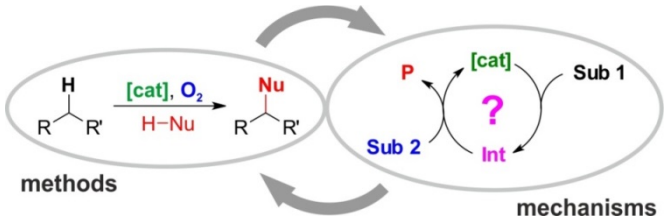
2.2.7 Research Area "Oxidative Coupling Reactions – Methods and Mechanisms" (M. Klußmann)

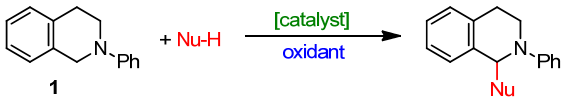
Involved: E. Böß, P. Karier, K. M. Jones, T. Hillringhaus, C. Schmitz, J. Demaerel, B. Schweitzer-Chaput, N. Gulzar, N. Uemiya

Objective: The transformation of two C–H bonds into a new C–C bond can be achieved by oxidative coupling, e.g. by using a catalyst together with a terminal oxidant.[38] We aim to develop sustainable oxidative coupling reactions, using simple and cheap catalysts and low molecular weight oxidants. Additionally, we investigate the mechanisms of these reactions to gain inspirations for the development of new and improved methods:



Scheme 1. Research interests of the Klußmann group.

Results: One area which has enjoyed rapid growth is the coupling α to nitrogen in tertiary amines, the most successful and widely studied being *N*-aryl tetrahydroisoquinolines (THIQ) **1**.[42] The mechanism of these reactions including the nature of intermediates and the role of catalyst and oxygen, however, remained essentially unknown.

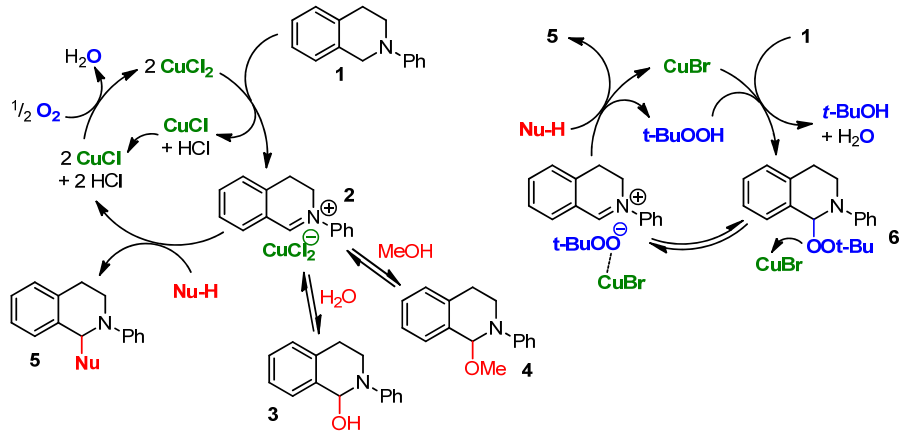


Scheme 2. Oxidative coupling reactions with *N*-phenyltetrahydroisoquinoline.

We have provided the first dedicated mechanistic studies in this field for two copper-catalyzed methods.[40,45] The first, using $CuCl_2$*$2H_2O$ as catalyst and oxygen as oxidant, was developed in our own group and still represents one of the simplest and most sustainable methods for this type of reaction which additionally has the broadest reported nucleophile scope. We could observe an iminium cuprate salt **2** as key intermediate, which is formed by oxidation of **1** with Cu(II).[40] In the presence of water

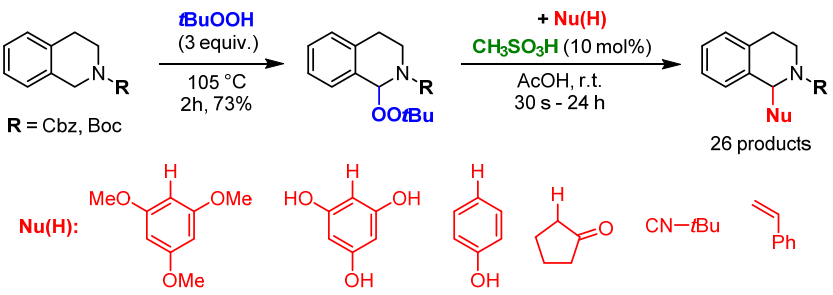
or methanol (a preferred solvent), this species is in equilibrium with a hemiaminal **3** or a hemiaminal ether **4** which provide a reservoir for the reactive iminium ion **2**. Addition of nucleophiles to the iminium provides the desired, thermodynamically preferred, coupling products **5**. Reoxidation of Cu(I) to Cu(II) by oxygen regenerates the catalyst.

