Programmable Microdroplet Cascade Reactions: Uncatalyzed Michael Addition for Carbon–Carbon Bond Formation via Plasma–Water Fusion

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Introduction

- Carbon–Carbon (C–C) bond forming steps have ubiquitous importance in all fields of chemical science
- C–C bond formation plays a critical role in the formation of bioactive chemicals, pharmaceuticals, biodegradable polymers, natural product and fine chemical synthesis, and agrochemicals
- Michael addition between a 1,3-dicarbonyl Michael donor and electron-deficient Michael acceptor represents a straightforward method for C–C formation
- Bulk Michael addition methods are limited by strong base catalysis, specialized reagent selection, and aprotic organic solvent – with unfavorable environmental and ecological implications
- Herein: A combination of the reactive environment of plasma discharge with the green medium of charged water microdroplets in a programmable reaction platform for uncatalyzed Michael addition

Approach

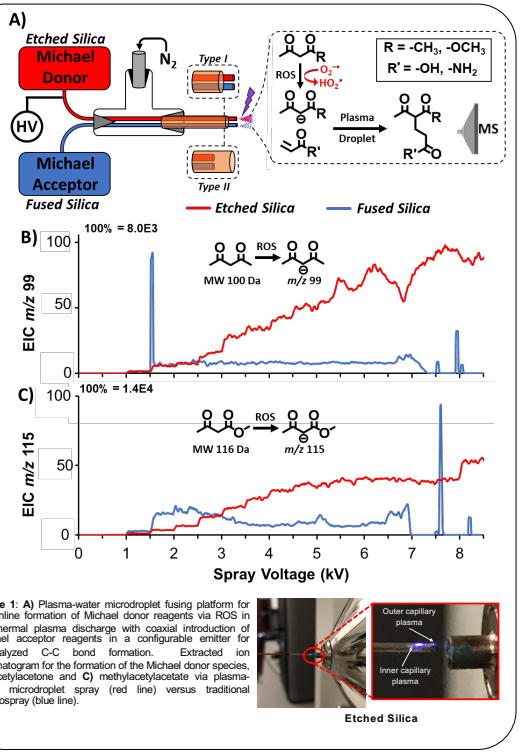

Figure 1: **A)** Plasma-water microdroplet fusing platform for the online formation of Michael donor reagents via ROS in non-thermal plasma discharge with coaxial introduction of Michael acceptor reagents in a configurable emitter for uncatalyzed C-C bond formation. Extracted ion chromatogram for the formation of the Michael donor species, **B)** acetylacetone and **C)** methylacetylacetate via plasma-water microdroplet spray (red line) versus traditional electrospray (blue line).

Results and Discussion

Plasma-Droplet Uncatalyzed Michael Addition

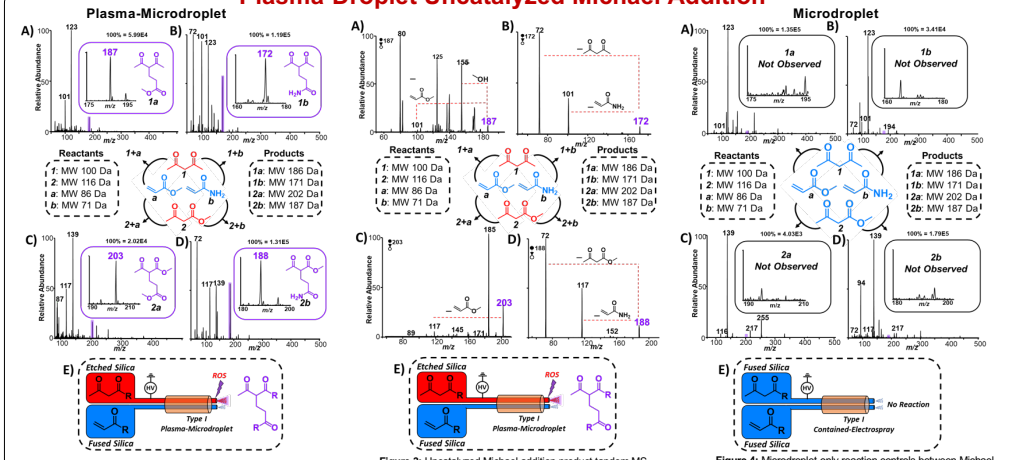

Figure 2: Uncatalyzed Michael addition between 1,3-dicarbonyl Michael donor reactants formed via plasma coaxial with α,β-unsaturated carbonyl Michael acceptor reactant

