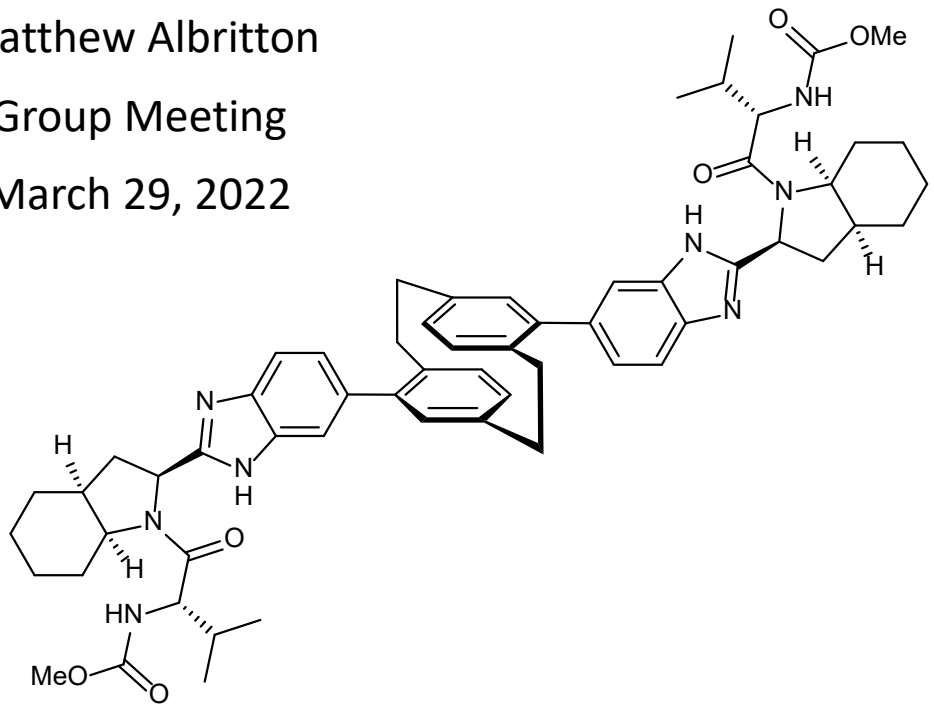
Development of a Commercial Process for Odalasvir

Matthew Albritton

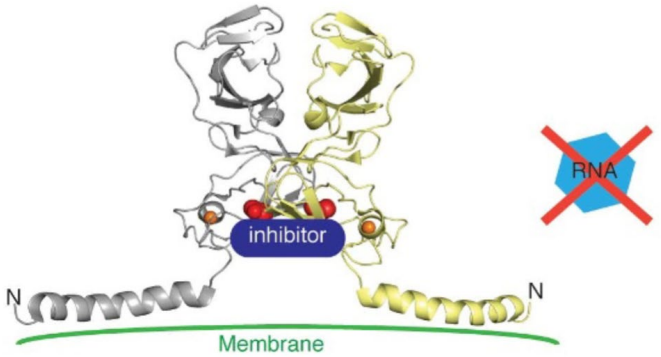
Group Meeting

March 29, 2022

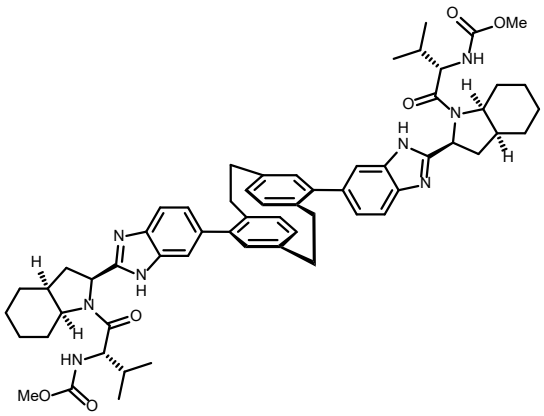


Development of a Commercial Process for Odalasvir

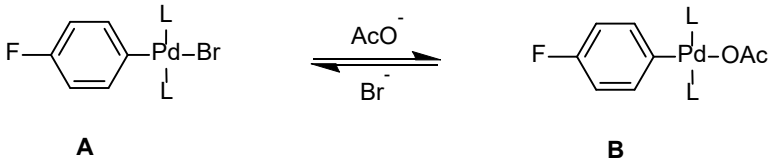
NS5A Inhibitors



Process-Scale
Synthesis Development

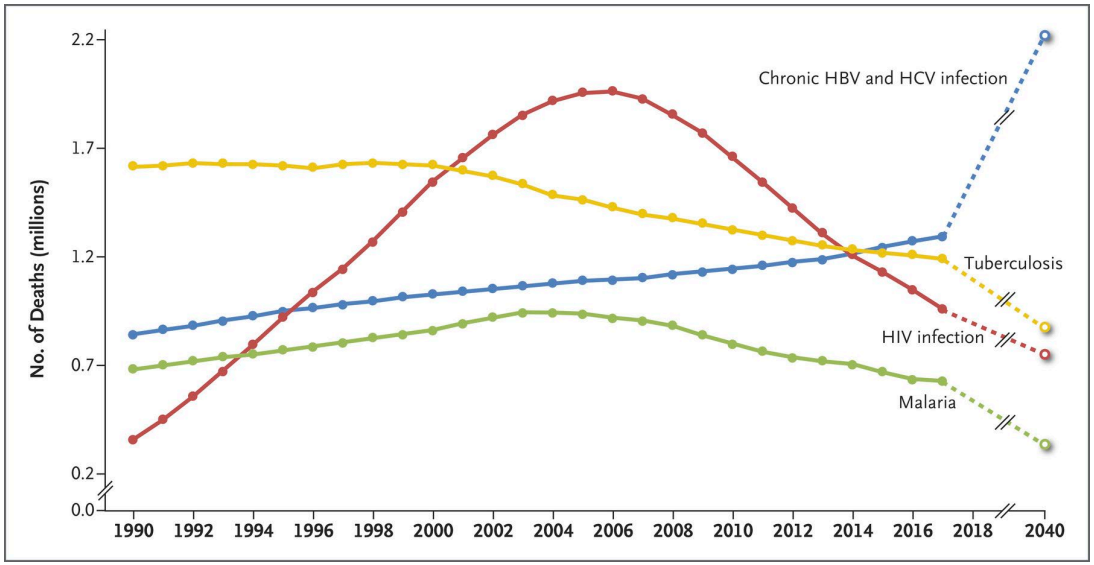


Miyaura Borylation
Kinetic Study

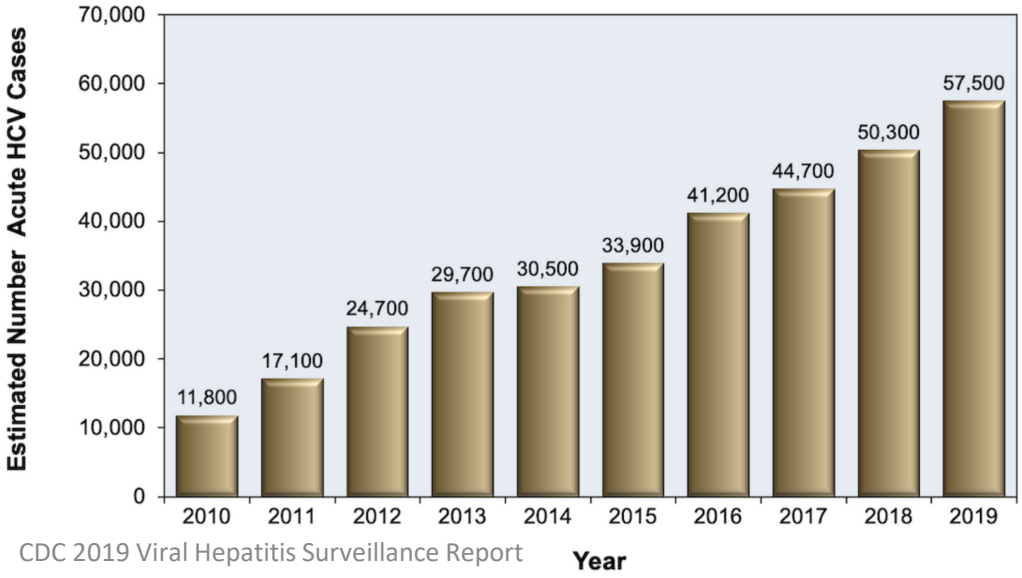


Hepatitis: Increasing Prevalence

- Deadliest infectious disease excluding COVID-19
- HBV: Effective vaccine but no cure
- HCV: No vaccine but curable



N Engl J Med 2019; 380:2041-2050

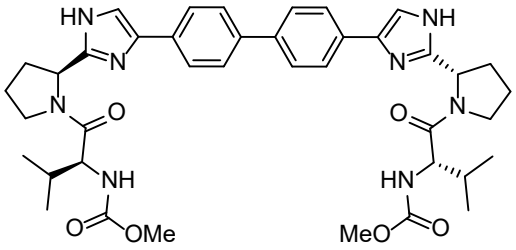


CDC 2019 Viral Hepatitis Surveillance Report

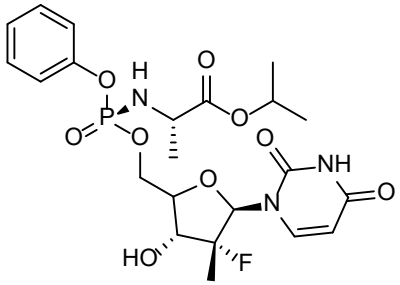
- Rise in prevalence in US largely attributable to opioid epidemic
- Intravenous drug use is main driver of transmission

First HCV Cure: NS5A Inhibitors

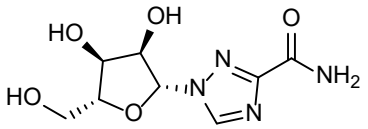
Daclatasvir



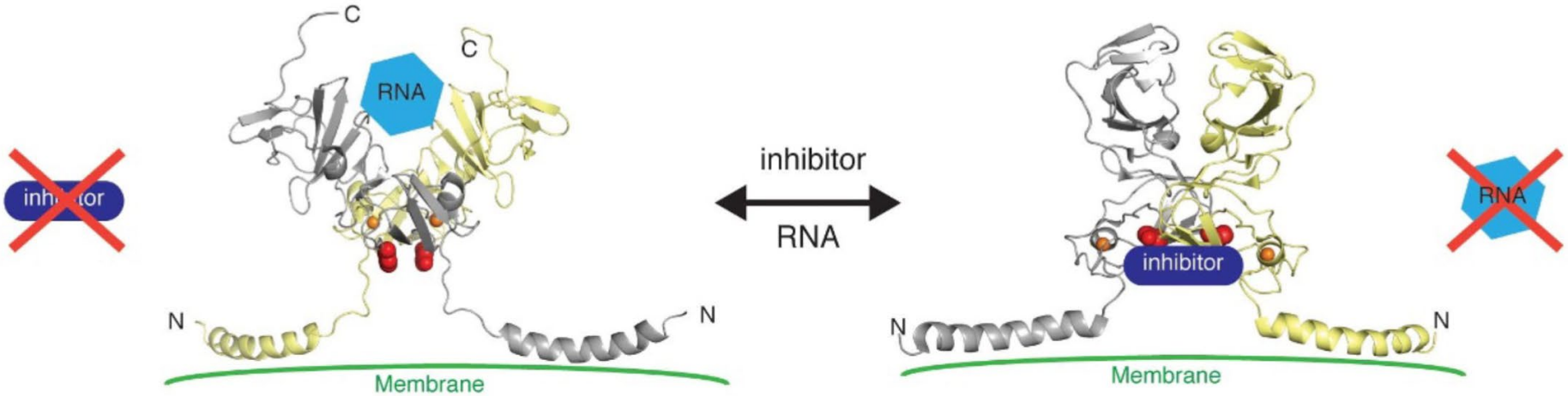
Bristol Myers Squibb™



Sofosbuvir



Ribavirin

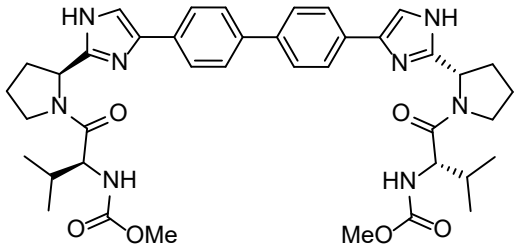


Pawlotsky JM. NS5A inhibitors in the treatment of hepatitis C. J Hepatol. 2013 Aug; 59(2):375-82.
Ascher, D., Wielens, J., Nero, T. et al. Potent hepatitis C inhibitors bind directly to NS5A and reduce its affinity for RNA. Sci Rep 4, 4765 (2014)

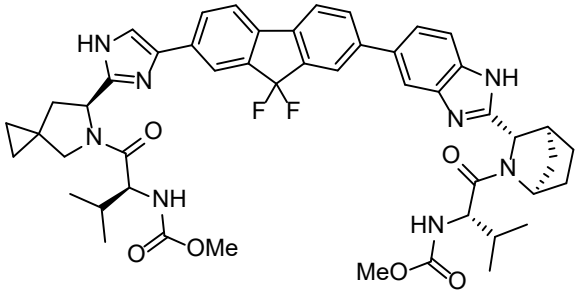
NS5A Inhibitors

First Generation

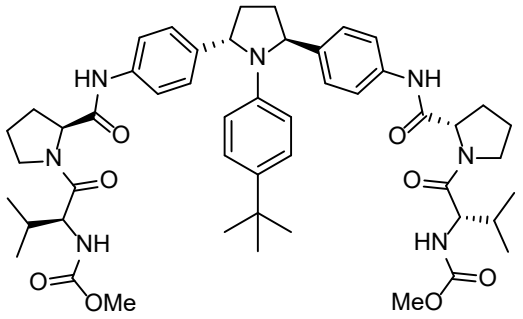
Daclatasvir
(Bristol-Myers Squibb)



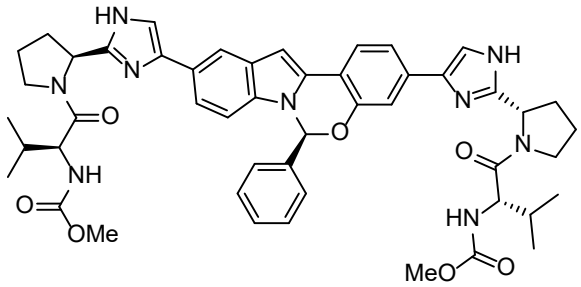
Ledipasvir
(Gilead Sciences)



Ombitasvir
(AbbVie)