The second method, using CuBr as catalyst and *tert*-butylhydroperoxide as oxidant, was reported by the group of C.-J. Li and has been most influential by inspiring many other research groups worldwide. We could establish a mechanism based on our studies which clarified the role of catalyst, oxidant and key intermediate **6**, a peroxide formed through a radical pathway initiated by CuBr and *tert*-butylhydroperoxide.[45]



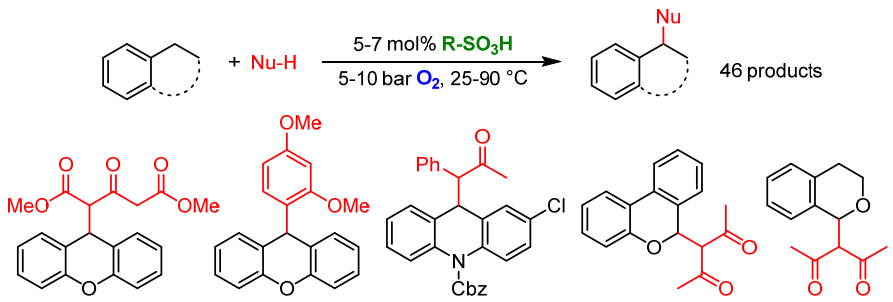
Scheme 3. Proposed reaction mechanisms of Cu-catalyzed oxidative coupling reactions with *N*-phenyltetrahydroisoquinolines.

The discovery that peroxide **6** converts to the reactive iminium ion intermediate by Lewis acid catalysis inspired us to develop an oxidative coupling of *N*-carbamate-protected THIQ's by Brønsted acid catalysis.[46] These compounds can be conveniently deprotected in contrast to *N*-aryl-THIQ's.



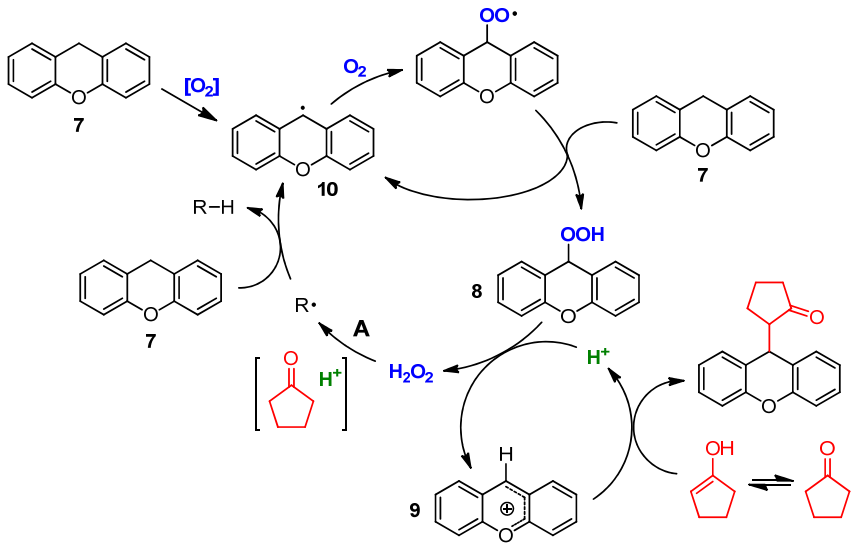
Scheme 4. Oxidative coupling with *N*-carbamoyltetrahydroisoquinolines *via* intermediate peroxides.

Recently, we had discovered a surprising oxidative coupling that proceeds without any redox-active catalyst. For example, xanthene is coupled with ketones by simply stirring the substrates under oxygen at ambient temperature and pressure in the presence of catalytic amounts of a strong Brønsted acid like methanesulfonic acid. The reaction is mostly limited to xanthene and ketones, but at high partial pressure of oxygen, the scope can be extended.[44]



Scheme 5. Autoxidative coupling at elevated partial pressure of oxygen.

