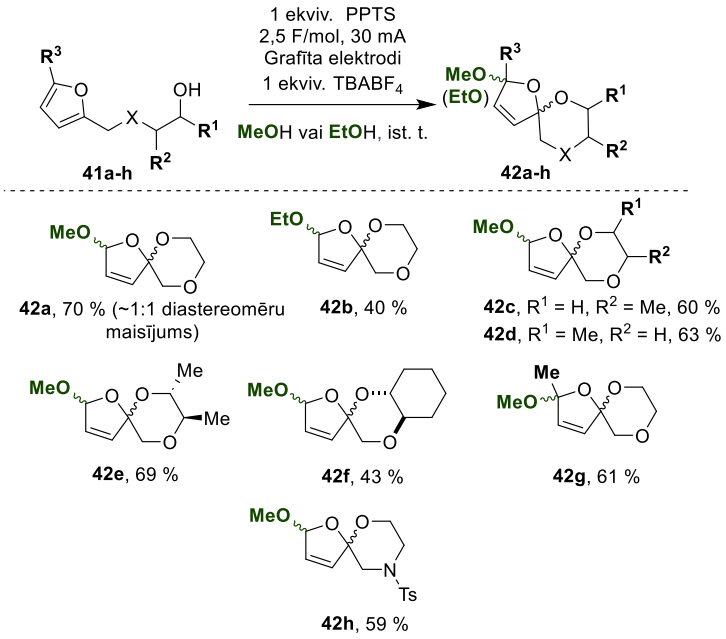
Paredzamie reakcijas produkti ir spirocikliski atvasinājumi **42**, ko tālāk varētu pakļaut fragmentācijai, lai iegūtu produktus **43** ar funkcionalizētu estera daļu. Produkti **43** varētu būt vērtīgi būvbloki tālākām ķīmiskām pārvērtībām. Spirocikla veidošanās sākas ar viena elektrona pāreju savienojumā **41a**, veidojot katjonradikāli **44a** (11. att., B), kas pēc deprotonēšanas un iekšmolekulāras ciklizēšanas dod starpproduktu **45a**. Tālāka **45a** oksidēšana dod oksonija jonu **46a,** kas pēc metanola pievienošanas dod spirociklu **42a**.



11. att. A) Torija tipa nepiesātināto esteru elektrosintēze;
B) spirocikla **42a** elektroķīmiskais veidošanās mehānisms.

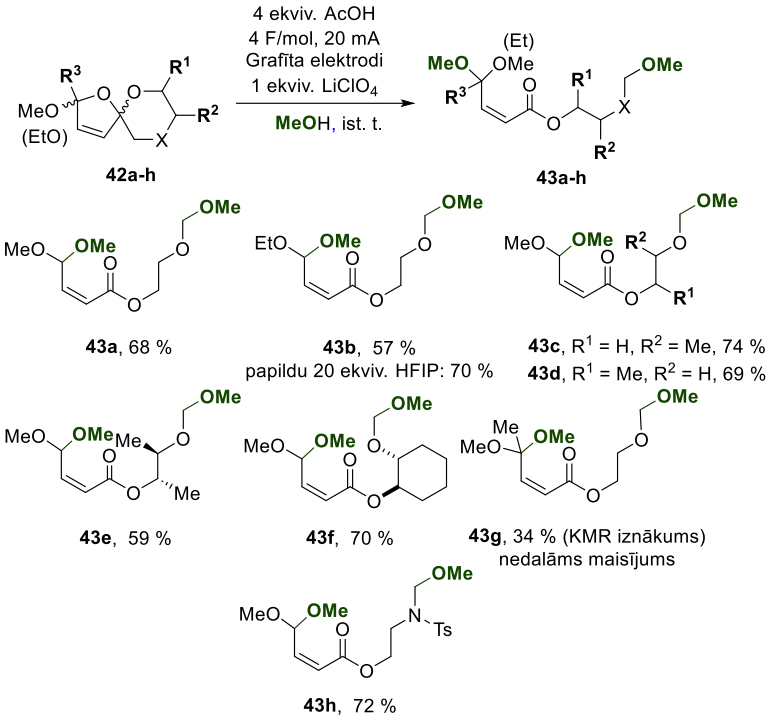
Elektroķīmiski ierosināta spirociklu **42** veidošanās tika realizēta nedalītā šūnā, izmantojot grafīta elektrodus (12. att.). Par šķīdinātāju tika izvēlēts metanols, jo tas spēj kalpot gan kā protonu donors katodiskajai reakcijai, gan arī kā nukleofīls, savukārt $TBABF_4$ tika izvēlēts kā fona elektrolīts. Lai novērstu iespējamo furāna gredzena dimetoksilēšanu (savienojums **47**, 11. att.) ar metoksīda anjonu, tika pētītas dažādas piedevas, kas veicinātu katodisko reakciju. Tika konstatēts, ka HFIP piedeva nodrošina spirociklu iegūšanu ar labu iznākumu, tomēr kā blakusprodukts veidojās ievērojams daudzums estera **43**, taču, pievienojot reakcijai PPTS,

vēlamais produkts veidojās ar augstu iznākumu bez ievērojama blakusproduktu daudzuma. Optimālie elektrolīzes apstākļi bija piemēroti spirta **41a** oksidēšanai līdz spirociklam **42a** līdz pat 500 mg izejvielas apjomam. Spirocikla sintēzes iespējas tika izpētītas arī no citiem furfurilfragmentu saturošiem etilēnglikola un aminoetanola atvasinājumiem, lai iegūtu produktus **42b–h** ar vidēji labiem vai labiem iznākumiem. Etanols bija piemērots šķīdinātājs un ārējais nukleofīls, lai attiecīgais produkts **42b** tiktu iegūts, lai arī ar zemāku iznākumu, nekā izmantojot metanolu.



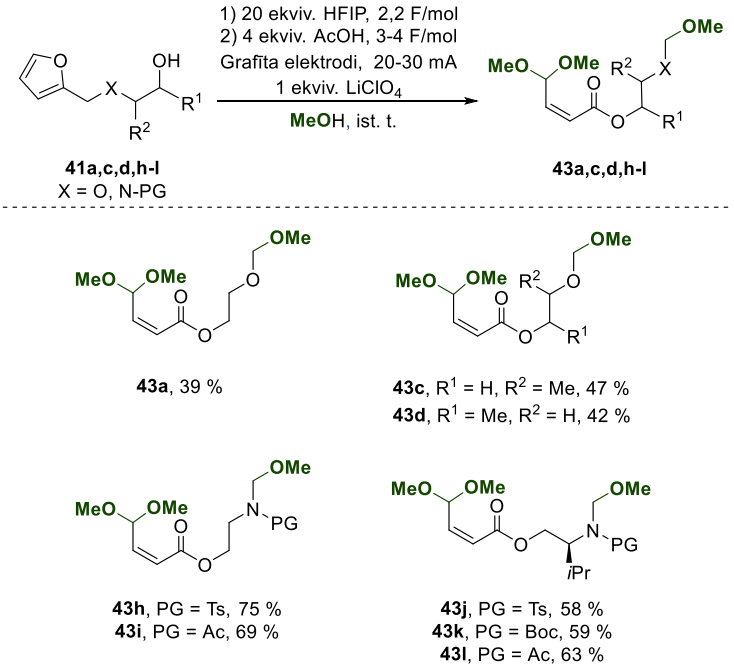
12. att. Spirociklu **42** elektroķīmiskās sintēzes klāsts.

Iegūto spirociklu elektrooksidatīvā fragmentēšana deva esterus **43**. Šim reakcijas solim PPTS nomainīja pret AcOH, jo PPTS blakusprodukti ar laiku mēdza nogulsnēties uz elektrodiem. Tika konstatēts, ka esteru veidošanai $LiClO_4$ ir labāks fona elektrolīts nekā $TBABF_4$. Optimizētajos apstākļos esteri **43a–h** veidojās selektīvi ar dubultās saites *Z* konfigurāciju (13. att.). Kad elektrolīzei tika pakļauts substrāts **42b**, transacetalizēšana ar metanolu netika novērota un veidojās tikai jauktais acetāls **43b**.



13. att. Elektroķīmiski iegūstamo esteru **43** klāsts no spirocikliem **42**

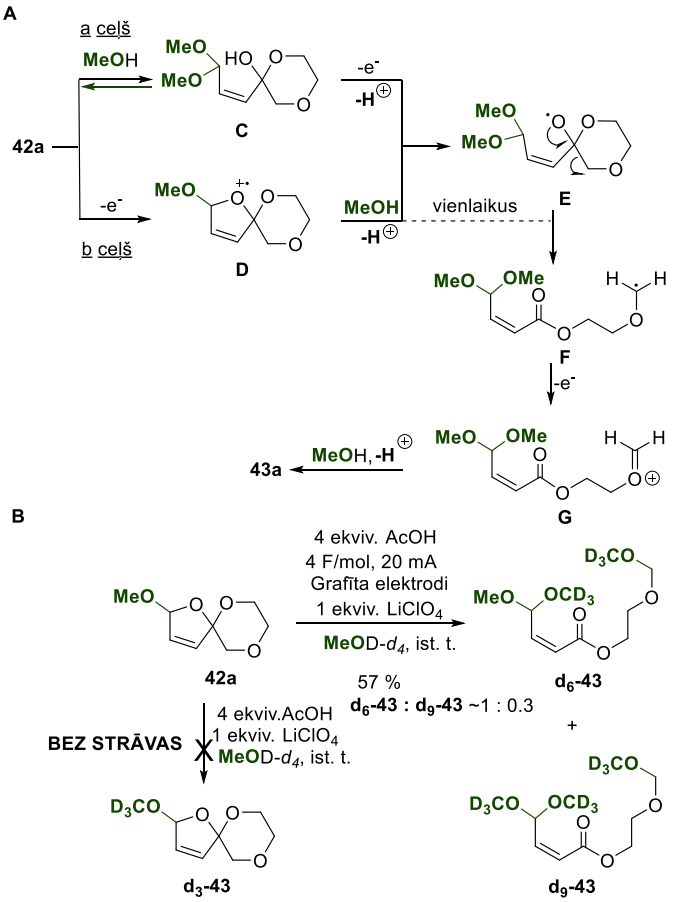
Spirtu **41** pārvērtību par esteriem **43** var veikt arī vienā solī (14. att.). Lai izvairītos no PPTS nogulsnēšanās ilgstošas elektrolīzes laikā, pirmajā posmā kā piedevu izmantoja HFIP, reakcijas otrā posma veicināšanai pievienoja AcOH. Pārvērtības veikšana vienā solī bija īpaši piemērota *N*-aizsargātu *O*-furfurilaizvietotu aminospirtu **43h–l** pārveidošanai. Viena soļa **43k** elektrosintēzi varēja veikt arī viena grama mērogā.



14. att. Spirtu **41** oksidatīvā fragmentēšanās vienā solī līdz esteriem **43**.

Piedāvātais estera **43** veidošanās mehānisms no spirocikla **42** sākas ar atgriezenisku S_N-tipa acetāla metanolīzi, kas rada starpproduktu **C**. Elektroķīmiska radikāļa **C** oksidēšana dod *O*-centrētu radikāli **E**, kas fragmentējas līdz *α*-oksi stabilizētam *C*-centrētam radikālim **F** (15. att., A, a ceļš). Otrs iespējamais reakcijas ceļš (b ceļš) paredz, ka, elektroķīmiski aktivējot acetāla grupu spirociklā **42a**, varētu veidoties katjonradikālis **D**. Pēc tam gredzens tiktu uzšķelts metanolīzes ceļā, iegūstot *O*-centrētu radikāli **E**.

Mehānisma izpētei elektrolīze tika veikta deiterētā metanolā gan elektriskās strāvas klātbūtnē, gan bez tās. Reakcijā, kurā netika izmantota strāvas padeve, neveidojās iespējamais produkts **d_3-43** (15. att., B), kas līdzsvara procesā veidotos caur a ceļu, tāpēc tika secināts, ka spirocikla metanolīzei ir nepieciešama elektroķīmiska aktivēšana (b ceļš).



15. att. A) Piedāvātais mehānisms estera **43a** iegūšanai no spirocikla **42a**;
B) deitērija iezīmēšanas eksperimenti, kas apstiprina estera **43a** veidošanās mehānismu caur *b* ceļu.

Apspriestie rezultāti ir publicēti 4. pielikumā pievienotajā dokumentā.

SECINĀJUMI

1. Trialkilstannilmetilgrupa ir piemērota elektropalīggrupa karbēnija jonu iegūšanai no trialkilstannilmetilēteriem, inicējot oksonija jona fragmentēšanos.
2. Karbēnija jonus var elektroķīmiski ģenerēt no stannilmetilēteriem nedalītā šūnā alilsilānu klātbūtnē. Elektroķīmiski ģenerētie karbēnija joni viegli reaģē ar alilsilāniem.
3. Elektroķīmiskā Frīdela–Kraftsa alkilēšana ar trialkilstannilmetilēteri 1,1,1,3,3,3-heksafluorpropān-2-olā , kā piedevu izmantojot $NaHCO_3$, ir lietota substrātiem, kas satur skābes jutīgas funkcionālās grupas, piemēram, TBDMS, Tr, THP, MOM un -$CHPh_2$.
4. Elektroķīmiski ierosinātas iekšmolekulāras Frīdela–Kraftsa alkilēšans ceļā, saslēdzoties sešlocekļu ciklam, iespējams iegūt kondensētus heterociklus. Produkta veidošanos kavē starpprodukta, oksonija jona, iekšmolekulāra stabilizēšana.
5. Etilēnglikola un aminoetanola atvasinājumi, kas satur furfurilgrupu, metanolā elektroķīmiski oksidējoties furāna gredzenam, veido spirociklus.
6. Spirociklu **42** elektroķīmiskā oksidēšana ļauj iegūt α,β-nepiesātinātus esterus. Pārvērtību iespējams veikt arī vienā solī no *O*-furfurilaizvietotiem etilēnglikoliem un aminospirtiem.
7. Eksperimenti ar deitērija iezīmētu metanolu apstiprina, ka elektroķīmiskai aktivēšanai ir izšķiroša nozīme spirocikla atvasinājumu pārveidošanā par α,β-nepiesātinātiem esteriem.

DOCTORAL THESIS PROPOSED TO RIGA TECHNICAL UNIVERSITY FOR THE PROMOTION TO THE SCIENTIFIC DEGREE OF DOCTOR OF SCIENCE

To be granted the scientific degree of Doctor of Science (Ph. D.), the present Doctoral Thesis has been submitted for the defence at the open meeting of RTU Promotion Council on June 1, 2023 at 14.00 at the Faculty of Materials Science and Applied Chemistry, 3/7 Paula Valdena Street, Room 272.

OFFICIAL REVIEWERS

Associate Professor Dr. chem. Kaspars Traskovkis,
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Assistant Professor Ph. D. Helena Lundberg,
KTH Royal Institute of Technology, Sweden

DECLARATION OF ACADEMIC INTEGRITY

I hereby declare that the Doctoral Thesis submitted for the review to Riga Technical University for the promotion to the scientific degree of Doctor of Science (Ph. D.) is my own. I confirm that this Doctoral Thesis had not been submitted to any other university for the promotion to a scientific degree.

Anna Lielpētere ……..….
(signature)
Date …...……...….

The Doctoral Thesis has been prepared as a collection of thematically related scientific publications complemented by summaries in both Latvian and English. The Doctoral Thesis unites four scientific publications. The scientific publications have been written in English, with a total volume of 79 pages, including supplementary data.

TABLE OF CONTENTS

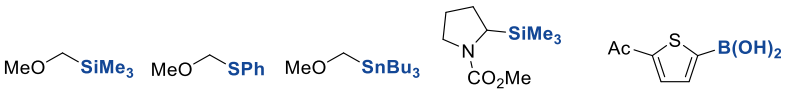
ABBREVIATIONS

Ac – acetyl
Alk – alkyl
Ar – aryl
Boc – *tert*-butoxycarbonyl
Bu – butyl
DCM – dichloromethane
EAux – electroauxiliary group
E^{ox} – peak oxidation potential
Equiv – equivalents
Et – ethyl
HFIP – 1,1,1,3,3,3-hexafluoro-2-propanol
Me – methyl
MeCN – acetonitrile
MOM – methoxymethyl
NMR – nuclear magnetic resonance spectroscopy
PG – protecting group
Ph – phenyl
Piv – pivalic
PPTS – pyridinium *p*-toluenesulfonate
r.t. – room temperature
SHE – standard hydrogen electrode
TBA - tetrabutylammonium
$TBABF_4$ – tetrabutylammonium tetrafluoroborate
TBDMS – *tert*-butyldimethylsilyl
THP – 2-tetrahydropyranyl
Tr – trityl
Ts – tosyl

GENERAL OVERVIEW OF THE THESIS

Introduction

In the last decade, synthetic organic electrochemistry has received renewed interest due to technological advances and its contribution to sustainable chemistry. Electrochemistry offers many advantages, such as new reaction pathways, scalability, ambient conditions, and controlled generation of reactive intermediates.[1–3] Reaction times can be predicted and modulated by changing the applied current.[4] Electrochemistry enables energy input directly into a molecule, avoiding using molecular energy carriers.[5] Electrons are directly transferred between the electrode surface and the organic molecule, producing reactive intermediate species. The concentration of the reactive intermediates depends on the current density applied, which is a measure of the rate of electron movement. Meanwhile, the electric potential characterises the driving force of the redox process. An electrochemical reaction can be performed either at constant potential or constant current mode. Constant potential electrolysis allows fine reactivity control, as the potential is controlled via the reference electrode. Usually, this type of reaction requires a divided cell where the working and the counter electrode are in separate compartments divided by a membrane or a frit, complicating the setup and increasing the resistance of the cell. On the other hand, constant current electrolysis can often be performed in a beaker-type cell. During constant current electrolysis, the species with the lowest redox potential are consumed, and chemoselectivity can be improved by using redox mediators or electroauxiliaries – functional groups that promote electron transfer.[3, 6] Known electroauxiliaries include silyl groups[7–9] (e.g. in Fig. 1, compounds **1**, **4**), stannanes[10–12] (e.g. in Fig. 1, compound **3**), arylthiols[13] (e.g. in Fig. 1, compound **2**) and organoboronic acids[14] (e.g. in Fig. 1, compound **5**) that have been used to lower the redox potential of carbamates[7, 11], alkoxycarbonyl compounds[10], ethers[8, 9, 11–13], alkenes[15], sulfides[15], and arenes[14].



1 1.60 V | **2** 1.40 V | **3** 0.91 V | **4** 1.23 V | **5** 2.5 V; 2.1 V in the presence of F^-

Fig. 1. Representative examples of known electroauxiliaries and their respective redox potentials (vs SHE).

One of this Thesis objectives is to explore the use of electroauxiliary groups for the generation of carbenium ions. Anodic oxidation enables the generation of carbenium ions (e.g. in Fig. 2 A, compound **7** from compound **6**) without the use of stoichiometric oxidants, while proton reduction to hydrogen at the cathode serves as a neutral paired reaction (Fig. 2 A). However, only some nucleophiles are compatible with the oxidation potential required for

substrate activation allowing to obtain compounds **8**. To expand the nucleophile scope, the Yoshida group developed an electrochemical cation pool methodology using starting materials **9** (Fig. 2 B) modified with an electroauxiliary (EAux) group. In this method, ions **10** (Fig. 2 B) are accumulated at low temperatures, followed by an "ex-cell" addition of a nucleophile to form products **11** (Fig. 2 B).[6] Even though the cation pool methodology is a powerful approach, it requires a complex setup with a divided cell, low temperatures and a large amount of trifluorosulfonic acid for the cathodic reaction. Preferable would be electrosynthesis in an undivided cell where carbenium ions are generated in the presence of nucleophiles. For this, the redox potential of substrates **6** and **9** must be lower than that of the nucleophile. Therefore, the use of electroauxiliary groups for carbenium ion generation enabled the use of various carbon nucleophiles in this Thesis.

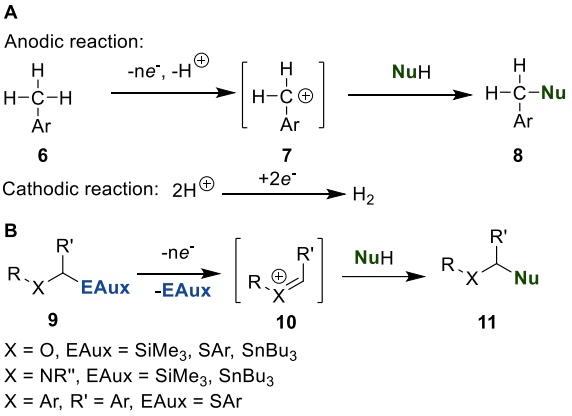


Fig. 2. A – Direct electrochemical oxidation followed by reaction with a nucleophile; B – electrochemical oxidation *via* electroauxiliary.

Additionally, electrochemistry can contribute to sustainable chemistry by offering methods for the valorisation of biomass.[2, 16, 17] Furan derivatives (e.g. in Fig. 3, compound **12**) are particularly suitable substrates for electrochemical functionalisation due to the low oxidation potential of the furan ring to form radical cations **12**$^{\bullet+}$, which allows transformation into various products like **14**, **15**, and **16** without the use of electroauxiliary groups (Fig. 3).