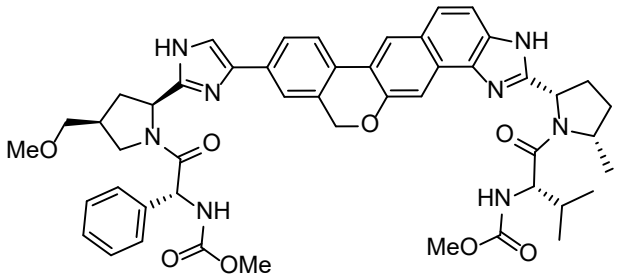
Second Generation

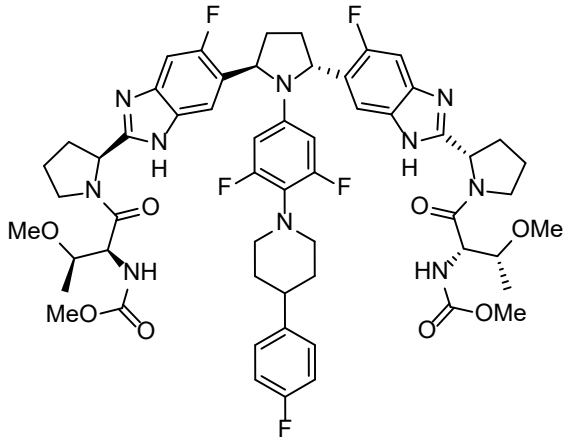


Elbasvir
(Merck)

$60,000 - $80,000

Velpatasvir
(Gilead Sciences)

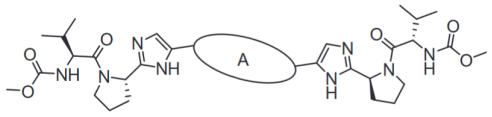




Pibrentasvir
(AbbVie)

Core variation, position of arms

EC_{50} (nM) values for compounds **22–28**[16]



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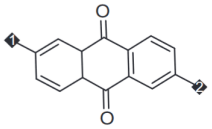
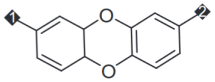
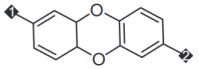
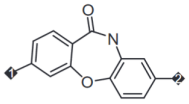
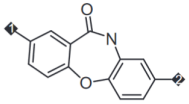
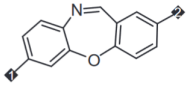
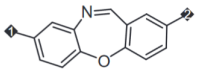
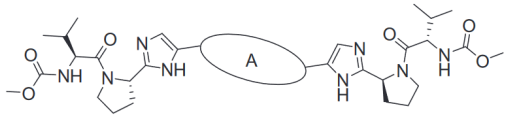
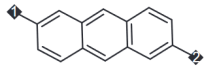
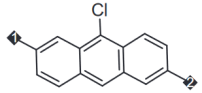
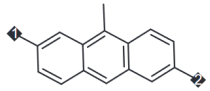
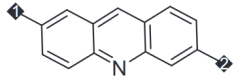
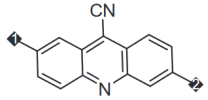
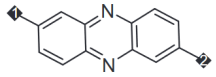
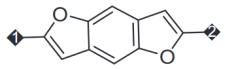
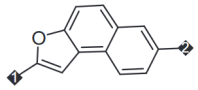
22		0.09	0.007	0.7	35
23		0.1	0.09	0.6	350
24		0.01	0.009	0.01	16
25[a]		145	0.2	310	nt
26[a]		950	40	>1000	nt
27[a]		220	0.06	55	nt
28[a]		40	0.5	55	nt

nt = not tested.

EC_{50} (nM) values for compounds **4**, **10–16**[16]

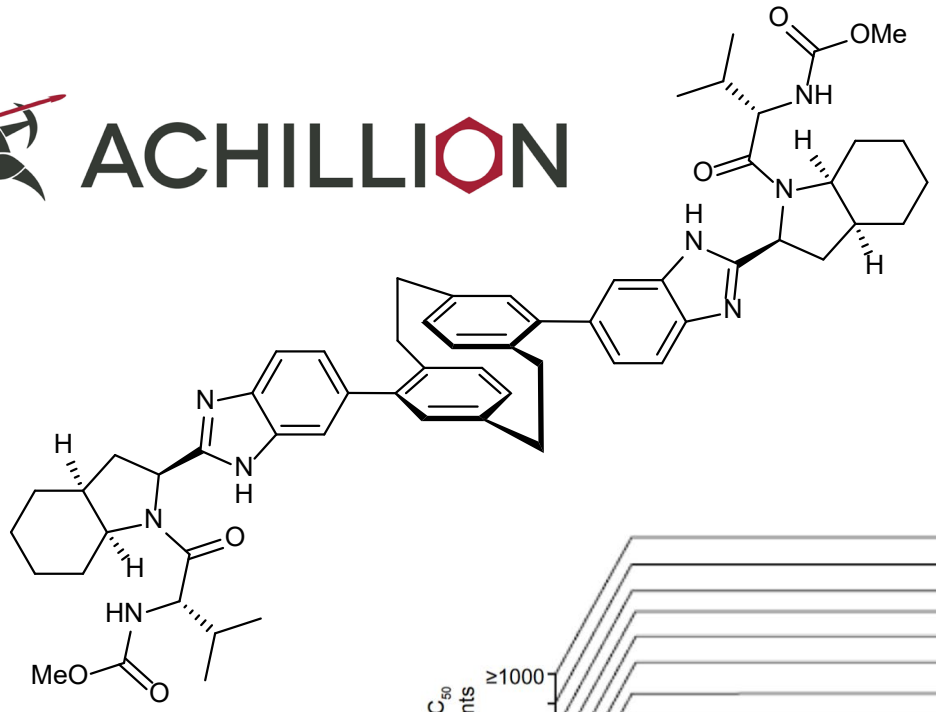


ID	A	GT-1a	GT-1b	GT-2a	GT-3a	GT-1a Y93H
4		0.006	0.001	0.005	0.06	87
10		0.05	0.003	0.01	0.6	66
11		0.02	0.005	0.005	0.5	42
12		0.05	0.01	0.04	nt	1050
13[a]		0.3	0.01	1	nt	nt
14		0.06	0.06	0.1	0.2	61
15		0.03	0.001	0.05	nt	nt
16		>10	0.01	0.3	nt	1400

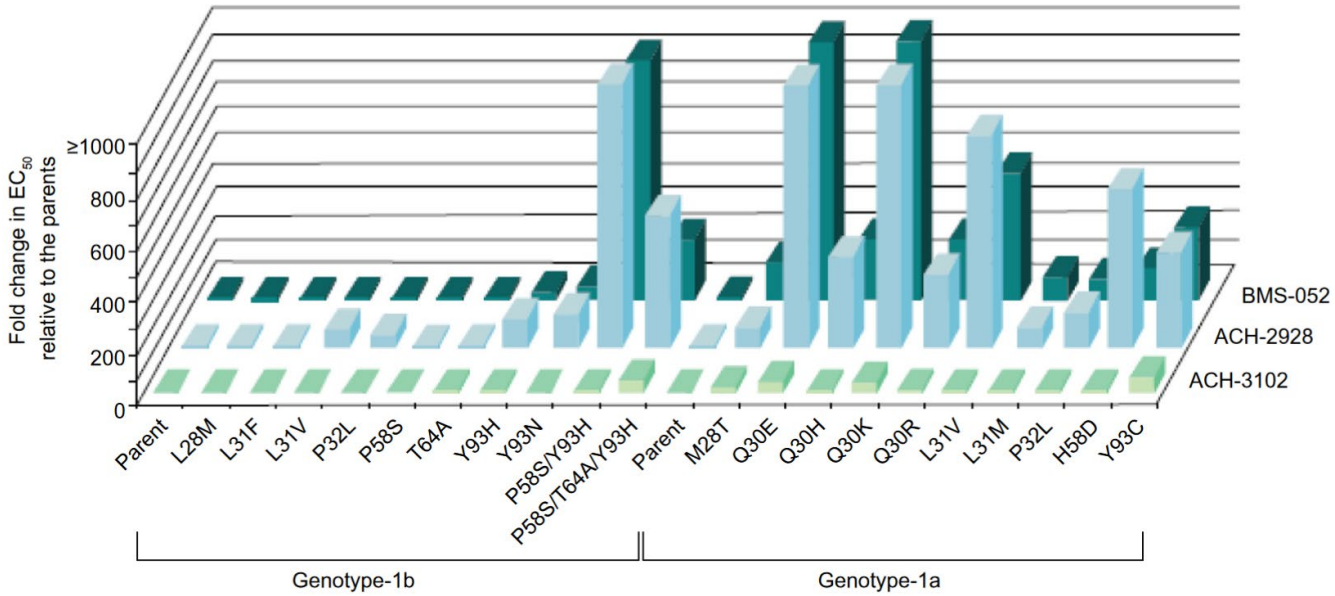
nt = not tested.

Odalasvir

ACHILLION

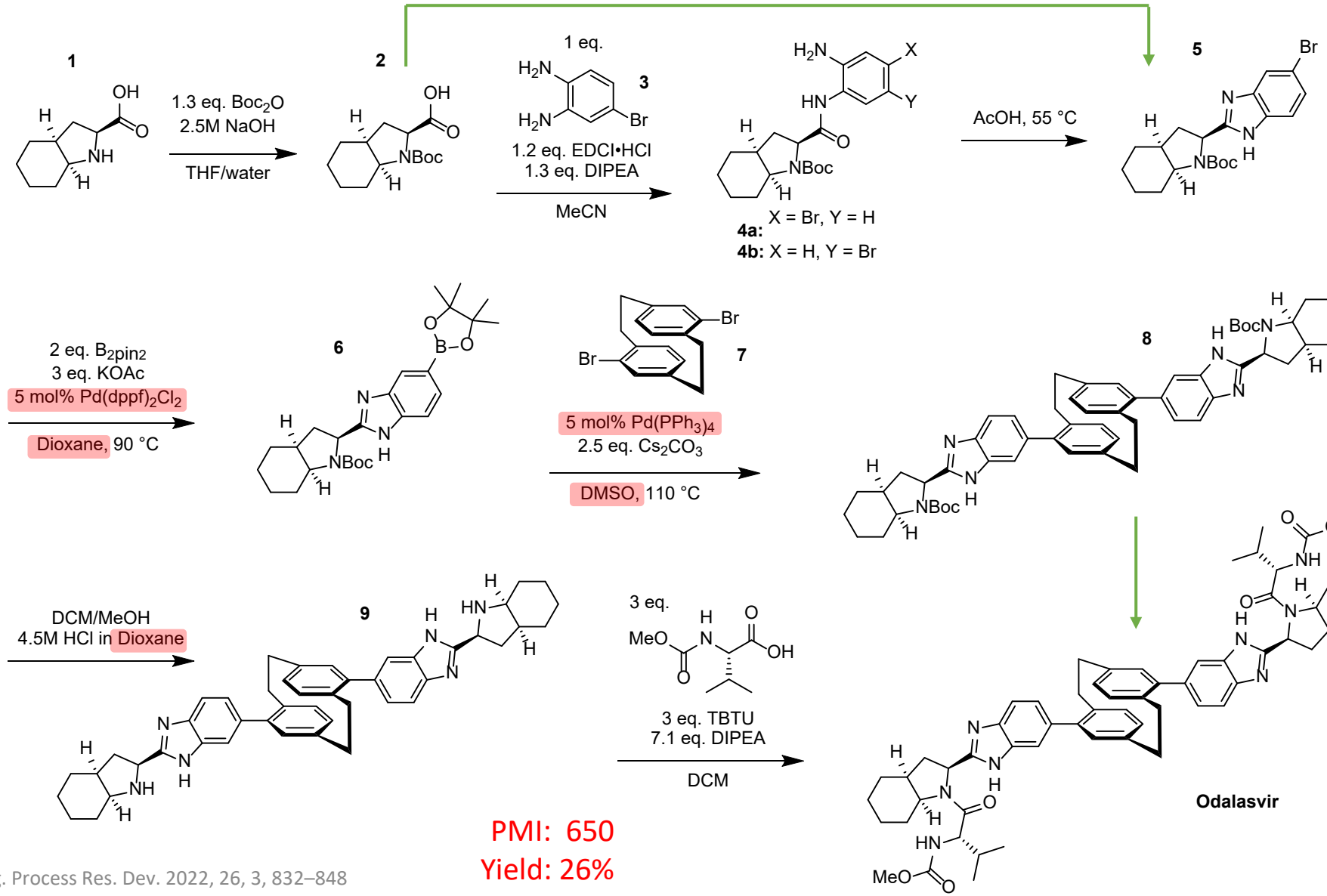


- Second generation NS5A inhibitor
- Effective against all genotypes
- Entering Phase 3 clinical trials



Pawlotsky JM. NS5A inhibitors in the treatment of hepatitis C. J Hepatol. 2013 Aug; 59(2):375-82.

Medicinal Chemistry Synthesis



PMI: 650
Yield: 26%

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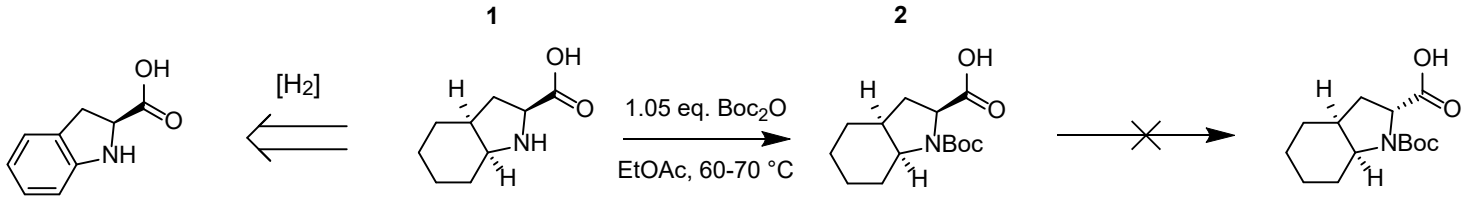
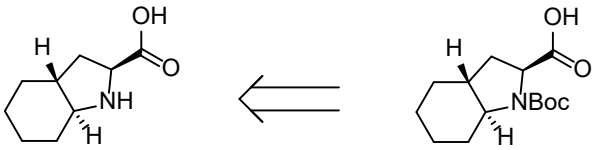
Boc protection



process	reaction and workup	yield	PMI
medicinal chemistry route	Boc_2O (1.3 equiv), NaOH, H_2O/THF; extraction, solvent switch, crystallization from EtOAc/heptane	100% in situ, 93% isolated	36
current process	Boc_2O (1.05 equiv), EtOAc (2 L/kg); distillation, crystallization from EtOAc/heptane	100% in situ, 92% isolated	8.5

