Palladium (II)-Catalyzed Enantioselective C-H Arylation of Cyclopropylmethylamines

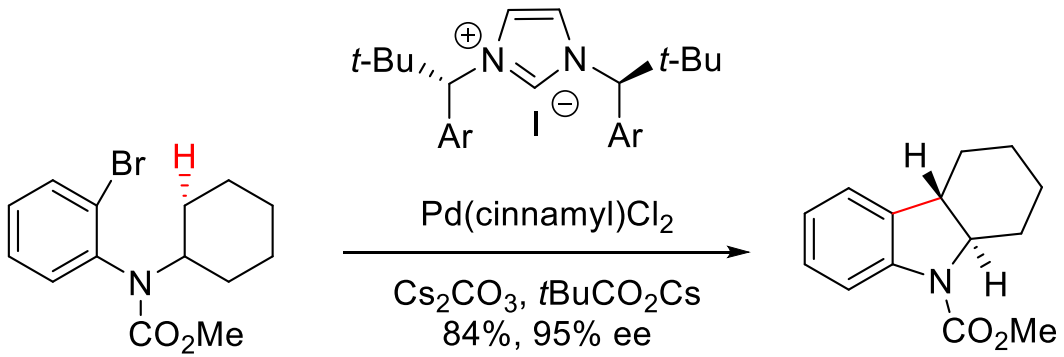
Chan, K. S. L.; Fu, H-Y.; Yu, J-Q.
J. Am. Chem. Soc. **2015**, *137*, 2042-2046.

John Milligan
Current Literature
Wipf Group Meeting- February 28, 2015

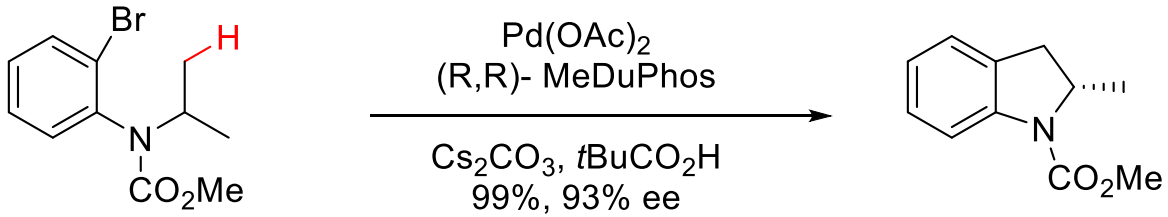
sp_3 C-H Activation

- "If we can find ways to use C-H bonds as versatile functional groups we can revolutionize the rules that have influenced our strategies for assembling molecules over the last 100 years" – L. McMurray, F. O'Hara, M. J. Gaunt. *Chem. Soc. Rev.* **2011**, *40*, 1885.
- See also: J. Hammill frontiers talk (9/28/12)

Enantioselective C-H activation

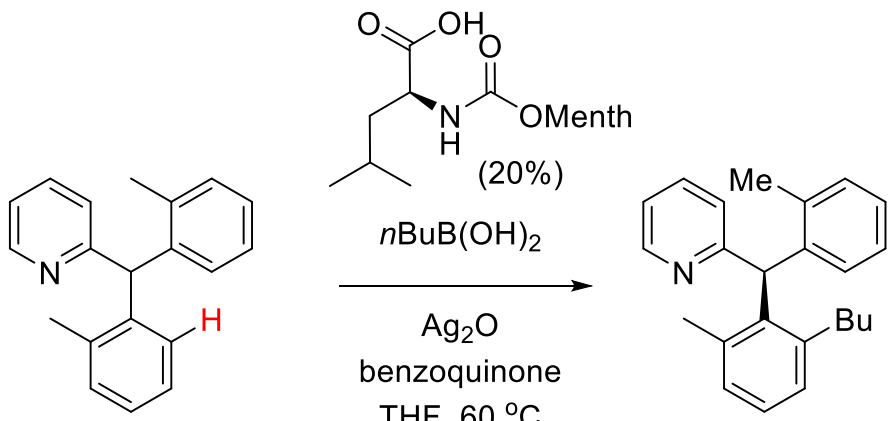


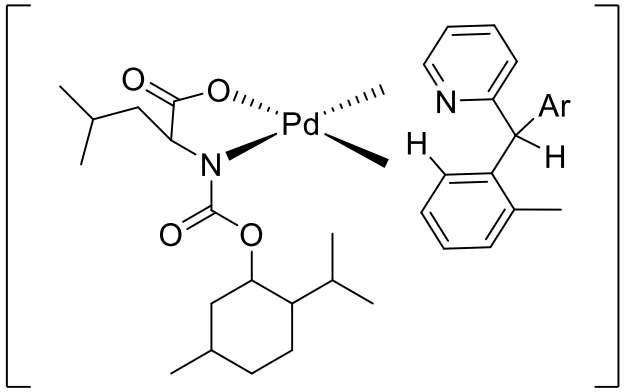
Nakanishi, M.; Kaayev, D.; Besnard, C.; Kundig, E. P. *Angew. Chem. Int. Ed.* **2011**, *50*, 7438-7441.



Anas, S.; Cordi, A.; Kagan, H. B. *Chem. Commun.* **2011**, *47*, 11483-11485.

