Advanced methods in synthesis

Team 1:

Mini project (Fluorophore click chemistry):

- Synthesis of Dap and Dab azido amino acids. Synlett 2011, 13, 1917–1919
- Synthesis of 7-alkenyl-4-methylcoumarin. Dyes Pigm. 2009, 82, 196–203
- Synthesis of endomorphin-2 with click label via solid phase peptide synthesis on Fmoc-Rink amide AM resin (scale: 1 mmol). Bachem SPPS guide.

More problems:

- Synthesis of Cbz-Ala-Oxazole-OMe JACS, 2006, 128, 10513-10520
- Synthesis of 5-/6-carboxy-tetramethylrhodamine *N*-succinimidyl ester from 3-(Dimethylamino)phenol. Org. Lett., 2008, 10, 4799-4801.

Teaching based research:

- Prepare trioxatriangulene (if not available).
- Identify substrate to test trioxatriangulene on as photoredox catalyst. See video on web page and see JOC, 2016 pp 7244). See http://pittelkow.kiku.dk/synmet/synmet_videoer/Nina%20photoredox.mp4

Fun useful exercises that can be done during the course:

- Kaiser test for primary amines
- Titration of organomagnesium, organozinc, and organolanthanide comp. MgI.
- Tetrakistriphenylphosphine palladium. Scale: 0.2 g $PdCl_2$. Opskr. K 116.
- Titration of DIBAL. OL 2005 2205.
- Reverse phase C18 silicagel separation

Advanced methods in synthesis

Team 2:

Mini project (Fluorophore chemistry):

- Synthesis of 5-/6-Carboxy-X-Rhodamine JOC 1987, 52, 1465-1468, Org. Lett., 2008, 10, 4799-4801. Scale: 0.1 mol (a lot).
- Synthesis of endomorphin-1 via solid phase peptide synthesis on Fmoc-Rink amide AM resin (scale: 1 mmol). Bachem SPPS guide.
- Label endomorphin-1 with rhodamine-X (scale: 0.01 mmol) (SPPS).

More problems:

- Synthesis of azido transfer reagent. Org. Lett. 2007, 9, 3797-3800.
- Synthesis of ε-azido Fmoc-lysine from Fmoc-Lys(Boc)-OH Synlett 2011, 13, 1917–1919.

Teaching based research:

- Prepare trioxatriangulene (if not available).
- Identify substrate to test trioxatriangulene on as photoredox catalyst. See video on web page and see JOC, 2016 pp 7244). See http://pittelkow.kiku.dk/synmet/synmet_videoer/Nina%20photoredox.mp4

Fun useful exercises that can be done during the course:

- Kaiser test for primary amines
- Titration of organomagnesium, organozinc, and organolanthanide comp. MgI.
- Tetrakistriphenylphosphine palladium. Scale: 0.2 g $PdCl_2$. Opskr. K 116.
- Titration of DIBAL. OL 2005 2205.
- Reverse phase C18 silicagel separation

Advanced methods in synthesis

Team 3:

Mini project

Synthesis of Labeled Albumin by S_NAr (chemistry on proteins, peptides and amino acids):

- Synthesis of pentafluorophenyl-sulphonylpiperidine. ACIE 2018, 57, 8022
- React Boc-cysteine with pentafluorophenyl-sulphonylpiperidine. ACIE 2018, 57, 8022
- Synthesis of DSKCGHfRWG peptides on Fmoc-rink amid-resin and label this with pentafluorophenyl-sulphonylpiperidine (scale: 1 mmol). Bachem SPPS guide.ACIE 2018, 57, 8022
- React Albumin with pentafluorophenyl-sulphonylamide PEG azide linker. ACIE 2018, 57, 8022

More problems:

- Synthesis of 5-/6-carboxy-tetramethylrhodamine *N*-succinimidyl ester from 3-(Dimethylamino)phenol. Org. Lett., 2008, 10, 4799-4801.
- Selenocarbamate. Scale: 1 gram of the phenol. Opskr: Selenocarbamate. Also do rearrangement reaction (ACIE 2013 p 12346).

Teaching based research:

- Prepare trioxatriangulene (if not available).
- Identify substrate to test trioxatriangulene on as photoredox catalyst. See video on web page and see JOC, 2016 pp 7244). See http://pittelkow.kiku.dk/synmet/synmet_videoer/Nina%20photoredox.mp4

Fun useful exercises that can be done during the course:

- Kaiser test for primary amines
- Titration of organomagnesium, organozinc, and organolanthanide comp. MgI.
- Tetrakistriphenylphosphine palladium. Scale: 0.2 g $PdCl_2$. Opskr. K 116.
- Titration of DIBAL. OL 2005 2205.
- Reverse phase C18 silicagel separation

Advanced methods in synthesis

Team 4:

Mini project (cross couplings, SNAr and click):

- Direct C-H activation cross coupling of pentafluorobenzene and 1-bromo-4-methoxybenzene under microwave conditions. *Org. Lett.*, 2014, 16, 3130-3133.
- SNAr reaction of imidazole and 1,2,3,5,6-pentafluoro-4'-methoxybiphenyl. *Org. Lett.*, 2014, 16, 3130-3133.
- Synthesis of ethynylpentafluorobenzene by Sonogashira reaction. Chem. Mater. 2005, 17, 1331-1345.
- Synthesis 3-Azido-7-hydroxy-coumarin and click on ethynylpentafluorobenzene. Org. Lett., 2004, 6, 4603-4606.

