

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



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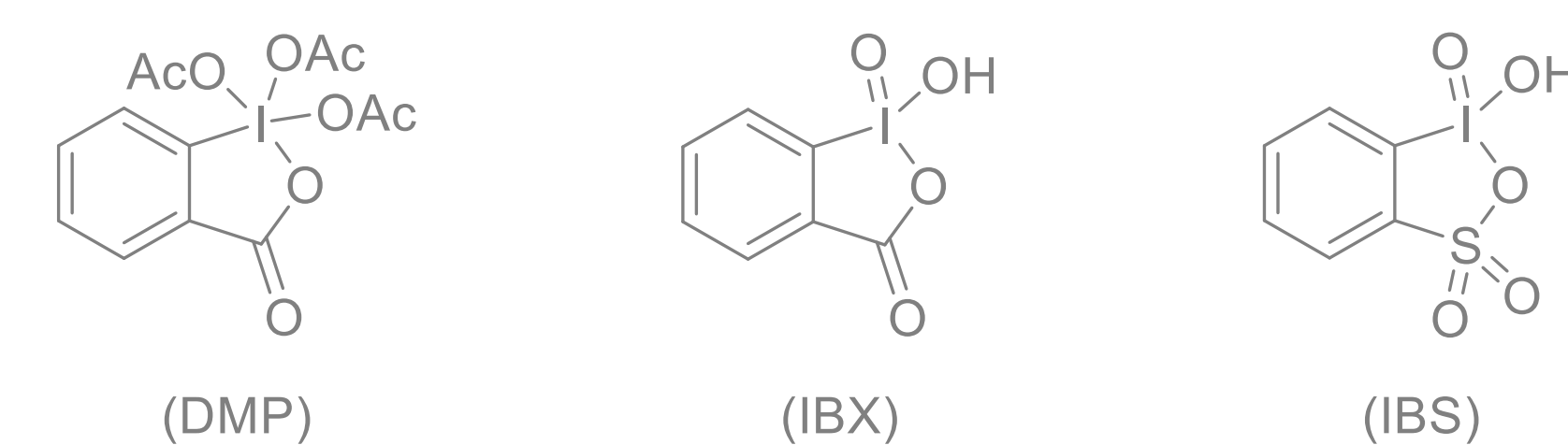
Introduction

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 plethora 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

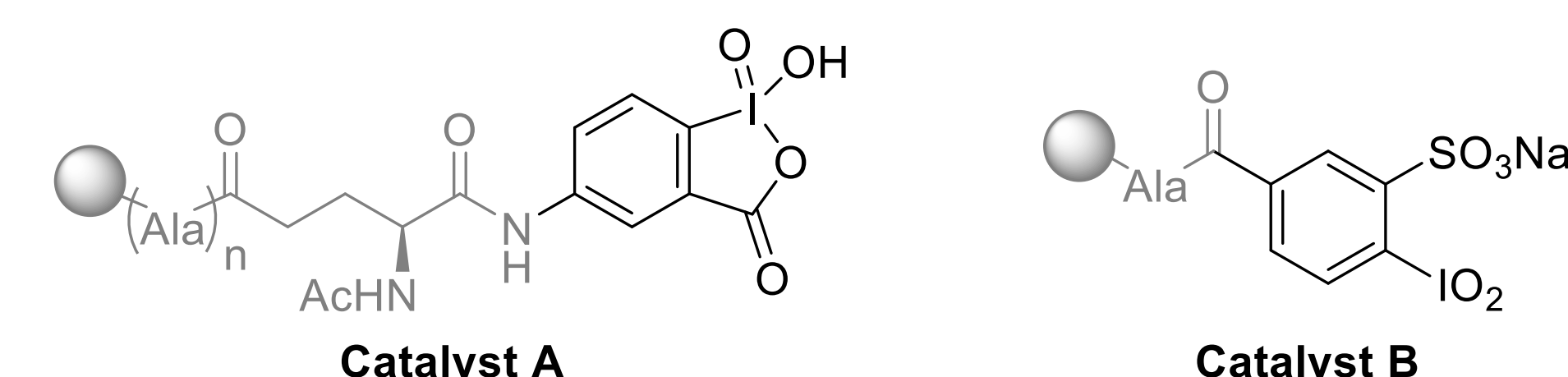
The development of hypervalent iodine reagents, such as DMP, IBX or IBS, were already an improvement regarding safety and sustainability.⁵ The chemical properties and reactivities of hypervalent iodine reagents are similar to heavy metals e.g. Pb(IV) or Hg(III) but are lacking environmental issues or toxicity.

