

Supporting Information

High-yield gram-scale organic synthesis using accelerated microdroplet/thin film reactions with solvent recycling

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Correction for ionization efficiency

The ionization efficiency correction factor f is used to correct for the difference in ionization efficiencies of product and reagent molecules in mass spectrum. It is defined in equation 1:

To determine f, the reaction mixture after reaction was quenched and analyzed by MS. We record the ratio of product peak intensity over reagent peak intensity, written as S_1 . Afterward, an equimolar amount of reagent (relative to the initial amount of reagent used for reaction) was spiked into the quenched solution, which was then used for MS analysis again. We recorded the ratio of product peak intensity over reagent peak intensity in this spectrum, written as S_2 . Since the reaction is quenched, adding reagents did not change reaction equilibrium. We have equation 2 and 3:

Solving equation 2 and 3 we can get:

A special case is when $S_1 \gg S_2$, equation 5 can then be approximated by equation 6, which usually occurs when reaction conversion is very high

For Claisen-Schmidt reaction we dissolved purified product and reagent in MeOH with 2 mM KOH to 1 mM solution to measure S_1 and S_2 . For the Schiff Base and Katritzky reactions, due to the very slow bulk reaction rates, we ran the accelerated reaction in the thin film format as reported before.¹ Briefly, 10 μ L reaction solution was dropcast on a glass slide covered with parafilm. These droplets were left to form a thin film at 25 °C for Katritzky reaction and at 65 °C for Schiff base reaction. The incubation time for all reactions was 10 min. Afterwards, the residual reaction mixture was washed using 100 μ L quench solution. A small fraction (10 μ L) of the quenched reaction solution was analyzed by nESI to get S_1 . 9 μ L of one reagent solution was spiked into the rest of the quenched solution to get S_2 . For the Suzuki reaction, we used 0.1 eq. Xphos and ran the bulk reaction under 65 °C for 1 hour. After reaction, 10 μ L of the solution was quenched by dilution using the quench solution shown in Table S1 and subjected to nESI analysis.

to get S_1 . Afterward, 10 μL reagent solution was spiked into the quenched solution and subjected to nESI analysis to get S_2 . The typical mass spectra used to measure S_1 and S_2 are shown in Figure S1. It is notable that 5-bromoquinoline contains one bromine atom so the sum of intensity of 208 and 210 was used to calculate S_1 and S_2 . Table S1 shows the quenching conditions, the measured S_1 and S_2 and the calculated f for each reaction.

Reaction Order

Many reversible organic reactions follow a 2nd-order rate equation. According to previous kinetics studies of the Claisen-Schmidt reaction², Schiff base reaction¹ and Katritzky reaction³, they all follow pseudo 2nd-order rate equations. Figure S6 shows the catalytic cycle of the Suzuki coupling reaction. Since the oxidation addition step is the rate determining step, the reaction rate is only dependant on the concentration of catalyst and aryl halide. The catalyst is regenerated in the catalytic cycle; therefore, the final rate equation is only dependent on the concentration of aryl halide, indicating that the Suzuki coupling reaction should follow 1st-order kinetics. In the main text, we have shown the AAF base when calculated using the 2nd-order rate equation for comparison with the other three reactions (they are all pseudo 2nd-order). Figure S7 shows a much smaller AAF of 10 based on calculation using 1st-order rate equation. It is notable that in the case of 1st-order reactions, the value of AAF is the ratio of intrinsic rate constant in microdroplet/thin reaction over that in bulk reaction, without any concentration effect in contribution to reaction acceleration.

Comparison of Collection Efficiency

The biggest difference between previous microdroplet/thin film reactions and the current one is that the reaction/collection sequence is now run in a closed system. As shown in Figure S2, microdroplet reactions generate different sizes of microdroplets, which inversely correlate with the reaction acceleration factor. Under ambient conditions, the smallest microdroplet/nanodroplets lack the kinetic energy to reach the collection substrate (paper, PTFE, etc.), while microdroplets with non-ideal spray angles, also fail to be collected on the substrate. In the current system, we can see many microdroplets with non-ideal spray angles collected on the wall of reaction chamber (Figure 4b). The vent for gas is open at the very top of the tall reaction chamber, which reduces the escape probability of the small size sprayed microdroplets, secondary microdroplets after collision and small microdroplets and vapors of reactants and products. In the solvent recycling mode, the collection efficiency can be further improved become these small microdroplets and particles can be captured in the condensation chamber and sent back to the reaction chamber again.