Up to 150kg per batch



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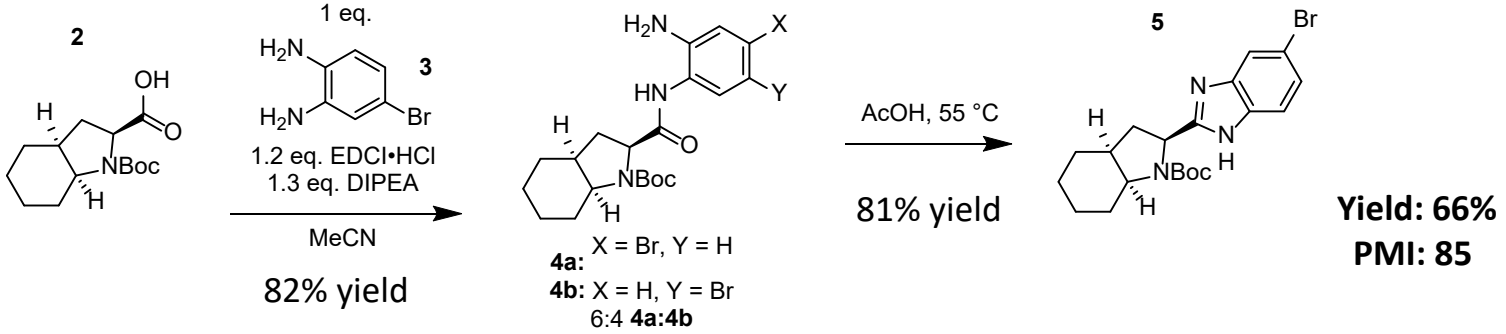
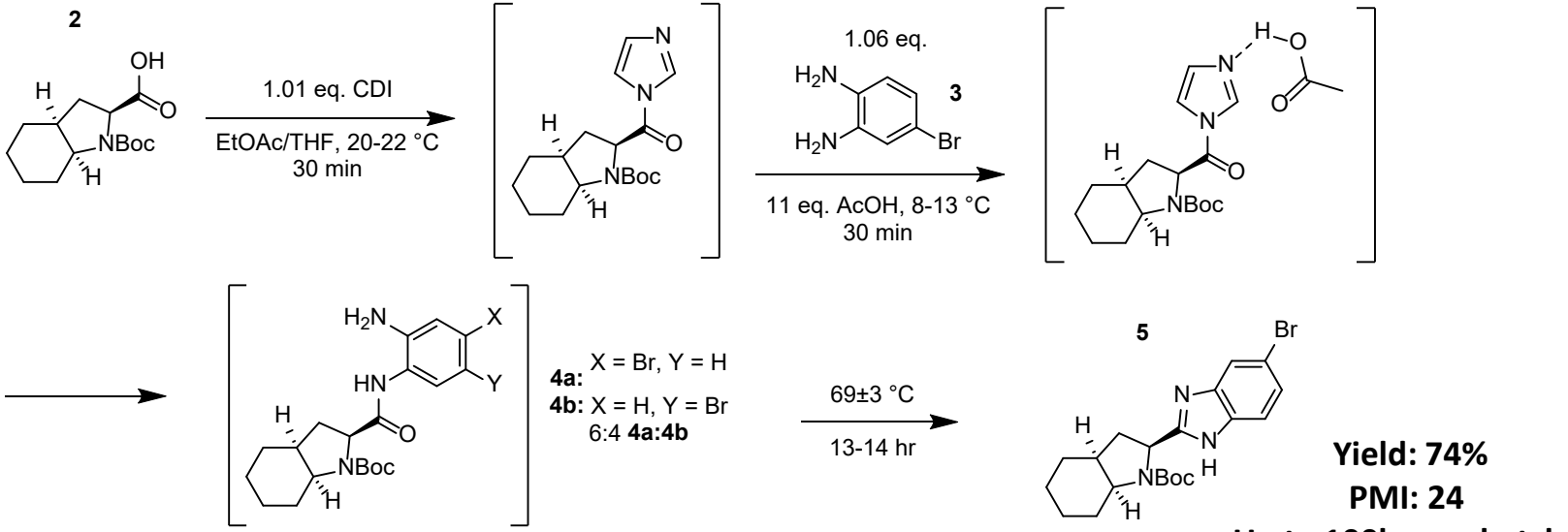
Telescoped Amidation/Cyclization

Original 2-Step Synthesis



Improved Telescoped Synthesis



Workup: Aqueous washes, solvent switch to IPA/heptane, **5**·IPA crystallized and desolvated in vacuo

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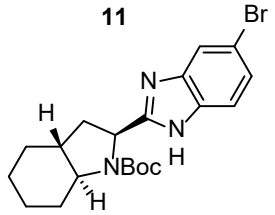
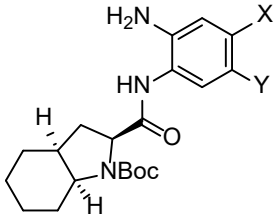
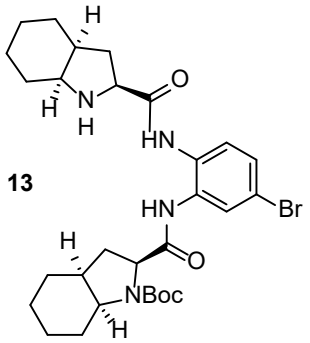
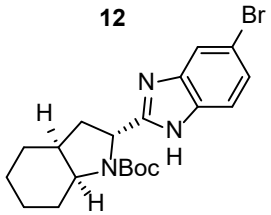
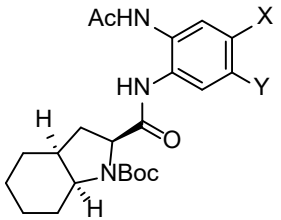
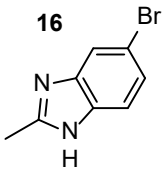
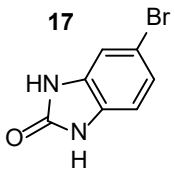
Telescoped Amidation/Cyclization Impurity Profile

Residual SM Impurity	Incomplete Reaction	Overreaction
11 	 **4a:** X = Br, Y = H **4b:** X = H, Y = Br	**13** 
Epimerization		**Excess CDI**
12 	 **14:** X = Br, Y = H **15:** X = H, Y = Br	**16**  **17** 

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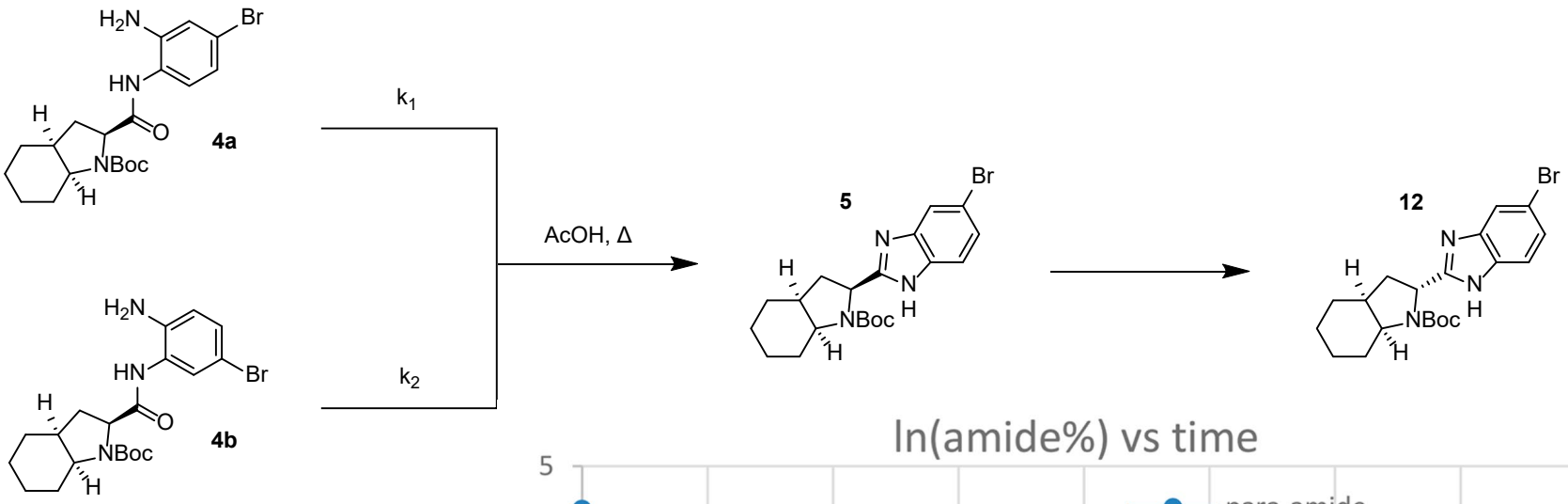
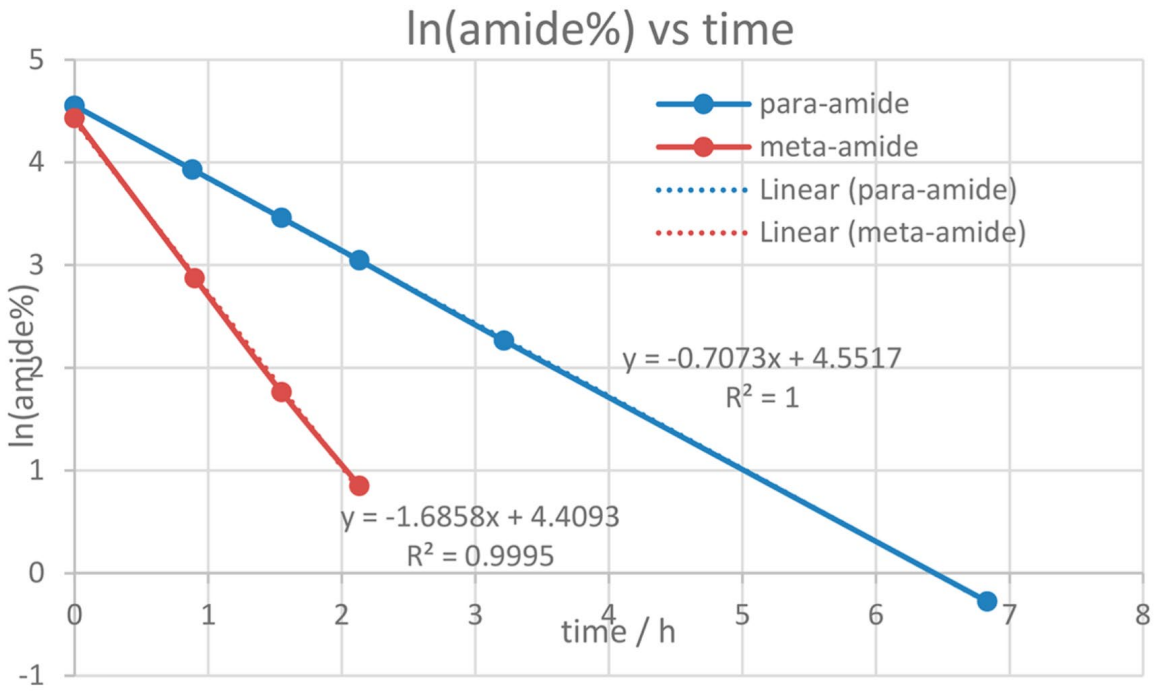
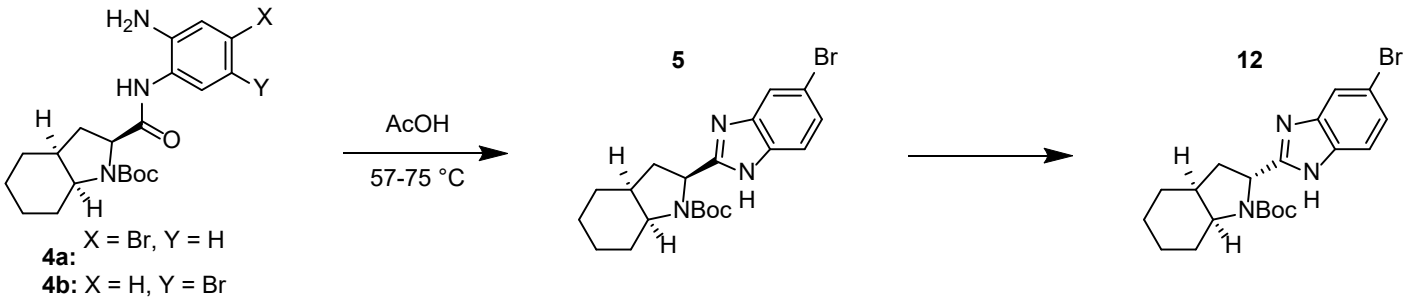
Telescoped Amidation/Cyclization Kinetic Study





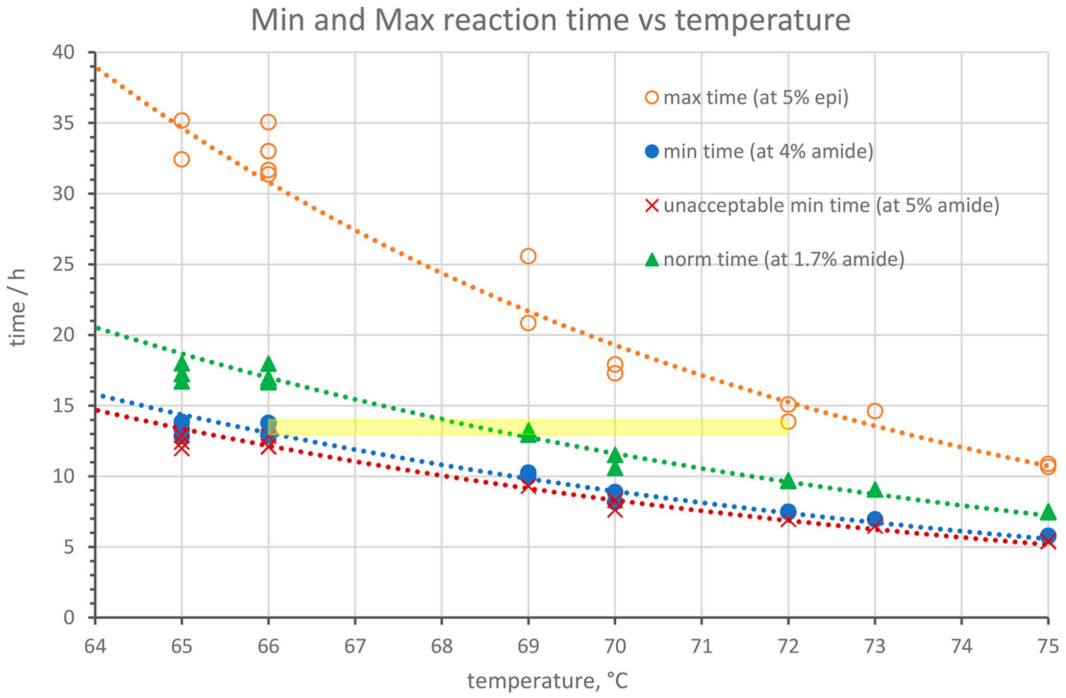
Org. Process Res. Dev. 2022, 26, 3, 832–848

