Flow-Chemistry Enabled Process Development Employing Organometallics

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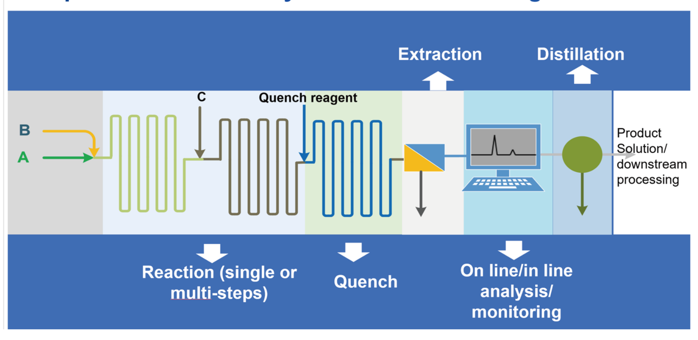
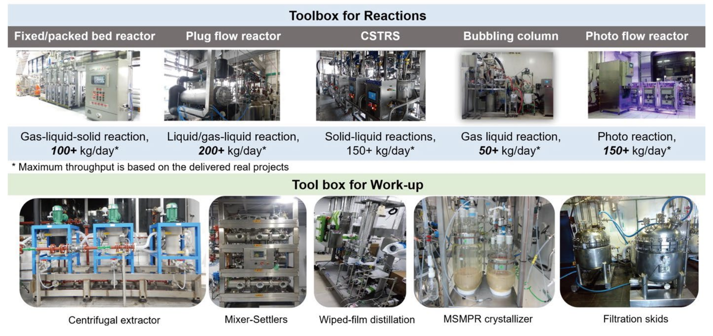
Introduction

- The rapid recent advances in flow chemistry have often provided an alternative approach to traditional batch chemistry
- Flow chemistry enables the use of highly reactive reagents in large-scale reactions, which would not be feasible with traditional flask chemistry
- Organometallic compounds, such as organolithium, organozinc, Grignard reagents, etc., are essential in many organic transformations but their highly reactive nature often impedes their scale-up
- WuXi STA has full suite capabilities to scale up organometallic reactions from lab to commercial scale safely and economically

Scope of Flow Chemistry for API Manufacturing



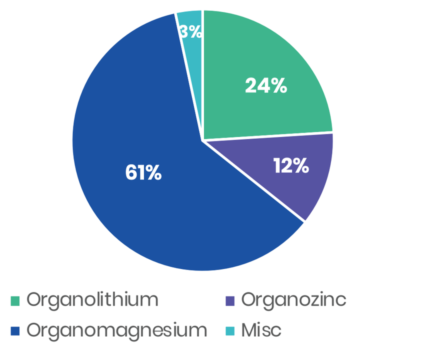
Available Flow Chemistry Toolbox at WuXi STA



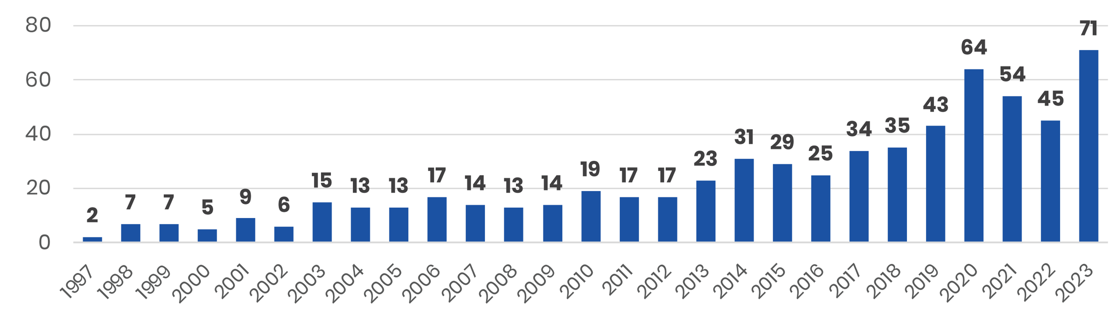
Organometallic Reactions on Scale – Flow Chemistry