More problems:

- Synthesis of N,N-bis(2-bromoethyl)aniline from 2,2'-(phenylazanediyl)bis(ethan-1-ol) Org. Lett. 2014, 16, 4984–4987.
- Synthesis of endomorphin-1 by SPPS.
- Selenocarbamate. Scale: 1 gram of the phenol. Opskr: Selenocarbamate. Also do rearrangement reaction (ACIE 2013 p 12346).

Teaching based research:

- Prepare trioxatriangulene (if not available).
- Identify substrate to test trioxatriangulene on as photoredox catalyst. See video on web page and see JOC, 2016 pp 7244). See http://pittelkow.kiku.dk/synmet/synmet_videoer/Nina%20photoredox.mp4

Fun useful exercises that can be done during the course:

- Kaiser test for primary amines
- Titration of organomagnesium, organozinc, and organolanthanide comp. MgI.
- Tetrakistriphenylphosphine palladium. Scale: 0.2 g $PdCl_2$. Opskr. K 116.
- Titration of DIBAL. OL 2005 2205.
- Reverse phase C18 silicagel separation

Advanced methods in synthesis

Team 5:

Mini project:

- Prepare sexiest molecule of 2019 (*Nature*, 574, 511–515(2019))

More problems:

- Methylisocyanid. Scale: 50%. Opskr: T. Morsing and methylisocyanide and picture.
- 2-Fluorophenyl boronic acid. Scale: to be agreed. Opskr. K 472.
- (E)-2-Methyltetradeca-1,3-diene. Scale: do on microscale – 1 mmol. Opskr. K 477, Opskr. K 481 Titration of Mg Zn and La.
- Selenocarbamate. Scale: 1 gram of the phenol. Opskr: Selenocarbamate.

Teaching based research:

- Prepare trioxatriangulene (if not available).
- Identify substrate to test trioxatriangulene on as photoredox catalyst. See video on web page and see JOC, 2016 pp 7244). See http://pittelkow.kiku.dk/synmet/synmet_videoer/Nina%20photoredox.mp4

Fun useful exercises:

- *N*-Pivaloyl-2-toluidine (Titration of Butyllithium). Scale: 100%. Opskr. K 101.
- Titration of organomagnesium, organozinc, and organolanthanide comp. Opskr K 481 Titration of Mg Zn and La.
- Sodium borohydride Titration. MgI. Opskr. K 473.
- Titration of organomagnesium, organozinc, and organolanthanide comp. MgI.
- Tetrakistriphenylphosphine palladium. Scale: 0.2 g $PdCl_2$. Opskr. K 116.
- Titration of Grignard reagents. Opskr. K 286.
- Titration OF DIBAL. OL 2005 2205.

Advanced methods in synthesis

Team 6:

Mini project (Levin chemistry):

- Make a chlorodiazine (https://pubs.acs.org/doi/10.1021/jacs.1c06287?fig=fig2&ref=pdf)
- Edit an indole (find example from paper)
- Edit tetraphenylporphyrin (not known)

More problems:

- 1,1-Di-*tert*-butyl ethylene. *tert*-BuLi. Scale 5 grams. *J. Org. Chem.* **1990**, *55*, 1792-1796.
- *cis*-2-Ethyl-1-hydroxy-2-pentene. Scale 10%. Opskr. DIBAL K 98.
- Lithiation (tBuLi) and methylation of dimethoxycarbazol. Scale: 1 gram (file: methylation of methoxycarbazole).

Teaching based research:

- Prepare trioxatriangulene (if not available).
- Identify substrate to test trioxatriangulene on as photoredox catalyst. See video on web page and see JOC, 2016 pp 7244). See http://pittelkow.kiku.dk/synmet/synmet_videoer/Nina%20photoredox.mp4

Fun useful exercises:

- *N*-Pivaloyl-2-toluidine (Titration of Butyllithium). Scale: 100%. Opskr. K 101.
- Titration of organomagnesium, organozinc, and organolanthanide comp. Opskr K 481 Titration of Mg Zn and La.
- Sodium borohydride Titration. MgI. Opskr. K 473.
- Titration of organomagnesium, organozinc, and organolanthanide comp. MgI.
- Tetrakistriphenylphosphine palladium. Scale: 0.2 g $PdCl_2$. Opskr. K 116.
- Titration of Grignard reagents. Opskr. K 286.
- Titration OF DIBAL. OL 2005 2205.