Figures and Tables

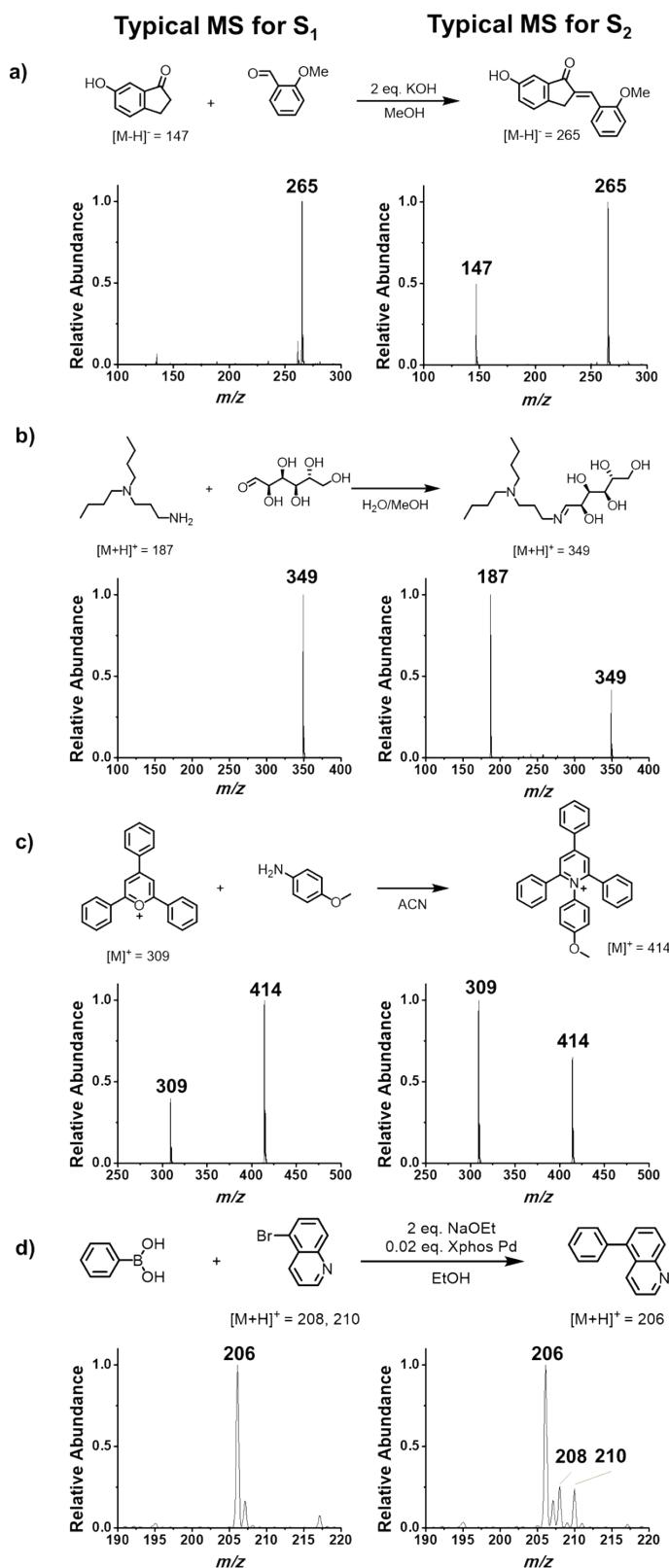


Figure S1. Typical mass spectra for measured S_1 and S_2 for different reactions.

Table S1. Ionization efficiency correction for the four reactions performed in this study

Name	Quenching condition	S1			S2			f
		1	2	3	1	2	3	
Claisen-Schmidt Reaction	Dilution 10X in MeOH	Too large	Too large	Too large	2.7	2.0	2.1	2.3
Katritzky Reaction	Dilution 10X in ACN	2.6	1.8	2.0	0.81	0.63	0.69	2.2
Schiff Base Formation	Dilution 10X in water	Too large	Too large	Too large	0.31	0.44	0.35	0.37
Suzuki Coupling	Dilution 1000X in ethanol with 1% Hac	Too large	Too large	Too large	1.9	2.0	2.0	2.0

