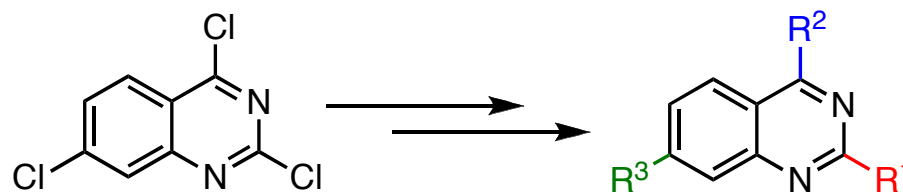


Regioselective Palladium Catalyzed Cross-Coupling Reactions of 2,4,7-Trichloroquinazoline and Progress Towards Small-Molecule Inhibitors for Protein Kinase D

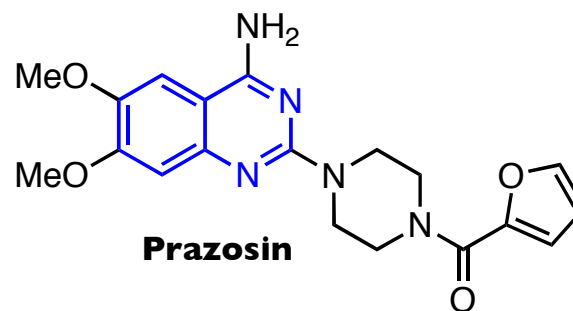
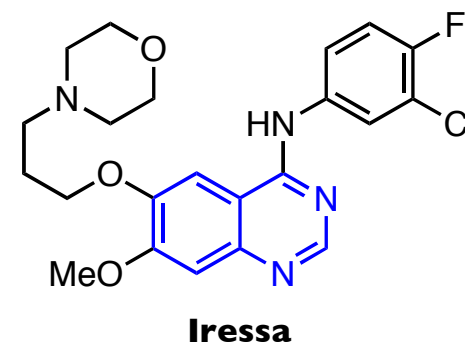
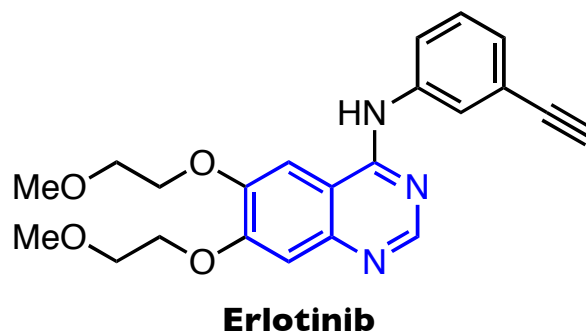
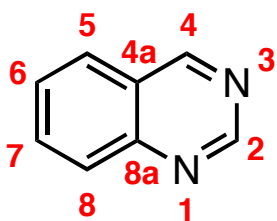
Kara George
Wipf Group Research Topic Seminar
5 June 2010

Regioselective Cross-Coupling Reactions of 2,4,7-Trichloroquinazoline



Quinazoline Scaffold: Overview and Biological Significance

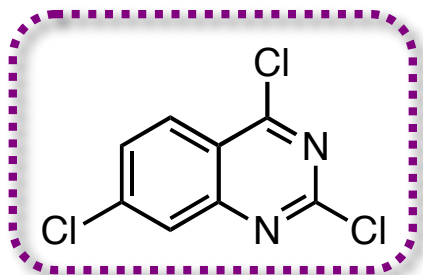
- Quinazoline skeleton is present in a variety of biologically active compounds
 - Among the most potent tyrosine kinase and cellular phosphorylation inhibitors
 - Exhibit remarkable activity as antitubercular, antiviral, antibacterial, and anticancer agents



Fry, D.W.; Kraker, A. J.; McMichael, A.; Ambroso, L.A.; Nelson, J. M.; Leopold, W. R.; Connors, R. W.; Bridges, A. J. *Science*. **1999**, 265, 1093.
Portela-Cubillo, F.; Scott, J. S.; Walton, J. C. *J. Org. Chem.* **2009**, 74, 4934.

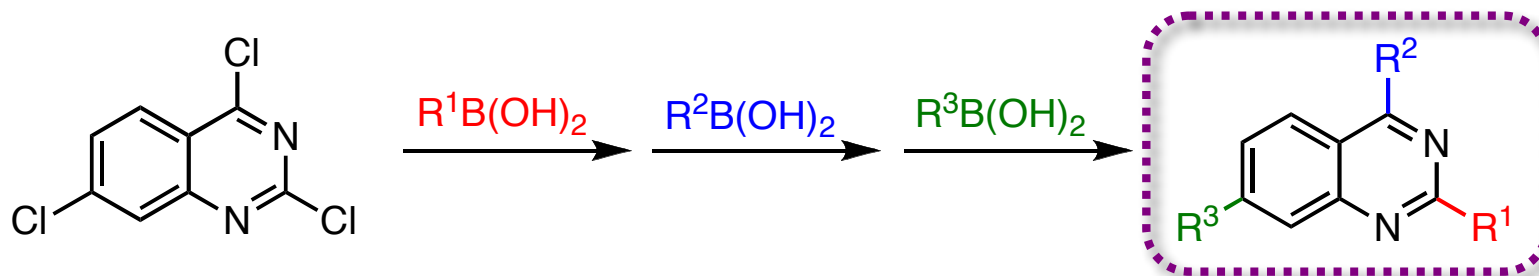
Regioselective Pd-Catalyzed Cross-Coupling of 2,4,7-Trichloroquinazoline

- Can we use consecutive Suzuki cross-coupling reactions to access tricarbo-substituted quinazolines?



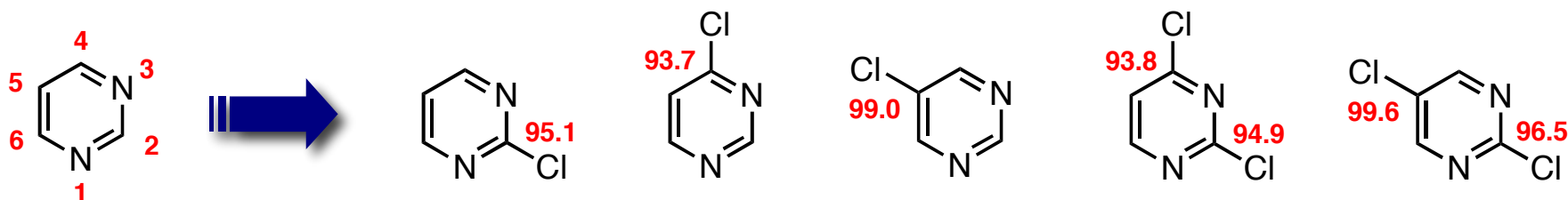
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Bond Dissociation Energy of Halo-Pyrimidines: Relationship to Regioselectivity

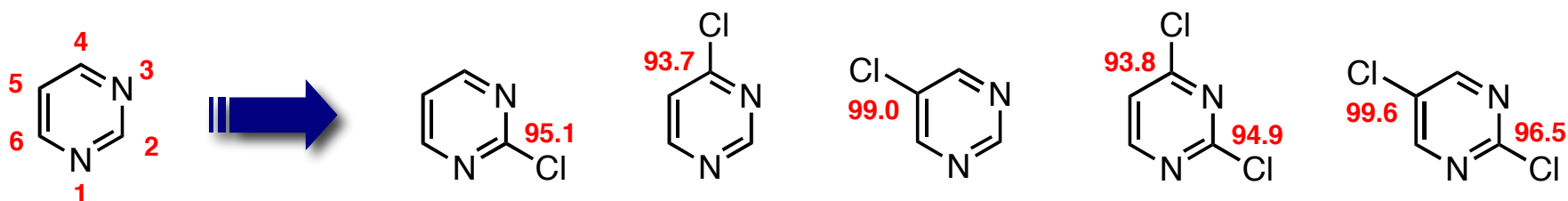
- Lowest C-Cl BDE at the 4-position, followed by the 2-position, then the 5-position



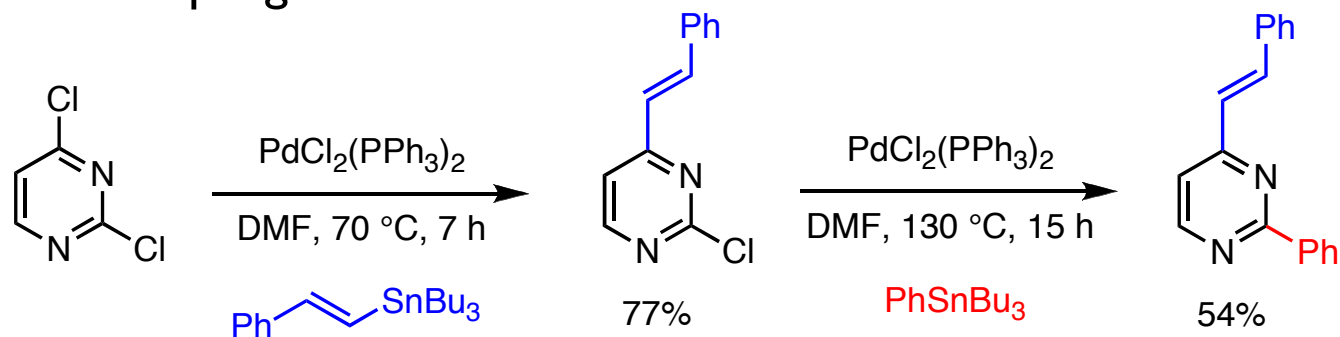
Garcia, Y.; Schoenebeck, F.; Legault, C. Y.; Merlic, C. A.; Houk, K. N. *J. Am. Chem. Soc.* **2009**, *131*, 6632.

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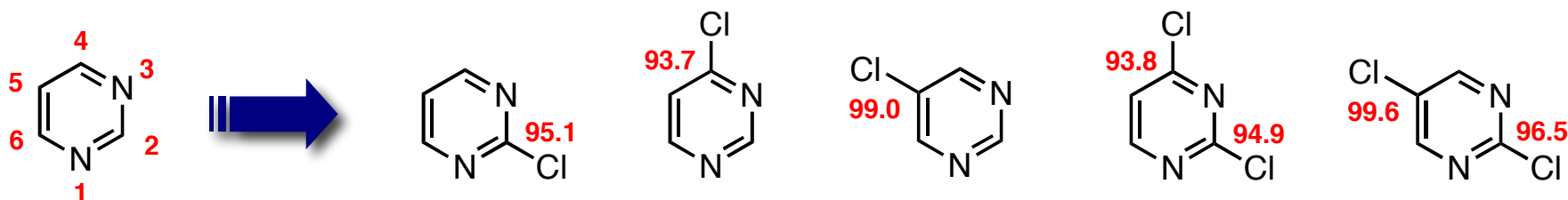
- Stille cross-coupling



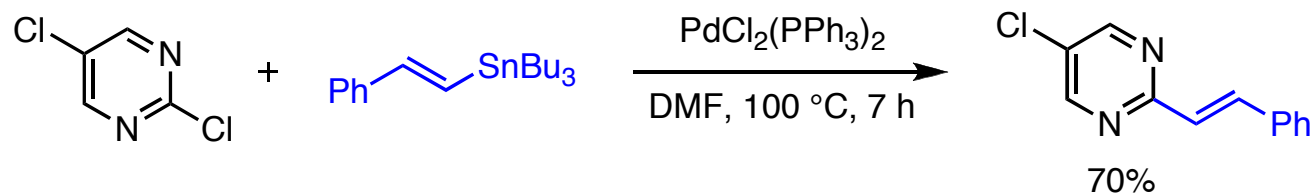
Garcia, Y.; Schoenebeck, F.; Legault, C. Y.; Merlic, C. A.; Houk, K. N. *J. Am. Chem. Soc.* **2009**, *131*, 6632.
Solberg, J.; Undheim, K. *Acta Chem. Scand.* **1989**, *43*, 62.

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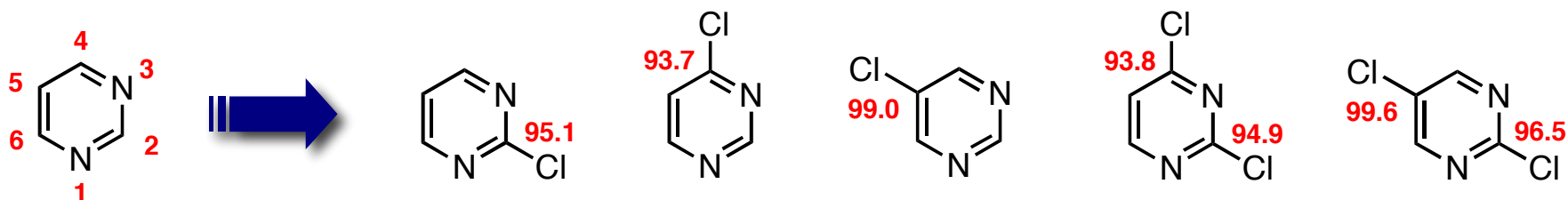
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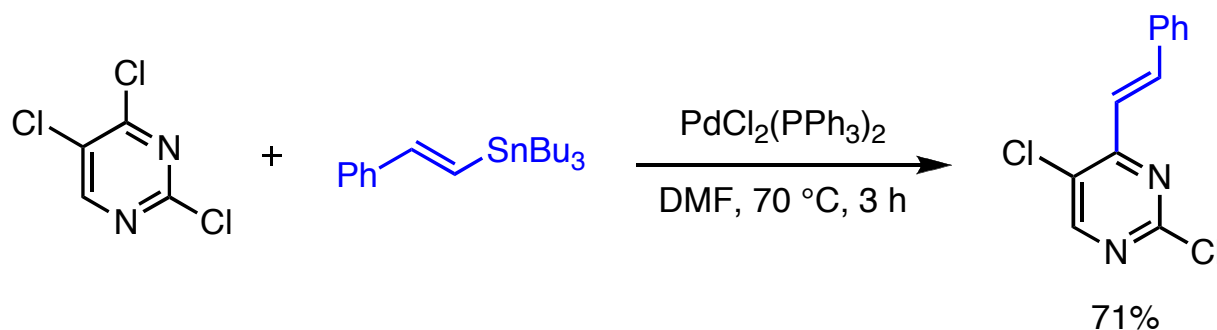
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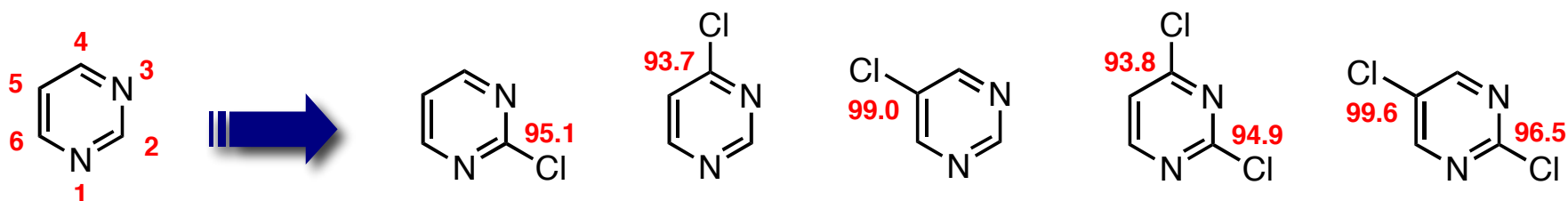
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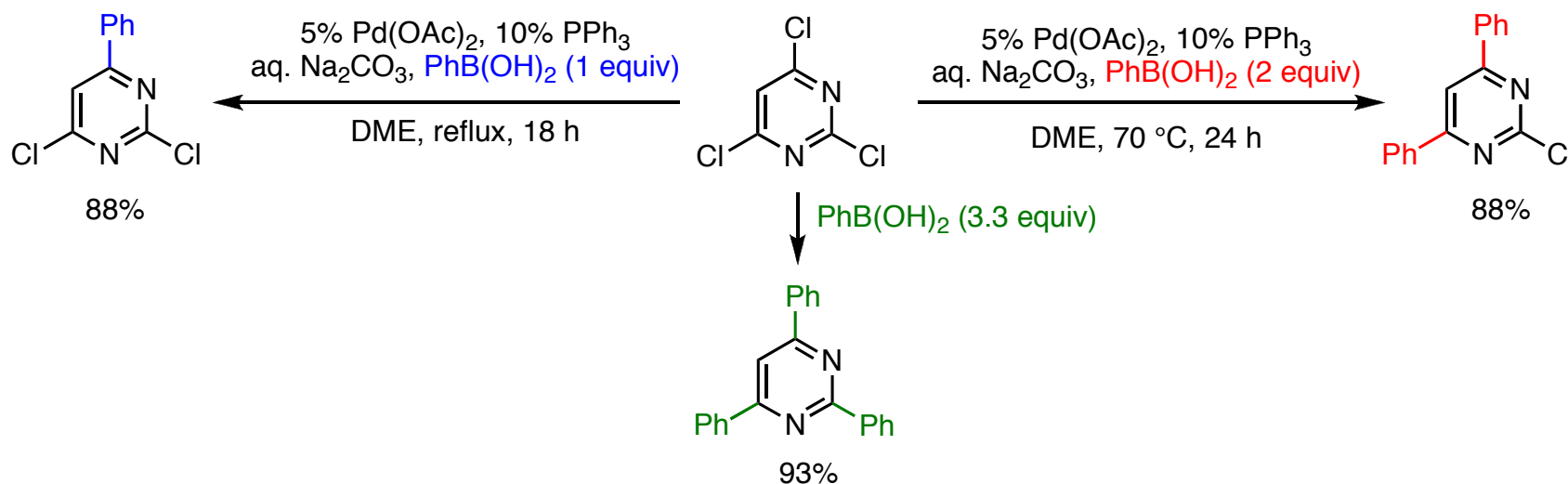
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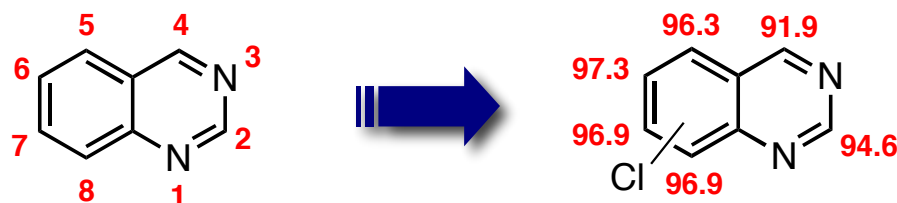
- Suzuki cross-coupling



Garcia, Y.; Schoenebeck, F.; Legault, C. Y.; Merlic, C. A.; Houk, K. N. *J. Am. Chem. Soc.* **2009**, *131*, 6632.
Schomaker, J. M.; Delia, T. J. *J. Org. Chem.* **2001**, *66*, 7125.

Bond Dissociation Energy of Halo-Quinazolines: Relationship to Regioselectivity

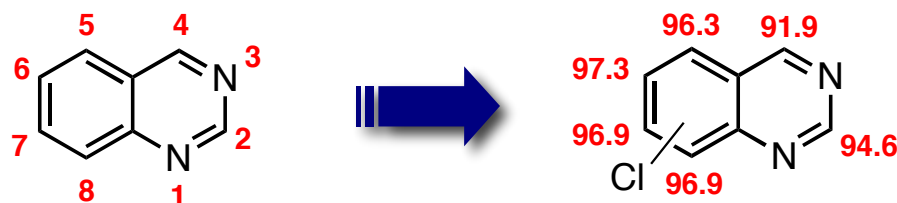
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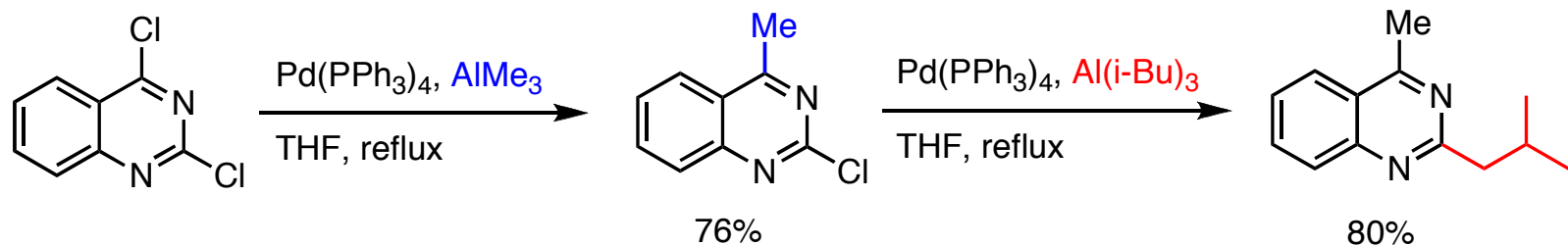
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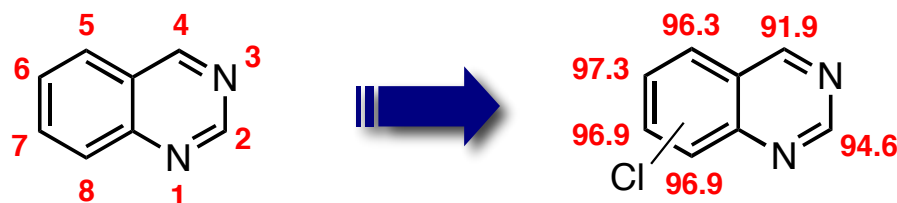
- Pd-catalyzed couplings of trialkylalanes



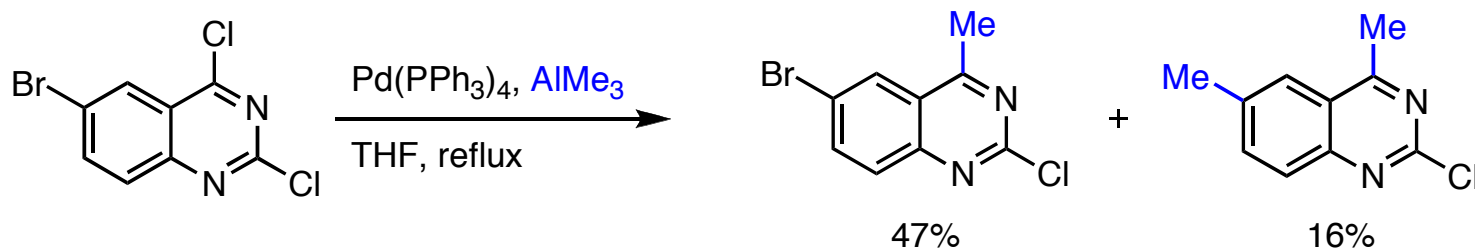
Garcia, Y.; Schoenebeck, F.; Legault, C. Y.; Merlic, C. A.; Houk, K. N. *J. Am. Chem. Soc.* **2009**, *131*, 6632.
Mangalagiu, I.; Benneche, T.; Undheim, K. *Acta Chem. Scand.* **1996**, *50*, 914.
Mangalagiu, I.; Benneche, T.; Undheim, K. *Tetrahedron Lett.* **1996**, *37*, 1309.

