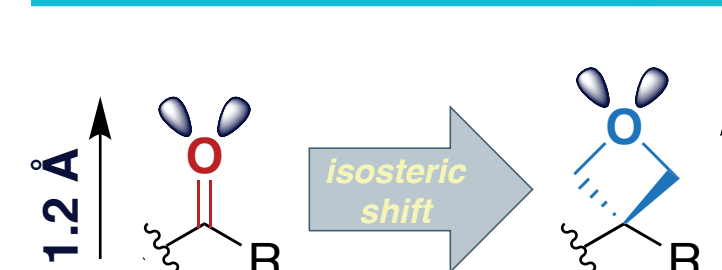


# Comprehensive oxetane building block's library: through a prism of 10 years' experience

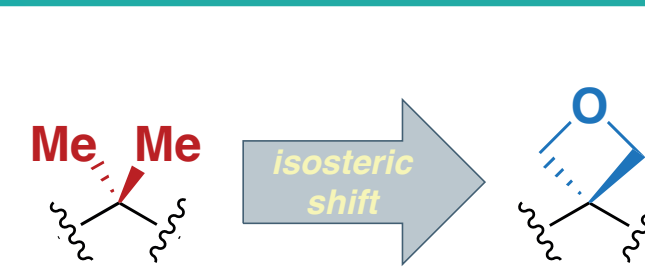
E. Litskan, O. Semenchenko, S. Lynnyk, D. Lega, D. Granat, D. Volochnyuk, S. Ryabukhin

## Background and synthetic strategy

### MEDICINAL CHEMISTRY PROSPECTS



- improves chemical and metabolic stability
- adds to three-dimensionality
- increases water solubility
- isostere for ketones, carboxylic acids and their derivatives (depending on R)