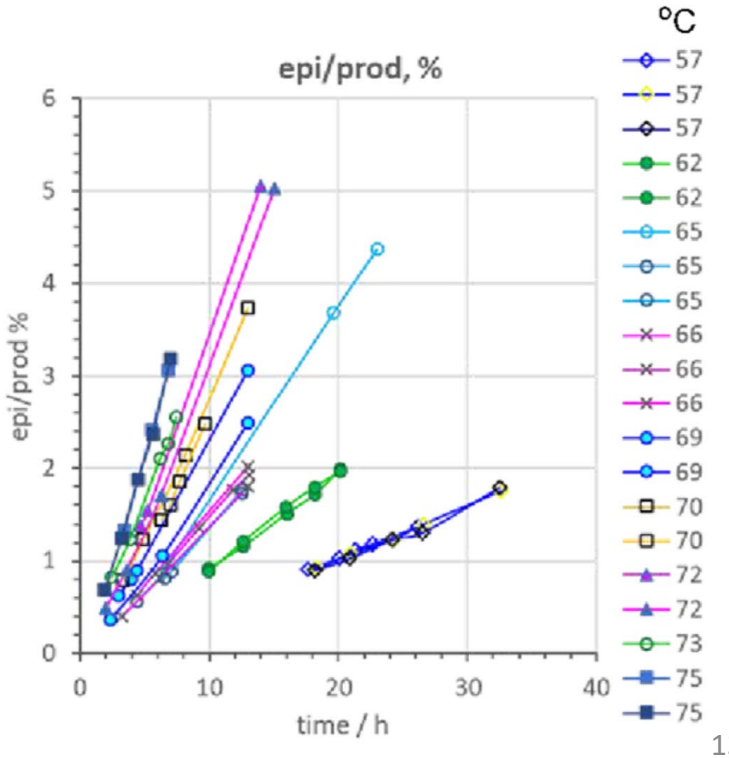
Telescoped Amidation/Cyclization Kinetic Study



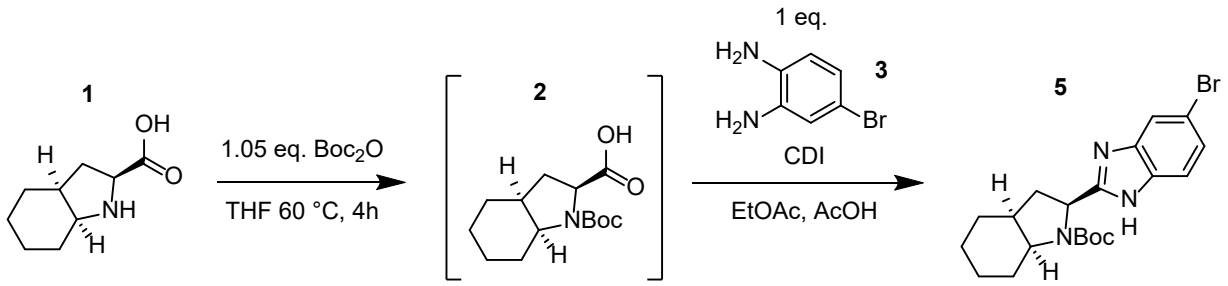
4a: X = Br, Y = H
4b: X = H, Y = Br

Hard Purity Limits: <5% **4a**, <10% **12**

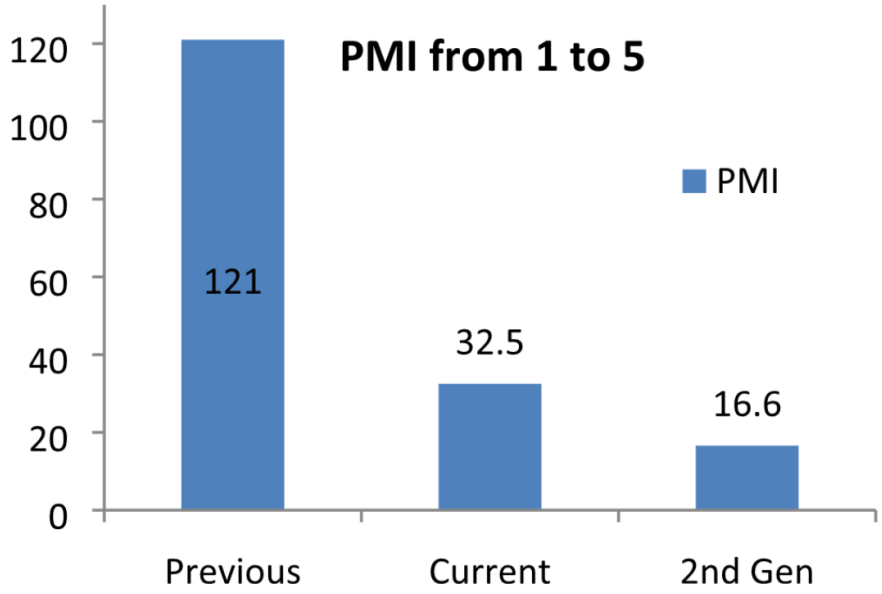




Telescoped Boc Protection/Amidation/Cyclization

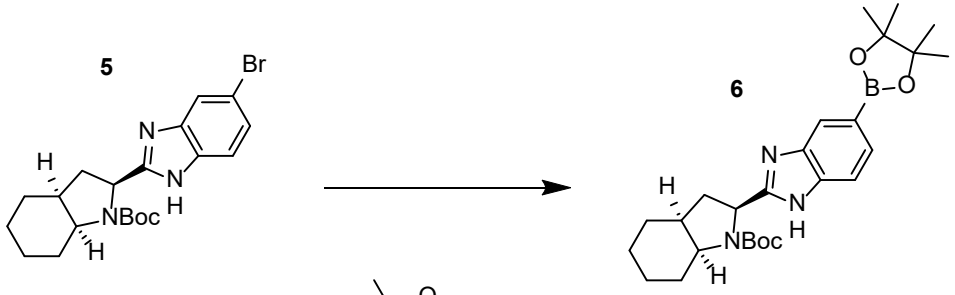


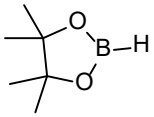
Crystallization of **5**·IPA from AcOH/IPA/H_2O system eliminates aqueous washes

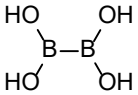


Org. Process Res. Dev. 2022, 26, 3, 832–848

Miyaura Borylation







Original Conditions

5 mol% $Pd(dppf)_2Cl_2$
3 eq. KOAc
2 eq. $B_{2}pin_{2}$
Dioxane, 90 °C

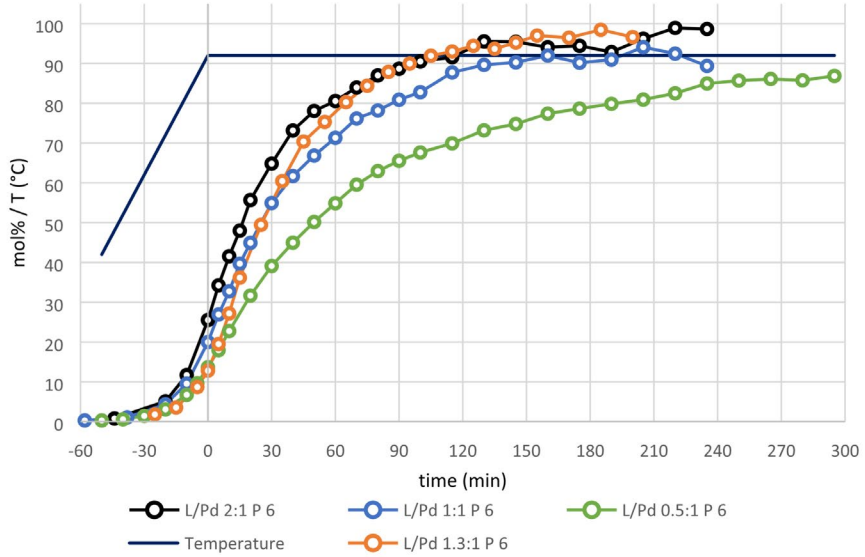
Optimized Conditions

1.02 eq. $B_{2}pin_{2}$
0.25 mol% $[Pd(allyl)Cl]_2$
0.65 mol% XPhos
IPAc, 90 °C
2 eq. KOAc **(jet-milled)**

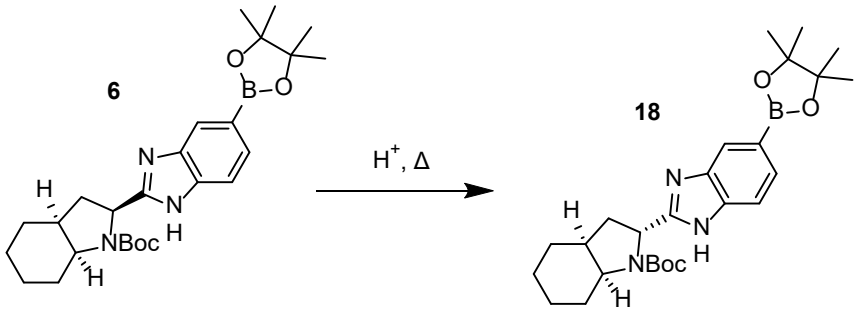
$B_{2}pin_{2}$ + Pd(XPhos)(allyl)Cl ⟶ ↓Pd

Order of Addition:

1. $[Pd(allyl)Cl]_2$ + XPhos
2. **5**
3. KOAc + $B_{2}pin_{2}$

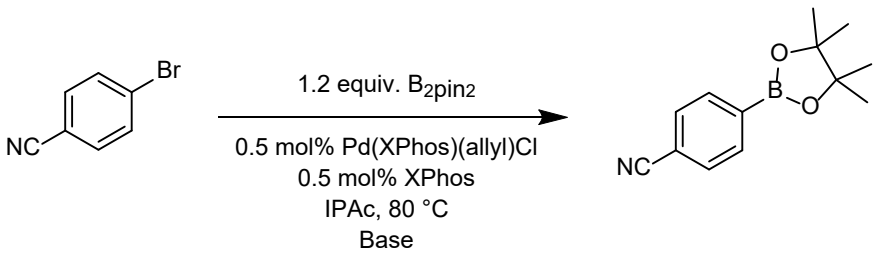


AcOBPin + H_2O ⟶ AcOH + HOBPin



Org. Process Res. Dev. 2022, 26, 3, 832–848

Miyaura Borylation Kinetic Study



entry	base	temperature (°C)	time (h)	conversion (%)	yield (%)
1	KOAc	80	0.5	100	90
2	NaOAc	80	21	63	53
3	AgOAc	80	0.5[a]	10	10
8	NMe_4OAc	55	1	100	89
9	CsOAc	55	1	100	96
10	NMe_4OAc	35	45	91	50
11	CsOAc	35	20	59	34

entry	base	temperature (°C)	time (h)	conversion (%)	yield (%)
1	KOAc	55	8	99	96
2	K propionate	55	3.5	100	96
3	K propionate	35	23	99	92
4	K *n*-butyrate	35	20	82	79
5	K *n*-hexanoate	35	48	83	68
6	K *n*-octanoate	35	48	99	87
7	K isobutyrate	35	23	88	82
8	KOPiv	35	4	97	97
9	K 2-ethyl hexanoate	35	1.5	100	95

Very hygroscopic. Fully soluble but forms thick gel when mixed with B_2pin_2. Thins out upon heating.

J. Org. Chem. 2021, 86, 1, 103–109

Miyaura Borylation Kinetic Study

entry	base	solvent	temperature (°C)	time (h)	conversion (%)	yield (%)
1	2-KEH	DMF	35	19	100	91
2	2-KEH	toluene	35	3	100	99
3	2-KEH	MeTHF	35	2.5	100	93
4	2-KEH	IPAC	35	1.5	100	95
5	2-KEH	methanol	55	0.5	100	96
6	2-KEH	heptane	80	1	90	87

Solvent / Salt	DMF	IPAC	toluene
cesium bromide	71.6 mM	n.d.	n.d.
cesium acetate	>500 nM at RT	58.2 mM	0.3 mM
cesium pivalate	>450 mM at RT	126.6 mM	11.8 mM
potassium bromide	86.9 mM	0.4 mM	55.3 mM
potassium acetate	11.8 mM	101.8 mM	n.d.
Potassium pivalate	>760 mM at RT	n.d.	0.06 mM
potassium 2-ethyl hexanoate	>1600 mM at RT	>570 mM at RT	0.1 mM
potassium 2-ethylhexanoate-B2Pin2 complex	303.0 mM	139.0 mM	n.d.
tetramethylammonium bromide	154.9 mM	n.d.	n.d.
tetramethylammonium acetate	>940 mM at RT	89 mM	>440 mM at RT
tetrabutylammonium bromide	>900 mM at RT	7.1 mM	41.2 mM
tetrabutylammonium acetate	>680 mM	440 mM	n.d.

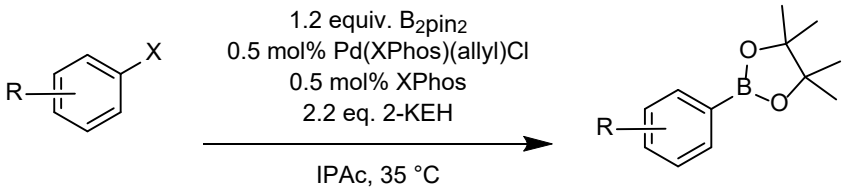
n.d. : non determined

“No clear correlation was found between reactivity and solubility of different bases / by-products”

J. Org. Chem. 2021, 86, 1, 103–109

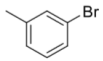
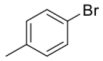
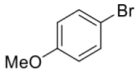
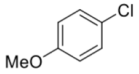
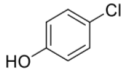
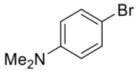
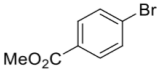
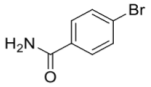
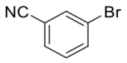
Miyaura Borylation Kinetic Study

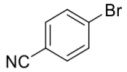
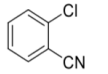
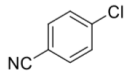
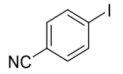
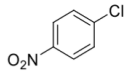
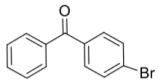
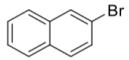
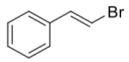
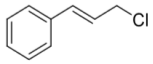
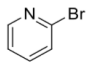
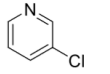
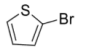
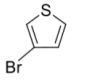
entry	pre-catalyst	ligand (equiv)	T (°C)	time (h)	conversion (%)	yield (%)
1	Xphos-Pd-G3	XPhos (1)	35	21	100	82
2	Xphos (allyl) PdCl	XPhos (1)	35	1.5	100	95
3	$Pd(dba)_2$	XPhos (2)	35	21	99	97
4	$Pd_2(dba)_3$	XPhos (2)	35	21	99	96
5	$Pd(OAc)_2$	XPhos (3)	35	21	100	93