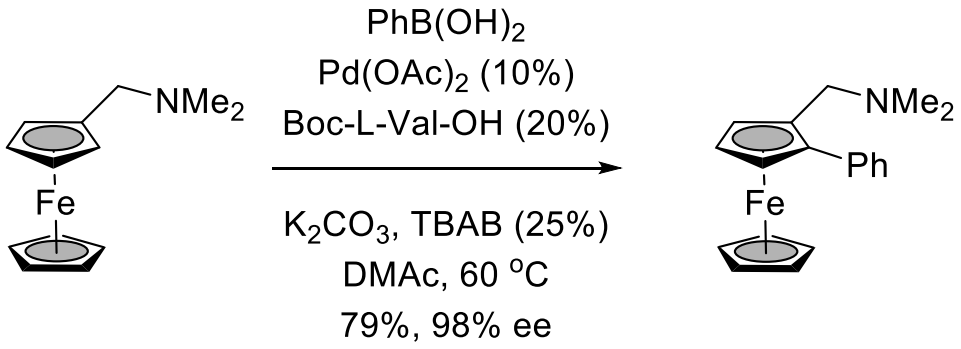
Yu Group: Amino Acid Ligands



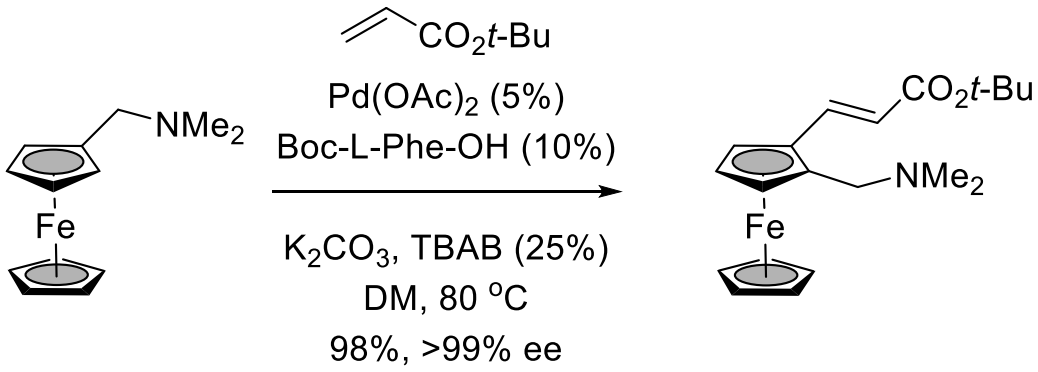


Shi, B-F.; Maugel, N.; Zhang, Y-H.; Yu, J-Q. *Angew. Chem. Int. Ed.* **2008**, *47*, 4882-4886.

Amino Acid Ligands

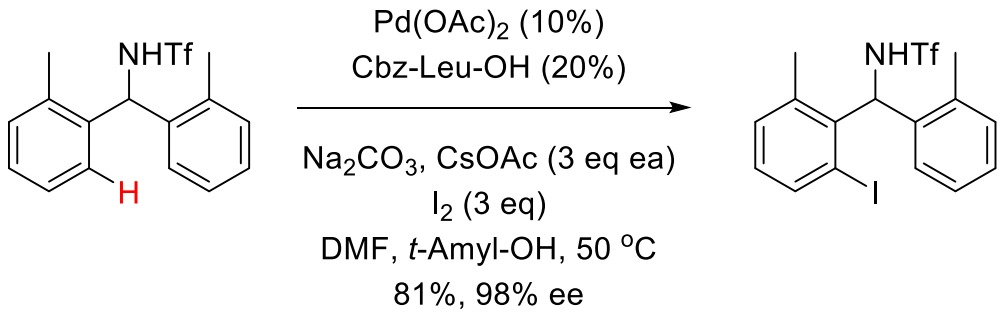


Gao, D-W.; Shi, Y-C.; Gu, Q.; Zhao, Z-L.; You, S-L. *J. Am. Chem. Soc.* **2013**, *135*, 86-89.

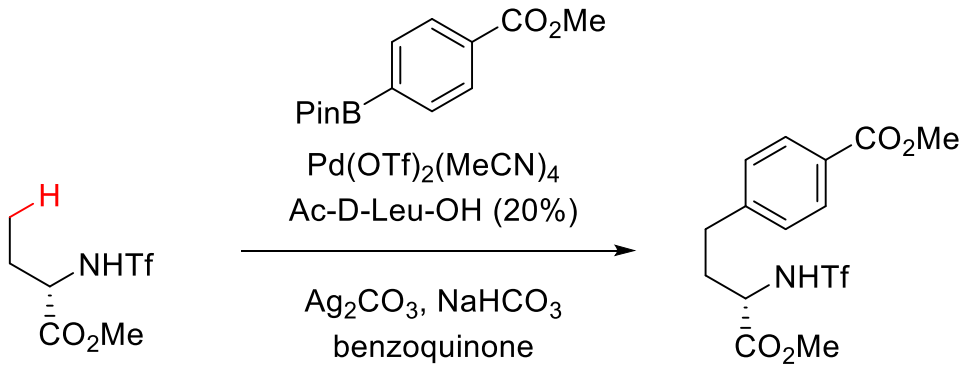


Pi, C.; Li, Y.; Cui, X.; Zhang, H.; Han, Y.; Wu, Y. *Chem. Sci.* **2013**, *4*, 2675.

