

Oxidation of alcohols using solid-phase hypervalent iodine reagents in batch and continuous flow



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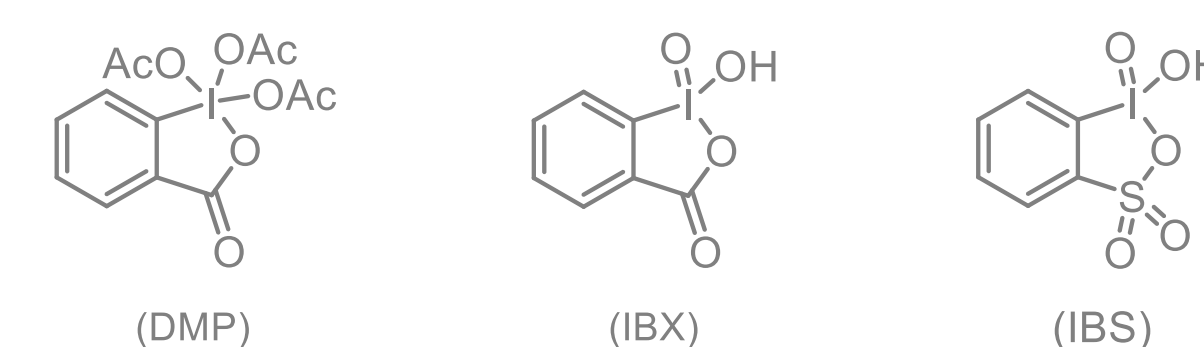
Introduction

The oxidation of alcohols towards carbonyls is one of the most fundamental reactions in organic chemistry. Decades of research have already been invested to investigate this apparent easy transformation.¹ Therefore, a myriad of methods have been invented, primarily using metals or toxic reagents (e.g., chromium-based). Nowadays, demands of chemistry to fulfil the 12 principles of green chemistry (atom economy, less hazardous chemical syntheses, or safer solvent use etc.) or its role to help create a more sustainable future do not match here.²⁻⁴

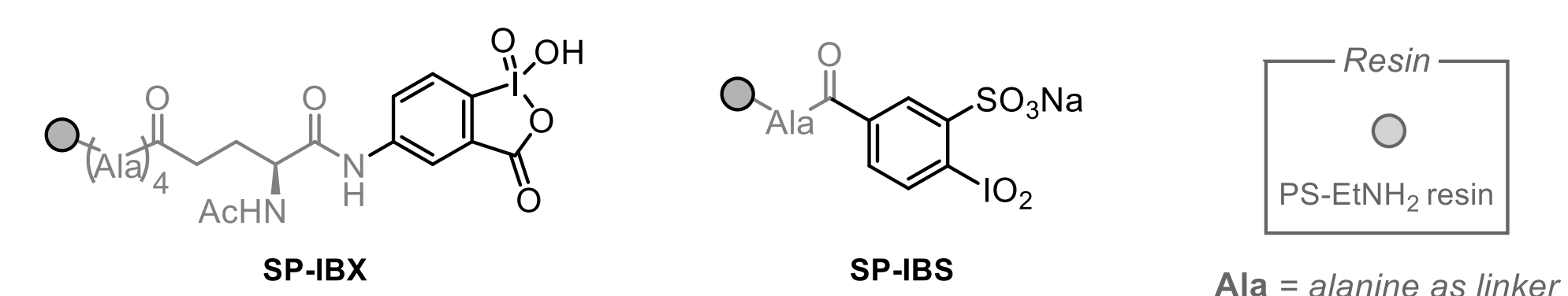
The development of hypervalent iodine reagents, such as DMP, IBX or IBS, are already an improvement in safety and sustainability.⁵

To address current needs of modern, organic synthesis and to make the catalytic use of hypervalent iodine reagents for oxidations more approachable, we developed a solid-phase catalyst system which proved to be suitable for the oxidation of alcohols.⁶

