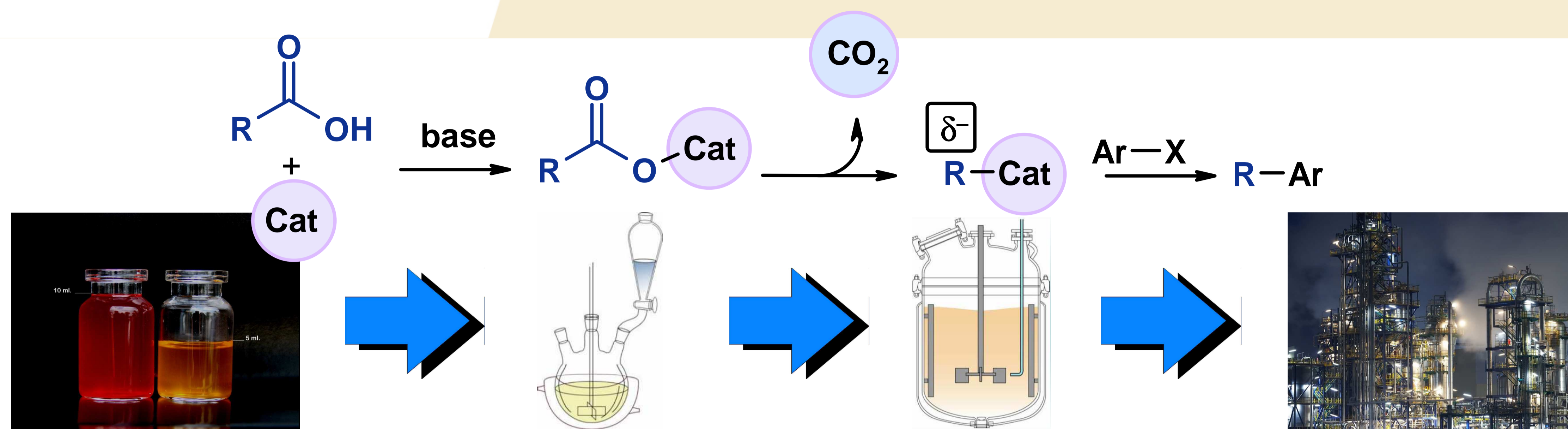


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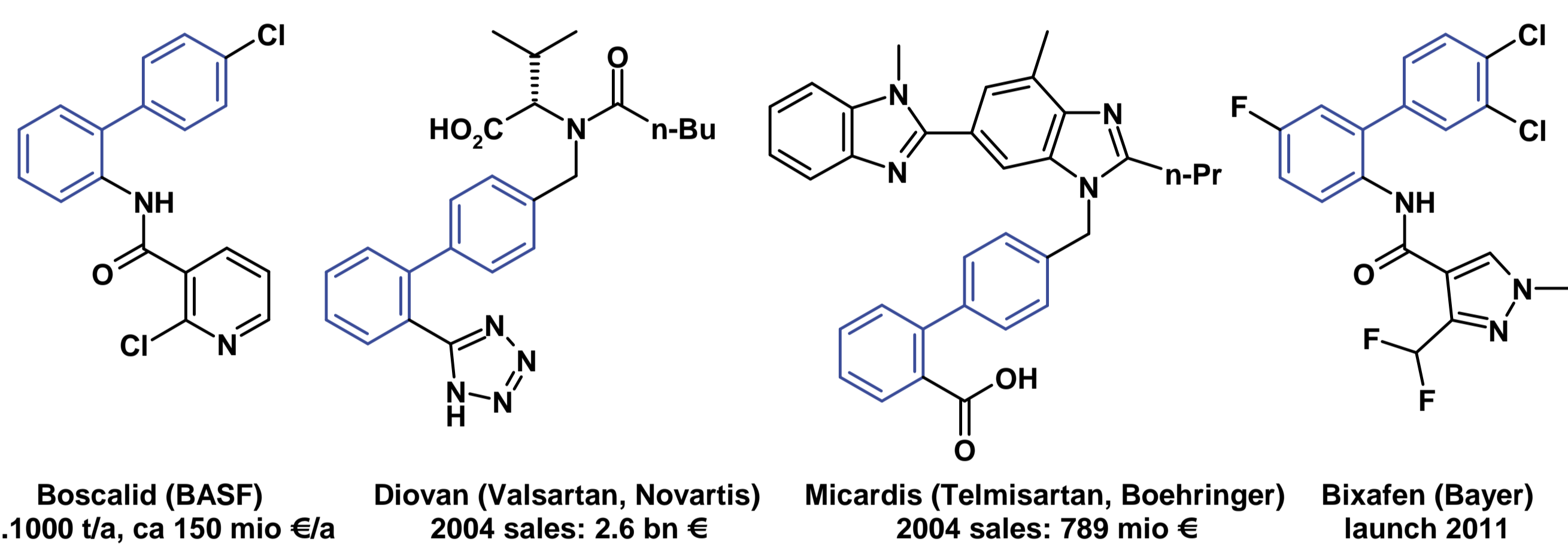
Our research is devoted to the development of sustainable catalytic transformations. We have reported that salts of carboxylic acids can be decarboxylated *in situ* to aryl metal species and utilized as *carbon nucleophiles* in catalytic cross-couplings. This new cross-coupling technique has high economic potential as expensive organometallic reagents are replaced by simple carboxylate salts in the synthesis of biaryls. In order to prove the applicability of this sustainable transformation on large scale, several industrially important biaryls have been synthesized in multi-gram to kg scales.



