

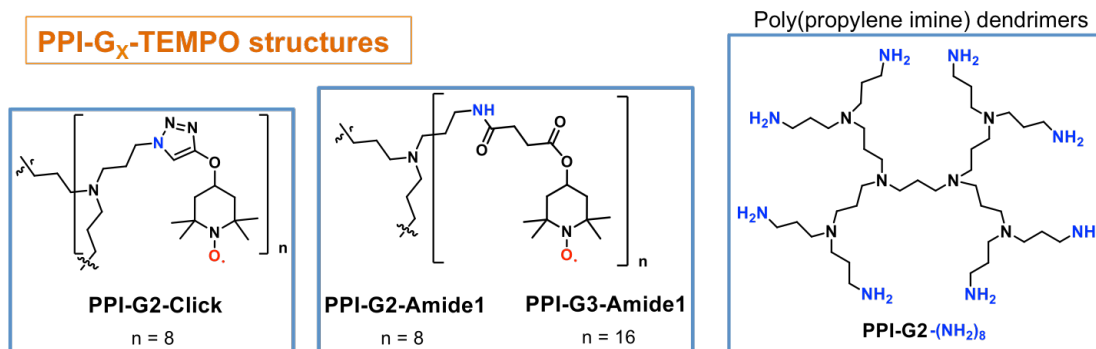
Final Report – MAX-BUCHNER-FORSCHUNGSSTIFTUNG Stipendium MBFSt-Kn.: 3355
Project: “Dialysis Techniques for Novel Oxidative Couplings of C(sp³)-H Bonds”

Abstract: The direct functionalization of C-H bonds has become a powerful and valuable tool for the construction of new C-C bonds. However, the selective C-H bond functionalization is still a challenge. In this project, TEMPO derivatives have been explored as non-toxic mild oxidants for oxidative C-H bond couplings using dialysis and flow-reactor techniques. Thus, the trimerization of indoles and the synthesis of difficult to access *N*-carbamoyl isoxazolines were achieved.

Project’s initial questions and objectives: In the last few years, the direct functionalization of C-H bonds has become a powerful and valuable tool for the construction of new C-C bonds. Despite the important advances already achieved in this area, the selective functionalization of demanding C(sp³)-H and C(sp²)-H bonds still constitutes a challenge.¹ In this regard, nitroxides and their oxoammonium salt derivatives are non-toxic, mild, environmentally friendly oxidants.² Recently, some reports by us and other research groups have showed their especial, sometimes unique, reactivity for the construction of C-C bonds by direct C-H functionalizations.³ Therefore, such oxidants would be further employed. In this project, we initially aimed at the integration of dialysis techniques and organic synthesis to:⁴

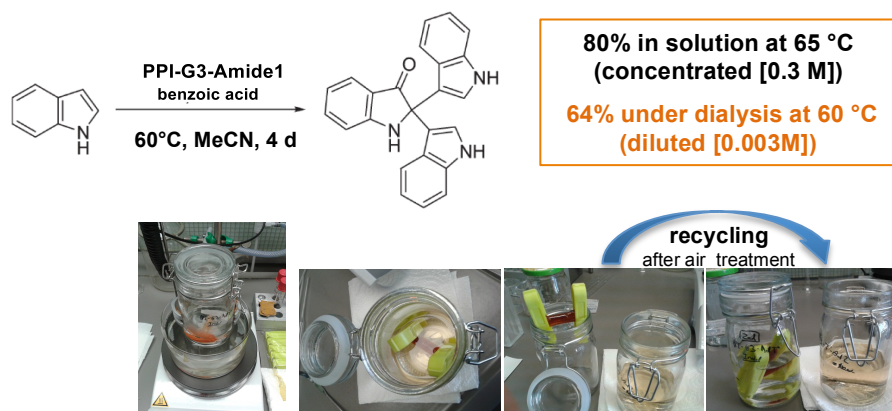
- 1) Develop new C-H transformations and recycle the TEMPO derivative-based oxidants
- 2) Study the compatibility of oxidative C(sp³)-H coupling reactions with (organo)catalysis

Project developments, results and discussion: We initially targeted the objective 1 (started at the University of Münster in 2013 and further carried out at University of Regensburg in early 2014). Consequently, different 4-substituted TEMPO nitroxides² were immobilized into a commercially available polystyrene resin (PS 200-400 mesh/Merrifield’s peptide resin) or dendrimers based on poly(propylene) imines (PPI), following literature known or slightly modified procedures (Scheme 1).⁵



Scheme 1. Representative covalent-immobilized nitroxide oxidants.