J. Org. Chem. 2021, 86, 1, 103–109

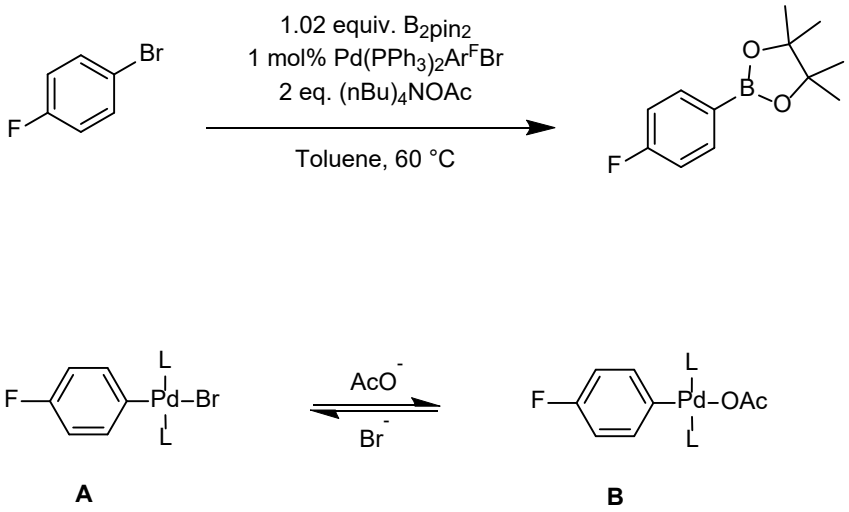
Miyaura Borylation Kinetic Study

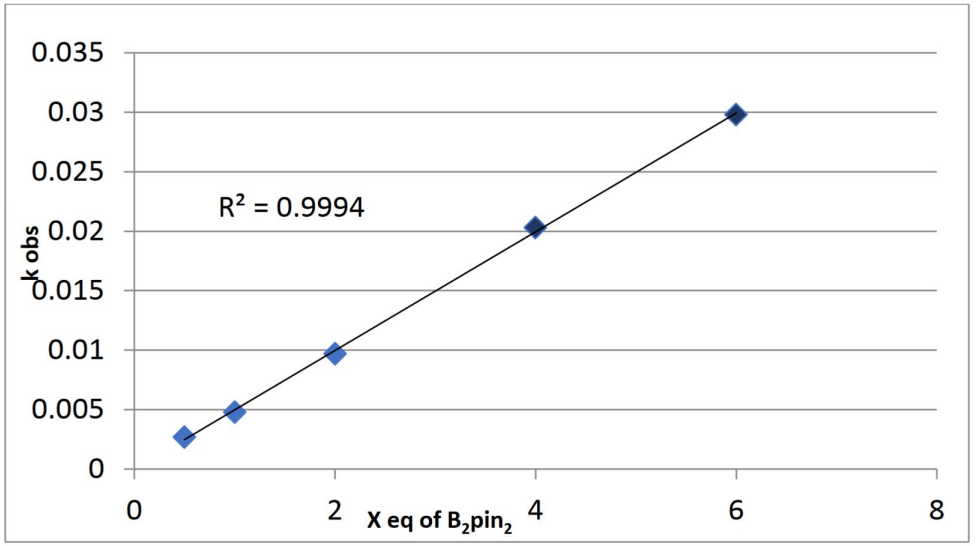
Entry[a]	Substrate	T (°C)	Time (h)	NMR yield (%)
1[2]		35	1	100
2[2]		45	5.5	99
3[11]		35 [b]	21	93
4		35	1.7	100
5[11]		35	1.5	100
6[11]		35 [c]	21	98
7[2]		80 [d]	16	27
8[2]		35	2.5	100
9[2]		35	4	90
10		35	24	75
11[2]		35	1	93
12[2]		35	2	100
13		35	1.2	95
14[12]		35	1	100

Entry[a]	Substrate	T (°C)	Time (h)	NMR yield (%)
15[2]		35	2	99
16[11]		35 [d]	5	93
17[2]		35	0.9	100
18[2]		35	13	98
19[11]		35	2	100 (84) [e]
20[7]		35	1	92
21		35	2	99
22[7]		35	16	83
23[13]		35	0.7	100
24		80	24	0
25		50 [f]	3.7	67
26[11]		35	6	90
27[11]		35	0.5	73

J. Org. Chem. 2021, 86, 1, 103–109

Miyaura Borylation Kinetic Study





Catalyst loading [mol%]	Reaction rate [%/min]
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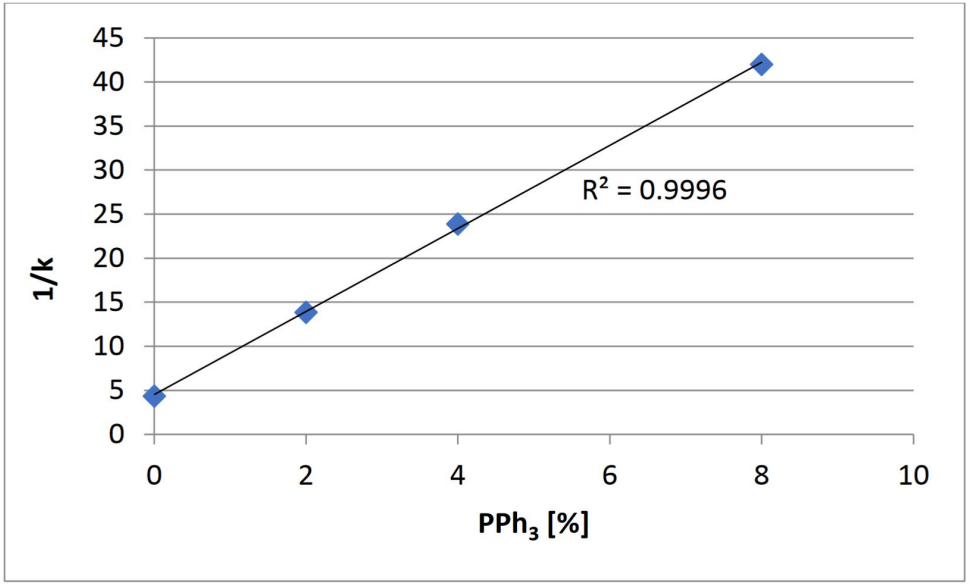
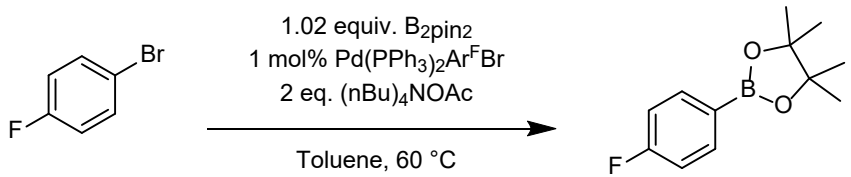
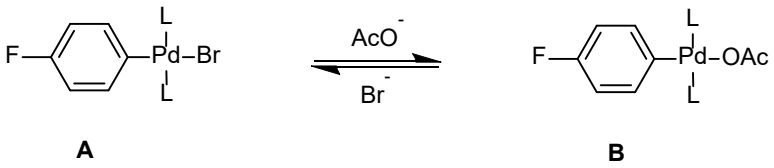
2.0	0.4209
4.0	0.7028
8.0	1.2576