- More and more organometallic transformations carried out in flow since the beginning of the new century
- An increasing number of industrial examples reported in the literature on multi-kilogram scale
- Majority of organometallic reagents involved organolithium, organomagnesium, and organozinc

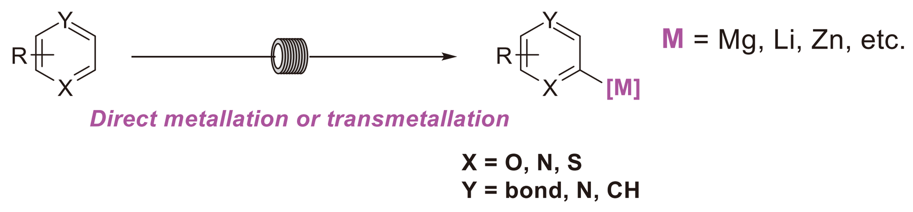
Organometallic in Flow (organo[metal] + "flow" in Reaxys)



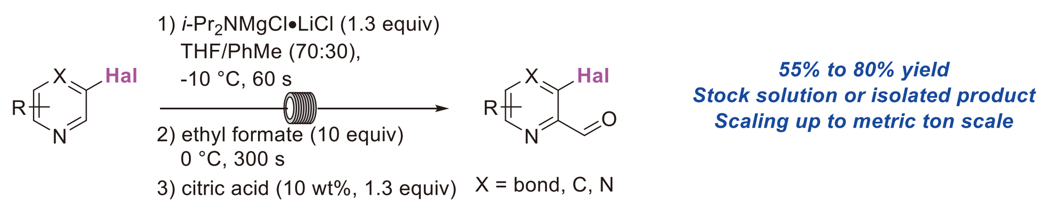
OPRD Publication from 1997 to 2023 (key words "flow" "organometallic")



Case 1: Preparation of Organometallic Reagent in Flow



- WuXi STA developed full suite capabilities to produce direct metalation or aryl/heteroaryl substrates under flow
- Great scalability and selectivity observed in general
- WuXi STA has been capable to incorporate subsequent functionalization of organometallic reagent in flow or batch modes

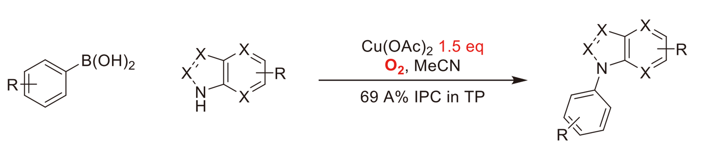


Main issue with batch mode:
Unstable deprotonated Grignard intermediate to from dimer or polymer (~ 30% starting material consumed) and potential scale-up issue in batch

Solution:
Flow process implemented & optimized; carefully gauged the flow rate to make sure reaction proceeded smoothly; introduction of active magnetic mixer to resolve clogging issue for longer term flow run

Key achievement:
Flow production at 15 kg scale was completed in 37 hrs without clogging; IPC purity ranged 89-93% with 2-4% SM remained and ~2% dimer impurity. IY is ~75%. All work was done in one month.

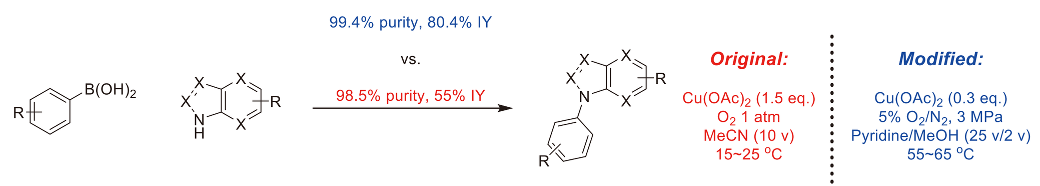
Case 2: Scaling Up Chan-Lam Coupling



Challenges:
Pure oxygen needed for the reaction
Superstoichiometric amount of Cu
Fairly low IPC purity
Need 20 kg within three weeks

