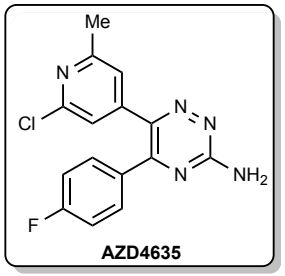
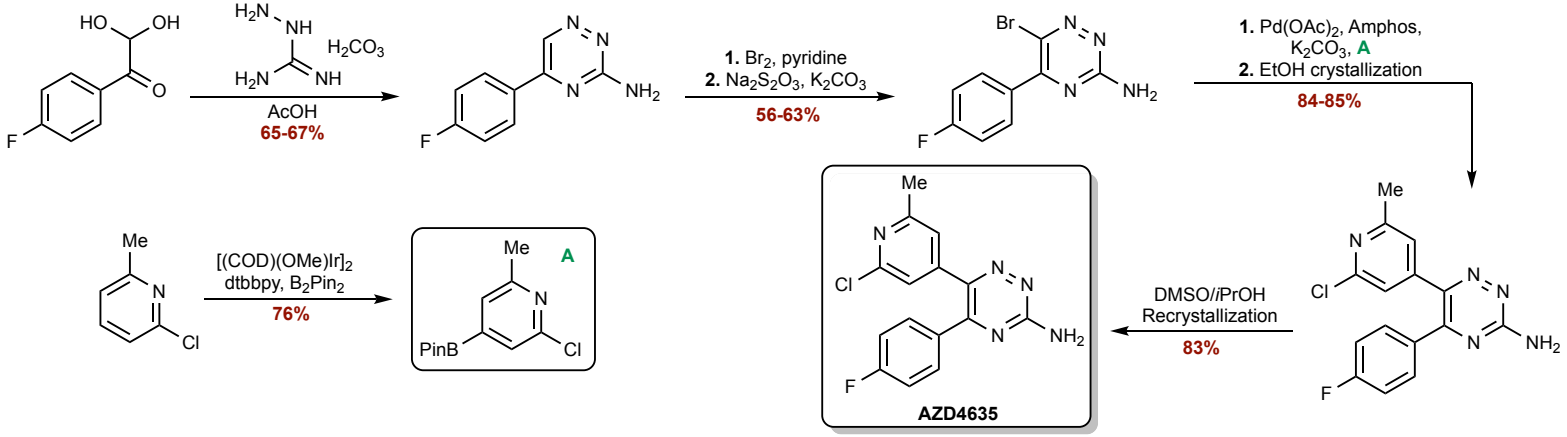
Route Design for AZD4635

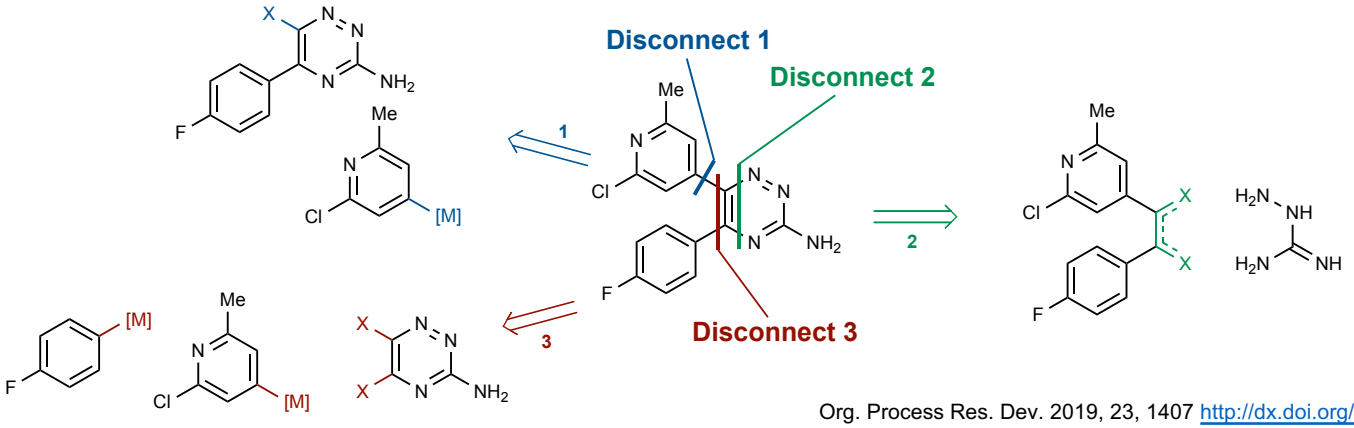


- $A_{2A}R$ antagonist in clinical trial for the treatment of solid tumors
- Discovery route was scaled up to provide material for clinical trials
  - ~30% yield over 5 steps
- Astra Zeneca underwent Route Design campaign to improve synthesis for process scale
  - Aimed to increase atom economy and decrease steps while improving impurity control
  - Prioritized risky strategies with high reward
- Scored potential routes on SELECT (Safety, Environment, Legal, Economic, Control, Throughput) criteria