Scale Up: From Lab Scale to Plant Scale

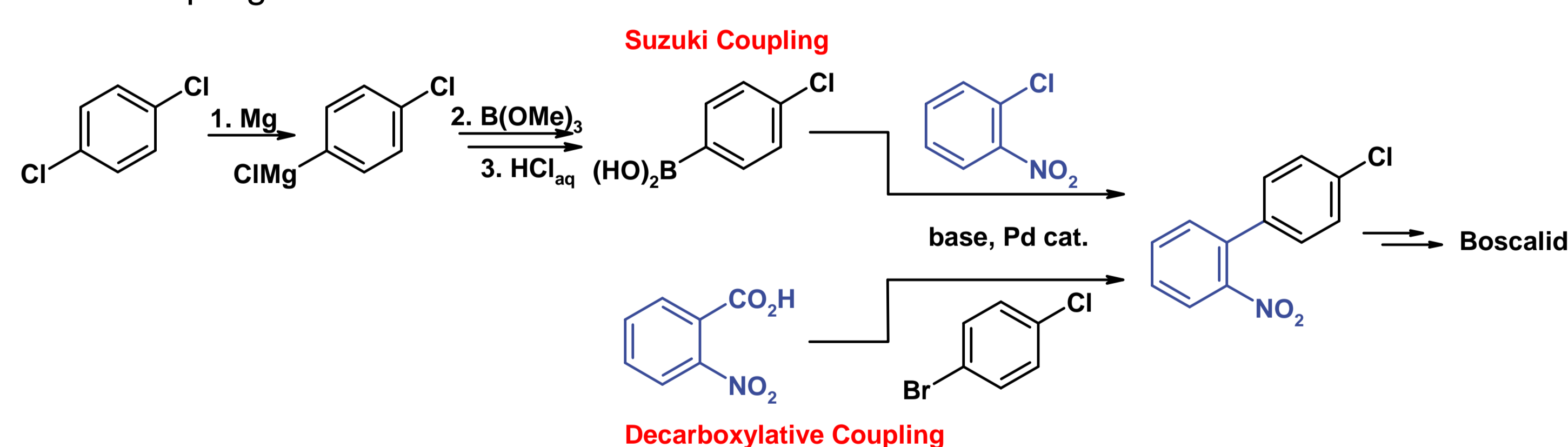
The Biaryl Substructure

The biaryl moiety is an important structural motif in a great number of biologically active compounds as demonstrated by the examples below.

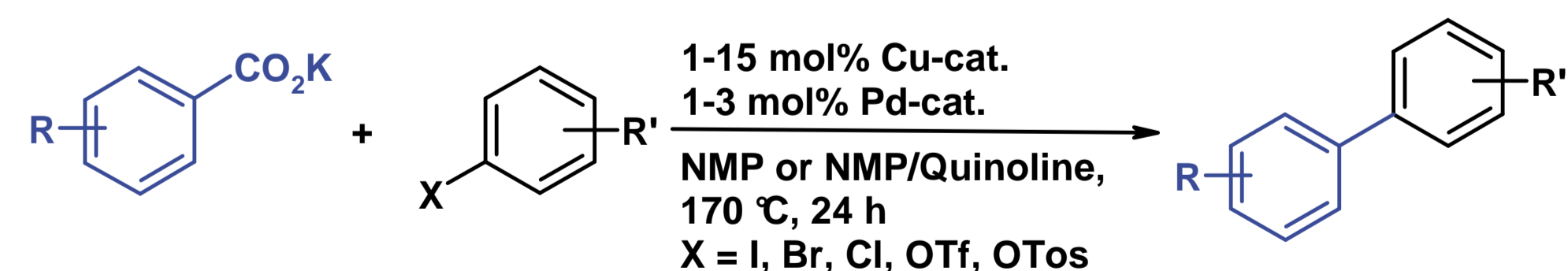


Synthesis of Unsymmetrical Biaryls Derivates

Over the past decades, the mild and selective Suzuki coupling has almost completely replaced the classical methods and become the method of choice for industrial applications.¹ However, the Suzuki reaction still suffers from a fundamental drawback: It requires the use of stoichiometric amounts of an expensive organometallic compound, in this case a boronic acid, which must generally be prepared from sensitive precursors under elaborate anaerobic conditions – on an industrial scale this is often more difficult than the cross-coupling itself.