Stoichiometric oxidants of alcohols – previous examples

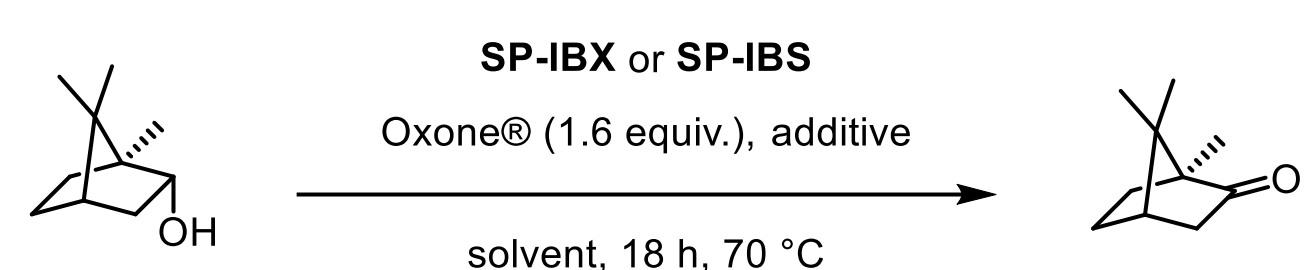
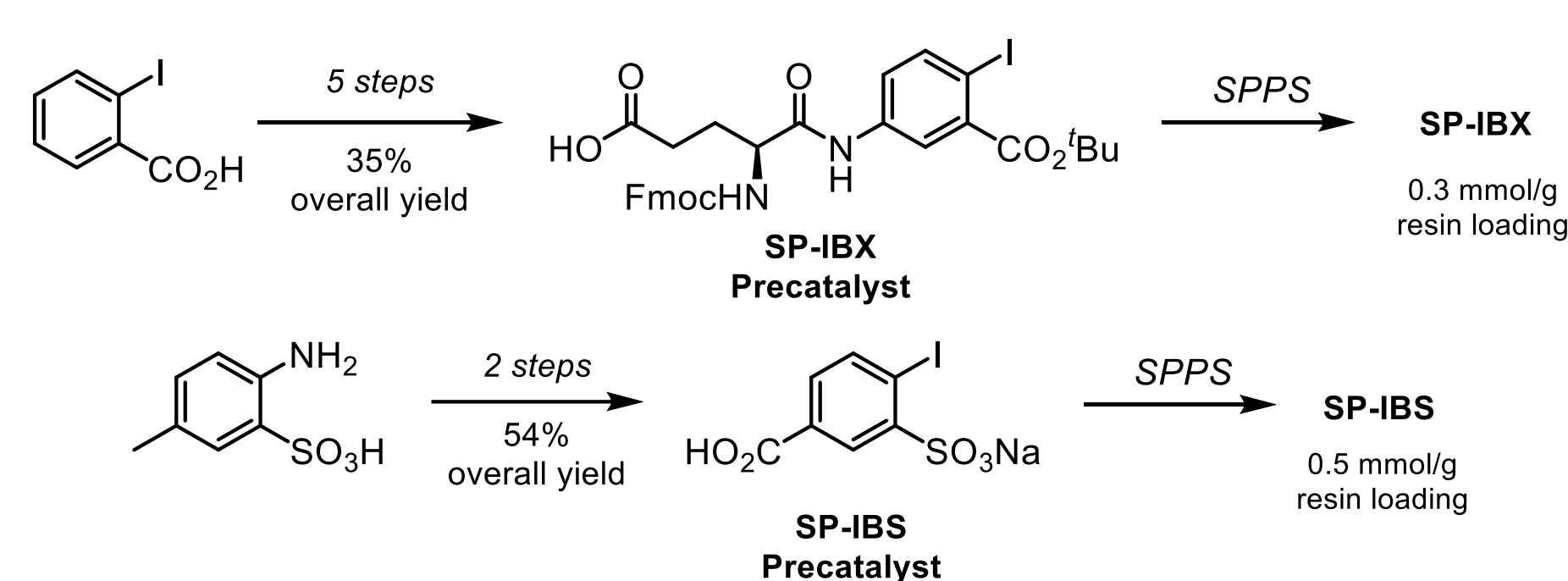