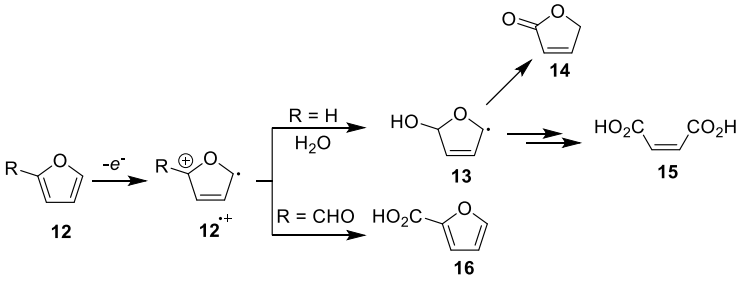


Fig. 3. Electrooxidative furan derivative valorisation products.[18].

To have a practical application in a synthetic lab, electrochemical methods benefit from operational simplicity, that is, employing an undivided cell, cheap electrode materials and simple equipment like the commercially available Electrasyn 2.0 potentiostat from IKA or even a battery.[1] For industrial applications, the safety, selectivity and yield as well as low energy and atom consumption of the electrosynthetic reactions are important factors. Electrochemical reactions such as the synthesis of adiponitrile (*Monsanto*), methoxylation of substituted toluene (*BASF*), oxidation of anthracene to anthraquinone (*ECRC*), reduction of maleic anhydride to succinic acid (*CERCI*) and methoxylation of 2-methyl-2,5-dimethoxyfuran as an intermediate for 2-methyl-3-mercaptofuranproduction (*Tengzhou Tianshui Biological Technology Co.)* are some examples of electrosynthetic reactions currently in practical industrial use.[19]

Both for laboratory and industrial application, especially attractive are methodologies that offer new reaction pathways, are usable for late-stage functionalisation with high functional group tolerance or show easy ways to perform traditionally complicated reactions without employing toxic or highly reactive reagents.[1] For these reasons, synthetic methodologies developed as part of this Thesis use an undivided cell and cheap graphite electrodes fitted to the commercially available Electrasyn potentiostat.

Aims and objectives

The main goal of the Thesis is to develop new operationally simple electrochemical methods for organic synthesis via electrochemically generated carbenium ions.

To fulfil this goal, the following tasks were set:

1. To find a suitable electroauxiliary for the generation of carbenium ions (via fragmentation of the oxonium ions).
2. To develop a new method for electrochemical allylation of carbenium ions formed by electrochemical activation of substrates modified with electroauxiliary.
3. To develop an electrochemical method for Friedel-Crafts alkylation in the presence of acid-labile substrates.
4. To demonstrate an intramolecular Friedel-Crafts alkylation for the synthesis of condensed heterocycles.
5. To investigate the valorisation of furan derivatives by the reactions of electrochemically generated radical cations.

Scientific novelty and main results

As the result of the Thesis, operationally simple electrochemical methods for new bond formation via carbenium ion generation have been developed. Trialkylstannylmethyl group has been established as a suitable electroauxiliary for carbenium ion formation via the

fragmentation of oxonium ion that enables the synthesis of carbenium ion precursors from alcohols as readily available starting materials. The low redox potential of trialkylstannylmethyl electroauxiliary allows selective electrooxidation in an undivided cell in the presence of nucleophiles. The carbenium ion formation was further promoted using 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as an additive. An electrochemical allylation method with allyltrimethylsilanes was demonstrated. The electrochemical carbenium ion generation method was further extended for Friedel-Crafts alkylation by using arenes as nucleophiles. The use of $NaHCO_3$ as a basic additive rendered the electrolysis conditions compatible with sensitive acid-labile functional groups, including TBDMS, Boc, Tr, MOM, THP, and $CHPh_2$ protecting groups. An intramolecular Friedel-Crafts alkylation was demonstrated where the formation of 6-membered cycles furnished new condensed heterocycles.

Ethylene glycol and amino ethanol derivatives containing furfuryl moiety formed spirocycles upon electrochemical oxidation in methanol. Upon further oxidation, the spirocycles could be transformed into α,β-unsaturated esters with complete *Z*-selectivity. The ester synthesis from biomass-derived starting materials can be done in two steps or by using a one-pot protocol giving multifunctional building blocks and tailored monomers for polymerisation.

Structure and volume of the Thesis

The Thesis is a collection of thematically related scientific publications on developing new electrochemical methods for carbenium ion generation and use in reactions. The Thesis compiles results from 4 original scientific papers indexed in Scopus and Web of Science.

Publications and approbation of the Thesis

The results of the Thesis have been published in 4 scientific papers. Additionally, the results have also been disseminated at 8 scientific conferences.

Publications:

1. **Lielpetere, A.**; Jirgensons, A. Carbenium ion formation by fragmentation of electrochemically generated oxonium ions. *Org. Biomol. Chem.*, **2018**, 16, 5094–5096.
2. **Lielpetere, A.**; Jirgensons. A. Friedel–Crafts Alkylation with Carbenium Ions Generated by Electrochemical Oxidation of Stannylmethyl Ethers. *Eur. J. Org. Chem.*, **2020**, 4510–4516.
3. Darzina, M.; **Lielpetere, A.**; Jirgensons, A. Torii-Type Electrosynthesis of *α,β*-Unsaturated Esters from Furfurylated Ethylene Glycols and Amino Alcohols. *Eur. J. Org. Chem.* **2021**, 4224.
4. **Lielpetere, A.**; Šilaks, A.; Jirgensons, A. Intramolecular Friedel–Crafts alkylation by electrochemical carbenium ion generation. *Chem. Heterocycl. Compd.* **2022**, 58(*12*), 732–736.

Conference participation:

1. **Lielpētere, A.**; Turovska, B.; Jirgensons, A. Electrochemical generation of carbocations and their reactions with nucleophiles. *Electrochemistry 2016*, Goslar, Germany, September 26–28, **2016**.
2. **Lielpētere, A.** Electrochemical generation of carbenium ions via Electroauxiliary. *10th Paul Walden Symposium on Organic Chemistry*. Riga, Latvia, June 5–16, **2017**.
3. **Lielpētere, A.** Electrochemical Generation of Carbenium Ions via Electroauxiliary and Their Reactions with Nucleophiles. *50t^{h} Heyrovský Discussion on Molecular Electrochemistry in Organic and Organometallic Research.* Třešť, Czech Republic, June 18–22, **2017**.
4. Dārziņa, M.; **Lielpētere, A.**; Jirgensons, A. Electrochemical Generation of Carbenium Ions and Their Reactions with Nucleophiles. *International Conference on Organic Synthesis BOS 2018*, Tallinn, Estonia, July 1–4, **2018**, PO58.
5. **Lielpetere, A.**; Jirgensons, A. Electrochemical generation of carbenium ions and their reactions with nucleophiles. *Electrochemistry 2018*, Ulm, Germany, September 24–26, **2018**, H059.
6. **Lielpētere, A.**; Jirgensons, A. Electrochemical generation of carbenium ions and their Friedel-Crafts reactions. *Beilstein Organic Chemistry Symposium "Electrifying Organic Synthesis"*, Mainz, Germany, April 9–11, **2019**.

7. **Lielpētere, A.**; Jirgensons, A. Friedel-Crafts reactions of electrochemically generated carbenium ions. *Giornate dell'Elettrochimica Italiana - GEI2019*, Padua, Italy, September 8–12, **2019**.
8. **Lielpētere, A.**; Jirgensons, A. Generation of carbenium ions by electrochemical leaving group activation. *11th Paul Walden Symposium*, Riga, September 19–20, **2019**.

MAIN RESULTS OF THE THESIS

1. Electrochemical carbenium ion generation via electroauxiliaries and their reactions with nucleophiles

For the electrochemical generation of carbenium ions, we envisioned a two-step process. The electrochemical activation of the electroauxiliary in starting material **17** would generate an oxonium ion **18**, which would undergo *in situ* fragmentation to carbenium ion **19** (Fig. 4 A). The two-step process would enable the generation of the substrates from alcohols as readily available starting materials.

We tested oxyacetic acid (**17a**), silylmethyl (**17b**) and stannylmethyl ether (**17b**) functional groups as electroauxiliaries (Fig. 4 B). From these, stannylmethyl ether had the lowest redox potential of 1.7 V in compound **17c** (vs SHE).

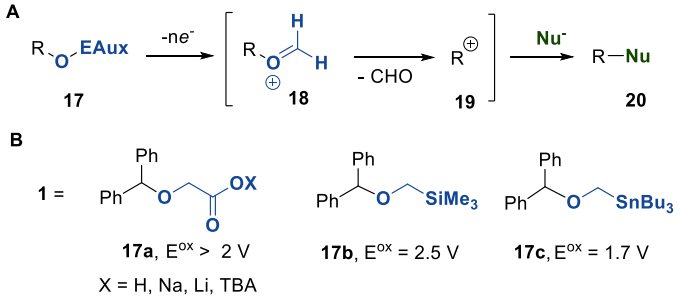


Fig. 4. A – Carbenium ion generation via oxonium ion fragmentation; B – tested electroauxiliaries and their oxidation potentials (vs SHE).

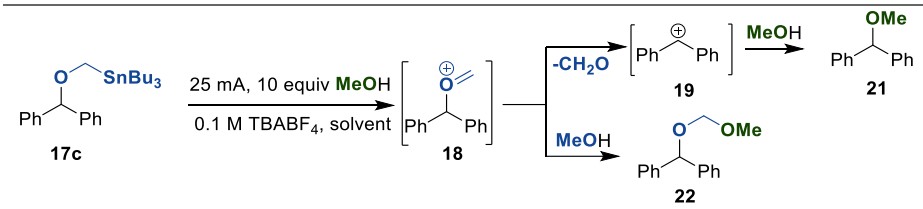
Stannylmethyl ether group was chosen as the electroauxiliary group for the generation of carbenium ions *via* oxonium ion fragmentation. The substrates were synthesised in one step from the corresponding alcohols. The reaction between alcohol and tributyl(iodomethyl)stannane required a strong base, KH.

The generation of carbenium ions from tributhylstannylmethylethers demanded not only the cleavage of *C–Sn* bond, but also an effective fragmentation of the oxonium ion in the electrolysis conditions. The effectiveness of the fragmentation was investigated by electrochemical methanolysis in various solvents (Table 1). In this case, methanol served as the proton donor for the cathodic reaction while the formed methanoate acted as a nucleophile for reaction with the electrochemically formed electrophilic species **18** and **19**. When ((benzhydryloxy)methyl)tributylstannane (**17c**) was subjected to a constant current electrolysis in methanol or acetonitrile as the electrolysis solvent, oxonium **18** and carbenium **19** ion products **21** and **22** formed in equimolar ratio in a moderate yield (Table 1, entries 1 & 2). A substantial improvement in selectivity and yield of carbenium ion product **21** was observed

with HFIP as the reaction solvent (Table 1, entry 4). HFIP is known to stabilise cation and radical cation intermediates due to its hydrogen bond donor ability, low nucleophilicity, and the ambivalent polarity domains of the molecule.[20] Some product formation due to ionisation of the starting materials promoted by the hydrogen bond donating character of the HFIP was also observed in the absence of electricity; however, the use of electrical current was crucial to provide products in high yields.

Table 1

Electrochemical activation of substrate **17c** in the presence of MeOH



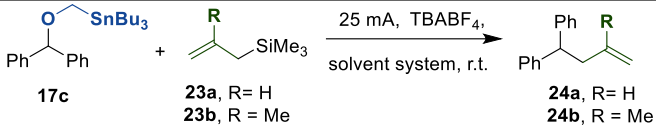
Entry	Solvent	Ratio **21** : **22**	Yield of **21** & **22** (%)[a]
1	MeOH	1 : 1.1	50
2	MeCN	1.3 : 1	50
3	DCM	7.5 : 1	85
4	**HFIP**	**>99 : 1**	**73**

[a] Total ^{1}H-NMR yield of products **21** and **22** using 1,4-bis-trichloromethylbenzene as the internal standard.

Next, the application of other nucleophiles for the reaction with electrochemically generated carbenium ions was explored. The optimal reaction conditions employed dichloromethane (DCM) as a solvent with HFIP as an additive to promote the cathodic reaction and fragmentation of the oxonium ion (Table 2, entries 2 & 3). The electrolysis was performed using a simple and robust setup in an undivided cell equipped with graphite electrodes at room temperature and ambient atmosphere. Allylsilanes **23a** and **23b** were compatible with the electrochemical reaction conditions for formation of a *C–C* bond upon reaction with the generated carbenium ions.

Table 2

Electrochemical activation of substrate **17c** in the presence of allylsilanes



17c | **23a**, R= H; **23b**, R = Me | **24a**, R= H; **24b**, R = Me

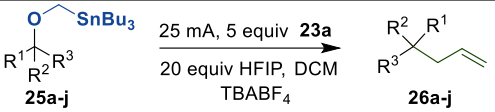
Entry	**23**, solvent system	**24**, yield (%)
1	**23a**, HFIP	**24a**, 40 (NMR)[a]
2	**23a**, DCM, 20 equiv HFIP	**24a**, 87 (isolated)
3	**23b**, DCM, 20 equiv HFIP	**24b**, 64 (isolated)

[a] ^{1}H-NMR yield using 1,4-bis-trichloromethylbenzene as the internal standard.

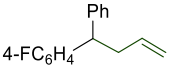
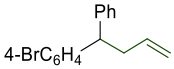
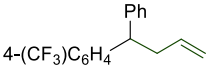
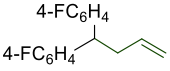
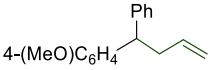
The scope of the stannylmethylethers (Table 3) included substrates derived from diphenylmethanols containing electron-withdrawing (products **26a-d**) and electron-donating (**26f**) substituents. Phenylcyclopropylmethyl and phenylcyclohexyl carbenium ions also provided the corresponding allylation products **26f** and **26i**. Tertiary carbenium ions reacted with allylsilane giving products **26g-h** in low yields. Less stable carbenium ions were formed inefficiently – methoxybenzylic ether gave product **26j** in a poor yield.

Table 3

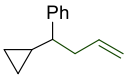
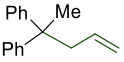
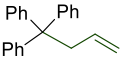
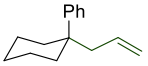
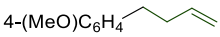
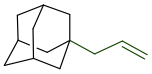
Substrate scope for the electrochemical allylation



25a-j | **26a-j**

Entry	Product	**26**, yield (%)
1		**26a**, 74
2		**26b**, 79
3		**26c**, 76
4		**26d**, 81
5		**26e**, 72

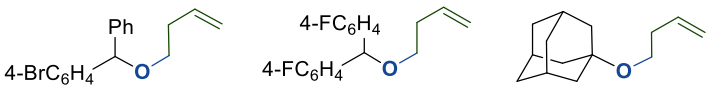
Continuation of Table 3

6		**26f**, 91
7		**26g**, 26[a]
8		**26h**, 42[b]
9		**26i**, 75
10		**26j**, 14
11		**26k**, 0

[a] 1,1-Diphenylethylene (20 %) was isolated as a side product.

[b] ^{1}H-NMR yield using 1,4-bis-trichloromethylbenzene as the internal standard; obtained as an inseparable mixture with triphenylmethane.

When less stable carbenium ions were formed, oxonium ion allylation products could be isolated (Fig. 5). In the case of the adamantlyl ether, oxonium ion addition product **29** was the major product. The results discussed have been published in the paper attached in Appendix 1.



27, 6 % **28**, 6 % **29**, 44 %

Fig. 5. Isolated oxonium ion allylation products.

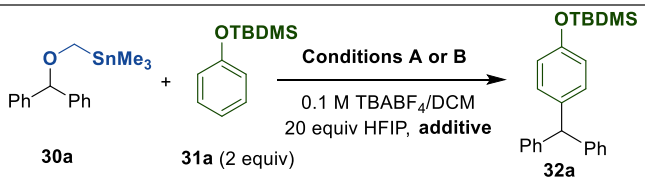
After successfully developing a method for carbenium ion formation *via* electrochemical oxidation of stannylmethyl ether and fragmentation of the intermediate oxonium ion, we explored using other nucleophiles for *C–C* bond formation. Electrochemistry offers an attractive tool for carbenium ion generation in an acid-free medium, while most carbenium ion generation techniques require a Lewis or Broensted acid. An important reaction proceeding through carbenium ion formation is Friedel-Crafts alkylation. To complement the recent advances in electrochemical arene functionalisation, we explored an electrochemical Friedel-Crafts reaction using stannylmethyl ethers as electrochemically activated carbenium ion precursors.

Trimethylstannylmethyl ethers were just as effective for the electrochemical carbenium ion generation as the tributylstannylmethyl ethers. Both functional groups exhibited a lower redox

potential than the nucleophiles (arenes). An electrochemically induced Friedel-Crafts reaction between stannylmethyl ether **30a** and *O*–TBS protected phenol **31a** was chosen as a model reaction. The product **32a** was obtained with a good yield and high *para*-selectivity when HFIP was used as an additive for the electrolysis (Table 4). However, due to the slightly acidic nature of HFIP, carbenium ion formation due to HFIP-induced solvolysis was observed even without the electric current when larger amounts of the additive were used (Table 4, entry 2). Therefore, basic additives were screened to render the reaction conditions compatible with acid-labile functional groups (Table 4, entries 3–6). $NaHCO_3$ was found to completely suppress the solvolysis of the starting material while delivering the product in a good yield (Table 4, entry 6).

Table 4

Reaction conditions for selective electrochemical activation of substrate **30a**



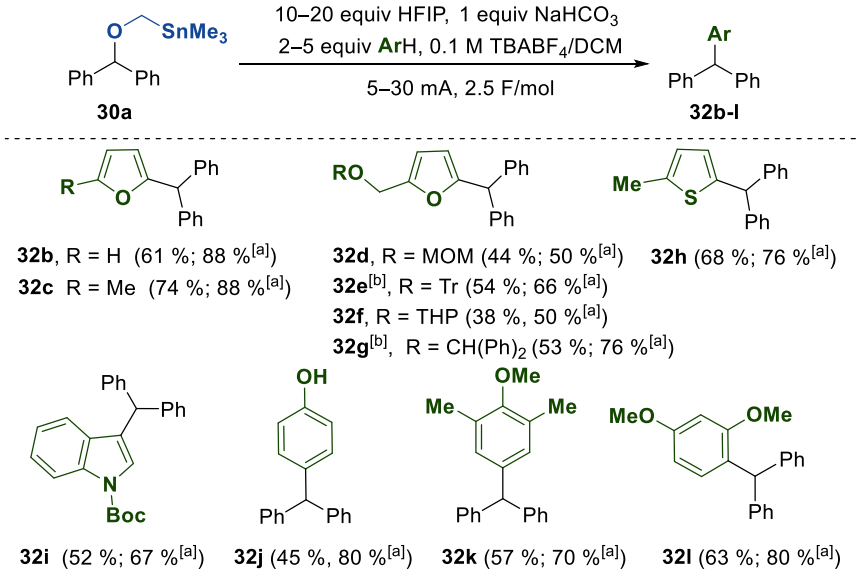
Conditions A: I = 2.5 F/mol, 20 mA, graphite electrodes, r.t., 40 min
Conditions B: no current, r.t., 18 h

Entry	Additive	Cond. A Yield[a] of **32a** (%)	Cond. B Yield[a] of **32a** (%)
1	none	63	9
2	additional HFIP[b]	56	74
3	1 equiv 2,6-lutidine	0	0
4	1 equiv PivONa	38	0
5	1 equiv $PhCO_2Li$	51	0
6	1 equiv $NaHCO_3$	64 (55[c])	0

[a] ^{1}H-NMR yield using EtOAcc as an internal standard.
[b] Solvent: HFIP:DCM 1:1
[c] Isolated yield.

With the electrolysis conditions established, the scope of arenes suitable for the electrochemical Friedel-Crafts reaction was investigated (Fig. 6). Furan and methylfuran reacted with the electrochemically generated carbenium ion to give products **32b** and **32c** in good yields. Moreover, furfuryl alcohols with acid-labile functional groups, such as MOM, Tr, THP, and Ph_2CH (products **32-g**), were also compatible with the reaction conditions, demonstrating to our knowledge the first example of Friedel-Crafts alkylation performed with acid-sensitive *O*–protecting group bearing substrates. Other heterocycles, such as thiophene

and *N*-protected indole, were also suitable for the alkylation reaction (products **32h**,**f**). Electron-rich phenol and anisole derivatives were compatible with the electrolysis conditions despite their low redox potentials. Unprotected phenol, dimethylanisole and 1,3-dimethoxybenzene all delivered products **32j-l** in good yields.

