Stereoselective Synthesis of Chiral β-Fluoro α-Amino Acids via Pd(II)-Catalyzed Fluorination of Unactivated Methylene C(sp^3)−H Bonds: Scope and Mechanistic Studies

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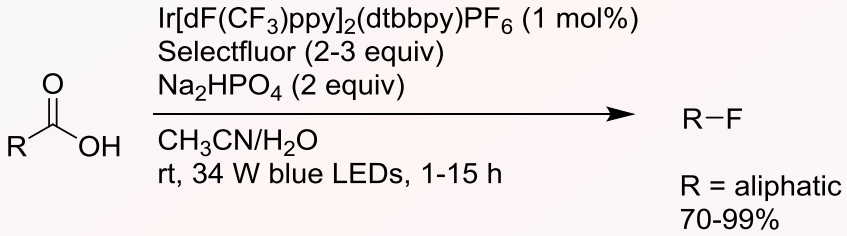
DOI: 10.1021/jacs.5b03989

Joseph Salamoun

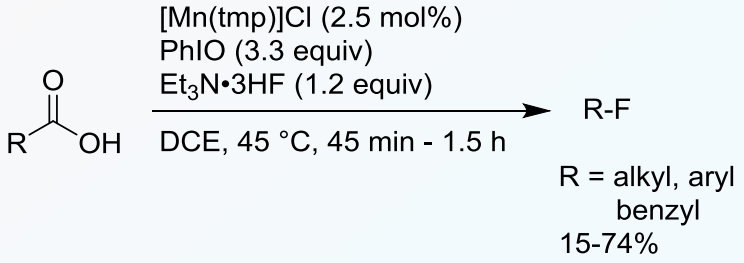
Current Literature 06/27/15

Wipf Group

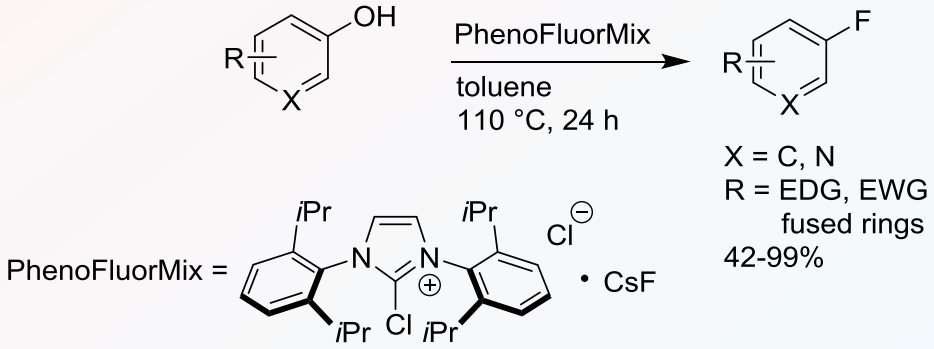
Selected Fluorination Methodologies (Jan–Jun 2015)



MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 5654.

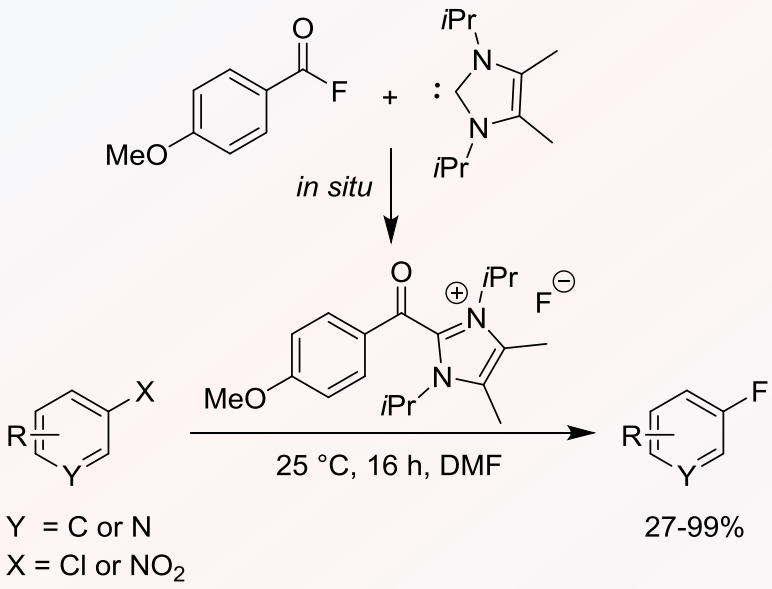


Groves, J. T. *Angew. Chem. Int. Ed.* **2015**, *54*, 5241.



Ritter, T. *Org. Lett.* **2015**, *17*, 544.