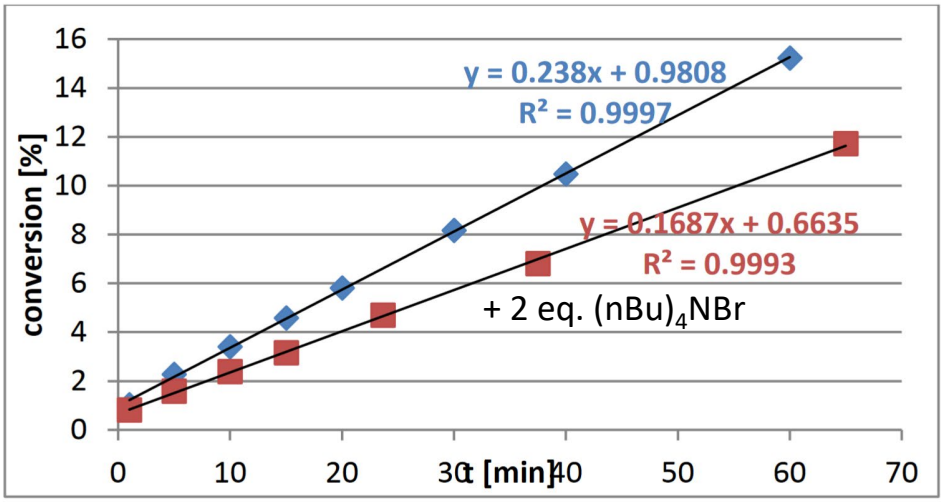


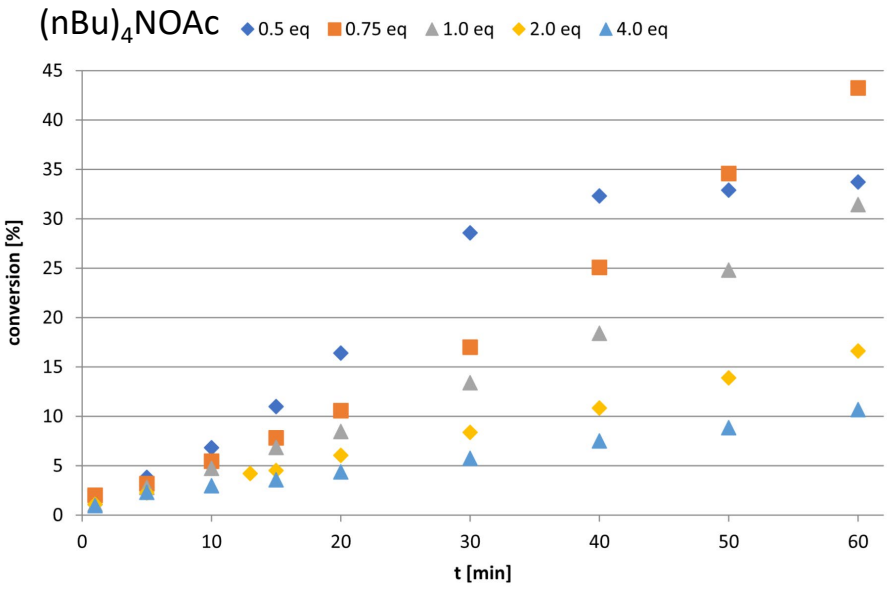
J. Org. Chem. 2021, 86, 1, 103–109

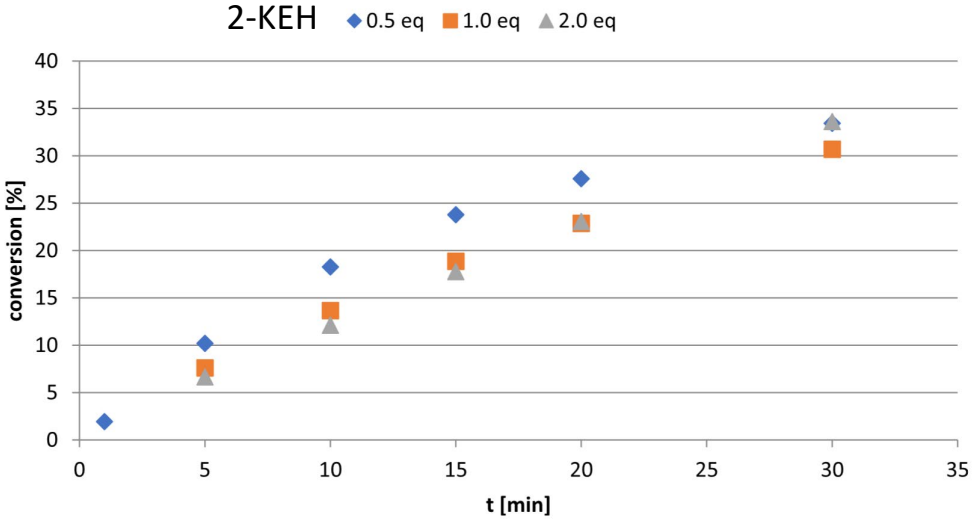
Miyaura Borylation Kinetic Study





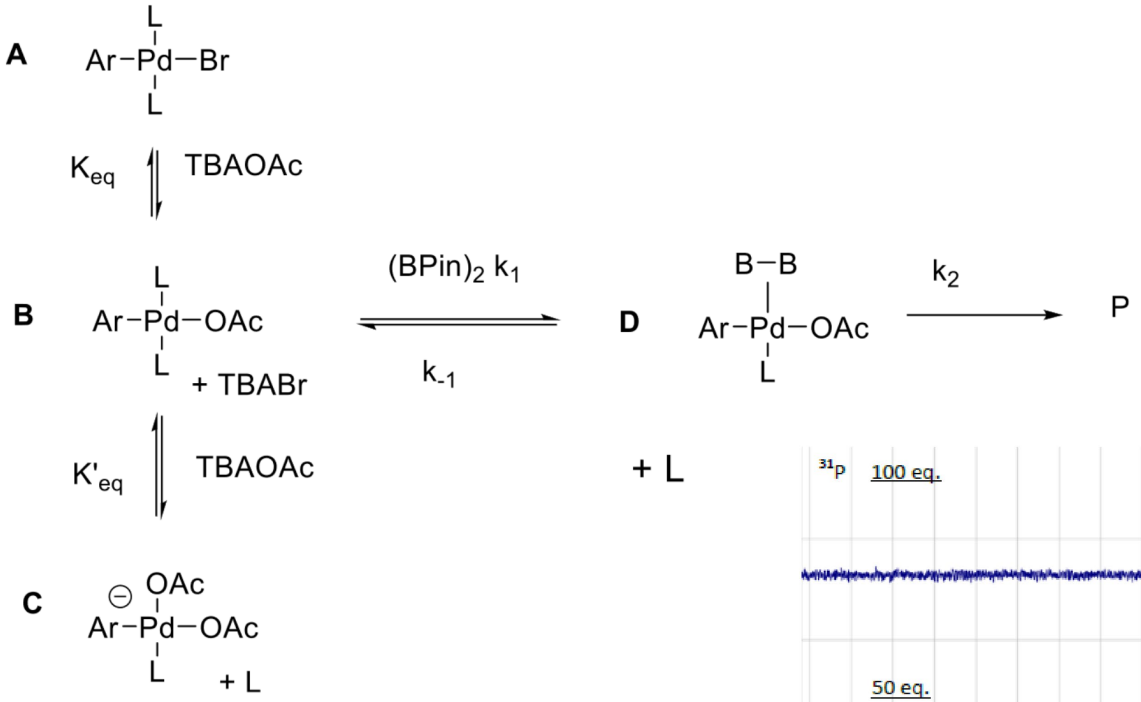


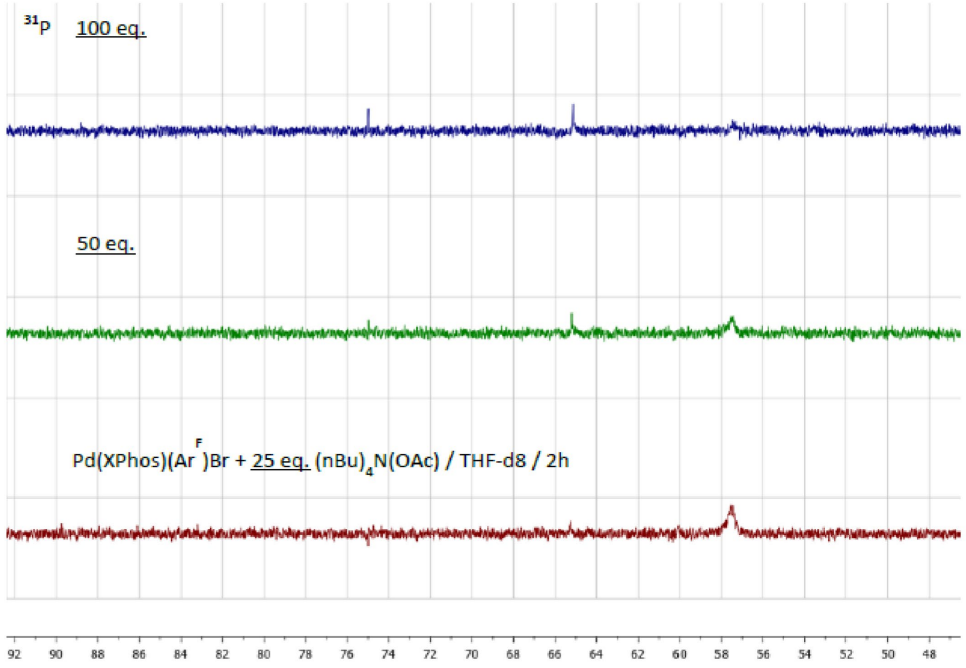




J. Org. Chem. 2021, 86, 1, 103–109

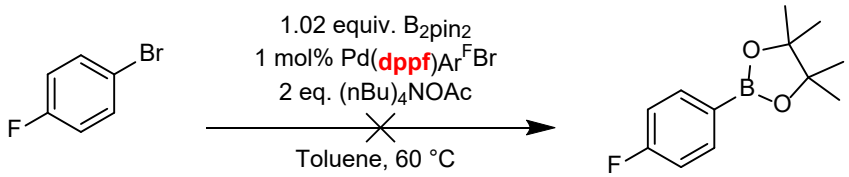
Miyaura Borylation Kinetic Study





J. Org. Chem. 2021, 86, 1, 103–109

Miyaura Borylation Kinetic Study



Role of dppf Monoxide in the Transmetalation Step of the Suzuki–Miyaura Coupling Reaction

Pierre-Adrien Payard,* Antoine Bohn, Damien Tocqueville, Khaoula Jaouadi, Emile Escoude, Sanaa Ajig, Annie Dethoor, Geoffrey Gontard, Luca Alessandro Perego, Maxime Vitale, Ilaria Ciofini,* Simon Wagschal,* and Laurence Grimaud*

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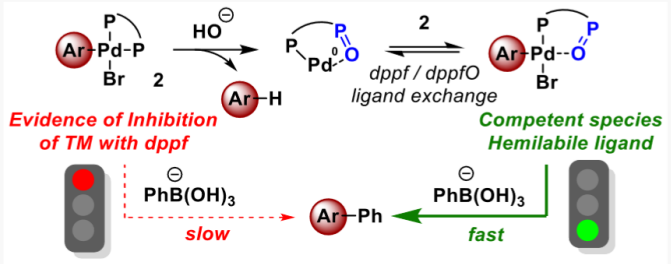
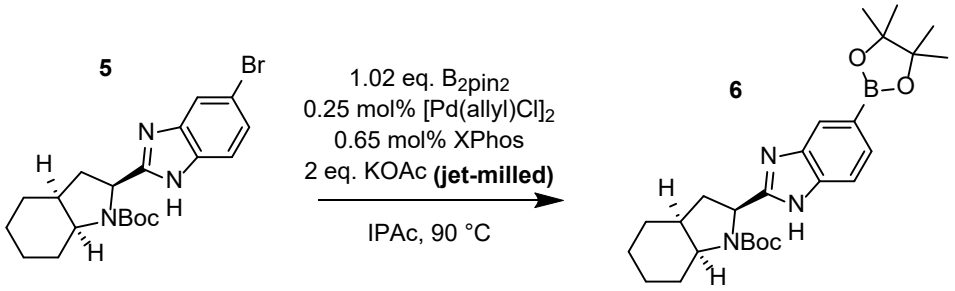
ABSTRACT: Diphosphine ligands are frequently used in palladium-catalyzed Suzuki–Miyaura (S-M) reactions. Despite their widespread application in both academic and industrial settings, their role in the B-to-Pd transmetalation has not been firmly established. We combined electrochemistry, NMR spectroscopy, and DFT calculations to elucidate the role of dppf (1,1′-bis(diphenylphosphino)-ferrocene) in this key elementary step of the S-M reaction. We observed that excess dppf inhibits transmetalation involving $PhB(OH)_2$ and dppf-ligated arylpalladium(II) complexes, while an optimal [base]/[$PhB(OH)_2$] ratio maximizes the concentration of a [Pd–O–B] key intermediate. *In situ* oxidation of dppf to the diphosphine monoxide dppfO can take place in the presence of base, leading to dppfO-ligated arylpalladium(II) complexes, which readily undergo transmetalation at room temperature. These findings suggest guidelines for the rational optimization of diphosphine-promoted S-M reactions.



J. Org. Chem. 2021, 86, 1, 103–109

Miyaura Borylation Workup

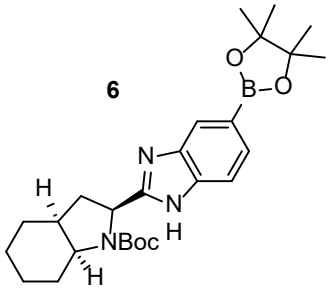


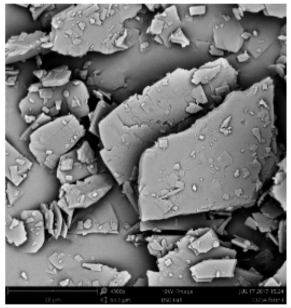
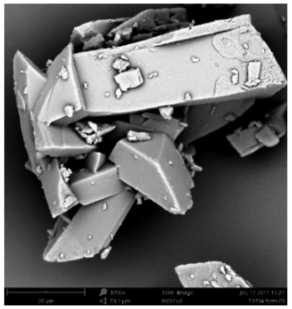
- Water workup resulted in palladium black contaminated product.
- N-acetyl-cysteine additive (0.13 eq.) to aqueous wash removes palladium.
- Reaction mixture is acidic at endpoint, acidic boron-containing side products not removed
- Washing with aqueous $NaHCO_3$ containing 0.13 eq. N-acetyl-cysteine removes palladium and acidic boron side products.
- Product crystallized from IPAc/heptane
- Scaled up to 1600L

parameter	medicinal chemistry	current process
isolated yield	70%	85%
Pd used for 1 kg of product	110 g	10.1 g
water usage for 1 kg of product	70.7 L	10.6 L
organic solvent usage for 1 kg of product	121.8 L	25.4 L
PMI	162.4	31.2

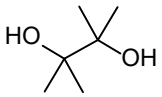
Org. Process Res. Dev. 2022, 26, 3, 832–848

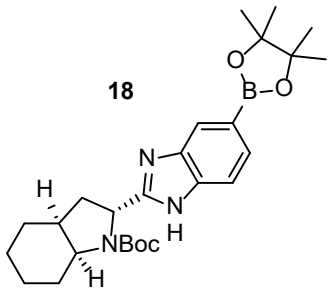
Miyaura Borylation Crystallization

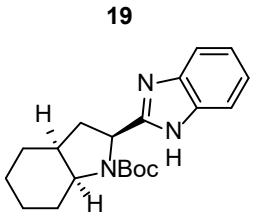


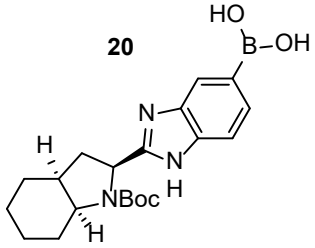
		
Form I mp = 198 °C plates	**Form II** mp = 216 °C needles	**Form III** (monohydrate) mp = 140 °C prisms

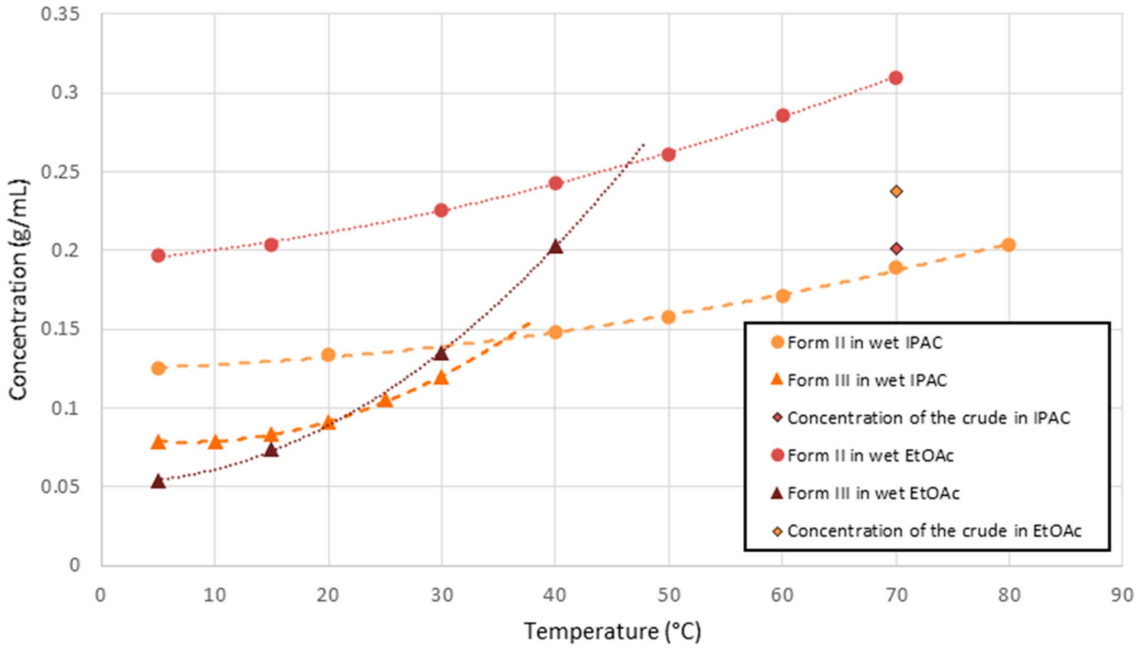
Impurity Profile





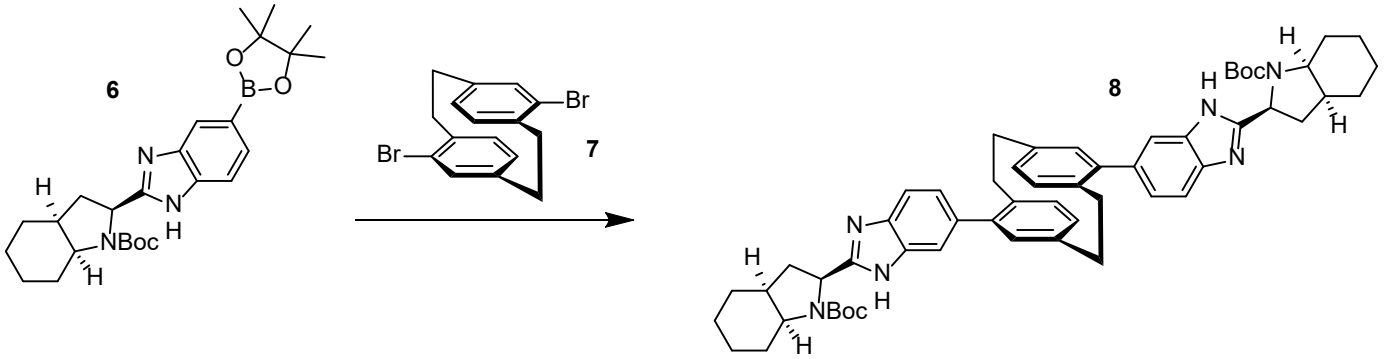






Org. Process Res. Dev. 2022, 26, 3, 832–848

Suzuki Coupling

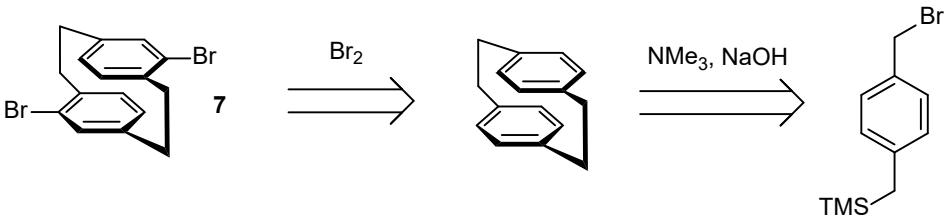


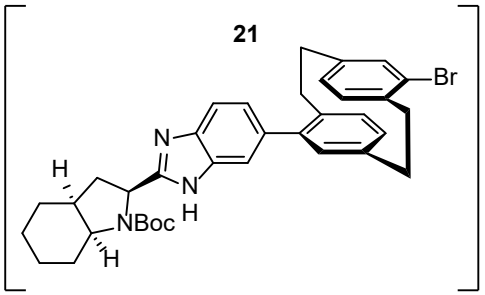
Original Conditions

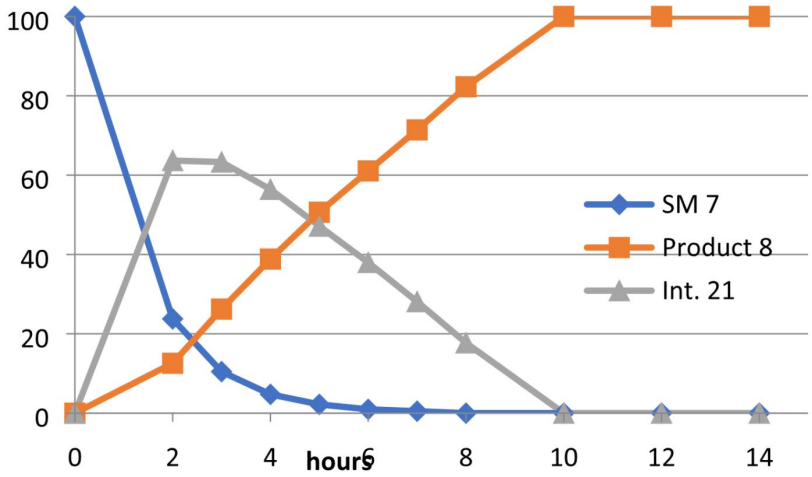
5 mol% $Pd(PPh_3)_4$
2.5 eq. Cs_2CO_3
DMSO, 110 °C, 2 hr