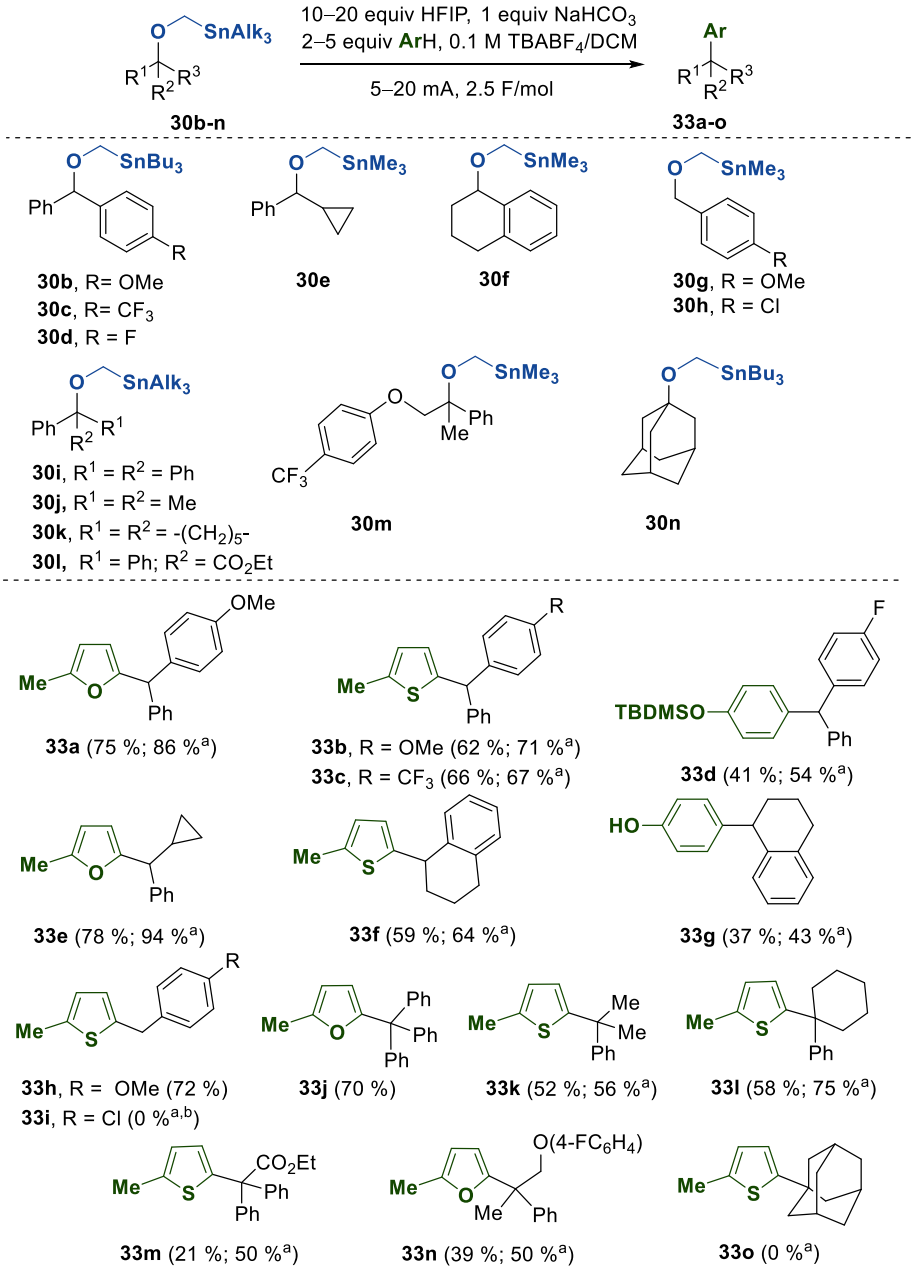


[a] ^{1}H-NMR yield using EtOAc as an internal standard [b] 10 equiv HFIP.

Fig. 6. Nucleophile scope for the electrochemically induced Friedel-Crafts reaction.

The range of stannylmethylethers included substrates derived from diphenylmethanol with various substituents at the 4-position of the phenyl ring (Fig. 7). Diarylmethyl cations with electron-donating (from **30b**) and electron-withdrawing (from **30c**) groups gave 2-methyl furan and 2-methyl thiophene alkylation products **33a-c** with good yields. Fluorine-containing diarylmethyl cation (from **30d**) reacted with *O*–TBDMS-protected phenol, giving a slightly lower product **33d** yield than the non-fluorinated analogue (product **32a**). The reaction was limited to benzyl cation precursor with a stabilising methoxy group (**30g**) as the 4-chlorobenzyl substrate **30h** failed to give the anticipated product **33i**. Tertiary carbenium ion precursors gave products in moderate yields except for the adamantyl cation precursor **30n** that did not yield the expected alkylation product **33o**.

The results discussed have been published in the paper attached in Appendix 2.



[a] ^{1}H-NMR yield using EtOAc as an internal standard [b] oxonium ion reaction product in 35% by NMR

Fig. 7. Scope of stannylmethylethers for the electrochemically induced Friedel-Crafts reaction.

An intramolecular Friedel-Crafts alkylation was demonstrated to obtain condensed heterocycles as reaction products. For this, we designed substrates **34** in which the internal (hetero)aromatic nucleophile was attached to the reaction centre *via* a tether of suitable length to form a 5- or 6-membered cycle upon intramolecular cyclisation (Fig. 8 A).

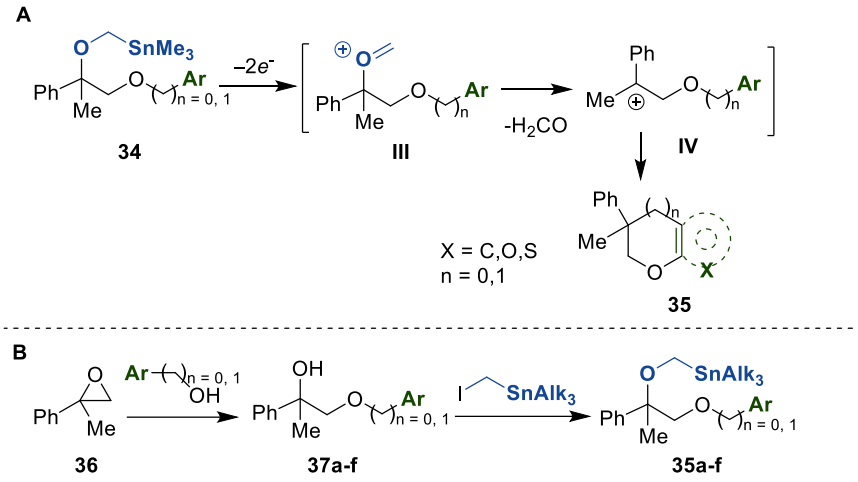


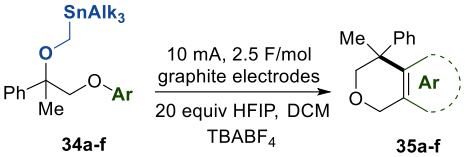
Fig. 8. Intramolecular electrochemically induced Friedel-Crafts reaction.

The synthesis of the substrates was achieved by a ring-opening reaction of the epoxide **36** with an aromatic alcohol introducing the intramolecular nucleophile to obtain alcohols **37a-f** which were then modified with the trialkylstannylmethyl group to provide the starting materials **34a–f** (Fig. 8 B).

Electrolysis with substrates containing 3-methoxyphenyl (**34a**), 3-furfuryl (**34b**), 3-benzofurfuryl (**34d**) and 3-thienyl (**34e**) group as internal nucleophiles all furnished the corresponding condensed 6-membered heterocycles **35a-b**,**d-e** in moderate to poor yields (Table 5). Formation of 5-membered cycle **35f** was not observed. Another substrate which failed to give the product was compound **34c**, in which the 2-furfuryl group was cleaved off during the electrochemical reaction.

Table 5

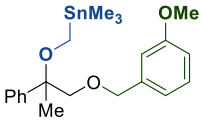
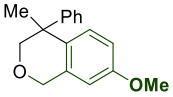
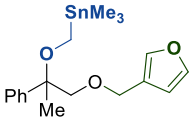
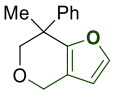
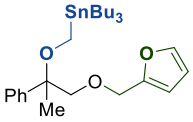
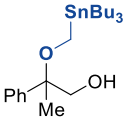
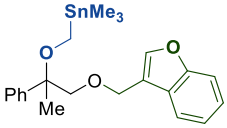
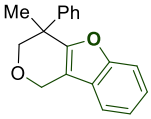
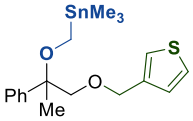
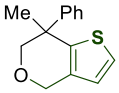
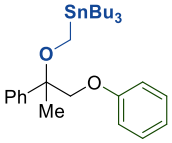
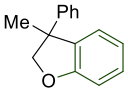
Scope of the intramolecular Friedel-Crafts alkylation



34a-f

Alk = Me, Bu

35a-f

Entry	Starting material **34**	Product **35**	Product, yield (NMR yield), %
1			**35a**, 46 (60[a])
2			**35b**, 30 (31[a])
3			**38**, 22
4			**35d**, 32 (39[a])
5			**35e**, 17 (32[a])
6			**35f**, 0

[a] ^{1}H-NMR yield using EtOAc as an internal standard

We hypothesised that the reduced yields compared to the intermolecular Friedel-Crafts reaction could be explained by poor fragmentation of intermediate oxonium ion III due to the stabilisation forming a transient cyclic system V (Fig. 9).

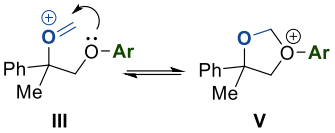


Fig. 9. Oxonium ion stabilisation by the lone electron pair of the ether linker.

Electrochemical methanolysis of the starting materials showed that methanol addition to the oxonium ion is the major pathway as the methoxymethylated products were obtained in excess over the methoxylated products. Furthermore, an analogue **39** incapable of oxonium ion stabilisation was synthesised and subjected to the electrolysis conditions (Fig. 10).

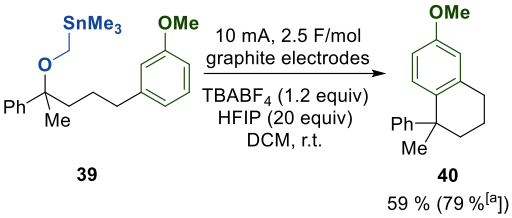


Fig. 10. Electrochemical formation of a carbocycle **40.**
[a] ^{1}H-NMR yield using EtOAc as an internal standard.

The corresponding carbocycle **40** formed in a higher yield compared to ether bond containing substrate **34a**, confirming the role of oxonium ion stabilisation in hindering the formation of the condensed heterocycles.

The results discussed have been published in the paper attached in Appendix 3.

2. Torii-Type electrochemical oxidation of furfurylated ethylene glycols

Electrochemical synthesis is a valuable tool not only for fine chemical synthesis but also for biomass valorisation. Furan derivatives are particularly suitable substrates for electrochemical functionalisation due to the furan ring's low oxidation potential, which allows transformation without the use of electroauxiliary groups. Our work was devoted to investigating the electrochemical oxidation of furyl methyl derivatives **41** bearing hydroxyl group as an internal nucleophile. Electrolysis in the presence of a nucleophile should provide spirocyclic derivatives **42** which would undergo fragmentation to give products **43** with functionalised ester moiety. Such products could be valuable building blocks for further chemical transformations. The spirocycle formation starts with one-electron oxidation of **41a**, giving a radical cation **44a** (Fig. 11 B) which undergoes proton elimination and intramolecular

cyclisation, yielding an intermediate **45a**. Further oxidation of **45a** followed by methanolysis gives spirocycle **42a**.

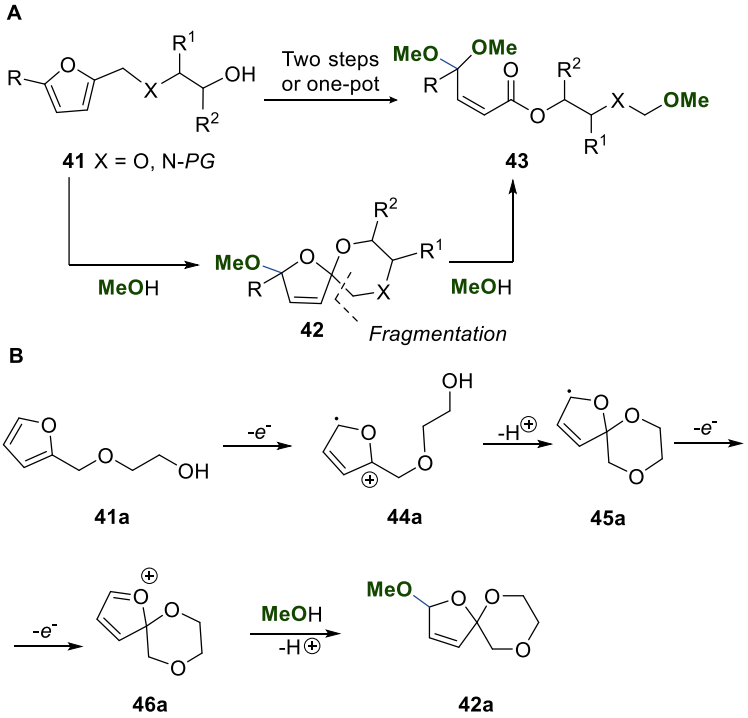


Fig. 11. A – Torii-type electrosynthesis of unsaturated esters; B – mechanistic steps for electrochemical formation of spirocycle **42a**.

Electrochemically induced formation of spirocycle **42** was realised in an undivided cell using graphite electrodes (Fig. 12). Methanol was chosen as the solvent due to its ability to serve both as the proton donor for the cathodic reaction and the external nucleophile, and $TBABF_4$ was found to be an effective electrolyte. Acidic additives were investigated to suppress the formation of methoxide ions, which would lead to methoxylation of the furan ring in favour of spirocyclization. HFIP was found to provide the spirocycle in a good yield; however, a significant amount of ester **43** formed as a byproduct. PPTS promoted the formation of the spirocycle in a high yield without large amounts of byproducts. Optimal conditions were suitable for the oxidation of alcohol **41a** to spirocycle **42a** on a 500 mg scale.

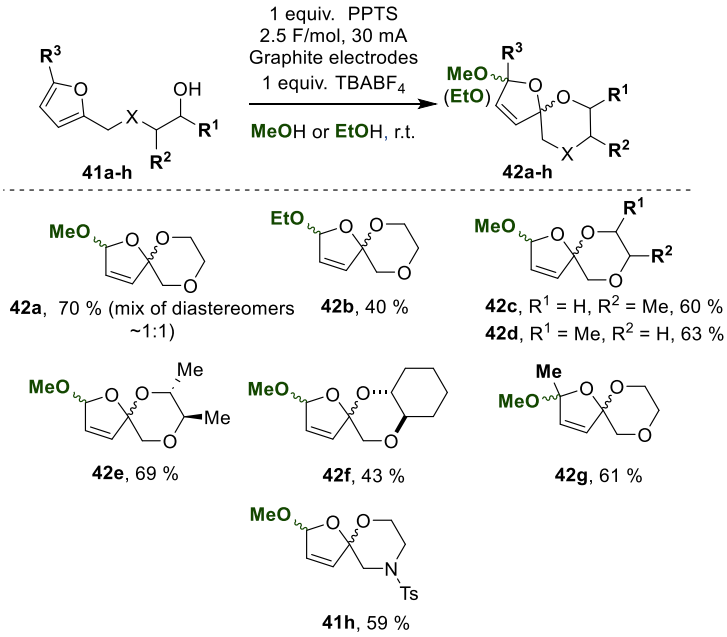


Fig. 12. Scope of spirocycle **42** synthesis.

The scope of spirocycle synthesis was explored for other ethylene glycol and amino ethanol derivatives containing furfuryl moiety to give products **42b-h** in moderate to good yields. Ethanol was also a suitable solvent and external nucleophile, although it provided the corresponding product **42b** in a lower yield.

An electrooxidative fragmentation of the obtained spirocycles provided esters **43**. For effective product formation, PPTS was exchanged for AcOH, since PPTS byproducts tended to accumulate on electrodes during longer electrolyses. $LiClO_4$ was also found to be a better electrolyte than $TBABF_4$ for the ester formation. In the optimised conditions, esters **43a-h** formed regioselectively with a *Z* configuration of the double bond (Fig. 13). No transacetalyzation with methanol was observed when the substrate **42b** was subjected to the electrolysis, and the mixed acetal **43b** formed exclusively.

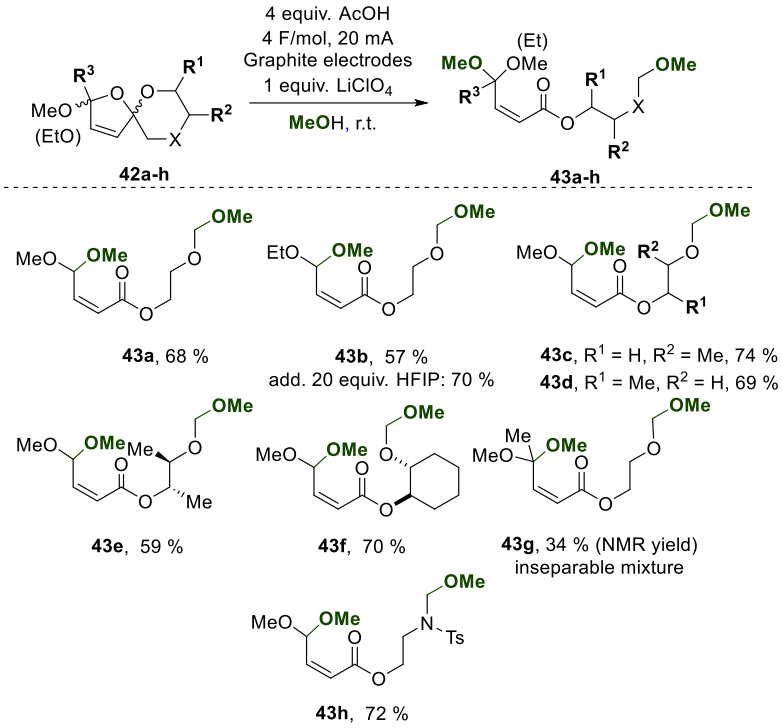


Fig. 13. Scope of oxidative fragmentation of spirocycles **42** to esters **43**.

One-pot transformation of alcohols **41** into esters **43** could also be realised (Fig. 14). To avoid precipitation of PPTS during prolonged electrolysis, HFIP was used instead as an additive for the first step, while AcOH was added to promote the second step of the reaction. The one-step approach was especially suitable for the transformation of *N*-protected *O*-furfuryl amino alcohols **43h-l**. Electrosynthesis of **43k** in one step could also be demonstrated on a gram scale.

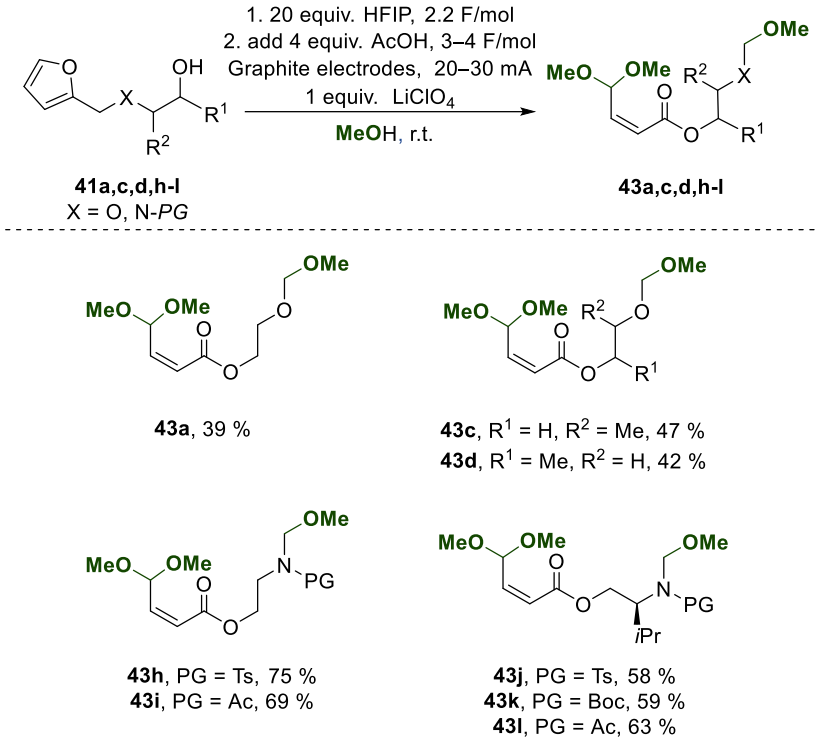


Fig. 14. One-pot oxidative fragmentation of alcohols **41** to esters **43**.

The proposed mechanism for ester **43** formation from spirocycle **42** starts with a reversible S_N-type methanolysis of the acetal leading to intermediate **C** which undergoes electrochemical oxidation to an *O*-centered radical **E** fragmenting to an *α*-oxy-stabilized *C*-centered radical **F** (Fig. 15 A, Path a). Alternatively, electrochemical activation of the acetal group in the spirocycle **26a** could form a radical cation **D**. Afterwards, the ring could be opened by methanolysis, leading to an *O*-centered radical **E**.

Mechanistic investigations performed in deuteromethanol in the presence and absence of electrical current showed that the electrochemical activation is crucial for the methanolysis of the spirocycle (Fig. 15 B), supporting Path b of the mechanism.

