Symeres

Making Molecules Matter. Together.

DRUG DEVELOPMENT

Leveraging copper-catalyzed Ullmann-type cross-coupling reactions in PR&D

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> **"Just because there's tarnish on the copper, doesn't mean there's not a shine beneath."**
>
> Laurence Yep

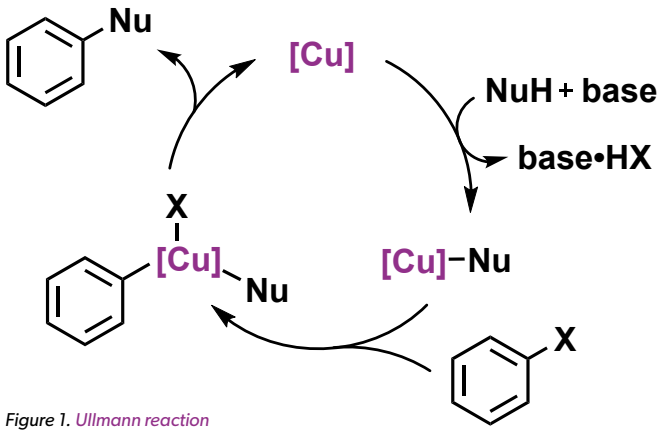

Figure 1. Ullmann reaction

The pharmaceutical industry is undergoing a significant change in how it creates complex molecules, with non-noble-metal catalysis emerging as a powerful tool in process chemistry. Copper-catalyzed cross-coupling reactions (Ullmann-type reactions) are increasingly replacing the well-established palladium-catalyzed alternatives in process chemistry projects at Symeres. Copper, as a catalyst in pharmaceutical synthesis, is considered 30 times less toxic than palladium, according to ICH guidelines,[2] providing a safer and more sustainable alternative for drug-manufacturing processes due to its lower environmental impact and cost-effective abundance.[1] Additionally, copper catalysis enables the synthesis of valuable compounds without sacrificing reaction efficiency.[1]

While the classical Ullmann reaction involves the homocoupling of aryl halides to form biaryls,[3] the Ullman-type cross-coupling reaction has found extensive applications in pharmaceutical process chemistry. Copper-catalyzed C–N couplings in particular have emerged as a superior alternative to palladium-catalyzed reactions in specific situations.[1] Ullmann reactions encompass various couplings, such as aryl and heteroaryl halides with amines, heterocycles (including indoles, imidazoles, and pyridones), amides, hydrazines, and hydroxylamines.[1] Additionally, the Ullmann reaction is often used to generate nitriles through copper-catalyzed cyanide coupling. Other examples of C–X bond formation are the formation of C–S bonds with thiols or sulfinic acids and C–P bonds with phosphines and phosphine oxides.[1]

Screening

Drawing on over 30 years of chemistry experience, Symeres leverages copper-catalyzed cross-coupling reactions to efficiently synthesize a diverse array of APIs, from the medicinal chemistry stage to Clinical Stage 2 manufacturing. Our extensive portfolio includes many successful collaborations with small and large pharmaceutical companies. What do we have in our toolkit to make your molecules matter?

1. Small-scale screening, including high-throughput experimentation (HTE) and design of experiments (DoE).
2. Gloveboxes with an extensive library of catalysts (>10 Cu sources, including preformed ligated complexes) and ligands (>50 ligands) to ensure a moisture and oxygen-free atmosphere on a small scale.
3. Initial scaleup using EasyMax or Mya4 equipment to mimic large-scale reactors.
4. Safety assessment, including reaction calorimetry and safety DSC studies.
5. Implementation of larger-scale demonstration batches to prepare batch records.
6. Large-scale synthesis through our pilot-plant production (multi-kg scale) supported by our Solid-State Center of Excellence to deliver desired polymorphs.