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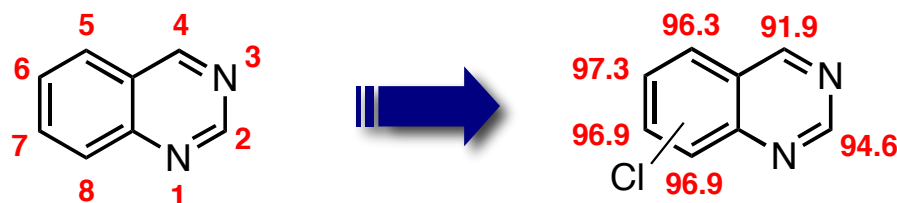
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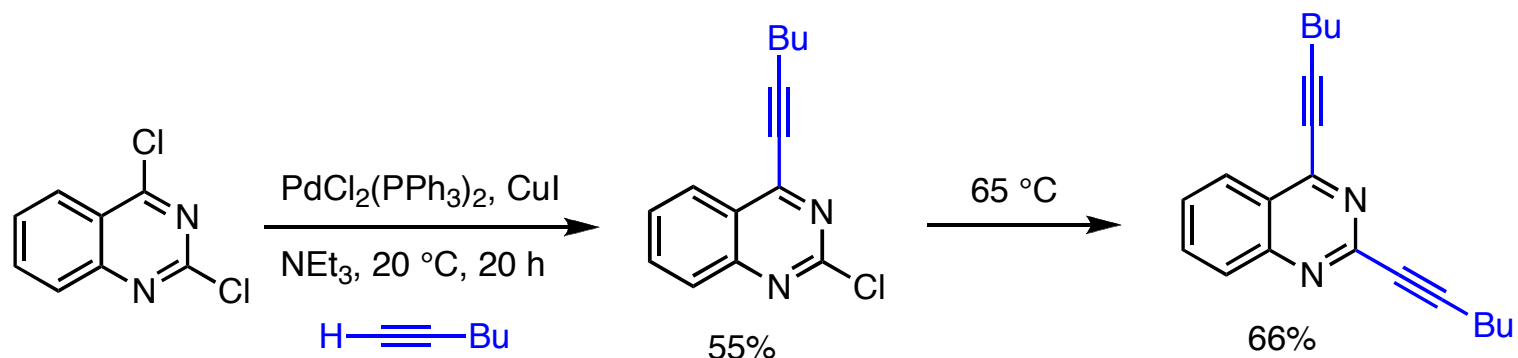
Garcia, Y.; Schoenebeck, F.; Legault, C. Y.; Merlic, C. A.; Houk, K. N. *J. Am. Chem. Soc.* **2009**, *131*, 6632.
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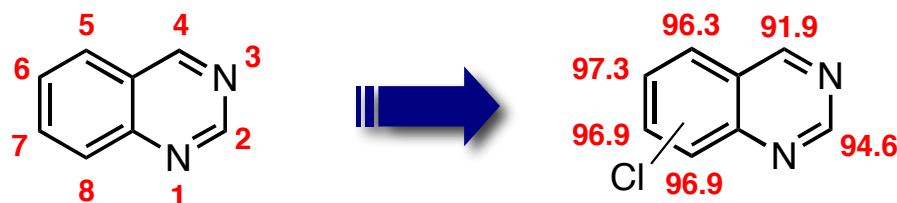
- Sonagashira cross-coupling



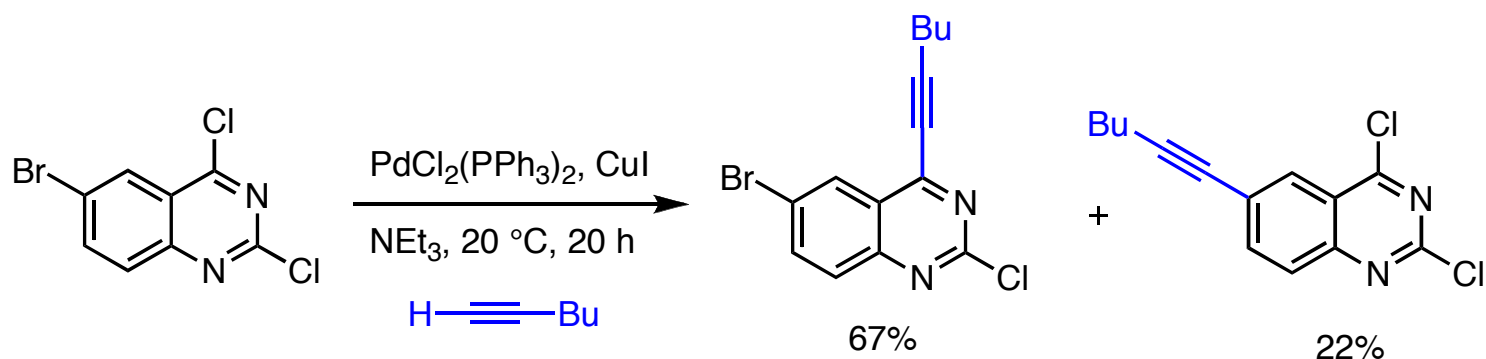
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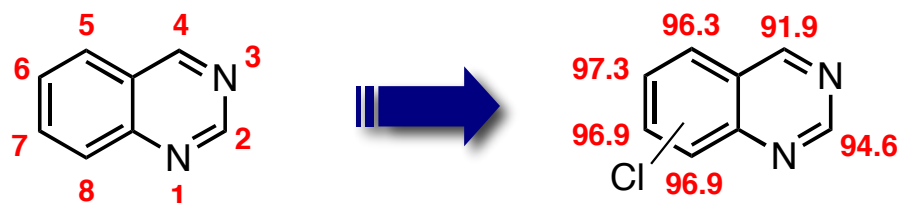
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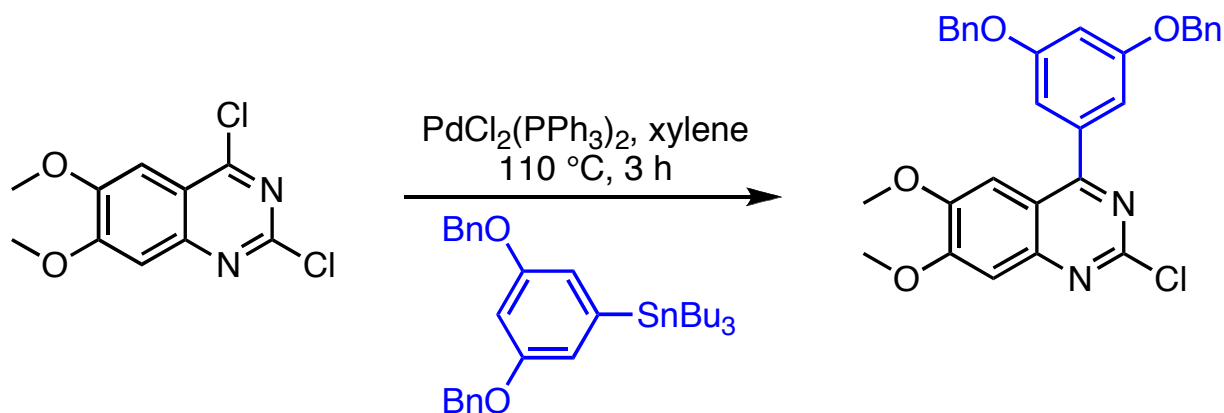
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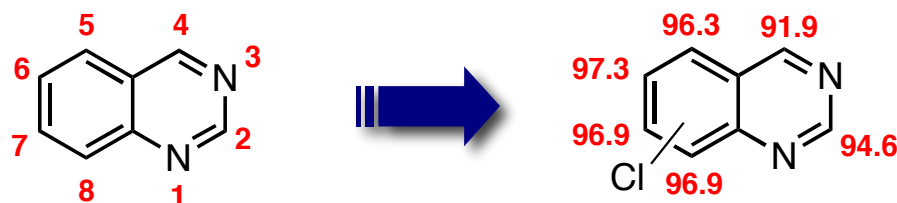
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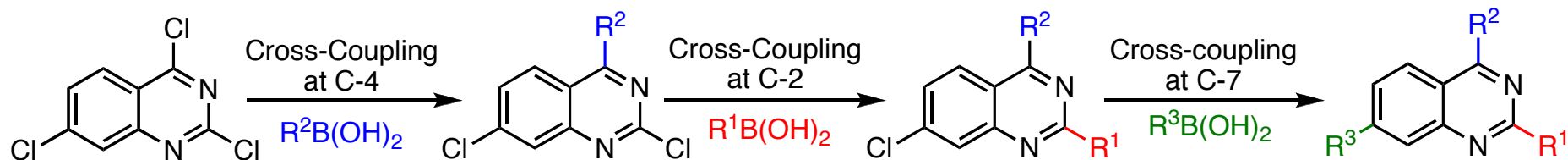
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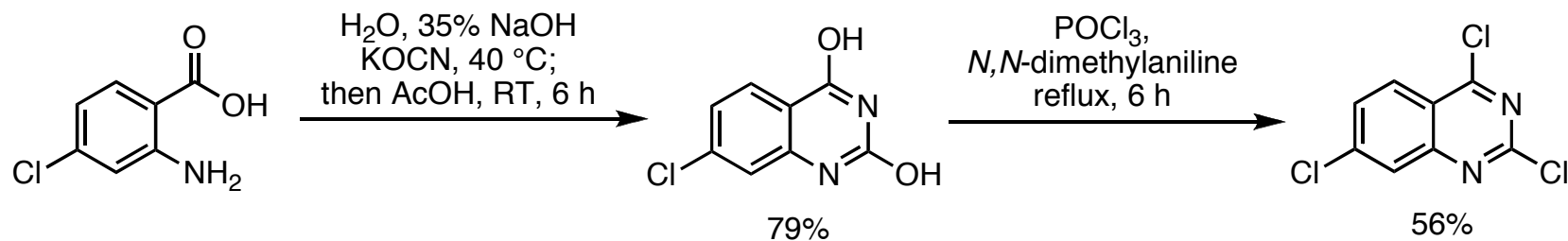


- Consecutive Pd-catalyzed Suzuki cross-couplings



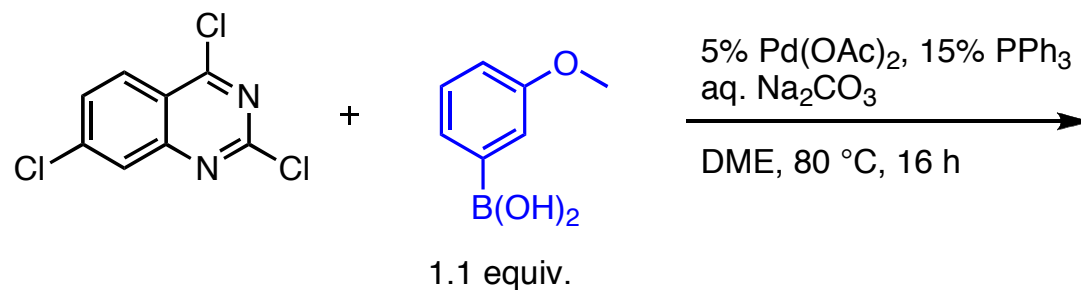
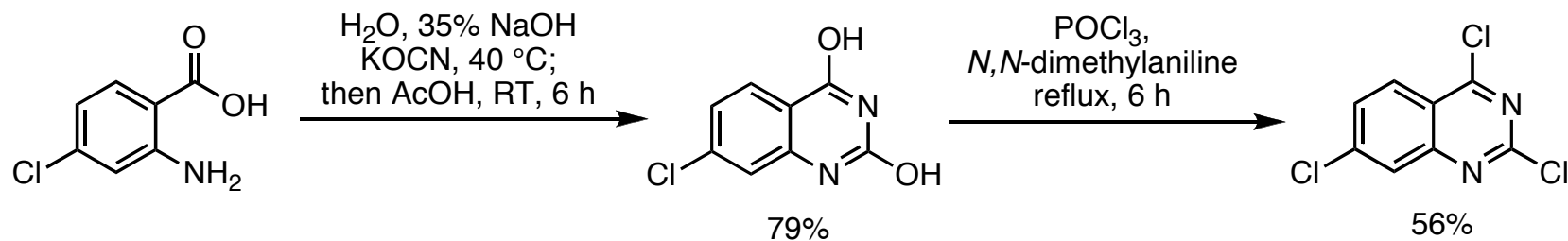
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Regioselective Suzuki Cross-Coupling at C-4



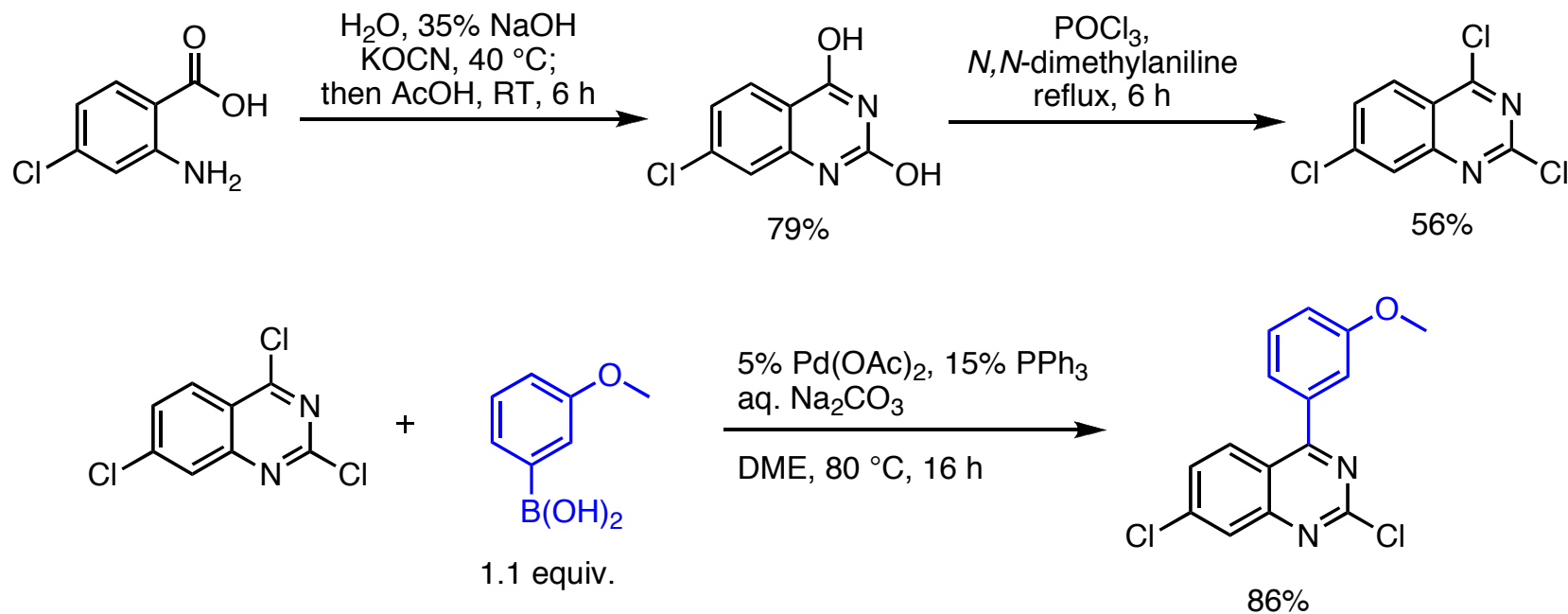
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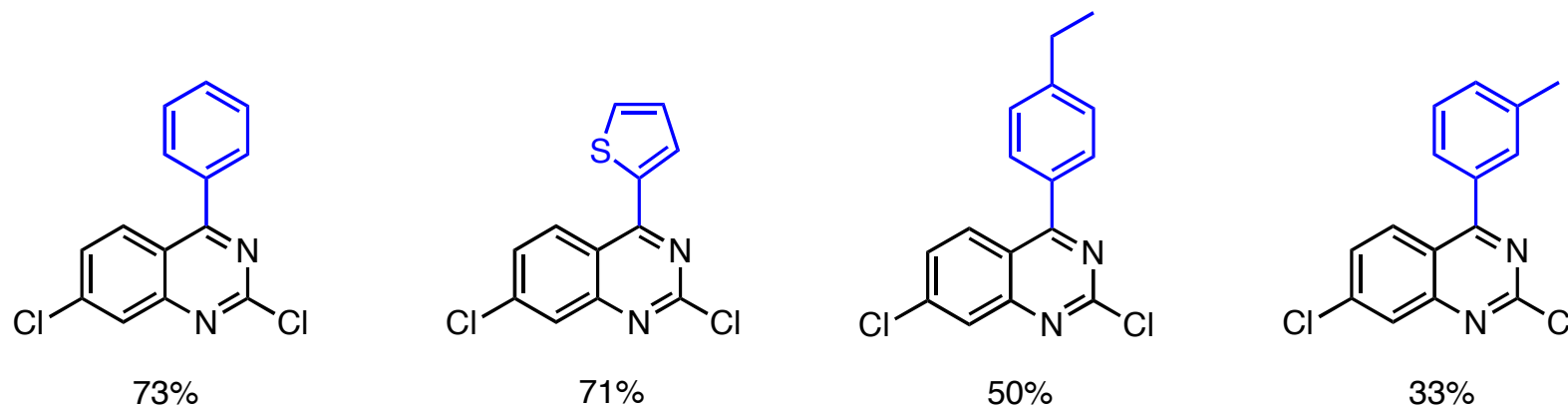
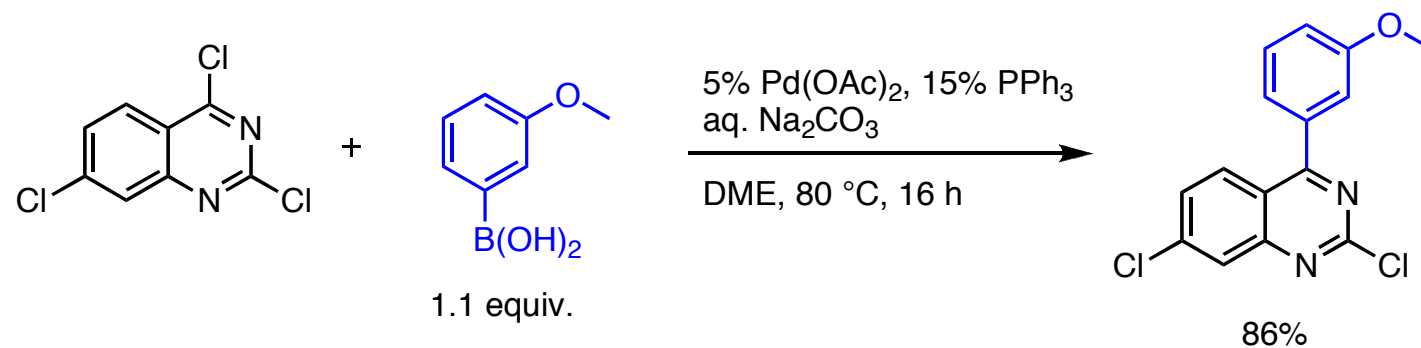
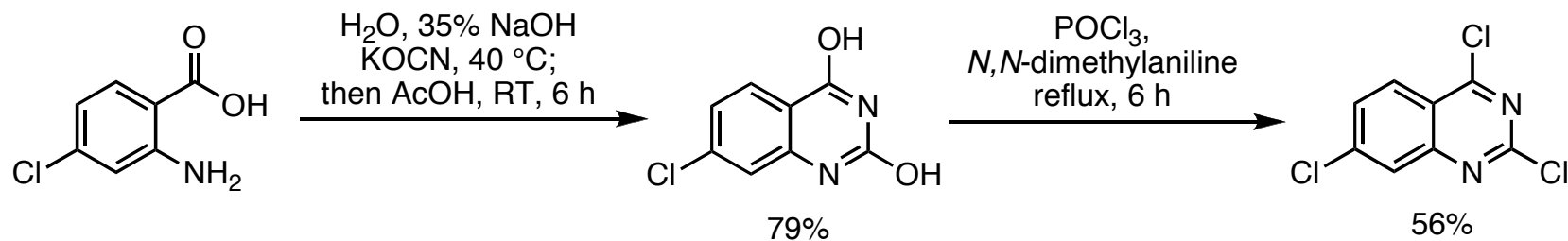
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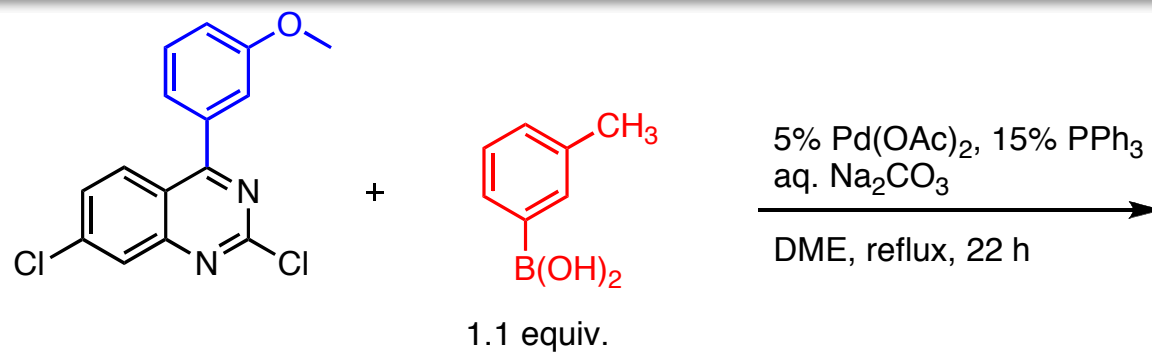
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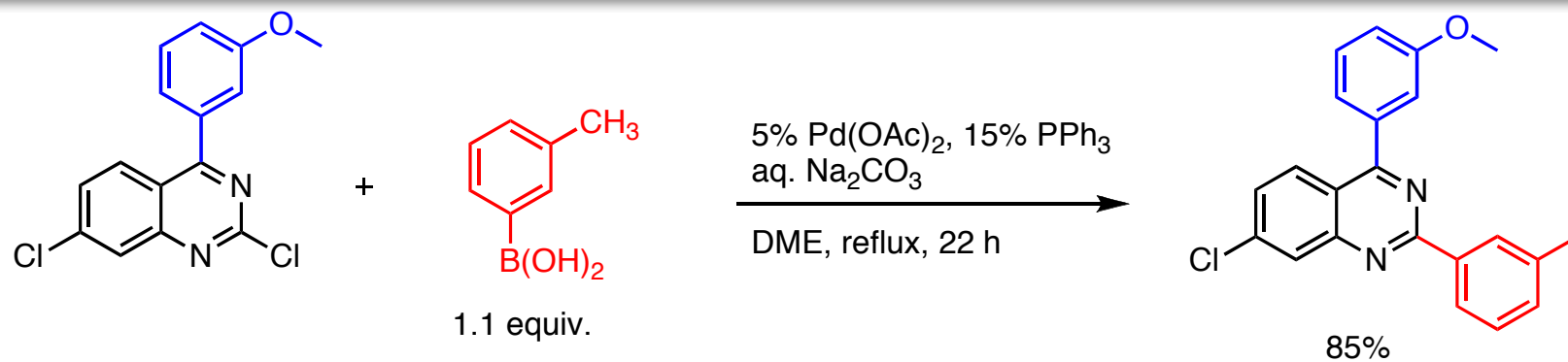


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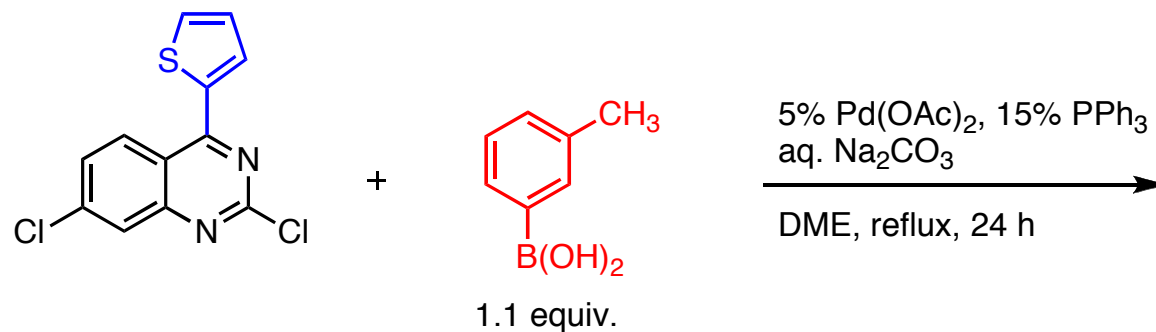
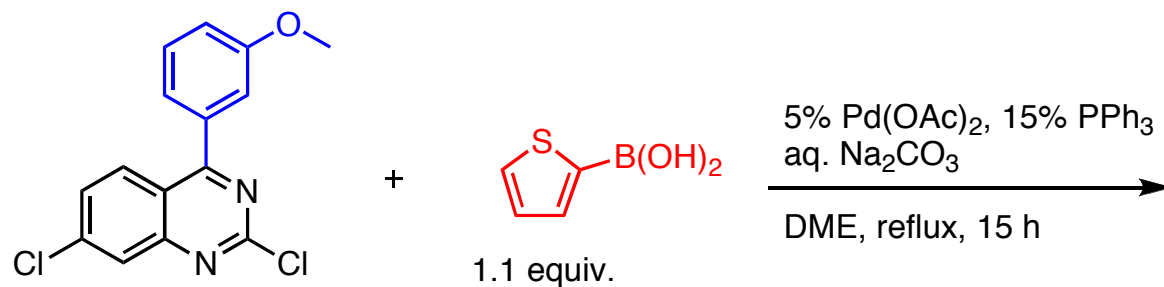
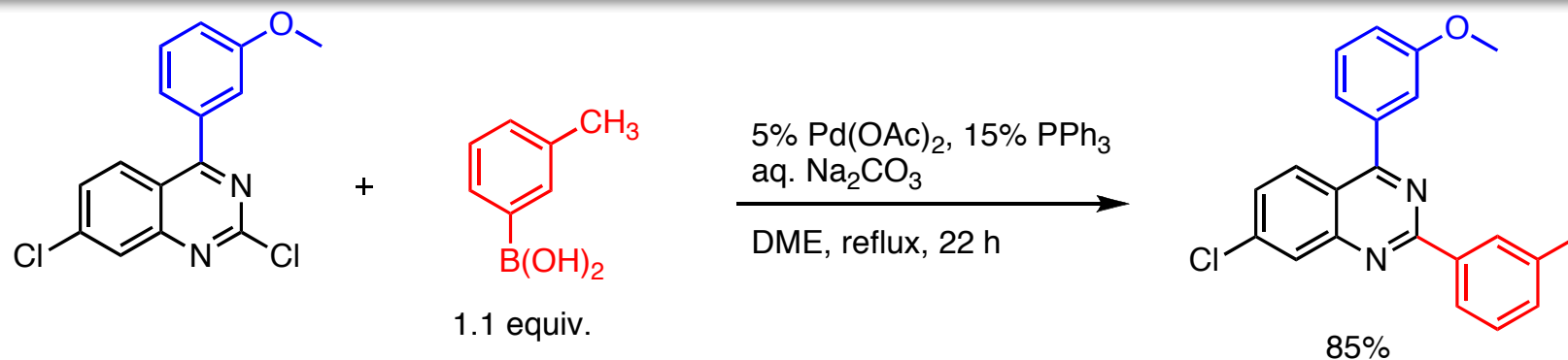
Regioselective Suzuki Cross-Coupling at C-2



