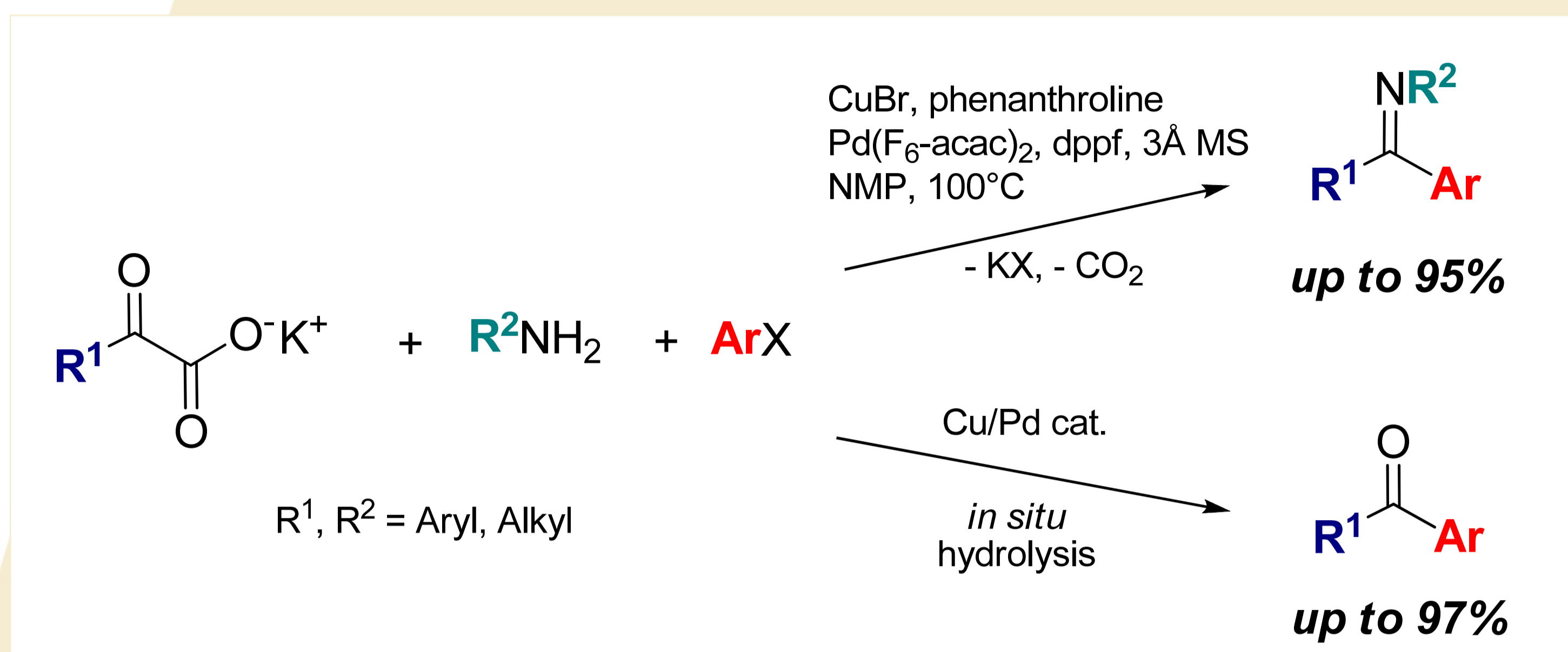




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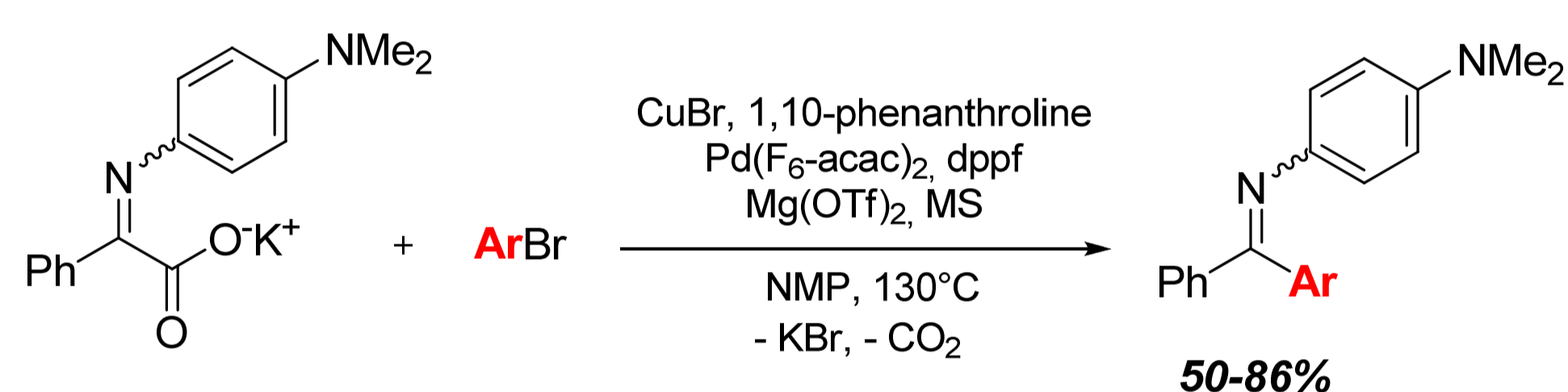
We herein present new one-pot three-component strategies for the synthesis of azomethines and ketones via decarboxylative coupling, starting from simple potassium  $\alpha$ -oxocarboxylates, primary amines and various aryl halides. These efficient procedures provide a straightforward access to a wide range of valuable substituted imines and ketones using an unprecedentedly low temperature for decarboxylative cross-coupling.