While copper-catalyzed Ullmann reactions offer a cost-effective alternative to palladium, challenges may arise during scaleup.[1] Issues such as air sensitivity and low catalyst stability, resulting

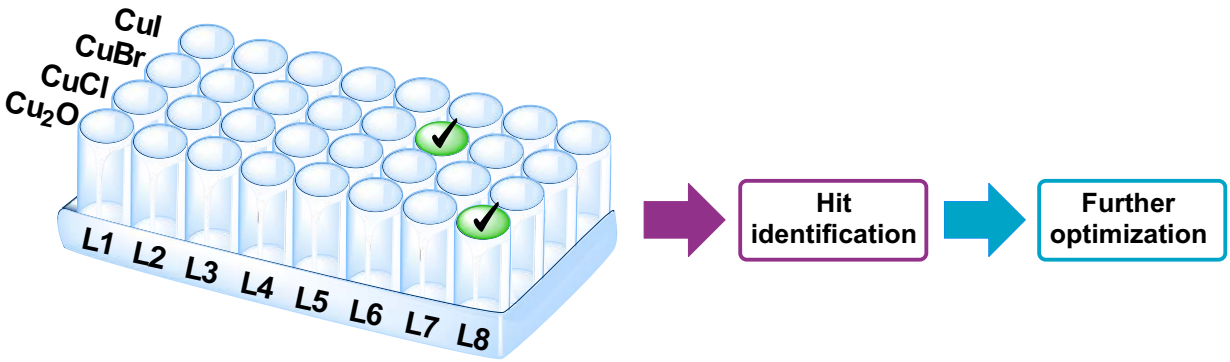

Figure 2. Hit identification

in prolonged reaction times or stalling, can hinder the efficient translation of laboratory-scale processes to manufacturing scales.[1] Experience of addressing these challenges is crucial for the widespread adoption of copper-catalyzed reactions in pharmaceutical manufacturing. The success of copper-catalyzed Ullmann reactions hinges on the careful selection of copper sources, ligands, bases, and solvents.[1] Optimal conditions can be identified through systematic screening of the Symeres Ullman coupling toolbox, consisting of more than 10 copper sources and 50 ligands, including amino acids, diketone and ß-keto ester ligands, diamine ligands, phenanthroline-based ligands, alcohols, oxo acids, and diamide ligands.

Scalability

Addressing the inherent challenge of Ullmann coupling, air sensitivity begins with the initial screening stages conducted within a glovebox. During scaleup, inert conditions are typically ensured by distillation of solvents under an inert atmosphere, which results in minimal oxyg en levels, as well as the removal of any residual water from reaction solvents. Visual kinetic analysis (VKA)[4] offers a simple technique to assess catalyst decomposition or product inhibition, if necessary. Timely implementation of

"large-scale" functions, such as mechanical stirring and the use of small vessels resembling the reactor's shape, together with an excellent supply of high-quality materials, allows us to avoid or mitigate unwanted scaleup effects. We aim to develop scalable (i.e., safe and efficient) processes and prioritize the use of green solvents to minimize their environmental impact. The continuous supply of solid bases of a particular particle size and careful documentation of all process steps under GMP conditions ensures reproducible batches across multiple recurring campaigns, facilitating transparent tech transfer from Symeres to your facilities.

Copper removal

After completion of the reaction, the removal of copper is pivotal for ensuring product purity. Several strategies can be employed, including the following:

1. **Filtration:** Simple filtration processes can effectively remove solid copper catalysts. This purification method works ideally in the case of CuI filtration, where residual Cu(I) particles form polymer complexes.
2. **Solvent extraction:** Copper can be extracted from the reaction mixture using suitable solvents. Sometimes Cu(I) requires further oxidation to Cu(II) to increase the solubility of copper-containing compounds. In this case, certain oxidizing agents can be used.
3. **Chelating agents:** Chelating agents, such as EDTA or DMG, can be employed to sequester copper ions. If Cu(I) is oxidized to Cu(II) in the process, then simple washing with aqueous ammonia can suffice.

Following isolation, we determine the copper levels in intermediates and APIs using inductively coupled plasma mass spectrometry (ICP-MS), ensuring the delivery of high-quality products.