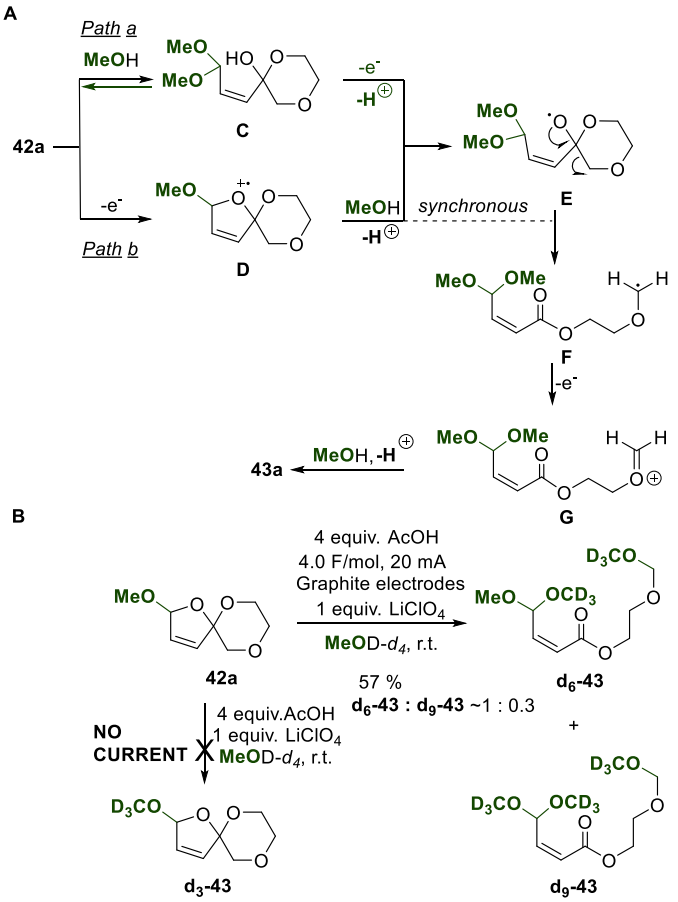


Fig. 15. A – Proposed mechanistic pathways for ester **43a** formation from spirocycle **42a**; B – Deuterium labelling experiments supporting Path b of ester **43a** formation mechanism.

The results discussed have been published in the paper attached in Appendix 4.

CONCLUSIONS

1. Trialkylstannylmethyl group is a suitable electroauxiliary for the generation of carbenium ions from trialkylstannylmethylethers via fragmentation of oxonium ions.
2. Carbenium ions can be generated electrochemically from stannylmethyl ethers in an undivided cell in the presence of allylsilanes. Electrochemically generated carbenium ions readily react with allylsilanes.
3. Electrochemical Friedel-Crafts alkylation with trialkylstannylmethylethers in HFIP as a solvent and using $NaHCO_3$ as an additive is compatible with substrates containing acid-labile functional groups like TBDMS, Tr, THP, MOM, and $CHPh_2$.
4. Intramolecular electrochemical Friedel-Crafts alkylation furnishes condensed heterocycles with the formation of a 6-membered cycle. Product formation is hindered by intramolecular stabilisation of the intermediate oxonium ion.
5. Ethylene glycol and amino ethanol derivatives containing furfuryl moiety form spirocycles upon electrochemical oxidation of the furan ring in methanol.
6. Further electrochemical oxidation of the spirocycles results in obtaining α,β-unsaturated esters in a one or two step electrolysis procedure.
7. Experiments with deuterium-labelled methanol confirm that the electrochemical activation is crucial for the transformation of spirocycle derivatives into α,β-unsaturated esters.

ATSAUCES

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PIELIKUMI

APPENDICES

Lielpetere, A.; Jirgensons, A. Carbenium ion formation by fragmentation of electrochemically generated oxonium ions. *Org. Biomol. Chem.*, **2018**, 16, 5094.

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Carbenium ion formation by fragmentation of electrochemically generated oxonium ions†

Anna Lielpetere and Aigars Jirgensons *

Fragmentation of electrochemically generated oxonium ions can be exploited to form carbenium ions at a low oxidation potential in the presence of a nucleophile. The application of this concept is demonstrated for the allylation of carbenium ions generated by the anodic oxidation of stannylmethylethers.

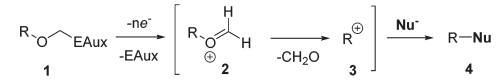
Electrochemical substrate activation is based on its redox potential enabling selective organic transformations with electric current as the principal reactant.[1–6] A well-known example is anodic oxidation for the generation of carbenium ions under near-neutral conditions and avoiding the use of stoichiometric oxidants.[5,6] However, only a limited number of nucleophiles are compatible with the oxidation potential required for substrate activation. To expand the nucleophile scope, the Yoshida group has developed an electrochemical cation pool methodology in which ions are accumulated at low temperatures followed by the addition of a nucleophile.[3,5,6–10] Less stable carbenium ions could be generated in the presence of a sulfilimine additive leading to stabilized yet very reactive electrophilic intermediates which are acquired at low temperatures.[11] Even though the cation pool methodology is a powerful approach, it requires a divided cell set-up and a large amount of expensive trifluorosulfonic acid for the cathode reaction.

Single cell electrolysis is more attractive due to the simplicity of the experiments; however, in this case, the carbenium ions should be generated in the presence of the nucleophile. This is feasible only if the oxidation potential of the substrate is lower than that of the nucleophile, which constitutes a major challenge for the application of single cell conditions.

Oxonium ions can be produced at a relatively low potential by the oxidative decarboxylation of oxyacetic acid[12,13] (non-Kolbe oxidation) or by the cleavage of silylmethyl[14,15] and stannylmethyl[16,17] ethers. We hypothesised that these substructures could be exploited as electroauxiliaries (EAux) in substrate **1** to produce carbenium ion **3** by the fragmentation of oxonium ion **2** (Scheme 1). To ensure the reaction with the more reactive carbenium ion **3**, the nucleophile reactivity should match the fragmentation rate of oxonium ion **2** which mainly depends on the stability of carbenium ion **3**.

Model substrates **1a–c** bearing oxycarbonylmethyl, trimethylsilyl-methyl and tributylstannylmethyl EAux groups were prepared from benzhydrol. The oxidation potentials of the compounds were determined, revealing that tributylstannylmethyl ether is most susceptible to electrochemical activation (Fig. 1).

This substrate, **1c**, was subjected to electrochemical oxidation under constant current conditions in the presence of methanol which served both as a nucleophile and a proton donor for the cathode reaction (Table 1). In methanol as the reaction solvent, both carbenium ion and oxonium ion methoxylation products **5** and **6** formed in equal amounts and in medium overall yield (Table 1, entry 1). Acetonitrile as the reaction media did not substantially change the product **5** and **6** ratio nor the yield (Table 1, entry 2). Considerable improvement of carbenium ion reaction product **5** formation was achieved in dichloromethane as the reaction solvent (Table 1,



Scheme 1 Generation and fragmentation of oxonium ions to carbenium ions.

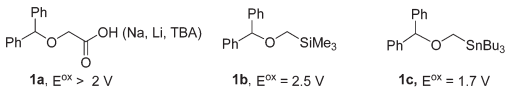


Fig. 1 Electroauxiliaries for oxonium ion **2** generation (electrochemical oxidation potentials determined by cyclic voltammetry: 0.1 M $TBABF_4$/MeCN, working electrode – glassy carbon, counter electrode – Pt wire, reference electrode – Ag/Ag^+ (potentials given *vs.* NHE)).

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†Electronic supplementary information (ESI) available: Experimental details, cyclic voltammograms, and NMR data. See DOI: 10.1039/c8ob01339j

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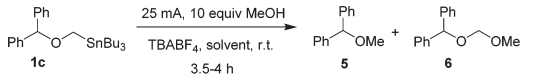
Table 1 Electrochemical activation of substrate **1c** in the presence of MeOH



Entry	Solvent	Ratio **5** : **6**	Yield of **5** & **6** [a] (%)
1	MeOH	1 : 1.1	50
2	MeCN	1.3 : 1	50
3	CH_2Cl_2	7.5 : 1	85
4	HFIP	>99 : 1	73

[a] Total ^{1}H-NMR yield of products **5** and **6** using 1,4-bis-trichloromethylbenzene as the internal standard.

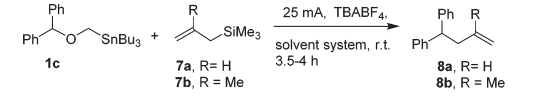
entry 3). Notably, almost complete selectivity for the desired product **5** formation was observed on performing the reaction in HFIP (Table 1, entry 4).[18,19]

Next the electrochemical activation of substrate **1c** was performed in the presence of allylsilanes **7a,b**[20] which led to useful C–C bond formation (Table 2).[21] Using HFIP as the solvent and proton donor, the reaction of stannylmethylether **1c** with allylsilane **7a** provided the desired product **8a**, albeit in a low yield due to the formation of several side products (Table 2, entry 1). Dichloromethane as the solvent with HFIP as an additive proved to be a more suitable reaction medium for an electrochemically induced reaction of stannylmethylether **1c** with allylsilanes **7a,b** to give the expected carbenium ion allylation products **8a,b** in good yields (Table 2, entries 2 and 3).

The substrate scope for the allylation of the carbenium ions was investigated using optimal reaction conditions for the electrochemical activation of stannylmethyl ether (Table 3).

Diphenylmethyl carbenium ion reaction products **10a–e** were obtained from substrates **9a–e** in good yields bearing both electron withdrawing and electron donating substituents in phenyl rings (Table 3, entries 1–5). The phenylcyclopropylmethyl carbenium ions generated from substrate **9f** were also efficiently allylated to give product **10f** (Table 3, entry 6). Tertiary carbenium ions generated from ethers **9g,h** provided the allylation products **10g,h** in low yields (Table 3, entries 7

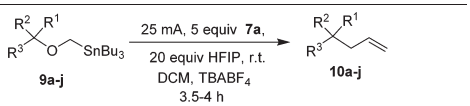
Table 2 Electrochemical activation of substrate **1c** in the presence of allylsilanes

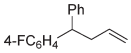
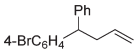
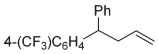
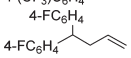
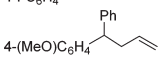
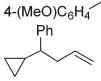
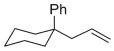
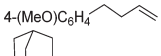
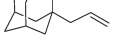


Entry	**7**, solvent system	**8**, yield (%)
1	**7a**, HFIP	**8a**, 40 (NMR)[a]
2	**7a**, CH_2Cl_2, 20 equiv. HFIP	**8a**, 87 (isolated)
3	**7b**, CH_2Cl_2, 20 equiv. HFIP	**8b**, 64 (isolated)

[a] ^{1}H-NMR yield using 1,4-bis-trichloromethylbenzene as the internal standard.

Table 3 Substrate scope for the reaction with allylsilane under electrochemical activation conditions



Entry	Product	**10**, yield (%)
1		**10a**, 74
2		**10b**, 79
3		**10c**, 76
4		**10d**, 81
5		**10e**, 72
6		**10f**, 91
7		**10g**, 26[a]
8		**10h**, 42[b]
9		**10i**, 75
10		**10j**, 14
11		**10k**, 0

[a] 1,1-Diphenylethylene (20%) was isolated as a side product. [b] ^{1}H-NMR yield using 1,4-bis-trichloromethylbenzene as the internal standard; obtained as an inseparable mixture with triphenylmethane.

and 8). However, the less stable phenylcyclohexyl cations generated from substrate **9i** gave the allylated product **10i** in good yield (Table 3, entry 9). Benzylic ether **9j** gave product **10j** in poor yield while no expected product **10k** was obtained from adamantyl ether **9k** (Table 3, entries 10 and 11). The poor performance of these substrates can be attributed to a slow fragmentation of the oxonium ion **2** to carbenium ion **3** due to the decreased stability of the latter. Oxonium ion allylation by-products **11–13** were isolated in the case of substrates **9b,d,k** providing less stable carbenium ions. Notably, in the case of adamantyl ether **9k**, homoallylether **13** formed as the major product (Fig. 2).

The hydrogen bonding properties of HFIP[22,23] can potentially promote the ionization of ethers **7** and **9** to give carbenium ions without electrochemical activation. Therefore,

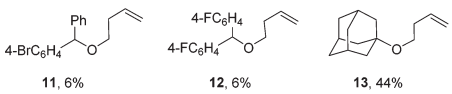


Fig. 2 Isolated oxonium ion allylation products.

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Table 4 Product **8** and **10** formation without electrochemical activation of the substrate

Entry	Time	Product, NMR yield[a] (%)
1	18 h	**8a**, 25
2	18 h	**10a**, 5
3	18 h	**10f**, 60
3	3 days	**10h**, 33

[a] ^{1}H-NMR yield using 1,4-bis-trichloromethylbenzene as the internal standard.

several control reactions were performed in the absence of an electric current (Table 4). Indeed, product **8a** and **10a,f,h** formation was observed; however, the reaction was very slow and resulted in a lower yield. These results indicate that the electrochemical activation of the substrates is crucial for efficient carbenium ion generation.

Conclusions

In summary, we demonstrated that carbenium ions can be formed in the presence of nucleophiles by the fragmentation of electrochemically generated oxonium ions. To achieve an acceptable oxidation potential of the substrate, the tributylstannylmethyl group was found to be an efficient electroauxiliary for oxonium ion formation. The application of this concept was demonstrated for the allylation of carbenium ions electrochemically generated from a range of stannylmethyl ethers in the presence of allylsilanes. Additional investigations are in progress to expand the scope of this reaction to other nucleophiles compatible with the oxidation potential needed for substrate activation.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Electrochemical Oxidation

Friedel–Crafts Alkylation with Carbenium Ions Generated by Electrochemical Oxidation of Stannylmethyl Ethers

Anna Lielpetere[a] and Aigars Jirgensons*[a]

Abstract: The electrochemical activation of stannylmethyl ethers was exploited for Friedel–Crafts alkylation of arenes at near-neutral conditions. Single cell anodic oxidation of stannylmethyl ethers leads to oxonium ions which fragment to carbenium ions in the presence of electron rich arenes. Low oxidation potential of stannylmethyl ethers and buffered conditions enable the Friedel–Crafts reaction with a wide range of arenes including the substrates with acid-sensitive groups.

Introduction

The Friedel–Crafts alkylation is a fundamental organic reaction for functionalization of arenes in their reaction with in situ generated carbenium ions.[1] Products of this reaction have found wide application in drug discovery and material science.[2–4] Consequently, a number of Friedel–Crafts alkylation versions has been developed, including the alkylation of arenes with alcohols,[5–10] halogens,[11,12] ethers,[13,14] acetates,[15,16] phosphonates,[17] sulfones,[18,19] trichloroacetimidates,[13] tosylamides,[20] epoxides,[21,22] and olefins.[23] Typically, these reactions rely on Broensted or Lewis acid catalysis to promote the carbenium ion formation. Limited number of methods for Friedel–Crafts alkylation has been developed using weak or non-acidic conditions which offer wider substrate scope for this useful transformation.[24–28]

Electrochemical generation of carbenium ions avoids the use of acidic conditions because the protons formed during the reaction are reduced to hydrogen at the cathode.[29,30] This provides an option to perform reactions of carbenium ions at near-neutral conditions which are compatible with acid-sensitive functionalities in substrates.

Recently, we have reported an operationally simple carbenium ion generation from stannylmethyl ethers **1** (Alk = *n*Bu) in single cell electrolysis at relatively low potential (Figure 1).[31] The method is based on the oxidation of stannylmethyoxy group in substrates **1** to form oxonium ions **A** which fragment to carbenium ion **B**. The proof of the concept was demonstrated for the reaction of carbenium ions **B** with allylsilane providing olefins **2**. With an aim to complement the recent advances in electrochemical arene functionalization,[32–34] we explored Friedel–Crafts reaction using stannylmethyl ethers **1** (Alk = *n*Bu, Me) as precursors for electrochemical generation of carbenium ions **B** to form alkylated arenes **3** (Figure 1).

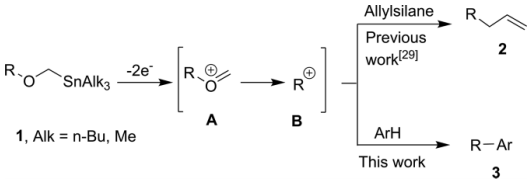

Figure 1. Electrochemical generation of carbenium ions from stannylmethyl ethers and their reaction with nucleophiles.

Results and Discussion

In a model reaction, stannylmethyl ether **1a** was subjected to anodic oxidation in the presence of *O*-TBS protected phenol **4** (Table 1, entry 1). Weekly nucleophilic HFIP was found as appropriate additive to secure the cathode reaction[35] and no significant competition with arene as reaction component was observed.[12,22] The electrochemically induced reaction proceeded in a relatively short time providing the expected product **3.1** in good yield and high *para*-selectivity (*ortho*-product **5** formed <5 % according to NMR: see Supporting Information). However, the control reaction without electric current was also productive, leading to observable formation of product **3.1** at longer reaction time (Table 1, entry 1).

Notably, the increased amount of HFIP facilitated non-electrochemical reaction leading to product **3.1** formation in good yield (Table 1, entry 2). This indicated the susceptibility of trimethylstannylmethyl ether **1a** to undergo ionization in the presence of HFIP. Moreover, such a result implied that the reaction conditions are not compatible with acid-labile functional groups.

To buffer the reaction media, various basic additives were tested. 2,6-Lutidine suppressed both electrochemically induced and solvolytic carbenium ion generation (Table 1, entry 3). Addition of sodium pivaloate and lithium benzoate to the reaction

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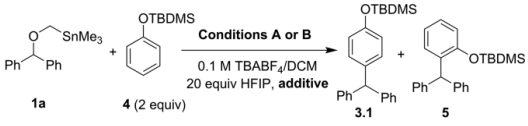
Table 1. Reaction conditions for selective electrochemical substrate activation.



Conditions A: I = 2.5 F/mol, 20 mA, graphite electrodes, r.t., 40 min
Conditions B: no current, r.t., 18 h

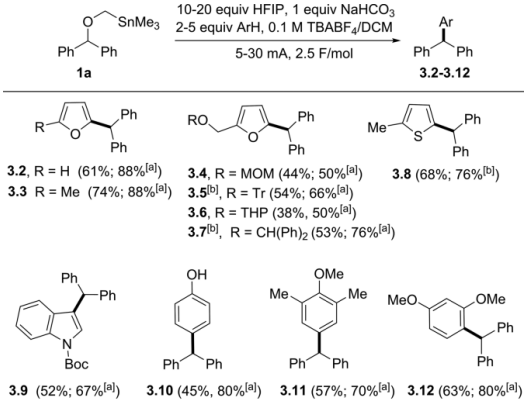
Entry	Additive	Cond. A Yield[a] of **3.1**,%	Cond. B Yield[a] of **3.1**,%
1	none	63	9
2	additional HFIP[b]	56	74
3	1 equiv. 2,6-lutidine	0	0
4	1 equiv. PivONa	38	0
5	1 equiv. $PhCO_2Li$	51	0
6	1 equiv. $NaHCO_3$	64 (55[c])	0

[a] NMR yield using ethyl acetate as an internal standard. [b] Solvent: HFIP/DCM, 1:1. [c] Isolated yield.

media gave Friedel–Crafts product **3.1** in medium yield and suppressed the solvolysis induced reaction (Table 1, entries 4,5). $NaHCO_3$ as additive induced the best yield of product **3.1** at electrochemical conditions and completely suppressed solvolytic carbenium ion generation (Table 1, entry 6). The oxidation potentials of the substrates **1a** (E^{ox} = 1.12 V) and **3.1** E^{ox} = 1.20 V) were determined at the conditions close to those used for the reaction (see Supporting Information). The difference of the oxidation potentials confirms that stannylmethyl ether **1a** can be selectively activated presumably leading to carbenium ion **B** as reactive intermediate (Figure 1).

With optimized conditions in hand, the stannylmethyl ether **1a** was subjected to electrochemically induced reaction with a range of arenes (Table 2). Alkylated furan derivatives **3.2** and **3.3** were prepared in good yield. Moreover, furfuryl alcohol derivatives bearing acid-labile *O*-protecting groups, such as MOM, Tr, THP and Ph_2CH, could also be alkylated with stannylmethyl

Table 2. Nucleophile scope for the electrochemically induced Friedel–Crafts reaction.



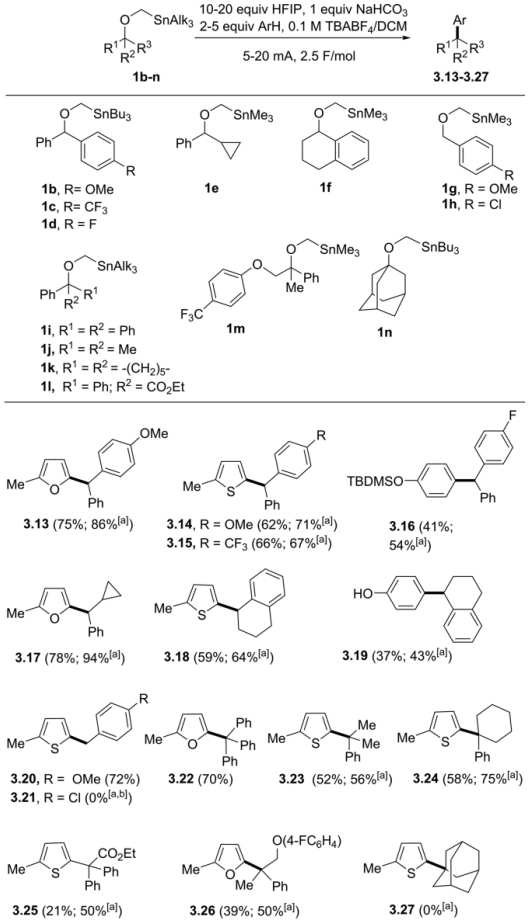
3.2, R = H (61%; 88%[a])
3.3 R = Me (74%; 88%[a])
3.4, R = MOM (44%; 50%[a])
3.5[b], R = Tr (54%; 66%[a])
3.6, R = THP (38%, 50%[a])
3.7[b], R = $CH(Ph)_2$ (53%; 76%[a])
3.8 (68%; 76%[b])
3.9 (52%; 67%[a])
3.10 (45%, 80%[a])
3.11 (57%; 70%[a])
3.12 (63%; 80%[a])

[a] NMR yield using ethyl acetate as an internal standard. [b] 10 equiv. HFIP.

ether **1a** to give the corresponding products **3.4**–**3.7**. To the best of our knowledge, these are the first examples of the compatibility of the acid-sensitive *O*-protecting groups with Friedel–Crafts alkylation conditions. Acid-sensitive heterocycles, such as thiophene and *N*-protected indole, also provided the desired alkylation products **3.8** and **3.9**. Electron rich phenols with low electrochemical potentials were also tested as substrates. Interestingly, unprotected phenol turned out to be a competent substrate to give *C*-alkylation product **3.10**. Anisole derivative and 1,3-dimethoxybenzene with low oxidation potentials (E^{ox} = 1.47 and 1.24 V, respectively) were also successfully alkylated to give products **3.11** and **3.12** in good yields.

