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Expanding the applicabilty of Buchwald-Hartwig amination by employing additives: screening, kinetics and mechanistic studies

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Highlights

- Additives[1] are shown to increase the substrate scope of Buchwald-Hartwig aminations
- Reaction progress kinetics reveal a shift in the rate limiting step and the formation of new catalytic intermediates
- Kinetic studies reveal cases in which catalyst deactivation is reduced, allowing lower catalyst loadings
- A new screening dimension for searching the optimal protocol is proposed

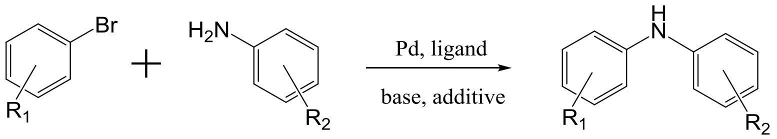
1. Introduction

The Buchwald-Hartwig amination reaction is the most used chemical transformation in the pharmaceutical industry[1], thus improvements that expand its scope and applicability are highly valuable. While several substrates require the use of strong organic bases, often this is undersirable due to substrate degradation and formation of impurities. On the contrary, the use of weaker inorganic bases may not result in the desired reaction performance. In this work, we disclose additives that enable the use of inorganic bases in cases where poor conversions would otherwise be observed. The origin of this improvement is explained mechanistically through a series of detailed kinetic studies.

2. Methods

Reaction development techniques were used to identify conditions to achieve desired conversions. Reaction progress kinetic analysis[2] was employed as a mechanistic probe to study the effect of additives on the rate of reaction, reaction orders and catalyst deactivation. High troughput experimentation (HTE) was used in order to screen additives and identify best conditions.

3. Results and discussion



Scheme 1: Buchwald-Harwig amination reaction

During development of a Buchwald-Hartwig amination (Scheme 1) where extensive screening was performed (on catalysts, ligands, solvents, bases) the best protocols that were found were not robust and could not be scaled-up in an industrial setting. A subsequent screening identified a new additive class[1] that enabled reaching full conversions. A process that included one of these additives was developed and scaled-up in a multi-kg production. Kinetic and mechanistic studies were carried out to identify the origin of this additive effect. The reaction was found to be first order in the amine and zero order in the aryl halide (Figure 1) and have a complex dependance on the additive. This was rationalized by considering that a new catalytic intermediate is formed as the catalyst resting state. Same excess experiments found cases in which, depending on the additive employed, catalyst deactivation could be reduced, suggesting that the exact nature of the additive could impact the stability of the catalyst resting state.

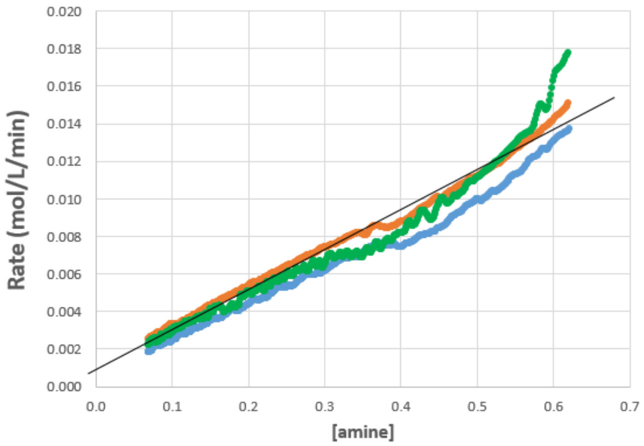


Figure 1: Different excess experiment. Rate data is obtained from reaction calorimetry. The reaction is first order in the amine and zero order in the aryl halide.

4. Conclusions

Additives that expand the applicability of Buchald-Harwtig amination to substrates that degrade in presence of strong organic bases were found. These additives greatly increase robustness, reaction rate and decrease catalyst deactivation. Detailed studies using reaction progress kinetics show that these additives generate a shift in the rate limiting step and the formation of new catalytic intermediates. Kinetic studies also show cases in which catalyst deactivation is reduced, enabling reduction of catalyst loadings. These additives provide a new screening dimension in the search for optimal protocols.

References

[1] Although we are not specifying the additives in this abstract, these will be discussed at the ISCRE meeting.

[2] P. Ruiz-Castillo, S.L. Buchwald, Chem Rev. 116 (2016) 12564–12649

[2] D.G. Blackmond, J. Am. Chem. Soc., 137 (2015) 10852–10866.

Keywords
Buchwald-Hartwig, kinetics, catalysis, mechanism