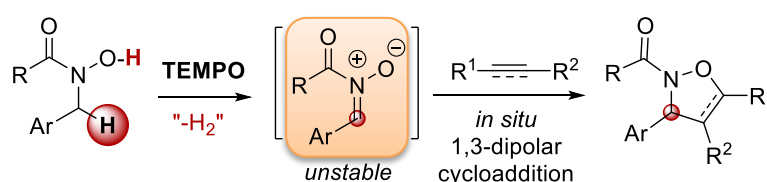
Next, the immobilized oxidants were placed into a dialysis membrane of type RC (Regenerated Cellulose), which is resistance to a broad variety of common organic solvents such as acetonitrile (MeCN), dichloromethane (DCM) or ethyl acetate to up to 60 °C. The nature-inspired oxidative trimerization of indoles was chosen as model study reaction⁶ since two new C-C bonds and interesting biologically relevant structures are formed in this transformation (Scheme 2).



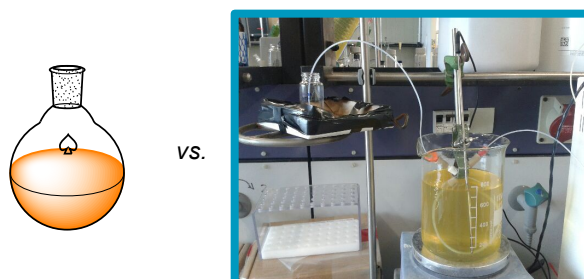
Scheme 2. Nitroxide/air system for oxidative C(sp³)-H coupling of indoles: Batch vs. Dialysis.

Satisfyingly, we could show that **dialysis techniques could be utilized for carrying out this type of oxidative C(sp³)-H coupling reaction**. Moreover, the oxidant inside the simple “home-made” dialysis device was employed with **air-oxygen as terminal oxidant** and the **immobilized nitroxide** could be **recycled up to 3 times**. However, **complications** associated to **inefficient diffusion, instability** of the commercially available semi-permeable dialysis membranes and **dialysis devices** against the organic solvents in the presence of oxidants at the RC-membranes limit range temperatures (aprox. 50-60 °C, which were required for the C-H functionalization reaction), as well as certain levels of irreproducibility were encountered.

Considering these last issues, **objective 2 was not further pursued** at the University of Regensburg. When the two new PhD students Andrea Gini and Dominik Kellner joined the freshly moved group (January and March, respectively), **the initial dialysis approach was replaced by microreactor/flow techniques**. Moreover, other oxidative C(sp³)-H coupling transformation was targeted: the in situ generation and trapping of unstable *N*-acyl nitrones to form isoxazoline derivatives (Scheme 3).⁷



Batch: 87%, 24 h, 70 °C, sealed tube under inert atmosphere (DCM)
Flow: 80%, 24 h, 70 °C, PPT tubing under air (DCE)



Scheme 3. Nitroxide-mediated formation of unstable *N*-acyl nitrones/trapping sequence: Batch vs. Flow.

This flow approach proved to be more efficient, leading to a **novel methodology for the preparation of synthetically valuable *N*-carbamoyl isoxazolines, not easily accessible by**

other available methods. Although similar results were obtained when carrying the reaction in batch and in a microreactor, **no inert atmosphere is required** in the second case, which simplifies the technical set-up of the reaction. Moreover, the **flow technique** also provides the possibility of **continuous synthesis** that will lead to a **more convenient and simple** preparation of large amounts of the targeted molecules.

Further studies in this area are currently carrying out in the research group. We are aiming at the finding of further innovative oxidative C-C coupling reaction from C-H bonds in flow systems, as well as the recycling of the oxidant and/or developing of “pseudo”-catalytic in TEMPO-type oxidant C-H bond coupling reactions.