The scope of stannylmethyl ethers **1** for alkylation of arenes was also investigated (Table 3). Diarylmethyl cations generated from stannylmethyl ethers **1b,c** gave furan and thiophene alkyl-

Table 3. Scope of stannylmethyl ethers for the electrochemically induced Friedel–Crafts reaction.



[a] NMR yield using ethyl acetate as an internal standard. [b] Oxonium ion reaction product in 35 % by NMR.

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ation products **3.13**–**3.15** in good yields. The reaction of fluorine-containing stannylmethyl ether **1d** provided alkylated protected phenol **3.16**, however, in slightly lower yield compared to non-fluorinated analogue **1a**. Alkylarylmethyl cations generated from stannylmethyl ethers **1e**,**f** gave furan, tiophene and phenol alkylation products **3.17**–**3.19**. Methoxy-substituted benzylic cation produced from substrate **1g** provided thiophene derivative **3.20** efficiently. However, chloro-substituted analogue **1h** failed to give the expected product **3.21**, likely due to the reduced stability of the intermediate carbenium ion. Tertiary carbenium ion precursors **1i**–**k** provided furan and thiophene alkylation products **3.22**–**3.24** in moderate yields. However, stannylmethyl ethers **1l**,**m** bearing EWG groups were considerably less productive, giving products **3.25**, **3.26** in low yield. Also, the electrochemical activation of less stable adamantyl cation precursor **1n** despite its low oxidation potential (E^{ox} = 0.9 V) failed to give the expected alkylation product **3.27**.

The proposed mechanism of electrochemically induced Friedel–Crafts reaction is shown in Figure 2. The cathode reaction involves the reduction of HFIP to generate the corresponding alkoxide and hydrogen. Stannate complex formed from substrate **1** undergoes anodic oxidation at low oxidation potential to form oxonium ion **A** with stannate $\mathbf{X}^-$ as the counterion. Fragmentation of oxonium ion **A** forms cation **B** which reacts with activated arene (**ArH**) providing Friedel–Crafts alkylation product **3** and non-acidic by-products (**HX**).

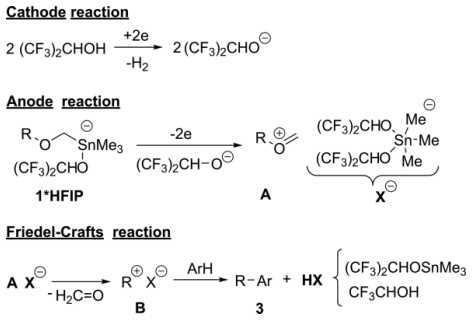

Figure 2. Proposed mechanism of electrochemically induced Friedel–Crafts reaction.

Conclusion

In summary, it was demonstrated that Friedel–Crafts reaction can be achieved by electrochemical activation of stannylmethyl ethers in the presence of electron rich arenes. The buffered electrolytic mixture contained HFIP as the cathode reactant and $NaHCO_3$ as proton scavenger. These conditions were found to be compatible with acid-labile *O*-protecting groups such as MOM, Tr, THP and Ph_2CH. We believe that electrochemical activation of substrates to form carbenium will expand the application of Friedel–Crafts reaction in the synthesis of useful products.

Experimental Section

General Remarks. All procedures were performed in oven-dried glassware under argon atmosphere unless noted otherwise. Reagents and starting materials were obtained from commercial sources and used as received unless otherwise noted. Tetrabutylammonium tetrafluoroborate (Fluorochem) was recrystallized from ethyl acetate and dried at 80 °C for 8 h before use. Solvents were purified and dried by standard procedures before use. Flash column chromatography was carried out using silica gel (230–400 mesh). Thin-layer chromatography (TLC) was performed on Merck TLC Silica gel 60 F254 Aluminium sheets and was visualized by UV lamp or staining with $KMnO_4$. NMR spectra were recorded on 300 or 400 MHz spectrometers with chemical shift values (δ) in parts per million using the residual solvent as an internal standard. HRMS analyses were performed on a hybrid quadrupole time-of-flight mass spectrometer equipped with an electrospray ion source. Electrochemical experiments were performed using electrochemical system Electrasyn 2.0.

Experimental Details. Synthesis of starting materials and characterization of side products is described in Supporting Information.

General Procedure for Electrochemical Friedel–Crafts Alkylation. Anodic oxidation was performed in Electrasyn beaker-type undivided cell (5 mL) equipped with two standard Electrasyn graphite plate electrodes (8 × 40 mm, ca. 15 mm submerged in the solution) in 0.1 M $TBABF_4$/dry DCM (2 mL) solution with the addition of HFIP (0.41 mL, 4.0 mmol unless noted otherwise) and $NaHCO_3$ (17.0 mg, 0.2 mmol). The trialkylstannylmethyl group bearing substrate (0.2 mmol) and nucleophile (2–5 equiv.) were added to the solution. Constant current electrolysis (5–30 mA) was carried out in air at ambient temperature with magnetic stirring and change of polarization every minute until approx. 2.5 F/mol were consumed. After the electrolysis, the reaction mixture was concentrated in vacuo and purified by flash column chromatography on silica gel.

(4-Benzhydrylphenoxy)(*tert*-butyl)dimethylsilane (3.1). Electrochemical oxidation of ((benzhydryloxy)methyl)trimethylstannane (**1a**) (72.6 mg, 0.20 mmol) in the presence of *tert*-butyldimethyl-(phenoxy)-silane (**4**) (84.0 mg, 0.40 mmol) according to the general procedure at 30 mA and purification by column chromatography on silica gel (eluent petroleum ether/Et_2O, 40:1) afforded 41.5 mg (55 %) of product as a white solid (m.p. 80–82 °C).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.33–7.25 (m, 4H), 7.24–7.16 (m, 2H), 7.14–7.07 (m, 4H), 6.99–6.92 (m, 2H), 6.78–6.72 (m, 2H), 5.49 (s, 1H), 0.98 (s, 9H), 0.19 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.12, 144.46, 136.70, 130.46, 129.55, 128.38, 126.33, 119.86, 56.23, 25.83, 18.32, –4.25.

HR-MS (ESI-TOF) *m/z*: calcd. for $C_{25}H_{29}OSi$ $[M - 1]^+$ 373.1988, found 373.1972.

Anal. calcd. for $C_{25}H_{30}OSi$: C, 80.16; H, 8.07; found C, 79.17; H, 8.08.

2-Benzhydrylfuran (3.2) Electrochemical oxidation of ((benzhydryloxy)methyl)trimethylstannane (**1a**) (71.9 mg, 0.2 mmol) in the presence of furan (0.1 mL, 1 mmol) according to the general procedure at 5 mA and purification twice by column chromatography on silica gel (eluent petroleum ether/diethyl ether, 20:1) afforded 28.4 mg (61 %) of product as a colourless oil. This compound has been reported in the literature.[28]

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 (d, *J* = 1.8 Hz, 1H), 7.31 (dd, *J* = 8.2, 6.6 Hz, 4H), 7.27–7.22 (m, 2H), 7.18 (dd, *J* = 7.0, 1.9 Hz, 4H), 6.31 (dd, *J* = 3.3, 1.9 Hz, 1H), 5.92 (d, *J* = 3.2 Hz, 1H), 5.46 (s, 1H).

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2-Benzhydryl-5-methylfuran (3.3) Electrochemical oxidation of ((benzhydryloxy)methyl)trimethylstannane (**1a**) (72.6 mg, 0.20 mmol) was carried out in the presence of 2-methylfuran (0.09 mL, 1.00 mmol) according to the general procedure at 5 mA until 2.87 F/mol has been consumed. Purification by column chromatography on silica gel (eluent petroleum ether/Et_2O, 20:1) afforded 36.7 mg (74 %) of product as an yellowish oil. This compound has been reported in literature.[27]

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.35–7.12 (m, 10H), 5.88 (m, 1H), 5.74 (m, 1H), 5.39 (s, 1H), 2.25 (m, 3H).

2-Benzhydryl-5-((methoxymethoxy)methyl)furan (3.4) Electrochemical oxidation of ((benzhydryloxy)methyl)trimethylstannane (**1a**) (71.8 mg, 0.20 mmol) was performed in the presence of 2-((methoxymethoxy)methyl)furan (56.5 mg, 0.40 mmol) according to the general procedure at 5 mA. Purification by column chromatography on silica gel (eluent petroleum ether/EtOAc, 10:1) afforded 27.2 mg (44 %) of product as an yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.24 (dd, *J* = 8.1, 6.5 Hz, 4H), 7.22–7.13 (m, 2H), 7.12 (dd, *J* = 7.0, 1.9 Hz, 4H), 6.21 (d, *J* = 3.1 Hz, 1H), 5.82–5.76 (m, 1H), 5.40 (s, 1H), 4.60 (s, 2H), 4.43 (s, 2H), 3.30 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.36, 150.90, 141.81, 128.90, 128.54, 126.84, 110.24, 109.33, 95.34, 77.36, 61.15, 55.46, 51.08.

HR-MS (ESI-TOF) *m/z*: calcd. for $C_{29}H_{19}O_3$ $[M - 1]^+$ 307.1334, found 307.1341.

2-Benzhydryl-5-((trityloxy)methyl)furan (3.5) Electrochemical oxidation of ((benzhydryloxy)methyl)trimethylstannane (**1a**) (71.4 mg, 0.20 mmol) was performed in the presence of 2-((trityloxy)methyl)furan (135.0 mg, 0.40 mmol) in a modified general procedure using 0.2 mL of HFIP at 5 mA. Purification by column chromatography on silica gel (eluent petroleum ether/EtOAc, 20:1 with 3 % triethylamine) afforded 54.1 mg (54 %) of product as an white amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49 (d, *J* = 7.7 Hz, 8H), 7.27 (m, 22H), 6.19 (d, *J* = 3.1 Hz, 1H), 5.87 (d, *J* = 3.3 Hz, 1H), 5.46 (s, 1H), 4.02 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.43, 151.92, 144.06, 142.10, 128.97, 128.85, 128.53, 127.98, 127.14, 126.81, 109.08, 108.70, 87.15, 59.57, 51.13.

HR-MS (ESI-TOF) *m/z*: calcd. for $C_{37}H_{29}O$ $[M - 1]^+$ 505.2168, found 505.2180.

2-((5-Benzhydrylfuran-2-yl)methoxy)tetrahydro-2*H*-pyran (3.6) Electrochemical oxidation of ((benzhydryloxy)methyl)trimethylstannane (**1a**) (72.5 mg, 0.20 mmol) was performed in the presence of 2-(furan-2-ylmethoxy)tetrahydro-2*H*-pyran (73.2 mg, 0.40 mmol) according to the general procedure at 5 mA. Purification by column chromatography on silica gel (eluent petroleum ether/Et_2O, 5:1) afforded 22.2 mg (38 %) of product as an yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 (m, 4H), 7.26–7.15 (m, 6H), 6.25 (d, *J* = 3.0 Hz, 1H), 5.84 (d, *J* = 3.0 Hz, 1H), 5.45 (s, 1H), 4.69 (d, *J* = 3.3 Hz, 1H), 4.61 & 4.47 (d & d, *J* = 12.9 Hz, 1H, 3.86 (m, 1H), 3.53–3.42 (m, 1H), 1.60 (m, 8H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.11, 151.33, 141.90, 128.93, 128.51, 126.81, 110.04, 109.26, 97.29, 62.16, 60.87, 51.08, 30.53, 25.55, 19.37.

HR-MS (ESI-TOF) *m/z*: calcd. for $C_{23}H_{24}O_3Na$ $[M + Na]^+$ 371.1623, found 371.1622.

2-Benzhydryl-5-((benzhydryloxy)methyl)furan (3.7) Electrochemical oxidation of ((benzhydryloxy)methyl) trimethylstannane (**1b**) (72.2 mg, 0.20 mmol) was performed in the presence of 2-((benzhydryloxy)methyl)furan (105.8 mg, 0.40 mmol) in a modified general procedure using 0.2 mL of HFIP at 5 mA. Purification by column chromatography on silica gel (eluent petroleum ether/Et_2O, 9:1) afforded 45.5 mg (53 %) of product as an yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33–7.15 (m, 21H), 6.21 (d, *J* = 3.1 Hz, 1H), 5.85 (dd, *J* = 3.0, 0.9 Hz, 1H), 5.43 (s, 1H), 5.41 (s, 1H), 4.42 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.14, 151.38, 141.90, 141.88, 128.95, 128.57, 128.48, 127.58, 127.45, 127.36, 126.85, 110.36, 109.17, 81.71, 62.63, 51.12.

HR-MS (ESI-TOF) *m/z*: calcd. for $C_{31}H_{26}O_2Na$ $[M + Na]^+$ 453.1830, found 453.1832.

2-Benzhydryl-5-methylthiophene (3.8) Electrochemical oxidation of ((benzhydryloxy)methyl)trimethylstannane (**1a**) (72.5 mg, 0.20 mmol) was performed in the presence of 2-methylthiophene (0.1 mL, 1.00 mmol) according to the general procedure at 5 mA. Purification by column chromatography on silica gel (eluent petroleum ether/DCM, 9:1) afforded 36.4 mg (68 %) of product as a colourless oil. Product has been reported in literature.[36]

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.28 (d, *J* = 6.7 Hz, 4H), 7.26–7.18 (m, 6H), 6.57 (d, *J* = 3.3 Hz, 1H), 6.45 (d, *J* = 3.3 Hz, 1H), 5.59 (s, 1H), 2.42 (s, 3H).

***tert*-Butyl-3-benzhydryl-1*H*-indole-1-carboxylate (3.9)** Electrochemical oxidation of ((benzhydryloxy)methyl)trimethyl-stannane (**1b**) (75.7 mg, 0.21 mmol) was performed in the presence of 1-Boc-1*H*-indole (43.4 mg, 0.20 mmol) and $NaHCO_3$ (16.8 mg, 0.2 mmol) according to the general procedure at 5 mA. Purification by column chromatography on silica gel (eluent petroleum ether/Et_2O, 9:1) afforded 40.0 mg (52 %) of product as an yellowish oil. Product has been reported in literature.[37]

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.08 (d, *J* = 8.2 Hz, 1H), 7.32 (s, 9H), 7.22 (m, 2H), 7.19–7.06 (m, 2H), 7.02 (s, 1H), 5.57 (s, 1H), 1.64 (s, 9H).

4-Benzhydrylphenol (3.10) Electrochemical oxidation of ((benzhydryloxy)methyl)trimethylstannane (**1a**) (72.9 mg, 0.20 mmol) in the presence of phenol (45.6 mg, 0.48 mmol) according to the general procedure at 20 mA and purification by column chromatography on silica gel (eluent DCM) afforded 23.8 mg (45 %) of product as a white solid. Product has been reported in literature.[38]

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.36–7.11 (m, 7H), 7.12–7.00 (m, 4H), 6.98–6.85 (m, 2H), 6.76–6.61 (m, 2H), 5.44 (s, 1H), 4.65 (br.s, 1H).

((4-Methoxy-3,5-dimethylphenyl)methylene)dibenzene (3.11) Electrochemical oxidation of ((benzhydryloxy)methyl)trimethylstannane (**1a**) (72.7 mg, 0.20 mmol) in the presence of 2,6-dimethylanisole (0.14 mL, 1.00 mmol) according to the general procedure at 30 mA and purification by column chromatography on silica gel (eluent petroleum ether/Et_2O, 20:1) afforded 34.9 mg (57 %) of product as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34–7.28 (m, 4H), 7.26–7.20 (m, 2H), 7.19 – 7.11 (m, 4H), 6.78 (s, 2H), 5.46 (s, 1H), 3.73 (s, 3H), 2.24 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.49, 144.33, 139.11, 130.58, 129.86, 129.53, 128.37, 126.31, 59.78, 56.46, 16.33.

HR-MS (ESI-TOF) *m/z*: calcd. for $C_{22}H_{21}O$ $[M - 1]^+$ 301.1592, found 301.1593.

((2,4-Dimethoxyphenyl)methylene)dibenzene (3.12) Electrochemical oxidation of ((benzhydryloxy)methyl)trimethylstannane (**1a**) (72.2 mg, 0.20 mmol) in the presence of 1,3-dimethoxybenzene (0.13 mL, 1.00 mmol) according to the general procedure at 20 mA

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and purification by column chromatography on silica gel (eluent petroleum ether/EtOAc, 20:1) afforded 38.3 mg (63 %) of product as a white solid. This compound has been reported in literature.[28]

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.13–7.05 (m, 4H), 6.74 (d, J = 8.4 Hz, 1H), 6.47 (m, 1H), 6.40 (m, 1H), 5.83 (s, 1H), 3.79 (s, 3H), 3.70 (s, 3H).

HR-MS (ESI-TOF) *m/z*: calcd. for $C_{21}H_{19}O_2$ $[M - 1]^+$ 303.1385, found 303.1382.

2-((4-Methoxyphenyl)(phenyl)methyl)-5-methylfuran (3.13) Electrochemical oxidation of tributyl(((4-methoxyphenyl)(phenyl)-methoxy)methyl)stannane (**1b**) (103.5 mg, 0.20 mmol) was performed in the presence of 2-methylfuran (0.09 mL, 1.0 mmol) according to the general procedure at 5 mA. Purification by column chromatography on silica gel (eluent petroleum ether/Et_2O, 20:1) afforded 41.5 mg (75 %) of product as an yellowish oil. Product has been reported in literature.[36]

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 (m, 2H), 7.25–7.19 (m, 1H), 7.17 (m, 2H), 7.13–7.06 (m, 2H), 6.90–6.80 (m, 2H), 5.87 (m, 1H), 5.77–5.70 (m, 1H), 5.34 (s, 1H), 3.79 (s, 3H), 2.25 (m, 3H).

2-((4-Methoxyphenyl)(phenyl)methyl)-5-methylthiophene (3.14) Electrochemical oxidation of tributyl(((4-methoxyphenyl)-(phenyl)-methoxy)methyl)stannane (**1b**) (104.1 mg, 0.20 mmol) was performed in the presence of 2-methylthiophene (0.1 mL, 1.0 mmol) according to the general procedure at 5 mA. Purification by column chromatography on silica gel (eluent petroleum ether/EtOAc, 20:1) afforded 36.5 mg (62 %) of product as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36–7.28 (m, 2H), 7.28–7.21 (m, 3H), 7.20–7.11 (m, 2H), 6.93–6.81 (m, 2H), 6.59 (dq, J = 3.5, 1.1 Hz, 1H), 6.47 (dd, J = 3.4, 1.1 Hz, 1H), 5.57 (s, 1H), 3.81 (s, 3H), 2.44 (d, J = 1.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.39, 146.08, 144.31, 139.04, 136.25, 129.92, 128.87, 128.45, 126.67, 126.08, 124.64, 113.82, 55.34, 51.61, 15.46.

HR-MS (ESI-TOF) *m/z*: calcd. for $C_{19}H_{17}OS$ $[M - 1]^+$ 293.1000, found 293.1009.

2-Methyl-5-(phenyl(4-(trifluoromethyl)phenyl)methyl)thiophene (3.15) Electrochemical oxidation of tributyl((phenyl(4-(trifluoro-methyl)phenyl)methoxy)methyl)stannane (**1c**) (111.9 mg, 0.20 mmol) was performed in the presence of 2-methylthiophene (0.1 mL, 1.0 mmol) according to the general procedure at 5 mA. Purification by column chromatography on silica gel (eluent petroleum ether/EtOAc, 10:1) afforded 44.0 mg (66 %) of product as an yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60 (d, J = 8.0 Hz, 2H), 7.43–7.33 (m, 4H), 7.33–7.27 (m, 1H), 7.27–7.21 (m, 2H), 6.63 (m, 1H), 6.51 (m, 1H), 5.69 (s, 1H), 2.47 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 148.0 (q, $^1J_{CF}$ = 1 Hz), 144.29, 143.06, 139.65, 129.31, 129.1 (q, $^2J_{CF}$ = 32 Hz), 28.92, 128.70, 127.15, 126.60, 125.5 (q, $^3J_{CF}$ = 4 Hz), 124.3 (q, $^2J_{CF}$ = 272 Hz),124.83, 52.18, 15.45.

^{19}F NMR (376 MHz, $CDCl_3$) δ = –62.36.

