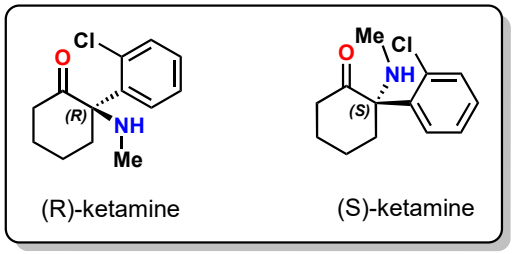
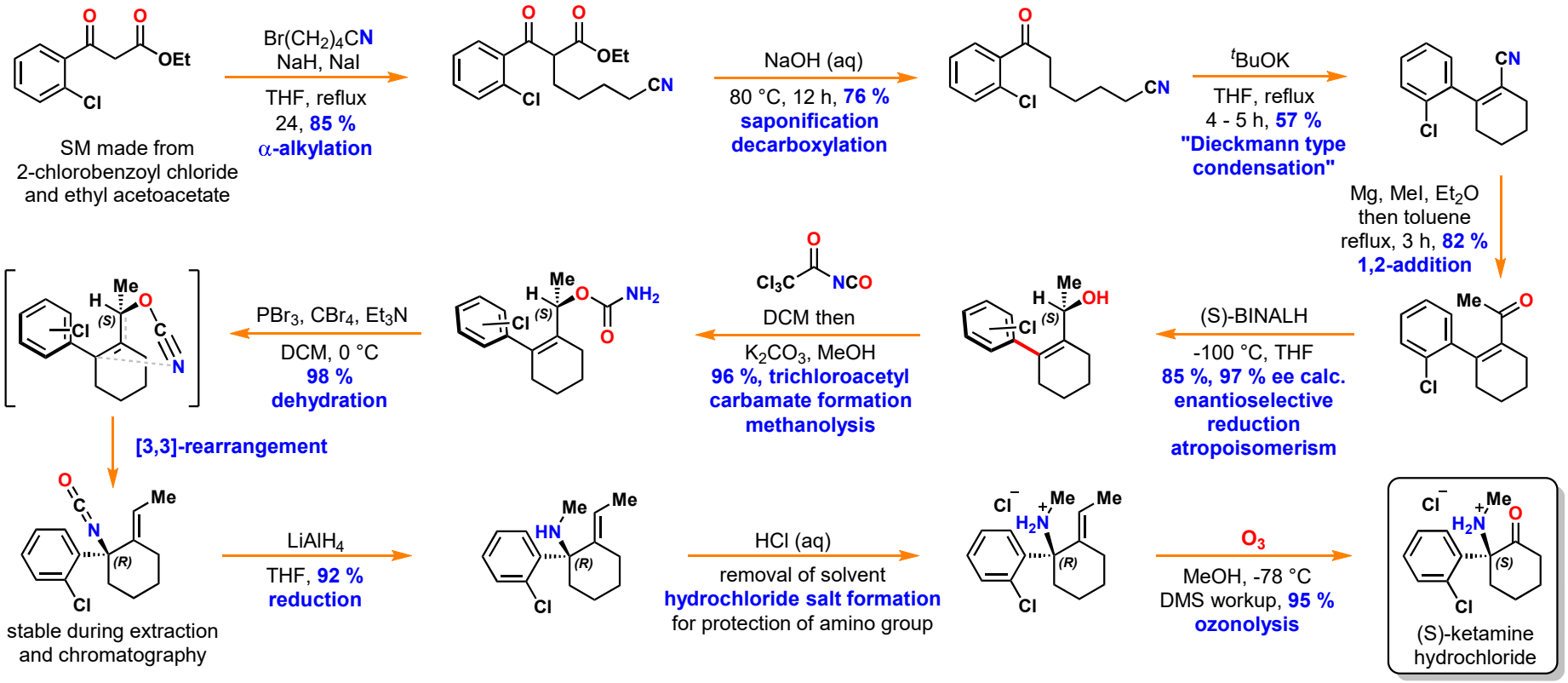
POTW: Ketamine (Esketamine)