### New Strategy for substituted imine synthesis

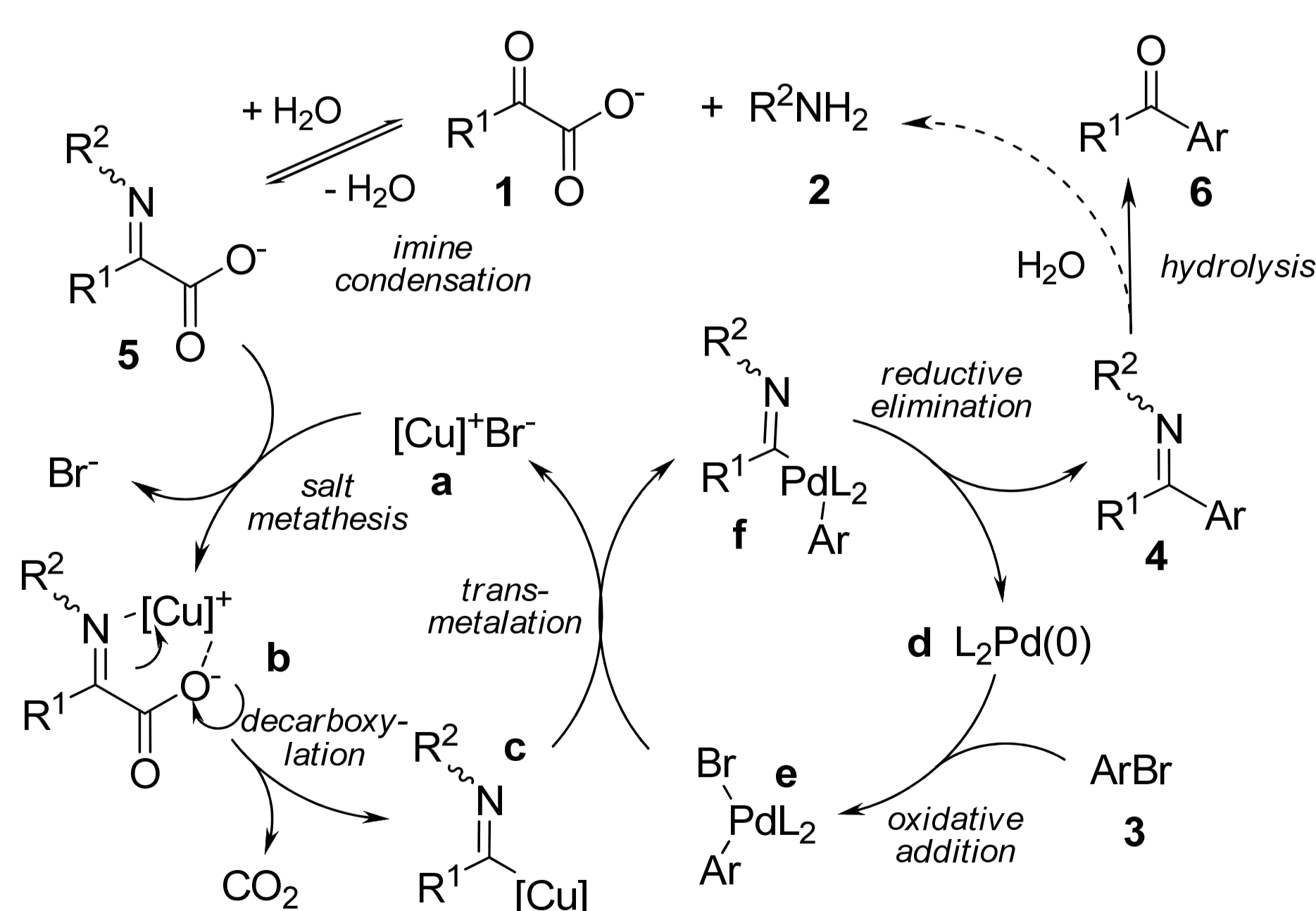
Imines are considered as the most valuable intermediates towards the synthesis of nitrogen-containing molecules.<sup>1</sup> In the last decades, new synthetic transformations have been developed that allow the direct synthesis of imines and ketones via transition-metal catalysis. However, they are often incompatible with sensitive functional groups due to the harsh reaction conditions or the use of organometallic reagents. Recently, decarboxylative couplings have emerged as powerful alternatives as they allow the use of simple and easily available carboxylic acids.<sup>2,3</sup> However, the requirement of high reaction temperatures remains as their main drawback.<sup>4</sup>

In search for concepts to lower the reaction temperature, we first investigated whether the conversion of  $\alpha$ -oxocarboxylic acids into  $\alpha$ -iminocarboxylates would reduce the activation barrier of the decarboxylation step. The first results were promising since the desired azomethines were isolated in good yields starting from the preformed  $\alpha$ -iminocarboxylate.