Advanced methods in synthesis

Team 7:

Mini project (MacMillan): Photo-redox chemistry

- Make Ir catalyst (Chem. Mater. 2005, 17, 5712-5719). This includes making a ligand via a Pd-tetrakis catalyzed Suzuki coupling (see Pd recipe below)
- Make Ni catalyst.
- Selective sp3- C-H alkylation (Nature 2017 vol 547 p 79-83). Make your own amine substrate.

More problems:

- DHA/VHF. Scale: to be agreed. Arkivoc, 2011, 51-67.
- Lithiation (tBuLi) and methylation of dimethoxycarbazol. Scale: 1 gram (file: methylation of methoxycarbazole). Titrate the lithium reagent (See below).

Teaching based research:

- Prepare trioxatriangulene (if not available).
- Identify substrate to test trioxatriangulene on as photoredox catalyst. See video on web page and see JOC, 2016 pp 7244). See http://pittelkow.kiku.dk/synmet/synmet_videoer/Nina%20photoredox.mp4

Fun useful exercises:

- *N*-Pivaloyl-2-toluidine (Titration of Butyllithium). Scale: 100%. Opskr. K 101.
- Titration of organomagnesium, organozinc, and organolanthanide comp. Opskr K 481 Titration of Mg Zn and La.
- Sodium borohydride Titration. MgI. Opskr. K 473.
- Titration of organomagnesium, organozinc, and organolanthanide comp. MgI.
- Tetrakistriphenylphosphine palladium. Scale: 0.45 g $PdCl_2$. Opskr. K 116.
- Titration of Grignard reagents. Opskr. K 286.
- Titration OF DIBAL. OL 2005 2205.

Advanced methods in synthesis

Team 8:

Mini project (Levin chemistry#2, https://www.nature.com/articles/s41586-021-03448-9):

- Prepare reagent.
- Choose substrate to edit…could be dibenzylamine.

More problems:

- Triphenylphosphine copper hydride (Strykers Reagent). Scale: 100%. Opskr. K 409 Stryker, Opskr. K Gen CuOAc2.
- 2-Fluorophenyl boronic acid. Opskr. K 472.
- 1-Butyne. Scale: 50%. Opskr. K 391 1-Butyne.
- Titration of NaH. Opskr. K 490.

Teaching based research:

- Prepare trioxatriangulene (if not available).
- Identify substrate to test trioxatriangulene on as photoredox catalyst. See video on web page and see JOC, 2016 pp 7244). See http://pittelkow.kiku.dk/synmet/synmet_videoer/Nina%20photoredox.mp4

Fun useful exercises:

- *N*-Pivaloyl-2-toluidine (Titration of Butyllithium). Scale: 100%. Opskr. K 101.
- Titration of organomagnesium, organozinc, and organolanthanide comp. Opskr K 481 Titration of Mg Zn and La.
- Sodium borohydride Titration. MgI. Opskr. K 473.
- Titration of organomagnesium, organozinc, and organolanthanide comp. MgI.
- Tetrakistriphenylphosphine palladium. Scale: 0.45 g $PdCl_2$. Opskr. K 116.
- Titration of Grignard reagents. Opskr. K 286.
- Titration OF DIBAL. OL 2005 2205.

Advanced methods in synthesis

Team 9:

Mini project – Tristan Lambert chemistry
(https://onlinelibrary.wiley.com/doi/abs/10.1002/anie.202100222):

- Prepare catalyst.
- Test hydroxylation reaction on a substrate from paper or on an alkyl-carbazol

More problems:

- 1-butyne (Opskr. K 391) + Sonogashira reaction with this in MW oven.
- Tetrakistriphenylphosphine palladium. Scale: 0.2 g $PdCl_2$. Opskr. K 116.
- Tropolone chemistry. Prepare Cu complex, then brominate and dimerize. The last step is not known, and should be discussed tith Pittelkow (or Jesper Bendix). Recipe from Jesper Bendix.

Teaching based research:

- Prepare trioxatriangulene (recipe from Pittelkow).
- Identify substrate to test trioxatriangulene on as photoredox catalyst. See video on web page and see JOC, 2016 pp 7244). See http://pittelkow.kiku.dk/synmet/synmet_videoer/Nina%20photoredox.mp4

Fun useful exercises:

- *N*-Pivaloyl-2-toluidine (Titration of Butyllithium). Scale: 100%. Opskr. K 101.
- Titration of organomagnesium, organozinc, and organolanthanide comp. Opskr K 481 Titration of Mg Zn and La.
- Sodium borohydride Titration. MgI. Opskr. K 473.
- Titration of organomagnesium, organozinc, and organolanthanide comp. MgI.
- Titration of Grignard reagents. Opskr. K 286.
- Titration OF DIBAL. OL 2005 2205.