Ketamine:
- Trade name Ketalar, anesthetic and analgesic
- Used since 1963, sold as a racemic mixture
- (S)-ketamine is 3-4 times more potent -> lower dosage (higher binding affinity for NMDA receptor)
- (R)-ketamine has more side effects (agitation, restlessness, halucination)
- Enantioselective syntheses are known (up to 50 %, 99 % ee)
- Chiral resolution with tartartic acid is still more viable for industrial scale
- In 2019, FDA approved ketamine nasal spray for treatment of treatment-resistant depression
- Good pharmacodynamics and pharmacokinetics



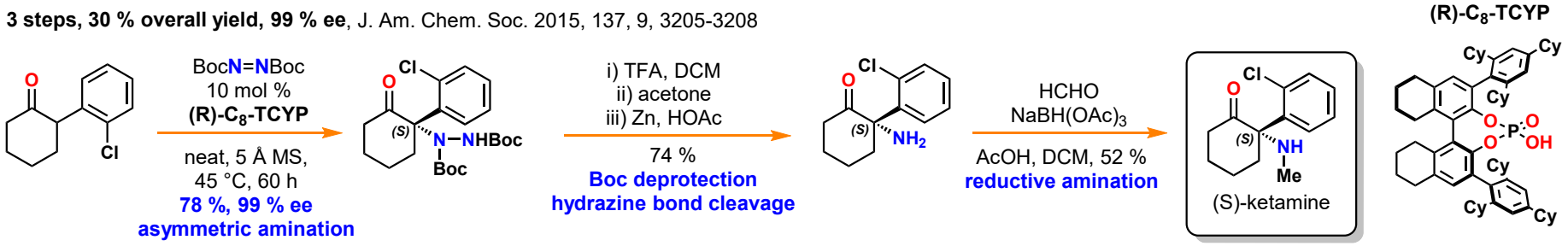
First asymmetric total synthesis (2009):
Tetrahedron 2009, 65, 27, 5181-5191
10 steps, 21 % overall yield, 99 % ee



Process Research and Impurity Control Strategy of Esketamine, Org. Process Res. Dev. 2020 ASAP

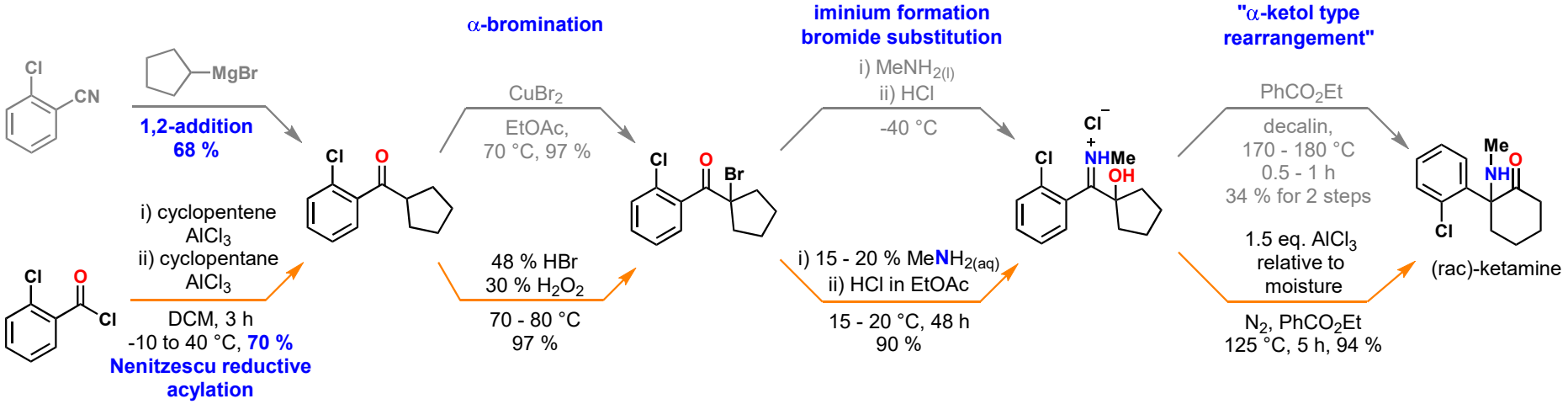
POTW: Ketamine (Esketamine)