Discovery Route Adapted for Scale



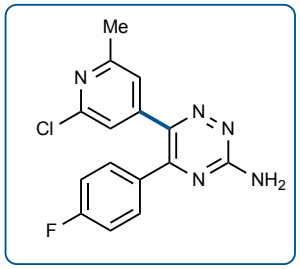
Disconnections Investigated in Route Design Campaign



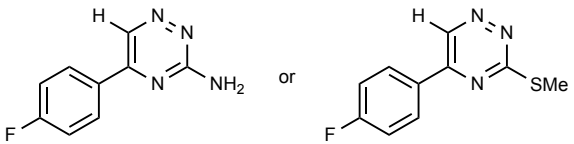
Org. Process Res. Dev. 2019, 23, 1407 http://dx.doi.org/10.1021/acs.oprd.9b00171

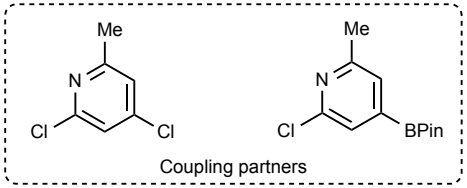
Route Design for AZD4635

Disconnect 1

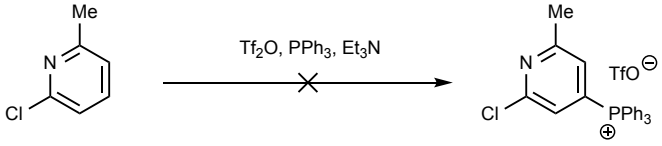


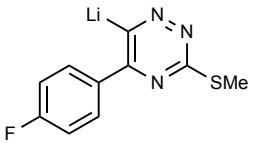
a) C-H activation