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

Previous examples:

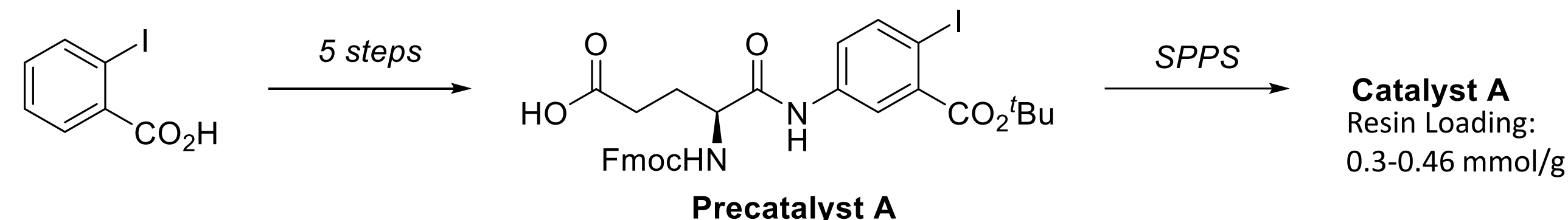


This work:

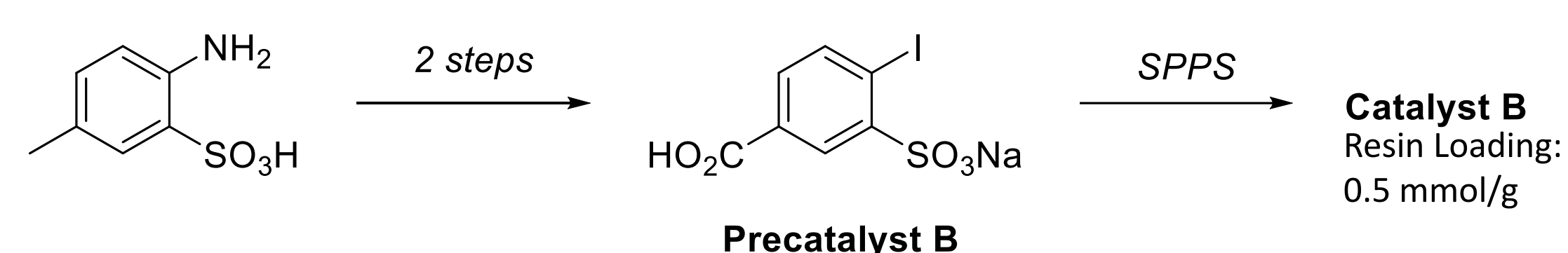


Synthesis of catalysts & Method development in batch⁶

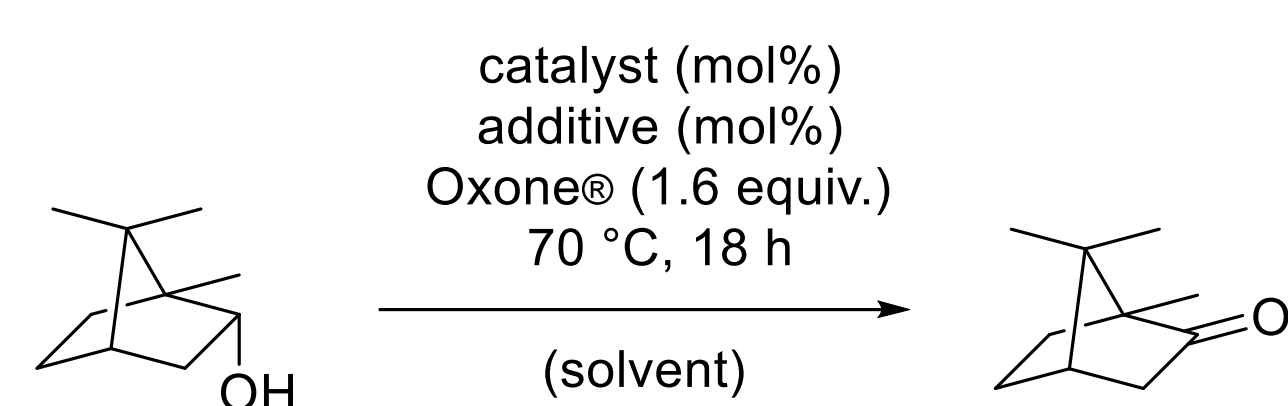
Synthesis of IBX-derived catalyst A



Synthesis of IBS-derived catalyst B



Method development in batch

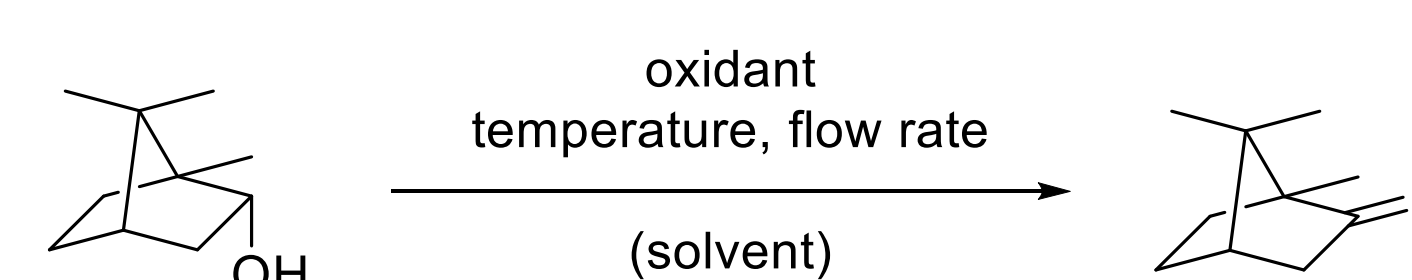
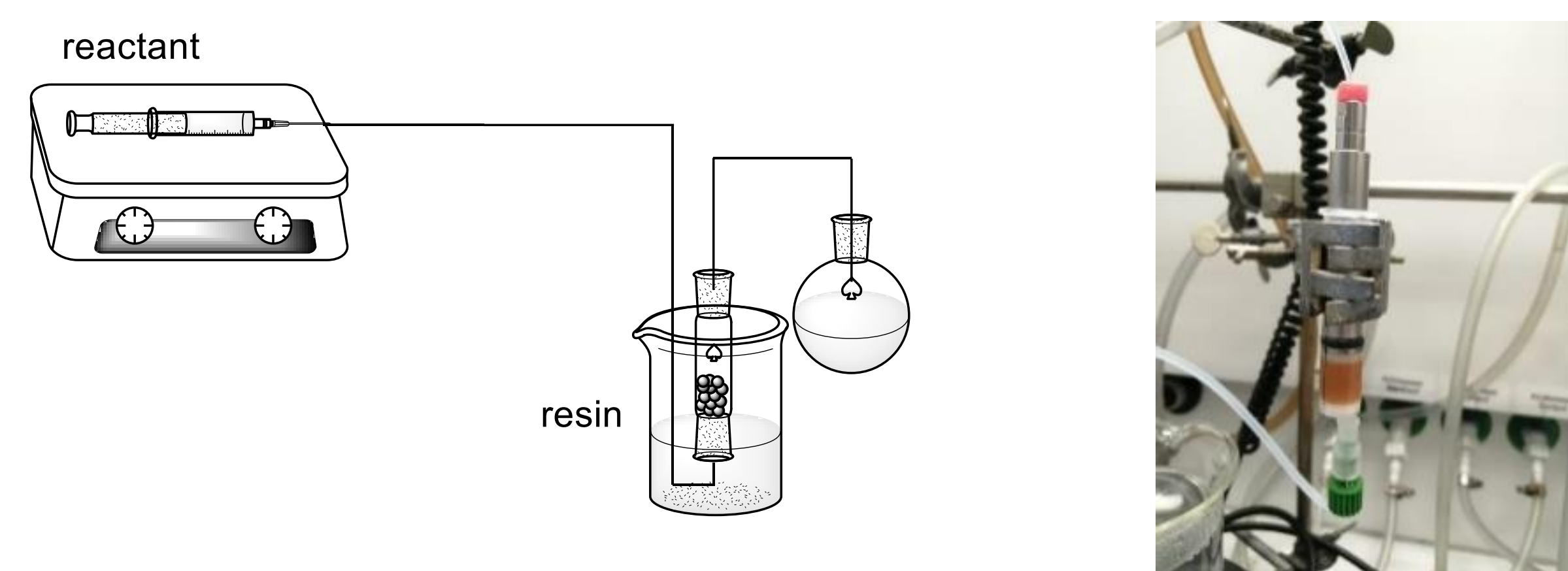


entry	catalyst (mol%)	additive (mol%)	solvent	R/P ^[a]
1 ^[b]	--	--	MeCN-H ₂ O (7:3)	92/8
2 ^[b]	A (5)	--	MeCN-H ₂ O (7:3)	>1/99
3 ^[c]	B (3)	--	MeCN-H ₂ O (7:3)	3/97
4 ^[d]	B (2.5)	--	MeCN	94/6
5 ^[d]	B (2.5)	--	MeNO ₂	91/9
6 ^[d]	B (2.5)	ⁿ Bu ₄ NHSO ₄ (10)	MeCN	43/57
7 ^[d]	B (2.5)	ⁿ Bu ₄ NHSO ₄ (10)	MeNO ₂	63/37
8 ^[d]	B (2.5)	ⁿ Bu ₄ NHSO ₄ (20)	MeCN	3/97
9 ^[e]	B (1)	ⁿ Bu ₄ NHSO ₄ (40)	MeCN	2/98
10 ^[f]	B(0.2)	ⁿ Bu ₄ NHSO ₄ (40)	MeCN	9/91
11 ^[e]	--	ⁿ Bu ₄ NHSO ₄ (40)	MeCN	94/6

[a] Ratio R/P was determined via GC-FID (calibrated with stock solutions of reactant and product), [b] 18 h, [c] 6 h, [d] 2 h, [e] 4 h, [f] 24 h.