Personal contributing to the project:

- Prof. Dr. Olga García Mancheño (June 2013 - June 2014; including a change of Universities: Münster to Regensburg, transition period September 2013 - January 2014)
- PhD Student Andrea Gini (January-March 2014 - PhD stipendium from project MBFSt 3355)
- PhD Student Dominik Kellner (March-May 2014 - PhD stipendium from project MBFSt 3355)

List of publications resulting from this project:

1. T. Stopka, O. García Mancheño, “TEMPO Derivatives as Alternative Mild Oxidants in C–C Coupling Reactions”, *Synthesis* **2013**, *45*, 1602-1611.
2. A. Gini, M. Segler, D. Kellner, O. García Mancheño, “Dehydrogenative TEMPO-Mediated Formation of Unstable *N*-Acyl Nitrones: Easy Access to *N*-Carbamoyl/-acyl Isoxazolines”, **2015**, *submitted manuscript under revision*.

Divuligation of the project's results in conferences and workshops:

1. **ProcessNet-Jahrestagung und 31. DECHEMA-Jahrestagung der Biotechnologen 2014**, Aachen (September-October 2014). *Oral communication*: O. García Mancheño, “Synthesis in a “Tea Bag”: Dialysis Techniques for Efficient Oxidative C–H Bond Functionalization Reactions”.
2. **Orchem 2014**, Weimar (September 2014). *Poster*: A. Gini, M. Segler, D. Kellner, O. García Mancheño, “Dehydrogenative TEMPO-Mediated Formation of Unstable Nitrones: Synthesis of *N*-Carbamoyl/-acyl Isoxazolines”.
3. **Summer School „Engineering and management across cultures“** TUM-WZS, Straubing (August 2014). *Lecture*: O. García Mancheño, “Flow reactor systems and dialysis techniques towards efficient synthesis”.
4. **Science Day 2014 – University of Regensburg** (June 2014). *Poster*: A. Gini, M. Segler, D. Kellner, O. García Mancheño, “Dehydrogenative TEMPO-Mediated Formation of Unstable *N*-Acyl Nitrones: Easy Access to *N*-Carbamoyl/-acyl Isoxazolines”.

¹ Recent review: S. A. Girard, T. Knauber, C.-J. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 74, and references cited therein.

² Recent reviews: a) L. Tebben, A. Studer, *Angew. Chem. Int. Ed.* **2011**, *50*, 5034; b) T. Stopka, O. García Mancheño, *Synthesis* **2013**, *45*, 1602.

³ See for example: a) H. Richter, O. García Mancheño, *Org. Lett.* **2011**, *13*, 6066; b) H. Richter, R. Fröhlich, C.-G. Daniliuc, O. García Mancheño, *Angew. Chem. Int. Ed.* **2012**, *51*, 8656; c) A. J. Neel, J. P. Hehn, P. F. Tripet, F. D. Toste, *J. Am. Chem. Soc.* **2013**, *135*, 14044, and references cited therein.

⁴ Selected examples on dialysis in (catalyzed)organic synthesis: a) M. Gaab, S. Bellemin-Laponnaz, L. H. Gade, *Chem. Eur. J.* **2009**, *15*, 5450; b) J. S. Willemsen, J. C. M. van Hest, F. P. J. T. Rutjes, *Beilstein J. Org. Chem.* **2013**, *9*, 960, and references cited therein.

⁵ PS-TEMPO derivatives: a) S. Weik, G. Nicholson, G. Jung, J. Rademann, *Angew. Chem. Int. Ed.* **2001**, *40*, 1436. Nitroxide-dendrimer derivatives: b) A. W. Bosman, R. A. J. Janssen, E. W. Meijer, *Macromolecules* **1997**, *30*, 3606.

⁶ W.-B. Qin, Q. Chang, Y.-H. Bao, N. Wang, Z.-W. Chena, L.-X. Liu, *Org. Biomol. Chem.* **2012**, *10*, 8814.

⁷ A. Gini, M. Segler, D. Kellner, O. García Mancheño, **2015**, *submitted manuscript under revision*.