

Palladium-Catalyzed Enantioselective Aza-Claisen Rearrangement Reactions

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Introduction

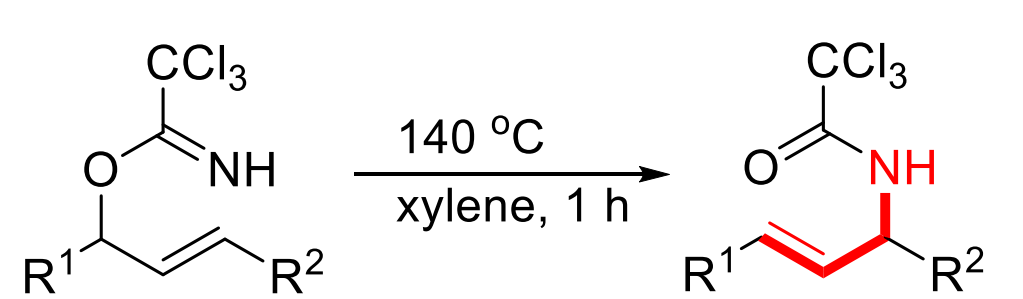
Claisen Rearrangement



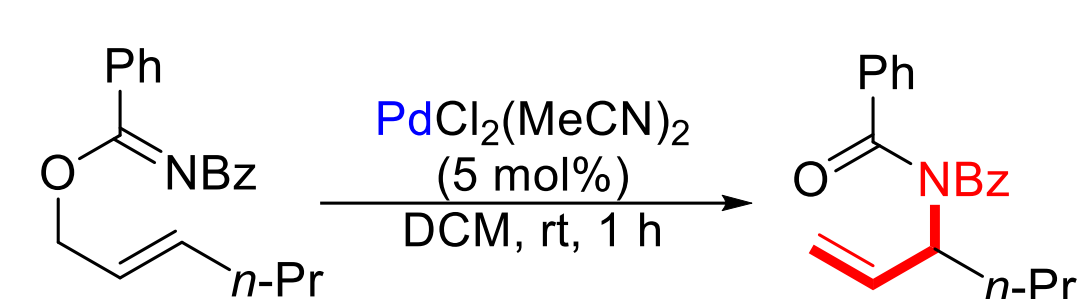
Aza-Claisen Rearrangement



Overman Rearrangement (1974)

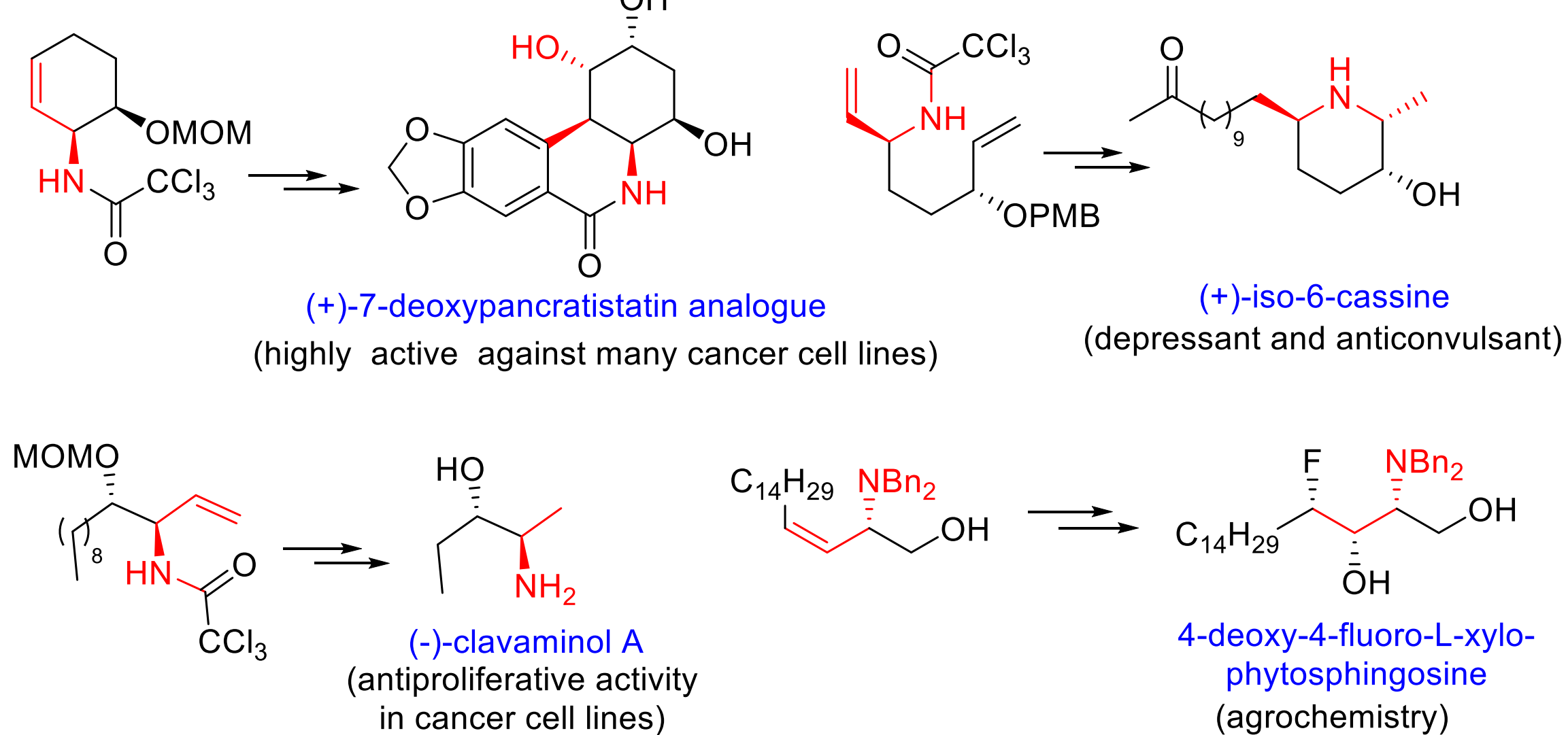


Pd(II) Catalyzed (1976)