3 steps, 30 % overall yield, 99 % ee, J. Am. Chem. Soc. 2015, 137, 9, 3205-3208



TOP: Janssen Pharmaceutical (Laboratory Scale) Route

BOTTOM: Improved Route



- Cheaper starting materials
- Purification by vacuum distillation (2 mmHg, 116 - 120 °C)

- Improved atom economy
- Cheaper reactants
- More environmentally friendly
- Purification by extraction (Na_2SO_3)

- Methylamine aqueous solution insead of liquid methylamine
- Product precipitates out
- Ambient temperatures

- Lower temperature
- Less carbonization
- Higher product quality

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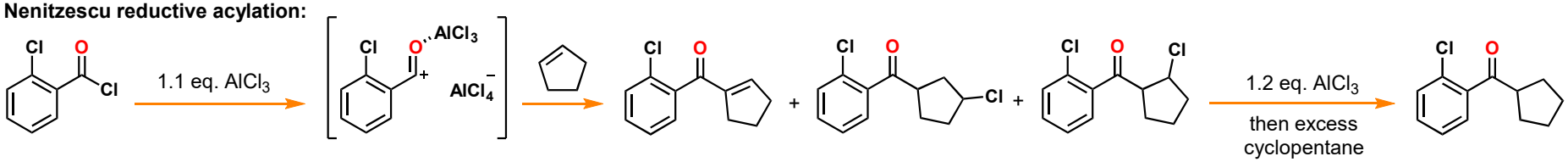
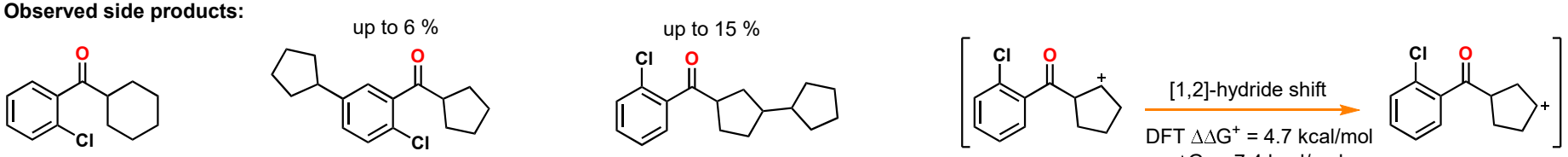
Sarlah Group

POTW: Ketamine (Esketamine)

Nenitzescu reductive acylation:



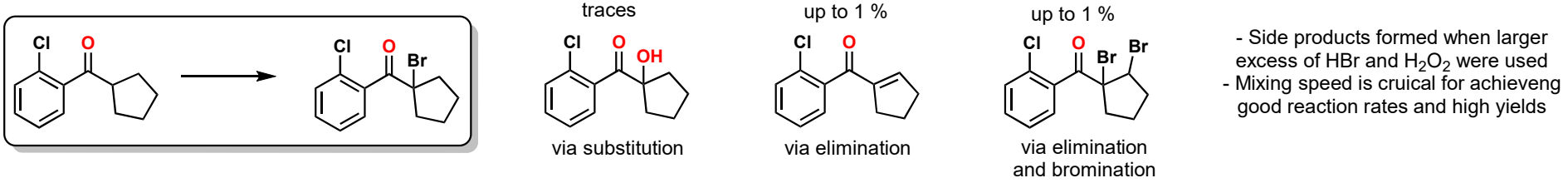
Observed side products:



