# Palladium-Catalyzed C-H Activation: A Versatile Gateway to Biologically Active Fused 1,2,3-Triazole (Dihydro)quinolines

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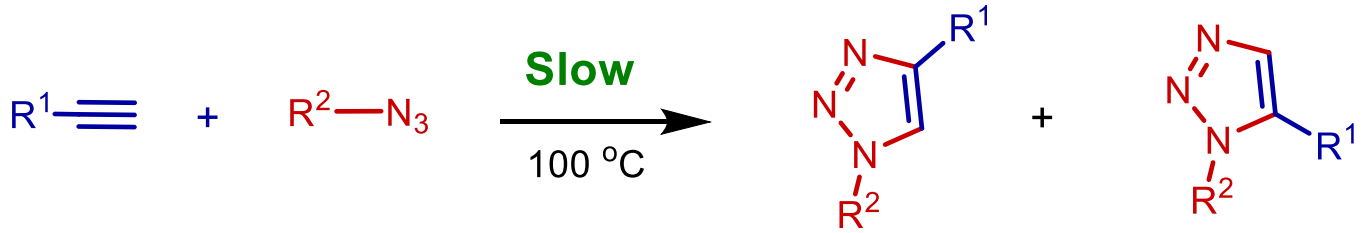
25 - 27 February 2026 | Catania, Italy

# Introduction to CuAAC Reaction/Click Chemistry

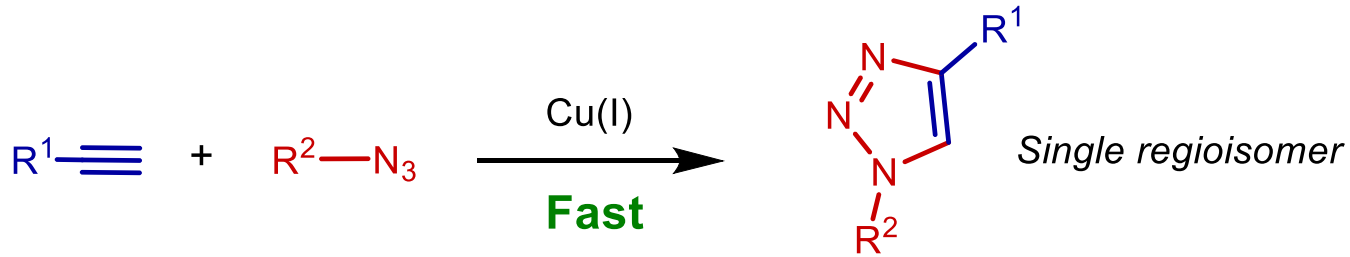
**A** ***Huisgen 1,3-dipolar cycloaddition (1960)***




*1,4-disubstituted 1,2,3-Triazoles*

*1,5-disubstituted 1,2,3-Triazoles*

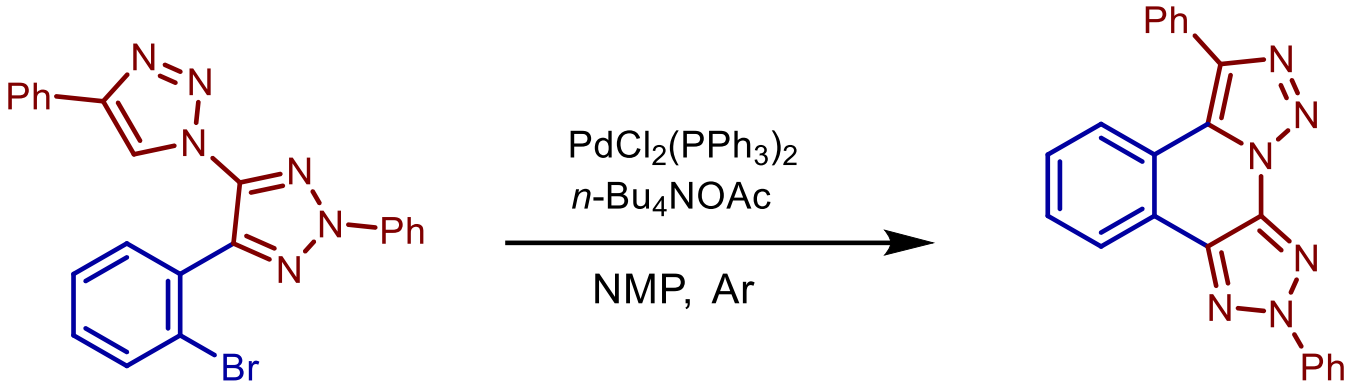
**B** ***Cu-catalyzed 1,3-dipolar cycloaddition (Sharpless, 2001)***