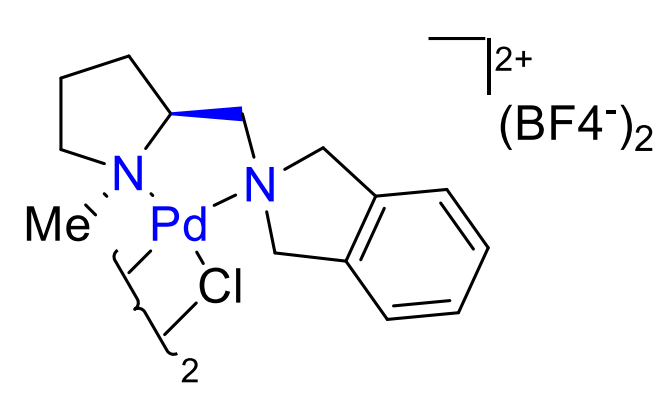
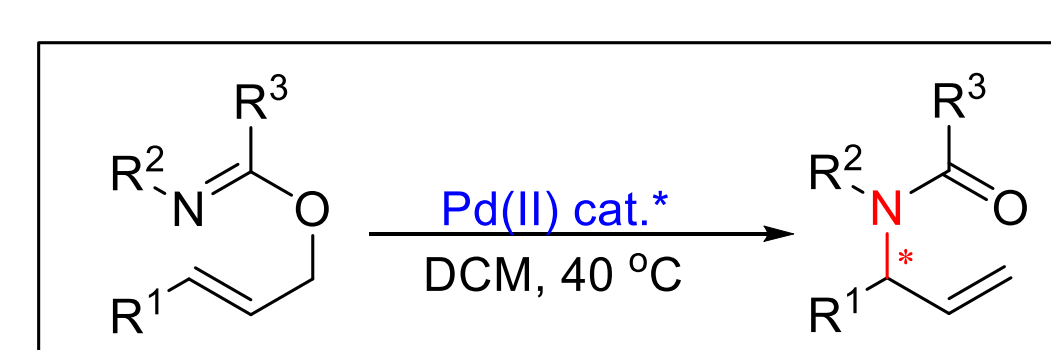


Synthesis of Natural Products Using Overman Rearrangement

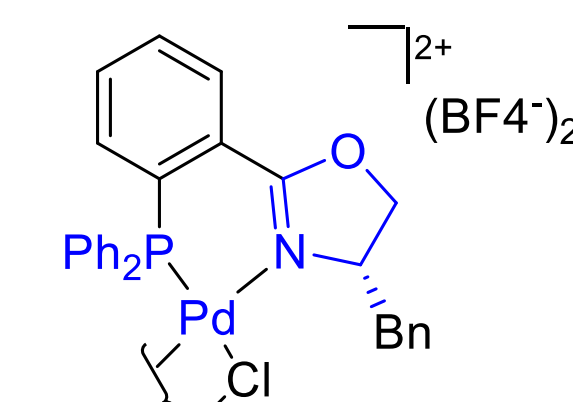
Allylic Amines: Antifungal, Antihistamine and Antidepressant properties



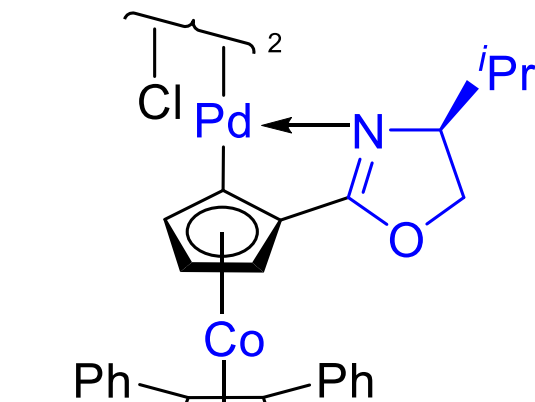
Prior Work



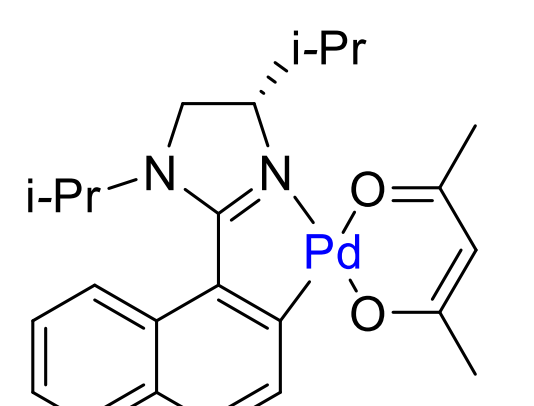
chiral diamine ligands
5 mol%, 40 °C, 2d
69%, 55% ee
(R¹ = n-Pr; R² = p-MeO-C₆H₄; R³ = Ph)