Replaced cyclohexane as a solvent with DCM

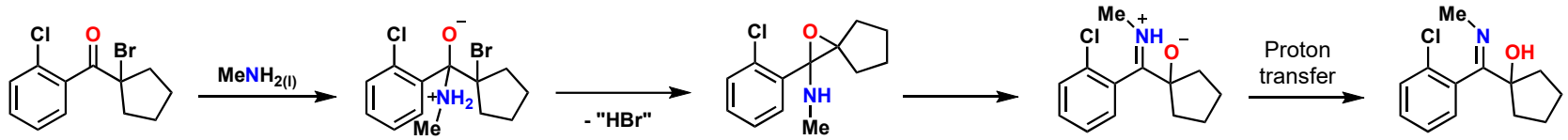
Decreaced yields of these impurities by lowering the amount of added cyclopentene and decreasing reaction times

Bromination side products:



- Side products formed when larger excess of HBr and H_2O_2 were used
- Mixing speed is cruical for achieveng good reaction rates and high yields

Methylamination:



Addition of 1 eq. $H_2{}^{18}O$ → No ^{18}O incorporation observed → Water plays no role in the reaction → $MeNH_{2(aq)}$

Jan Petrovcic, April 10, 2020

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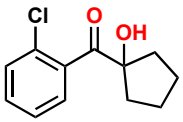
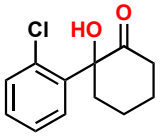
POTW: Ketamine (Esketamine)

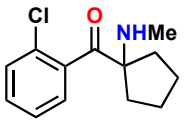
Methylamination side products:



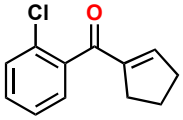
up to 6 %
via hydrolysis



up to 4 %
via hydrolysis
and rearrangement



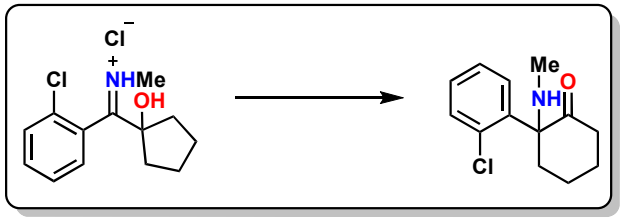
up to 25 %
via substitution

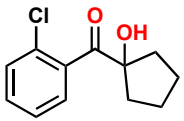


up to 1 %
via elimination

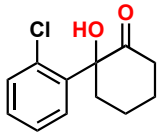
Side product yields were lowerer by:
- choosing an appropriate solvent (water)
- decreasing $MeNH_2$ concentration
- lowering reaction temperature

Thermal rearrangement side products:





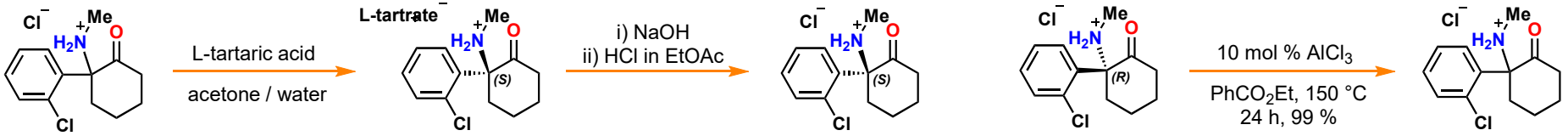
up to 25 %
via hydrolysis



up to 9 %
via hydrolisis
and rearrangement

- Moisture in starting material and solvent
- Karl Fisher titration
- Added 1.5 eq. of $AlCl_3$ relative to moisture
- Reaction could be preformed at 125 °C

Chiral resolution and racemization:



(rac)-ketamine
hydrochloride

(S)-ketamine
(L)-tartrate dihydrate

(S)-ketamine
hydrochloride

(R)-ketamine
hydrochloride

(rac)-ketamine
hydrochloride

3 recycling cycles: 87 % yield of resolution

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