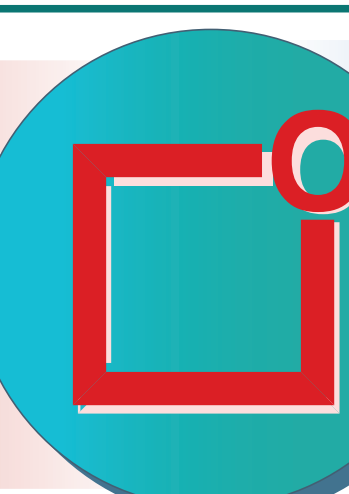


- increases metabolic stability
- adds to three-dimensionality
- lowers logD

narrow chemical space

synthetic challenge due to ring lability

high price for simple building blocks



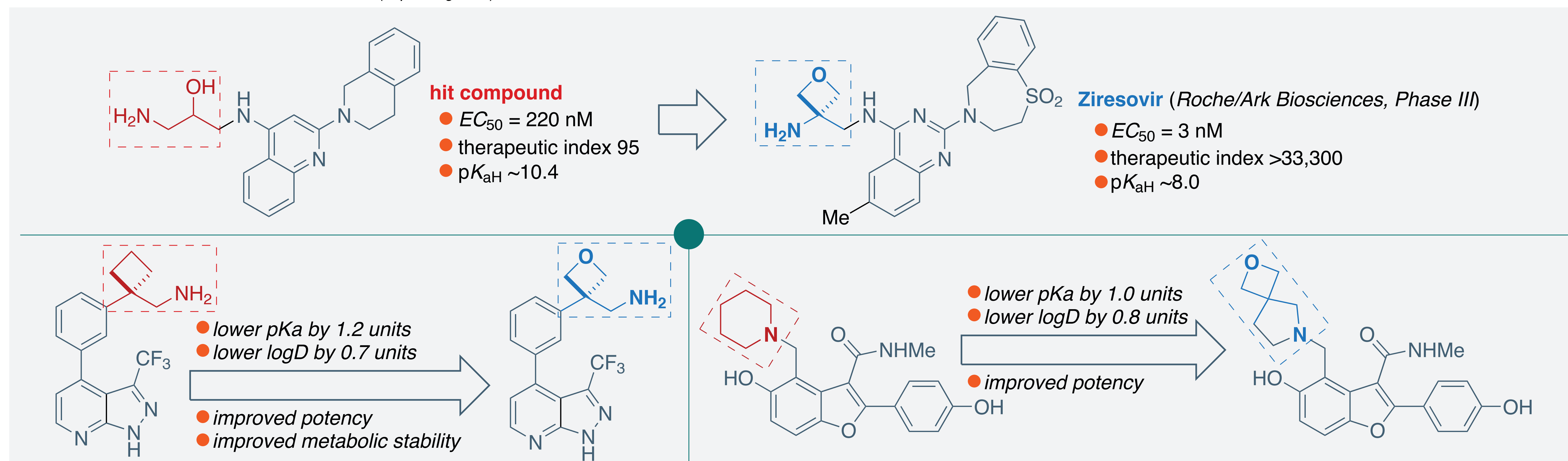
about 10 drug candidates

sp<sup>3</sup>-enriched 3D-shaped core

isostere to C=O and gem-di-Me