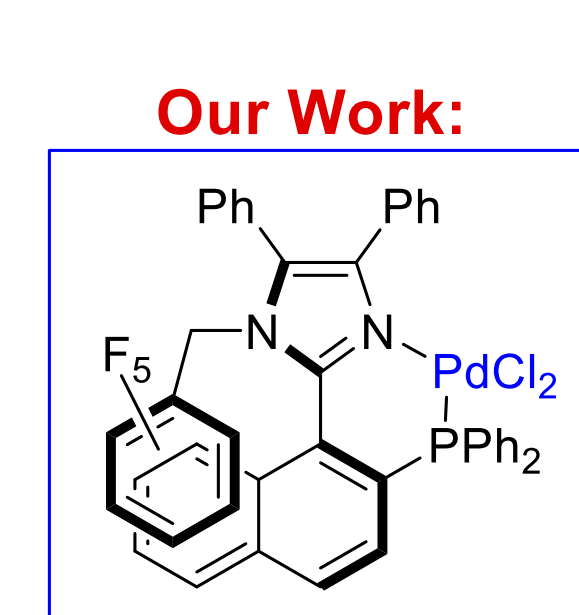
phosphino-oxazoline ligands
5 mol%, 40 °C, 1d
41%, 76% ee
(R¹ = n-Pr; R² = p-MeO-C₆H₄; R³ = Ph)



COP-Cl
5 mol%, rt, 60 h
(R¹ = n-Pr; R² = p-MeO-C₆H₄; R³ = CF₃)
Z-isomer 92%, 92% ee
E-isomer 78%, 89% ee

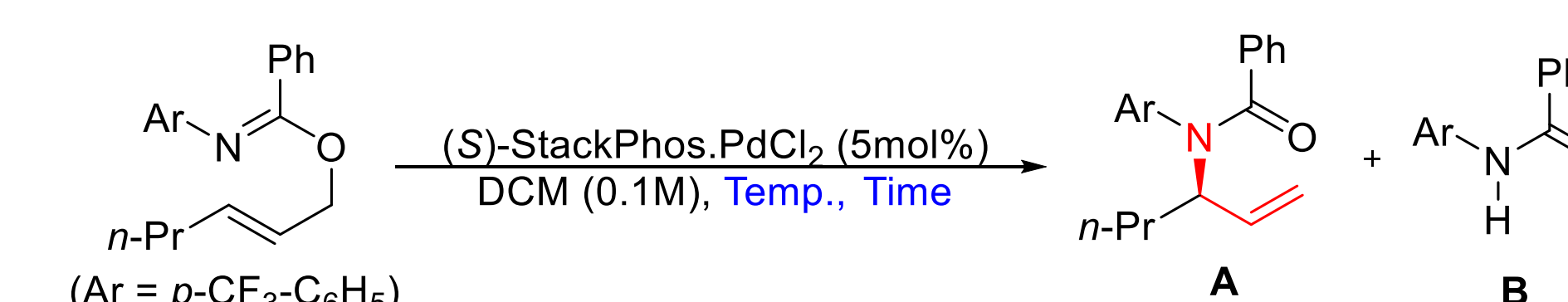


PIN
10 mol%, 40 °C, 24 h
10%, racemic
(R¹ = n-Pr; R² = H; R³ = CCl₃)



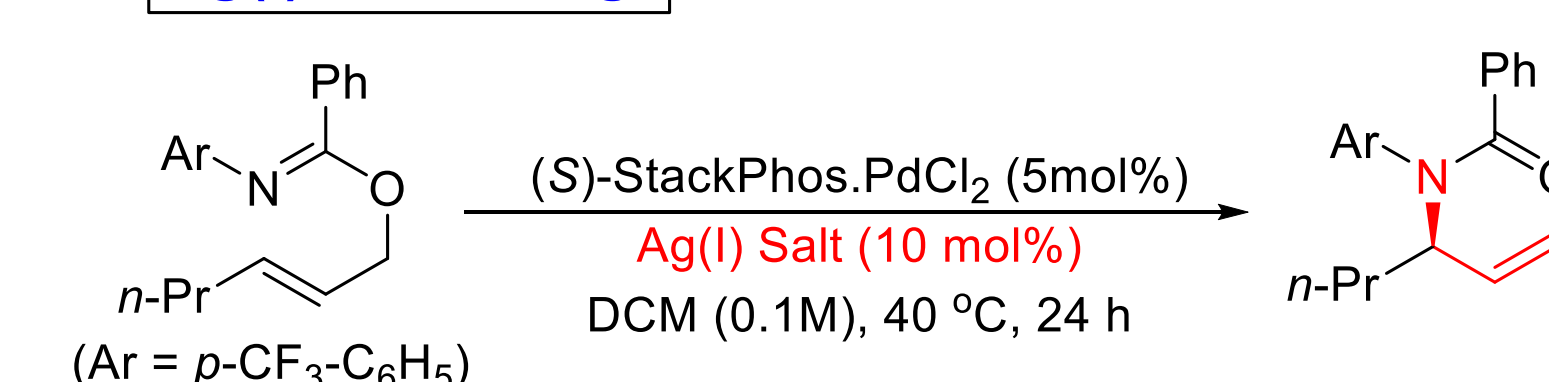
(S)-StackPhos.PdCl₂
Axially Chiral P,N-Ligand-Pd complex

