2.2.6 Research Area “Oxidative Coupling Reactions for the Formation of Carbon-Carbon Bonds” (M. Klußmann)

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**Objective:** The activation of carbon-hydrogen bonds for chemical synthesis is a longstanding goal in the chemical community. The direct substitution of hydrogen in C-H bonds by the desired fragment creates interesting synthetic alternatives to the more common multi-step approach of first introducing reactive functional groups. Instead, only one step is needed and very simple substrates can be used, as C-H bonds are basically ubiquitous in organic compounds. The transformation of two C–H bonds into a new C-C bond can be achieved by oxidative coupling, requiring a stoichiometric amount of an oxidizing reagent or a catalyst together with a terminal oxidant:

\[
\text{RH} + \text{R'H} \xrightarrow{[\text{cat}]} \text{ROx} \xrightarrow{OxH_2} \text{RR'}
\]

Many of these reactions, however, still need harsh conditions, expensive noble metal catalysts or synthetic oxidants, producing unwanted cost and waste. We aimed to develop oxidative coupling reactions for the formation of C-C bonds using mild conditions and preferably elemental oxygen as oxidant to create more sustainable methods for organic synthesis.

**Results:** We have developed two different methods for the coupling of tertiary amines with ketones using transition metal catalysis. Using copper catalysis, amines can be oxidatively coupled with silyl enolates or ketene acetals, furnishing amino-ketones, aldehydes and esters. The reaction requires only a simple copper salt and elemental oxygen; it proceeds fast at ambient temperature and generally gives high yields:

\[
\text{N}_{\text{Ph}} \quad \text{N} \quad \text{O} \\
\text{Ph} \quad \text{OTMS} \\
\text{5eq.} \\
\text{CuCl}_2*2\text{H}_2\text{O} (10 \text{ mol}%) \\
\text{solvent, O}_2, \text{RT} \\
\text{2.5h-1d} \\
\text{N}_{\text{Ph}} \quad \text{O} \\
\text{N} \quad \text{OMe} \\
83\% \\
91\% \\
46\% \\
21 \text{ examples}
\]

\[
\text{N}_{\text{Ph}} \\
\text{N} \\
\text{OHC} \\
\text{StBu} \\
\text{95}\
\]
In order to utilize free ketones instead of preformed enolates, we developed a combined metal- and organocatalysis approach. The combination of a simple vanadium complex and tert-butyl hydroperoxide was used to oxidatively activate tertiary amines while proline was used to activate ketone nucleophiles via enamine catalysis, resulting in an oxidative Mannich-type reaction. This method could be applied to the one-step total synthesis of the alkaloid hygrine.

\[
\text{N} \begin{array}{c}
\text{Ph} \\
\text{Ar}
\end{array} \text{O} + \text{O} \begin{array}{c}
\text{Ph} \\
\text{Ph}
\end{array} \text{N} + \text{O} \begin{array}{c}
\text{Ph} \\
\text{Ph}
\end{array} \text{N} \xrightarrow{\text{VO(acac)}_2 (10\text{mol\%})} \left[ \begin{array}{c}
\text{N} \\
\text{Ph}
\end{array} \text{O} \begin{array}{c}
\text{Ph} \\
\text{Ph}
\end{array} \text{N} \right] \xrightarrow{\text{L-Prolin (10\text{mol\%})}} \text{MeOH, RT, 24h} \quad \begin{array}{c}
\text{N} \\
\text{Ph}
\end{array} \text{O} \begin{array}{c}
\text{Ph} \\
\text{Ph}
\end{array} \text{N} \xrightarrow{1.5\text{eq. tBuOOH}} \text{11 examples}
\]

Attempts at performing these reactions stereoselectively have failed so far, giving at best an enantiomeric excess of 17\% with a prolinol-derivative as chiral organocatalyst.

Recently, we have discovered a surprising oxidative coupling that proceeds without any redox-active catalyst. Xanthene, acridanes and tetrahydroisoquinolines are coupled with ketones or activated esters simply by stirring the substrates without additional solvents under oxygen in the presence of catalytic amounts of a strong Brønsted acid like methanesulfonic acid:

\[
\text{X} \xrightarrow{7\text{mol\% CH}_3\text{SO}_3\text{H}} \left[ 1-6 \text{ bar O}_2, \text{r.t./40°C} \right] \text{R'} \text{O} \begin{array}{c}
\text{R'} \\
\text{R'}
\end{array} \xrightarrow{5 \text{ eq.}} \text{20 examples}
\]

The reactions are believed to proceed via hydroperoxides formed by autooxidation, which would then undergo acid-catalyzed substitution reactions with the carbonyl
nucleophiles. Accordingly, we have termed this reaction “autoxidative coupling”. Its unprecedented simplicity and sustainability could serve as a model for future developments of green cross-coupling reactions.

**Publications resulting from this research area:** 265, 266, 339, 375

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