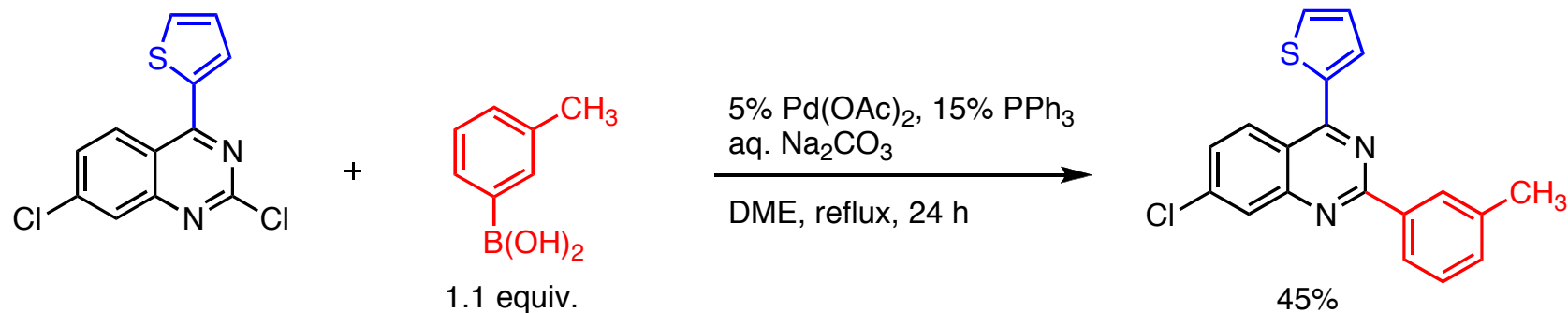
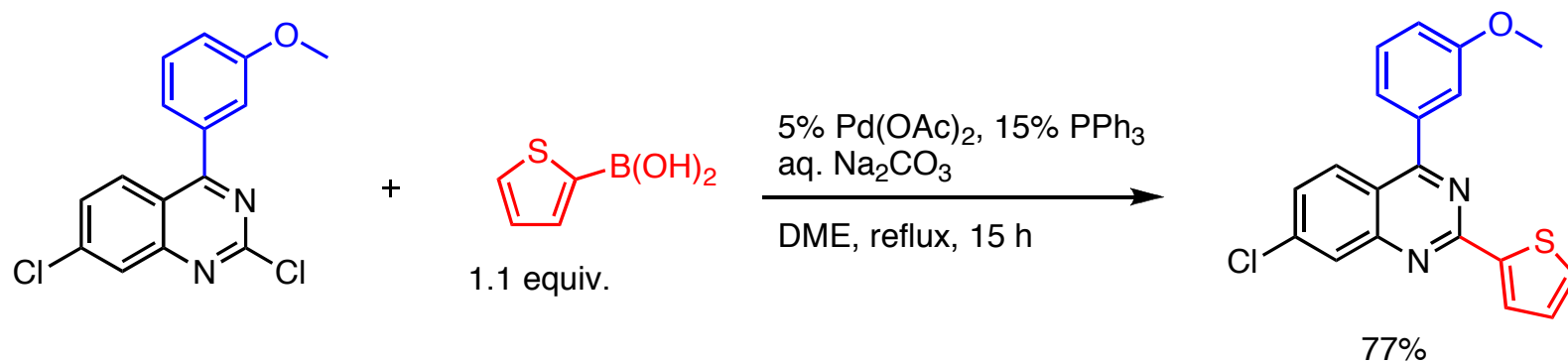
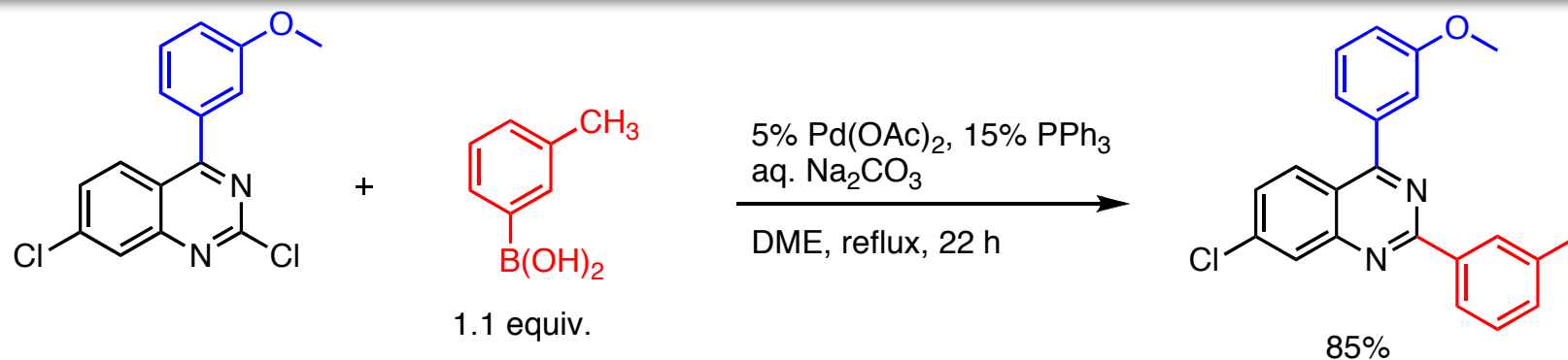
Regioselective Suzuki Cross-Coupling at C-2



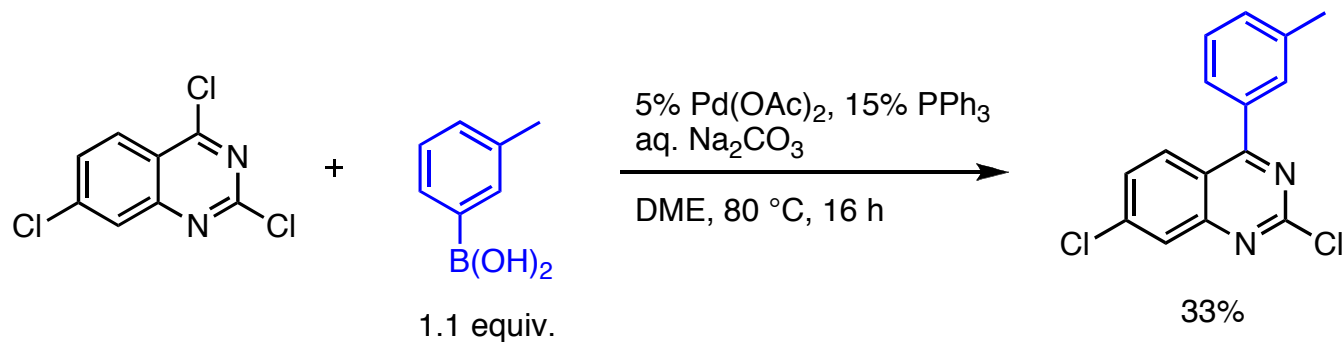
Regioselective Suzuki Cross-Coupling at C-2



Regioselective Suzuki Cross-Coupling at C-2

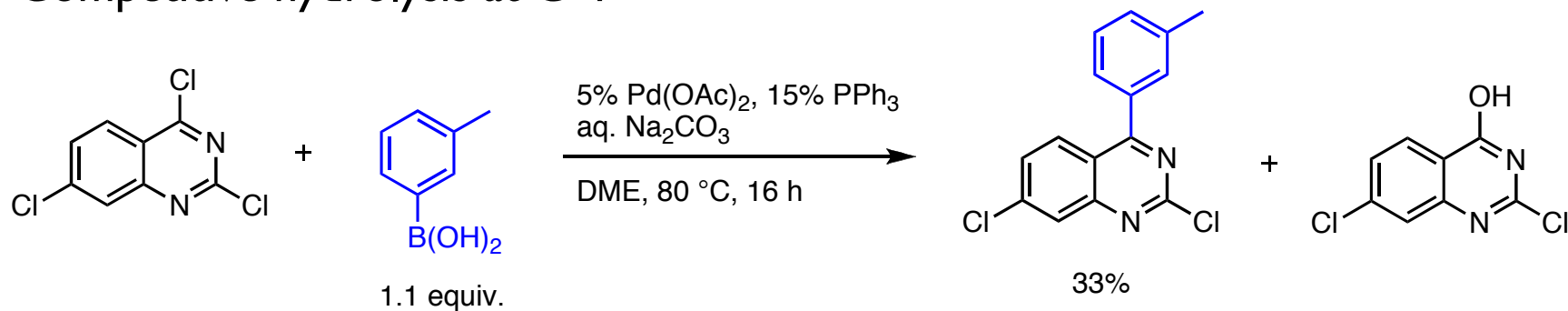


Alternative Route to Sequential Cross-Coupling Reactions of 2,4,7-Trichloroquinazoline



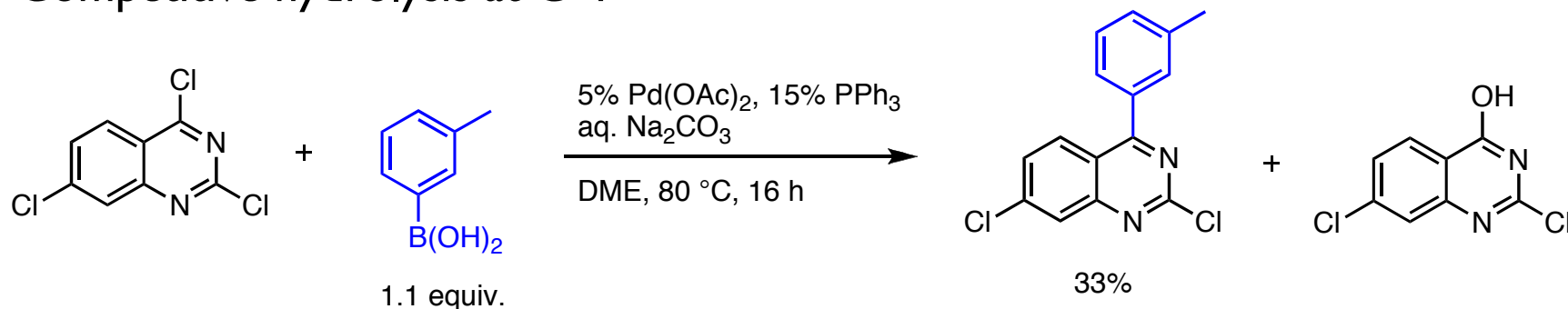
Alternative Route to Sequential Cross-Coupling Reactions of 2,4,7-Trichloroquinazoline

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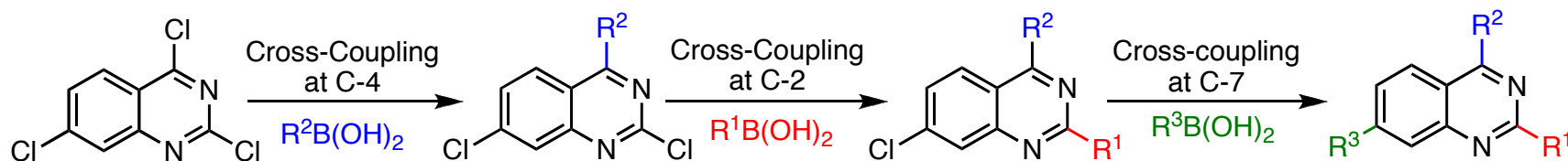


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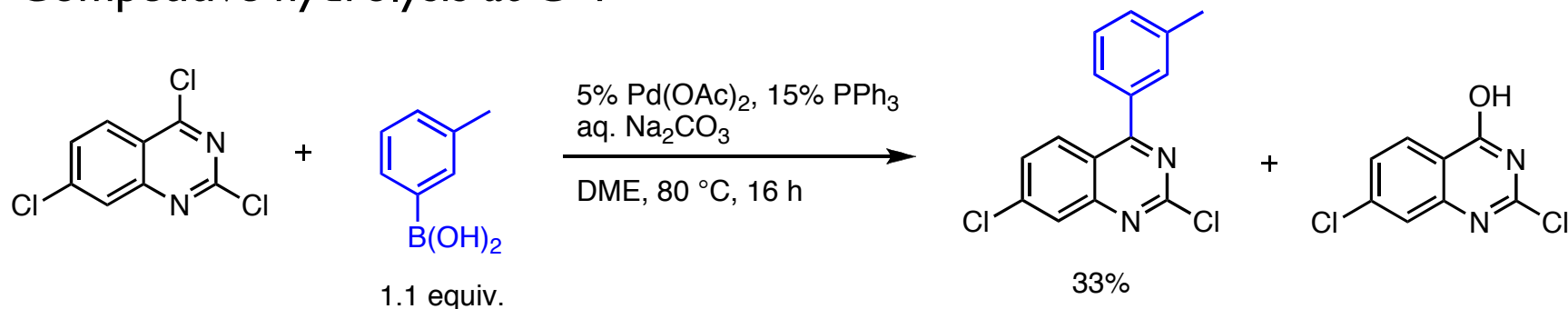


- Initial Approach

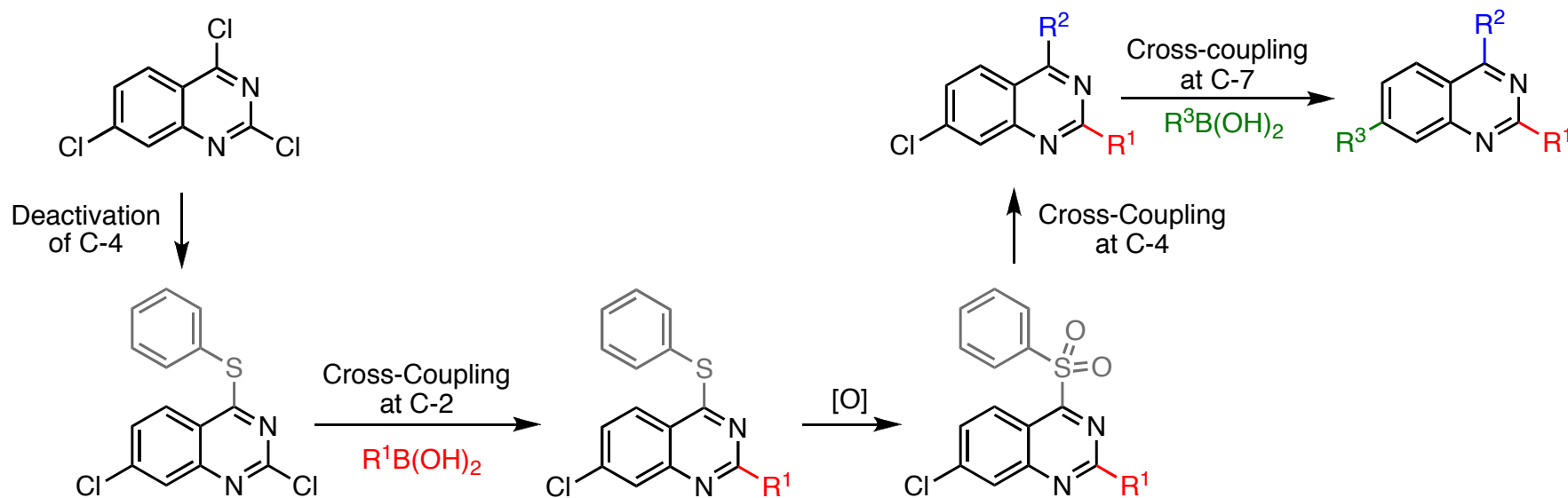


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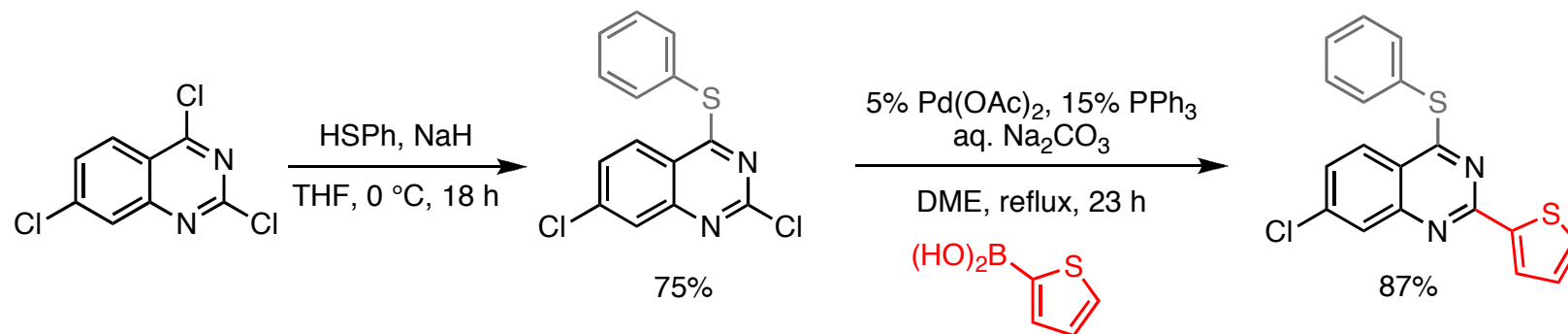
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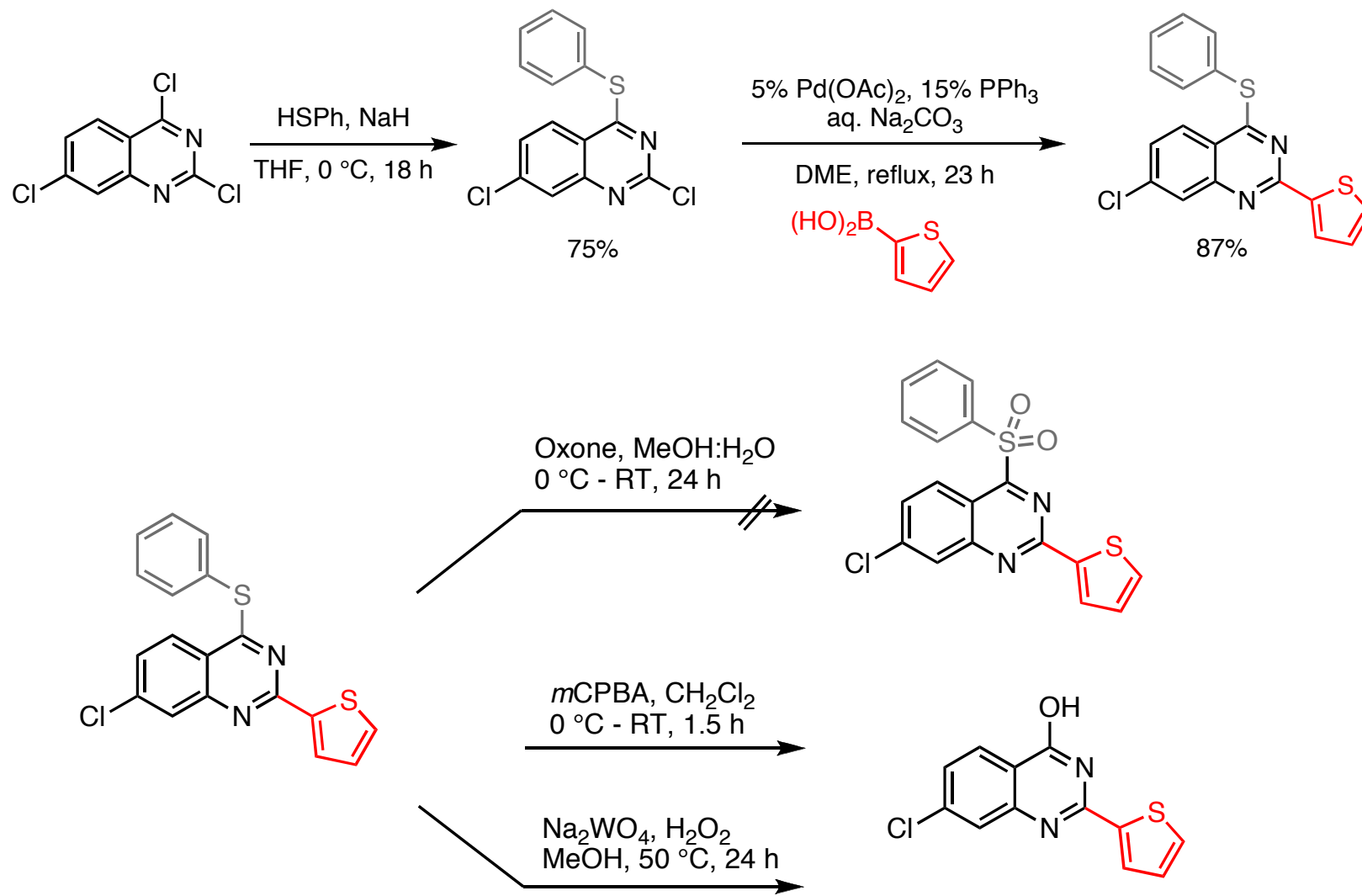
- New Approach



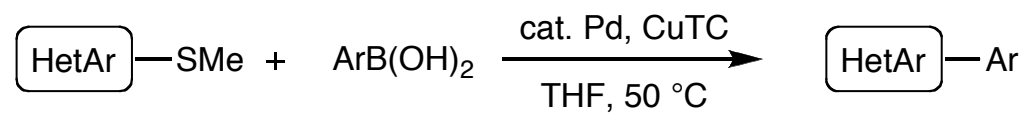
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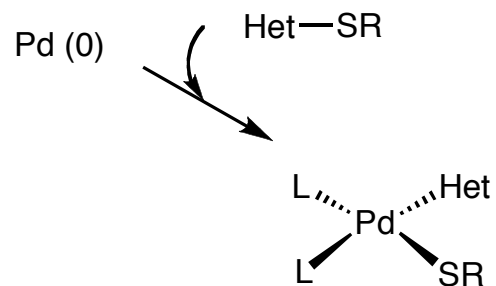
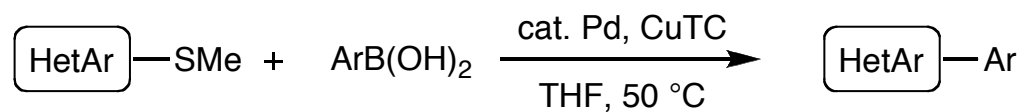


Pd-Catalyzed, Cu-Mediated Cross-Coupling



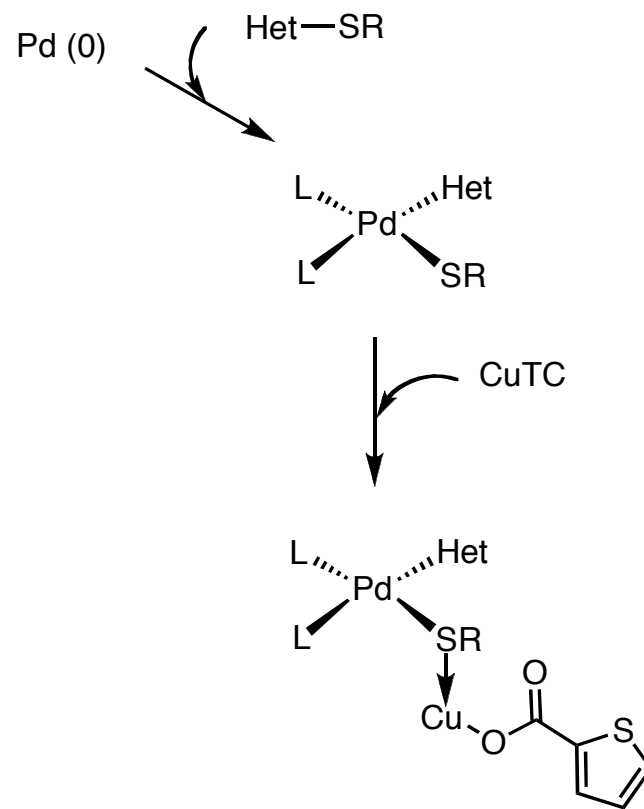
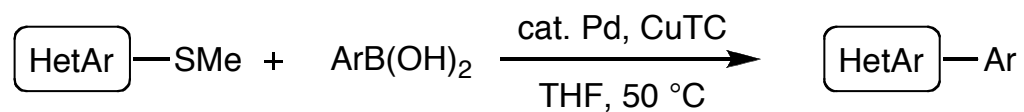
Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979.