Optimization



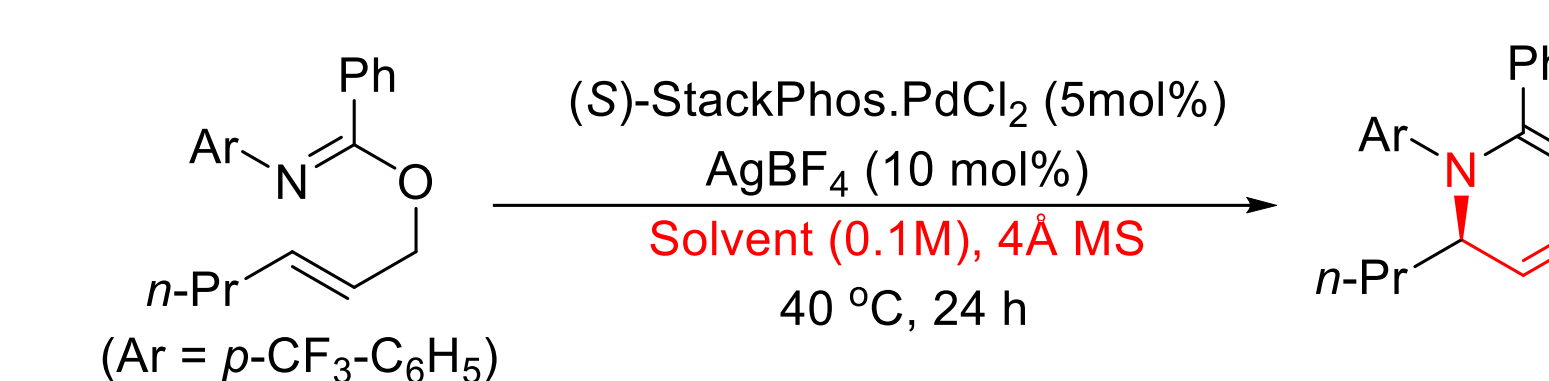
Modification of reaction conditions	Isolated yield of A	ee of product A	Unreacted SM: A: B
No Ag(I) salt, rt, 16 h	93%	0% ee	Only Pdt A
AgBF ₄ (10 mol%), rt, 44 h	14%	92% ee	5: 1: 1
AgBF ₄ (10 mol%), 40 °C, 20 h	62%	95% ee	_: 1: 0.6
(S)-StackPhos.Pd(MeCN) ₂ (BF ₄) ₂ [instead of (S)-stackPhos.PdCl ₂ + AgBF ₄ , 40 °C, 24 h	25%	69% ee	2.5: 1: 0.3

Ag(I) Screening:



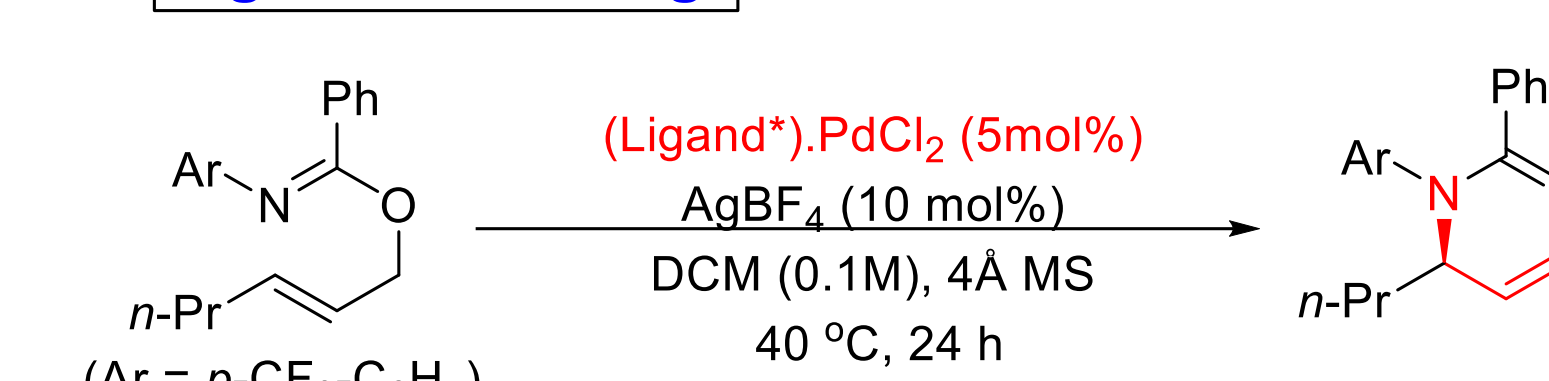
Ag(I) Salt	Yield	ee
AgBF ₄	70%	95%
AgOTf	50%	94%
AgOTs	35%	79%
AgPF ₆	32%	75%
No Ag(I)	92%	0%
AgBF ₄ (5 mol%)	95%	88%

Solvent Screening:

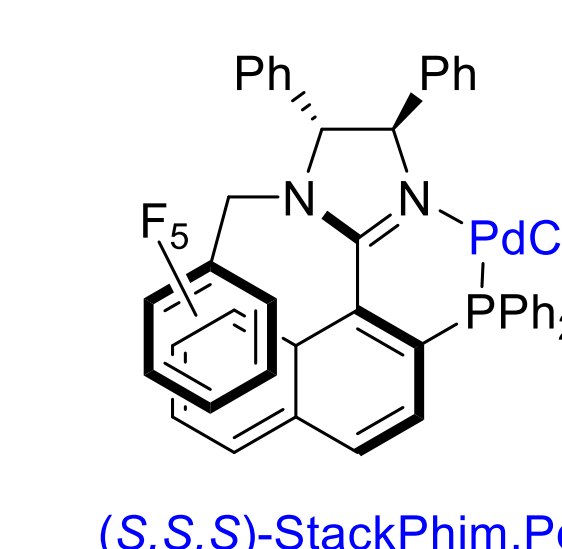
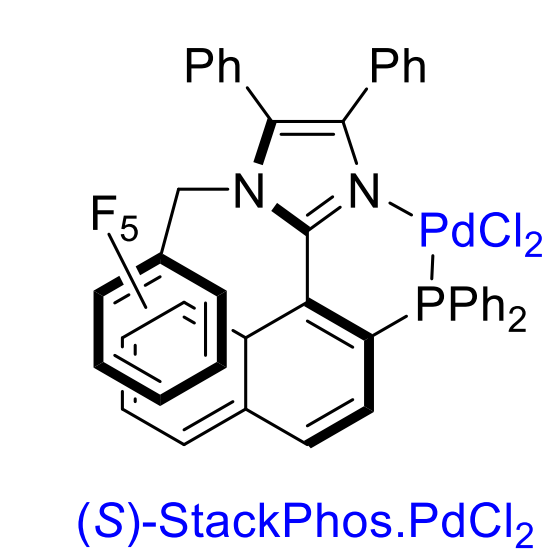


Solvent	Yield	ee
DCM	82%	92%
CHCl ₃	90%	94%

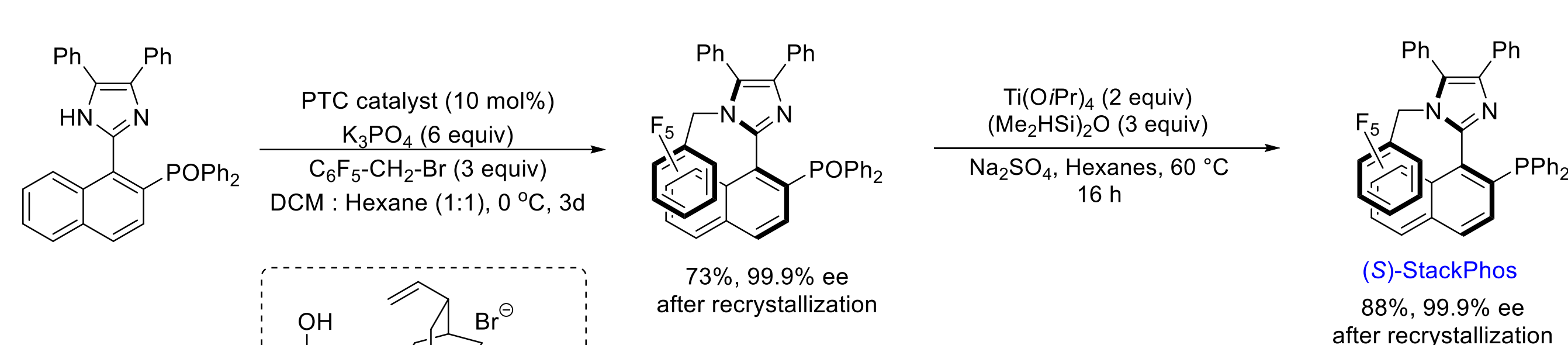
Ligand Screening:



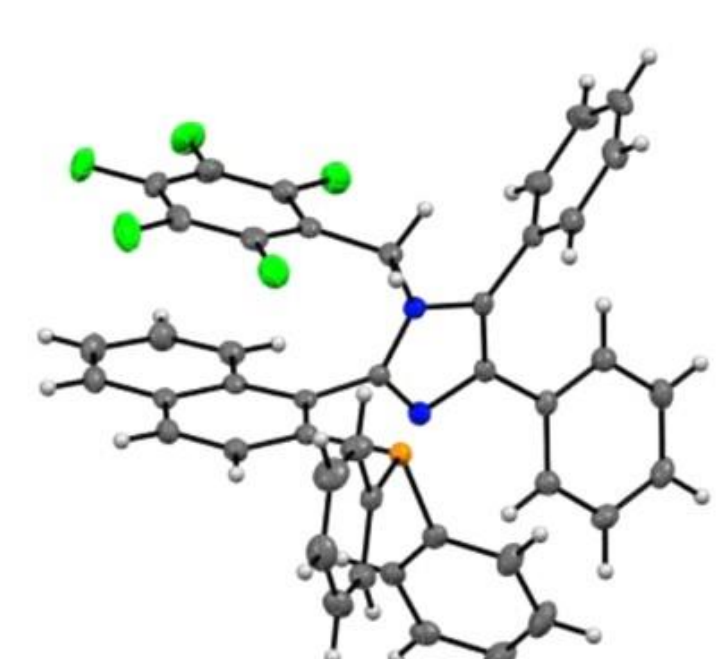
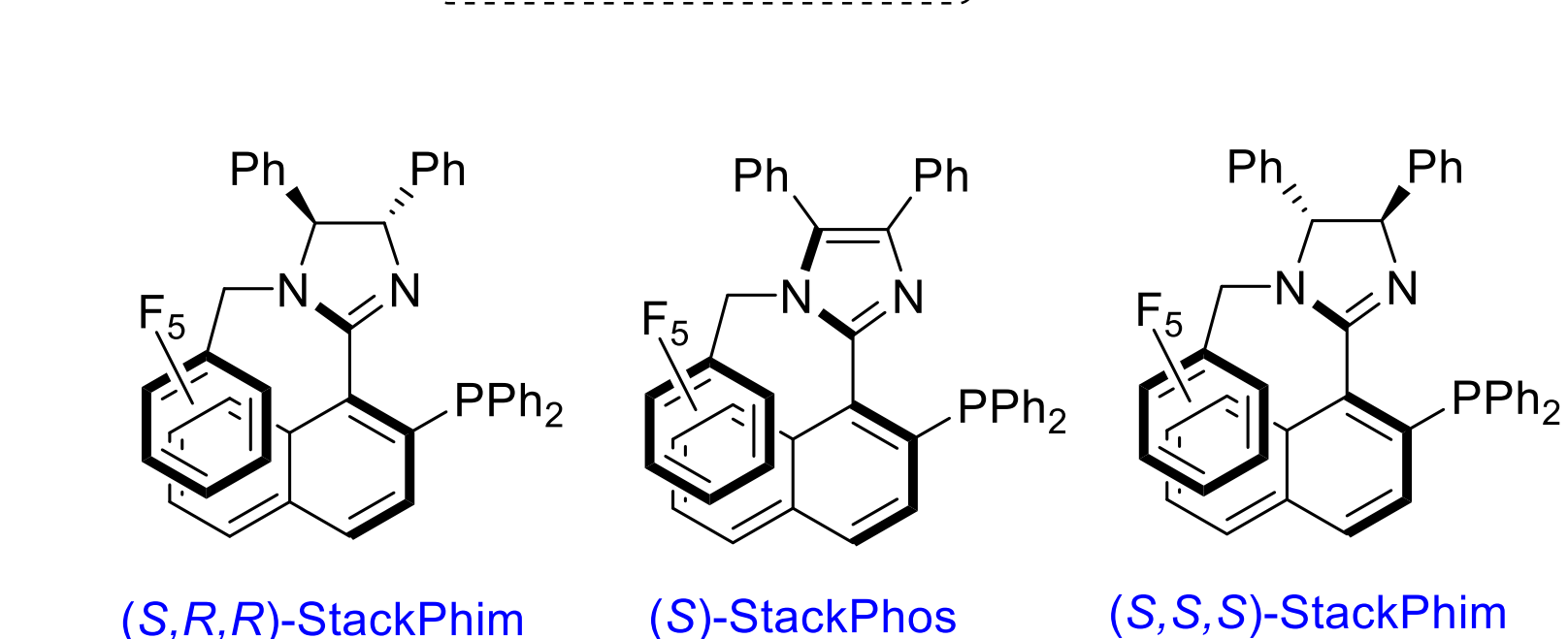
Pd(II)-Ligand*	Yield	ee
(S)-StackPhos.PdCl ₂	91%	94%
(S,S,S)-StackPhim.PdCl ₂	20% (in 48h)	87%