Solid-phase oxidants for stoichiometric and catalytic use – this work

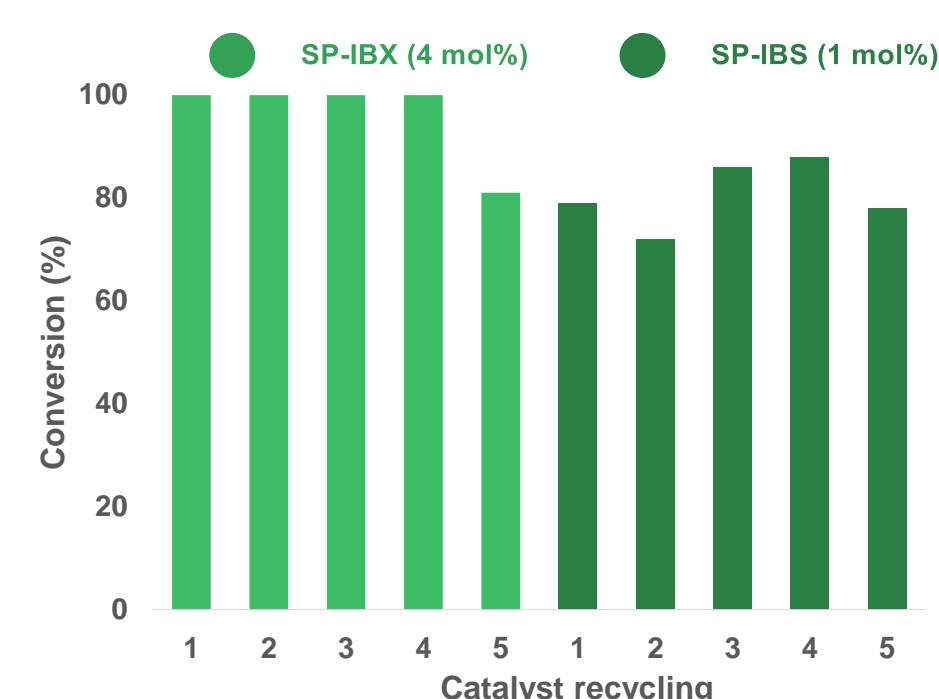


Ala = alanine as linker

Synthesis of catalysts & Method development in batch⁶



Entry	Catalyst [mol%]	Additive [mol%]	Solvent	Conversion ^[a]
1 ^[b]	--	--	MeCN-H ₂ O ^[e]	2%
2 ^[b]	SP-IBX [5]	--	MeCN-H ₂ O ^[e]	>99%
3 ^[c]	SP-IBS [3]	--	MeCN-H ₂ O ^[e]	97%
4 ^[d]	SP-IBS [2.5]	--	MeCN	6%
5 ^[d]	SP-IBS [2.5]	--	MeNO ₂	9%
6 ^[d]	SP-IBS [2.5]	ⁿ Bu ₄ NHSO ₄ [10]	MeCN	57%
7 ^[d]	SP-IBS [2.5]	ⁿ Bu ₄ NHSO ₄ [10]	MeNO ₂	37%
8 ^[d]	SP-IBS [2.5]	ⁿ Bu ₄ NHSO ₄ [20]	MeCN	97%
9 ^[e]	SP-IBS [1]	ⁿ Bu ₄ NHSO ₄ [40]	MeCN	98%
10 ^[f]	SP-IBS [0.2]	ⁿ Bu ₄ NHSO ₄ [40]	MeCN	91%
11 ^[e]	--	ⁿ Bu ₄ NHSO ₄ [40]	MeCN	6%



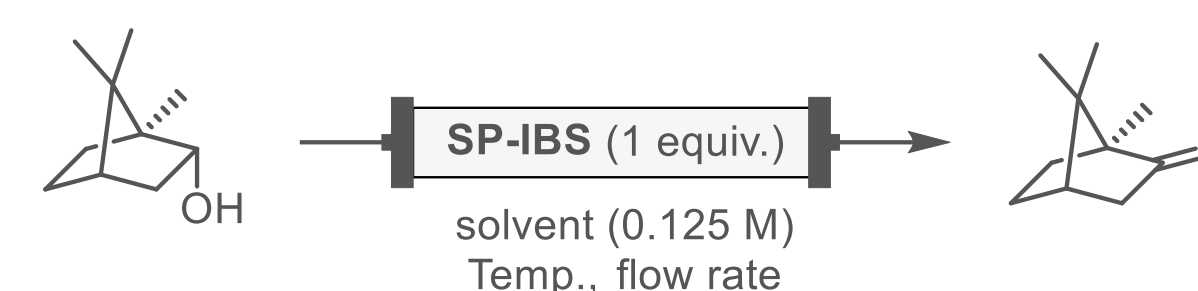
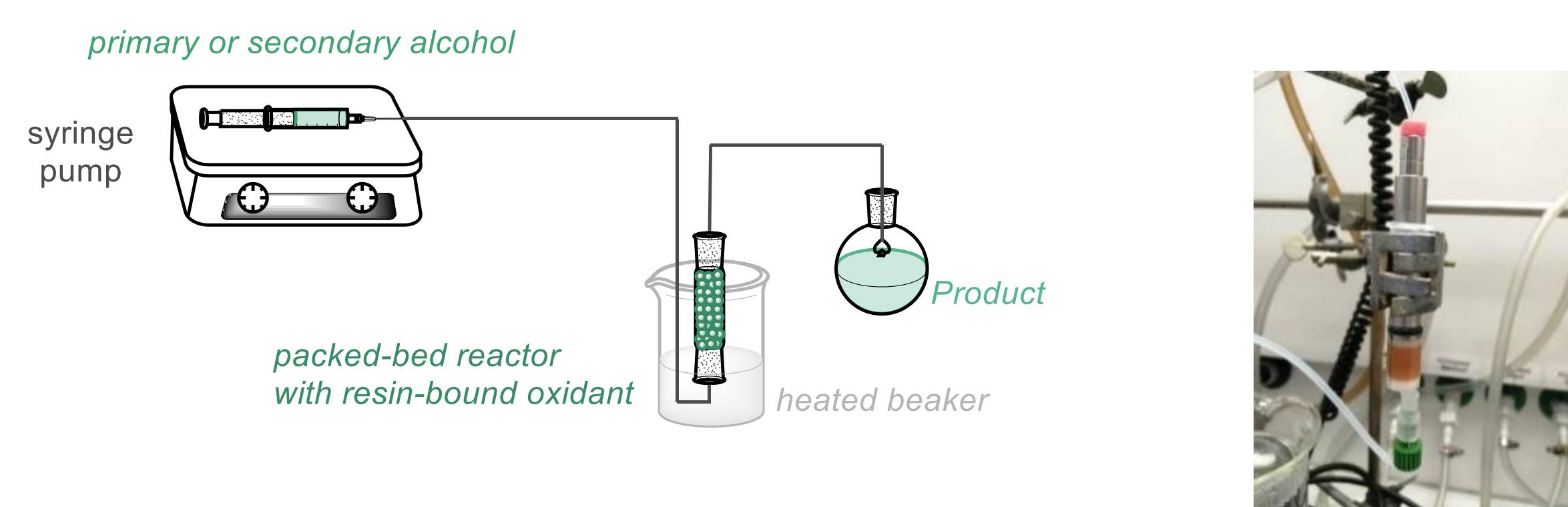
Key features