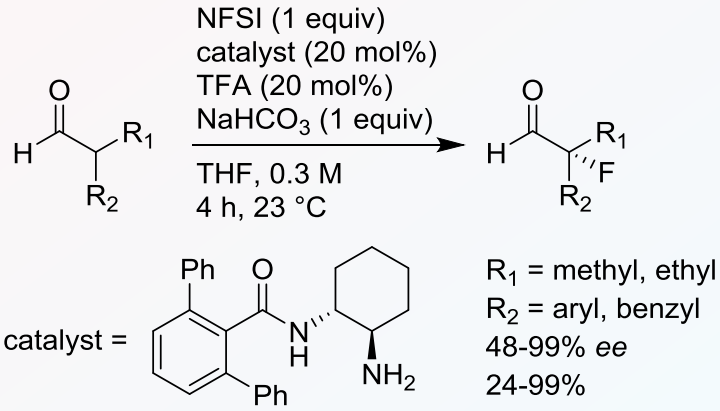
Selected Fluorination Methodologies (Jan–Jun 2015)



Y = C or N
X = Cl or NO_2

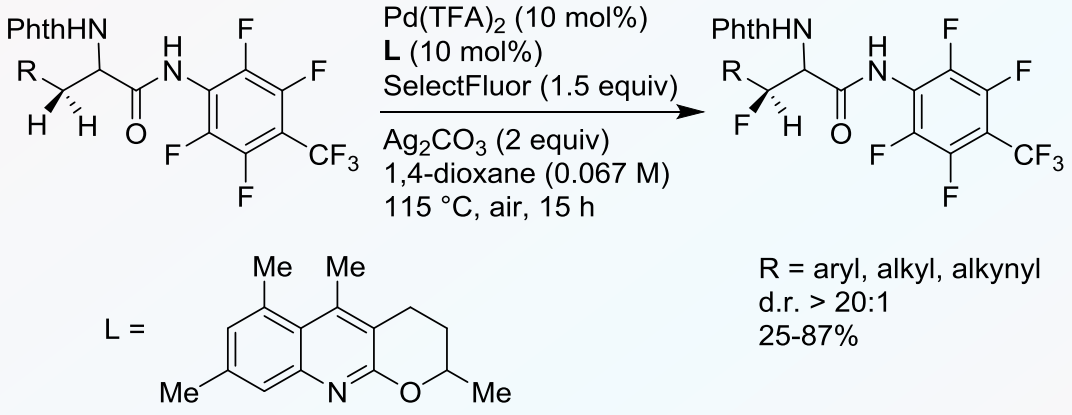
27-99%

Sanford, M. S. *Org. Lett.* **2015**, *17*, 1866.



R_1 = methyl, ethyl
R_2 = aryl, benzyl
48-99% *ee*
24-99%

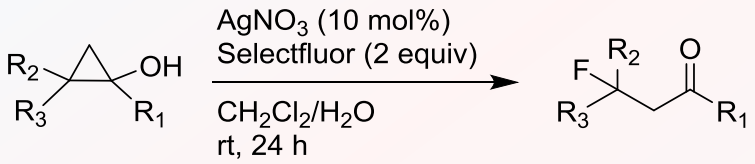
Jacobsen, E. N. *Org. Lett.* **2015**, *17*, 2772.



R = aryl, alkyl, alkynyl
d.r. > 20:1
25-87%

Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 7067.

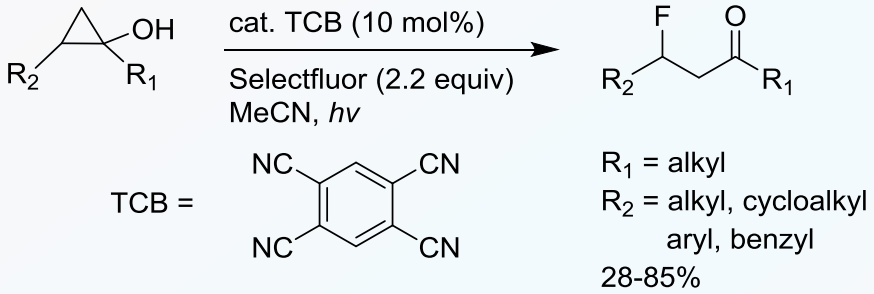
Selected Fluorination Methodologies (Jan–Jun 2015)



*Also $Fe(acac)_3$ as catalyst.

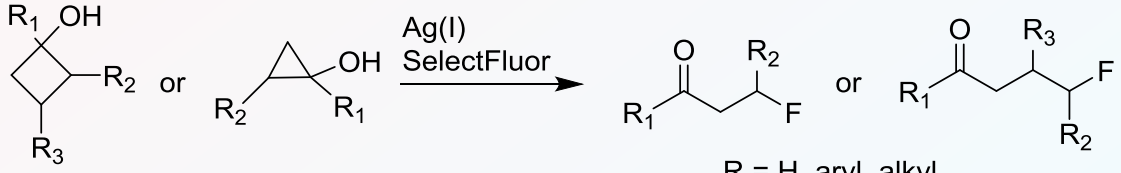
R_1 = alkyl, aryl, benzyl
$R_{2,3}$ = H, alkyl, aryl, benzyl
74-99%

Loh, T.-P. *Org. Biomol. Chem.* **2015**, *13*, 5105.