Axially Chiral P,N-Ligands



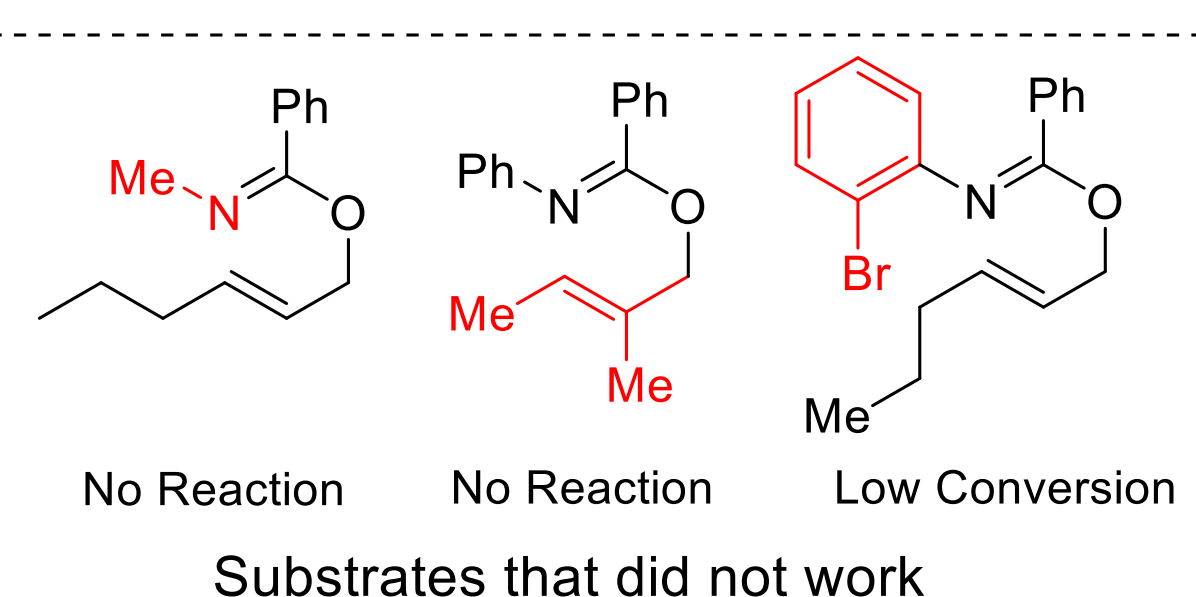
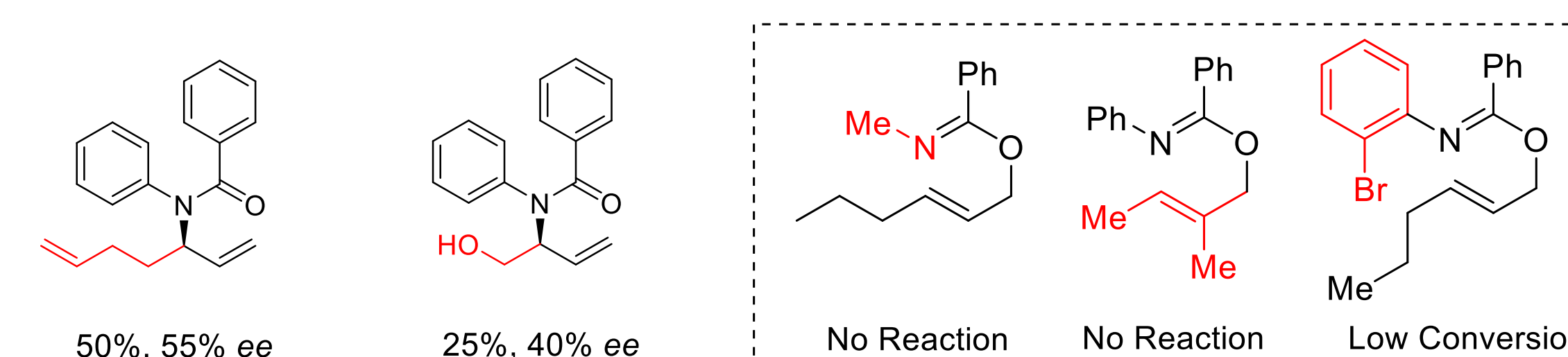
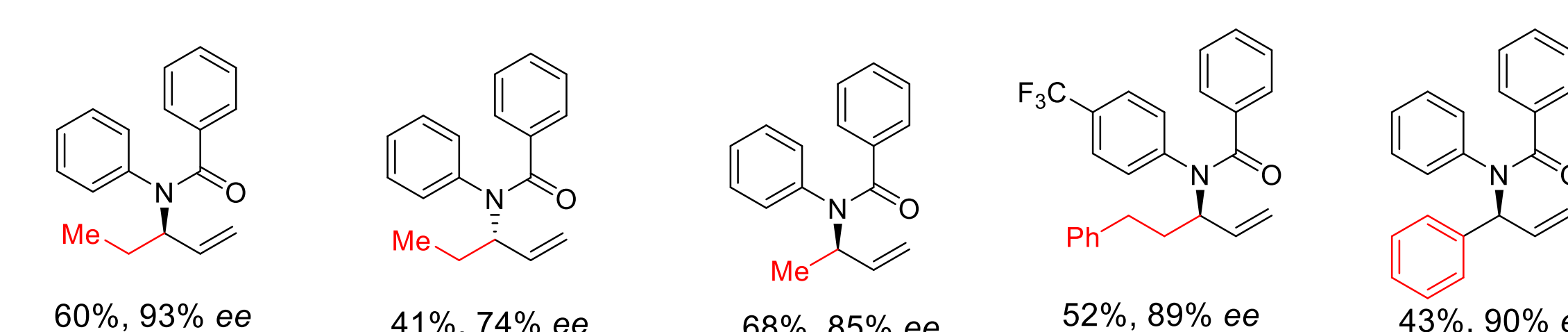
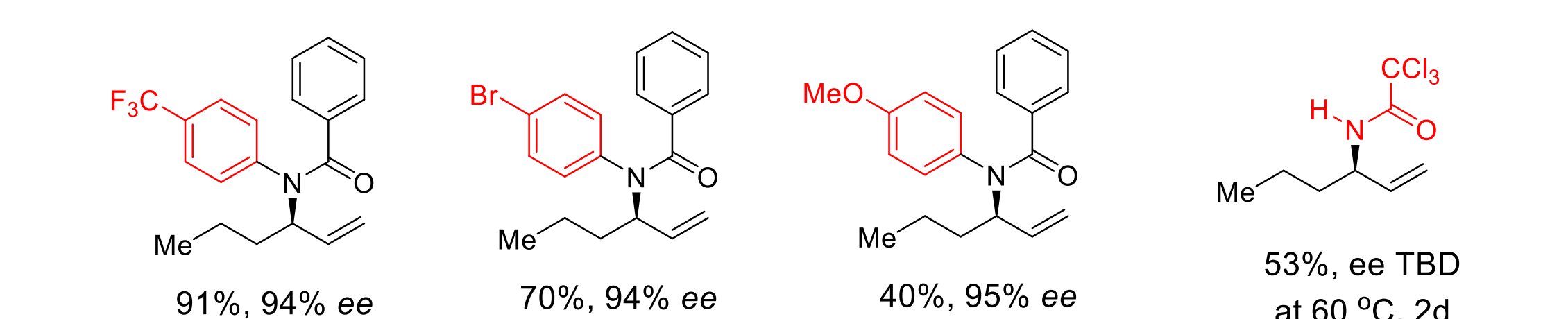