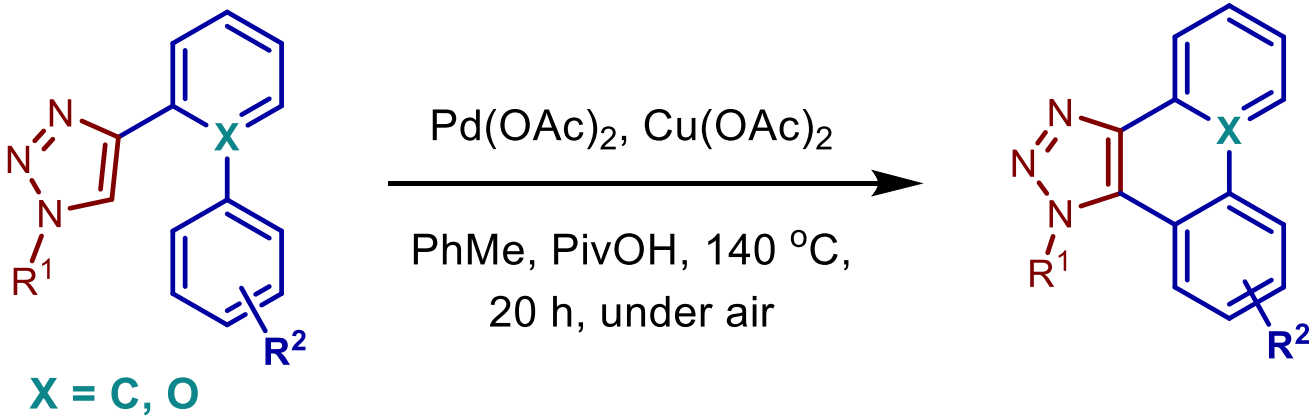

*Single regioisomer*

*1,4-disubstituted 1,2,3-Triazoles*

# Pd-catalyzed intramolecular heterocyclic fused 1,2,3-triazole

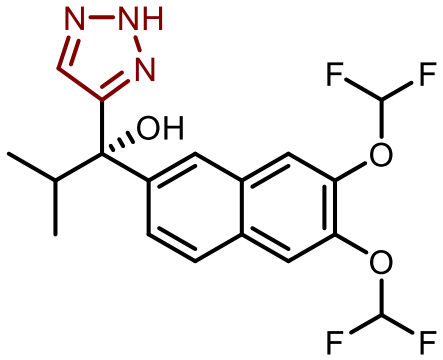



B. Tsyrenova, V. Khrustalev, V. Nenajdenko, J. Org. Chem. 2020, 85, 7024–7035:

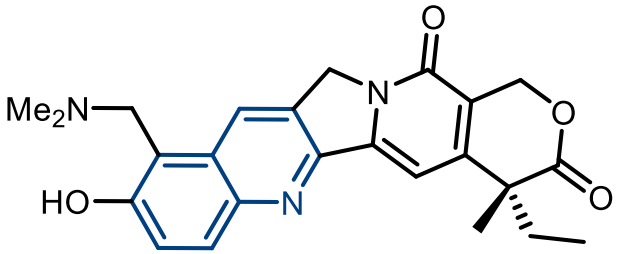



L. Ackermann, R. Jeyachandran, H. K. Potukuchi, P. Novak, L. Büttner, Organic Letters 2010, 12, 2056-2059

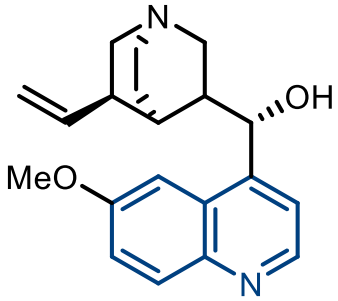
# Some examples of pharmacologically active molecules