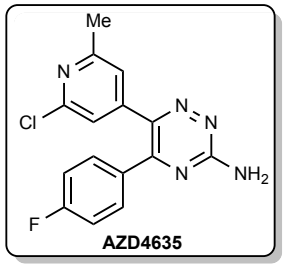




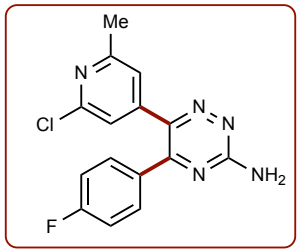
b) Phosphonium salt coupling

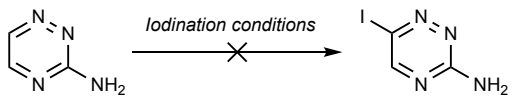


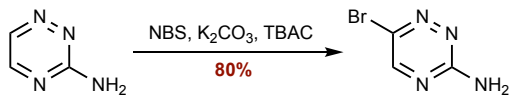




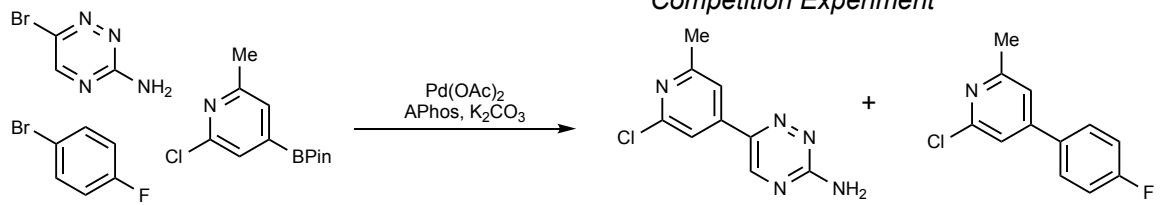
Disconnect 2





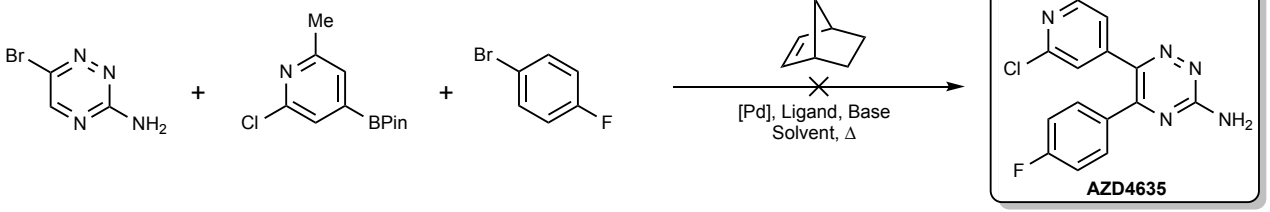


Competition Experiment



87:13
desired:undesired

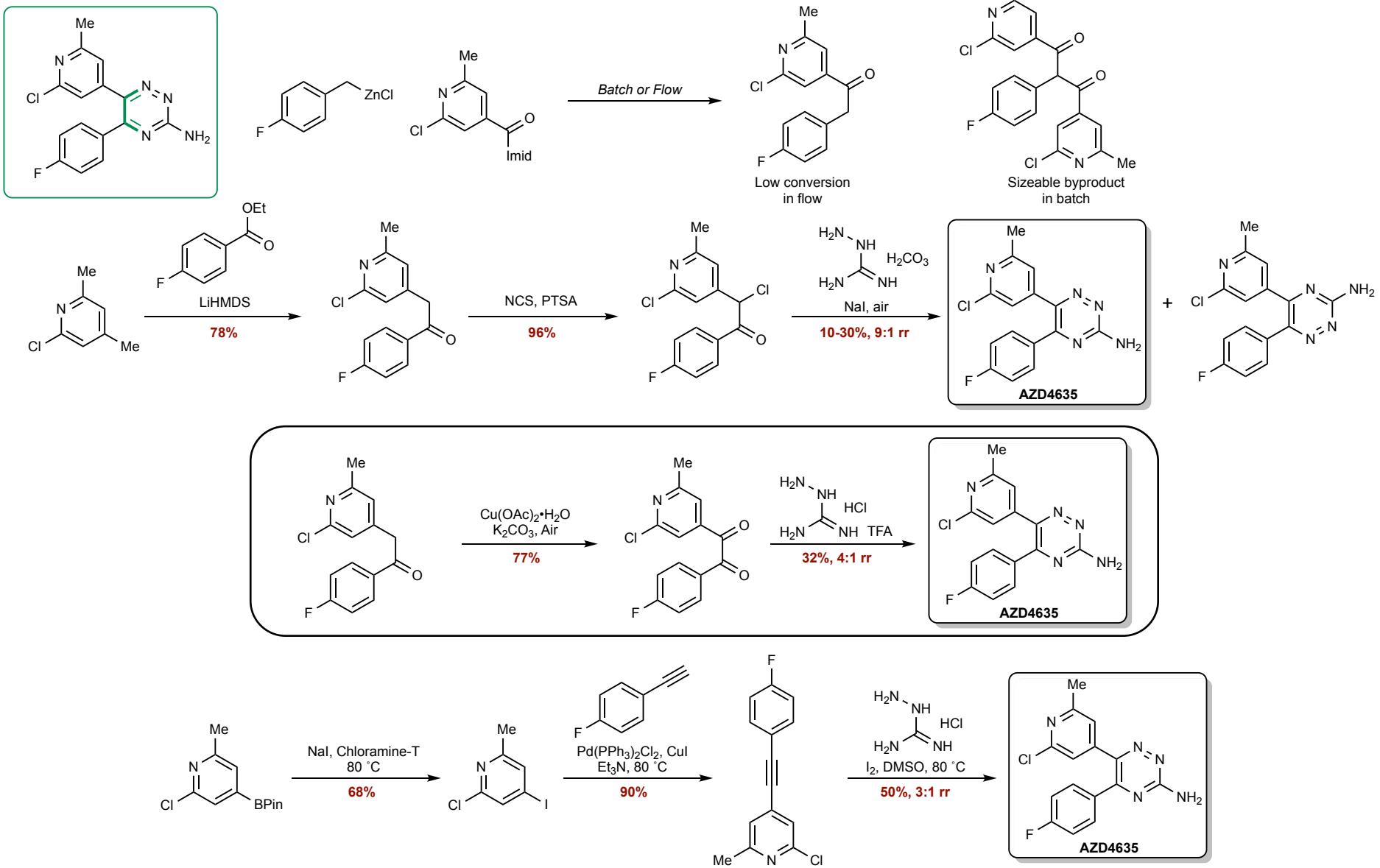
Triazine coupling occurs first
Catellani reaction possible



