https://doi.org/10.17952/38EPS.2026.P280
European Peptide Symposium, 6th – 11th September 2026, Vienna, Austria

RACEMIZATION-FREE PEPTIDE SYNTHESIS IN WATER UNDER BATCH AND FLOW CONDITIONS

Sri Hari Anandhi Rajendran[a,b], Sándor B. Ötvös[a,b], C. Oliver Kappe[a,b], Wilfried M. Braje[c], Matthew Burns[d]

[a] Research Center Pharmaceutical Engineering GmbH (RCPE), Inffeldgasse 13, A-8010 Graz, Austria
[b] Institute of Chemistry, University of Graz, NAWI Graz, Heinrichstrasse 28, A-8010 Graz, Austria
[c] *AbbVie Deutschland GmbH & Co. KG, 67061 Ludwigshafen, Germany*
[d] *Chemical Development, Pharmaceutical Technology & Development, Operations, AstraZeneca, Macclesfield SK10 2NA, United Kingdom*

hari.rajendran@rcpe.at | www.goflow.at

INTRODUCTION

Established technology — Reactions in Organic Solvents

- ✓ Excellent solubility for organic compounds
- ✓ Well-understood, well-established protocols
- ✓ Readily scalable



- ✗ Harmful and toxic: **DMF, NMP, DCM, MTBE**
- ✗ Make up most of the waste generated
- ✗ Expensive, and restricted by legislation

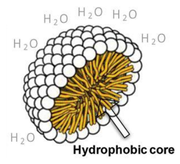


'New' approach — Reactions in Water

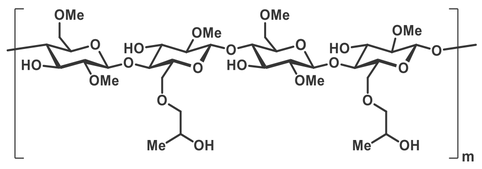
- ✓ Non-toxic, not flammable
- ✓ Inexpensive and readily available
- ✓ Mild conditions, Rate enhancement



- ✗ Poor solubility of organic compounds
- ✗ Enablers, e.g. surfactants are needed
- ✗ Designer surfactants are expensive!

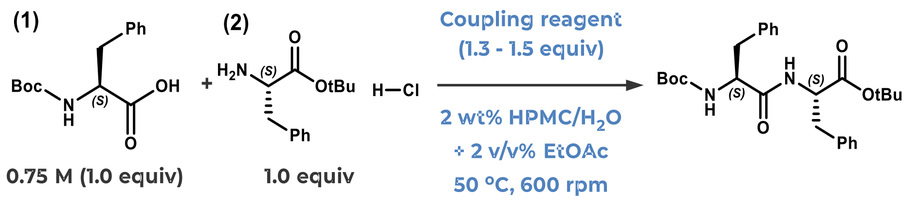


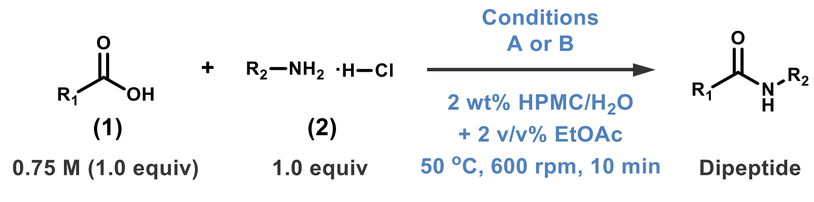
This work — Why HPMC?



- ✓ **Bulk commodity**, not a designer surfactant
- ✓ Pharma excipient (E464) — cheap, non-toxic
- ✓ **Hydrophobic pockets** concentrate the reagents

BATCH OPTIMIZATION & SUBSTRATE SCOPE





Screening coupling reagents

Reagent	Base	t [min]	Conv [%]	Sel [%]	d.r
COMU	2,6-Lutidine	60	94	93	>99 : 1
EDC·HCl	Pyridine	60	80	94	—
CDI	—	10	60	95	—
EEDQ	**none***	**≤10**	**>99**	**97**	**>99 : 1**