N-Tf Directing Group

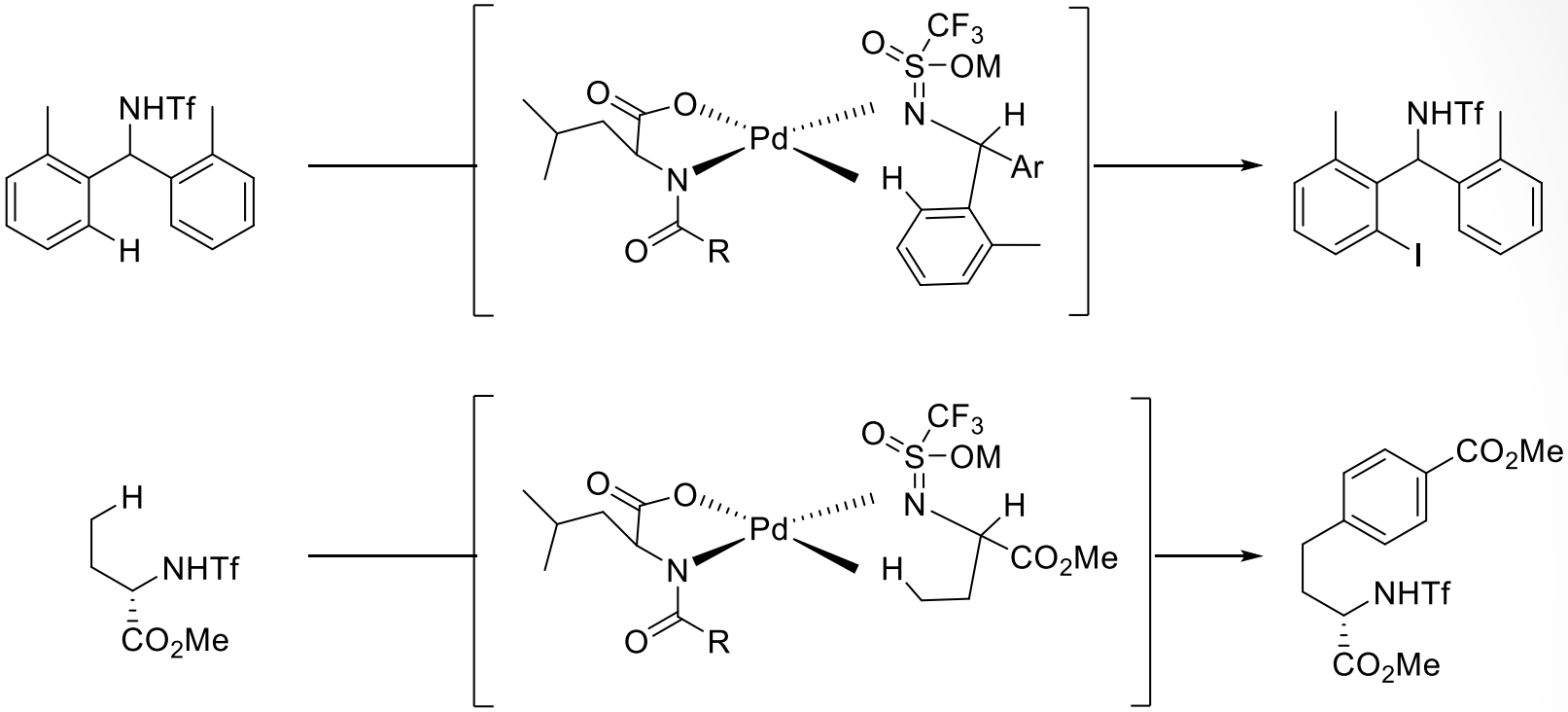


Chu, L.; Wang, X-C.; Moore, C. E.; Rheingold, A. L.; Yu, J-Q. *J. Am. Chem. Soc.* **2013**, 135, 16344-16347.

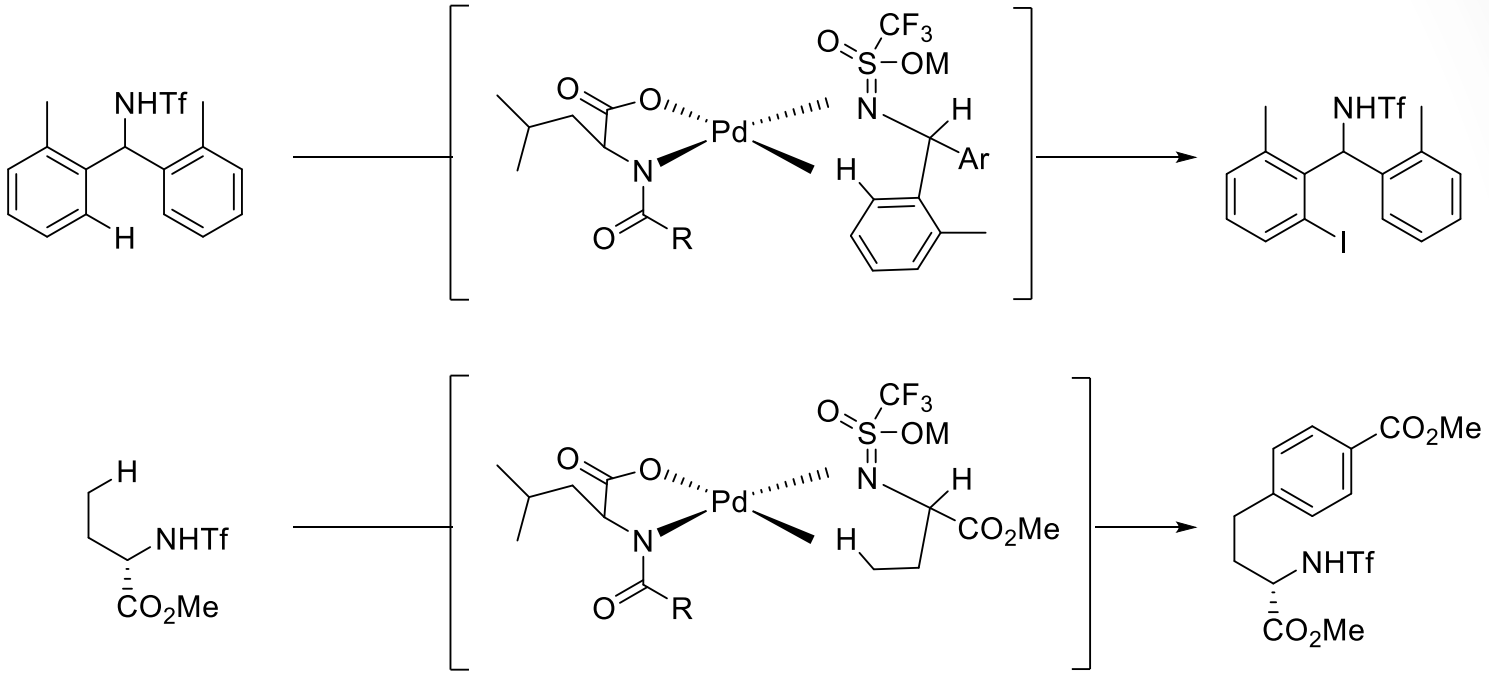


Chan, K. S. L.; Masayuki, W.; Chu, L.; Laforteza, B. N.; Miura, M.; Yu, J-Q. *Nature Chem.* **2014**, *6*, 146.

Previous Work:



Previous Work:



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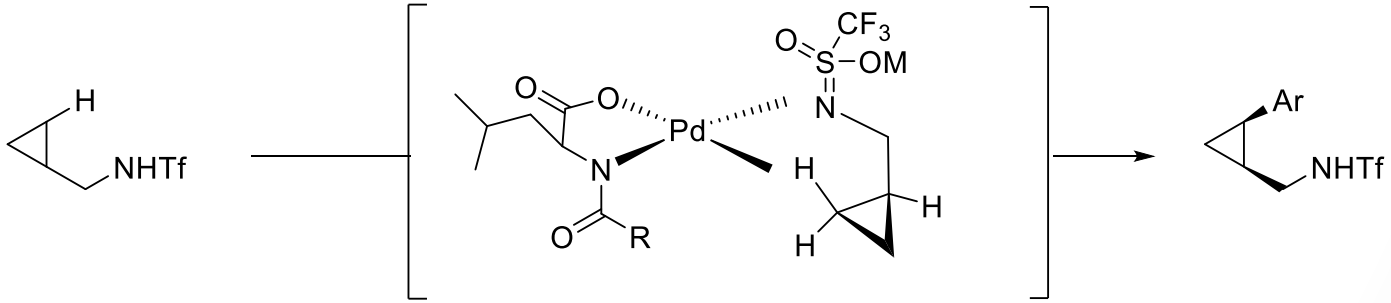