No product observed
Significant direct Suzuki coupling

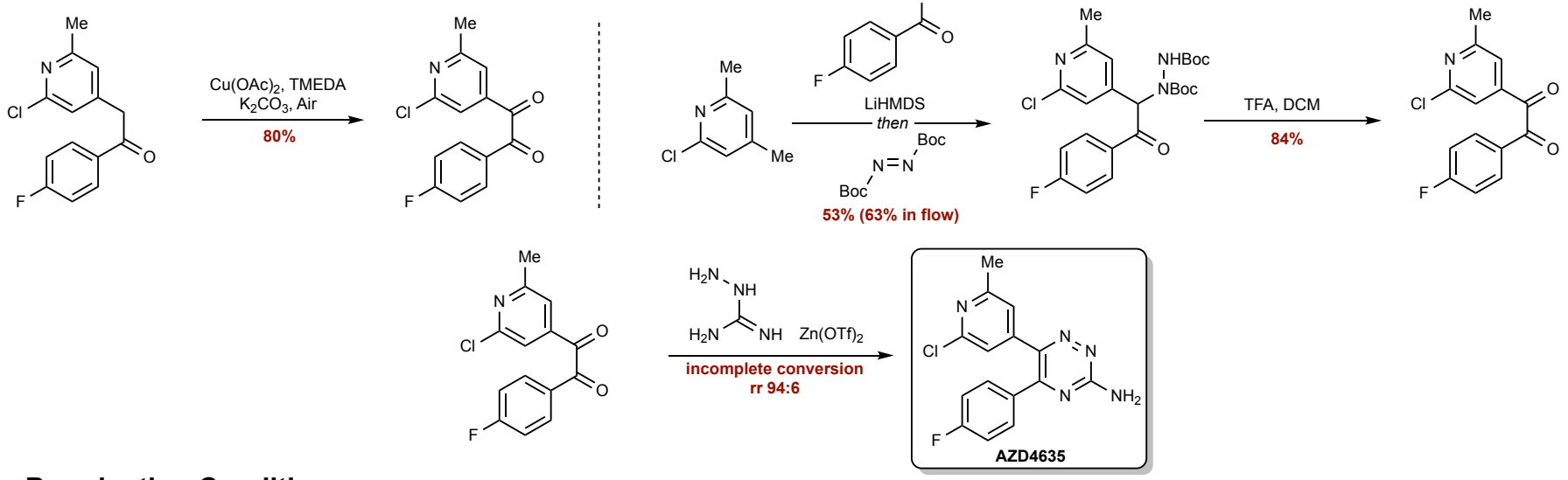
Route Design for AZD4635

Disconnect 3

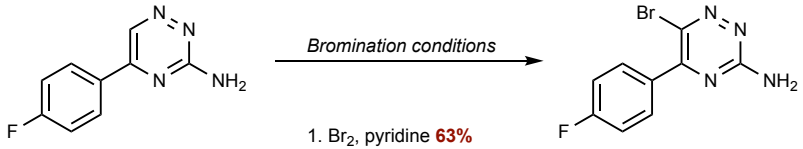


Route Design for AZD4635

Optimizing Disconnect 3



New Bromination Conditions



1. Br_2, pyridine **63%**
2. NBS, K_2CO_3 **98%**
3. NBS, TBACl, K_2CO_3 **64% at 1 mmol scale**

Due to time constraints, original route with reoptimized bromination was used for process scale

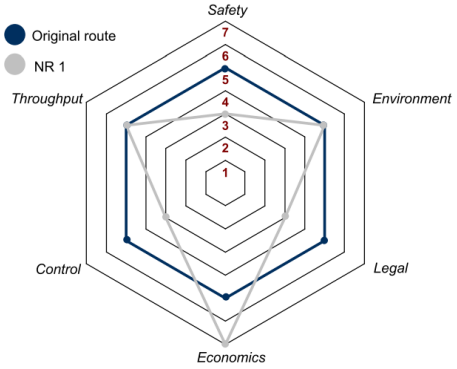


Table 3. Direct Comparison of Key Parameters

parameter	NR1	original route (new bromination)
step count	3 linear	4 (3 linear)
yield	predicted 30%	predicted 35%
atom economy	high	bromination and borylation