R_1 = alkyl
R_2 = alkyl, cycloalkyl
aryl, benzyl
28-85%

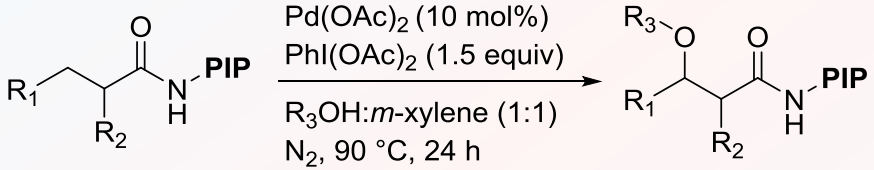
Lectka, T. *Chem. Eur. J.* **2015**, *21*, 8060.



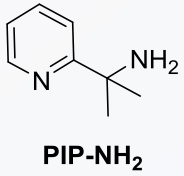
R = H, aryl, alkyl
ring expansion
32-83%

Zhu, C. *J. Am. Chem. Soc.* **2015**, *137*, 3490.

Previous Work from the Shi Group

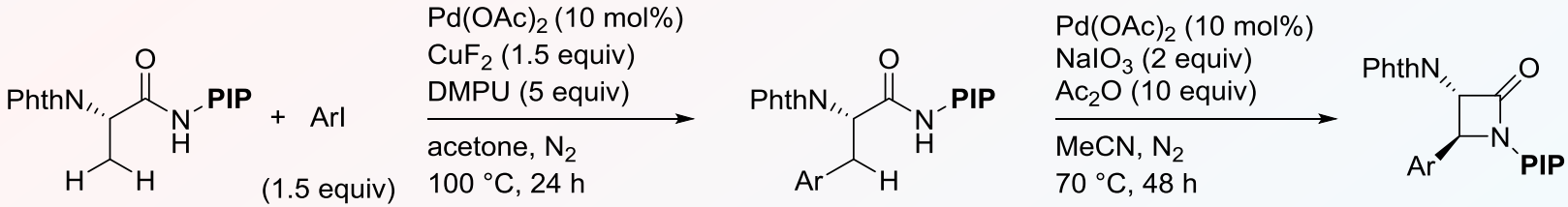


R_1 = H, alkyl
R_2 = H, alkyl, aryl, benzyl, heteroatom
R_3 = aliphatic, deuterated
19-90%



PIP-NH_2

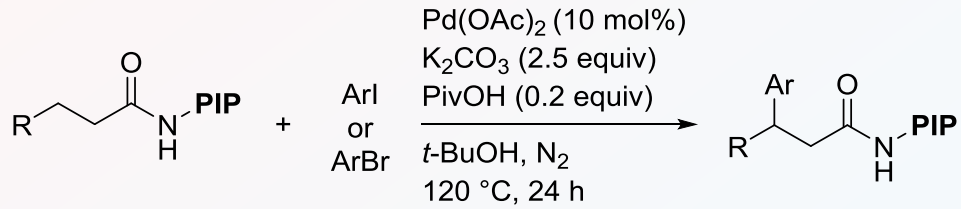
Chem. Sci. **2013**, *4*, 4187.



35-89% (mono/di 25-30:1)

46-86%

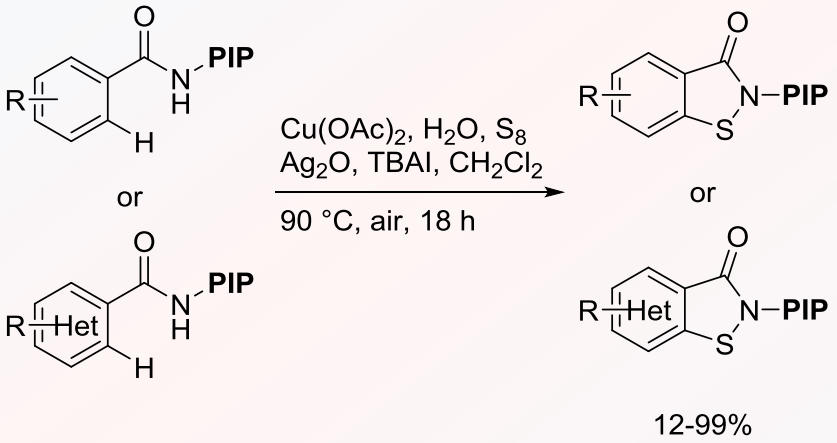
Angew. Chem. Int. Ed. **2013**, *52*, 13588.



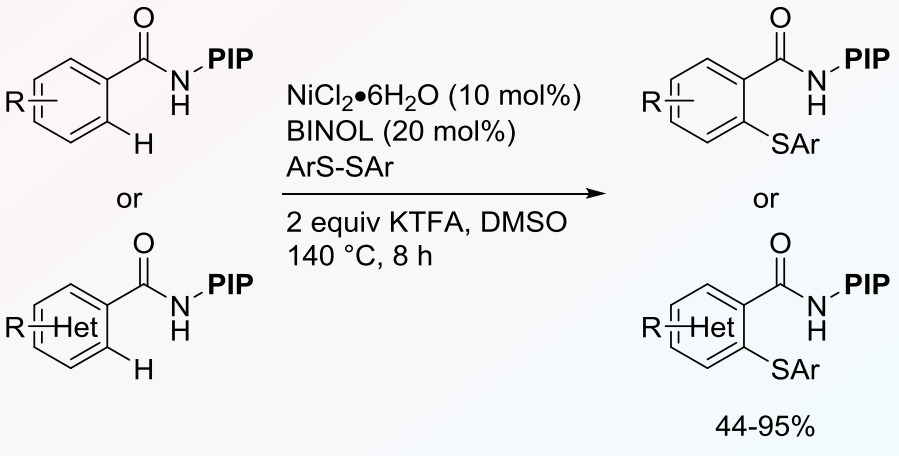
23-90%

Chem. Commun. **2014**, *50*, 8353.