HR-MS (ESI-TOF) *m/z*: calcd. for $C_{19}H_{14}F_3S$ $[M - 1]^-$ 331.0768, found 331.0778.

***tert*-Butyl(4-((4-fluorophenyl)(phenyl)methyl)phenoxy)dimethyl-silane (3.16)** Electrochemical oxidation of tributyl(((4-fluoro-phenyl)-(phenyl)methoxy)methyl)stannane (**1d**) (101.0 mg, 0.20 mmol) was performed in the presence of *tert*-butyldimethyl(phenoxy)silane (83.3 mg, 0.4 mmol) according to the general procedure at 20 mA. Purification by column chromatography on silica gel (eluent petroleum ether/DCM, 9:1) afforded 32.2 mg (41 %) of product as an yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 (m, 2H), 7.25–7.19 (m, 1H), 7.12–7.04 (m, 4H), 7.01–6.91 (m, 4H), 6.80–6.73 (m, 2H), 5.47 (s, 1H), 0.98 (s, 9H), 0.19 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.51 (d, $^1J_{CF}$ = 244.8 Hz), 154.24, 144.28, 140.21, 136.51, 130.93 (d, $^3J_{CF}$ = 7.8 Hz), 130.37, 129.44, 128.47, 126.47, 119.95, 115.15 (d, $^2J_{CF}$ = 21.3 Hz), 55.43, 25.81, 18.32, –4.26.

^{19}F NMR (376 MHz, $CDCl_3$) δ = –117.04.

HR-MS (ESI-TOF) *m/z*: calcd. for $C_{25}H_{28}OFSi$ $[M - 1]^+$ 391.1893, found 391.1888.

2-(Cyclopropyl(phenyl)methyl)-5-methylfuran (3.17) Electrochemical oxidation of ((cyclopropyl(phenyl)methoxy)methyl)trimethyl-stannane (**1d**) (64.8 mg, 0.20 mmol) was performed in the presence of 2-methylfuran (0.09 mL, 1.0 mmol) according to the general procedure at 5 mA. Purification by column chromatography on silica gel (eluent petroleum ether/Et_2O, 20:1) afforded 30.8 mg (78 %) of product as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.36–7.21 (m, 5H), 6.09 (m, 1H), 5.91 (m, 1H), 3.23 (d, J = 9.3 Hz, 1H), 2.25 (m, 3H), 1.38–1.28 (m, 1H), 0.73–0.64 (m, 1H), 0.61–0.52 (m, 1H), 0.43–0.22 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.18, 151.07, 142.95, 128.41, 128.07, 126.59, 106.55, 105.86, 49.91, 16.02, 13.76, 5.30, 4.43.

HR-MS (ESI-TOF) *m/z*: calcd. for $C_{15}H_{17}O$ $[M + 1]^+$ 213.1279, found 213.1281.

2-Methyl-5-(1,2,3,4-tetrahydronaphthalen-1-yl)thiophene (3.18) Electrochemical oxidation of trimethyl(((1,2,3,4-tetrahydronaphth-alen-1-yl)oxy)methyl)stannane (**1f**) (65.1 mg, 0.20 mmol) was performed in the presence of 2-methylthiophene (0.10 mL, 1.0 mmol) according to the general procedure at 5 mA. Purification by column chromatography on silica gel (eluent petroleum ether/EtOAc, 20:1) afforded 27.2 mg (59 %) of product as a colourless oil. Product has been reported in literature.[40]

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.21–7.06 (m, 4H), 6.61–6.53 (m, 1H), 6.50 (d, J = 3.3 Hz, 1H), 4.34 (t, J = 6.1 Hz, 1H), 2.98–2.75 (m, 2H), 2.45 (s, 3H), 2.26–2.11 (m, 1H), 2.07–2.00 (m, 2H), 1.88–1.71 (m, 1H).

4-(1,2,3,4-Tetrahydronaphthalen-1-yl)phenol (3.19) Electrochemical oxidation of trimethyl(((1,2,3,4-tetrahydronaphthalen-1-yl)oxy)-methyl)stannane (**1f**) (65.4 mg, 0.20 mmol) was performed in the presence of phenol (40.0 mg, 0.4 mmol) according to the general procedure at 5 mA. Purification by column chromatography on silica gel (eluent petroleum ether/EtOAc, 20:1) afforded 16.9 mg (37 %) of product as a white solid. Product has been reported in literature.[40]

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.20–6.90 (m, 5H), 6.84 (d, J = 7.7 Hz, 1H), 6.74 (d, J = 8.4 Hz, 2H), 4.56 (s, 1H), 4.05 (t, J = 6.5 Hz, 1H), 3.00–2.74 (m, 2H), 2.14 (m, 1H), 2.01–1.65 (m, 3H).

2-(4-Methoxybenzyl)-5-methylthiophene (3.20) Electrochemical oxidation of (((4-methoxybenzyl)oxy)methyl)trimethylstannane (**1g**) (63.5 mg, 0.20 mmol) was performed in the presence of 2-methyl-thiophene (0.1 mL, 1.0 mmol) according to the general procedure at 5 mA. Purification by column chromatography on silica gel (eluent petroleum ether/EtOAc, 10:1) afforded 31.5 mg (72 %) of product as a colourless oil. Product has been reported in literature.[27]

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.16 (m, 2H), 6.84 (m, 2H), 6.55 (s, 2H), 4.01 (s, 2H), 3.79 (s, 3H), 2.41 (s, 3H).

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2-Methyl-5-tritylfuran (3.22) Electrochemical oxidation of tributyl((trityloxy)methyl)stannane (**1i**) (112.9 mg, 0.20 mmol) was performed in the presence of 2-methylfuran (0.09 mL, 1.0 mmol) according to the general procedure at 5 mA. Purification by column chromatography on silica gel (eluent petroleum ether/DCM, 9:1) afforded 45.6 mg (70 %) of product as a white solid. Product has been reported in literature.[28]

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33–7.25 (m, 10H including residual $CHCl_3$), 7.18–7.11 (m, 6H), 5.95–5.90 (m, 1H), 5.88 (d, J = 3.2 Hz, 1H), 2.31 (s, 3H).

2-Methyl-5-(2-phenylpropan-2-yl)thiophene (3.23) Electrochemical oxidation of trimethyl(((2-phenylpropan-2-yl)oxy)methyl)-stannane (**1j**) (62.4 mg, 0.20 mmol) was performed in the presence of 2-methylthiophene (0.10 mL, 1.0 mmol) according to the general procedure at 5 mA. Purification by column chromatography on silica gel (eluent petroleum ether/EtOAc, 20:1) afforded 22.5 mg (52 %) of product as a colourless oil. Product has been reported in literature.[41]

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.37–7.27 (m, 4H), 7.23–7.14 (m, 1H), 6.60 (d, J = 3.4 Hz, 1H), 6.56 (m, 1H), 2.41 (d, J = 1.1 Hz, 3H), 1.74 (s, 6H).

2-Methyl-5-(1-phenylcyclohexyl)thiophene (3.24) Electrochemical oxidation of tributyl(((1-phenylcyclohexyl)oxy)methyl)stannane (**1k**) (96.6 mg, 0.20 mmol) was performed in the presence of 2-methylthiophene (0.1 mL, 1.0 mmol) according to the general procedure at 5 mA. Purification by column chromatography on silica gel (eluent petroleum ether/DCM, 9:1) afforded 30.0 mg (58 %) of product as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43–7.27 (m, 4H), 7.21–7.16 (m, 1H), 6.63 – 6.53 (m, 2H), 2.42 (d, J = 1.2 Hz, 3H), 2.38–2.18 (m, 4H), 1.74–1.38 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 152.79, 148.32, 137.83, 128.38, 126.70, 125.92, 124.47, 123.30, 45.50, 38.76, 26.23, 23.03, 15.44.

HR-MS (ESI-TOF) m/z: calcd. for $C_{17}H_{21}S$ $[M + 1]^+$ 257.1364, found 257.1356.

Ethyl 2-(5-methylthiophen-2-yl)-2,2-diphenyl acetate (3.25) Electrochemical oxidation of (80 mg, 0.18 mmol) was performed in the presence of 2-methylthiophene (0.1 mL, 1.0 mmol) according to the general procedure at 5 mA. Purification by twice column chromatography on silica gel (eluent petroleum) afforded 13.2 mg (21 %) of product as an yellowish oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.36–7.27 (m, 6H), 7.17–7.06 (m, 4H), 6.58 (dd, J = 3.6, 1.1 Hz, 1H), 6.43 (d, J = 3.6 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 2.44 (d, J = 1.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.18, 143.63, 143.42, 140.86, 129.84, 129.61, 127.83, 127.40, 124.09, 64.79, 62.17, 15.32, 14.12.

HR-MS (ESI-TOF) m/z: calcd. for $C_{21}H_{21}O_2S$ $[M + 1]^+$ 337.1262, found 337.1245.

2-Methyl-5-(2-phenyl-1-(4-(trifluoromethyl)phenoxy)propan-2-yl)furan (3.26) Electrochemical oxidation of trimethyl(((2-phenyl-1-(4-(trifluoromethyl)phenoxy)propan-2-yl)oxy)methyl)stannane (94.8 mg, 0.20 mmol) was performed in the presence of 2-methylfuran (0.09 mL, 1.0 mmol) according to the general procedure at 5 mA. Purification by column chromatography on silica gel (eluent petroleum ether/Et_2O, 20:1) afforded 28.0 mg (39 %) of product as an yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54 (d, J = 8.7 Hz, 2H), 7.26 (s, 6H), 6.98 (d, J = 8.5 Hz, 2H), 6.65 (d, J = 3.5 Hz, 1H), 6.59 (m, 1H), 4.37 (s, 2H), 2.43 (s, 3H), 1.91 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.33, 148.71, 145.62, 138.86, 128.37, 127.07, 127.01 (q, J = 3.8 Hz), 126.90, 124.5 (q, J = 271 Hz), 123.3 (q, J = 32.8 Hz), 114.85, 46.13, 26.69, 15.38.

Unstable under the conditions of HR-MS.

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Keywords: Friedel–Crafts reaction · Electrochemistry · Carbenium ion · Anodic oxidation · Stannylmethyl ethers

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Intramolecular Friedel–Crafts alkylation by electrochemical carbenium ion generation

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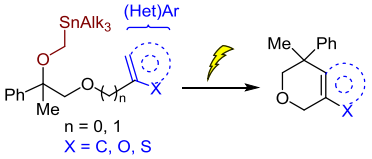


Electrochemical activation of trialkylstannylmethyl group as an electroauxiliary for carbenium ion generation enables the intramolecular Friedel–Crafts alkylation. Electrochemical activation of stannylmethyl group forms carbenium ion which can be trapped by intramolecular (het)aromatic nucleophiles for the formation of new 6-membered cycles.

Keywords: carbenium ion, chromenes, pyrans, condensed heterocycles, electroauxiliary, electroorganic synthesis, Friedel–Crafts alkylation.

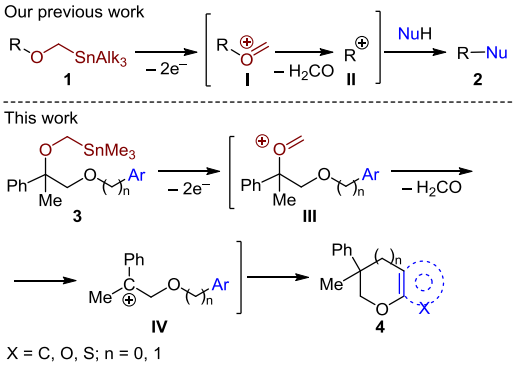
Friedel–Crafts alkylation enables functionalization of arenes by their reaction with *in situ* generated carbenium ions.[1] Classical realization of the reaction relays on the use of catalytic or stoichiometric amounts of Brønsted or Lewis acids for carbenium ion generation rendering the reaction incompatible with acid-labile functional groups. In the recently reported electrochemically induced Friedel–Crafts alkylations, redox mediators[2,3] or ring-opening reactions[3,4] are used to generate the carbenium ions. Alternatively, carbenium ions could be generated using electroauxiliaries – electrochemical leaving groups that promote electron transfer.[5,6] Some reported electroauxiliaries include silyl,[7] stannyl,[8] arylthio[9] groups, organoboronic acid[10] and carboxylic acid.[11]

Recently we reported a new method for electrochemical generation of carbenium ions which offers acid-free conditions for Friedel–Crafts alkylation.[12] The method is based on trialkylstannylmethyl group as an electroauxiliary originally introduced by Yoshida et al.[8] We showed that anodic oxidation of stannylmethyl ethers **1** can be used for the generation of carbenium ions **II** *via* fragmentation of oxonium ions **I**[12,13] (Scheme 1).

The electrochemically generated carbenium ions **II** were engaged in a reaction with allylsilane[13] and also with various (het)arenes to realize Friedel–Crafts reaction in nonacidic conditions.[12] Trialkylstannylmethyl group as an electroauxiliary with low oxidation potential was the key to avoiding the oxidation of electron-rich aromatic systems.

In this work, we demonstrate the use of trialkylstannylmethyl ethers for electrochemical generation of carbenium ions to perform intramolecular Friedel–Crafts alkylation providing condensed heterocycles. For this study, we have designed substrates **3** in which the internal (het)aromatic nucleophile was attached to the reaction center *via* a tether of suitable length to form a 5- or 6-membered cycle upon intramolecular cyclization. The substrates were synthesized by ring-opening reaction of epoxide **5** with an alcohol introducing the intramolecular nucleophile to obtain alcohols **6a–f** which were modified with the trialkylstannylmethyl electroauxiliary to provide products **3a–f** (Scheme 2).

Scheme 1. Strategies for inter- and intramolecular Friedel–Crafts alkylation using electroauxiliary for carbenium ion generation



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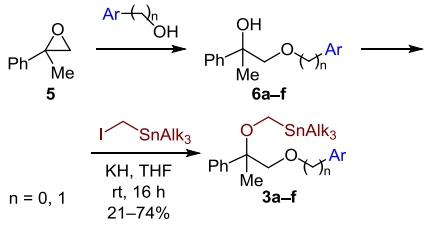
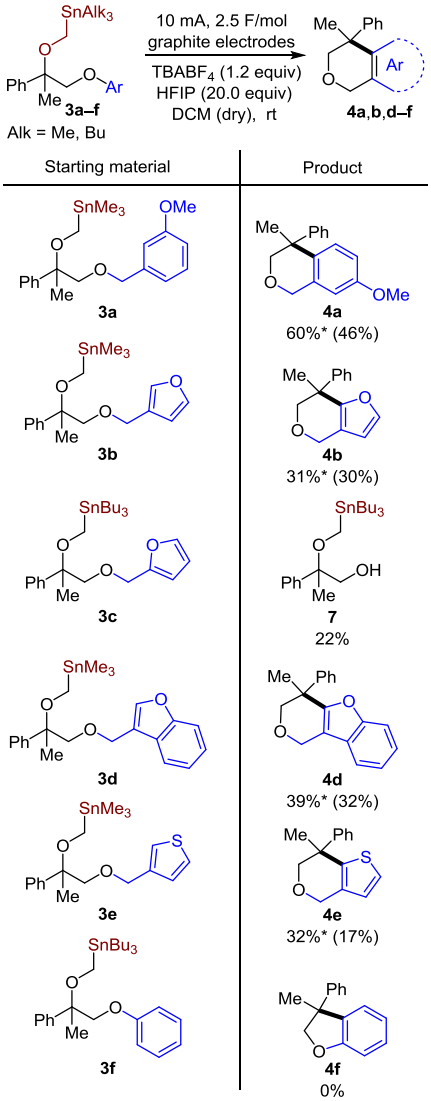
Scheme 2. Synthesis of the starting materials **3a–f** for intramolecular Friedel–Crafts alkylation



Scheme 3. Scope of intramolecular Friedel–Crafts alkylation



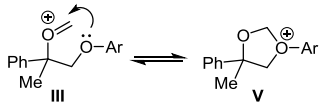
* ^{1}H NMR yield using 1,4-bis(trichloromethyl)benzene or EtOAc as the internal standard, in brackets – isolated yield.

The electrolysis of substrates **3a–f** was performed under conditions optimized for intermolecular Friedel–Crafts alkylation with trialkylstannylmethyl ethers.[12] Constant current was applied to the reaction mixture in an undivided cell equipped with graphite electrodes. The electrolyte was tetrabutylammonium tetrafluoroborate ($TBABF_4$) in dichloromethane (DCM) with hexafluoroisopropanol (HFIP) as an additive. HFIP served both as a proton donor for the cathodic reaction of hydrogen evolution and presumably to promote the ionization of trialkylstannylmethyl ether by formation of ate complex with the hexafluoroisopropanoate ion formed at the cathode.

Substrate **3a** with 3-methoxyphenyl group as internal nucleophile gave product **4a** in a good yield with excellent regioselectivity – no formation of the regioisomers was observed (Scheme 3). 3-Furfuryl (substrate **3b**) and 3-benzofurfuryl groups (substrate **3d**) were also suitable internal nucleophiles providing products **4b**,**d** in moderate yields. 2-Furfuryl group in substrate **3c** was cleaved off during electrolysis, giving alcohol **7** as the major side product. Poor yield of Friedel–Crafts alkylation product **4e** was obtained when 3-thienyl group (substrate **3e**) served as the internal nucleophile. The formation of 5-membered ring (product **4f**) from substrate **3f** bearing phenyl group as an internal nucleophile was not observed.

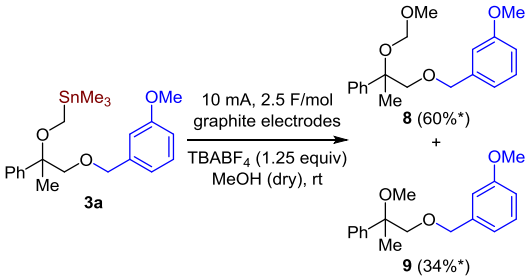
The yields for intramolecular Friedel–Crafts reaction (Scheme 3) were relatively lower compared to the intermolecular reaction.[2] We hypothesized that the reduced yields could be explained by poor fragmentation of intermediate oxonium ion **III** due to the stabilization through forming a transient cyclic system **V**[14] (Scheme 4).

Scheme 4. Oxonium ion stabilization by the lone electron pair of the ether linker



To test the effectiveness of oxonium ion **III** fragmentation to carbenium ion **IV**, electrolysis of compound **3a** in MeOH was conducted (Scheme 5). The product analysis showed that the ratio of compounds **8** and **9** was 2:1 with oxonium ion addition product in excess.

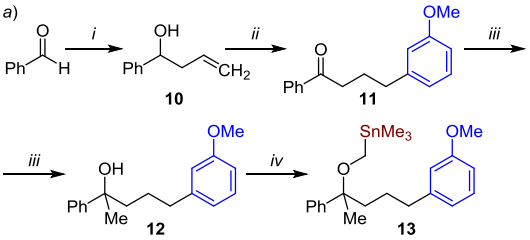
Scheme 5. Methanolysis of substrate **3a** to determine the ratio of oxonium and carbenium ion reaction products



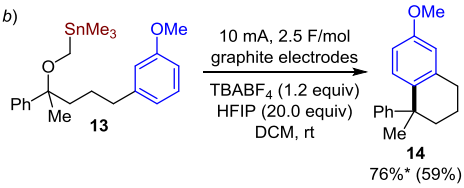
* ^{1}H NMR yield using 1,4-bis(trichloromethyl)benzene as the internal standard.

To further investigate the effect of oxonium ion stabilization, analog **13** was synthesized where oxygen in the linker was substituted for a CH_2 group (Scheme 6*a*) incapable of stabilizing oxonium ion **I**. Alcohol **12** was prepared in three steps starting from benzaldehyde (Scheme 6*a*). Reaction with allylmagnesium bromide afforded intermediate **10** which was coupled with 3-iodoanisole in a Pd-catalyzed Heck reaction to obtain ketone **11**. Grignard reaction between ketone **11** and methylmagnesium bromide furnished alcohol **12** which was further modified with trimethylstannylmethyl electroauxiliary to give starting material **13**.

Scheme 6. *a*) Synthetic pathway to obtain substrate **13**; *b*) electrochemical cyclization to substrate **14**



i: allylmagnesium bromide (1.2 equiv), THF, 0°C, 1 h
ii: $Pd(OAc)_2$ (2.0 mol %), LiCl (3.0 equiv), DIPEA (1.5 equiv), 3-iodoanisole (1.0 equiv), DMF, Ar, 80°C, 18 h
iii: MeMgBr (3 M, 2.0 equiv), Et_2O, 0°C, 3 h, then aq NH_4Cl
iv: 30% KH in oil (2.0 equiv), (iodomethyl)trialkylstannane (1.05 equiv), THF, Ar, 16 h



* ^{1}H NMR yield using 1,4-bis(trichloromethyl)benzene as the internal standard, in brackets – isolated yield.

When substrate **13** was subjected to the electrolysis conditions (Scheme 6*b*), carbocycle **14** was formed in a higher yield compared to substrate **3a** containing ether bond, further confirming the role of oxonium ion stabilization hindering the formation of the condensed heterocycles.