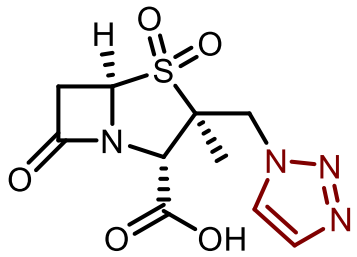
***Seviteronel*** **- Anticancer**



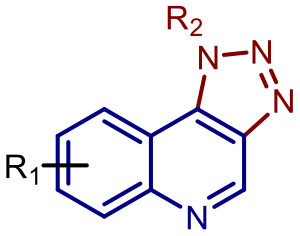
***Topotecan*** **- Chemotherapeutic**



***Quinine*** **- Antimalaric**



***Tazobactam*** **- Antibiotic**

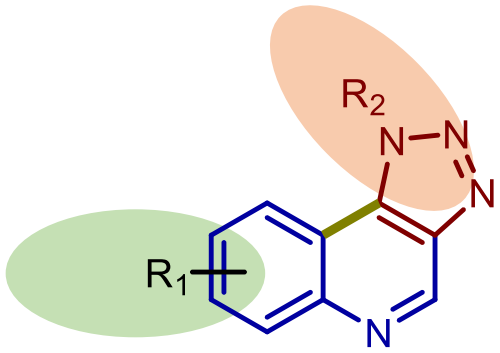


**Class of Ataxia-Telangiectasia Mutated Kinase Inhibitors[1]** & **Class of Hippo signaling pathway inhibitors[2]**

[1] Zhang S. et al. Discovery of [1,2,3]Triazolo[4,5-c]quinoline Derivatives as a New Class of Ataxia-Telangiectasia Mutated Kinase Inhibitors. 2023, ACS Medicinal Chemistry Letters. 8, 14, 746 – 756.

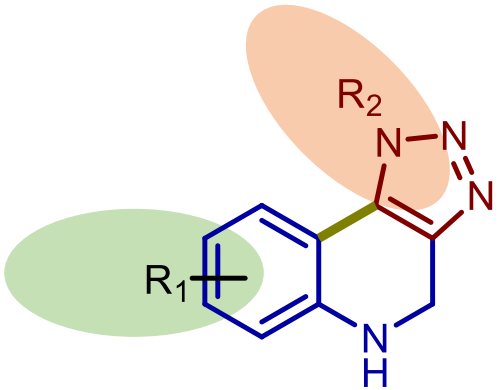
[2] Qiao J. et al. Discovery of 1,8-disubstituted-[1,2,3]triazolo[4,5-c]quinoline derivatives as a new class of Hippo signaling pathway inhibitors. 2019, Bioorganic & Medicinal Chemistry Letters, 18, 29, 2595 – 2603.