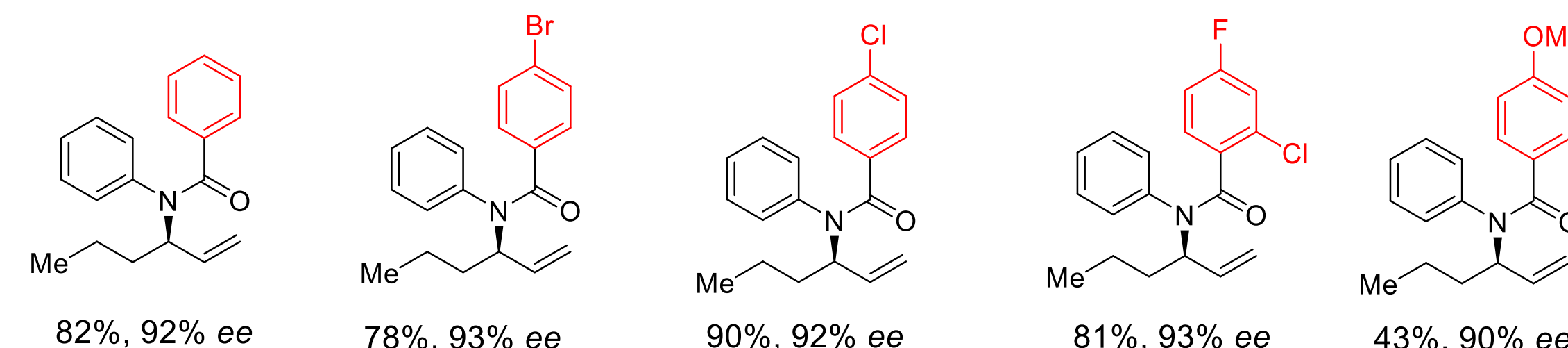
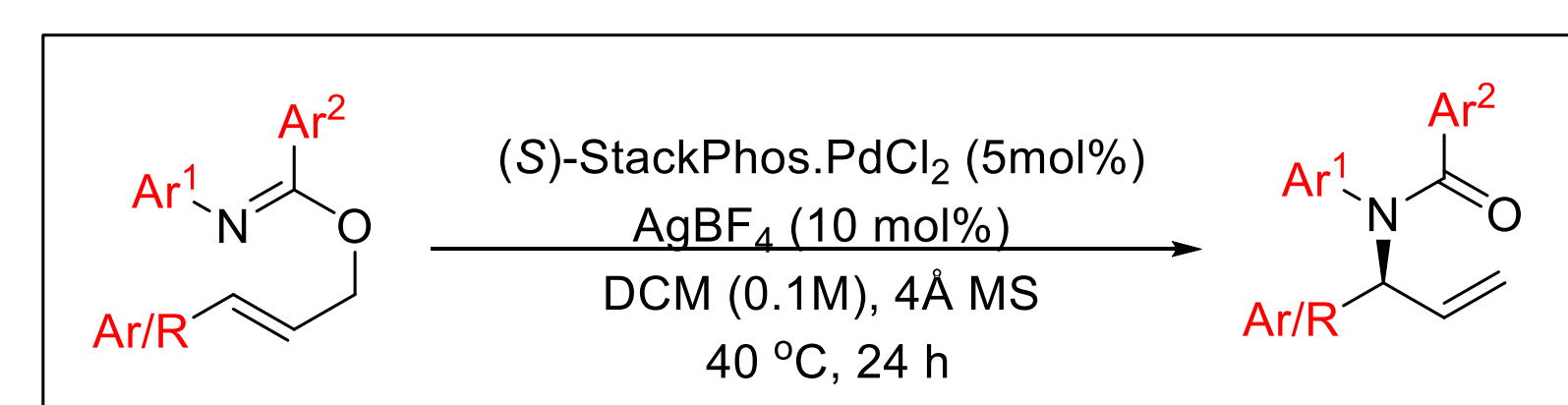
- ✓ Gram scale synthesis
- ✓ Axially chiral 6,5-biaryls
- ✓ Configurationally stabilized by π-π stacking