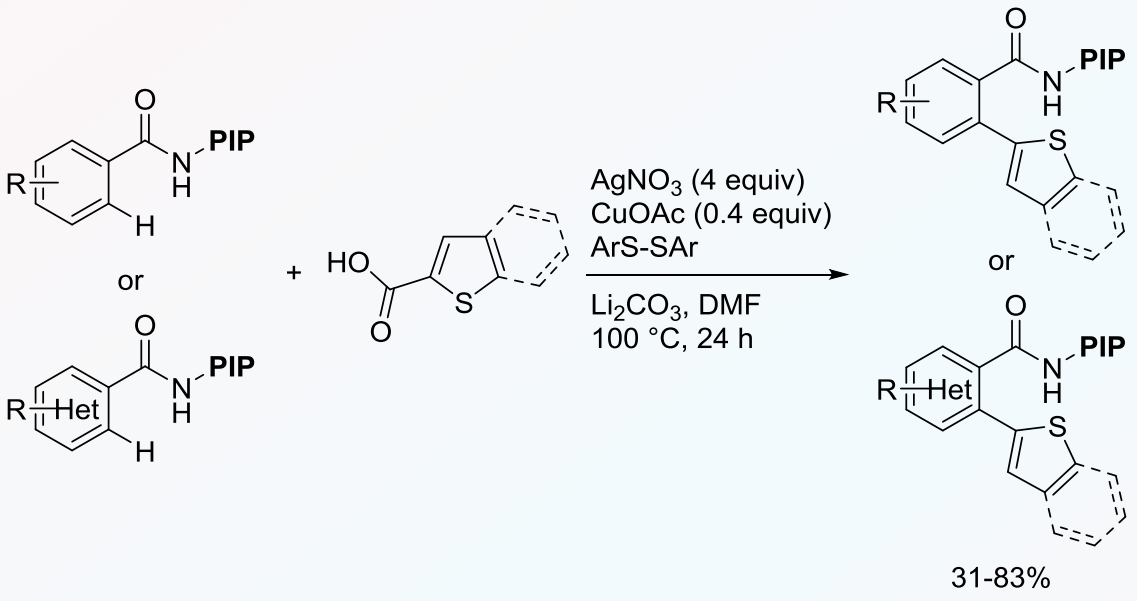
Previous Work from the Shi Group



Org. Lett. **2014**, *16*, 5644.



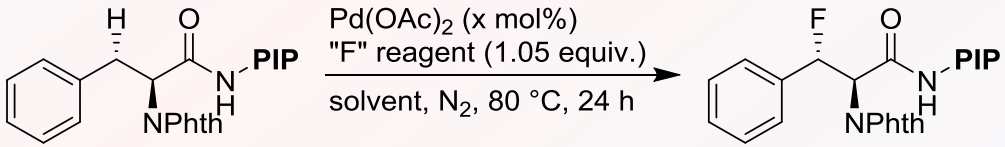
Chem. Commun. **2015**, *51*, 4069.



Org. Lett. **2015**, *ASAP*.

- PIP-NH_2 is available via Sigma-Aldrich (500 mg for $50).

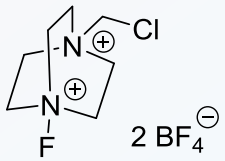
Reaction Conditions Optimization



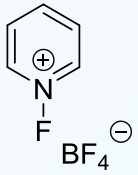
1a **2a**

entry	$Pd(OAc)_2$	"F" reagent	solvent	yield (%)[a]	rsm (%)[b]
1	10 mol%	Selectfluor	MeCN	8	15
2	10 mol%	Selectfluor	Toluene	22	51
3	10 mol%	Selectfluor	DCM	28	40
4	10 mol%	Selectfluor	DCM/MeCN (30:1)	51	12
5	10 mol%	Selectfluor	DCM/*i*-PrCN (30:1)	64	15
6	**6 mol%**	**Selectfluor**	**DCM/*i*-PrCN (30:1)**	**73 (65)[c]**	**21**
7	2 mol%	Selectfluor	DCM/*i*-PrCN (30:1)	53	35
8	6 mol%	FP	DCM/*i*-PrCN (30:1)	10	9
9	6 mol%	FTMP	DCM/*i*-PrCN (30:1)	70	21
10	6 mol%	NFSI	DCM/*i*-PrCN (30:1)	10	61

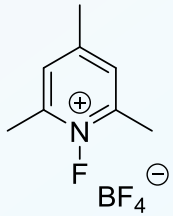
[a]NMR yield with dimethyl malonate as internal standard. [b]rsm = recovered starting material. [c]Isolated yield.