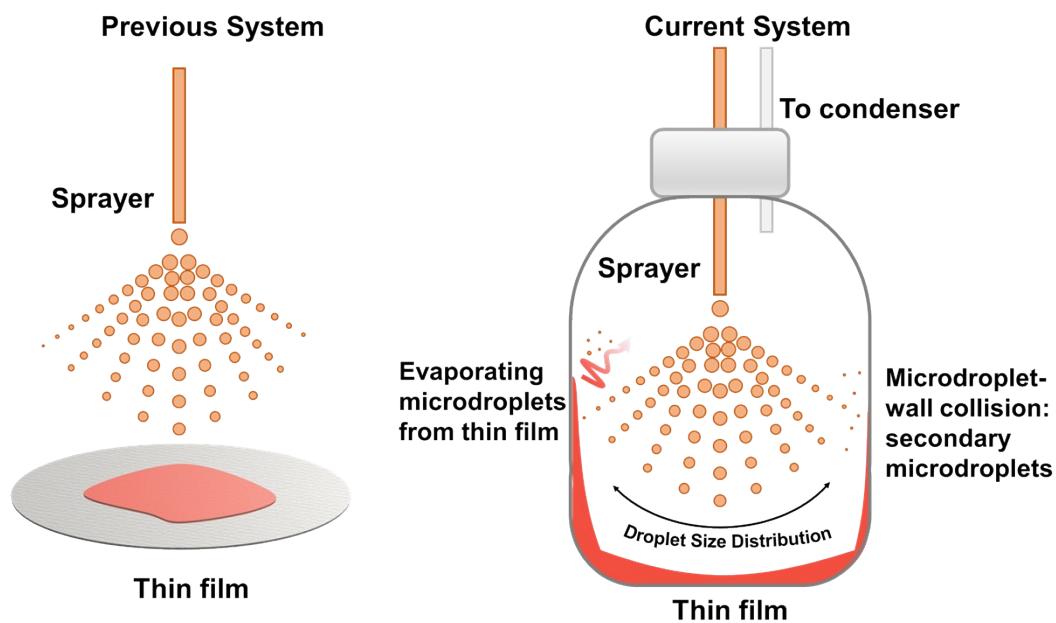


Figure S2. Comparison of product collection efficiency in our previous reported² system and the current system

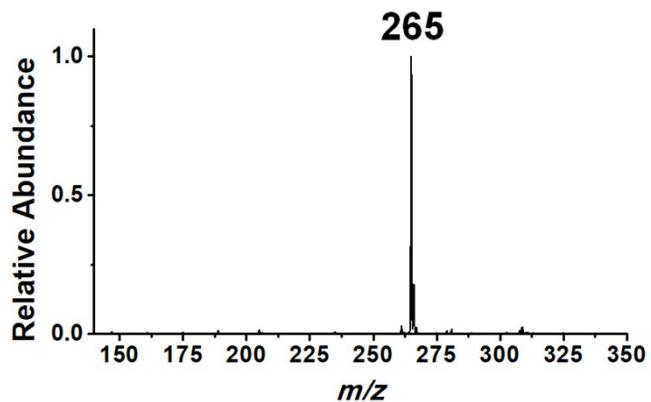


Figure S3. Mass spectrum of purified product of scaled-up Claisen-Schmidt reaction. The product was diluted to 1 mM and 1 mM DMAP was added to increase ionization in negative mode analysis.