- Synthetically easy precatalyst
- Catalytical oxidation
- Recyclable catalyst
- Possible use in peptide conjugate catalysis

[a] Conversion was determined via GC-FID, [b] 18 h, [c] 6 h, [d] 2 h, [e] 4 h, [f] 24 h, [g] Ratio MeCN-H₂O 7:3.

SPSS = solid-phase peptide synthesizer

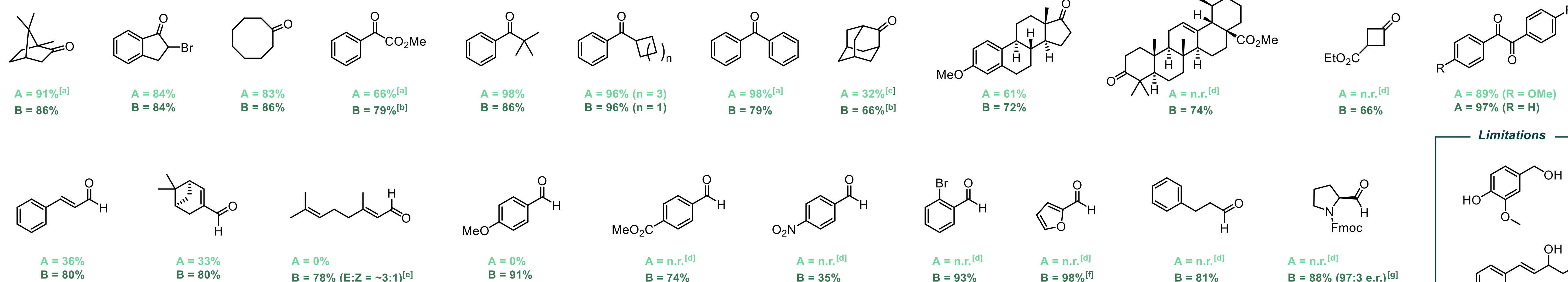
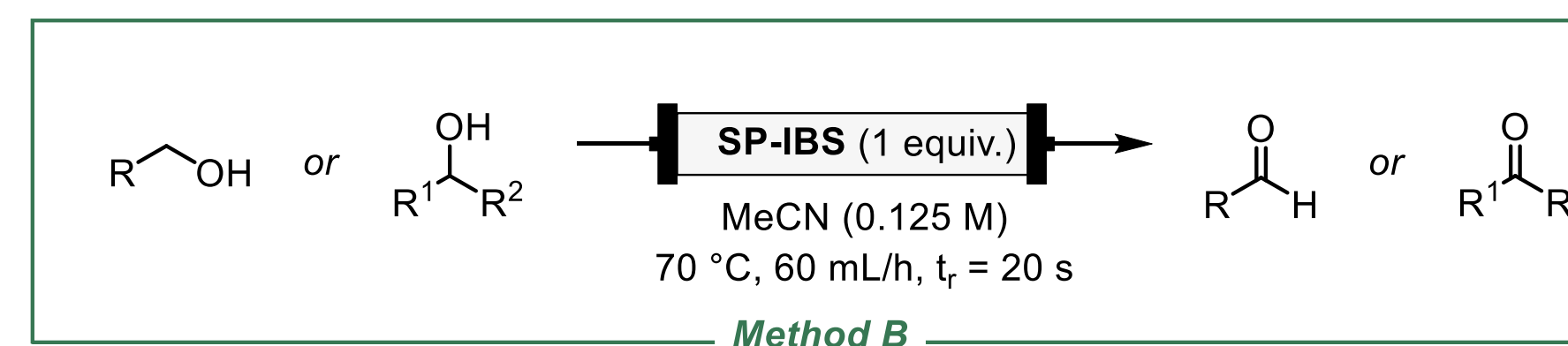
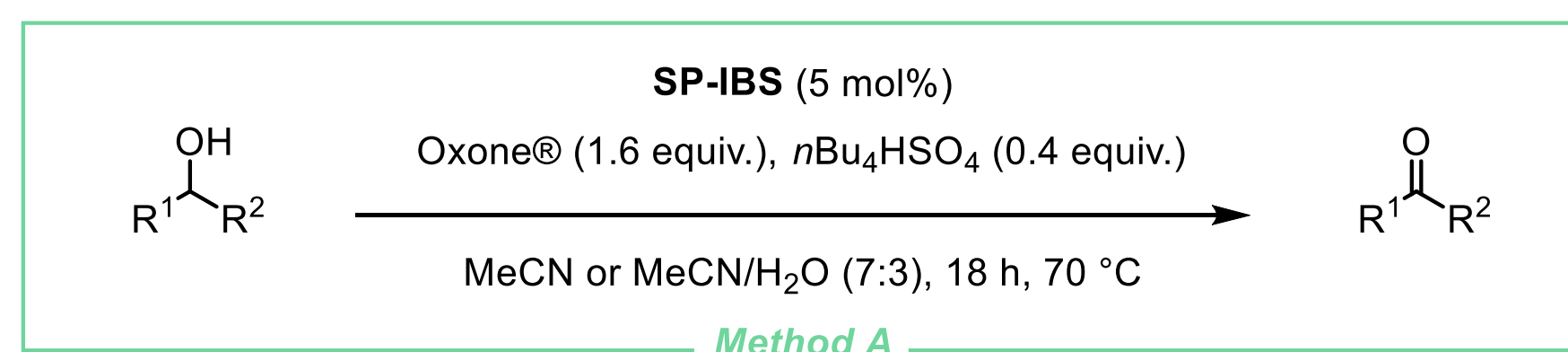
Method development in flow



Entry	Oxidant [equiv.]	Flow rate [mL/h]	Temperature [°C]	Solvent	Conversion ^[a]
1	SP-IBS [1]	10	70	MeCN	>99
2	SP-IBS [1]	20	70	MeCN	>99
3	SP-IBS [1]	40	70	MeCN	>99
4	SP-IBS [1]	60	70	MeCN	>99
5	--	60	70	MeCN	0%
6	SP-IBS [1]	120	70	MeCN	84%
7	SP-IBS [1]	60	60	MeCN	>99
8	SP-IBS [1]	60	80	MeCN	>99
9	SP-IBS [1]	60	70	AcOH	>99
10	SP-IBS [1]	120	70	AcOH	84%
11	--	60	70	AcOH	0%

[a] Conversion was determined via GC-FID.

Selected Scope & Limitations



[a] 3 h, [b] in AcOH, [c] 72 h in acetone, [d] n.r. = experiment was not run, [e] E:Z ratio determined via ¹H-NMR, [f] determined via GC-FID (calibrated), [g] determined via chiral HPLC.

Outlook

- Employing a catalytic strategy in flow
- Expand to other oxidative transformations
- Expand to peptide conjugates



References

- [1] F. Cavani and J. H. Teles, *ChemSusChem*, 2009, **2**, 508–534. [2] P. Anastas and N. Eghbali, *Chem. Soc. Rev.*, 2010, **39**, 301–312. [3] E. S. Beach, Z. Cui and P. T. Anastas, *Energy Environ. Sci.*, 2009, **2**, 1038. [4] S. A. Matlin, G. Mehta, H. Hopf and A. Krief, *Nat. Chem.*, 2015, **7**, 941–943. [5] M. Uyanik, M. Akakura and K. Ishihara, *J. Am. Chem. Soc.*, 2009, **131**, 251–262. [6] F. Ballaschk and S. F. Kirsch, *Green Chem.*, 2019, **21**, 5896–5903.