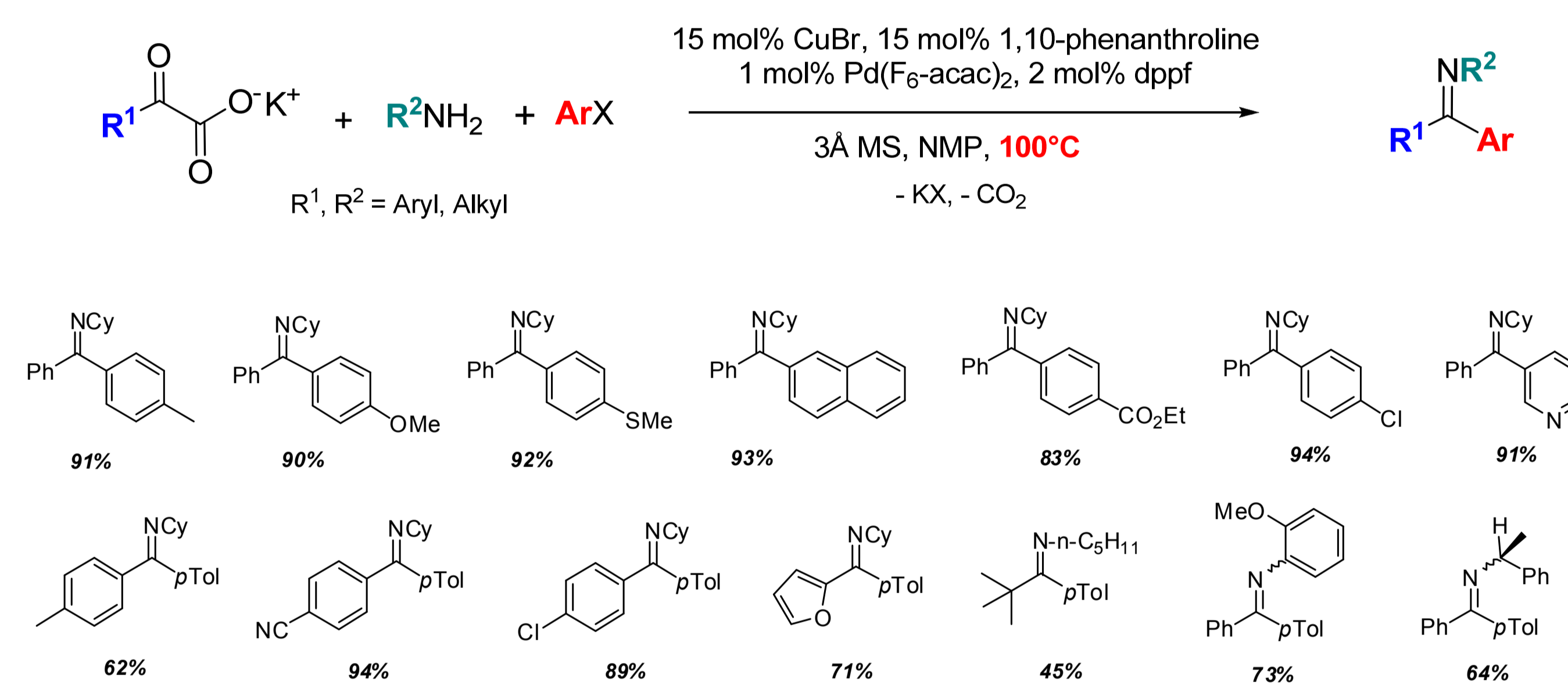
Encouraged by those good results, the idea was then to combine the condensation of the amine with the reactive carbonyl group of an  $\alpha$ -oxocarboxylate to give the  $\alpha$ -iminocarboxylate, and its decarboxylative cross-coupling reaction with aryl halides into a one-pot process.

We herein disclose a highly modular entry to azomethines, involving the decarboxylative coupling of aryl halides and  $\alpha$ -iminocarboxylates, generated *in situ* from potassium  $\alpha$ -oxocarboxylates and primary amines.<sup>5</sup> Through the formation of imido-metal species, an unprecedentedly low temperature for decarboxylative cross-couplings can be used.