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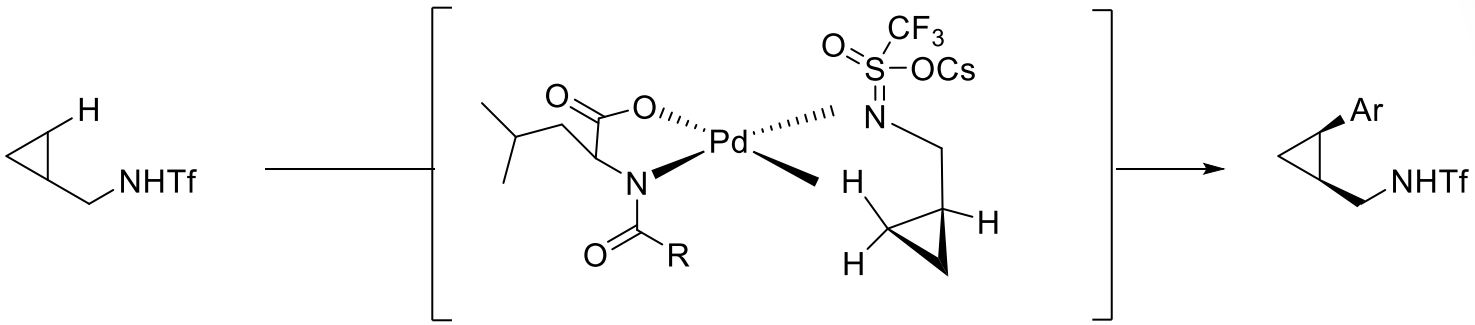
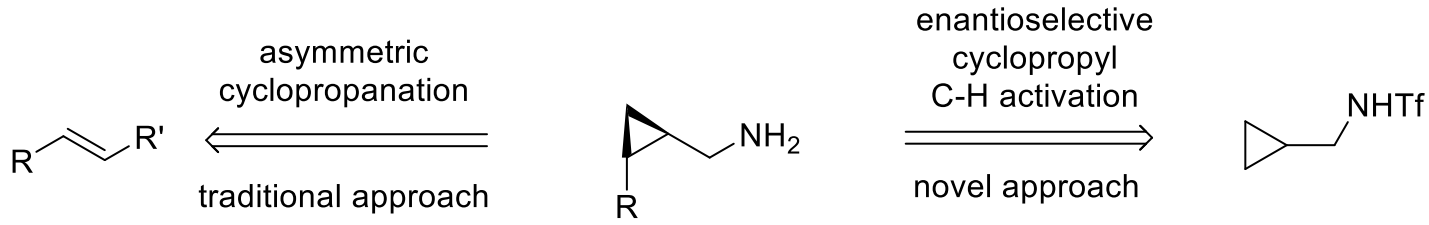
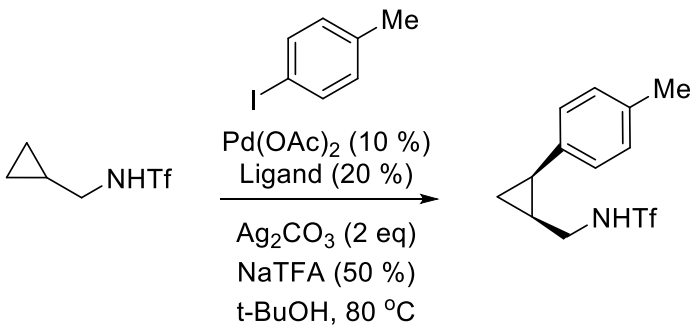




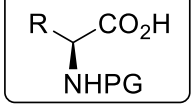
Lebel, H.; Marcoux, J-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 911-1050.

Optimization

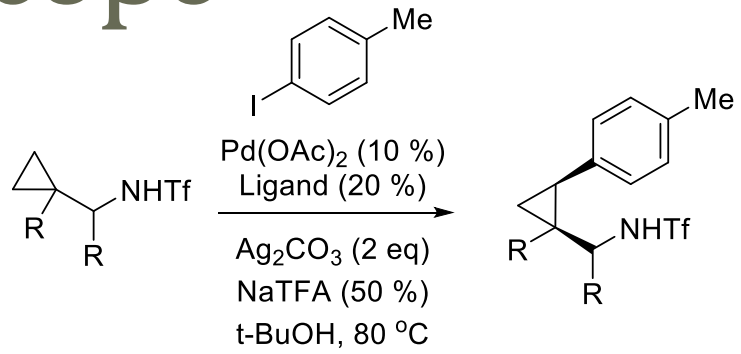


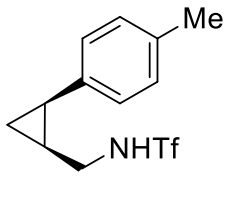
entry	R	PG	yield	ee
1	Me	Ac	84	76.3
2	*n*-Pr	Ac	89	93.6
3	*i*-Bu	Ac	87	96.0
4	*s*-Bu	Ac	94	96.0
5	*i*-Pr	Ac	94	87.8
6	*i*-Pr	Formyl	40	55.8
7	*i*-Pr	COBn	64	89.9
8	*i*-Pr	CO*t*-Bu	37	56.3
9	*i*-Pr	$COCF_3$	70	94.2
10	*i*-Pr	CO_2Me	70	98.1
11	*s*-Bu	Boc	94	98.5
12	*i*-Pr	Boc	91	98.8
13	*i*-Pr	Fmoc	93	98.2
14	*i*-Pr	Cbz	85	98.5
15	*i*-Pr	Troc	76	95.3

Ligand:



Amine Scope





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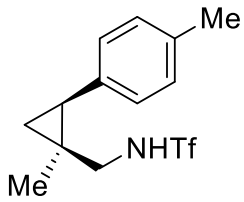

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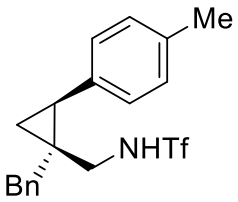

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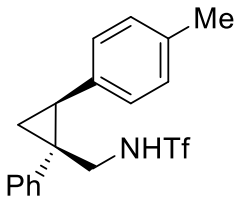

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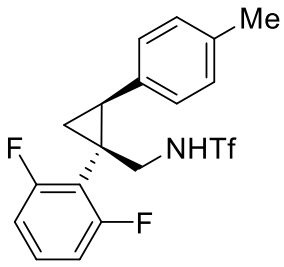

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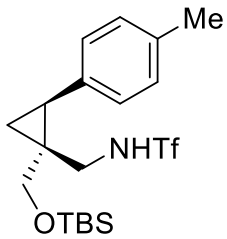

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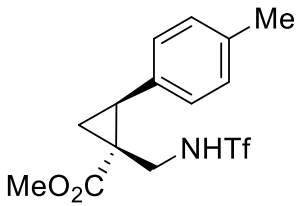

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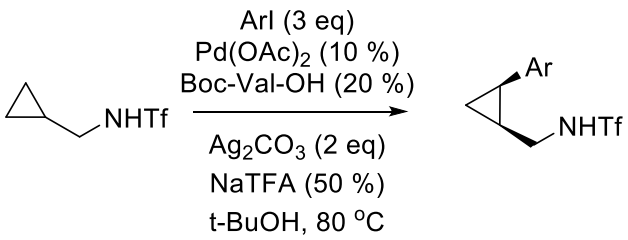
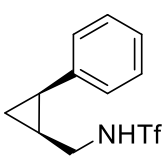
Aryl Iodide Scope





