

## Automated reaction optimisation of the enantioselective $\alpha$ -arylation of aldehydes via SOMO catalysis

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### Introduction

Recent work in the MacMillan group has demonstrated a new mode of organocatalytic activation (SOMO catalysis). The proposed mechanism involves the participation of a  $3\pi$ -radical cation species in a variety of unprecedented asymmetric bond forming reactions.<sup>1</sup> These studies have included the first examples of stereoselective  $\alpha$ -allylic alkylation,<sup>1b</sup>  $\alpha$ -enolation<sup>1c</sup> and  $\alpha$ -vinylation<sup>1d</sup> of aldehydes. Based on these results it was hypothesised that the  $\alpha$ -arylation of aldehydes might be plausible via SOMO catalysis (Fig. 1). This was, indeed, found to be the case.<sup>2</sup> Herein we describe the automated optimisation of the reaction conditions for this novel transformation.

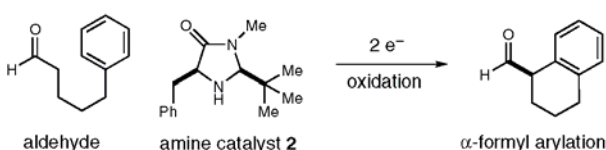


Figure 1. Enantioselective  $\alpha$ -arylation of aldehydes via SOMO catalysis.

### Experimental

Reactions to optimise the number of equivalents of pivalic acid and water and find the ideal concentration of the reaction were carried out in 2 mL reactors at 0.05 mmol (aldehyde) scale, according to the following protocol:

- [Fe(phen)<sub>3</sub>](PF<sub>6</sub>)<sub>3</sub> was delivered by the overhead gravimetric solid dispensing unit (SDU).
- NaHCO<sub>3</sub> was delivered by the SDU.
- The atmosphere within the accelerator hood was purged out with N<sub>2</sub> for 1 h.
- The reactors were evacuated (5 mbar) and filled with N<sub>2</sub> five times.
- The reactors were cooled to -20 °C and kept under a N<sub>2</sub> atmosphere.
- Degassed CH<sub>3</sub>CN was dispensed by the 4-needlehead (4NH).
- Stock solutions of catalyst, water, additive and substrate were added with the 4NH.
- The reactors were degassed again by evacuating (5 mbar) and filling with N<sub>2</sub> five times.
- Under a N<sub>2</sub> atmosphere, the reactors were vortexed at 800 rpm for 24 h.
- Internal standard (methyl benzoate) was added as a stock solution to the reactions (by the 4NH).
- To precipitate out the solids 1.5 mL of ether was added, and the reactions warmed to room temperature
- To avoid any precipitate, the 4-needlehead was then used to sample 100  $\mu$ L of the reaction mixture from 1 cm above bottom of the reactor into a 96-well plate. The sample was then diluted with 1 mL of toluene and analysed by GC-FID. The yield was referenced to the response of the internal standard.

### Results

The number of equivalents of pivalic acid was varied between 0 and 1, the results are summarised in Fig. 2. 0.3 eq was found to be the optimum amount. Next the relationship between concentration and number of

equivalents of water was investigated. The results of this screen are shown in Fig. 3. The starting point of 1 eq H<sub>2</sub>O at 0.1 M, gave 70 % yield and 97 % ee; after optimisation, a yield of 80 % with 98 % ee was achieved using 0.5 eq H<sub>2</sub>O at 0.2 M.

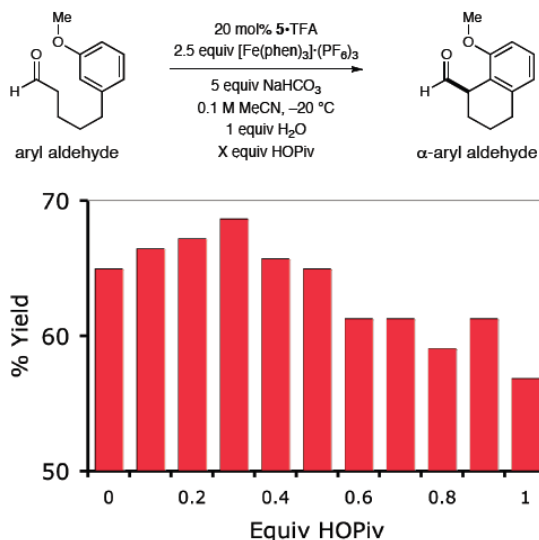


Figure 2. Optimisation of the equivalents of pivalic acid.

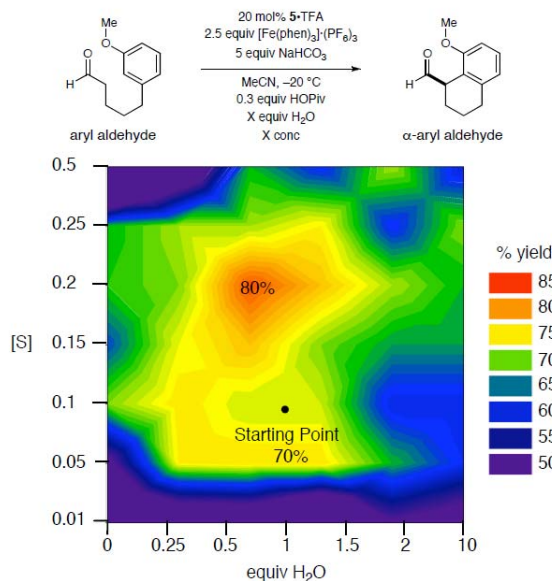


Figure 3. Optimisation of the reaction concentration; and equivalents of H<sub>2</sub>O.

### Summary

The fast and efficient optimisation of reaction conditions on the Chemspeed Synthesizer Catest, has boosted the development of a new, important asymmetric bond forming reaction.

### References

- (a) Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582. (b) Jang, H.-Y.; Hong, J.-B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 7004. (c) Kim, H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 398. (d) Graham, T. H.; Jones, C. M.; Jui, N. T.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 16494.
- Conrad, J. C.; Kong, J.; Laforteza, B. N.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 11640.