### Development of one-pot three-component azomethine synthesis

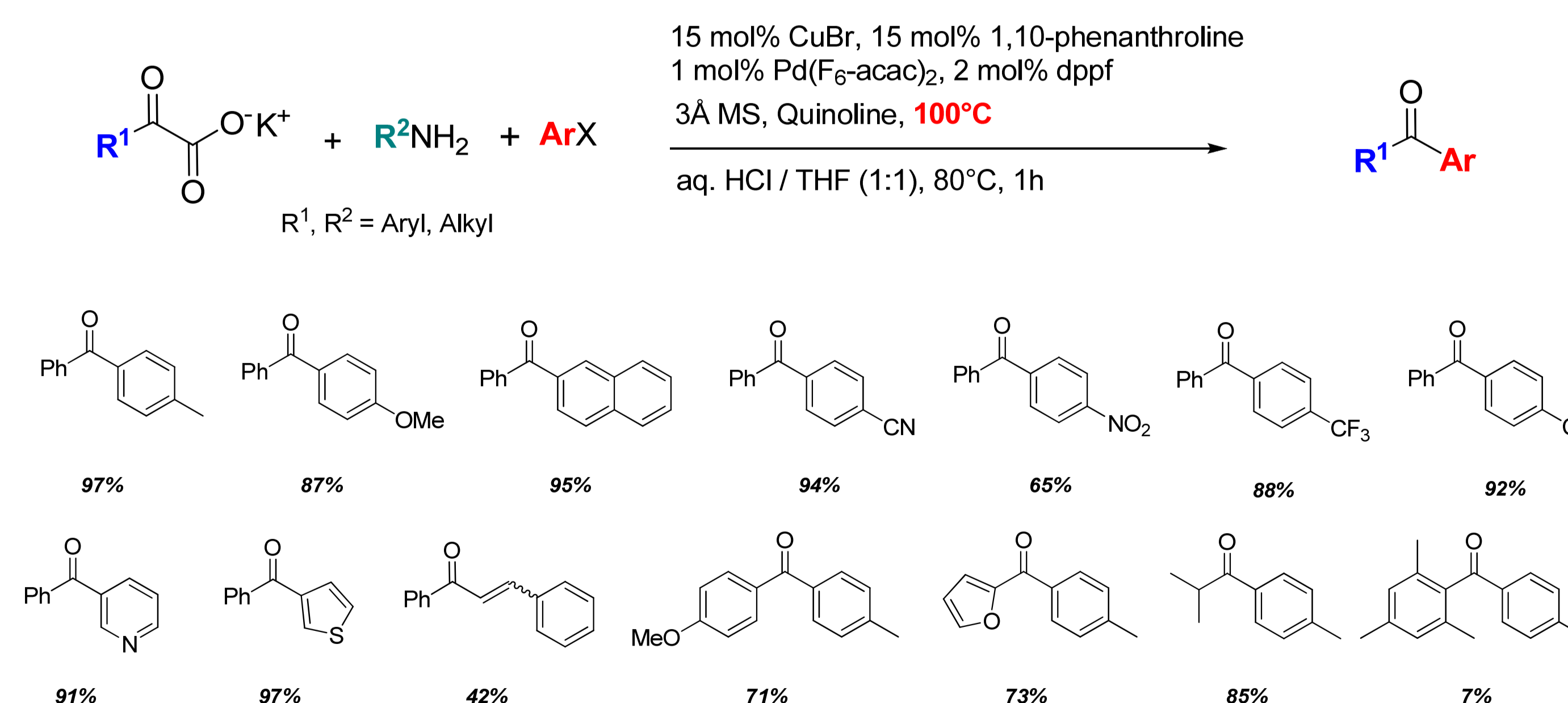
Upon mixing all reagent components, and in an attempt to decrease the reaction temperature, we then evaluated several parameters including palladium cross-coupling catalysts in combination with different copper decarboxylation co-catalysts. The optimized Pd/Cu catalyst system is represented below.



The reaction is widely applicable with regard to the aryl bromide. A plethora of electron-rich and electron-deficient aryl- and heteroaryl bromides containing various functional groups, e.g. thioether, halide, nitro or ester moieties, were coupled in high yields with potassium phenylacetate and cyclohexylamine. The molecular diversity can also be reached by varying the oxocarboxylate component as well as the nature of the primary amine.

### Extension to the ketone synthesis

Having identified such an effective catalyst system, we decided to synthesize the corresponding ketones from  $\alpha$ -oxocarboxylates by their *in situ* conversion to imines, cross-coupling and subsequent hydrolysis of the azomethine intermediates. This procedure appeared to be compatible with the same substrates and functionalities as for the three-component imine synthesis.



### Conclusion

These new one-pot three-component protocols showed remarkably broad substrate scope and excellent functional group tolerance, providing a straightforward access to a wide range of valuable imines using an unprecedentedly low-temperature for decarboxylative cross-couplings. The discovery, that  $\alpha$ -iminocarboxylate salts can so easily be generated and decarboxylate at such mild conditions under formation of imido-metal species, opens up new opportunities for the design of various related decarboxylative transformations.

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### Literature and Further Reading

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