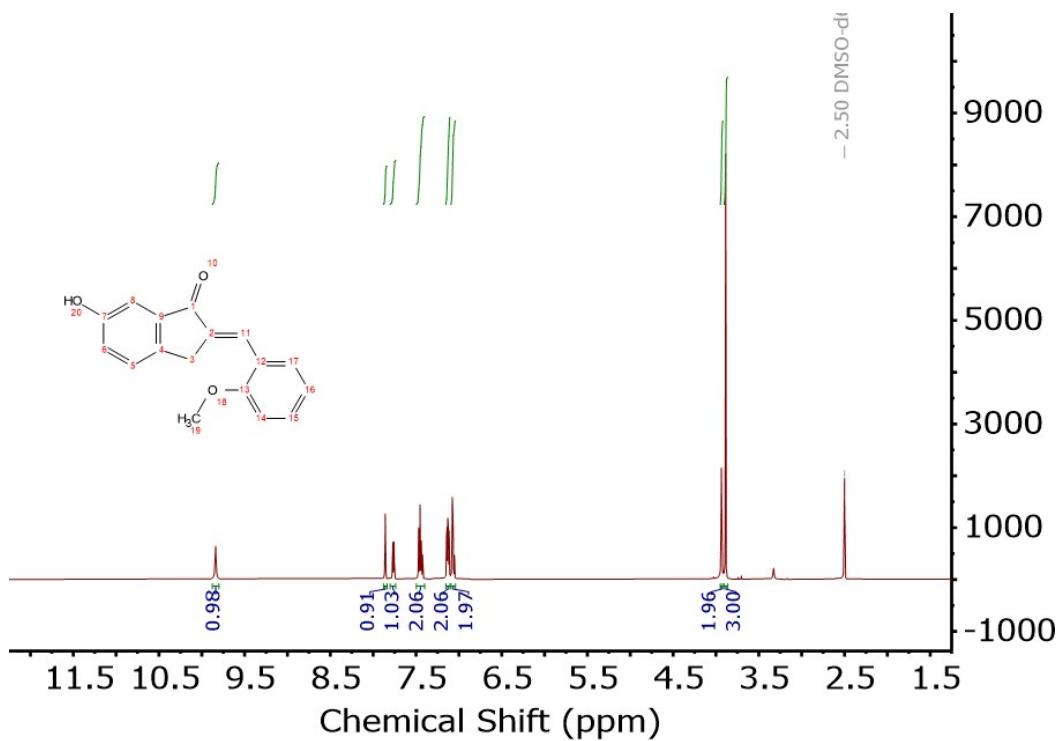


Figure S4. H-NMR spectrum of the purified product of scaled-up Claisen-Schmidt reaction. The product was dissolved in deuterated DMSO. The frequency is 500 MHz. Peaks: 9.84 (s, 1H), 7.86 (t, 1H), 7.76 (dd, 1H), 7.46 (, 1H), 7.44 (td, 1H), 7.13 (m, 2H), 7.08 (d, 1H), 7.06 (td, 1H), 3.94 (d, 2H), 3.89 (s, 3H).

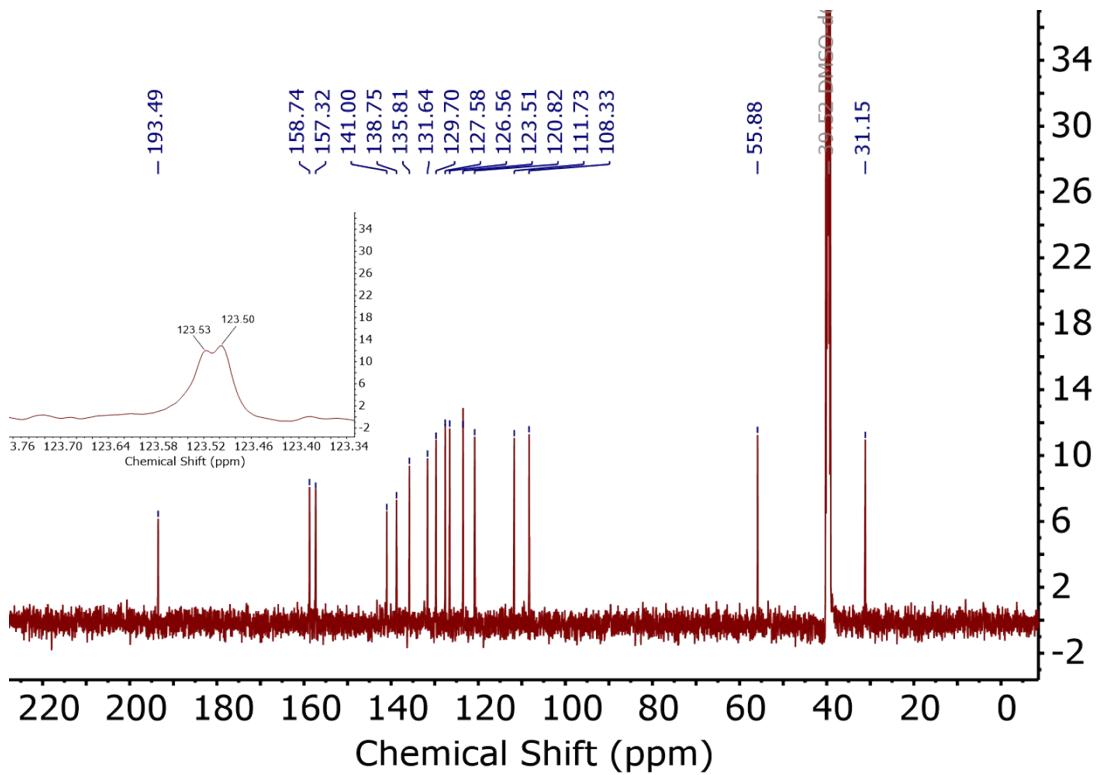


Figure S5. H-NMR spectrum of the purified product of scaled-up Claisen-Schmidt reaction. The product was dissolved in deuterated DMSO. The frequency is 500 MHz. Peaks: 193.5, 158.7, 157.3, 141.0, 138.8, 135.8, 131.6, 129.7, 127.6, 126.6, 123.5 (two peaks: 123.53 and 123.50), 120.8, 111.7, 108.3, 55.9 and 31.2.

