

A continuous flow platform for the safe use of ozone in Medicinal Chemistry

Alexandra Bosnidou¹, M.^a Carmen Campanero, Graham Cumming¹, Carlos Mateos¹, Gabriel A. Hrehoret, Pablo García Losada¹,
Juan A. Rincón¹, María José Nieves¹

¹ Centro de Investigación Lilly S.A.U, Avda. de la Industria 30, 28108 Alcobendas, Madrid, Spain.

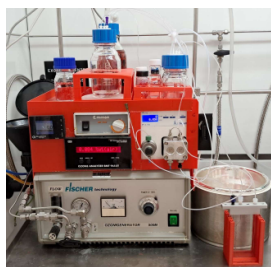
Lilly A MEDICINE COMPANY

KEY FEATURES

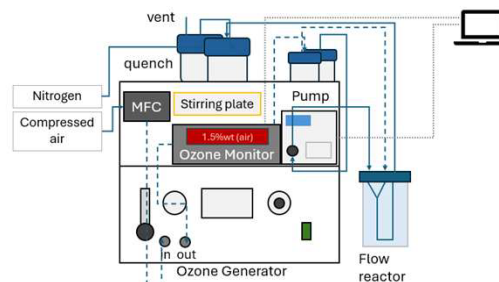
- Ozone reactions GO ACCESSIBLE for Medicinal Chemistry
- Developed an inherently SAFE flow platform: NO NEED OF NEAT OXYGEN, uses laboratory hood compressed air
- Precise control of OZONE STOICHIOMETRY
- FULLY VALIDATED with a broad scope of substrates
- ON-DEMAND PRODUCTION of Medicinal Chemistry relevant compounds

TYPICAL REACTION CONDITIONS:

- SM concentration = 0.05 - 0.1 M
- Air flowrate = 80 ml/min
- Liquid flowrate = 0.1 - 0.8 ml/min
- O₃ concentration = 1.0 - 2.0 %wt./wt.
- Residence time = 4 - 34 s
- Ambient temperature
- Easy reductive work-up with solid-supported PPh₃

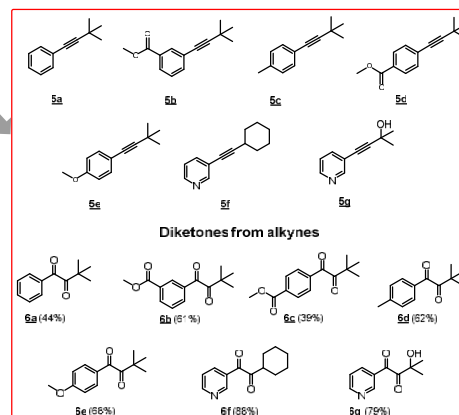
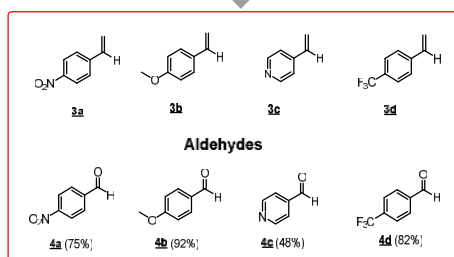
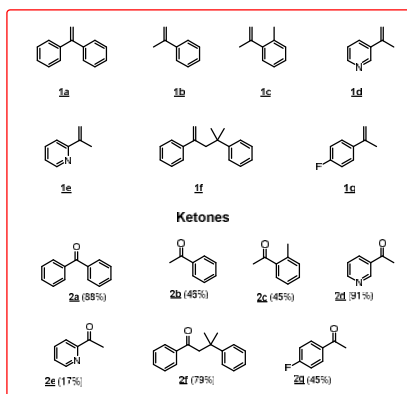


IN-HOUSE FLOW OZONOLYSIS PLATFORM

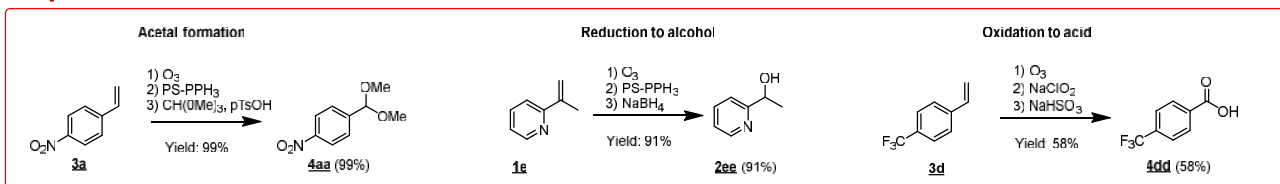


- Easy-to-use platform with in-house software control
- Real-time ozone concentration monitoring
- Low-volume reactor chip for better heat and mass transfer

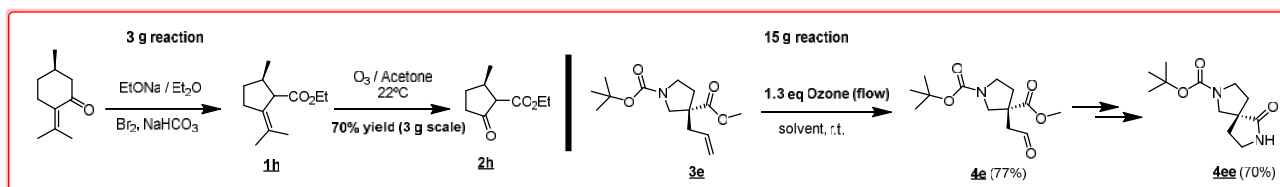
PLATFORM VALIDATION AND SCOPE OF SUBSTRATES



Sequential transformations



Multigram examples



CONCLUSIONS

- Fast, convenient setup to perform ozonolysis reactions from mg to > 10 gr
- Automated and unattended control of ozone/substrate equivalents
- Validated with scope of substrates, from alkenes to alkynes
- On-demand production of aldehydes for telescope processes

REFERENCES

1. Nieves-Remacha, M.J.; Jensen, K.F. *J Flow Chem* **5**(3):1-6. (2015)
2. Lou, F.; Cao, Q.; Zhang, C. *et al. J Flow Chem* **12**, 307-315 (2022)
3. Polterauer, D.; Roberge, D. M.; *et al. Reaction Chemistry & Engineering*, **6** (12), 2253-2258 (2021)
4. Vaz, M.; Courboin, D.; *et al. Organic Process Research & Development* **25** (7), 1589-1597 (2021)
5. Alterman, J. L.; Vang, D. X.; *et al. Organic Letters*, **22** (19), 7424-7426 (2020)
6. Roydhouse, M. D.; Motherwell, W. B. *et al. RSC Advances* **3** (15), 5076-5082. (2013)
7. MsThesis M.^a Carmen Campanero, Universidad Autónoma de Madrid, 2022
8. MsThesis Gabriel A. Hrehoret, Universidad Complutense de Madrid, 2023