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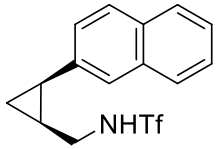

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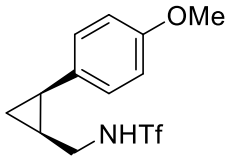

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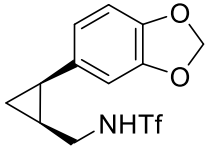

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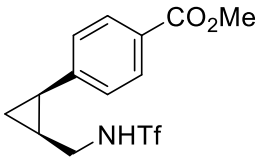

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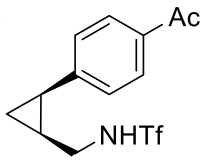

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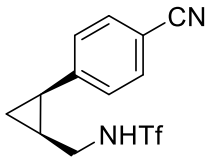

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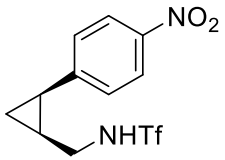

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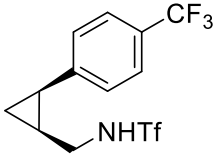

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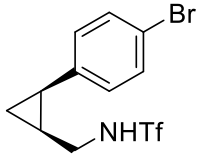

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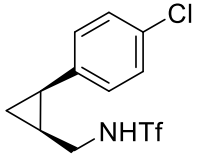

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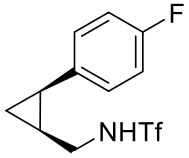

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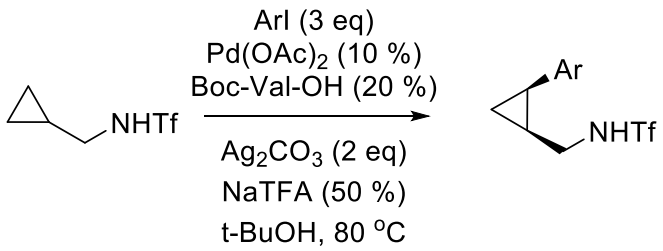

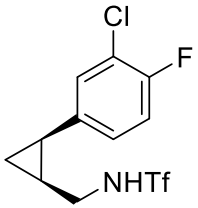

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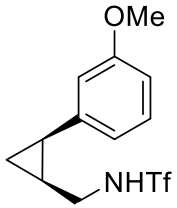

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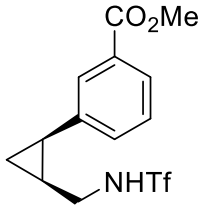

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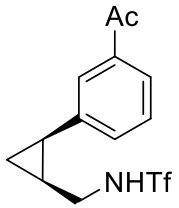

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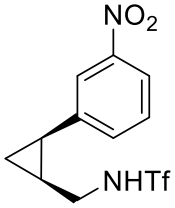

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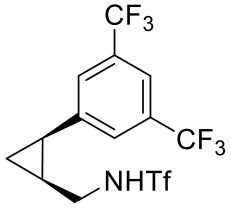

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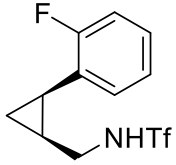

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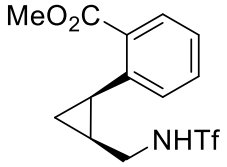

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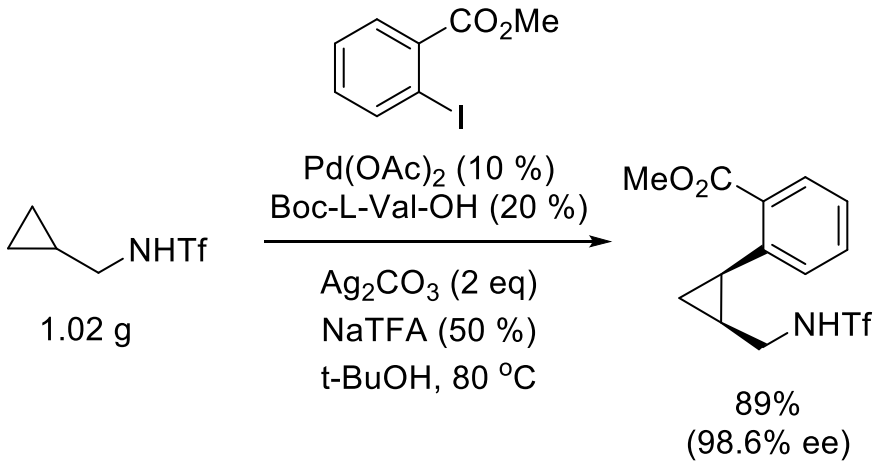
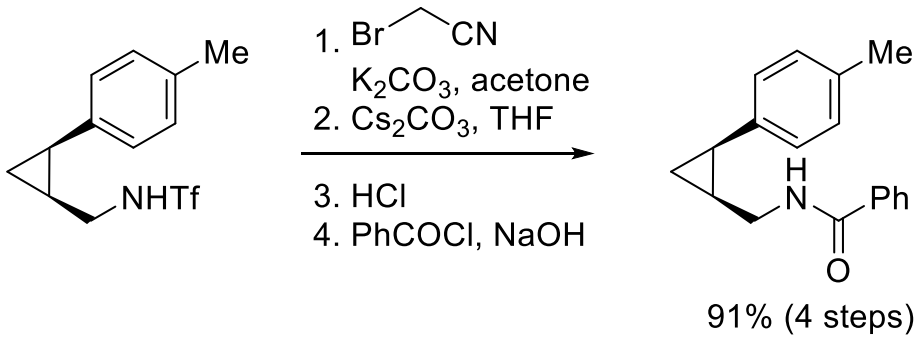
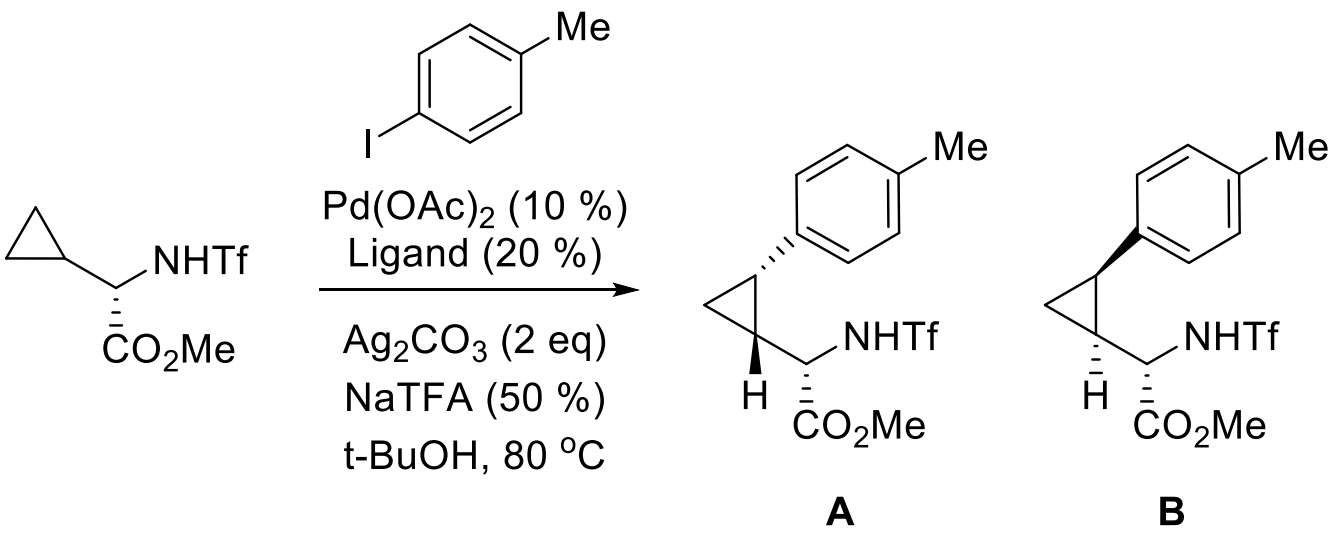
Scale up and deprotection