Catalytic Cycle: Pd-Catalyzed, Cu-Mediated Cross-Coupling



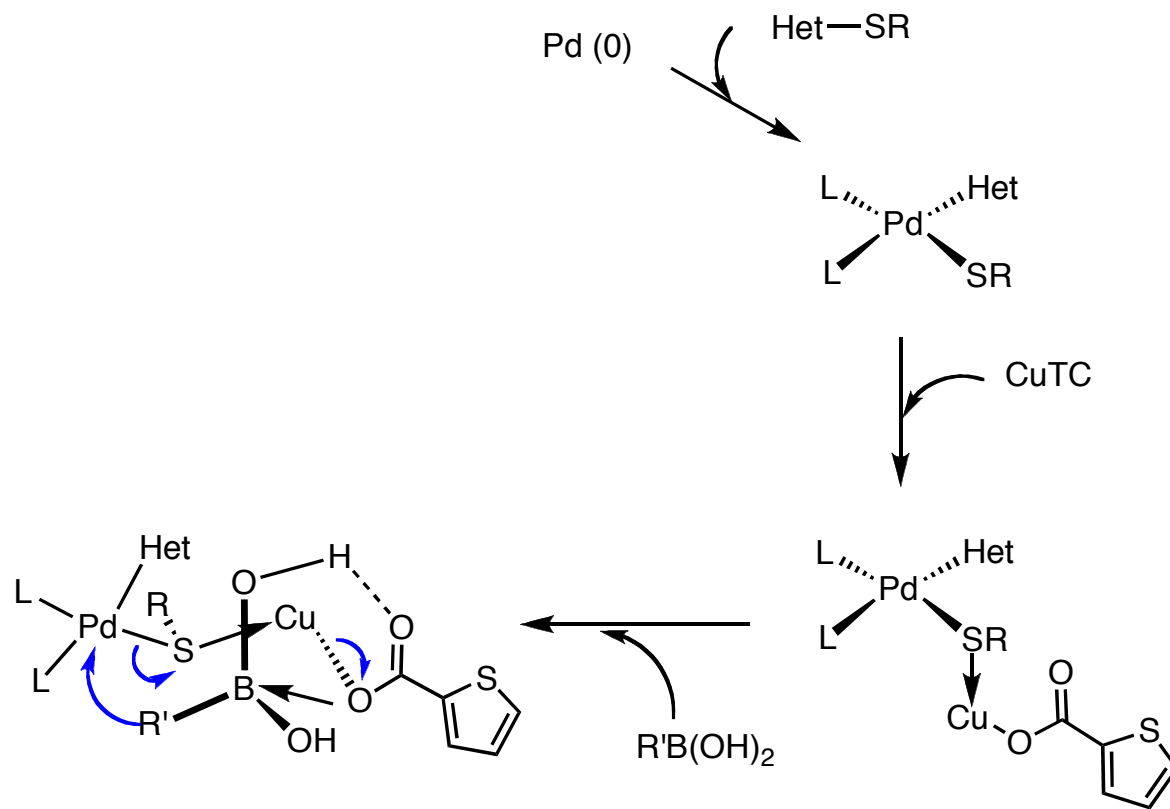
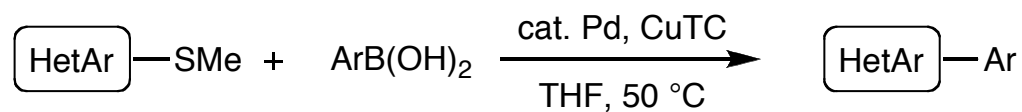
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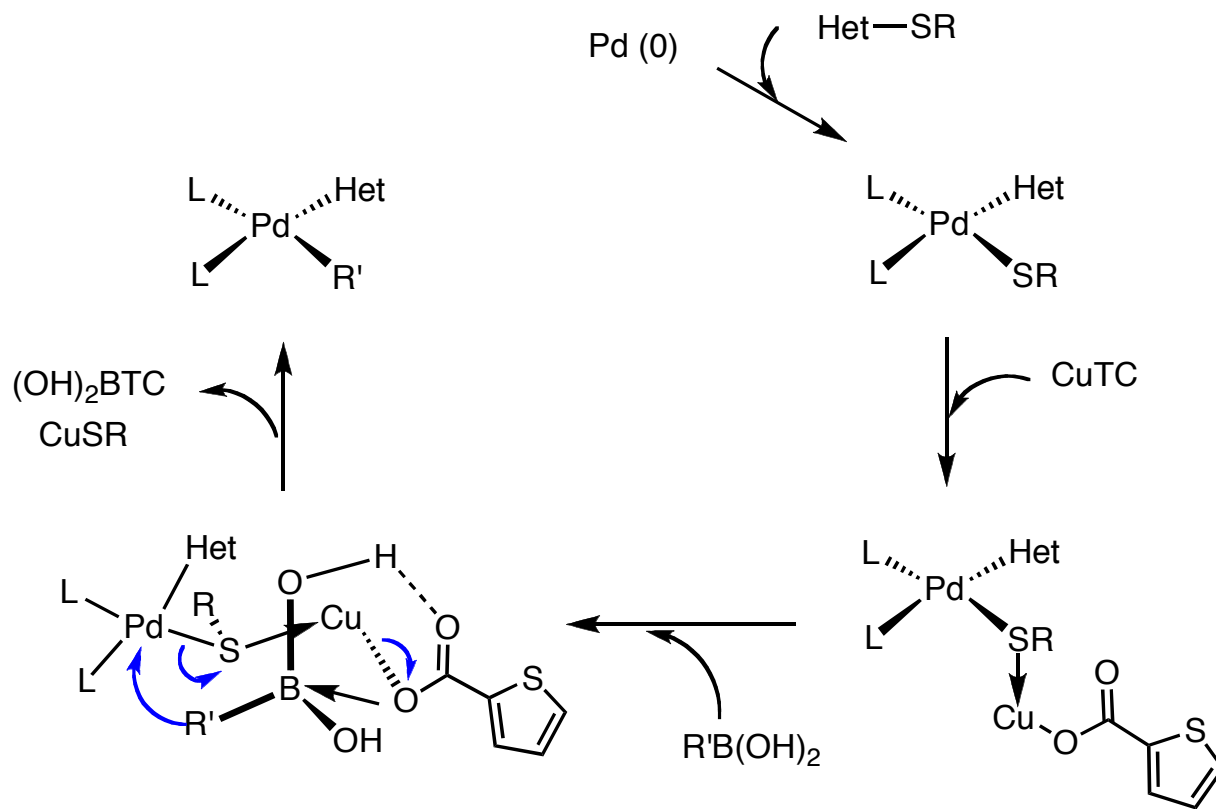
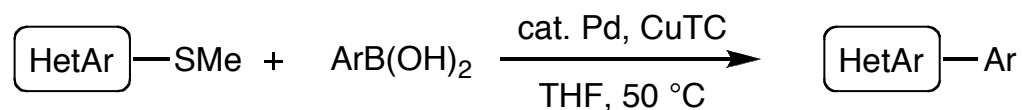
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Catalytic Cycle: Pd-Catalyzed, Cu-Mediated Cross-Coupling



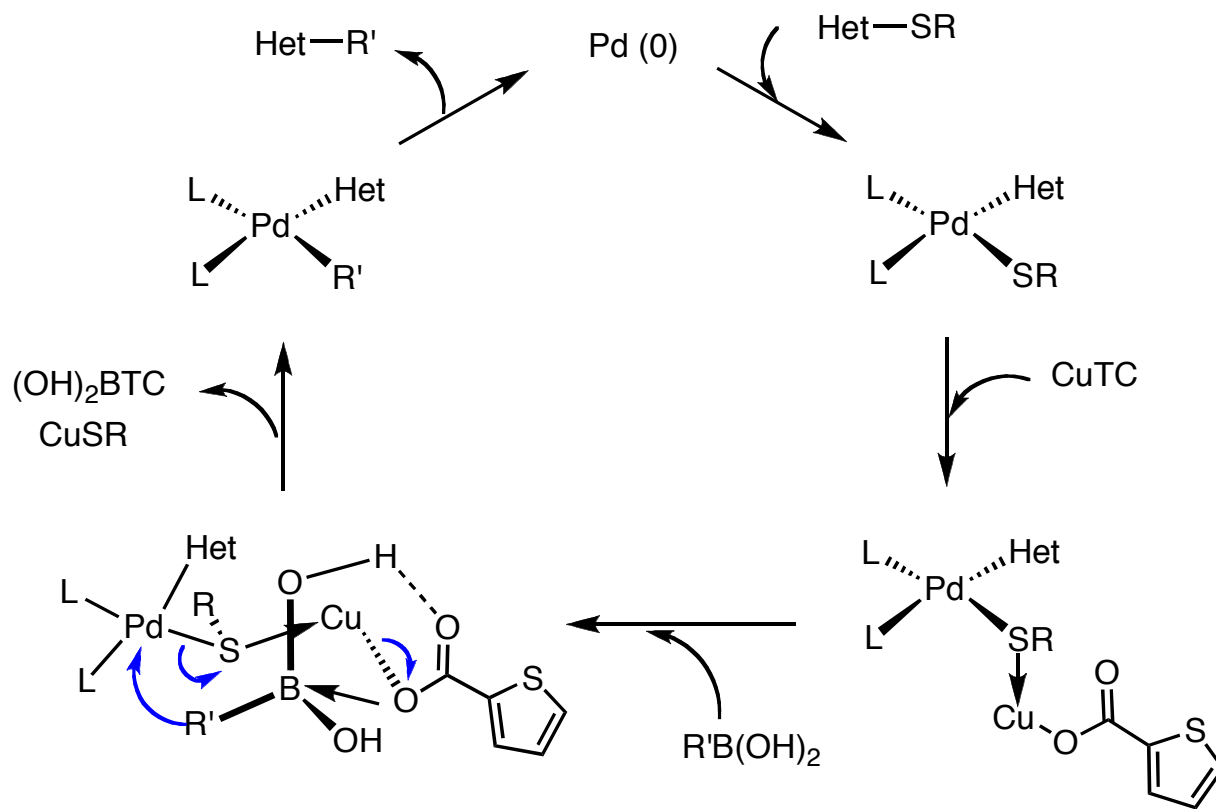
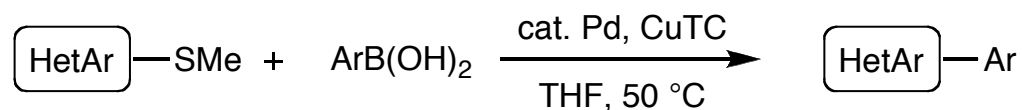
Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979.

Catalytic Cycle: Pd-Catalyzed, Cu-Mediated Cross-Coupling



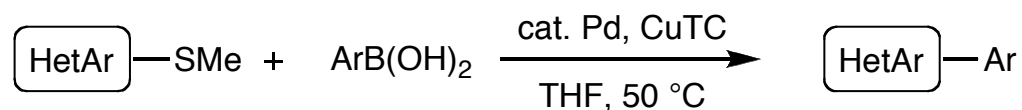
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Catalytic Cycle: Pd-Catalyzed, Cu-Mediated Cross-Coupling

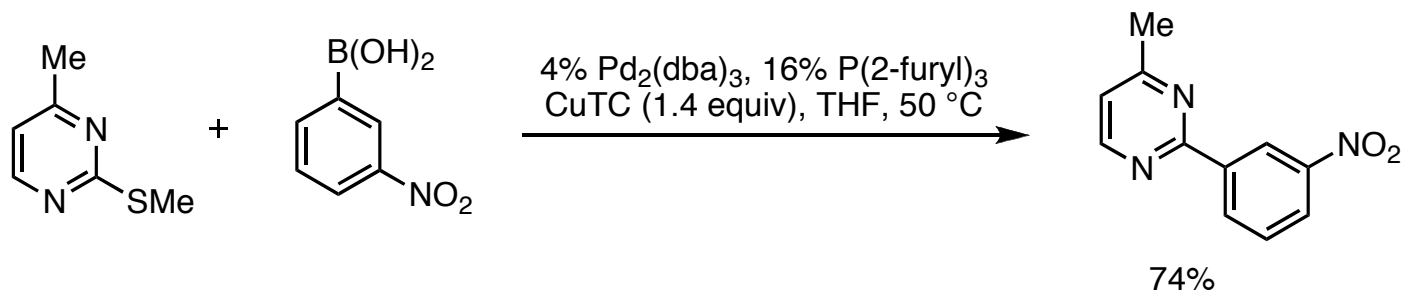


Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979.

Pd-Catalyzed, Cu-Mediated Cross-Coupling

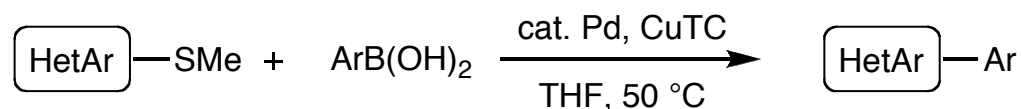


- Efficient Pd-catalyzed, Cu-mediated coupling of heteroaromatic thioethers with boronic acids by Liebeskind and co-workers

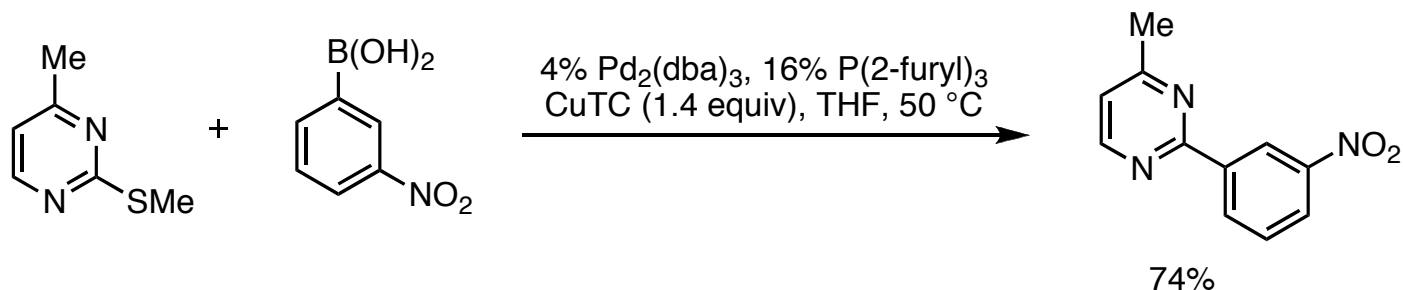


Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979.

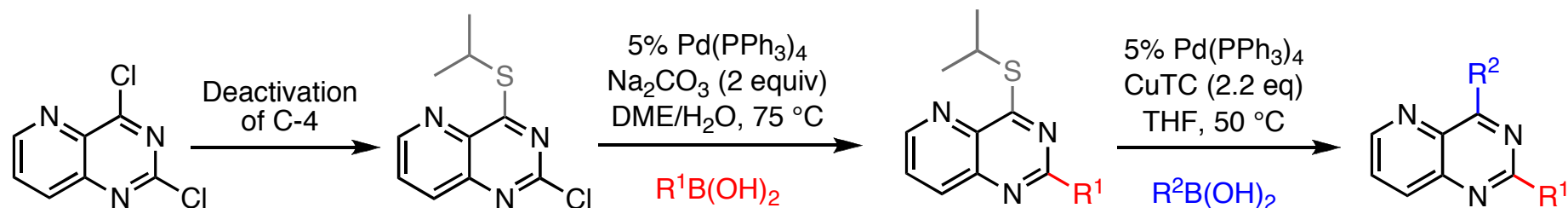
Pd-Catalyzed, Cu-Mediated Cross-Coupling



- Efficient Pd-catalyzed, Cu-mediated coupling of heteroaromatic thioethers with boronic acids by Liebeskind and co-workers



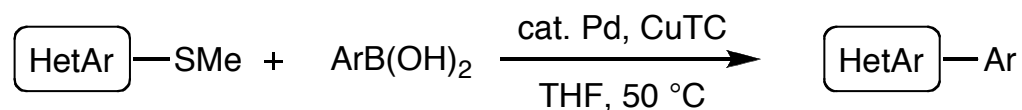
- Preparation of bis-fuctionalized pyridopyrimidine derivatives by Guillaumet and co-workers



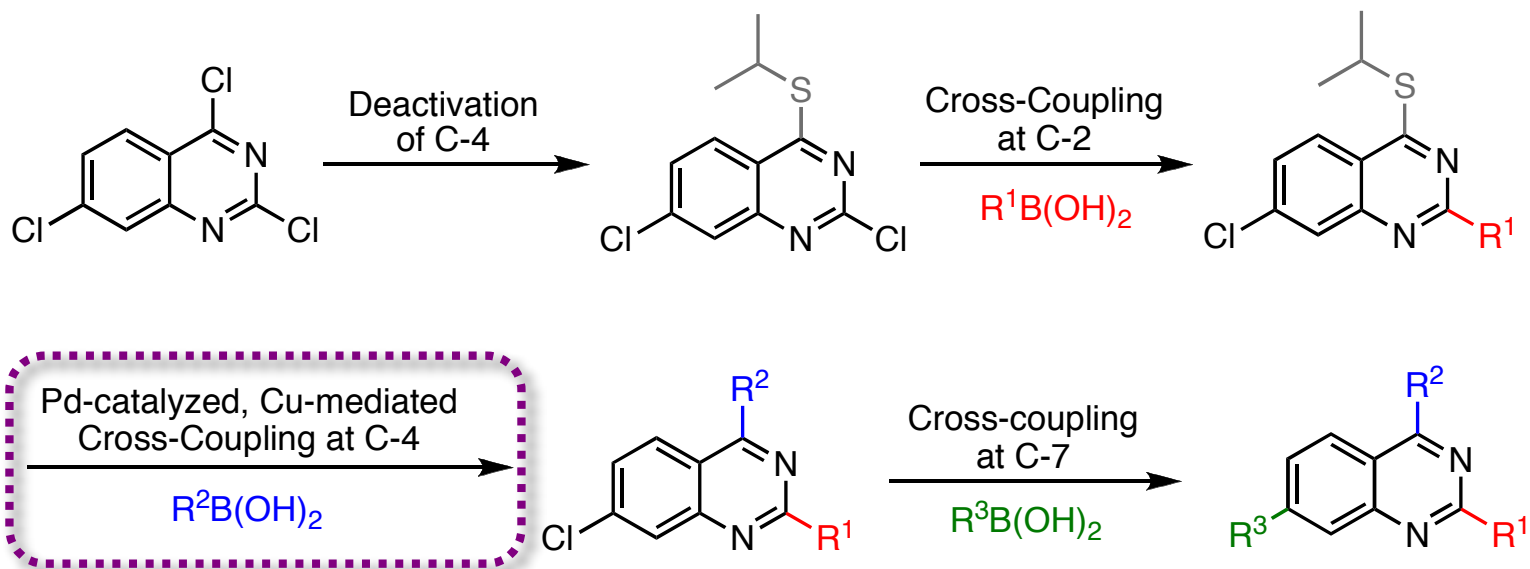
Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979.

Abdellatif, T.; Routier, S.; Akssira, M.; Leger, J.-M.; Jarry, C.; Guillaumet, G. *Org. Lett.* **2007**, *9*, 4673.

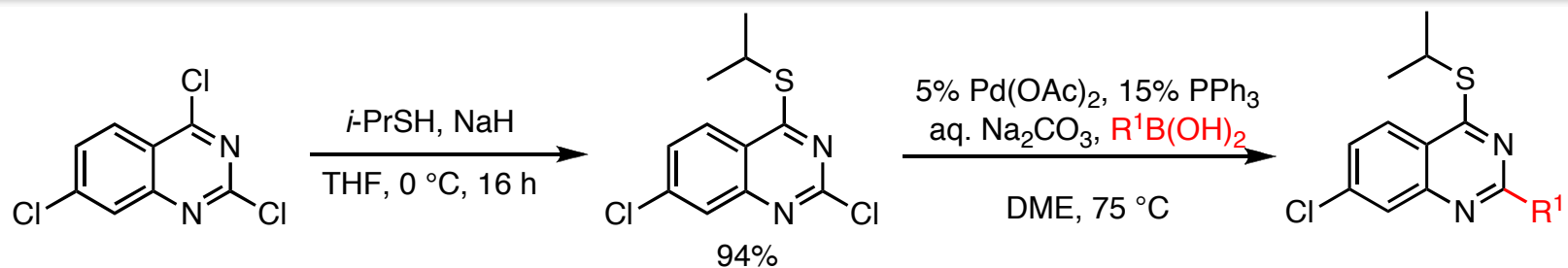
A Third Approach: Pd-Catalyzed, Cu-Mediated Cross-Coupling



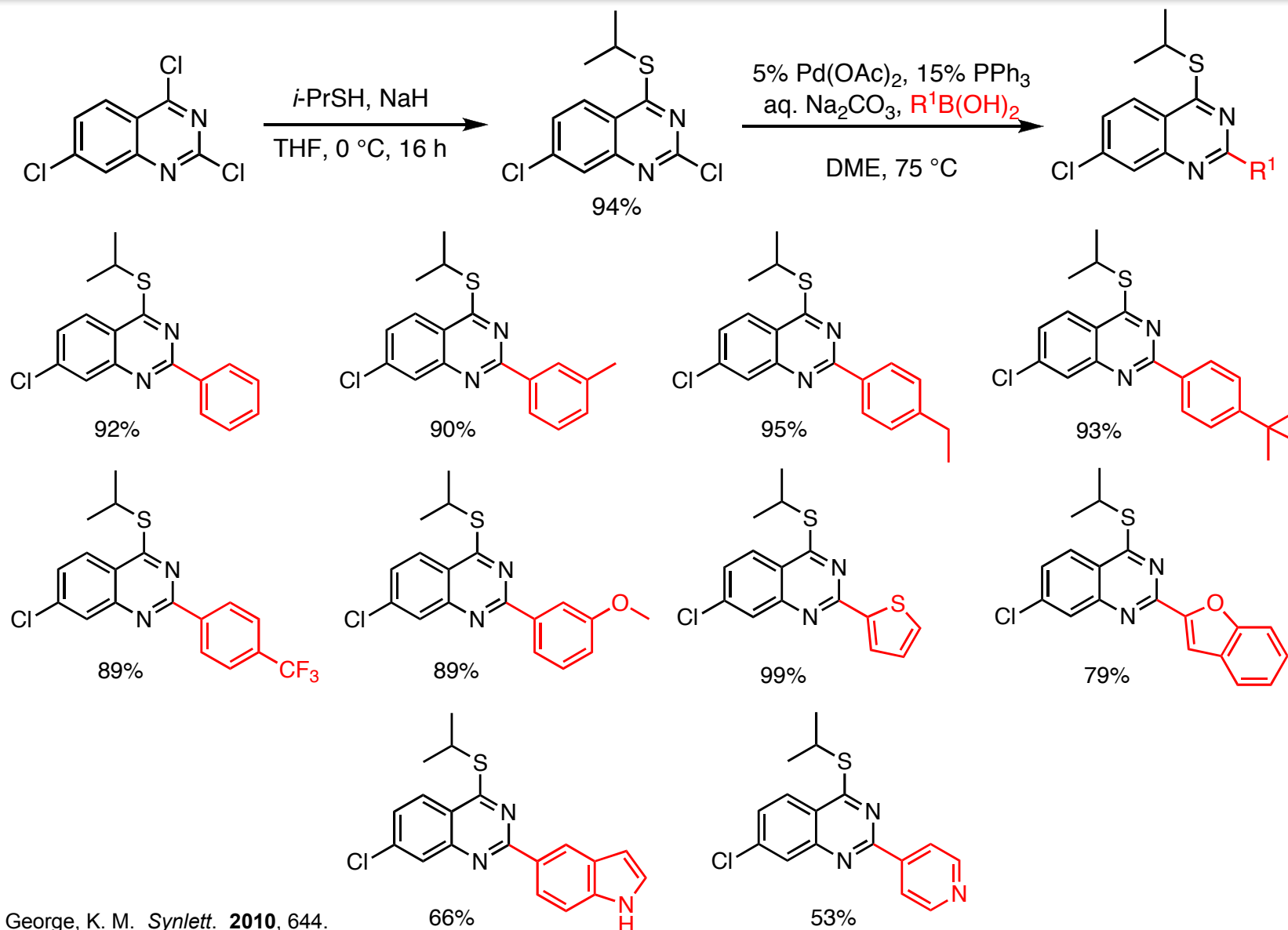
■ New Approach:



Regioselective Pd-Catalyzed Cross-Coupling at C-2

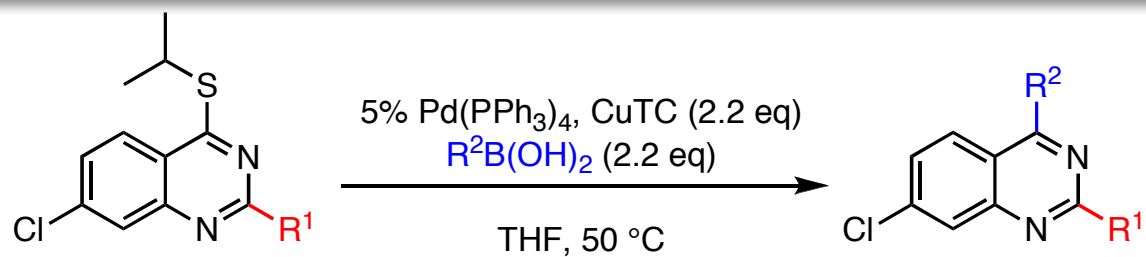


Regioselective Pd-Catalyzed Cross-Coupling at C-2

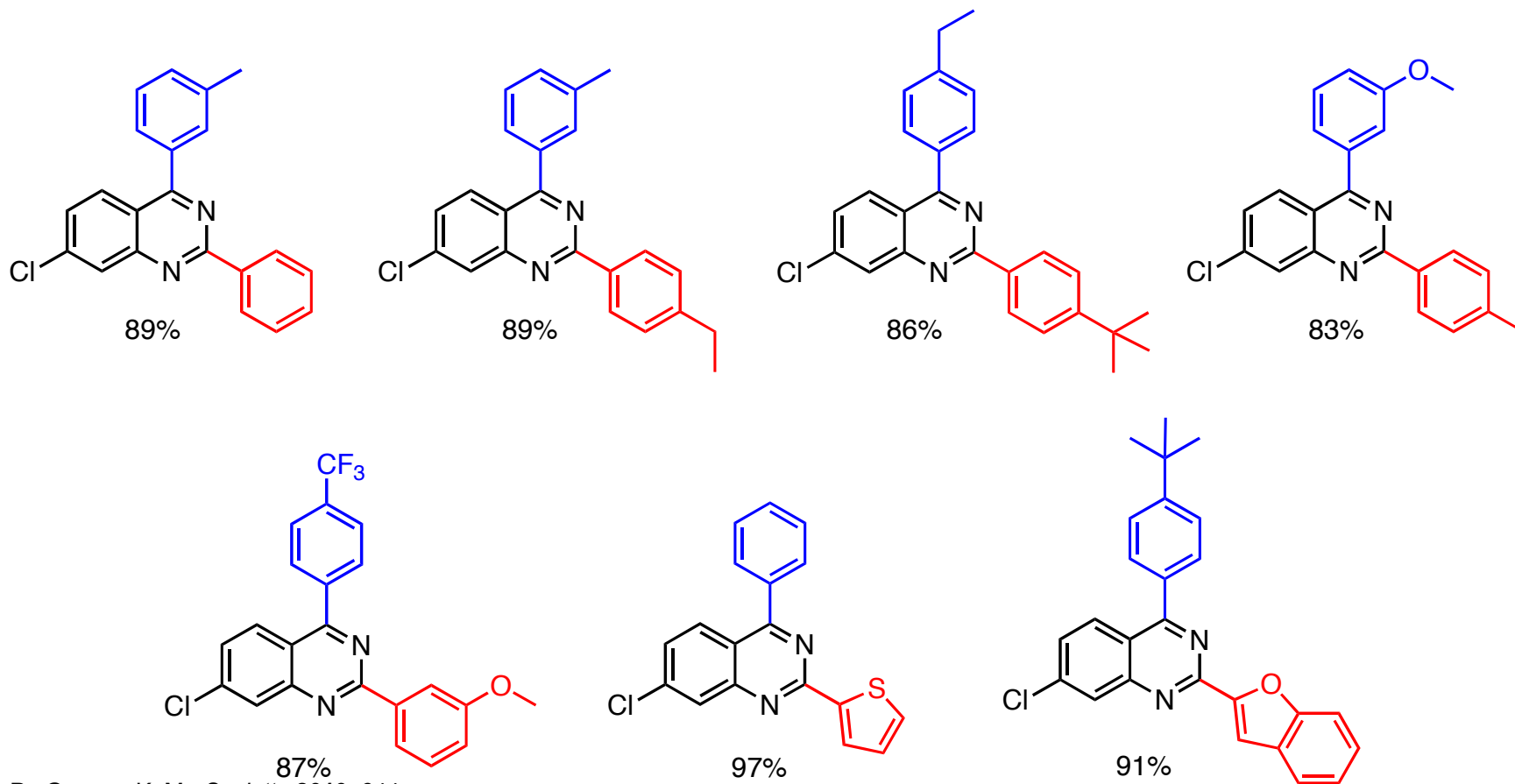
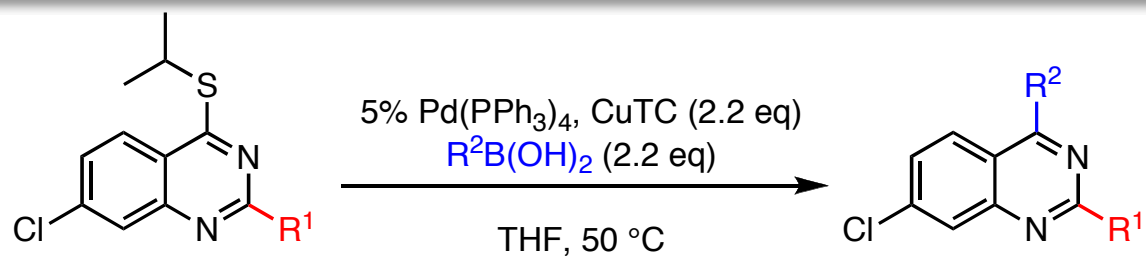


Wipf, P.; George, K. M. *Synlett*. 2010, 644.

Pd-Catalyzed, Cu-Mediated Cross-Coupling at C-4

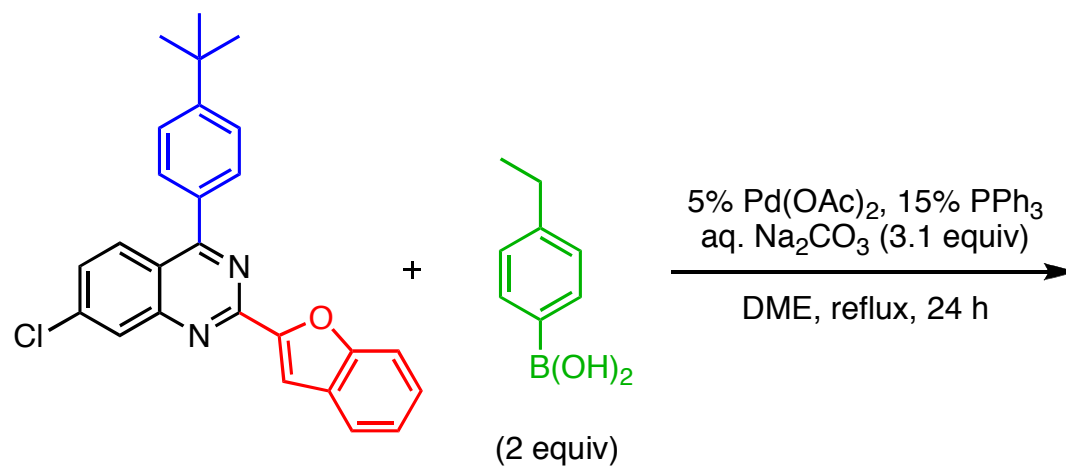


Pd-Catalyzed, Cu-Mediated Cross-Coupling at C-4

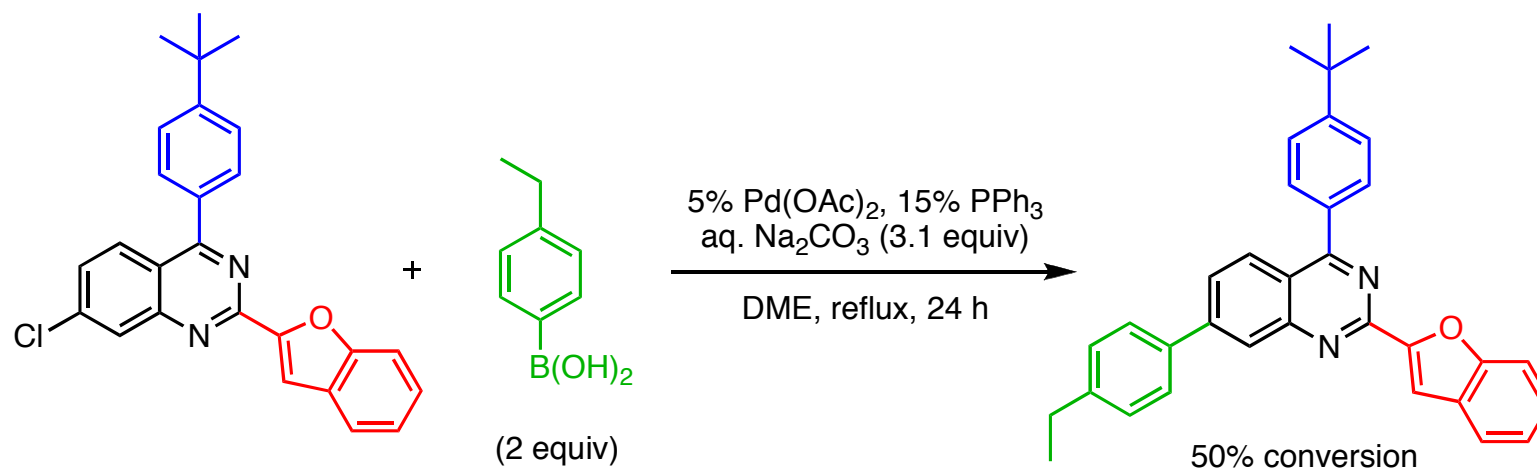


Wipf, P.; George, K. M. *Synlett*. 2010, 644.

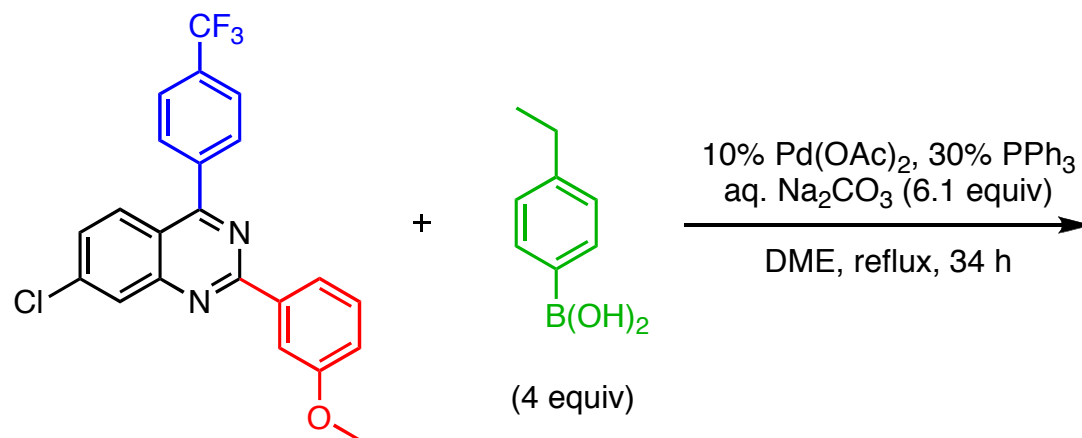
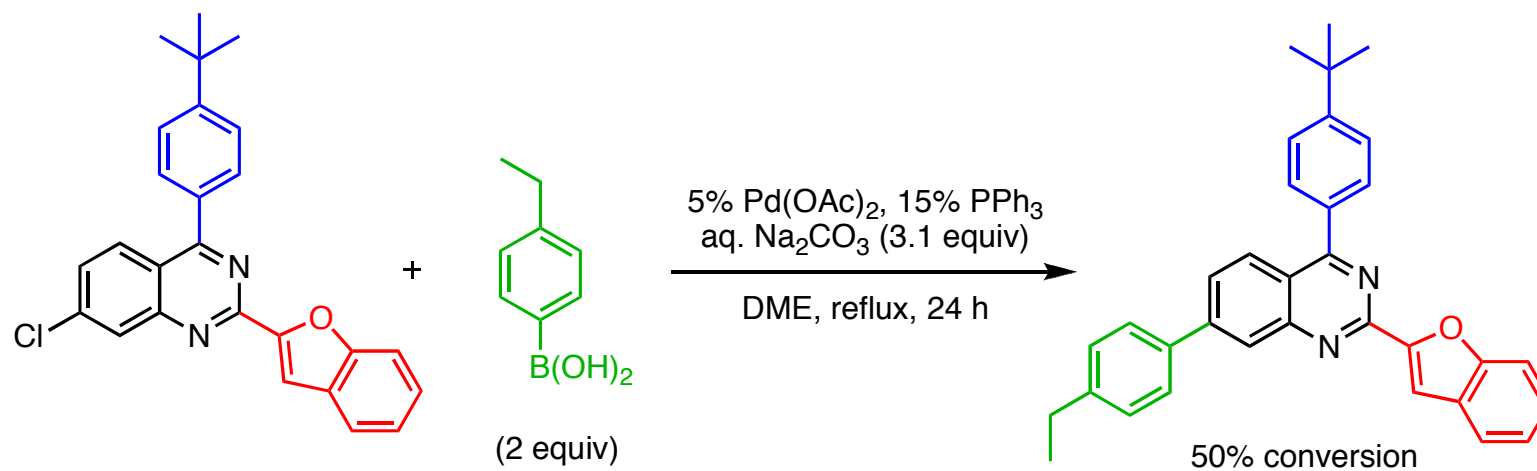
Final Cross-Coupling at C-7



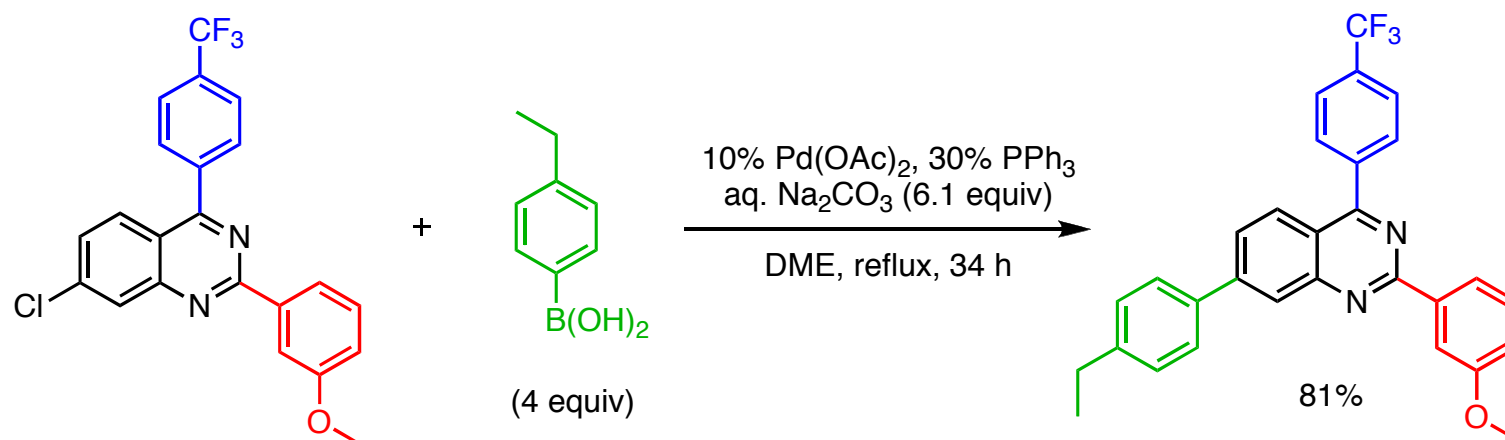
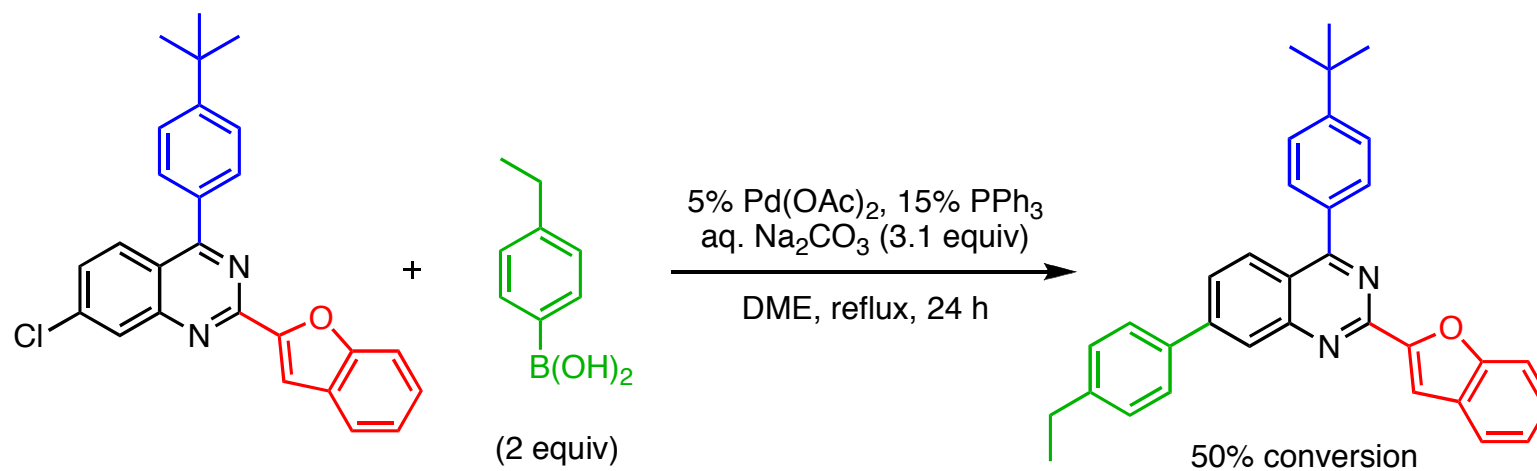
Final Cross-Coupling at C-7



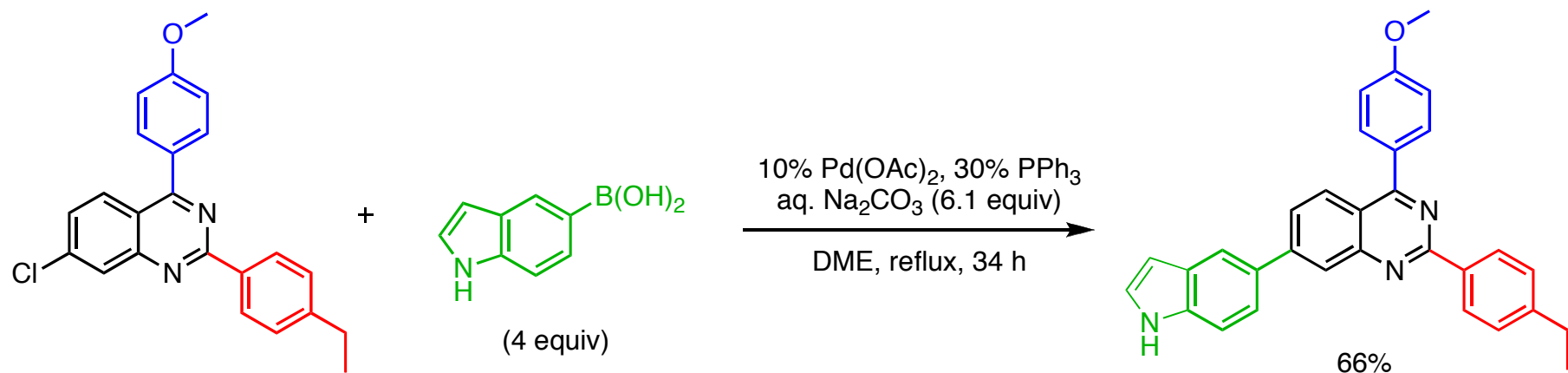
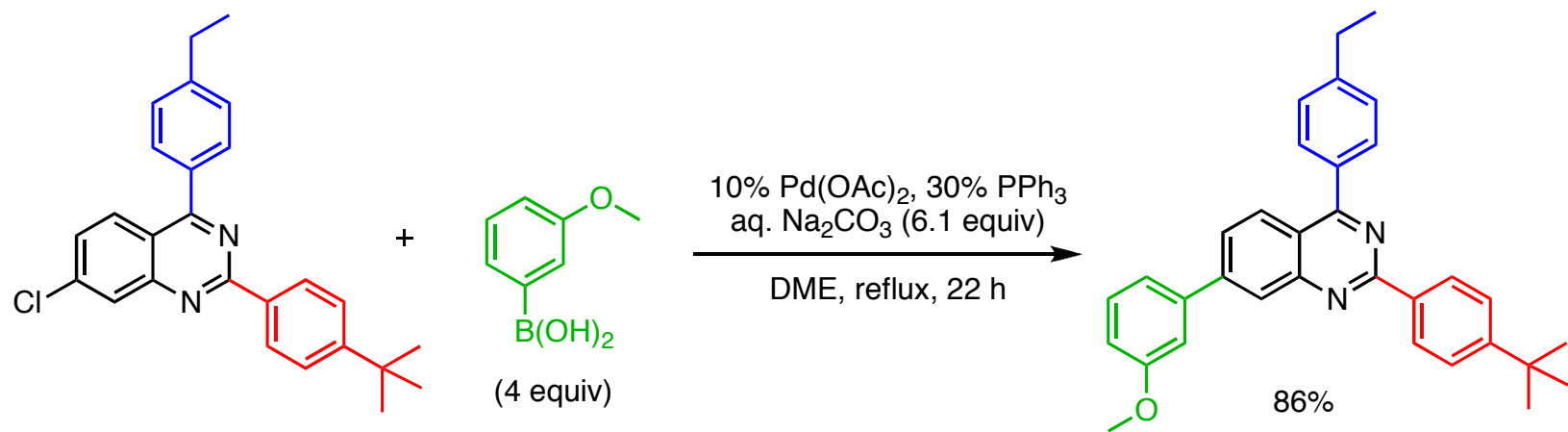
Final Cross-Coupling at C-7



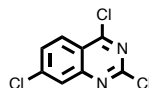
Final Cross-Coupling at C-7



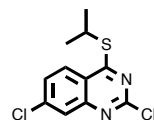
Final Cross-Coupling at C-7



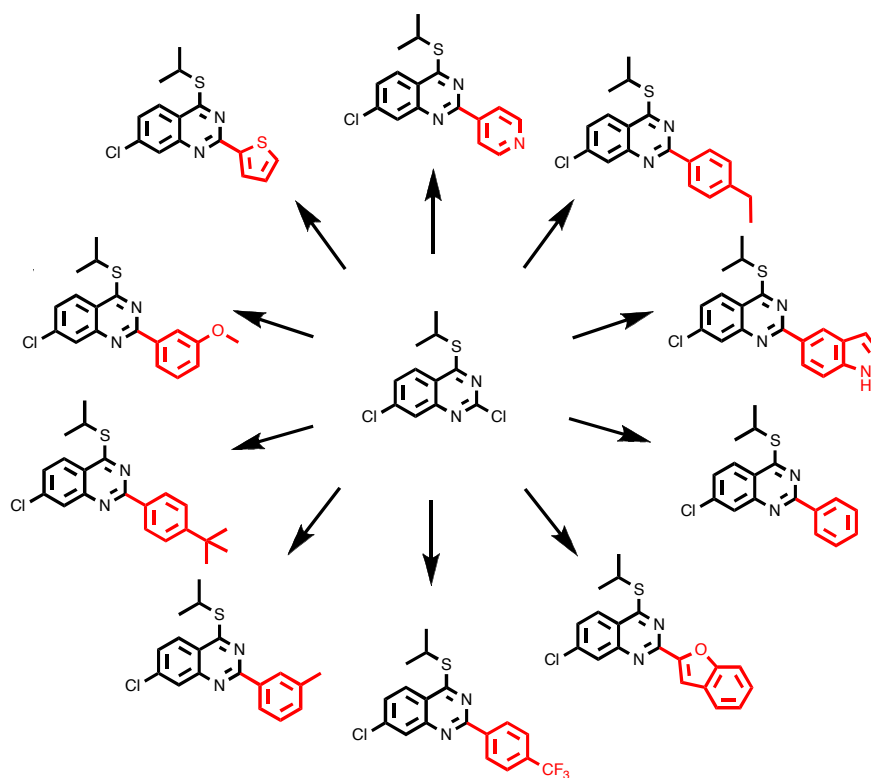
Subsequent Regioselective Cross-Coupling Reactions of 2,4,7-Trichloroquinazoline