# Synthesis of 1,2,3-triazole fused heterocycles

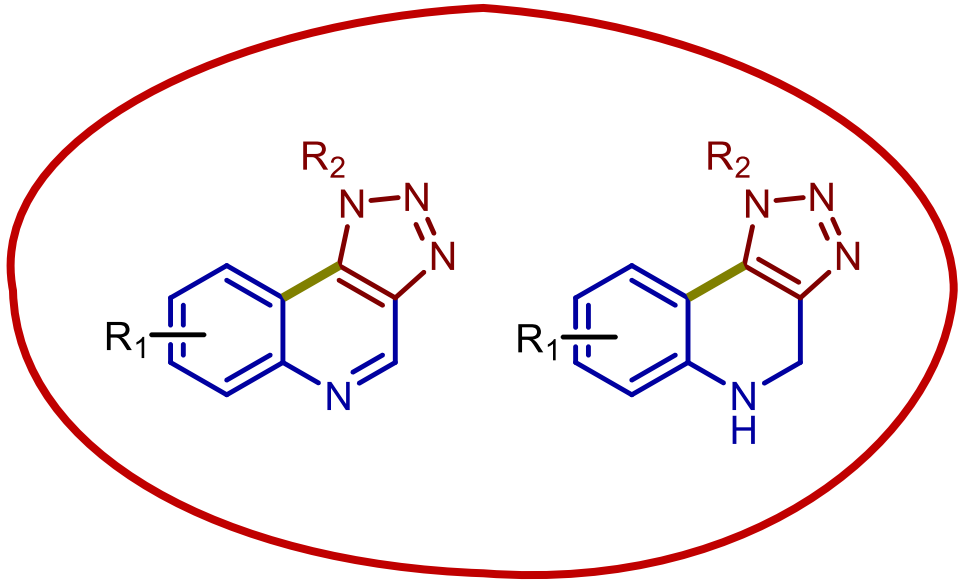



**Research Goals**

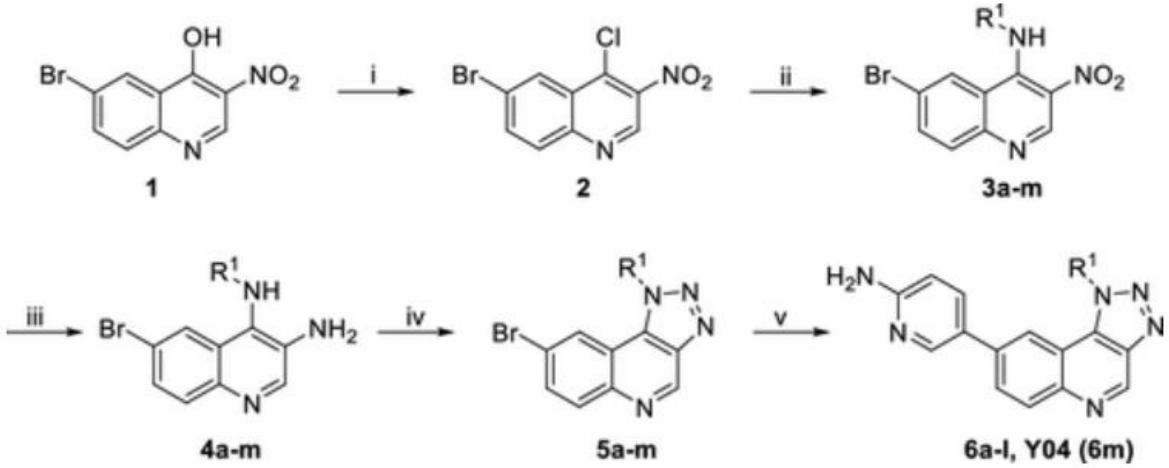
- Easy and fast synthesis of possible active compounds
- High group tolerance
- High selectivity towards quinoline and dihydroquinoline compounds