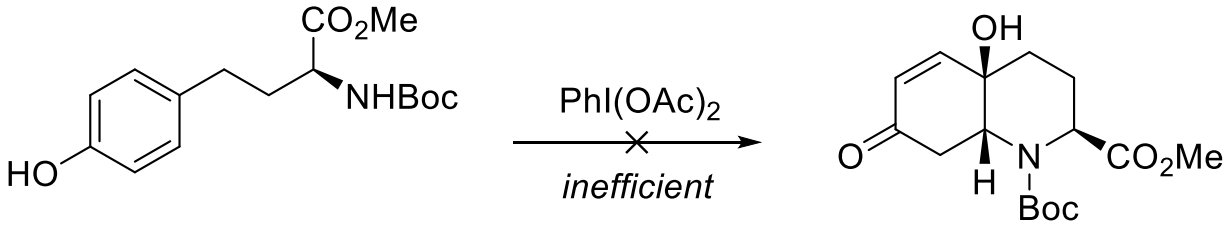


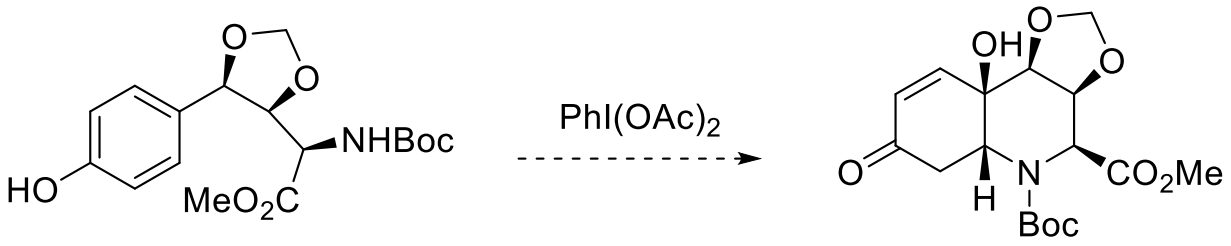
Overriding Stereochemistry

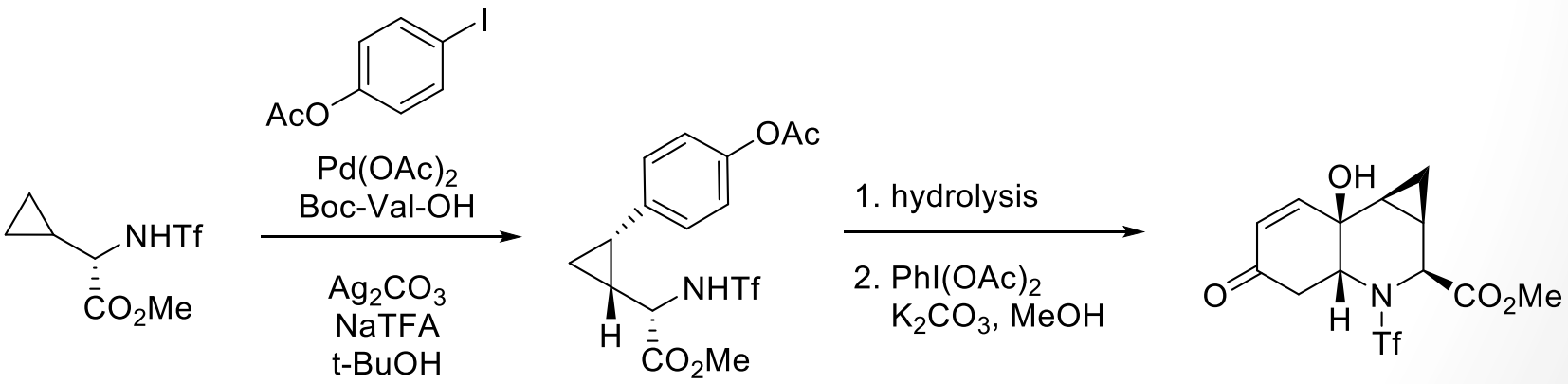


entry	ligand	yield	**A:B**
1	Boc-L-Val-OH	35%	>20:1
2	Boc-Gly-OH	11%	2:1
3	Boc-D-Val-OH	28%	1:>20

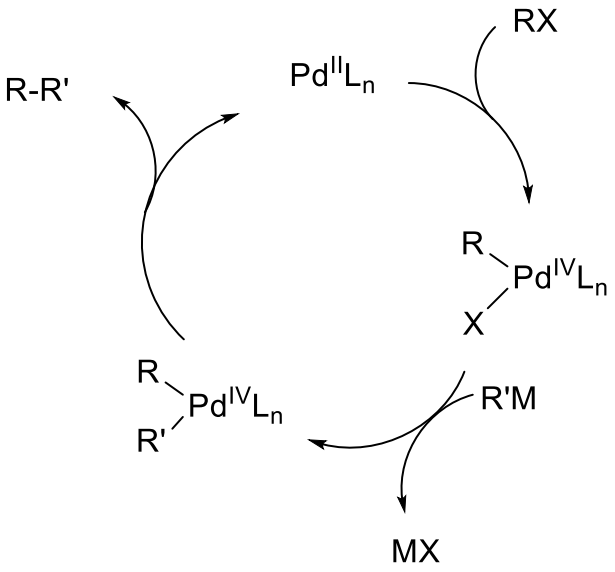
Wipf Group Application?