Subsequent Regioselective Cross-Coupling Reactions of 2,4,7-Trichloroquinazoline

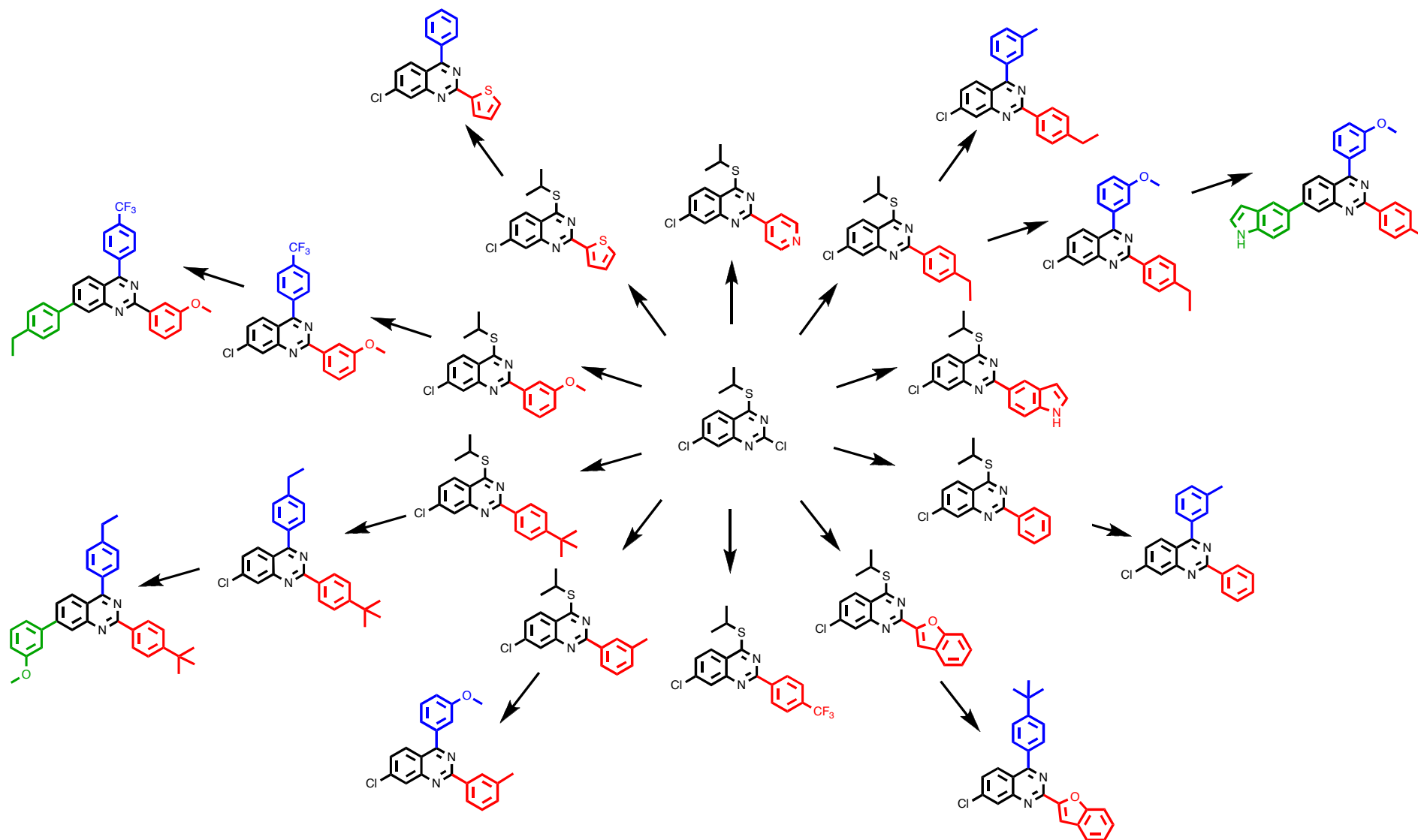


Subsequent Regioselective Cross-Coupling Reactions of 2,4,7-Trichloroquinazoline



Wipf, P.; George, K. M. *Synlett.* **2010**, 644.

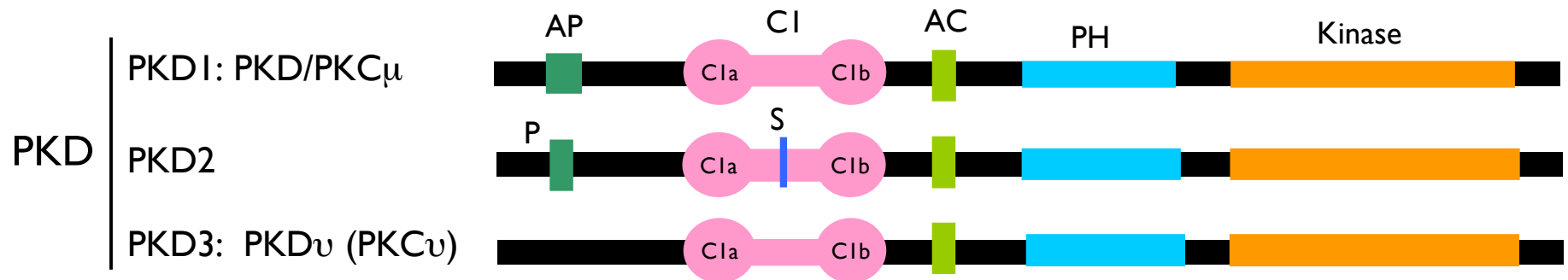
Subsequent Regioselective Cross-Coupling Reactions of 2,4,7-Trichloroquinazoline



Wipf, P.; George, K. M. *Synlett*. 2010, 644.

Introduction: Protein Kinase D

- Constitutes a novel family of serine/threonine kinases and diacylglycerol (DAG) receptors that belong to the Ca^{2+} /calmodulin-dependent kinase (CaMK) superfamily
- Three PKD isoforms: PKD1 ($\text{PKC}\mu$), PKD2, PKD3 ($\text{PKC}\nu$)
- PKD has been linked to a diverse set of signal transduction pathways involved in tumor development and cancer progression

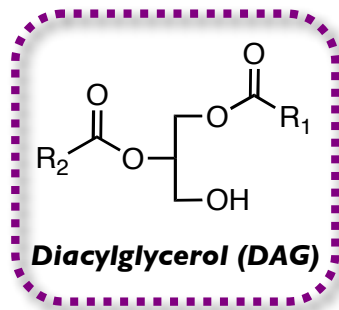
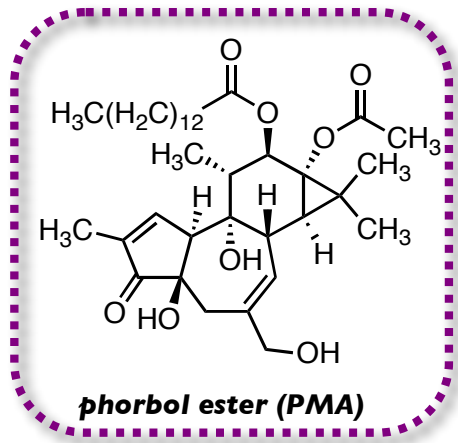
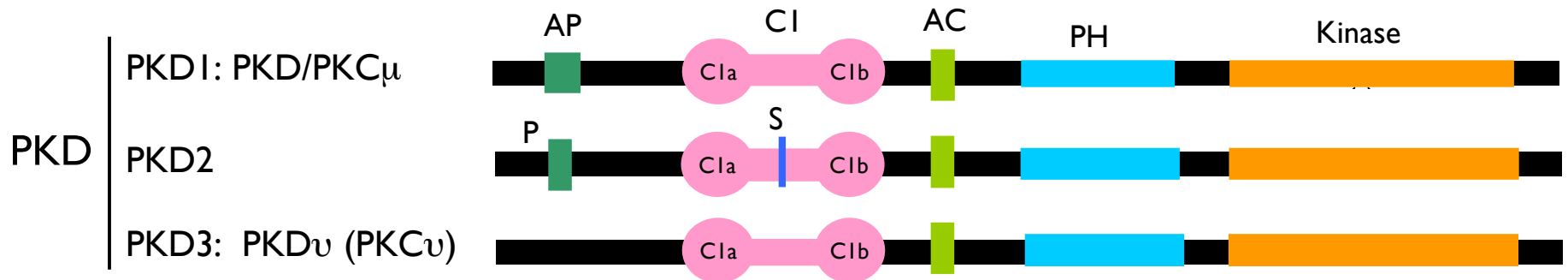


Wang, Q. J. *Trends in Pharmacol. Sci.* **2006**, 27, 317.

For reviews see: Rozengurt, E.; Rey, O.; Waldron, R. T. *J. Bio. Chem* **2005**, 280, 13205.

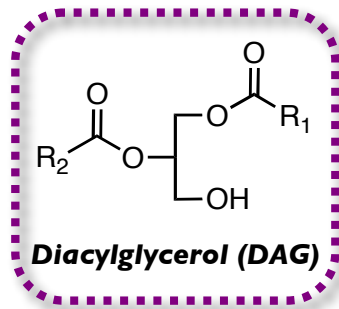
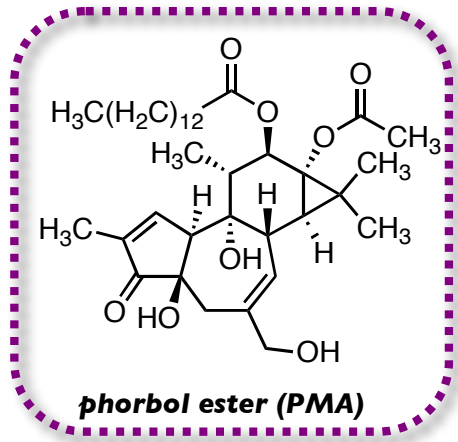
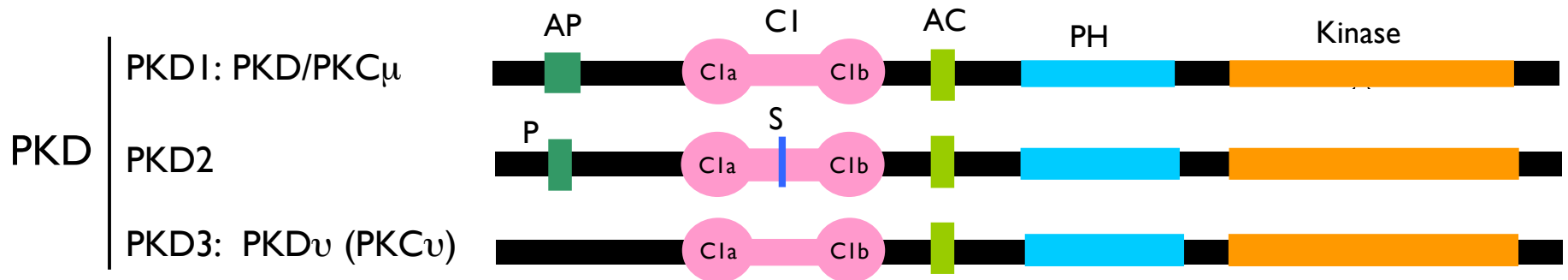
LaValle, C. R.; George, K. M.; Sharlow, E. R.; Lazo, J. S.; Wipf, P.; Wang, Q. J. *BBA Rev. Cancer.* **2010**, in press

Introduction: Protein Kinase D



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Introduction: Protein Kinase D

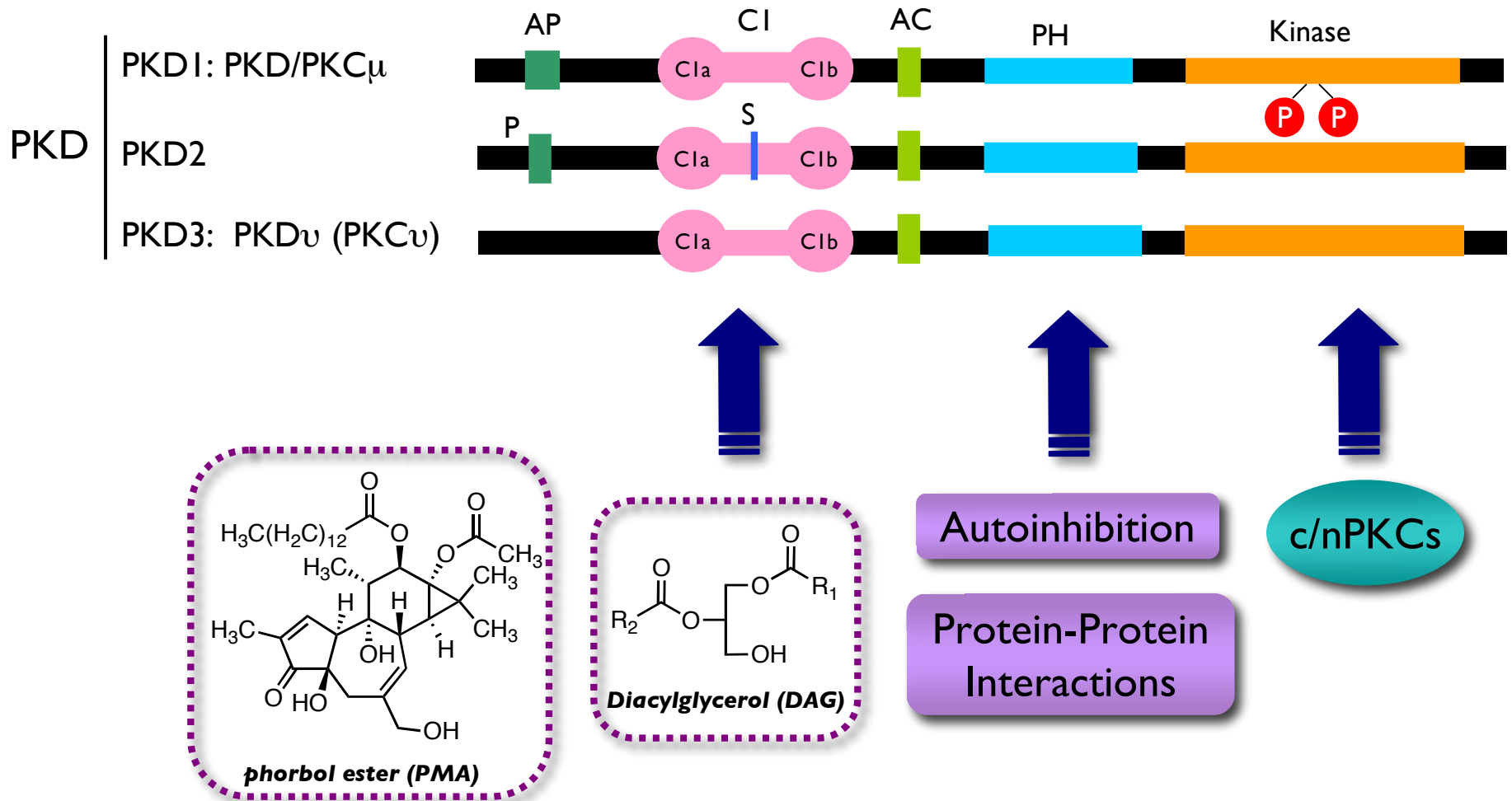


Autoinhibition

Protein-Protein Interactions

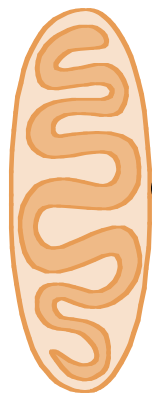
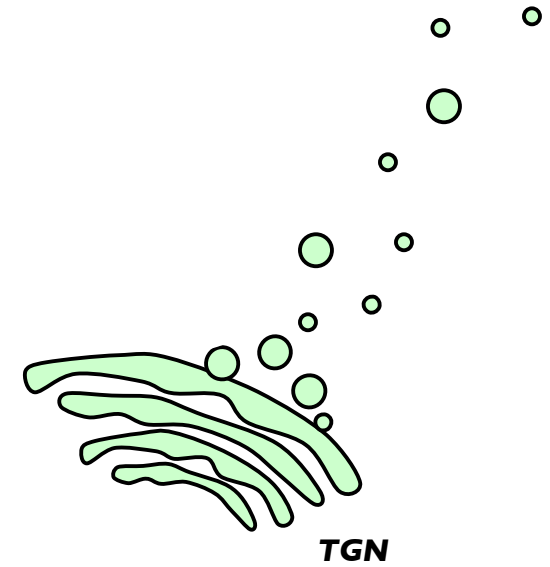
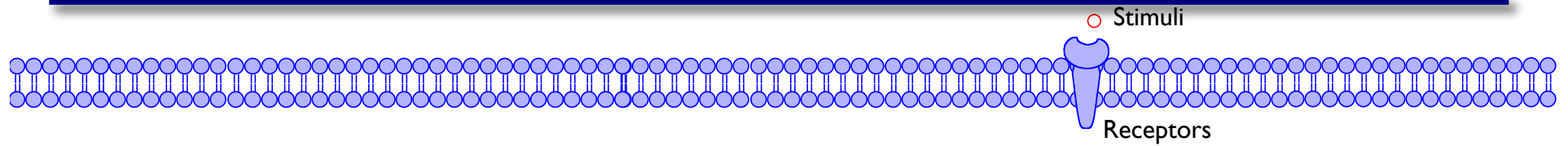
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Introduction: Protein Kinase D

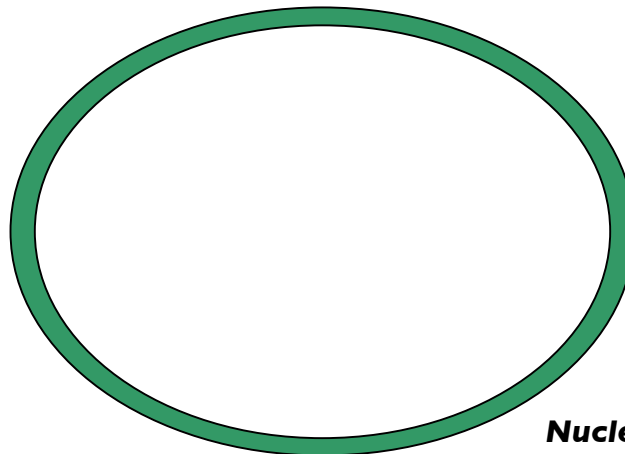


Wang, Q. J. *Trends in Pharmacol. Sci.* **2006**, 27, 317.

Protein Kinase D Signaling Pathway



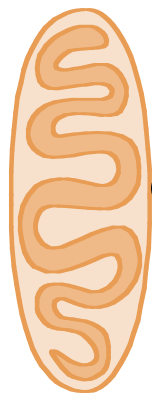
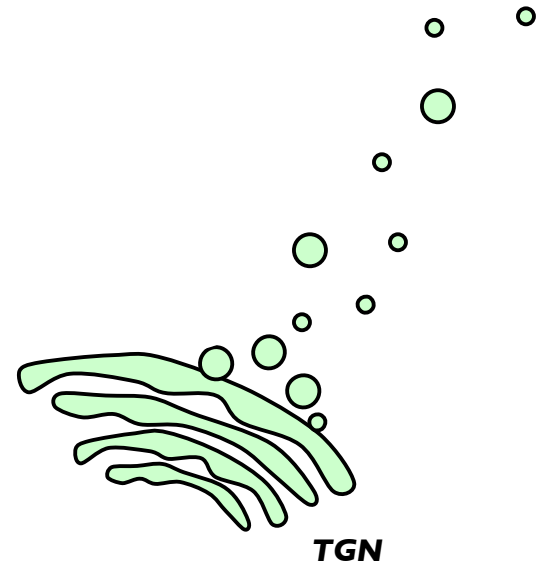
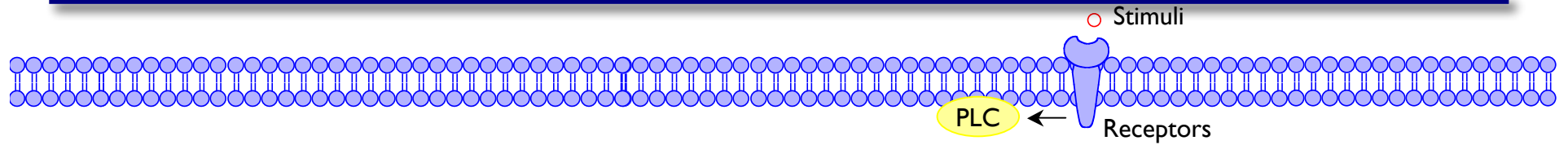
Mitochondria



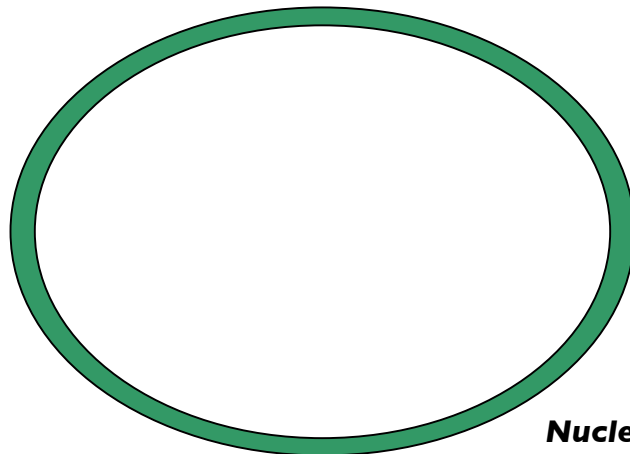
Nucleus

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Protein Kinase D Signaling Pathway



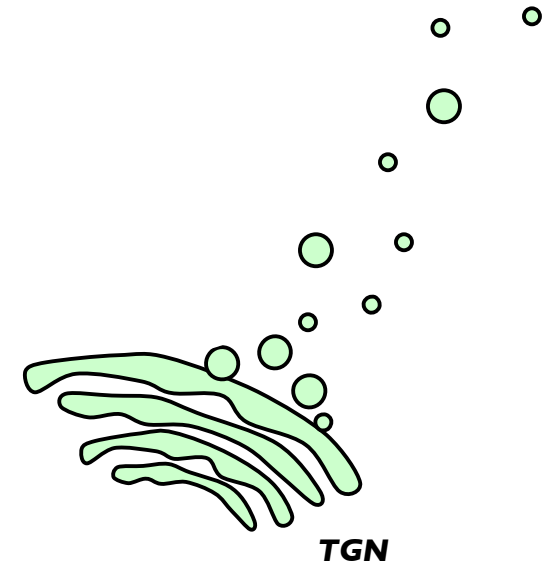
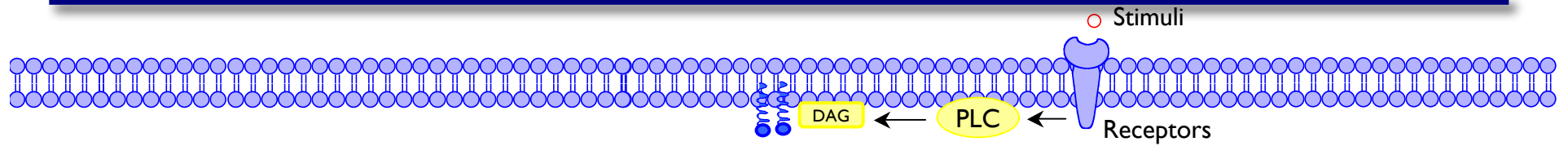
Mitochondria



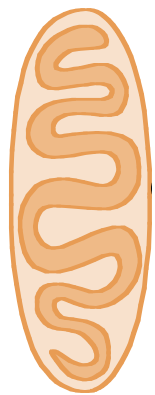
Nucleus

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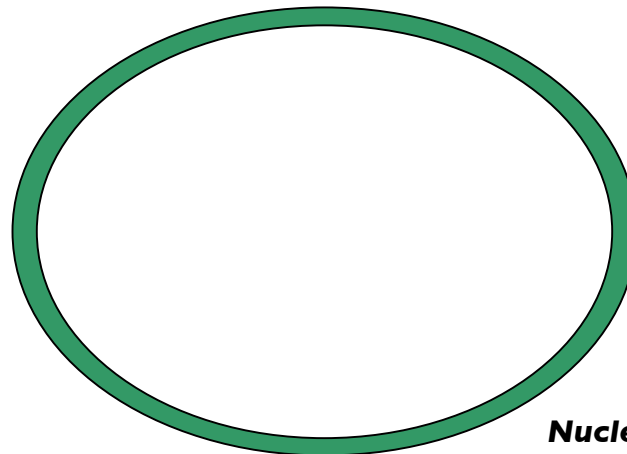
Protein Kinase D Signaling Pathway