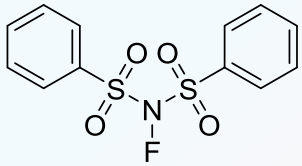
Selectfluor®



FP



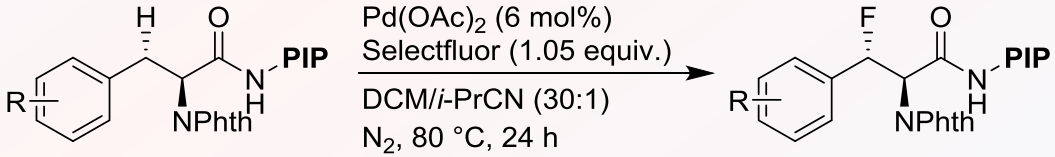
FTMP



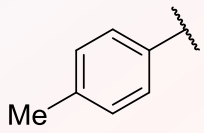
NFSI

DOI: 10.1021/jacs.5b03989

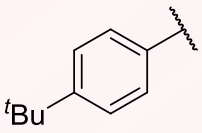
Fluorination of Benzylic Methylene C(sp^3)-H Bonds



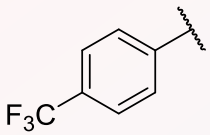
1 (0.3 mmol) **2**



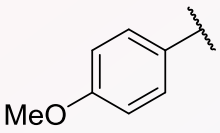
2b, 60%[a]



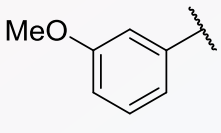
2c, 60%[a]



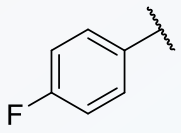
2d, 57%



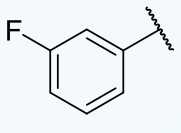
2e, 33%



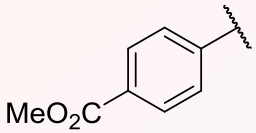
2f, 58%



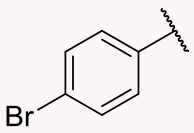
2g, 66%



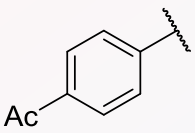
2h, 66%[a]



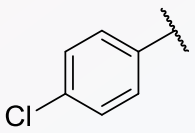
2i, 64%[a]



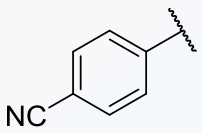
2j, 73%



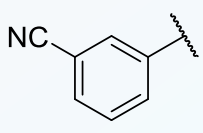
2k, 70%



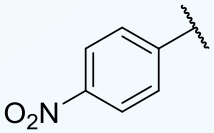
2l, 70%



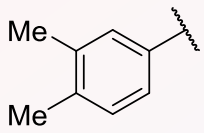
2m, 58%



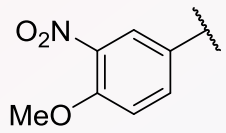
2n, 56%



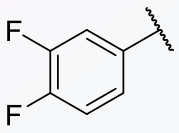
2o, 44%



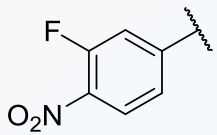
2p, 54%



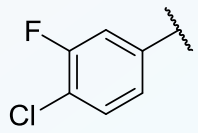
2q, 73%



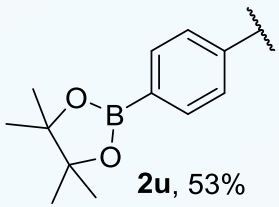
2r, 66%



2s, 44% (53%)[b]



2t, 67%

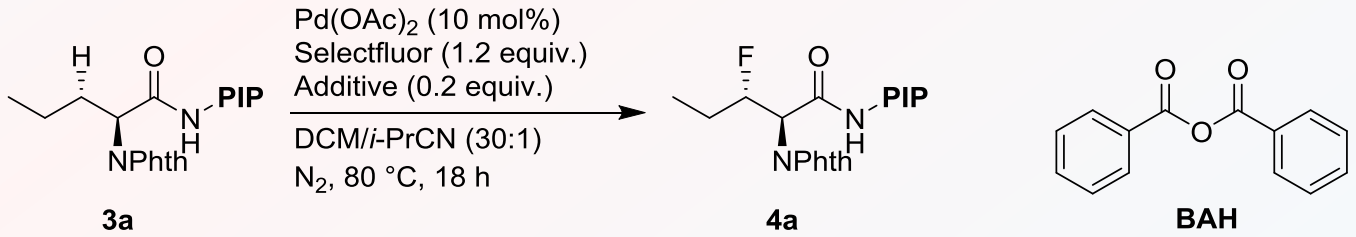


2u, 53%

[a]Structure confirmed by single crystal X-ray diffraction. Syn diastereomer not observed.
[b]10 mol% of $Pd(OAc)_2$.