# Synthesis of of 1,2,3-triazole fused heterocycles



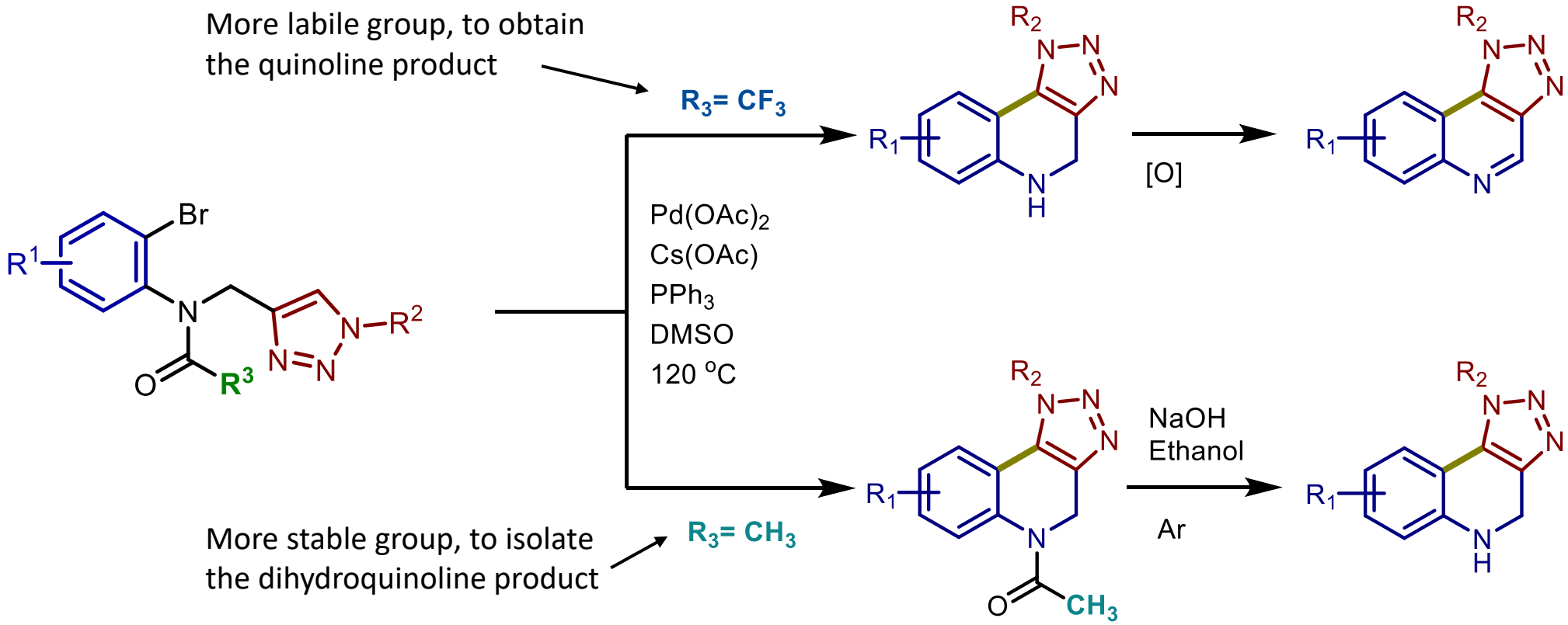

## Reported synthesis strategy – An example[1]



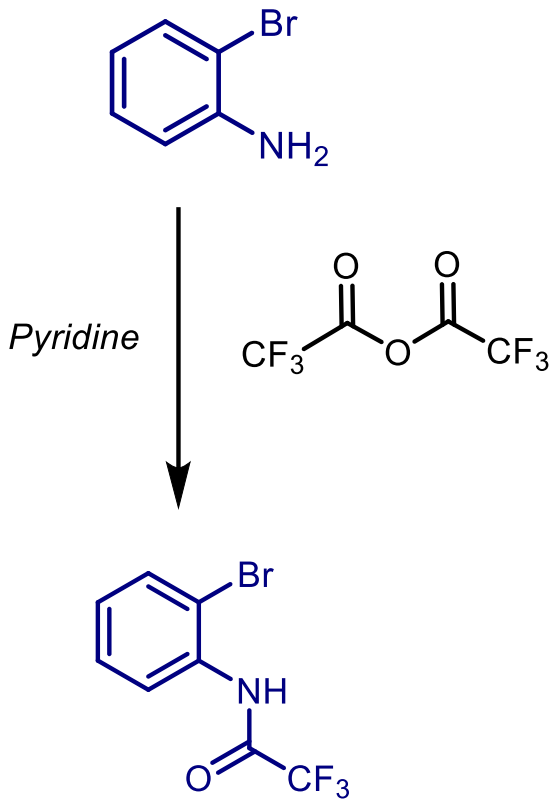

[a]Reagents and conditions: (i) $POCl_3$, reflux; (ii) substituted amine, triethylamine, EtOH, reflux; (iii) Fe, AcOH, 60 °C; (iv) $NaNO_2$, AcOH/$H_2O$; (v) (6-aminopyridin-3-yl)boronic acid, Pd(dppf)$Cl_2$, $K_2CO_3$, 1,4-dioxane/$H_2O$, 100 °C, 24 h.

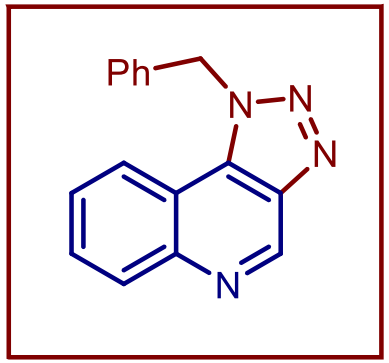
[1] Zhang S. et al. Discovery of [1,2,3]Triazolo[4,5-c]quinoline Derivatives as a New Class of Ataxia-Telangiectasia Mutated Kinase Inhibitors. 2023, ACS Medicinal Chemistry Letters. 8, 14, 746 – 756.

# Cu/Pd-catalyzed controlled intramolecular C-H activation for the synthesis of quinoline or dihydroquinoline fused-1,2,3-triazole