TGN



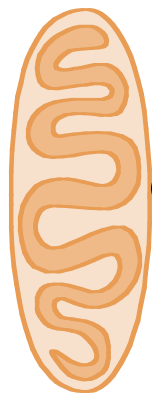
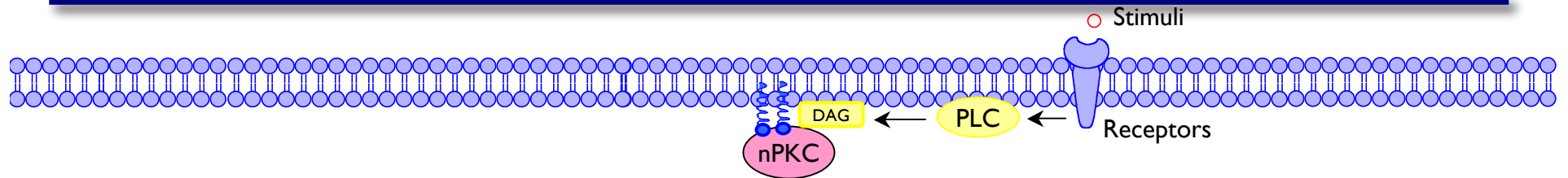
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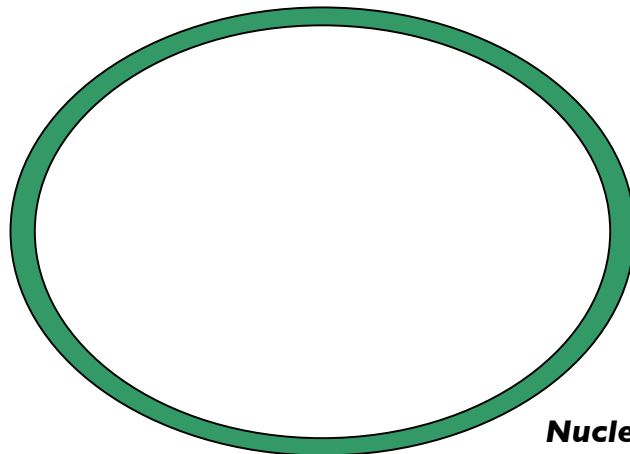
Nucleus

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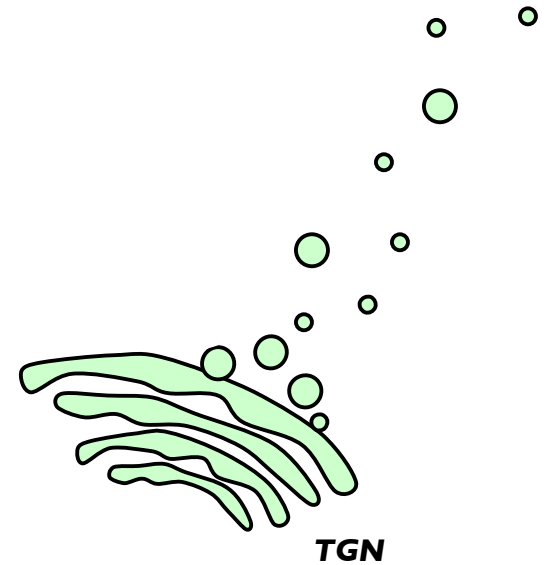
Protein Kinase D Signaling Pathway



Mitochondria

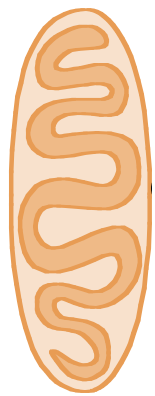
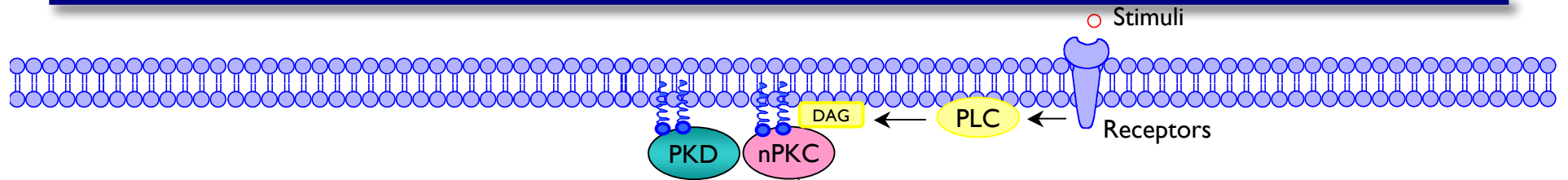


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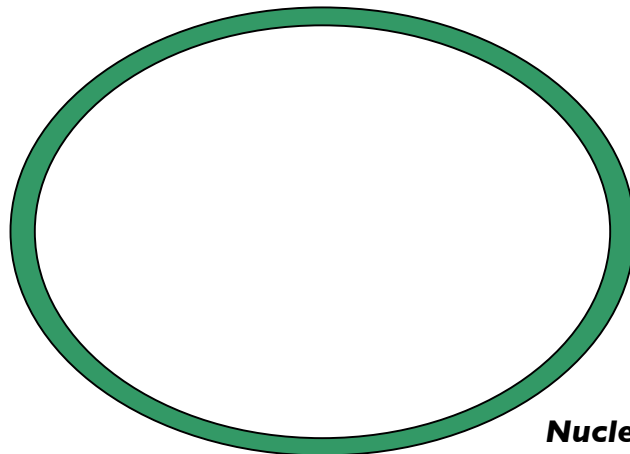


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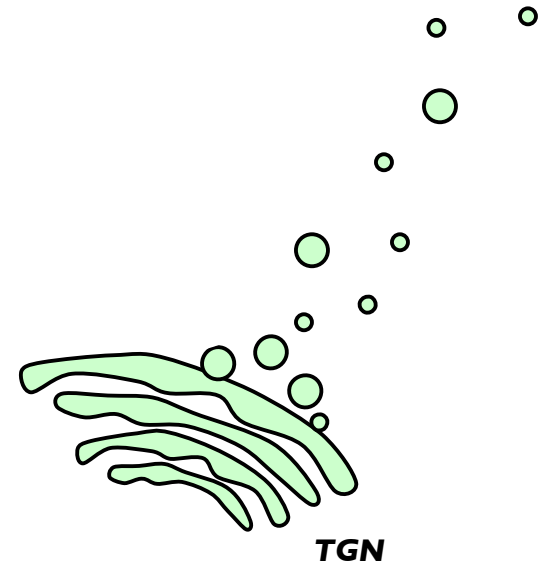
Protein Kinase D Signaling Pathway



Mitochondria



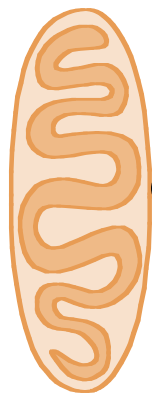
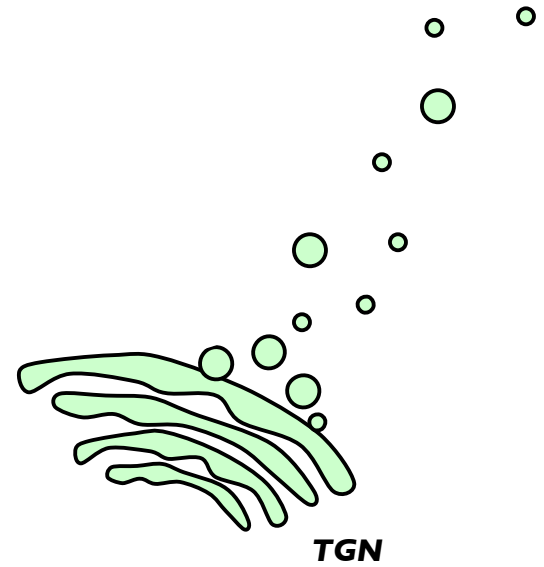
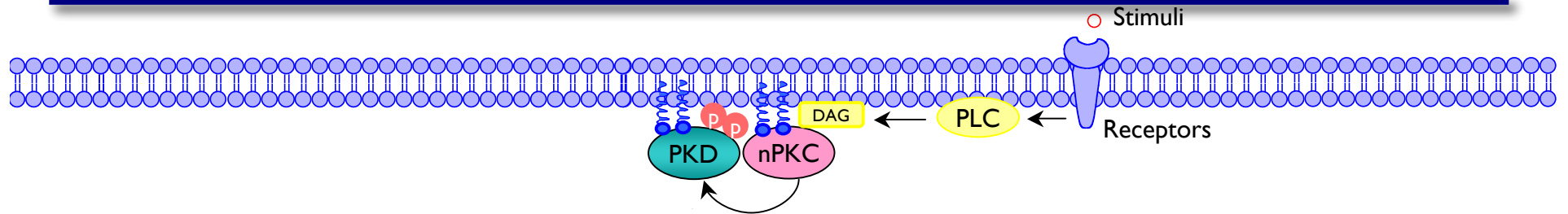
Nucleus



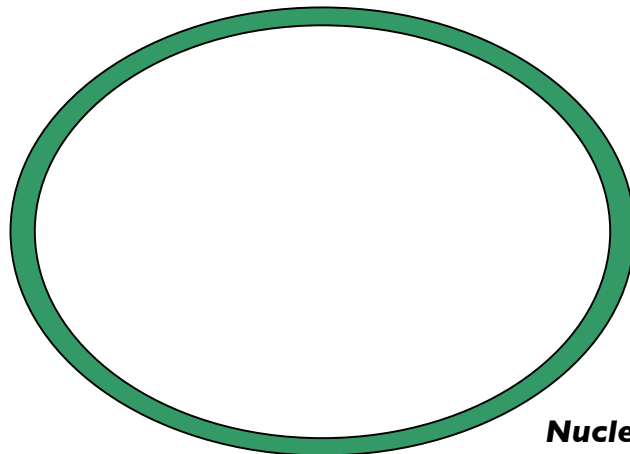
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Protein Kinase D Signaling Pathway



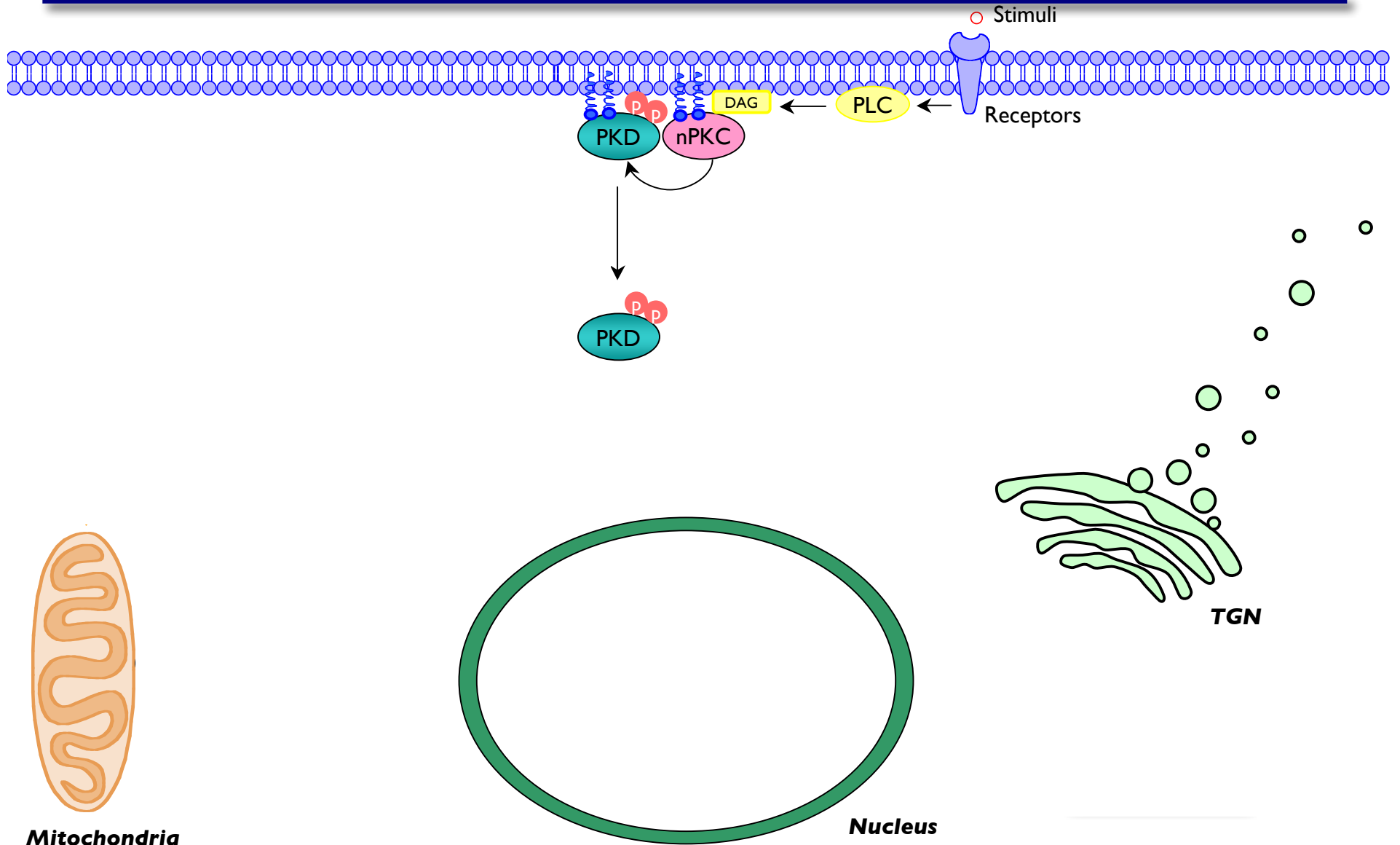
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Nucleus

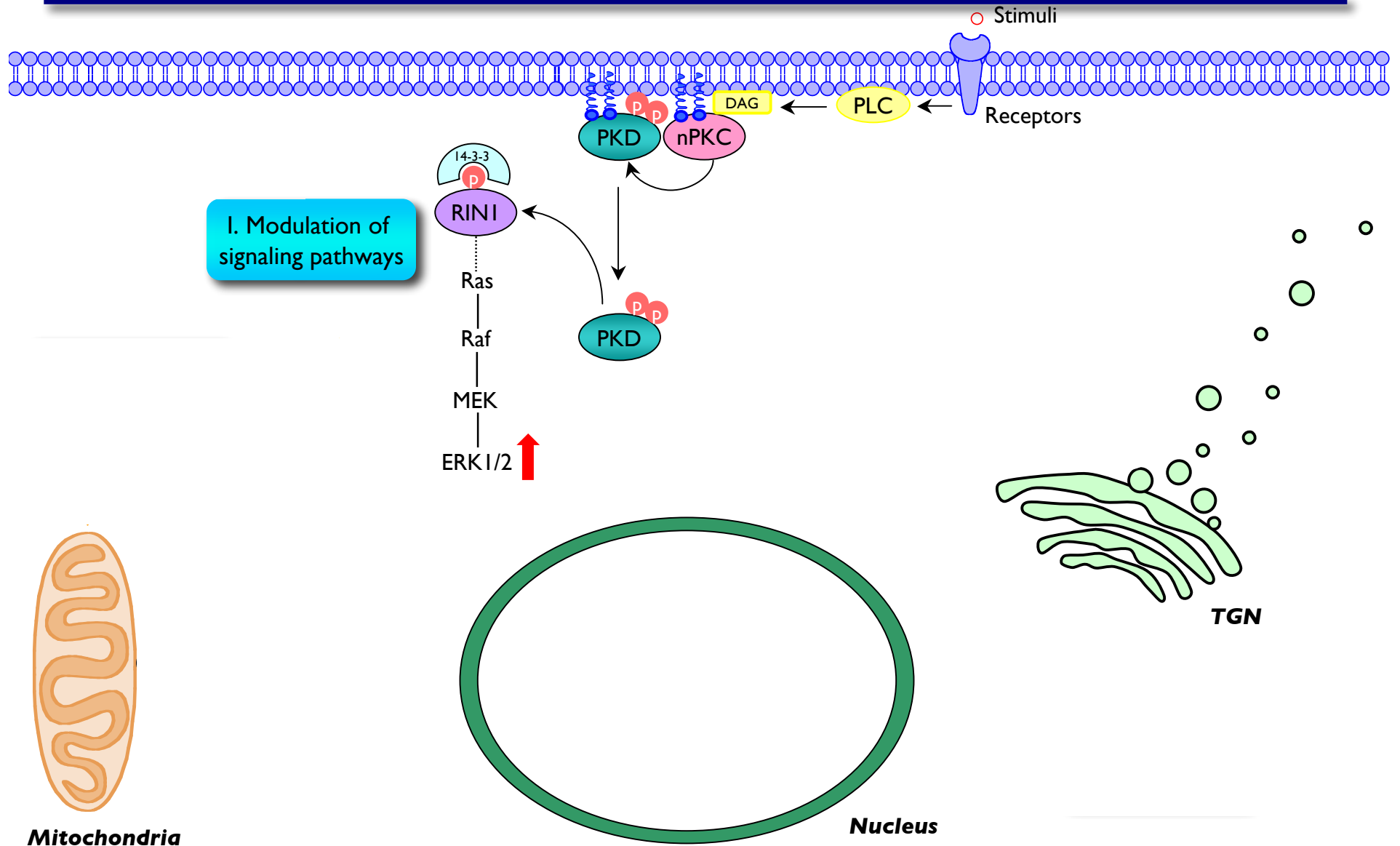
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Protein Kinase D Signaling Pathway



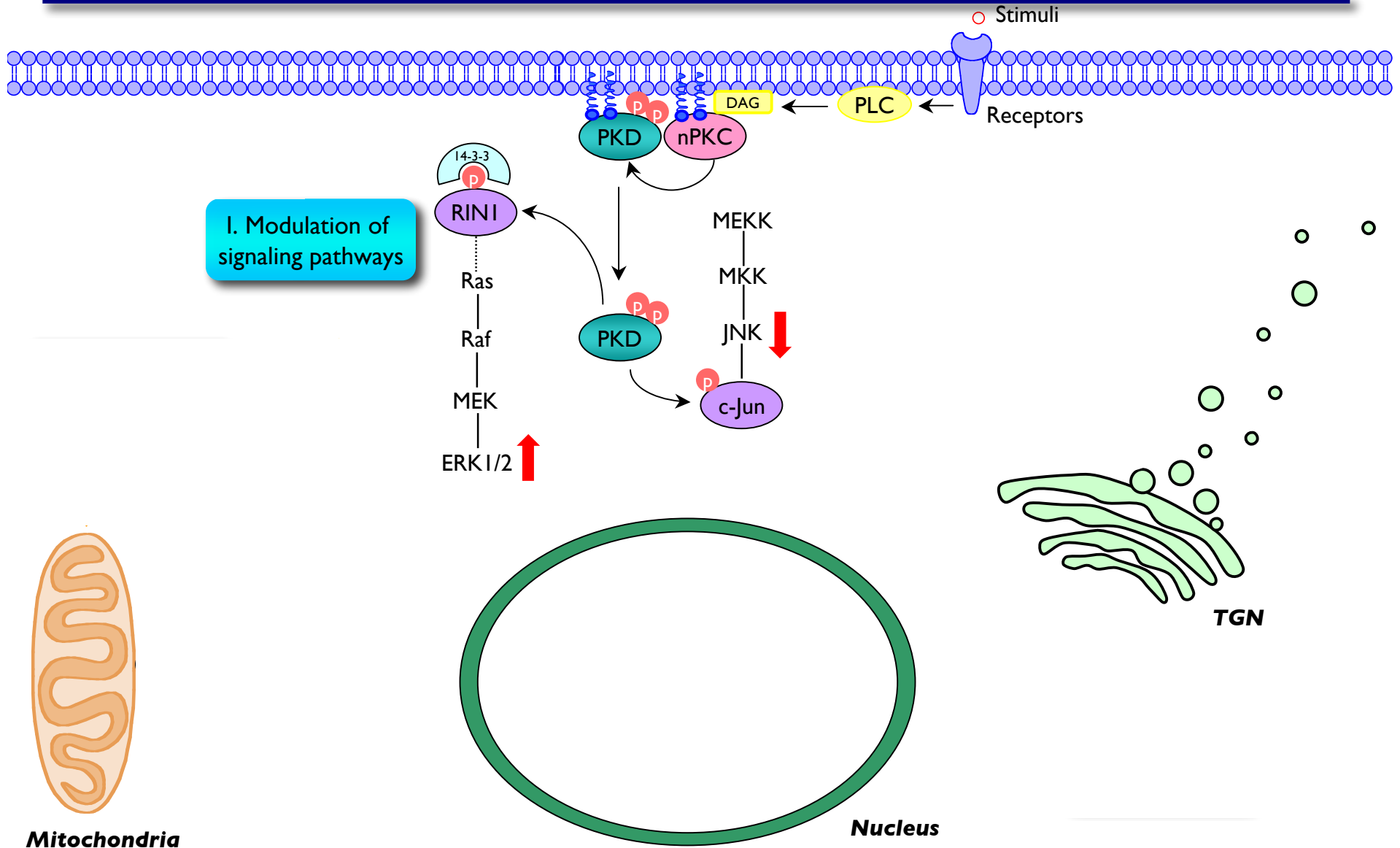
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Protein Kinase D Signaling Pathway



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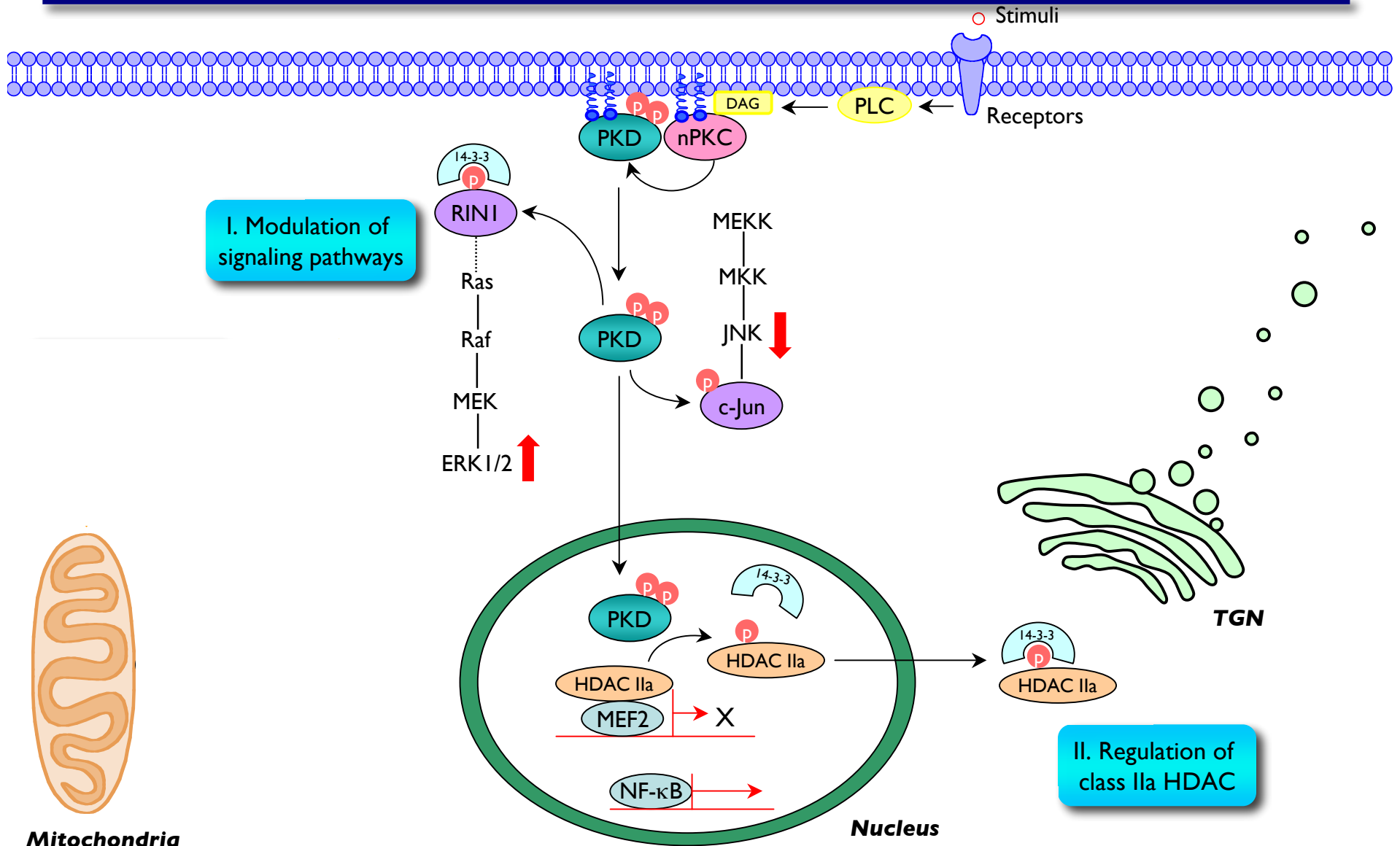
Protein Kinase D Signaling Pathway