Optimized Conditions

2.2 eq. **6**
1 mol% $Pd(OAc)_2$
2 mol% SPhos
5 mol% TBAB
2.5 eq. Cs_2CO_3
5:1 Toluene:H_2O, 90 °C, 10 hr

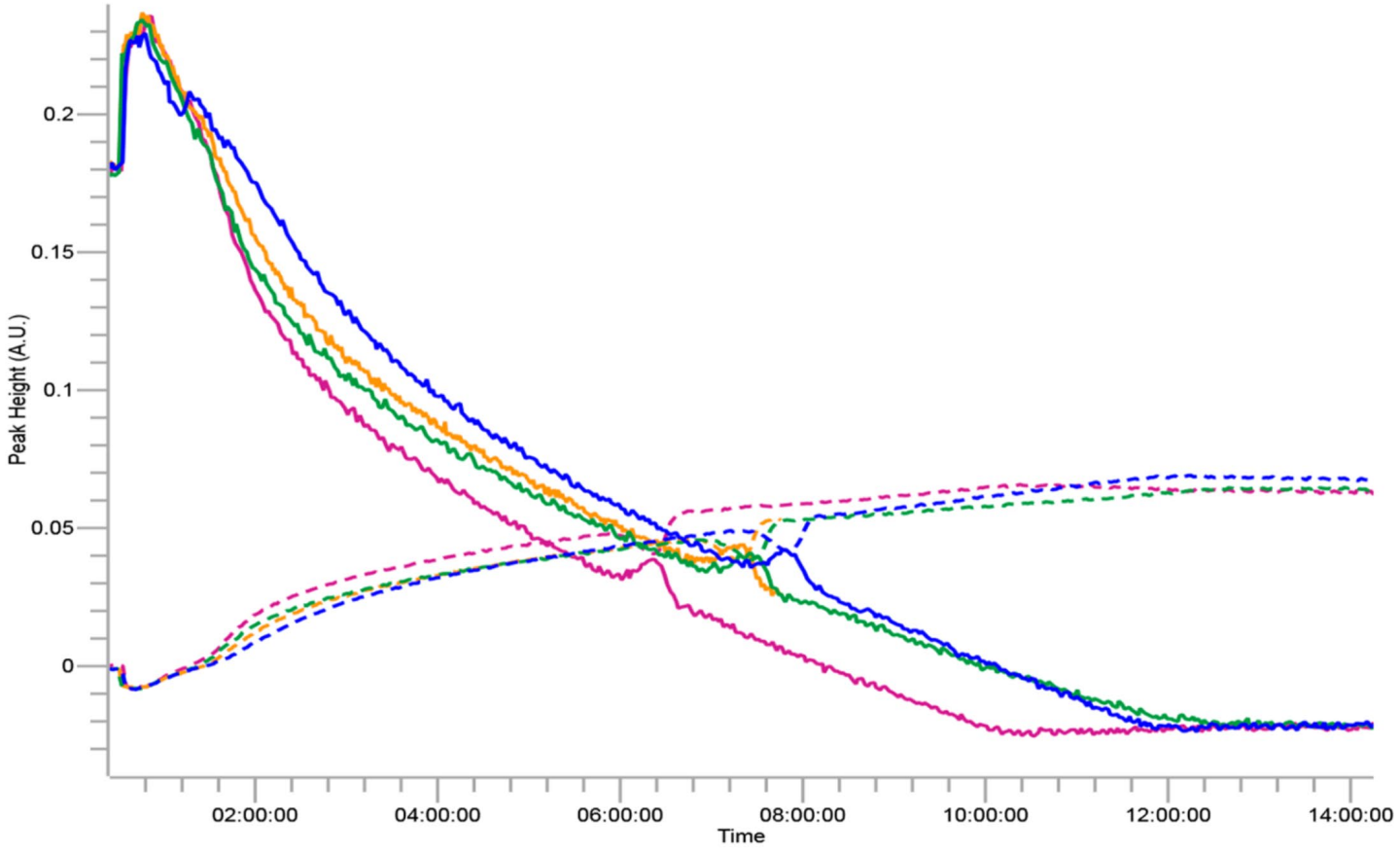






Org. Process Res. Dev. 2022, 26, 3, 832–848

Suzuki Coupling FTIR Monitoring



FTIR traces at 1355 cm^{-1} of different batches size at the reaction temperature (1 L, purple; 400 L, yellow; 1600 L, green and blue).

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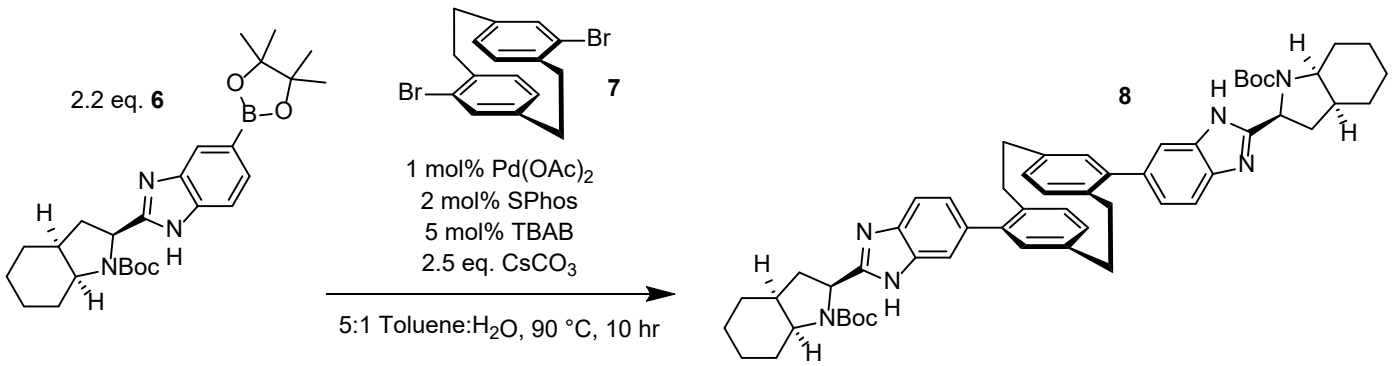
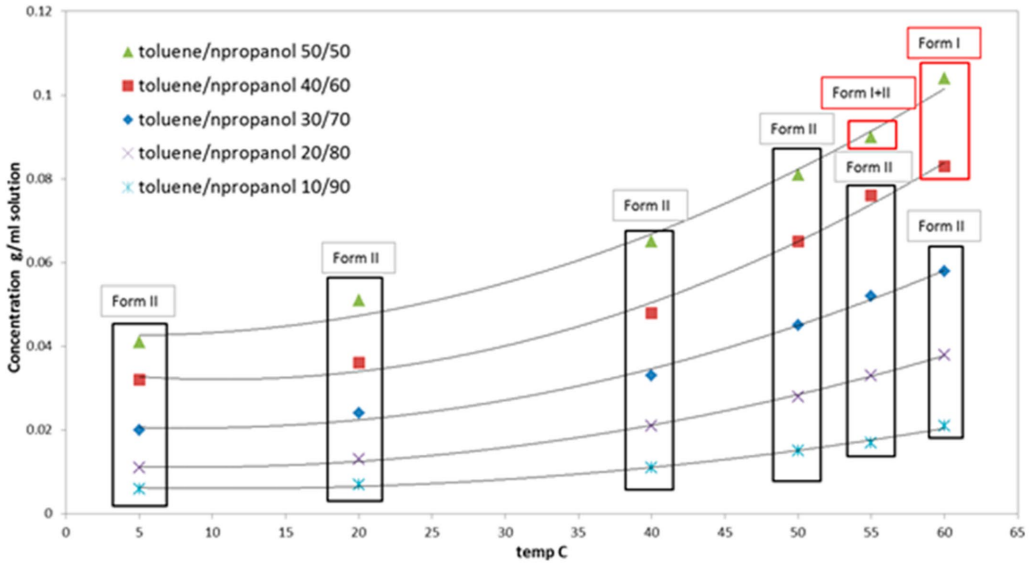
Suzuki Coupling Crystallization



- **8** is very soluble in DMF, DMSO but sparingly soluble in less polar organic solvents
- Synergistic solubility found in 1:1 n-butanol/toluene (120 g/L) vs. neat n-butanol or toluene (<10 g/L)
- Distillation resulted in excess nucleation, **Form I** crystals unsuitable for filtration
- 1-propanol/toluene yielded **Form II**, bis(1-propanol) solvate **8B**

parameter	medicinal chemistry	current process
isolated yield	70%	75–83%
Pd used for 1 kg of product	7.8 g	1.4 g
water usage for 1 kg of product	8.1 L	6.0 L
organic solvent usage for 1 kg of product	106.8 L	17.0 L
PMI	117.5	22.5



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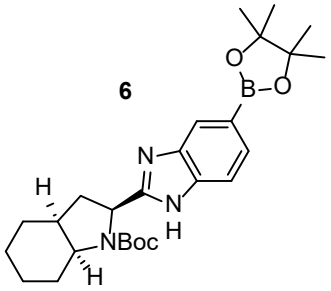
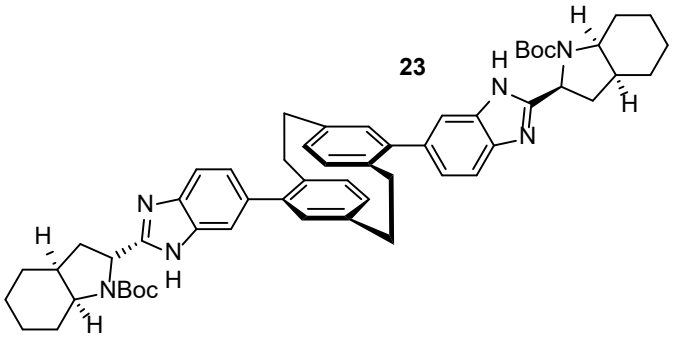
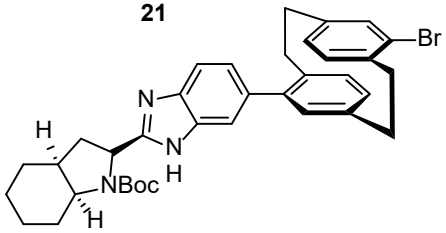
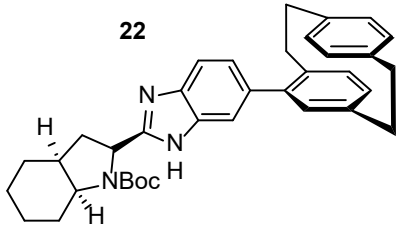
Suzuki Coupling Impurity Profile









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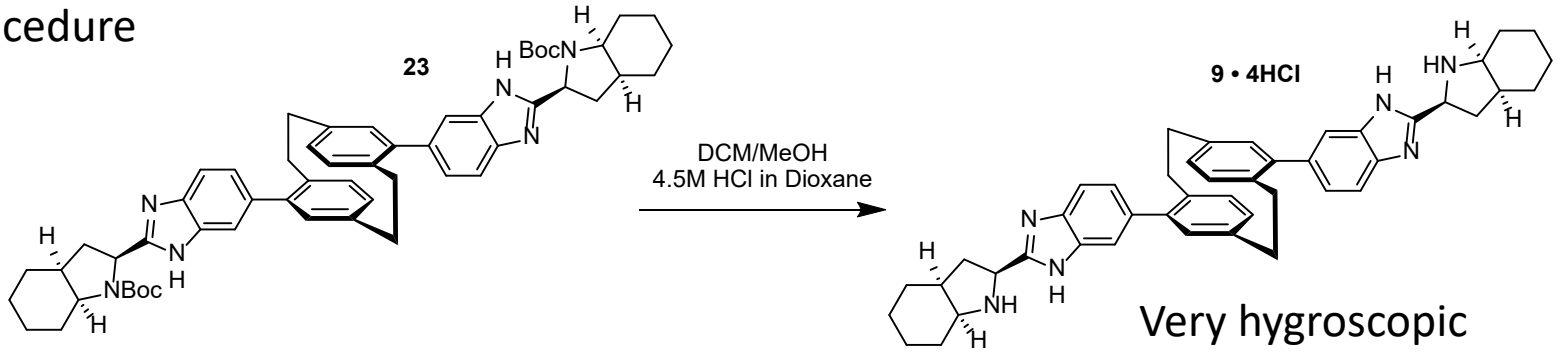
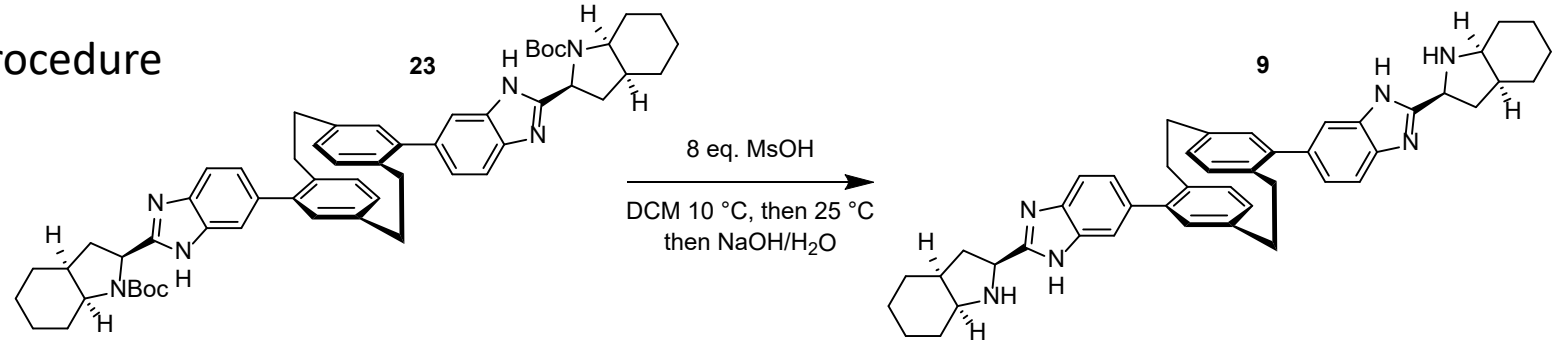
Boc Deprotection