Figure 3: Uncatalyzed Michael addition product tandem MS analysis for product validation from Type I plasma-microdroplet operation

Figure 4: Microdroplet-only reaction controls between Michael donor and acceptor species in a co-axial contained-ESI emitter yielding null product formation in the absence of plasma

Programmable Michael Addition

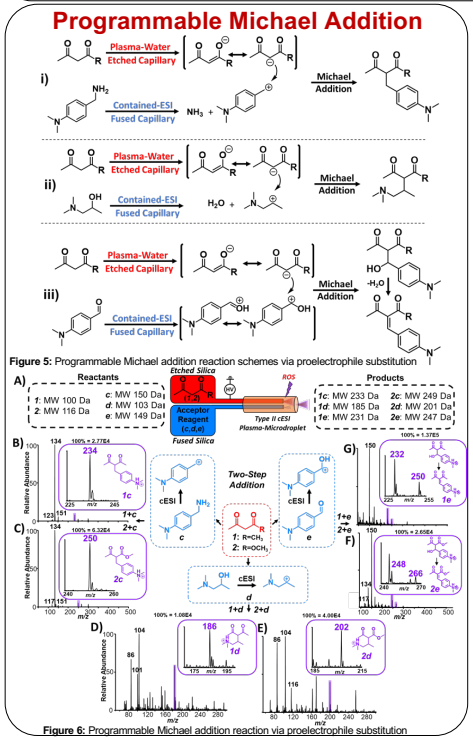

Figure 5: Programmable Michael addition reaction schemes via proelectrophile substitution

Figure 6: Programmable Michael addition reaction via proelectrophile substitution

Programmable Hantzsch Cascade Reactions

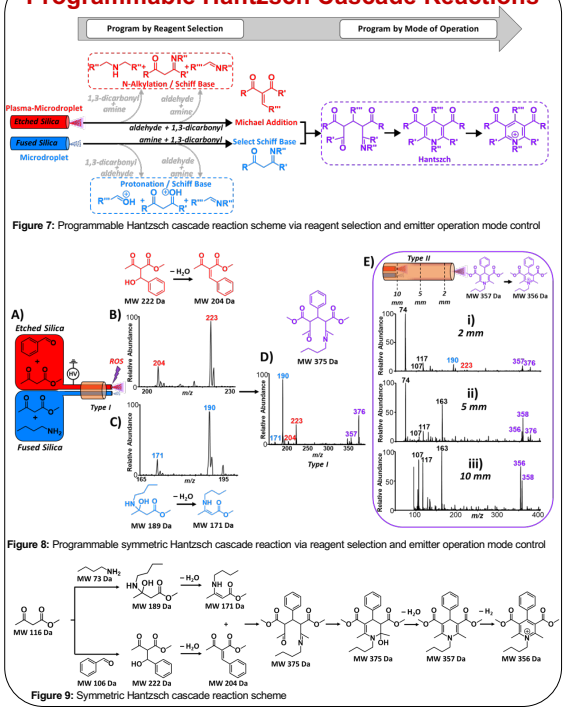

Figure 7: Programmable Hantzsch cascade reaction scheme via reagent selection and emitter operation mode control

Figure 8: Programmable symmetric Hantzsch cascade reaction via reagent selection and emitter operation mode control

Figure 9: Symmetric Hantzsch cascade reaction scheme

Summary

- The contained-ESI source with chemically etched spray capillaries is capable of online plasma-droplet fusing reactions
- This phenomena is applied here to uncatalyzed Michael addition reactions
- Reaction programmability is achieved via:
  - Reagent selection in etched silica capillaries for plasma generation and fused silica capillaries for microdroplet reactivity
  - Emitter operational mode control
- Tandem MS of products generated online yield structural information
- Programmable Hantzsch reaction demonstrated for symmetric product generation

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