I. Modulation of signaling pathways

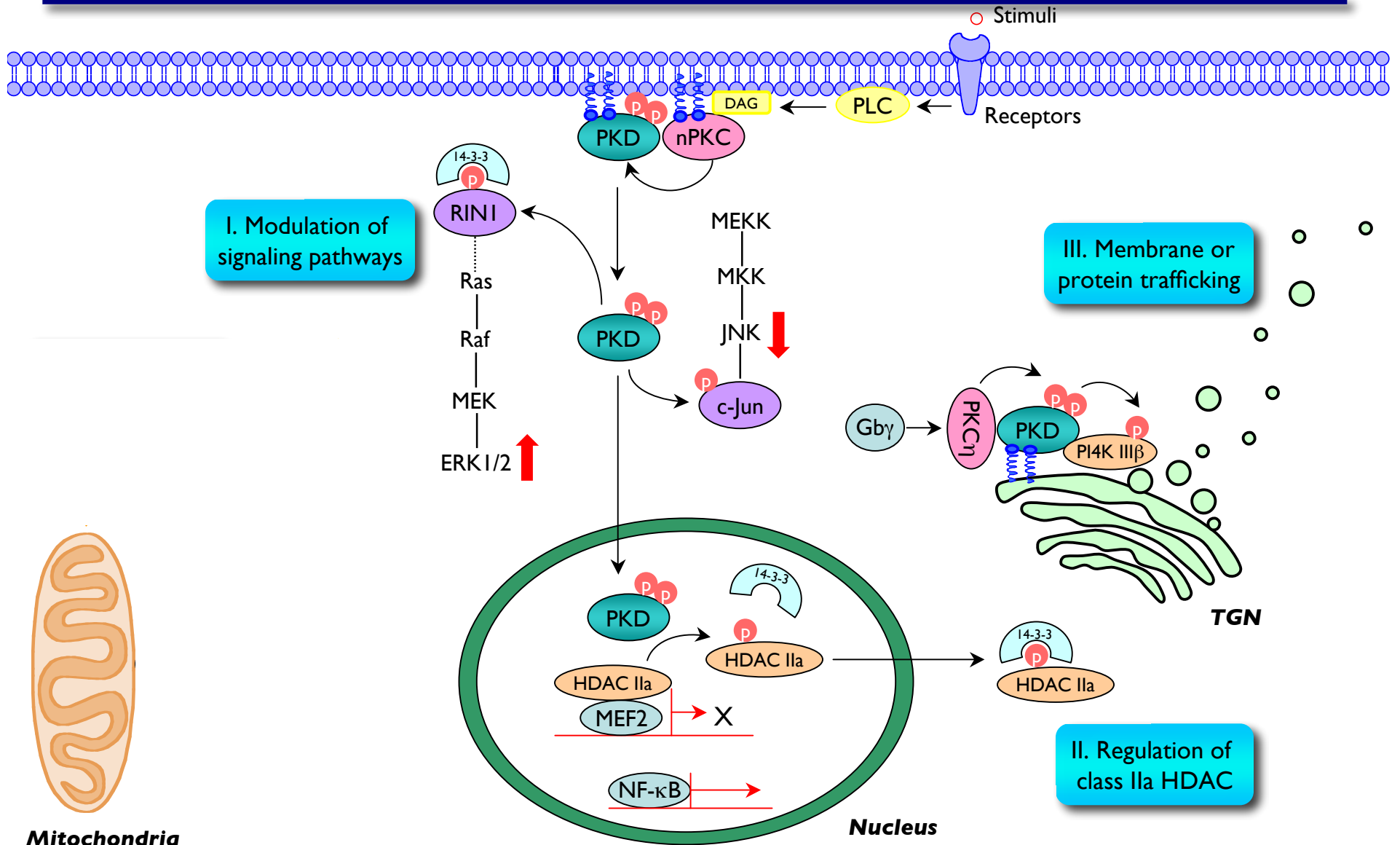
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Protein Kinase D Signaling Pathway



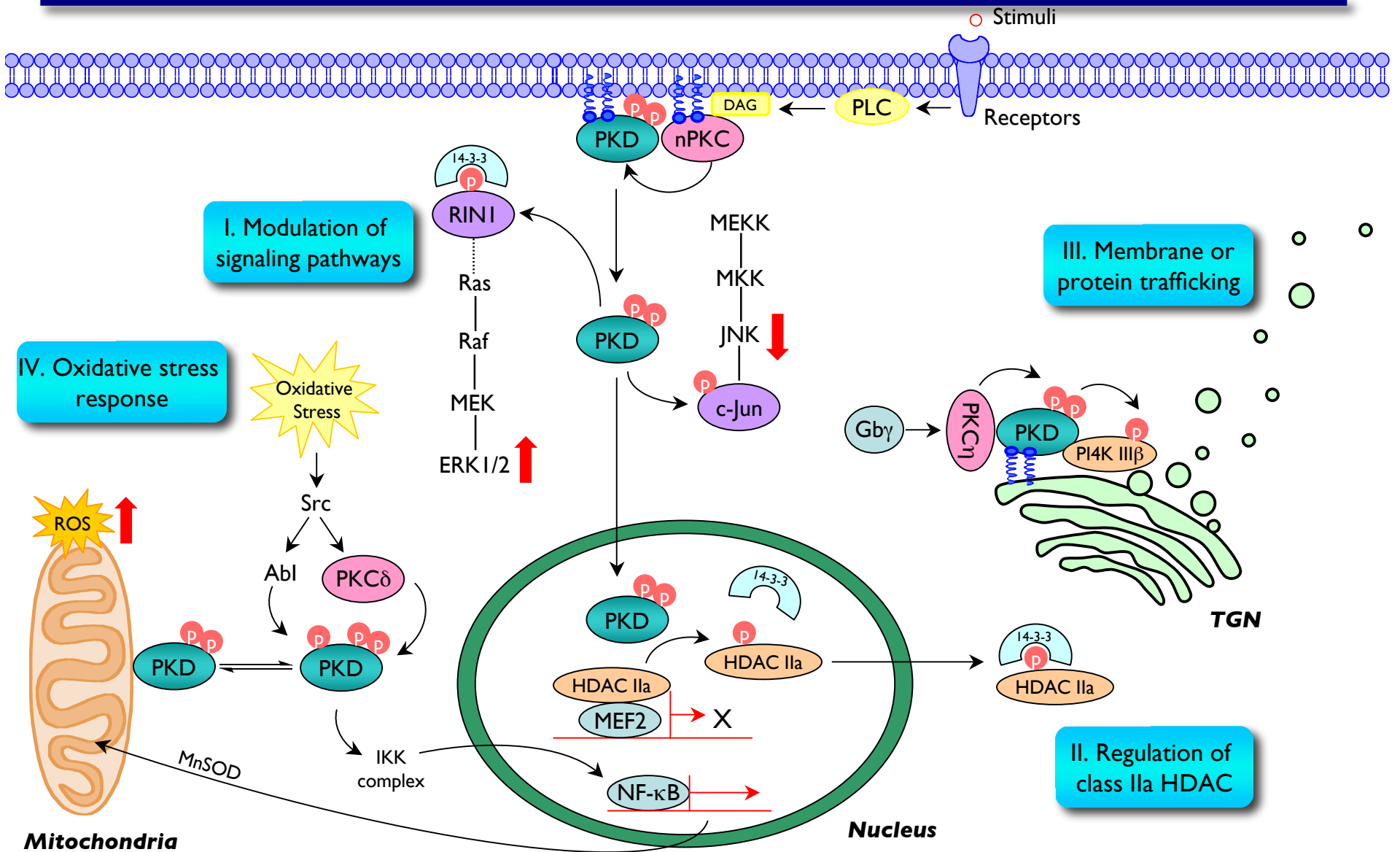
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Protein Kinase D Signaling Pathway



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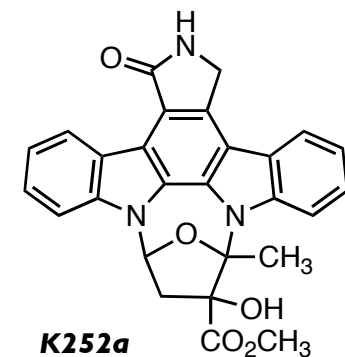
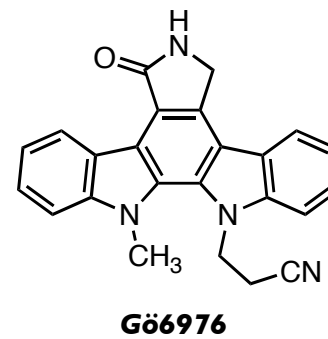
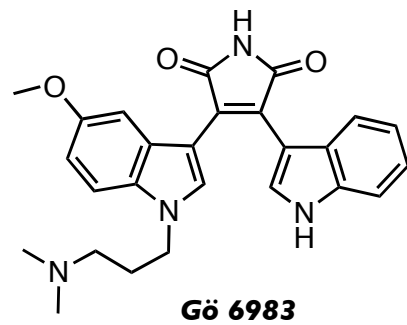
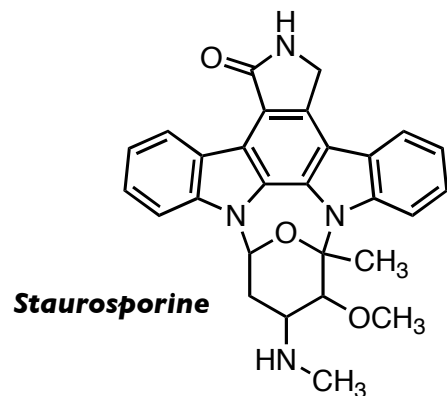
Protein Kinase D Signaling Pathway



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Chemical Inhibitors of PKD

- ATP competitive
- Staurosporine and staurosporine-derived compounds



Inhibitor	PKC α	PKC β	PKC γ	PKC δ	PKC ζ	PKC μ /PKD
Staurosporine	330 nM	330 nM	430 nM	>10,000 nM	>10,000 nM	40 nM
Gö 6983	7 nM	7 nM	6 nM	10 nM	60 nM	20,000 nM
Gö 6976	2.3 nM	6.2 nM	n.d.	>10,000 nM	>10,000 nM	20 nM
K252a	17 nM	15 nM	18 nM	3000 nM	10 nM	7 nM

Abbreviation: n.d., not determined

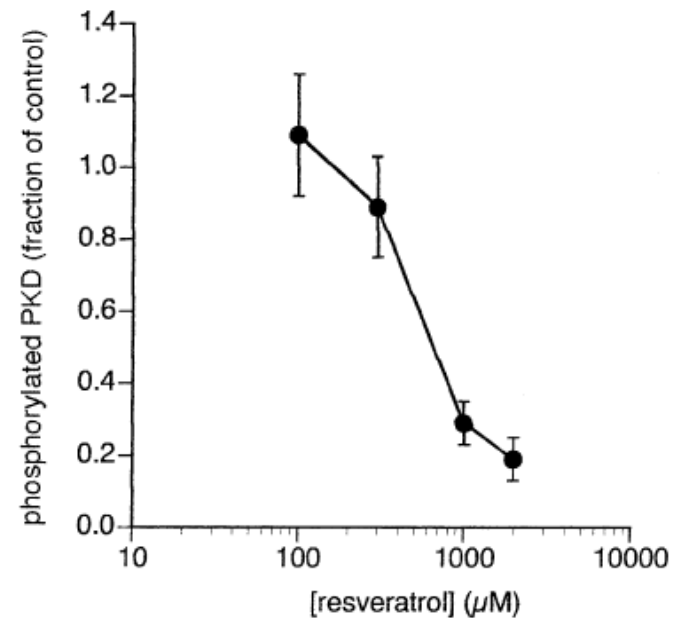
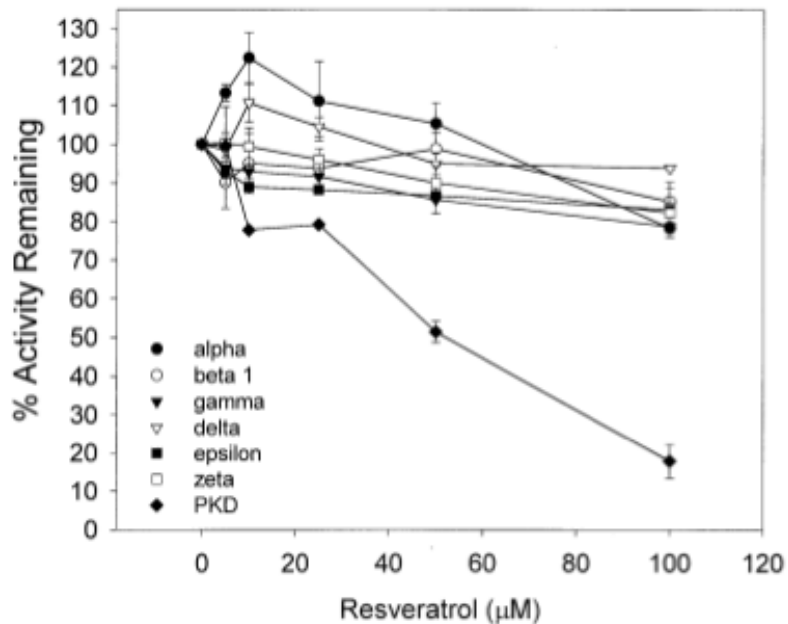
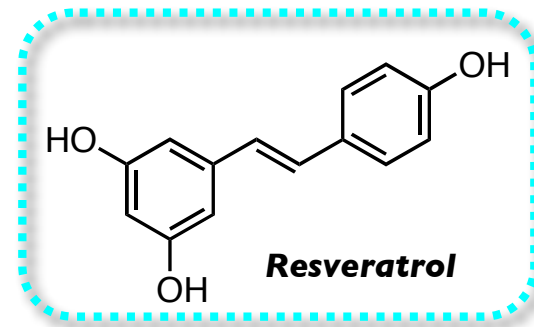
Gschwendt, M.; Dieterich, S.; Rennecke, J.; Kittstein, W.; Mueller, H.-J.; Johannes, F.-J. *FEBS Letters* **1996**, 392, 77.

Martiny-Baron, G.; Kazanietz, M. G.; Mischak, H.; Blumberg, P. M.; Kochs, G.; Hug, H.; Marme, D.; Schachtele, C. *J. Biol. Chem.* **1993**, 268, 9194.

Zang, R.; Mueller, H.-J.; Kielbassa, K.; Marks, F. *Biochem. J.* **1994**, 304, 641.

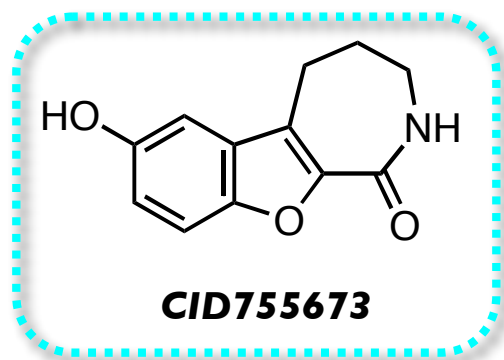
Chemical Inhibitors of PKD

- ATP competitive
- Resveratrol
 - *In vitro* IC₅₀ (PKD) = 52 - 200 μM
 - *In vivo* IC₅₀ (PKD) = 760 μM



Stewart, J. R.; Christman, K. L.; O'Brian, C. A. *Biochem. Pharmacol.* **2000**, *60*, 1355.
Haworth, R. S.; Avkiran, M. *Biochem. Pharmacol.* **2001**, *62*, 1647.

First Potent and Selective Inhibitor of PKD: CID755673

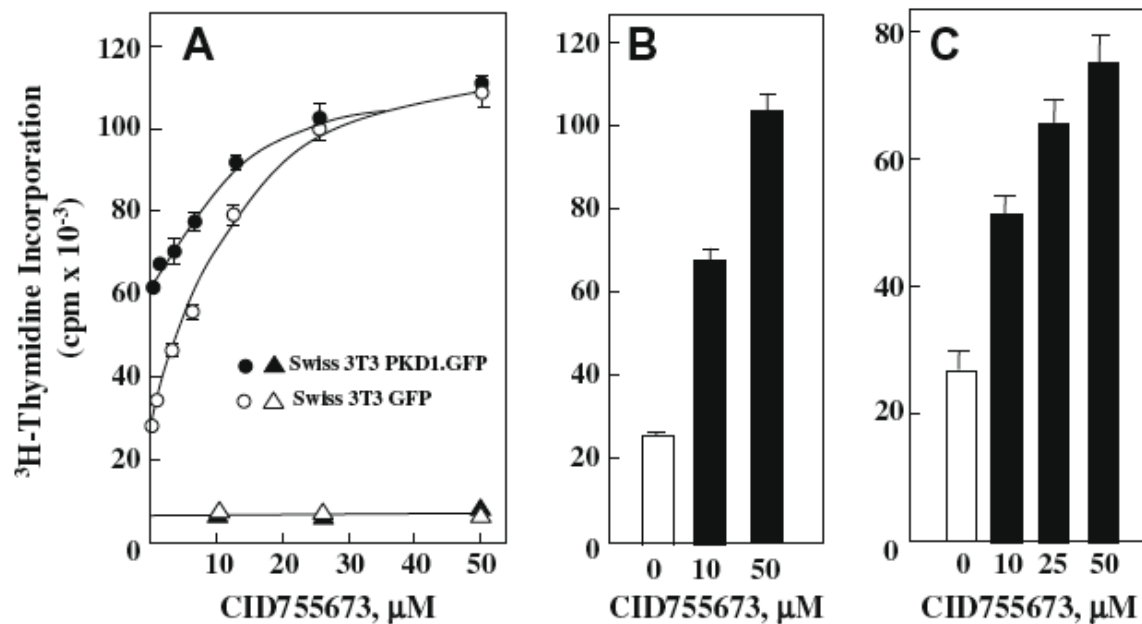
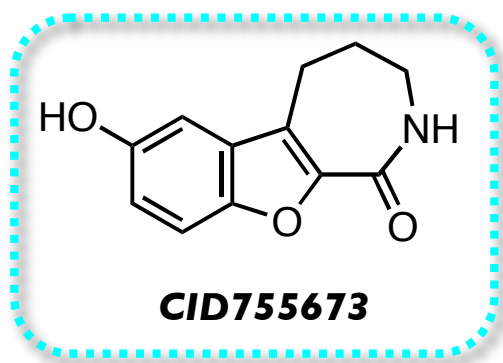


Kinase	IC ₅₀ (μM)
PKD1	0.5 ± 0.03
PKD2	0.3 ± 0.002
PKD3	0.2 ± 0.02
PLK1	20.3 ± 10.9
CAK	15.3 ± 1.8
AKT	18.6 ± 2.0
PKCα	not significant
PKCδ	no activity
CAMPKα	40.5 ± 4.6

- Non-competitive with respect to ATP and substrate
- Effective at blocking PKD-mediated cell functions
- Reduced cell migration, invasion, and proliferation in prostate cancer cells

Sharlow, E. R.; Giridhar, K. V.; LaValle, C. R.; Chem, J.; Leimgruber, S.; Barrett, R.; Bravo-Altamirano, K.; Wipf, P.; Lazo, J.; Wang, Q. J. *J. Biol. Chem.* **2008**, 283, 33516.

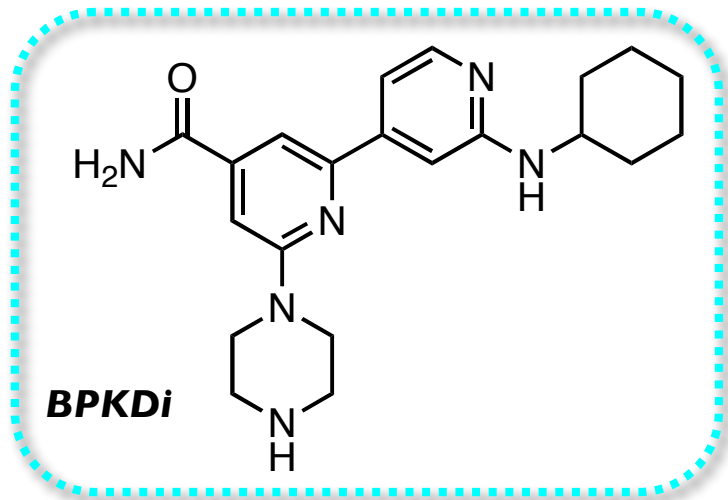
First Potent and Selective Inhibitor of PKD: CID755673



- Cellular activity relatively weak: $\text{IC}_{50} = 10 - 30 \mu\text{M}$
- May possess unintended PKD-independent effects

Torres-Marquez, E.; Sinnott-Smith, J.; Guha, S.; Kui, R.; Waldron, R. T.; Rey, O.; Rosengurt, E. *Biochem. Biophys. Res. Comm.* **2010**, *391*, 63.

Chemical Inhibitors of PKD

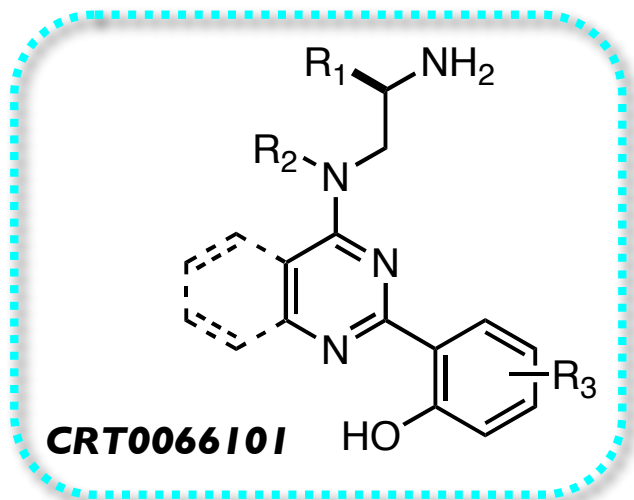


Kinase	% Inhibition at 1 μ M BPKDi	IC ₅₀ (μ M)
PKD1	102	0.001
PKD2	102	0.009
PKD3	109	0.001
CaMKI δ	6	n.d.
CaMKII α	0	n.d.
CaMKII β	3	n.d.
CaMKII δ	26	n.d.
CaMKIV	1	n.d.
MARK1	24	n.d.
MARK2	27	n.d.
SIK1	7	n.d.
GRK5	2	n.d.
PKC δ	22	n.d.
PKC ϵ	-3	n.d.

- Blocks signal-dependent phosphorylation and nuclear export of class IIa HDACs in cardiomyocytes, thereby suppressing hypertrophy of these cells
- ATP competitive

Monovich, L.; Vega, R. B.; Meredith, E.; Miranda, K.; Rao, C.; Capparelli, M.; Lemon, D. D.; Phan, D.; Koch, K. A.; Chapo, J. A.; Hood, D. B.; McKinsey, T. A. *FEBS Letters* **2010**, 584, 631.

Chemical Inhibitors of PKD



Kinase	IC ₅₀ (μM)
PKD1	0.001
PKD2	0.003
PKD3	0.002

- First orally bioavailable PKD inhibitor
- Blocks pancreatic cancer growth both *in vitro* and *in vivo*
- Specificity confirmed in an *in vitro* assay comprising a panel of >90 protein kinases
- ATP competitive

Harikumar, K. B.; Kunnumakkara, A. B.; Ochi, N.; Tong, Z.; Deorukhkar, A.; Sung, B.; Kelland, L.; Jamieson, S.; Sutherland, R.; Raynham, T.; Carles, M.; Bagherzadeh, A.; Foxton, C.; Boakes, A.; Farooq, M.; Maru, D.; Diagaradjane, P.; Matsuo, Y.; Sinnott-Smith, J.; Gelovani, J.; Krishnan, S.; Aggarwal, B. B.; Rozengurt, E.; Ireson, C. R.; Guha, S. *Mol. Cancer Ther.*, **2010**, *9*, 1136.

Conclusion and Future Work

- Methoxy derivative successfully synthesized and biological testing is in progress



- Optimize deprotection and submit for biological testing



- Photoaffinity labeled derivative to gain insight into binding site



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