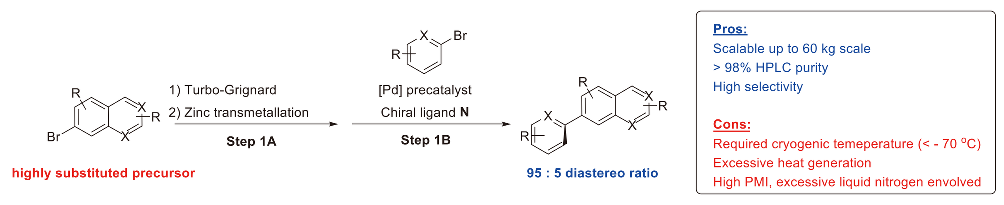
- Quick modification within four days reached to the conclusion that the scalability of the original protocol could not be scaled up
- A protocol safe to scale up was needed in a hurry by the project team and the client

Attempted modification for batch mode	
Use air or 5% oxygen in nitrogen as reaction atmosphere	Sluggish reaction (500 g batch, needed > 84 hours to reach to 80% conversion)
Use oxidants other than oxygen such as pyridine oxide	Failed to provide meaningful conversion; desired product < 25 A% in IPC
Screen solvents to make the reaction homogeneous	Pyridine was used to replace MeCN which allowed to lower down the cupper loading from 1.5 eq to 0.3 eq



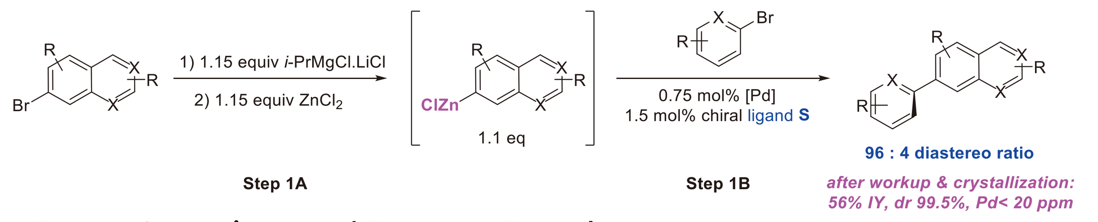
- WuXi STA quickly developed a flow chemistry protocol to allow on time delivery of the advanced intermediate which subsequently enabled IND filing on time
- Employed flow condition ($Cu(OAc)_2$, 5% O_2/N_2, pyridine/MeOH) provided 99.4 A% purity and 80.7% yield vs 98.5 A% purity and 55% yield (not scalable)

Case 3: A Challenging Negeshi Coupling



This protocol was put on hold due to potential scalability issues

- A protocol capable to produce > 500 kg of the advanced intermediate was requested with very short lead time
- Direct organozinc formation using Knochel protocol successful on model system but provided only 35% conversion on the target molecule
- Envisioned a flow protocol might be the saver of the game



- Route Scouting and Process Development
  - Conducted a rigorous investigation of the atroposelective Negishi Coupling reaction and implemented the process on production scales (HTE involved)
  - Optimized the process and improved the overall yields
  - Developed an efficient and cost-effective route
- Productivity
  - Delivered > 600 kg of advanced intermediates on time
- Flexibility: Quickly adjust resources to accommodate our additional requests and accelerated timelines
- Portfolio Impact: "*Timely delivery of the SMs and intermediate is critical for our API manufacturing in expediting the project in clinical development*"

Developed flow chemistry step and received recognition from the client

Asymmetric Negishi coupling, after work up residual Pd < 20 ppm

Set up on 2 MT of starting materials, delivered ~150 kg of final API via 17 steps

Summary

- Flow chemistry offers a solution to many of the challenges faced in organometallic batch chemistry
  - Efficient mass and heat transfer
  - Precise control of residence times
  - Advanced mixing apparatus
- WuXi STA built a flow chemistry platform to deliver superior solutions for the pharmaceutical industry leveraging cutting-edge technology to meet demanding processing requirements

Organometallic + Flow