For further investigation of the electrochemical behavior of the substrates, compounds **3a** and **13** were characterized by cyclic voltammetry in the presence and absence of HFIP (Table 1). The peak potential of the irreversible oxidation was decreased by 100 mV in presence of HFIP. We propose that the lowering of the redox potential is caused by the formation of a stannate by complexation of the corresponding substrate and the hexafluoropropanoate formed at the cathode.[12] Additionally, HFIP is known to stabilize cationic and radical cation species.[15]

Table 1. Cyclic voltammetry data for substrates **3a** and **13** in 0.1 M $TBABF_4$/DCM in the presence and absence of HFIP

Substrate	E^{ox}, V *vs* Ag/AgCl	E^{ox} in presence of HFIP, V *vs* Ag/AgCl
3a	1.81	1.72
13	1.94	1.85

In summary, we have demonstrated that an intramolecular Friedel–Crafts alkylation by electrochemical carbenium ion formation from stannylmethyl ethers can be performed to obtain various condensed heterocycles. The product formation is hindered by oxonium ion stabilization when an ether linker is used to attach the internal nucleophile to the reaction center. The irreversible electrochemical oxidation of the stannylmethyl group is promoted by HFIP as shown by cyclic voltammetry.

Experimental

IR spectra were recorded on a Shimadzu IR Prestige-21 spectrometer in thin layer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400-MR spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ using the residual solvent peaks as internal standard (7.26 ppm for ^{1}H nuclei, 77.2 ppm for ^{13}C nuclei). HRMS analyses were performed on a hybrid quadrupole time-of-flight mass spectrometer equipped with an electrospray ion source. Flash column chromatography was carried out using silica gel (35–70 mesh). Electrochemical experiments were performed using an electrochemical system Electrasyn 2.0. Cyclic voltammetry was conducted with a PARSTAT 2273 potentiostat/galvanostat/FR analyzer using three-electrode setup with glassy carbon working electrode, platinum counter electrode, and Ag/AgCl pseudoreference electrode.

All procedures for starting material synthesis were performed in oven-dried glassware under argon atmosphere unless noted otherwise. Reagents and starting materials were obtained from commercial sources and used as received unless noted otherwise. Tetrabutylammonium tetrafluoroborate (Fluorochem) was recrystallized from EtOAc and dried in vacuum at 60°C for 6 h before use. Solvents were obtained from a MBraun MB-SPS-800 solvent purification system.

Synthesis of stannylmethyl ethers 3a–f, 13 from alcohols 6a–f, 12 (General method). Oven-dried flask was charged with 30% KH suspension in oil (2.00 equiv) in dry THF (80 ml) under argon. Alcohol **6a–f**, **12** (1.00 equiv) was added to the suspension in portions, and the solution was stirred for 2–3 min at room temperature. Afterward, (iodomethyl)trialkylstannane (1.05 equiv) was added and the reaction mixture was stirred for 16 h. Then, the excess KH was quenched by slow addition of ice-cold H_2O, the reaction mixture was diluted with Et_2O and extracted 2 times, and then the combined organic phase was washed with H_2O and brine. The organic phase was dried over Na_2SO_4, and the solvent was evaporated to give a crude mixture which was purified by flash column chromatography on silica gel using petroleum ether – EtOAc, 20:1 (except for compound **3c** where 8:1 ratio was used) as eluent to obtain the corresponding product.

[({1-[(3-Methoxybenzyl)oxy]-2-phenylpropan-2-yl}oxy)methyl]trimethylstannane (3a) was prepared from 30% KH (1.44 g, 10.8 mmol), 1-[(3-methoxybenzyl)oxy]-2-phenylpropan-2-ol (**6a**) (1.47 g, 5.4 mmol), and (iodomethyl)-

trimethylstannane (1.73 g, 5.7 mmol). Yield 1.27 g (52%), yellow oil. IR spectrum, ν, cm^{-1}: 3056 (C–H Ar), 2903 (C–H), 1034 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.14 (9H, s, $J^{117/119}_{Sn-^1H}$ = 52.0, $Sn(CH_3)_3$); 1.64 (3H, s, CH_3); 3.25 (1H, d, $J^{117/119}_{Sn-^1H}$ = 36.0, *J* = 9.7, $SnCH_2$); 3.49 (2H, d, *J* = 9.3, $ArCH_2$); 3.58 (1H, d, *J* = 10.1, $SnCH_2$); 3.78 (3H, s, OCH_3); 6.79–6.85 (3H, m, H Ar); 7.19–7.40 (6H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: −10.3; 20.1; 53.3; 55.3; 73.5; 78.2; 81.2; 112.7; 113.2; 119.8; 127.0; 127.2; 128.2; 129.4; 140.6; 143.5; 159.8. Found, *m*/*z*: 473.1099 $[M+Na]^+$. $C_{21}H_{30}NaO_3Sn$. Calculated, *m*/*z*: 473.1115.

({[1-(Furan-3-ylmethoxy)-2-phenylpropan-2-yl]oxy}methyl)trimethylstannane (3b) was prepared from 30% KH (1.40 g, 10.5 mmol), 1-(furan-3-ylmethoxy)-2-phenylpropan-2-ol (**6b**) (1.22 g, 5.3 mmol), and (iodomethyl)trimethylstannane (1.68 g, 5.5 mmol). Yield 1.5 g (70%), light-yellow oil. IR spectrum, ν, cm^{-1}: 2904 (C–H), 1884 (C–H Ar), 768 (C–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.13 (9H, s, $J^{117/119}_{Sn-^1H}$ = 56.0, $Sn(CH_3)_3$); 1.60 (3H, s, CH_3); 3.23 (1H, d, $J^{117/119}_{Sn-^1H}$ = 36.0, *J* = 9.7, $SnCH_2$); 3.38–3.59 (3H, m, $SnCH_2$, CH_2); 4.35 (1H, d, *J* = 12.4, OCH_2); 4.45 (1H, d, *J* = 12.4, OCH_2); 6.32 (1H, s, H HetAr); 7.23–7.40 (7H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: –10.3; 20.0; 53.3; 65.0; 77.8; 81.2; 110.4; 122.8; 126.9; 127.2; 128.2; 140.6; 143.3; 143.5. Found, *m*/*z*: 433.0795 $[M+Na]^+$. $C_{18}H_{26}NaO_3Sn$. Calculated, *m*/*z*: 433.0802.

Tri-*n*-butyl({[1-(furan-2-ylmethoxy)-2-phenylpropan-2-yl]oxy}methyl)stannane (3c) was prepared from 30% KH (2.08 g, 15.5 mmol), 1-(furan-2-ylmethoxy)-2-phenylpropan-2-ol (**6c**) (1.80 g, 7.8 mmol), and tributyl(iodomethyl)stannane (2.51 g, 8.2 mmol). Yield 0.89 g (21%), light-yellow oil. IR spectrum, ν, cm^{-1}: 2925 (C–H), 1097 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.75–0.91 (15H, m, $3CH_3CH_2$); 1.23 (6H, s, *J* = 7.3, $3EtCH_2$); 1.39–1.51 (6H, m, $3EtCH_2CH_2$); 1.51 (3H, s, CH_3); 3.16 (1H, d, $J^{117/119}_{Sn-^1H}$ = 32.0, *J* = 9.5, $SnCH_2O$); 3.40 (2H, d, *J* = 9.5, CCH_2); 3.49 (1H, d, *J* = 10.5, $SnCH_2O$); 4.34 (1H, d, *J* = 13.1, OCH_2); 4.43 (1H, d, *J* = 13.1, OCH_2); 6.15 (1H, d, *J* = 3.1, C=C<u>H</u>–CH); 6.24 (1H, dd, *J* = 3.0, *J* = 1.9, CH–C<u>H</u>=CHO); 7.16–7.32 (6H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 9.1; 13.9; 19.8; 27.5; 29.3; 51.9; 65;7; 78.1; 81.3; 109.0; 110.3; 127.0; 127.2; 128.1; 142.6; 143.4; 152.4. Compound is unstable under HRMS conditions.

({[1-(Benzofuran-3-ylmethoxy)-2-phenylpropan-2-yl]oxy}methyl)trimethylstannane (3d) was prepared from 30% KH (0.54 g, 4.0 mmol), 1-(benzofuran-3-ylmethoxy)-2-phenylpropan-2-ol (**6d**) (0.57 g, 2.0 mmol), and (iodomethyl)trimethylstannane (0.64 g, 2.1 mmol). Yield 0.92 g (60%), light-yellow oil. IR spectrum, ν, cm^{-1}: 2901 (C–H), 1582 (C–H Ar), 746 (C–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.13 (9H, s, $J^{117/119}_{Sn-^1H}$ = 56.0, $Sn(CH_3)_3$); 1.62 (3H, s, CH_3); 3.24 (1H, d, $J^{117/119}_{Sn-^1H}$ = 40.0, *J* = 9.7, $SnCH_2$); 3.45–3.54 (3H, m, $SnCH_2$, CCH_2); 3.61 (1H, d, *J* = 10.1, $SnCH_2$); 4.62 (1H, d, *J* = 12.5, OCH_2); 4.74 (1H, d, *J* = 13.1, OCH_2); 7.16–7.23 (1H, m, H Ar); 7.24–7.40 (6H, m, H Ar); 7.43–7.54 (3H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: –10.3; 19.2; 53.3; 64.4; 78.2; 81.2; 111.5; 118.2; 120.5; 122.7; 124.5; 127.0; 127.3 (2C); 128.2; 142.8; 143.4; 155.7. Compound is unstable under HRMS conditions.

Trimethyl({[2-phenyl-1-(thiophen-3-ylmethoxy)propan-2-yl]oxy}methyl)stannane (3e) was prepared from 30% KH (1.02 g, 4.0 mmol), 2-phenyl-1-(thiophen-3-ylmethoxy)-propan-2-ol (**6e**) (0.95 g, 3.8 mmol), and (iodomethyl)-trimethylstannane (1.22 g, 4.0 mmol). Yield 1.2 g (74%), light-yellow oil. IR spectrum, ν, cm^{-1}: 2903 (C–H), 1602 (C–H Ar), 770 (C–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.13 (9H, s, $J^{117/119}_{Sn-^1H}$ = 56.0, $Sn(CH_3)_3$); 1.61 (3H, s, CH_3); 3.24 (1H, d, $J^{117/119}_{Sn-^1H}$ = 36.0, *J* = 9.7, $SnCH_2$); 3.47 (2H, dd, *J* = 9.7, *J* = 3.2, CCH_2); 3.56 (1H, d, *J* = 10.1, $SnCH_2$); 4.49 (1H, d, *J* = 12.5, OCH_2); 4.58 (1H, d, *J* = 12.5, OCH_2); 6.97 (1H, d, *J* = 4.9, H Ar); 7.09 (1H, s, H Ar); 7.23–7.27 (2H, m, H Ar); 7.32–7.39 (4H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: –10.3; 20.0; 53.3; 78.1; 81.2; 122.4; 125.8; 127.0; 127.2; 127.3; 128.2; 140.1; 143.5. Found, *m*/*z*: 411.0431 $[M–Me]^+$. $C_{17}H_{23}O_2SSn$. Calculated, *m*/*z*: 411.0441.

Tri-*n*-butyl{[(1-phenoxy-2-phenylpropan-2-yl)oxy]methyl}stannane (3f) was prepared from 30% KH (1.87 g, 16.3 mmol), 1-phenoxy-2-phenylpropan-2-ol (**6f**) (1.86 g, 8.2 mmol), and tributyl(iodomethyl)stannane (3.69 g, 8.7 mmol). Yield 1.92 g (44%), light-yellow oil. IR spectrum, ν, cm^{-1}: 3061 (C–H Ar), 2926 (C–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.79–0.91 (15H, m, $3CH_3CH_2$); 1.23 (6H, sext, *J* = 7.2, $3EtCH_2$); 1.39–1.47 (6H, m, $3EtCH_2CH_2$); 1.62 (3H, s, CCH_3); 3.24 (1H, d, $J^{117/119}_{Sn-^1H}$ = 32.0, *J* = 9.4, $SnCH_2O$); 3.44 (1H, d, $J^{117/119}_{Sn-^1H}$ = 32.0, *J* = 9.5, $SnCH_2O$); 3.89 (1H, d, *J* = 9.3, CH_2O); 3.96 (1H, d, *J* = 9.3, CH_2O); 6.78–6.84 (3H, m, H Ar); 7.13–7.22 (3H, m, H Ar); 7.28 (2H, t, *J* = 7.5, H Ar); 7.37 (2H, d, *J* = 7.4, H Ar). ^{13}C NMR spectrum, δ, ppm: 9.1; 13.9; 20.4; 27.5; 29.3; 52.0; 75.5; 80.1; 114.9; 120.7; 127.0; 128.2; 129.4; 143.1; 159.4. Found, *m*/*z*: 475.1650 $[M–Bu]^+$. $C_{24}H_{35}O_2Sn$. Calculated, *m*/*z*: 475.1654.

({[5-(3-Methoxyphenyl)-2-phenylpentan-2-yl]oxy}methyl)trimethylstannane (13) was prepared from 30% KH (0.44 g, 3.3 mmol), 5-(3-methoxyphenyl)phenylpentan-2-ol (**12**) (0.45 g, 1.7 mmol), and (iodomethyl)trimethylstannane (0.53 g, 1.7 mmol). Yield 0.47 g (67%), light-yellow oil. IR spectrum, ν, cm^{-1}: 2943 (C–H), 1601 (C–O), 768 (C–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.14 (9H, s, $J^{117/119}_{Sn-^1H}$ = 56.0, $Sn(CH_3)_3$); 1.49 (3H, s, CH_3); 1.50–1.60 (2H, m, CH_2); 1.70–1.85 (2H, m, CH_2); 2.52 (2H, t, *J* = 7.6, CH_2); 3.21 (1H, d, $J^{117/119}_{Sn-^1H}$ = 40.0, *J* = 9.6, $SnCH_2$); 3.36 (1H, d, $J^{117/119}_{Sn-^1H}$ = 40.0, *J* = 9.7, $SnCH_2$); 3.79 (3H, s, OCH_3); 6.65–6.76 (3H, m, H Ar); 7.12–7.28 (2H, m, H Ar); 7.28–7.38 (4H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: –10.4; 23.1; 25.7; 36.4; 42.0; 52.7; 55.2; 80.4; 111.1; 114.2; 121.0; 126.4; 126.6; 128.1; 129.3; 144.4; 146.1; 159.7. Found, *m*/*z*: 433.1179 $[M–Me]^+$. $C_{21}H_{29}O_2Sn$. Calculated, *m*/*z*: 433.1190.

Electrochemical cyclization for the synthesis of products 4a–e, 7, 14 (General method). Undivided electrochemical cell (5 ml) equipped with graphite electrodes was charged with trialkylstannylmethyl ether **3a–f**, **13** (0.2 mmol, 1.0 equiv), $TBABF_4$ (80 mg, 0.24 mmol, 1.2 equiv), and dry DCM (2 ml). HFIP (0.4 ml, 4.0 mmol, 20.0 equiv) was added to the solution, and the electrolysis was conducted at 10 mA until 2.5 F/mol were consumed. Polarization of the

electrodes was automatically reversed each minute. After electrolysis, the mixture was transferred to a flask, evaporated in vacuum, analyzed with NMR with addition of 1,4-bis-(trichloromethyl)benzene (15.6 mg, 0.05 mmol, 0.25 equiv) or EtOAc (19.6 µl, 0.2 mmol, 1.0 equiv) as internal NMR standard and finally purified with column chromatography.

7-Methoxy-4-methyl-4-phenyl-3,4-dihydro-1*H*-isochromene (4a). Purified by column chromatography using petroleum ether – EtOAc, 8:1, as eluent. Yield 24 mg (46%), light-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.76 (3H, s, CH_3); 3.82 (1H, d, *J* = 11.3, CCH_2O); 3.85 (3H, s, OCH_3); 3.97 (1H, d, *J* = 11.2, CCH_2O); 4.93 (2H, d, *J* = 2.5, OCH_2Ar); 6.62 (1H, d, *J* = 2.6, H Ar); 6.78 (1H, dd, *J* = 8.6, *J* = 2.7, H Ar); 6.94 (1H, d, *J* = 8.6, H Ar); 7.21–7.37 (5H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 26.0; 42.0; 55.4; 69.2; 78.5; 108.4; 113.5; 126.4; 127.8; 128.17; 129.7; 134.4; 135.3; 147.0; 157.8. Found, *m/z*: 208.0885 $[M–Me–OMe]^+$. $C_{15}H_{12}O$. Calculated, *m/z*: 208.0877.

7-Methyl-7-phenyl-6,7-dihydro-4*H*-furo[3,2-*c*]pyran (4b). Purified by column chromatography using petroleum ether – EtOAc, 9:1, as eluent. Yield 13 mg (30%), light-yellow oil. IR spectrum, ν, cm^{-1}: 2924 (C–H), 1446 (C–O), 699 (C–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.64 (3H, s, CH_3); 3.72 (1H, d, *J* = 11.1, CCH_2O); 3.99 (1H, d, *J* = 11.1, CCH_2O); 4.68 (2H, d, *J* = 3.0, $ArCH_2O$); 6.25 (1H, s, H Ar); 7.18–7.38 (6H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 22.3; 41.9; 65.0; 78.0; 107.0; 116.1; 126.62; 126.65; 128.3; 141.6; 144.3; 152.9. Found, *m/z*: 215.1063 $[M+H]^+$. $C_{14}H_{15}O_2$. Calculated, *m/z:* 215.1072.

4-Methyl-4-phenyl-3,4-dihydro-1*H*-pyrano[4,3-*b*][1]-benzofuran (4d). Purified by column chromatography using hexane–Et_2O, 5:1, as eluent. Yield 17 mg (32%), colorless oil. IR spectrum, ν, cm^{-1}: 2848 (C–H), 1451 (C–O), 749 (C–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.75 (3H, s, CH_3); 3.84 (1H, d, *J* = 11.2, CCH_2O); 4.10 (1H, d, *J* = 11.2, CCH_2O); 4.87–5.00 (2H, m, $ArCH_2O$); 7.20–7.36 (7H, m, H Ar); 7.39–7.49 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 22.3; 42.3; 64.1; 78.2; 111.8; 112.3; 118.9; 122.8; 124.0; 125.9; 126.9; 127.0; 128.6; 143.5; 154.6; 156.0. Found, *m/z*: 265.1225 $[M+H]^+$. $C_{18}H_{17}O_2$. Calculated, *m/z:* 265.1229.

7-Methyl-7-phenyl-6,7-dihydro-4*H*-thieno[3,2-*c*]pyran (4e). Purified by column chromatography using petroleum ether – EtOAc, 8:1, as eluent. Yield 8 mg (17%), light-yellow oil. IR spectrum, ν, cm^{-1}: 2967 (C–H), 1444 (C–O), 698 (C–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.78 (3H, s, CH_3); 3.78 (1H, d, *J* = 11.0, CCH_2O); 4.04 (1H, d, *J* = 11.0, CCH_2O); 4.80–4.93 (2H, m, $ArCH_2O$); 6.82 (1H, d, *J* = 5.2, H Ar); 7.23–7.38 (6H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 26.3; 42.3; 67.1; 78.0; 123.1; 124.1; 126.7; 127.1; 128.3; 134.1; 142.7; 146.3. Found, *m/z*: 213.0743 $[M–OH]^+$. $C_{14}H_{13}S$. Calculated, *m/z:* 213.0738.

2-Phenyl-2-[(tributylstannyl)methoxy]propan-1-ol (7). Purified by column chromatography using petroleum ether – DCM, 2:1, as eluent. Yield 21 mg (22%), yellow oil. Cyclization product was not observed. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.88–0.95 (15H, m, $3CH_3CH_2$); 1.26–1.36 (7H, m, $3EtCH_2CH_2$); 1.48–1.56 (5H, m, $3EtCH_2CH_2$); 1.61 (3H, s, CCH_3); 2.00 (1H, br. s, OH); 3.29 (1H, d, $J^{117/119}_{Sn–^1H}$ = 30.0, $SnCH_2$); 3.45–3.53 (2H, m, CH_2O); 3.63 (1H, d, *J* = 11.0, $SnCH_2$); 7.26–7.39 (5H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 9.1; 13.9; 19.1; 27.5; 29.4; 51.9; 71.6; 81.2; 126.8; 127.5; 128.4; 152.5. Compound is unstable under HRMS conditions.

6-Methoxy-1-methyl-1-phenyl-1,2,3,4-tetrahydro-naphthalene (14). Purified by column chromatography using hexane–Et_2O, 9:1, as eluent. Yield 31 mg (59%), light-yellow oil. IR spectrum, ν, cm^{-1}: 2932 (C–H), 1736 (C–H Ar), 1493 (C–O), 701 (C–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.20–1.32 (1H, m, CH_2); 1.58–1.81 (1H, m, CH_2); 1.71 (3H, s, CH_3); 1.83–1.92 (1H, m, CH_2); 2.00–2.09 (1H, m, CH_2); 2.83 (2H, t, *J* = 6.5, $ArCH_2$); 3.80 (3H, s, OCH_3); 6.64–6.72 (2H, m, H Ar); 6.93 (1H, d, *J* = 8.5, H Ar); 7.08–7.18 (3H, m, H Ar); 7.19–7.28 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 19.7; 30.2; 30.8; 41.7; 42.5; 55.3; 112.5; 113.2; 125.5; 127.5; 127.9; 130.3; 136.7; 138.5; 151.9; 157.5. Found, *m/z*: 251.1434 $[M–H]^-$. $C_{18}H_{19}O$. Calculated, *m/z:* 251.1436.

Supplementary information file containing procedures for synthesis of starting compounds **6a–f**, **12** and ^{1}H and ^{13}C NMR spectra of the synthesized compounds is available at the journal website at http://hgs.osi.lv.