SPPS = solid-phase peptide synthesizer

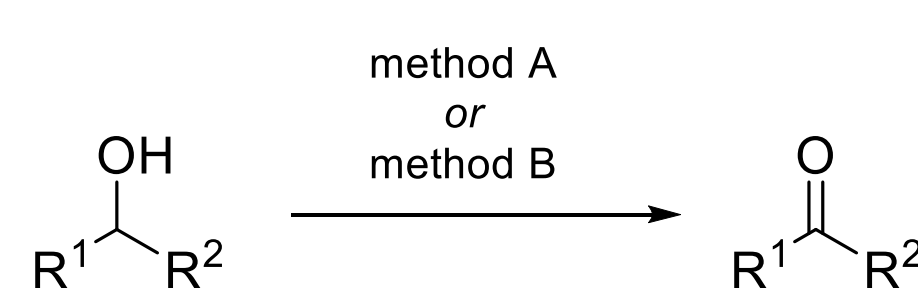
Method development in flow



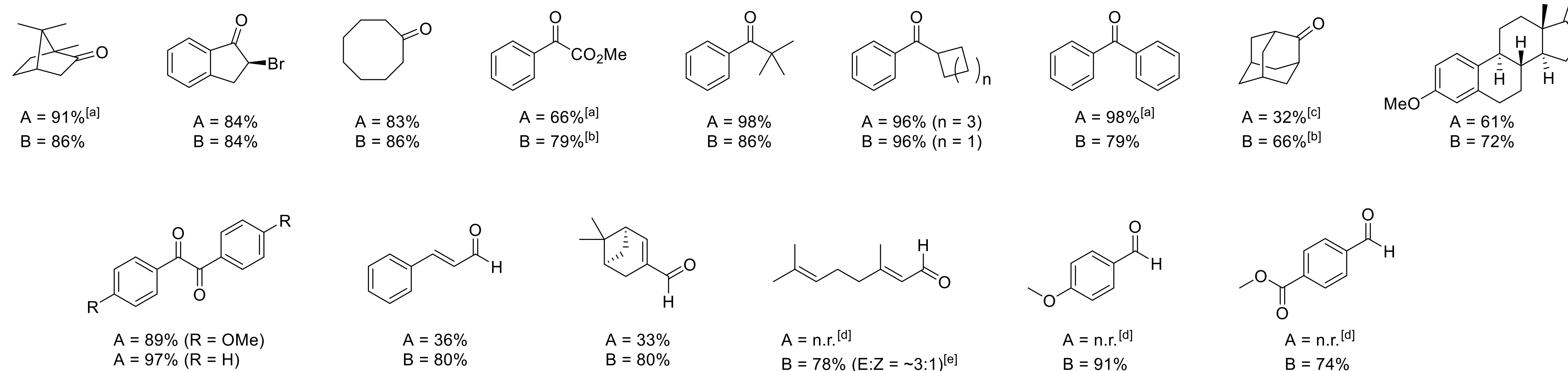
entry	oxidant (equiv.)	flow rate (mL/h)	temperature (°C)	solvent	R/P ^[a]
1	--		70	MeCN	100/0
2	B (1)	10	70	MeCN	>1/99
3	B (1)	20	70	MeCN	>1/99
4	B (1)	40	70	MeCN	>1/99
5	B (1)	60	70	MeCN	>1/99
6	B (1)	120	70	MeCN	16/84
7	B (1)	60	60	MeCN	>1/99
8	B (1)	60	80	MeCN	>1/99
9	B (1)	60	70	AcOH	>1/99
10	B (1)	120	70	AcOH	16/84
11	--	60	70	AcOH	100/0

[a] Ratio R/P was determined via GC-FID (calibrated with stock solutions of reactant and product)

Selected Scope & Limitations



method A: B (5 mol%), Oxone® (1.6 equiv.), ⁿBu₄NHSO₄ (0.4 equiv.), 70 °C, 18 h, MeCN
method B: B (1 equiv.), 20 mL/h, 70 °C, MeCN



[a] 3 h, [b] in AcOH [c] 72 h in acetone. [d] n.r. = no reaction [e] E:Z ratio determined via ¹H-NMR

Limitations