DOI: 10.1021/jacs.5b03989

Additive Screening for Aliphatic Methylene C(sp^3)-H Bonds



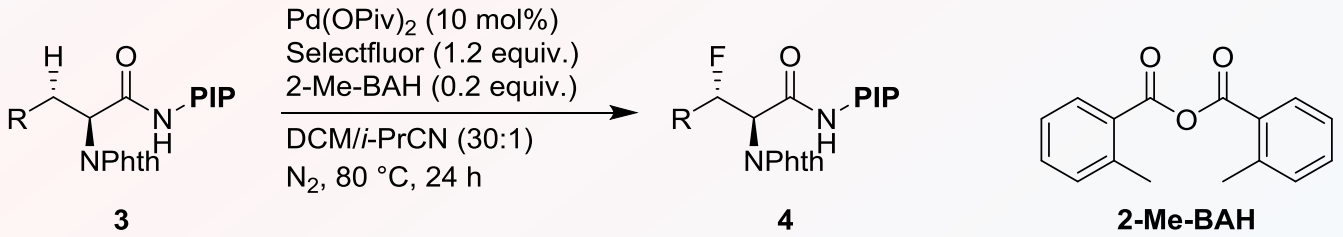
3a **4a** **BAH**

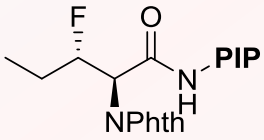
entry	additive	yield (%)[a]	entry	additive	yield (%)[a]
1	none	35	10	BAH	40
2	AcOH	25	11	2-Cl-BAH	33
3	PivOH	30	12	4-AcNH-BAH	36
4	4-MeO-$PhCO_3H$	33	13	4-NO_2-BAH	30
5	TFA	13	14	2-MeO-BAH	32
6	Ac_2O	39	15	2-Me-BAH	50
7	succinic anhydride	27	**16[b]**	**2-Me-BAH**	**54 (46)[c]**
8	isobutyric anhydride	43	17	2,4,6-*tri*-Me-BAH	29
9	Boc_2O	33	18	2-Ph-BAH	30

[a]NMR yield with dimethyl malonate as internal standard. [b]$Pd(OPiv)_2$ instead of $Pd(OAc)_2$ 24 h. [c]Isolated yield.

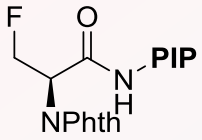
DOI: 10.1021/jacs.5b03989

Fluorination of Aliphatic Methylene C(sp^3)-H Bonds

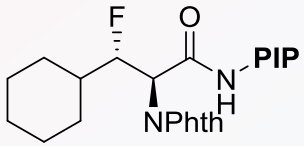




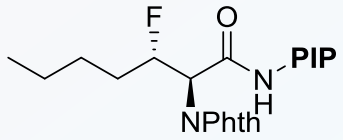
4a, 46%, 99% ee (rsm = 23%)



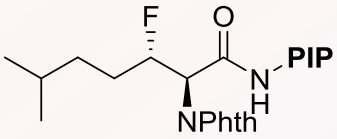
4b, 33% (rsm = 37%)



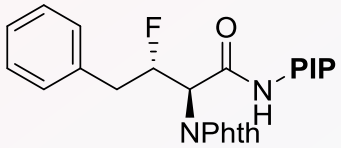
4c, 32% (rsm = 42%)



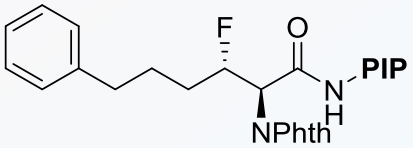
4d, 45% (rsm = 15%)



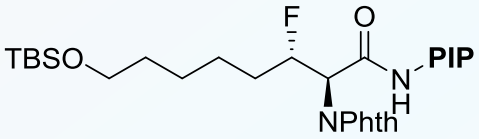
4e, 39% (rsm = 14%)



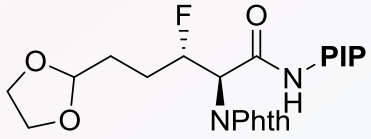
4f, 32% (rsm = 34%)



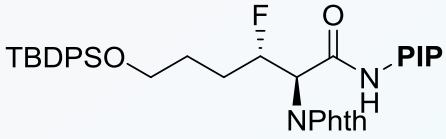
4g, 42% (rsm = 26%)



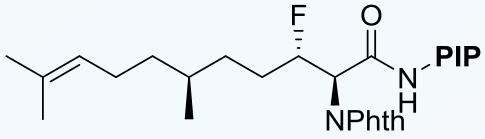
4h, 46% (rsm = 25%)



4i, 41% (rsm = 25%)



4j, 44% (rsm = 24%)



4k, 37% (rsm = 31%)

Syn diastereomer not observed.