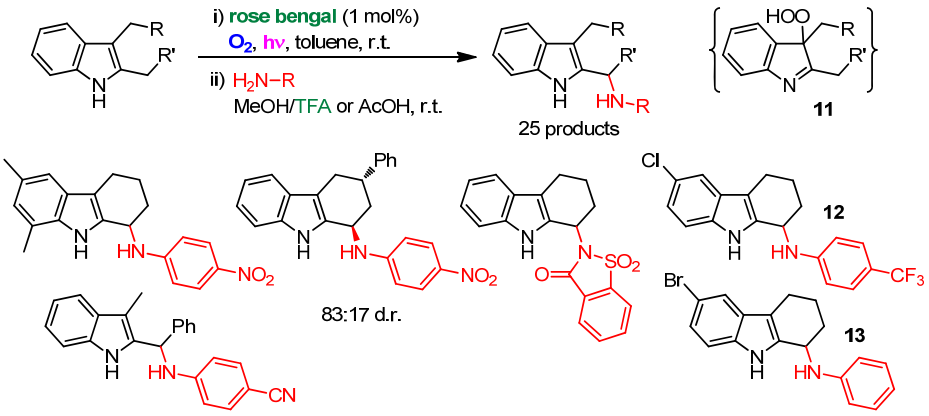
A mechanistic study of this reaction, with the coupling of xanthene **7** with cyclopentanone as model reaction, revealed the autoxidation of xanthene to hydroperoxide **8** as the key step.[49] In the presence of a strong Brønsted acid, the hydroperoxide group is substituted by the ketone nucleophile, probably *via* xanthylium ion **9**. Interestingly, the reaction proceeds faster than the rate limiting autoxidation. The waste product hydrogen peroxide accelerates the reaction by a synergistic action of Brønsted acid and ketones that generates radicals (path **A**, mechanism not yet fully understood).



Scheme 6. Proposed mechanism of the autoxidative coupling of xanthene with cyclopentanone.

We assume that under these conditions, perketals or related structures are formed that decompose into radicals, which in turn abstract a hydrogen atom from xanthene. The resulting xanthenyl radicals **10** are quickly trapped by oxygen, thereby accelerating the autoxidation to form more of the key intermediate **8**.

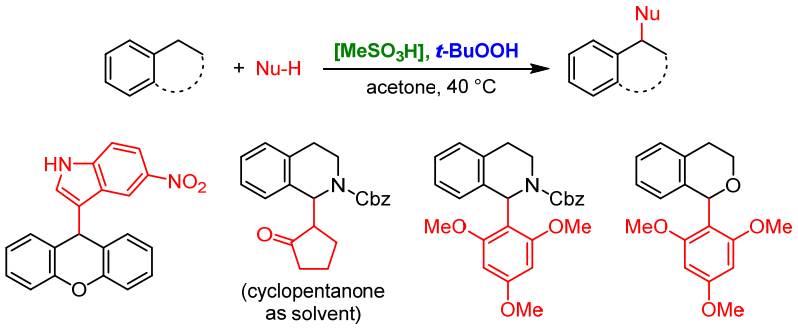
This discovery has inspired several still ongoing research projects. For example, we have developed a programme of C–H functionalization *via* Intermediate PeroxideS, termed CHIPS, which will provide means to derive valuable products from C–H bonds in a sustainable manner, only requiring catalysis and oxygen as the only stoichiometric reagent. As a proof-of-principle, we have developed a photochemical and Brønsted acid catalyzed two-step method to functionalize tetrahydrocarbazole derivatives *via* hydroperoxides **11**, which enables the synthesis of potent antiviral compounds like **12**- and **13**.[48]



Scheme 7. C–H amination of indole-derivatives *via* intermediate hydroperoxides.

In a related project, we have used hydroperoxides derived from the reaction of phenols with singlet oxygen to synthesize spirolactones.[47] And by applying the discovery of the synergistic effect of hydro(gen)-peroxide, ketones and Brønsted acid catalysis, we have developed novel ways of performing oxidative coupling reactions without involvement of redox-active catalysts.[49]

These studies are expected to have broader implications for the understanding of radical and autoxidation chemistry.



Scheme 8. Oxidative coupling reactions by the synergistic action of a Brønsted acid catalyst, hydroperoxide and ketone solvents.

Future directions

Our group will continue with a combination of mechanistic studies and method development, with the goal of developing novel sustainable methods for the C–H functionalization of various organic compounds and gaining an improved understanding of the underlying reaction mechanisms. In particular, we will focus on the principle of CHIPS (C–H functionalization *via* Intermediate PeroxideS) and on the newly gained mechanistic insight into the synergistic action of acid, hydroperoxide and ketone solvents.

Using the principle of CHIPS, we want to develop one-pot methods to functionalize C–H bonds by visible light and simple acid catalysts, for C–H bonds in allylic or heterocyclic compounds (along the lines of Scheme 7).

The mechanistic insight from the autoxidative coupling reaction (Scheme 6) has already allowed us to develop oxidative coupling reactions without the use of redox-active catalysts (Scheme 8). We have found indications that the intermediate radicals (“R·” in Scheme 6) are ketone-derived, this knowledge will be used to develop novel radical reactions to functionalize ketones. We have already achieved a hydrofunctionalization and a 1,2-difunctionalization of olefins with ketones, depending on reaction conditions. The reactions are reminiscent of the so-called SOMO-catalysis. Further studies towards the extension of these methods as well as an elucidation of their mechanisms are expected to be a major focus of our group’s future research activities.