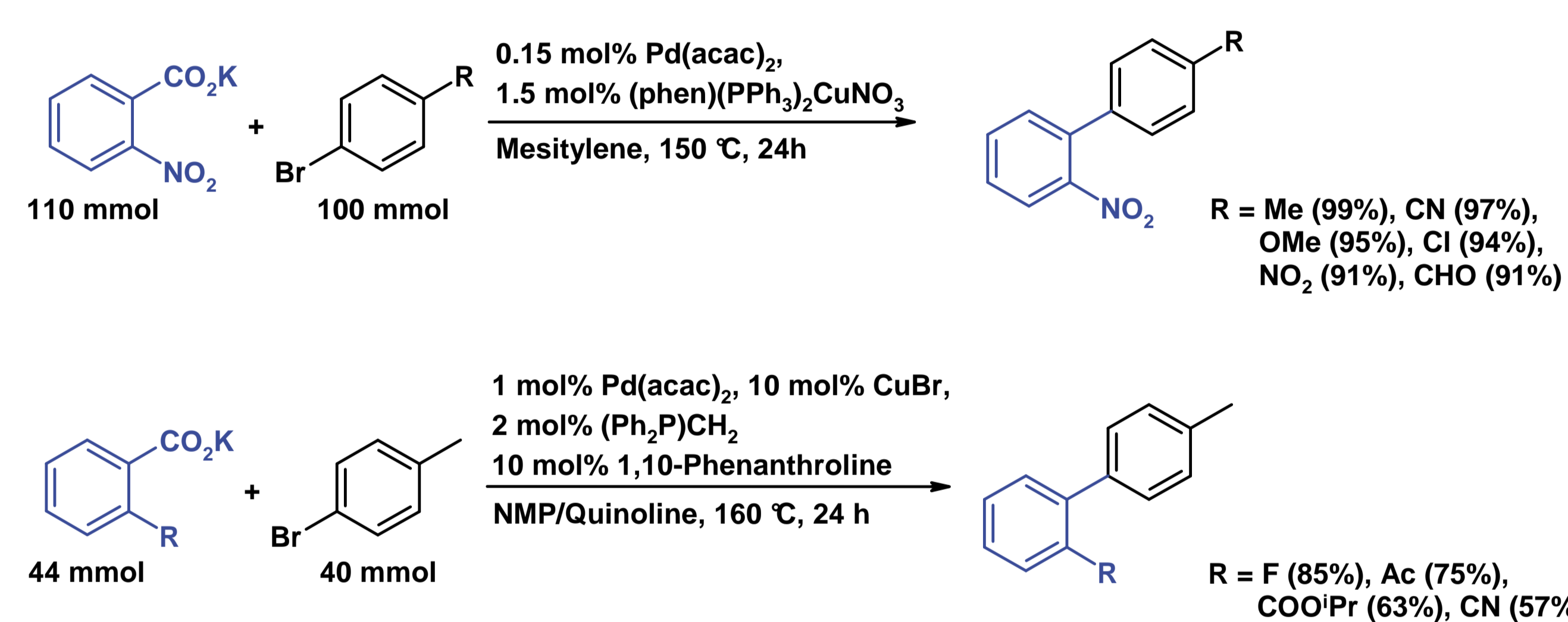
In this respect, the *in situ* generation of carbon nucleophiles via decarboxylation of carboxylic acid salts arguably offers a true synthetic alternative of immediate economical potential.² The viability of this concept has been confirmed by coupling various aryl halides,³ triflates⁴ and tosylates^{4b} with a broad range of aromatic carboxylic acids.



The reaction mechanism presumably includes the strongly exothermic extrusion of CO₂ from these substrates within the coordination sphere of a copper/phenanthroline catalyst, giving rise to organocopper intermediates, which are directly coupled with carbon electrophiles by a palladium co-catalyst.

Scale Up of the Decarboxylative Cross-Coupling Reaction

Recently, we have presented a safe and convenient cross-coupling strategy for the large scale synthesis of biaryls.⁵ The goal of this work was not only to provide reliable recipes for the application of decarboxylative cross-coupling reactions for preparative chemists inexperienced in the field of transition metal catalysis, but also to evaluate the potential for an industrial application.



In the case of the 2-nitrobenzoic derivatives, the protocol could easily be scaled up from millimolar to molar quantities without a decrease in yields. Due to their high reactivity, a commercially available and easy-to-handle copper-phenanthroline complex can be used. Since it is possible to use an inexpensive, non-polar solvent, the reaction work-up is simple: The products are obtained in pure form after removal of the solvent and Kugelrohr distillation or crystallization, this issue being the key achievement for the application in an industrial process.



However, scale up a reaction does not mean a simple linear increase in size whilst maintaining geometric similarity. It is crucial to ensure an efficient stirring to minimize differences in temperature and concentrations. Time, heat up/cool down rates, material handling and safety issues were some of the most important variables to control during the scale up process.

The industrial applicability of the reaction has been demonstrated in cooperation with the Saltigo GmbH in the kg scale synthesis of an *o*-nitrobiaryl intermediate. In the final process less than 0.5 mol% of copper(I) bromide and less than 0.05 mol% palladium(II) acetylacetonate have been employed, and mesitylene (70% by weight) as the only solvent was required. The product was obtained in pure form by a simple crystallization.⁶

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Literature and Further Reading (see also www.chemie.uni-kl.de/goossen)

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