# Synthetic Strategy for quinoline fused 1,2,3-Triazole



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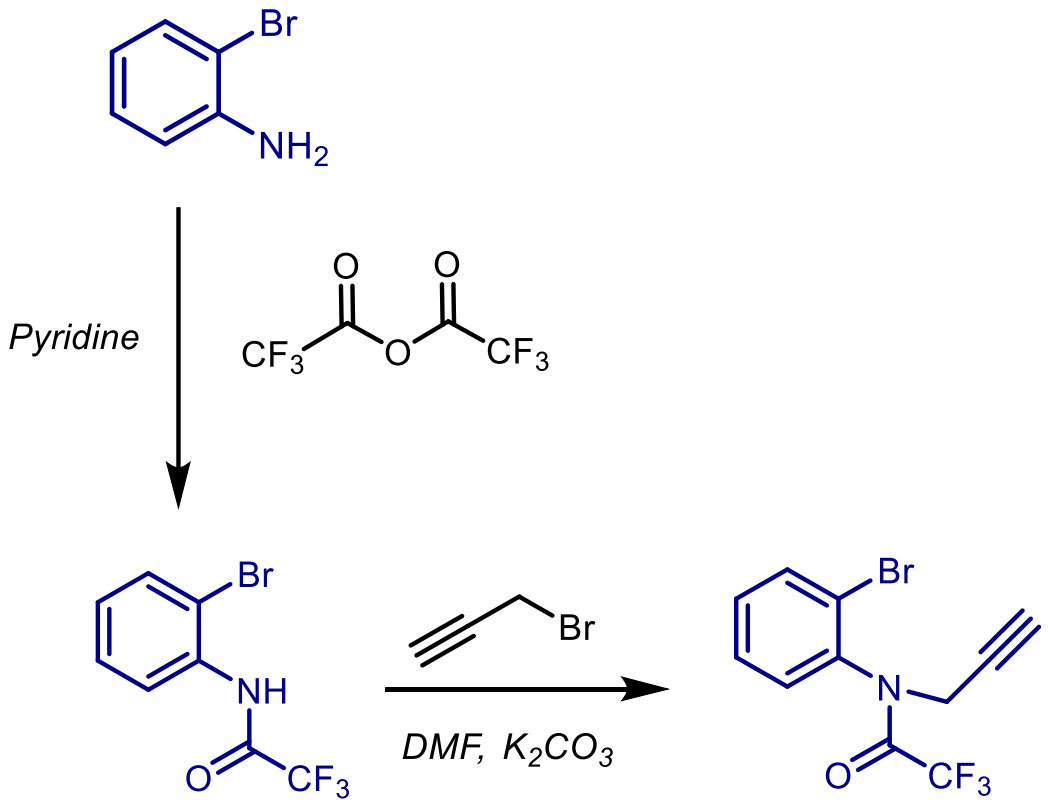

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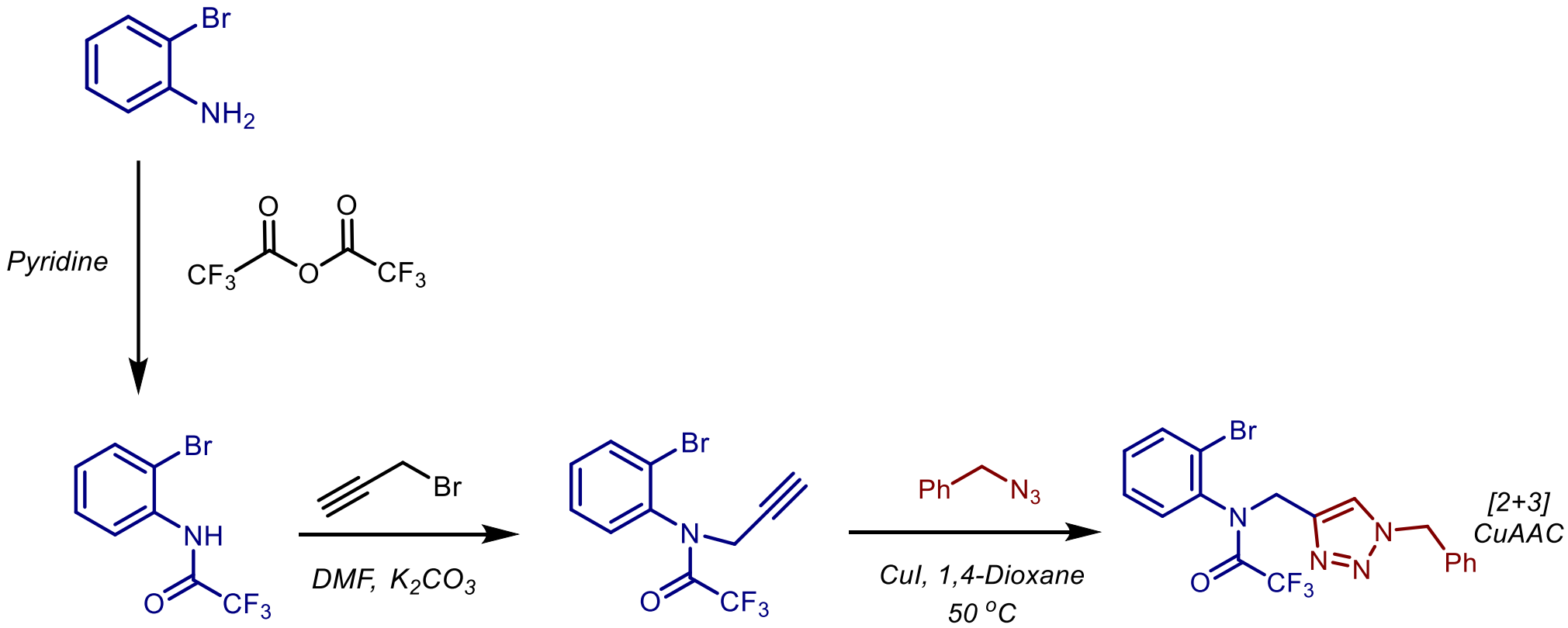