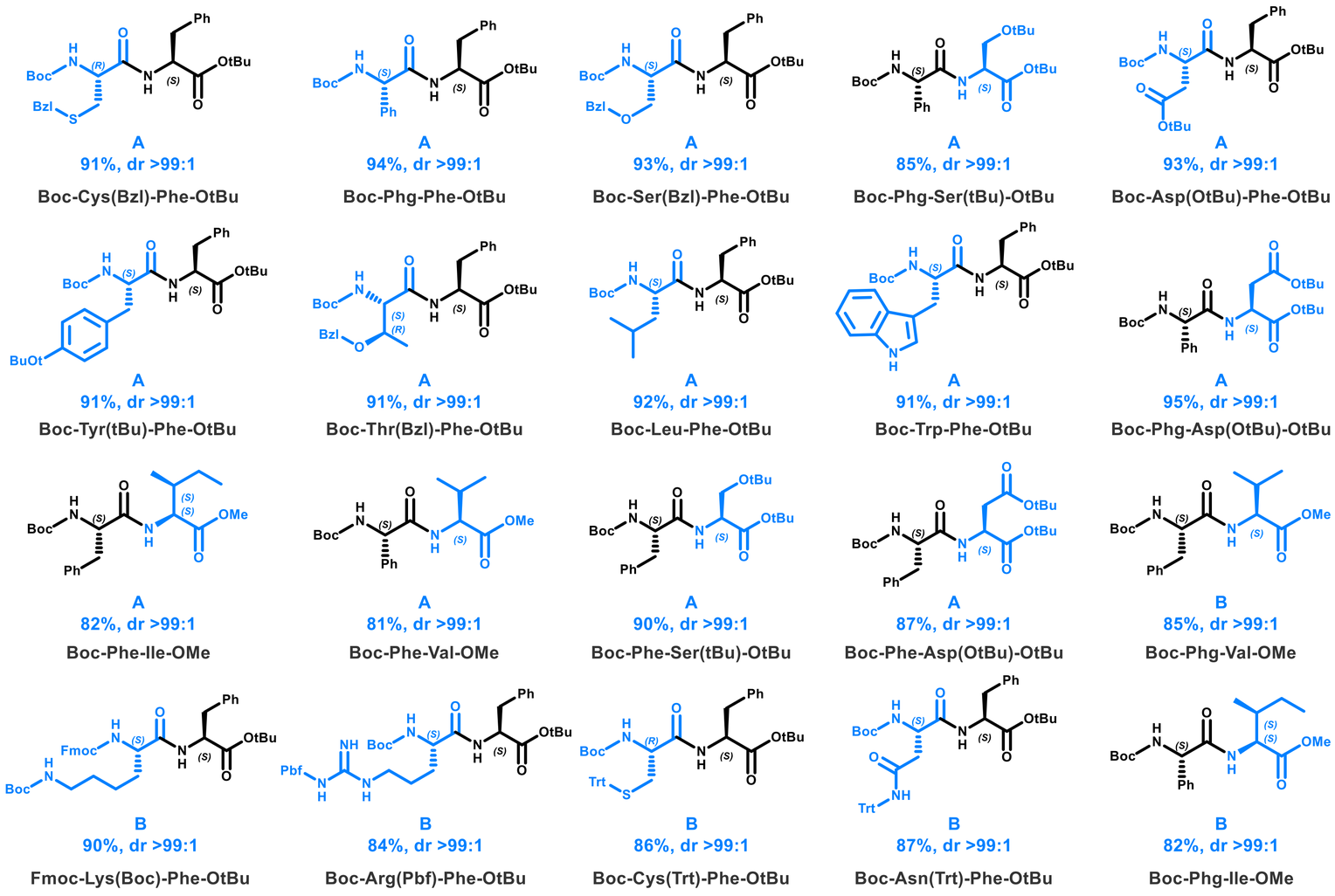
Advantages of EEDQ

- ✓ **Racemization-free** - d.r >99 : 1
- ✓ **No external base** - quinoline in situ
- ✓ **Easy and simple work-up**
- ✓ **Fast** - ≤10 min
- ✓ **Improved atom economy**
- ✓ **Low cost per mole**

Scale-up

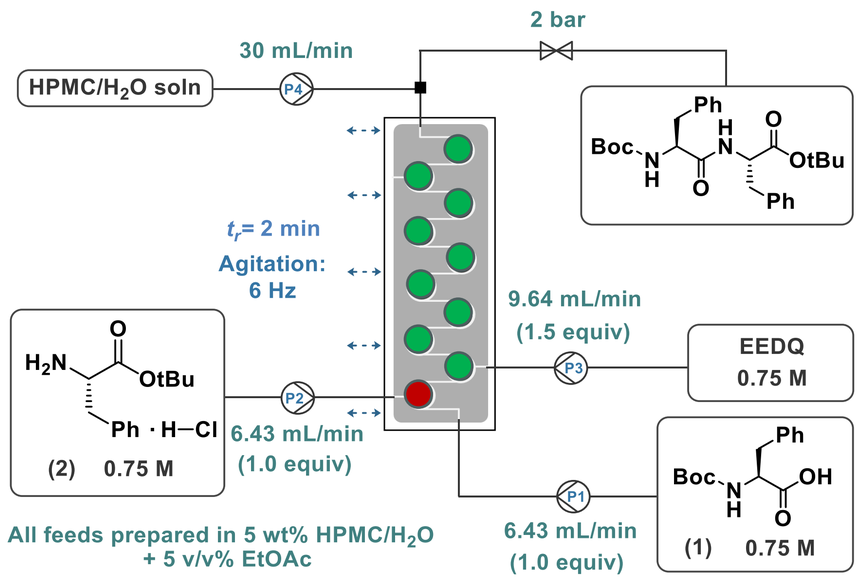
Volume	Isolated yield	d.r
5 mL	89 %	>99 : 1
100 mL	91 % (32 g)	>99 : 1
500 mL	92 % (163 g)	>99 : 1

Chemistry scales well in batch but CO_2 evolution becomes significant at higher volumes, making flow chemistry an attractive approach!



plus 13 additional substrates...