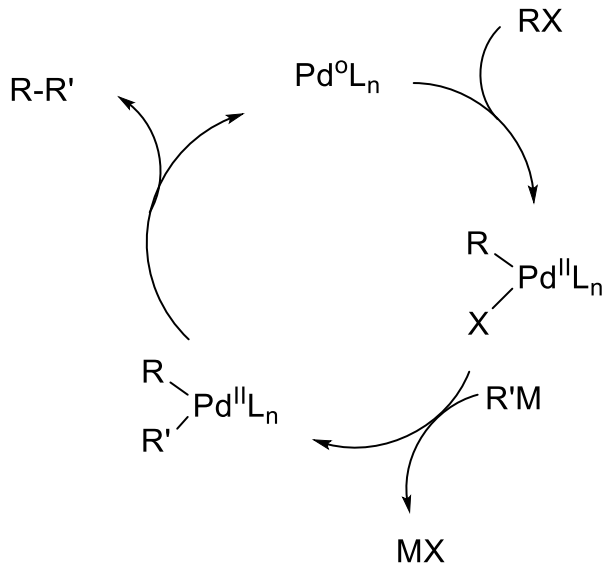




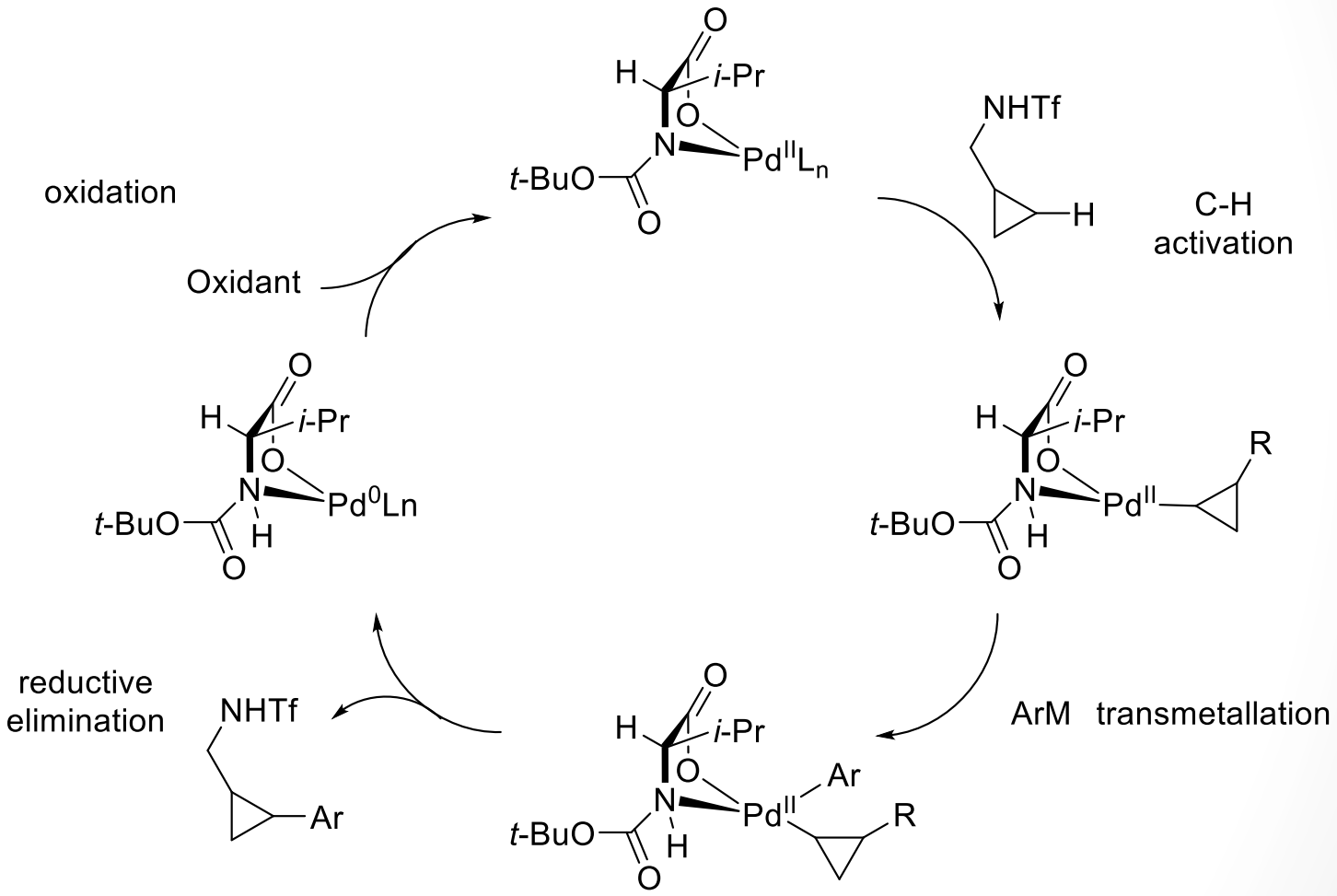


Pd(0)/Pd(II) vs. Pd(II)/Pd(IV)