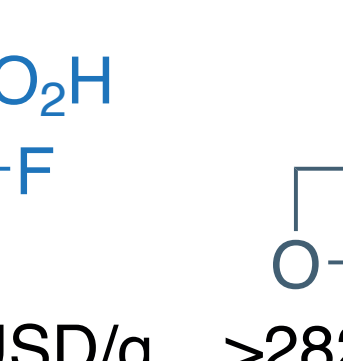
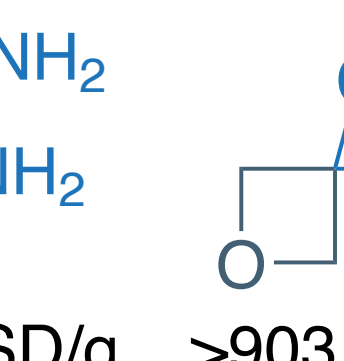
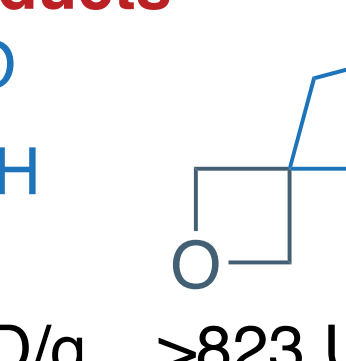
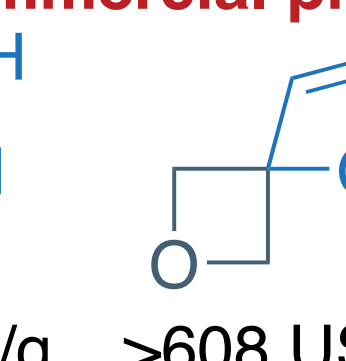
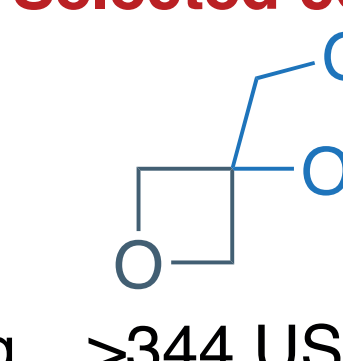
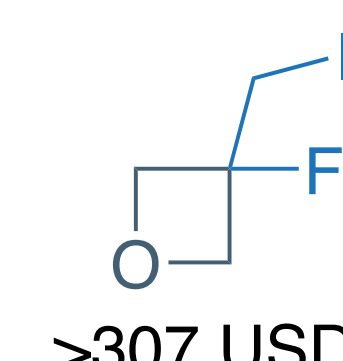
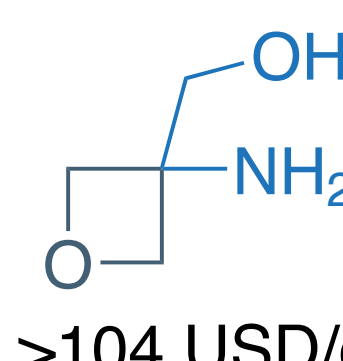
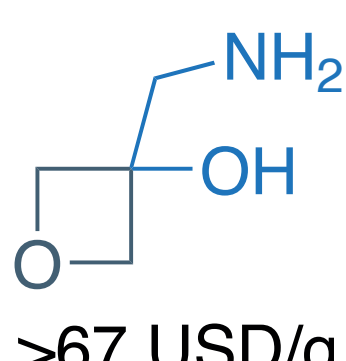
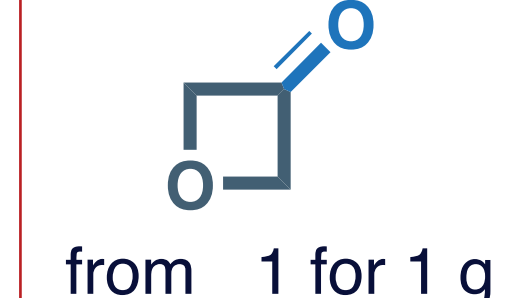
increases metabolic stability