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Torii-Type Electrosynthesis of α,β-Unsaturated Esters from Furfurylated Ethylene Glycols and Amino Alcohols

Madara Darzina,[a] Anna Lielpetere,[a] and Aigars Jirgensons*[a]

Electrosynthesis of unsaturated esters from furan derivatives, reported by Torii et al. in 1976, is an attractive method for the valorization of furanoic platform chemicals. Nevertheless, it has received practically no attention, presumably due to specific reaction conditions including the use of expensive Pt electrodes. With the aim of expanding the application of Torii-type ester electrosynthesis, we explored the electrochemical transformation of *O*-furfuryl ethylene glycols and N-furfuryl amino alcohols to esters **5**. These can be obtained in two consecutive electrochemical steps: bis-alkoxylation of the furan derived substrates **3** to give spirocycles **4**, followed by ring-opening involving oxidative fragmentation of the C–C bond. Both steps can be carried out at ambient conditions, using inexpensive graphite electrodes; however, each step required a different supporting electrolyte and acidic additive to achieve good yields of the product. Additionally, conditions were found for efficient one-pot transformation of N-furfuryl amino alcohols to esters **5** while O-furfuryl ethylene glycols under the same conditions gave esters **5** in moderate yields.

Introduction

The utilization of biomass has received increasing attention as an alternative to replace the dwindling fossil resources for the production of value-added products.[1] Biomass-derived platform chemicals are central to this initiative. Among them, furanoics, accessible in bulk amounts from lignocellulosic feedstocks, are versatile starting materials to achieve a range of chemicals with an application in material science, drug discovery, and agriculture.[2] Electrochemistry has been demonstrated as a useful tool for valorization of biomass-derived compounds.[3] Furanoics are particularly suitable substrates for electrochemical functionalization due to the low oxidation potential of the furan ring[4] (see also Supporting Information). Notable examples include oxidative dihydroxylation[5] and dialkoxylation[6] of furan derivatives. Anodic oxidative dialkoxylation was also employed in electrochemical synthesis of unsaturated ester **2** from furfuryl alcohol **1a**, furfural **1b**, and 2-furoic acid **1c** in the presence of methanol, first demonstrated by Torii *et al* (Figure 1).[7] According to their proposed mechanism, oxidative dimethoxylation of the furan ring leads to intermediate **A**. Further oxidation leads to cleavage of the *C–C* bond resulting in oxonium ion **B** and subsequent ring opening by methanol gives ester **2**. Despite the high potential value of the Torii ester electrosynthesis products, surprisingly limited application of this transformation has been demonstrated in the scientific literature.[8] Our work was focused on the electrochemical oxidation of furylmethyl derivatives **3** bearing hydroxyl group as an internal nucleophile (Figure 1). In this case, oxidative methoxylation should provide spirocyclic derivatives **4** which would undergo fragmentation to give products **5** with functionalized ester moiety. These products are valuable building blocks for further chemical transformations, including tailored polymer synthesis.

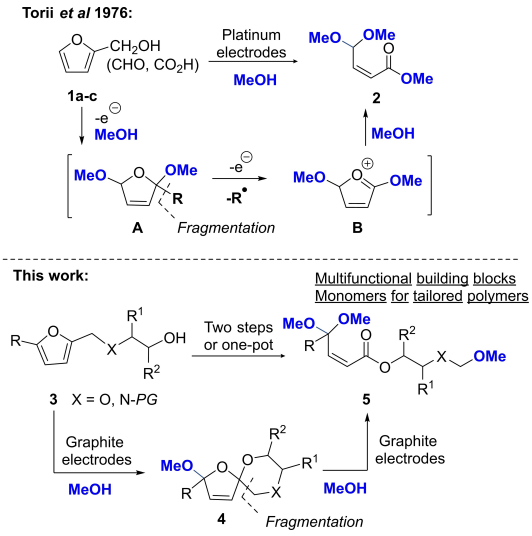

Figure 1. Torii-type electrosynthesis of unsaturated esters.

Results and Discussion

O-Furfuryl ethylene glycol (**3a**) was used as the model substrate to find efficient conditions for the spirocycle (**4a**) formation by

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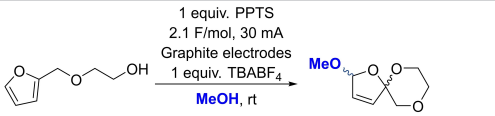
electrochemical oxidation of the furan ring (Table 1). The reaction previously has been described using one-pot two-step transformation which includes electrochemical bromination of furan using NH_4Br and a carbon anode/nickel cathode, followed by addition of sodium methoxide.[9] Given the low oxidation potential of furan, we explored direct spirocycle formation[6a] with a simple electrochemical setup using undivided cell and graphite electrodes. Methanol was used as a solvent and proton reduction as the cathode reaction. We found that the addition of PPTS (1 equiv.) was beneficial to achieve a good yield of the product **4a** (Table 1, entry 1). Decreasing or increasing the amount of PPTS led to a reduced yield of the product **4a** (Table 1, entries 2–4). It can be hypothesized that the addition of PPTS prevents formation of methoxide as the reduction product of methanol which may decrease the dimethoxylation of furane favoring formation of spirocycle **4a**.[6a] A slight increase of the total charge passed through the solution (measured in faradays per mole of substrate (F/mol)) led to a slightly higher yield (Table 1, entry 5), while significant increase of the charge was detrimental to the product **4a** formation (Table 1, entry 6). $LiClO_4$ as an electrolyte was less efficient compared to $TBABF_4$ (Table 1, entry 7). If HFIP was used as an additive instead of PPTS, a relatively good yield of product **4a** was observed at increased charge. However, in this case, a significant amount of ester **5a** formed as a by-product (Table 1, entry 8). If HFIP was used as an additive and $LiClO_4$ as an electrolyte, poor yield of spirocycle **4a** was obtained due to competing dimethoxylation of the furane (Table 1, entry 9). Optimal conditions were suitable also for the oxidation of alcohol **3a** to spirocycle **4a** in 0.5 g scale (Table 1, entry 10).

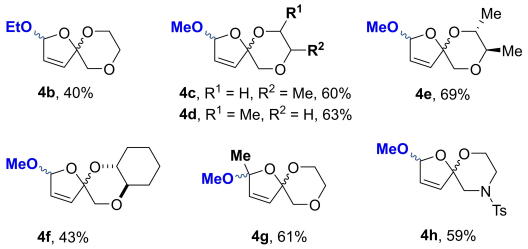
Table 1. Oxidative cyclization of alcohol **3a** to spirocycle **4a**.



3a (0.7 mmol) **4a** (mix of diastereomers ~1:1)

Entry	Conditions[a]	Yield of **4a**[b]
1	none	70%
2	no PPTS	50%
3	0.5 equiv. PPTS	58%
4	2.0 equiv. PPTS	55%[c]
5	2.5 F/mol	77%
6	4.0 F/mol	59%
7	$LiClO_4$ instead of $TBABF_4$	59%
8	no PPTS, 20 equiv. HFIP, 4 F/mol	52%[d]
9	no PPTS, 20 equiv. HFIP, $LiClO_4$ instead of $TBABF_4$,	38%[e]
10	45 mA, 500 mg scale	71%

[a] Deviation from the conditions given in the scheme. [b] Isolated yields are given; [c] Precipitate deposition on cathode observed; [d] Formation of **5a** was observed, isolated yield 15%. [e] dimethoxylation product of furane is a major by-product according to ^{1}H-NMR of a crude mixture



4b, 40%

4c, R^1 = H, R^2 = Me, 60%
4d, R^1 = Me, R^2 = H, 63%

4e, 69%

4f, 43%

4g, 61%

4h, 59%

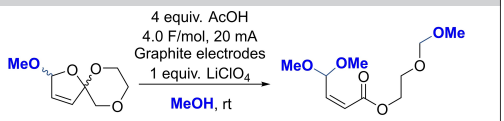
Scheme 1. Scope of spirocycle **4** synthesis.

The scope for spirocycle **4b–h** synthesis was investigated for a wider range of ethylene glycol and amino ethanol derivatives **3a–h** bearing furfuryl substituent (Scheme 1). Ethanol was also found to be a competent nucleophile to form ethoxy-substituted product **4b**, although in a lower yield than **4a** formed with methanol as nucleophile. Moreover, electrolysis in ethanol led to precipitate formation on the cathode. Substitution at ethylene glycol linker in starting materials **3c–f** gave products **4c–f** with good yields. Methyl substitution at furan 5th position in the starting material did not significantly affect the yield of the product **4g**. *N*-substituted amino ethanol derivative **3h** was also subjected to electrochemical cyclization to give spirocycle **4h** in good yield.

With spirocycles **4** in hand, their electroxidative fragmentation was investigated with an aim to obtain esters **5**. Spirocycle **4a** was used as a model compound to establish the conditions for this step (Table 2). PPTS as an additive and $TBABF_4$ as an electrolyte used for spirocycle **4a** formation were not suitable for obtaining ester **5a** due to precipitation of the PPTS decomposition products on the cathode during prolonged electrolysis (Table 2, Entry 1).

When acetic acid and HFIP were used as additives, the yield of product **5a** was considerably increased, however, the formation of an inseparable side-product along ester **5a** was observed (Table 2, entry 2). To obtain ester **5a** in a good yield, AcOH (4 equiv.) as an additive and $LiClO_4$ as electrolyte were

Table 2. Conditions for the oxidative fragmentation of spirocycle **4a**.



4a (0.6 mmol) **5a**

Entry	Conditions[a]	Yield of **5a**[b]
1	1 equiv. PPTS instead of AcOH $TBABF_4$ instead of $LiClO_4$	9%[c]
2	Add 20 equiv. HFIP $TBABF_4$ instead of $LiClO_4$	58%[d]
3	None	68% (77%)[e]
4	no AcOH	11%
5	1 equiv. AcOH	58%
6	2 equiv. AcOH	55%
7	add. 20 equiv. HFIP	67%
8	2.0 F/mol	(59%)[e,f]
9	3.0 F/mol	(74%)[e,g]

[a] Deviation from the conditions given in the scheme. [b] Isolated yields are given if not indicated otherwise. [c] Unreacted starting material (isolated yield: 55%). [d] Contains unidentified inseparable by-product ~15% [e] ^{1}H-NMR-yield using 1,4-bis(trichloromethyl)benzene as an internal standard. [f] Unreacted starting material (^{1}H-NMR yield: 20%) [g] Unreacted starting material (^{1}H-NMR yield: 5%).

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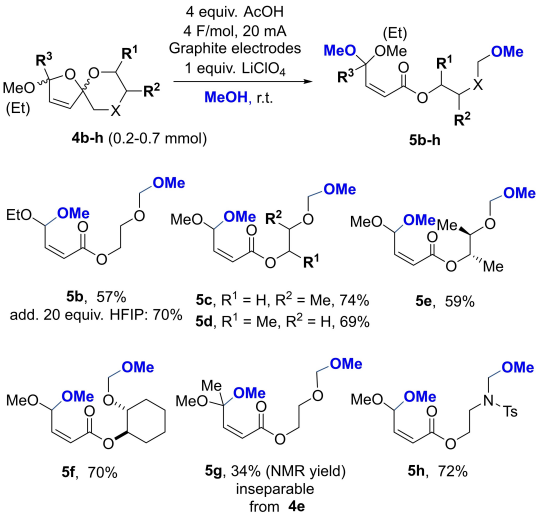
found to be crucial reaction components (Table 2, Entry 3). Decreasing the amount of AcOH reduced the yield of product **5a** (Table 2, Entries 4–6). Addition of HFIP did not have an impact on product **5a** formation (Table 2, Entry 7). Notably, 4.0 F/mol of charge were needed to achieve complete consumption of the starting material **4a** (Table 2, Entries 8,9). This indicated a parallel competitive oxidation process since in theory only 2.0 F/mol are needed for the desired transformation (*vide infra*). In all the experiments, the formation of ester **5a** with a Z-configuration double bond was observed while *E*-isomer formation was not detected. *Z*-Configuration of ester **5a** was confirmed by characteristic coupling constant of double bond protons (J = 11.8 Hz) and their cross peaks in NOESY spectra (see Supporting Information)

Spirocycles **4b–h** were subjected to electrochemical oxidative fragmentation to esters **5b–h** using the optimized conditions found for model substrate **4a** (Scheme 2). Ethoxy substituted spirocycle **4b** gave product **5b** in a slightly lower yield compared to the methoxy analogue **5a**. Noteworthy, mixed acetal **5b** formed exclusively, indicating that no transacetalyzation with methanol takes place during the reaction. Addition of HFIP to the reaction of substrate **4b** improved the yield of product **5b** – such an effect was not observed in the reaction of the model substrate **4a** (Table 2, entry 8). Substrates **4c–f** with a substituted ethylene linker gave the desired esters **5c–f** in good yields using standard conditions with no HFIP additive. Methyl substituted substrate **4g** also gave the expected product **5g**, however, it was difficult to separate from the unreacted starting material. In this case full conversion of spirocycle **4g** could not be achieved after 4.0 F/mol of charge passed. Morpholine derivative **4h** was efficiently transformed to the *O*-acylated *N*-protected amino alcohol **5h**.

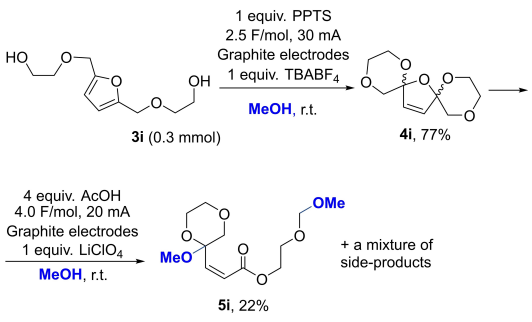


Scheme 2. Scope of oxidative fragmentation of spirocycles **4** to esters.

Diol **3i** derived from bis-hydroxymethylfuran was also successfully transformed into the spirocycle **4i** by anodic oxidation (Scheme 3). However, electrochemical oxidative fragmentation of the spirocycle **4i** gave the expected product **5i** in a relatively low yield (22%).

One-pot synthesis of esters **5** from alcohols **3** was also explored (Scheme 4). PPTS additive which was found beneficial for the transformation of substrates **3** to spirocycles **4** could not be applied for this purpose because the transformation of intermediates **4a** to ester **5a** was low yielding in the presence of this additive. Therefore, HFIP was used for the first step given the good conversion of substrate **3a** to the mixture of compounds **4a** and **5a** using this additive (Table 1, entry 8). After complete conversion of the starting material **3** at the first stage (equal to 2.2 F/mol of passed charge), acetic acid was added, and the electrolysis was continued for additional 4.0 F/mol of passed charge to obtain products **5**. This procedure led to moderate yields of esters **5a,c,d** from *O*-furfuryl ethylene glycols **3a,c,d**. Gratifyingly, this approach was more productive in the case of synthesis of esters **5h–m** containing protected amine functionality from *O*-furfuryl amino alcohols **3h–m**. It should be noted that ester **5k** synthesis was successfully performed on 0.9 g scale.

Mechanisms of electrochemical bis-alkoxylation of furan and (methoxy) anisole derivatives have been proposed previously depending on the reaction conditions.[6a,10] For the oxidative fragmentation of spirocycle **4a** to ester **5a** two possible pathways are provided in Scheme 5. Path A involves reversible S_N type methanolysis of the acetal in the dihydrofuran part of spirocycle **4a**, leading to intermediate **C**. Electrochemical oxidation of the hemi-acetal would give the *O*-centered radical **E** which fragments to α-oxy-stabilized *C*-centered radical **F**. Further oxidation of intermediate **F** would give oxonium ion **G** which reacts with methanol giving ester **5a**. The alternative path B starts with electrochemical activation of acetal group in spirocycle **4a** to give radical cation **D** after which the ring opens by methanolysis, leading to *O*-centered radical **E**. It cannot be excluded that methanolysis of activated acetal **D** and fragmentation occurs in a simultaneous fashion leading directly to intermediate **F.**



Scheme 3. Transformation of alcohol **3i** to spirocycle **4i** and its fragmentation to ester **5i**.

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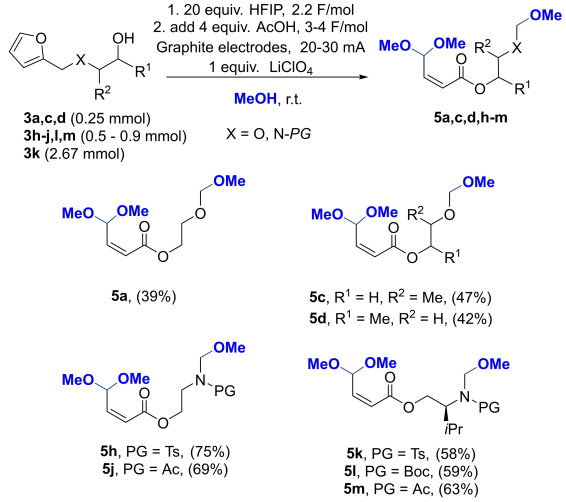
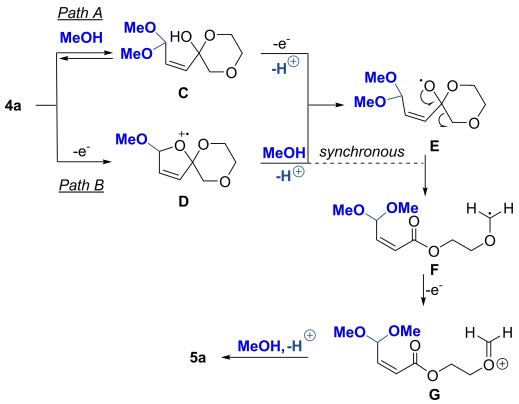
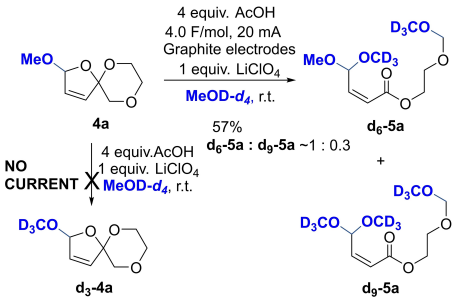


Scheme 4. One-pot synthesis of esters **5** from alcohols **3**.



Scheme 5. Proposed mechanistic pathways for ester **5a** formation from spirocycle **4a**.



Scheme 6. Deuterium labelling experiments supporting path B of ester **5a** formation mechanism.

To establish if path A is operational, spirocycle **4a** was subjected to the reaction conditions with no current passing through the reaction mixture and using deuterated methanol as the reaction solvent (Scheme 6). In this case, no deuterium incorporation was observed by ^{1}H-NMR even after 24 hours. However, when the current was passed through the reaction mixture, incorporation of deuterated methanol took place, forming a mixture of the products ***d*$_6$-5a** and ***d*$_9$-5a** (ratio 1 : 0.3, detected by ^{1}H-NMR). These results clearly indicated the necessity of electrochemical activation for the methanolysis of spirocycle **4a** and supported path B of the product **5a** formation mechanism.

Conclusion

In summary, we have demonstrated an extended application of Torii-type ester electrosynthesis from biomass-derived furan conjugates with glycols and amino alcohols. The ester synthesis from furanoics can be done in two steps or by using one-pot protocol giving multifunctional building blocks and tailored monomers for polymerization. Notably, the reactions can be performed using undivided cell commercial electrochemical set-up using inexpensive graphite electrodes.

Demonstration of the application for the reaction products is planned as the next step of our research work.

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Experimental Section

Optimized conditions for spirocycle formation: Substrate (1.0 equiv.), $TBABF_4$ (1.0 equiv.) and PPTS (1.0 equiv.) were transferred to an undivided cell (10 mL) and dissolved in freshly distilled MeOH (7 mL). Graphite electrodes were fitted to the cell and electrolysis was performed in constant current (30 mA) conditions until 2.5 F/mol of charge were passed through the cell. Afterwards the solvent was evaporated, and the product was purified using column chromatography.

Optimized conditions for α,β-unsaturated ester formation: Substrate (1.0 equiv.) and $LiClO_4$ (1.0 equiv.) were transferred to an undivided cell (10 mL) and dissolved in freshly distilled MeOH (7 mL). AcOH (4.0 equiv.) was added. Graphite electrodes were fitted to the cell and electrolysis was performed in constant current (20–30 mA) conditions until 4.0 F/mol of charge were passed through the cell. After electrolysis was done, TEA (4.0 equiv.) was added, and the reaction mixture was filtered through a silica plug. The solvent was evaporated, and product was purified using column chromatography.

Optimized conditions for one-pot transformation of alcohols to α,β-unsaturated esters: Substrate (1.0 equiv.) and $LiClO_4$ (1.0 equiv.) were transferred to an undivided cell (10 mL) and dissolved in freshly distilled MeOH (7 mL). HFIP (20.0 equiv.) was added. Graphite electrodes were fitted to the cell and electrolysis was performed using constant current (20–30 mA) conditions until 2.2 F/mol of charge were passed through the cell. Then AcOH (4.0 equiv.) was added, and electrolysis was continued for another 4.0 F/mol. After electrolysis was done, TEA (4.0 equiv.) was added, and the reaction mixture was filtered through a silica plug. The solvent was evaporated, and the product was purified using column chromatography.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Anodic oxidation · Biomass · Electrochemistry · Furan · α,β-Unsaturated ester

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