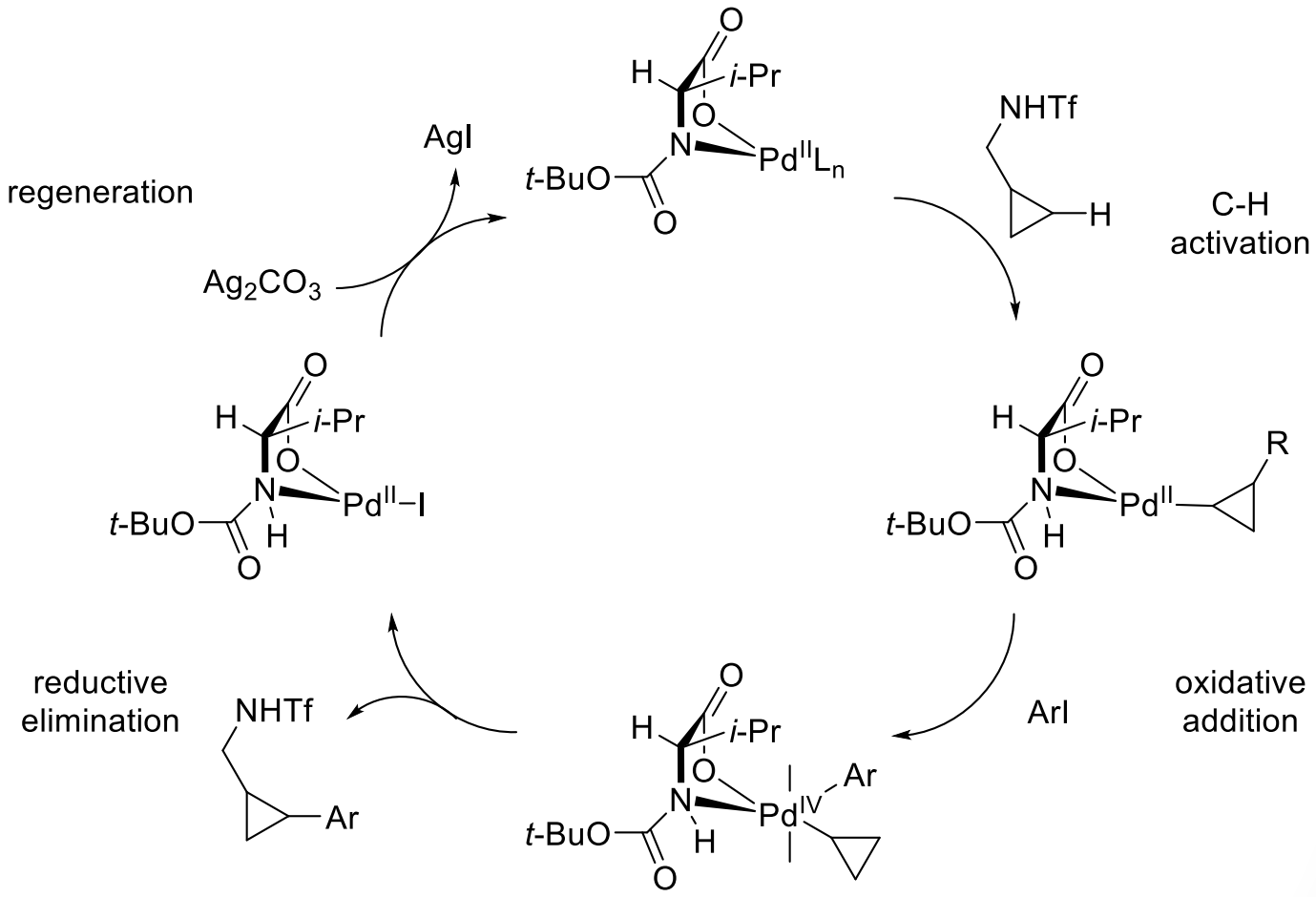




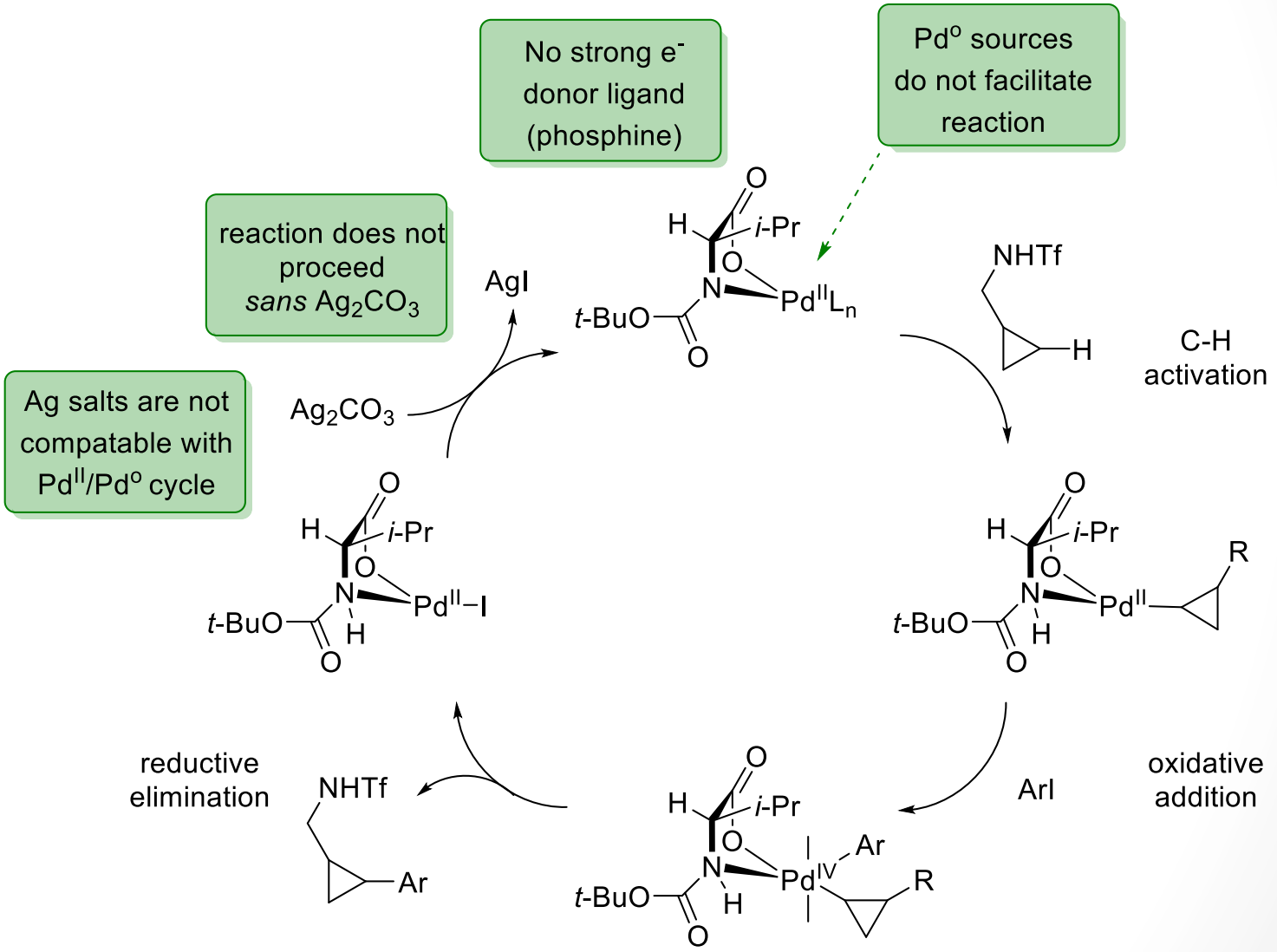
Pd(0)/Pd(II) cycle



Pd(II)/Pd(IV) cycle



Pd(II)/Pd(IV) cycle: support



Conclusion

- A highly enantioselective C-H arylation of cyclopropylmethylamines has been developed
- This constitutes the first enantioselective C-H arylation via a Pd(II)/Pd(IV) catalytic cycle
- Useful method for the synthesis of diverse chiral cylcopropanes