enhances water solubility



### PRICES FOR COMMERCIALLY AVAILABLE OXETANES

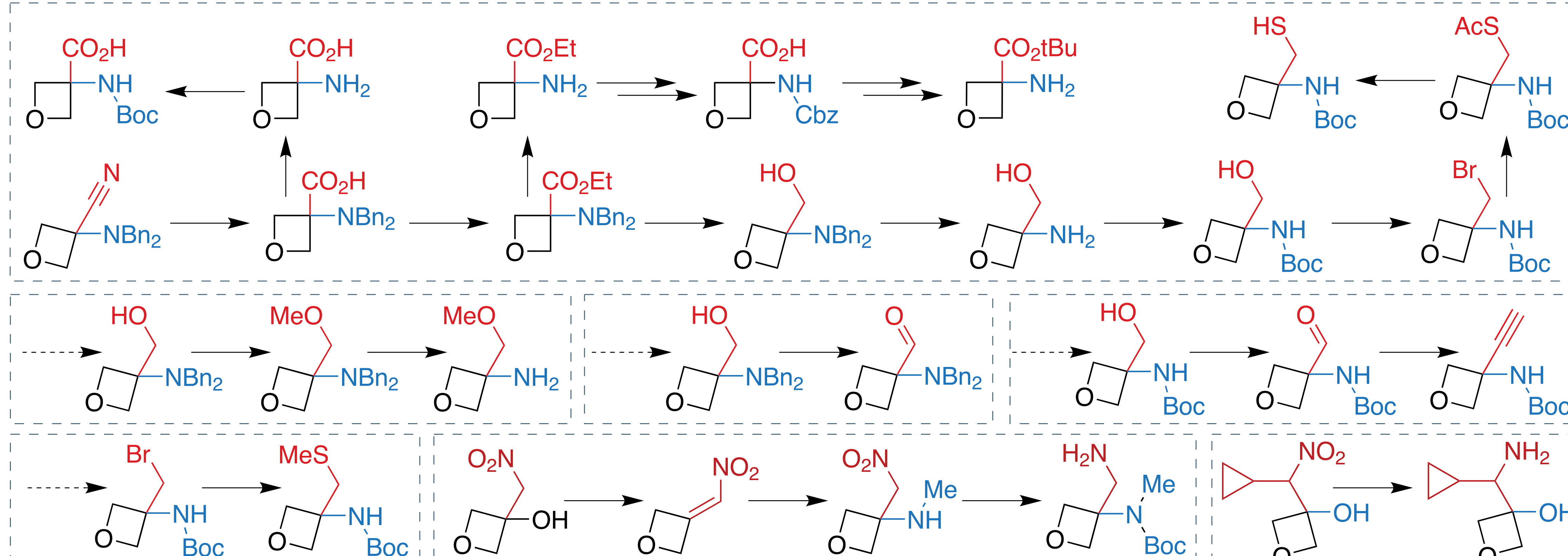
cheap & in bulk chemical for



Selected commercial products

## Synthetic results

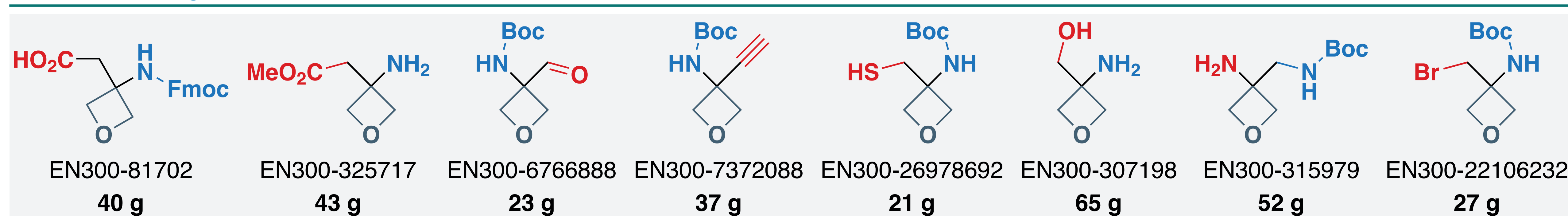
### SELECTED EXAMPLES OF ELABORATED, OPTIMIZED & SCALED SYNTHETIC SEQUENCES



## EXPERIMENTAL DATA ON THE STABILITY OF OXETANE RING DURING COMMON LABORATORY PROTOCOLS

CN → CO <sub>2</sub> H	CONR <sub>2</sub> → CH <sub>2</sub> NR <sub>2</sub>	CN → CH <sub>2</sub> NH <sub>2</sub>	Me, Et ester → CH <sub>2</sub> OH	CO <sub>2</sub> H → CH <sub>2</sub> OH	Boc-deprotection
✓ basic hydrolysis ✗ acidic hydrolysis	✓ AlH <sub>3</sub> , -78 to -50°C ✗ LiAlH <sub>4</sub> or BH <sub>3</sub>	✓ Co(BH <sub>4</sub> ) <sub>2</sub> , MeOH, Boc <sub>2</sub> O ✓ Ni Raney, 80 atm/60°C ✗ LiAlH <sub>4</sub> , any temperature	✓ LiAlH <sub>4</sub> , -10 to -30°C ✓ NaBH <sub>4</sub> , 0°C, for α-NBoc ✗ LiAlH <sub>4</sub> , >0°C	✓ mixed anhydride + NaBH <sub>4</sub> , 20% ✗ LiAlH <sub>4</sub> , <0°C doesn't go ✗ BH <sub>3</sub> , LiAlH <sub>4</sub> , >0°C ring opens	✓ TFA, DCM, 1 hour ✗ HCl/Et <sub>2</sub> O, 1 hour ✗ HCl/dioxan, 1 hour
N <sub>3</sub> → NH <sub>2</sub>	ketone → OH	2° OH → ketone	CO <sub>2</sub> H → CO <sub>2</sub> Me	ester → CO <sub>2</sub> H	CF <sub>3</sub> CO-deprotection
✓ Staudinger reaction conditions ✗ H <sub>2</sub> /Pd, low purity & yields	✓ LiAlH <sub>4</sub> , -30°C ✗ NaBH <sub>4</sub> , -30°C to rt	✓ Dess-Martine reagent, rt ✓ PCC, rt, 3 hours	✓ acid catalysis, ring opens ✗ MeI, DIPEA, MeCN, 60°C	✓ basic hydrolysis ✗ acidic hydrolysis	✓ KOH, MeOH, 60°C

## Showcasing in stock examples



## Contact

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