Original Procedure

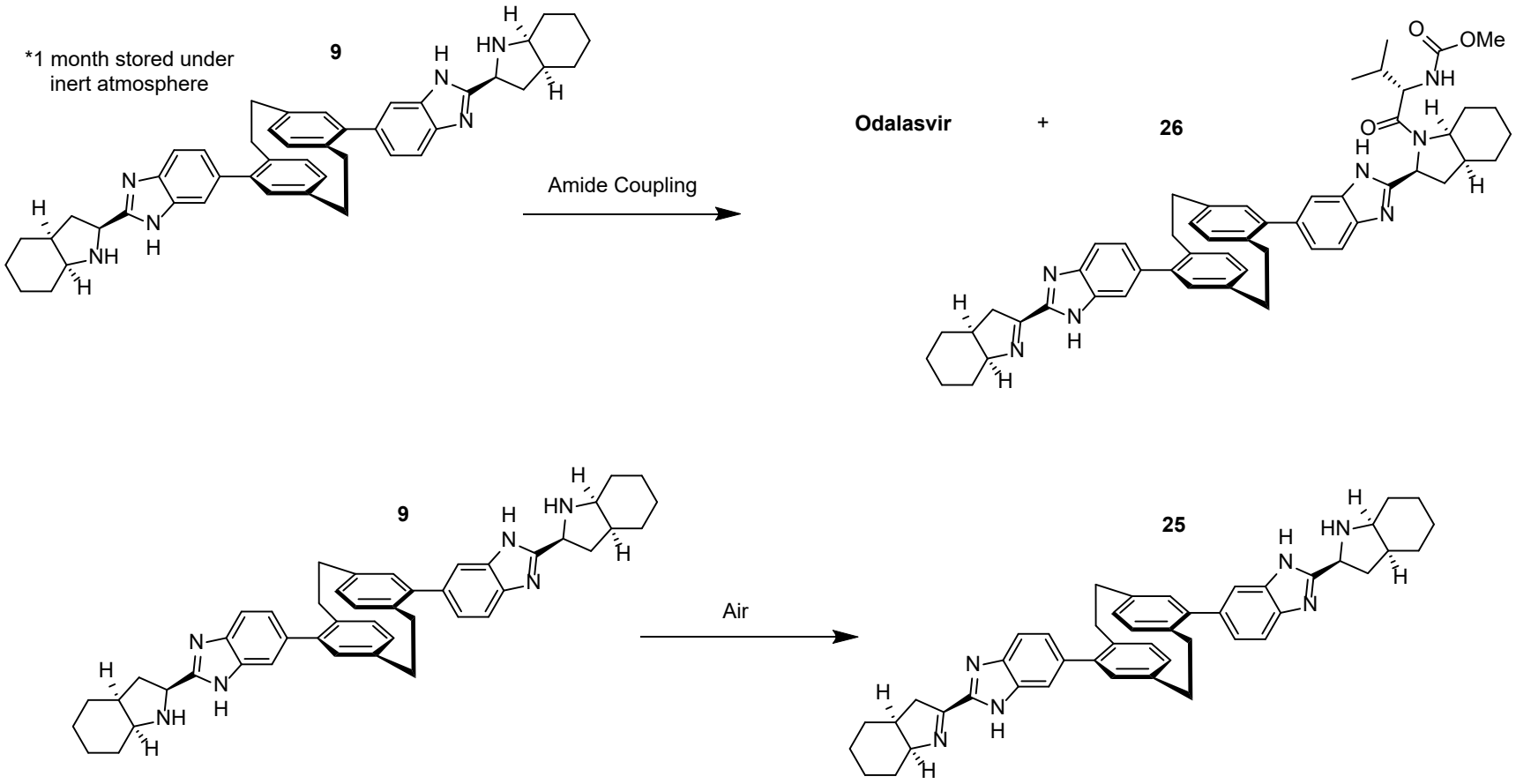


Freebase Procedure



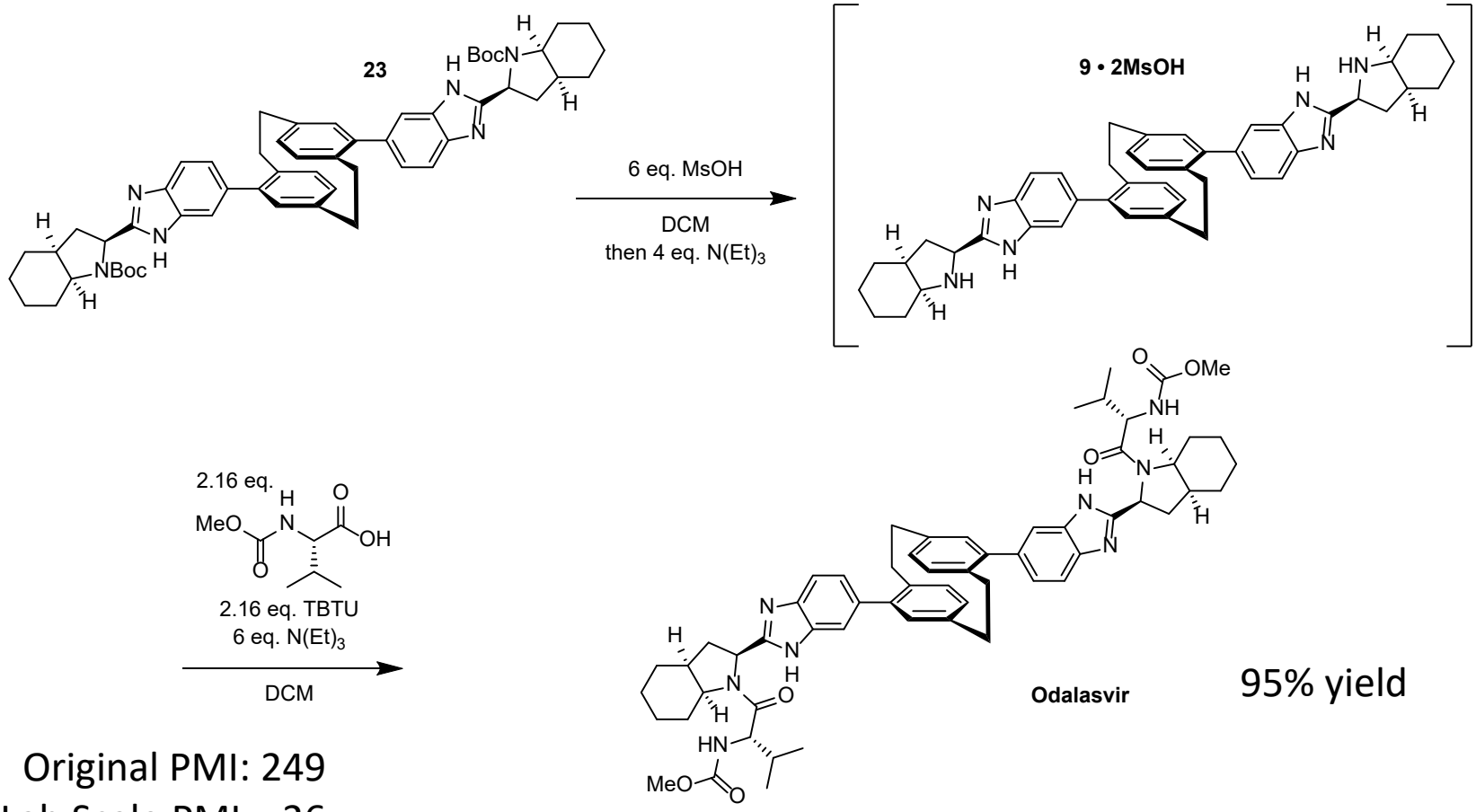
Org. Process Res. Dev. 2022, 26, 3, 832–848

Boc Deprotection



Org. Process Res. Dev. 2022, 26, 3, 832–848

Telescoped Boc Deprotection/Amide Coupling



95% yield

Original PMI: 249
Lab Scale PMI: 26
Process Scale PMI: 41

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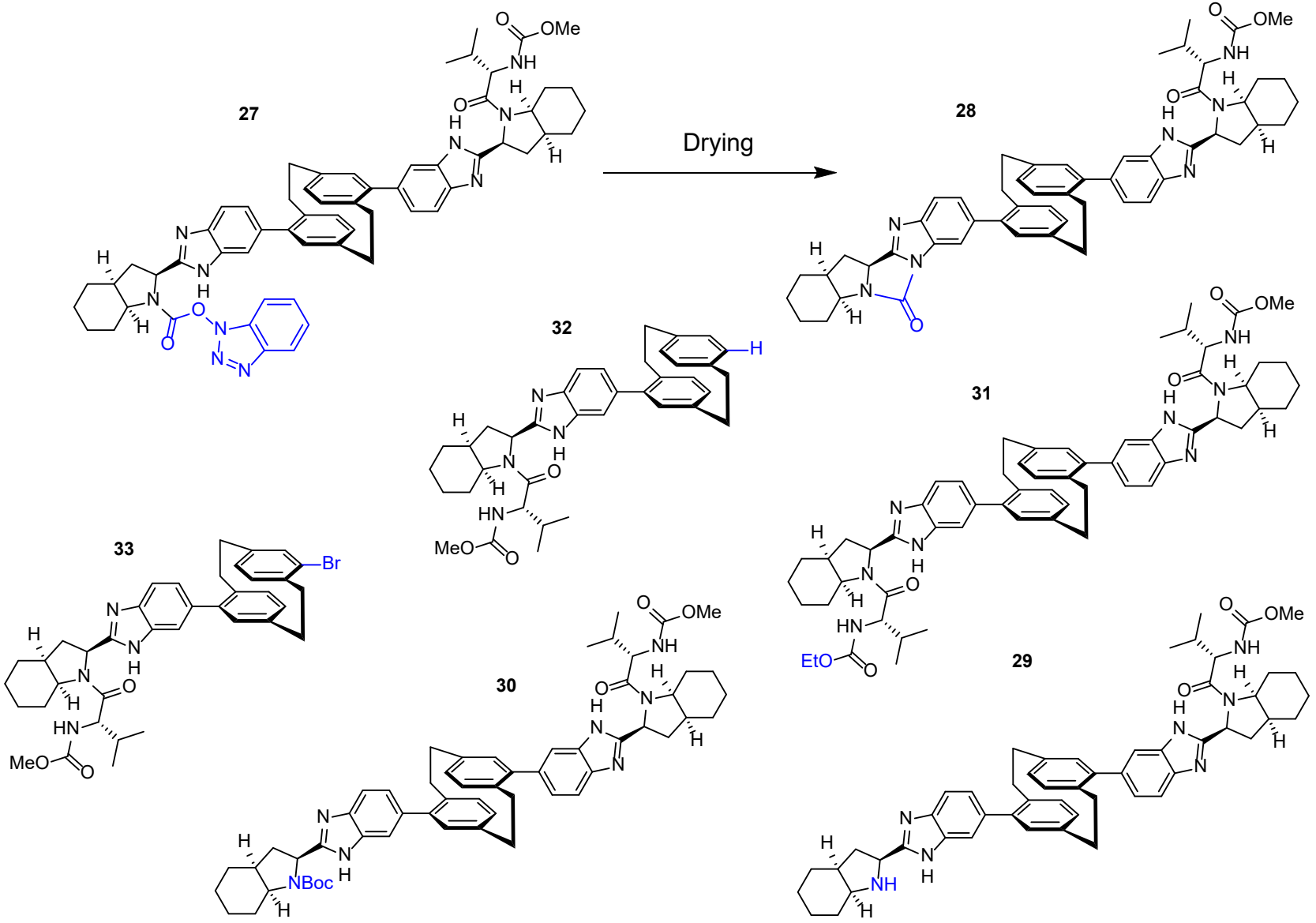
Telescoped Boc Deprotection/Amide Coupling Impurity Profile



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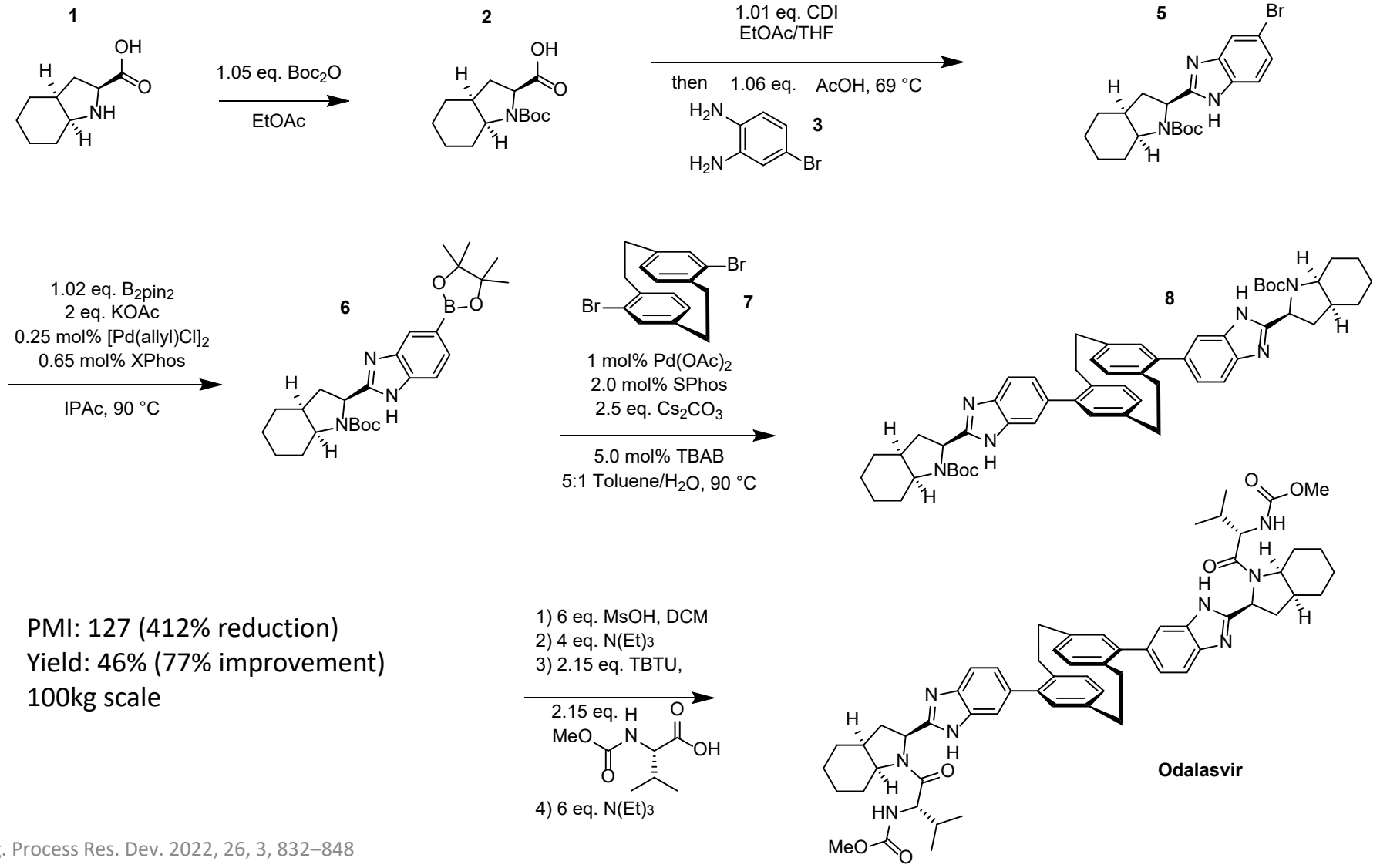
Process-Scale Odalasvir Synthesis



PMI: 127 (412% reduction)
Yield: 46% (77% improvement)
100kg scale

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