Case study

Below is a selected example of a process that started from route scouting and proceeded further to our pilot plant:

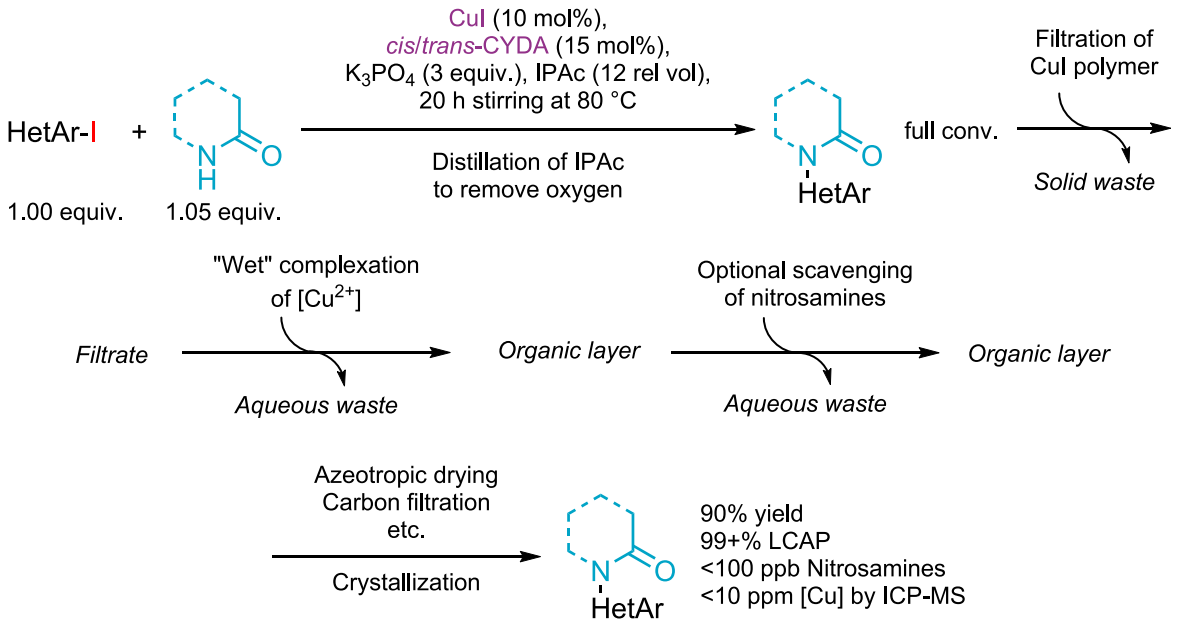

Figure 3. A simplified process scheme showing the relevant isolation steps

Through internal collaboration across multiple departments, we have developed an efficient, scalable process. Using an environmentally friendly solvent and a primary amine as a ligand to minimize the risk of nitrosamines, we produced over 10 kg of final material in high yield and excellent purity.

Our interdisciplinary development strategy ensured rapid, precise production at every step, which is vital for toxicological batches and a smooth transition to clinical stages. The Symeres catalysis screening group supports the optimization of reaction conditions in the "research" step. Once the optimal solvent, temperature, copper source, and ligand are determined, the process development team comes together to provide reliable and safe isolation of the material at a larger scale.

If a particular parameter needs to be changed due to isolation issues, the process research or process development team can conduct an additional round of conditions testing. Some problems, such as the scaleup effect, only become more pronounced when moving to larger vessels (1, 2, 5, 10, 20 L, etc.). When these issues are discovered, our process development team makes process adjustments in our pilot-plant facilities before actual production begins. Crystallization development, supported by our Solid-State team, is another critical step in material isolation, if required. Together with synthetic efforts, our analytical team can perform testing and development of the final methods to ensure a smooth transition of the process to production under R&D or GMP conditions.

Our experience in overcoming scaleup challenges and harnessing the benefits of non-noble-metal catalysis makes Symeres the CRO of choice for challenging steps, such as the Ullmann reaction. We are dedicated to enhancing the efficiency, sustainability, and cost-effectiveness of your API manufacturing processes.

[1] *Org. Process Res. Dev. 2022, 26, 1690−1750*
[2] *https://www.ich.org/page/quality-guidelines*
[3] *Chem. Rev. 2007, 107, 1, 133–173*
[4] *Chem. Sci. 2019, 10, 348−353*

For further inquiries or collaboration opportunities, please contact us via: science@symeres.com
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