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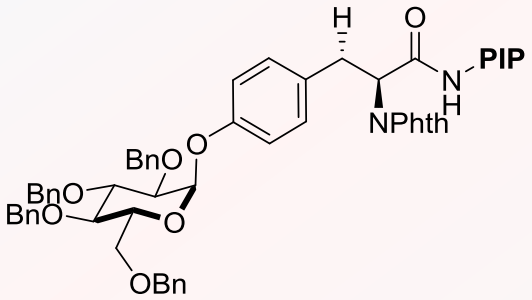
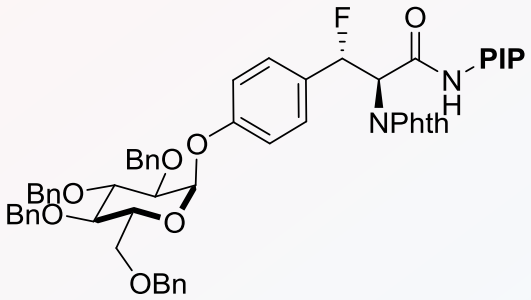
Fluorinations of Complex Molecules



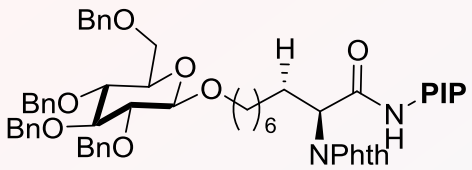
5

$Pd(OAc)_2$ (6 mol%)
Selectfluor (1.05 equiv)

DCM/*i*-PrCN (30:1)
N_2, 80 °C, 24 h



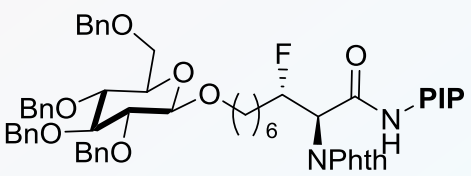
6, 53%



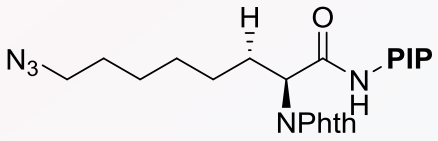
7

$Pd(OPiv)_2$ (10 mol%)
Selectfluor (1.2 equiv)
2-Me-BAH (0.2 equiv)

DCM/*i*-PrCN (30:1)
N_2, 80 °C, 24 h



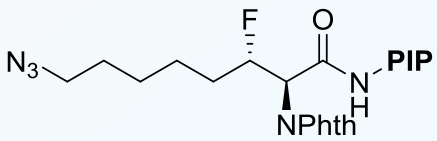
8, 30%



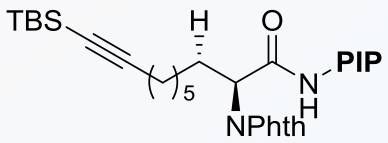
9

$Pd(OPiv)_2$ (10 mol%)
Selectfluor (1.2 equiv)
2-Me-BAH (0.2 equiv)

DCM/*i*-PrCN (30:1)
N_2, 80 °C, 24 h



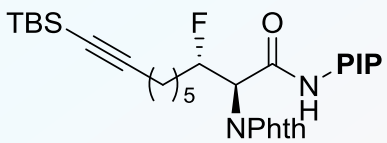
10, 31%



11

$Pd(OPiv)_2$ (10 mol%)
Selectfluor (1.2 equiv)
2-Me-BAH (0.2 equiv)

DCM/*i*-PrCN (30:1)
N_2, 80 °C, 24 h



12, 46%

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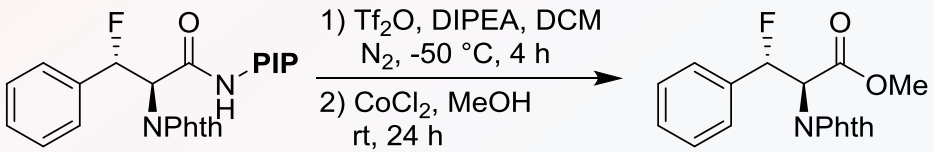
Removal of PIP Group



2a

13, 52% (98.8% ee)

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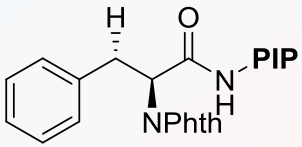
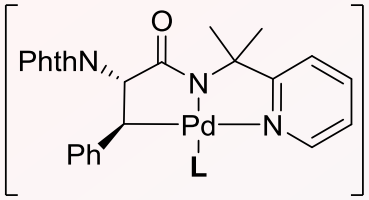
Mechanistic Considerations



1a

$Pd(OAc)_2$ (1 equiv)
i-PrCN (10 equiv), DCM

rt, o/n, 87%

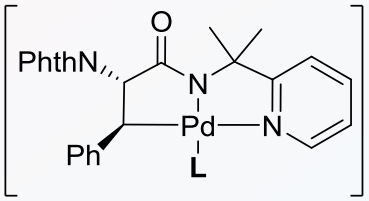


INT-A (**L** = *i*-PrCN)

^1H and ^{13}C NMR

pyridine (2 equiv)

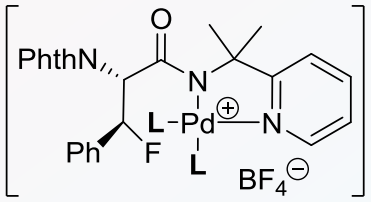
DCM, rt, 5 h, 84%



14 (**L** = pyridine)

X-ray

Selectfluor (1.05 equiv)
d_3-MeCN, rt, 5-10 min
78%

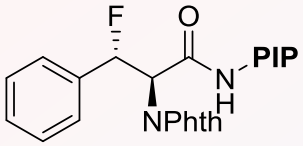


INT-C (**L** = d_3-MeCN)