PEPTIDE COUPLINGS IN FLOW



PREPARATIVE RUN (2 h)
248 g
91.5 % yield · 124 g/h · ≈ 3 kg/day

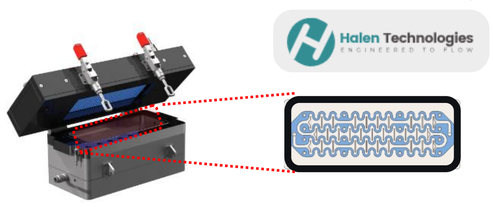
E-factor : 2.1

PMI : 3.1

Halen XFR 200

Serpentine design, oscillatory mixing, 11.6 mL

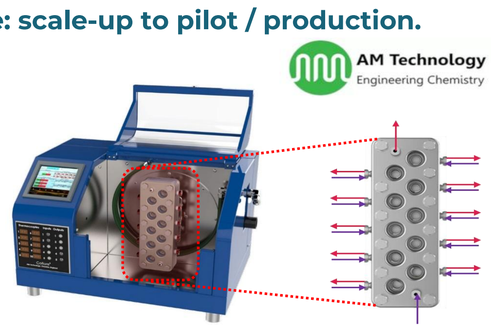
Role: process development & screening.



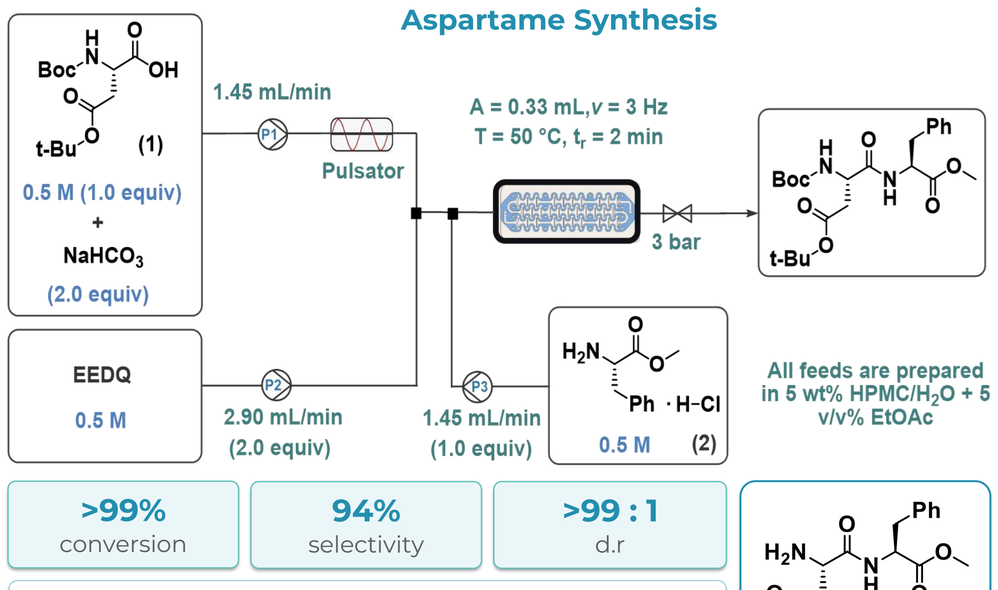
Coflore ACR

10 CSTRs in series, lateral agitation, 30–90 mL

Role: scale-up to pilot / production.



Aspartame Synthesis



>99% conversion	94% selectivity	>99 : 1 d.r

1. **Flow coupling** — steady state in < 5 min
2. **Boc/OtBu removal** — TFA/DCM, rt, 30 min
3. **Anti-solvent wash** — by-products removed

82%
isolated yield

This project is supported by the Innovative Health Initiative Joint Undertaking (IHI JU) under grant agreement No 101165889. The JU receives support from the European Union's Horizon Europe research and innovation programme and COCIR, EFPIA, Europa Bio, MedTech Europe, and Vaccines Europe.

Federal Ministry Republic of Austria Climate Action, Environment, Energy, Mobility, Innovation and Technology
Federal Ministry Republic of Austria Labour and Economy
FFG Promoting Innovation.
Das Land Steiermark Wirtschaft, Tourismus, Regionen, Wissenschaft und Forschung
SFG NEUES DENKEN. NEUES FÖRDERN.