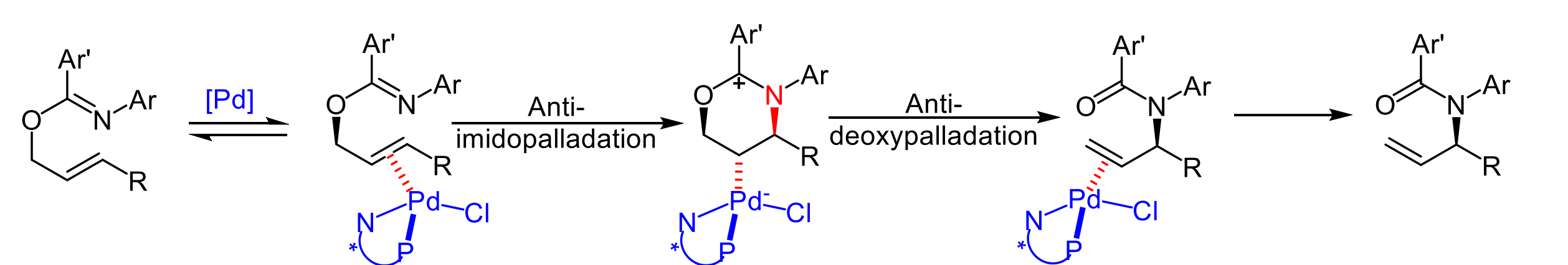
- ✓ Tunable axially chiral Imidazole/ Imidazoline backbone
- ✓ Position tuning and size tuning with different substituents

X-ray crystal structure showing π-stacking

Substrate Scope



Plausible Mechanism



- Cyclization induced rearrangement
- Deoxypalladation yields rearranged products
- Allylic imidates to allylic amides
- Imidate nitrogen attacks Pd-complexed alkene

References

Org. Biomol. Chem. 2017, 15, 2672. Overman, L. J. Org. Chem. 1997, 62, 1449. Uozumi, Y.; Hayashi, T. Tetrahedron: Asymmetry. 1998, 9, 1065. Pavan, M.; Overman, L. Org. Lett. 2003, 5, 1809. Anderson, C.; Overman, L. J. Am. Chem. Soc. 2003, 125, 12412. Overman, L. J. Org. Chem. 2012, 77, 1939. Yin, S.; Liu, J.; Weeks, k.; Aponick, A. J. AM. Chem. Soc. 2023, 145, 51, 28176

Acknowledgements

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