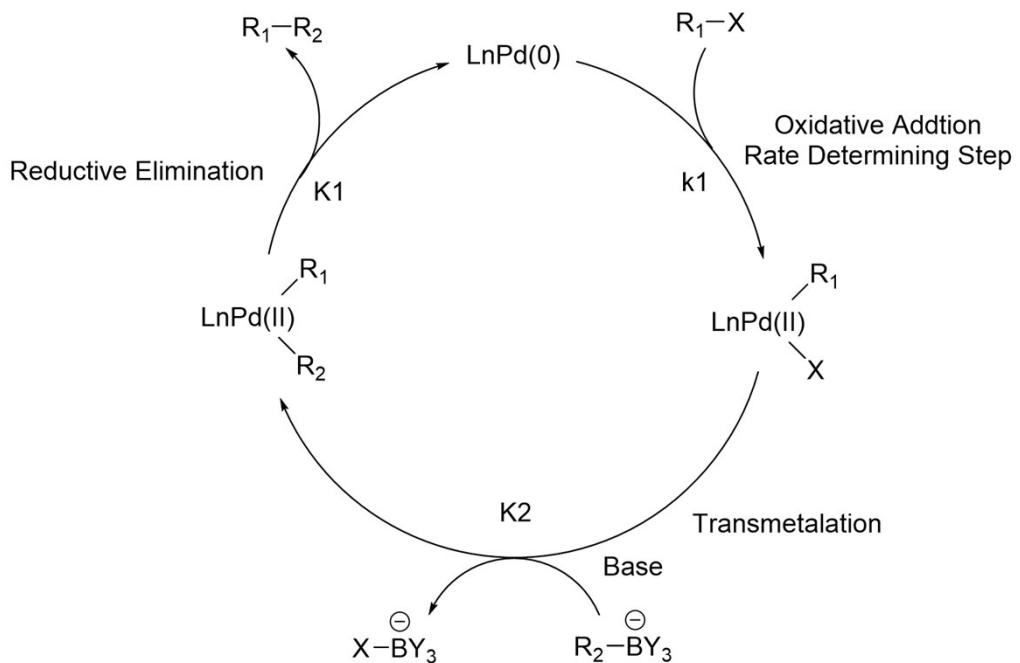


Figure S6. Mechanism of Suzuki coupling reaction. Oxidative addition is the rate determining step.

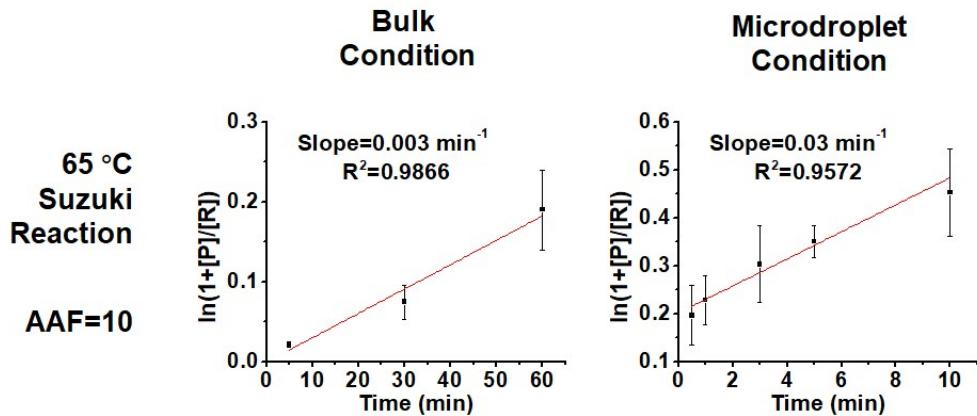


Figure S7. Kinetics curve of Suzuki coupling reaction based on 1st-order rate equation. The AAF is 10 in microdroplets. It is notable that in the case of 1st-order reaction, the value of AAF reflects the ratio of intrinsic rate constant in microdroplet/thin film reaction vs. bulk reaction.

References

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