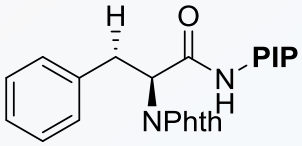
observed by ^1H and ^{19}F NMR

NH_4Cl, Na_2S

rt, 10 min, 86%



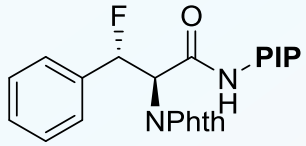
2a



1a

INT-A (6 mol%)
AcOH (12 mol%)
Selectfluor (1.05 equiv)

DCM/*i*-PrCN (30:1)
N_2, 80 °C, 24 h



2a, 70% (18% RSM)
w/o AcOH: 12% (75% RSM)

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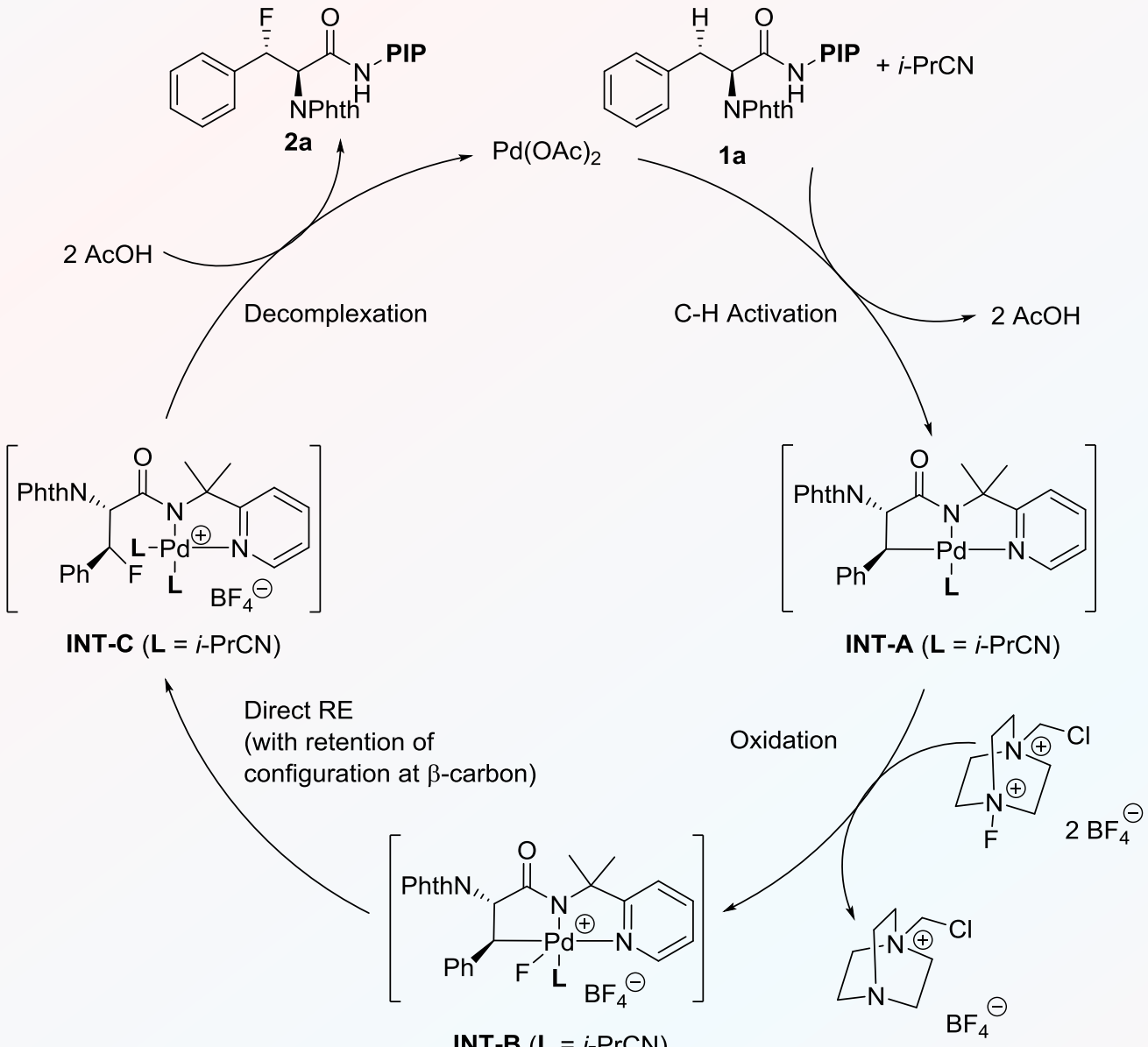
Proposed Mechanism



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Conclusions

- Strengths:
  - Expansion of the PIP/Pd(II) methodology.
  - PIP-NH_2 is easy to make/install.
  - Excellent stereoselectivity/regioselectivity.
  - A range of functional group tolerance.
  - Mechanism based on isolated reaction intermediates.

- Weaknesses:
  - Lots of recovered SM (better optimization can address this).
  - Methodology requires a linear sequence to place and remove PIP group (especially with moderate yields).
  - Removal of phthalimide protecting group?