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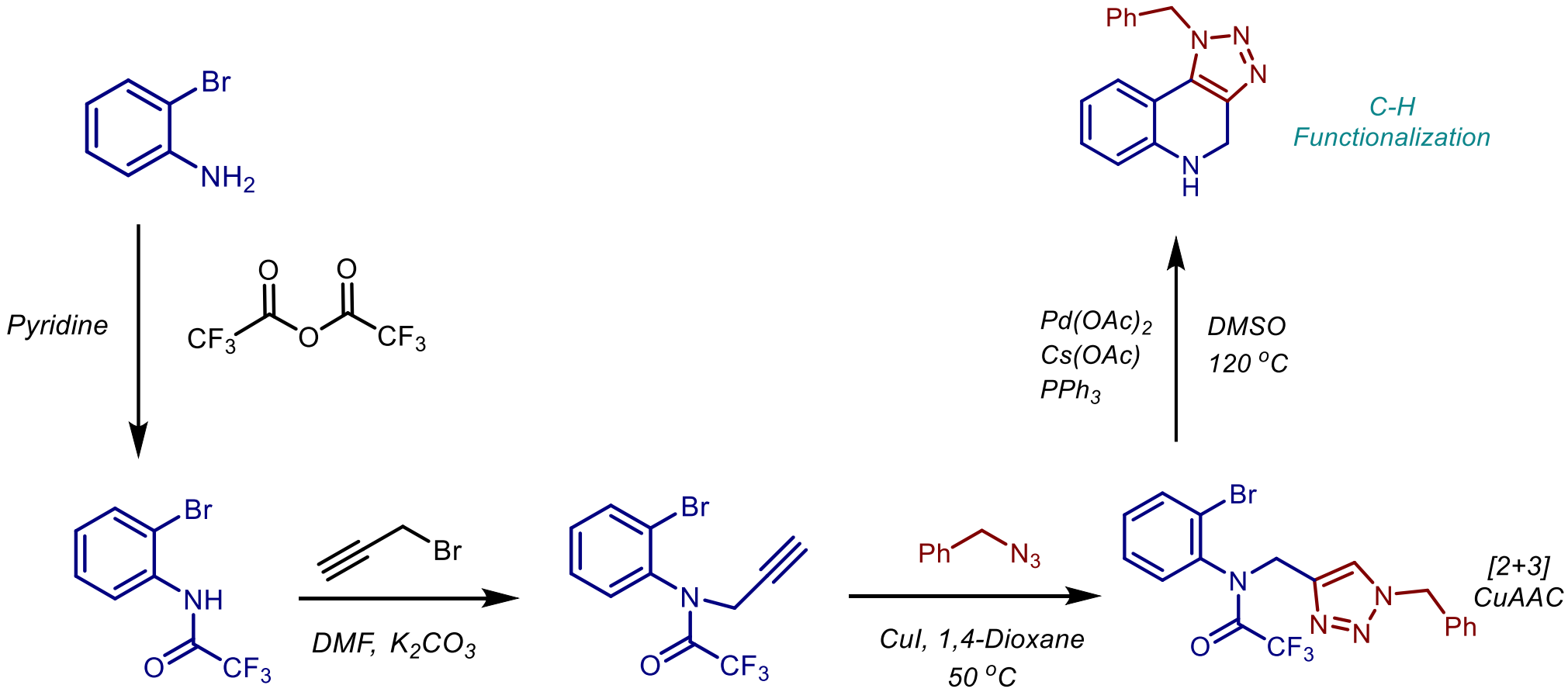

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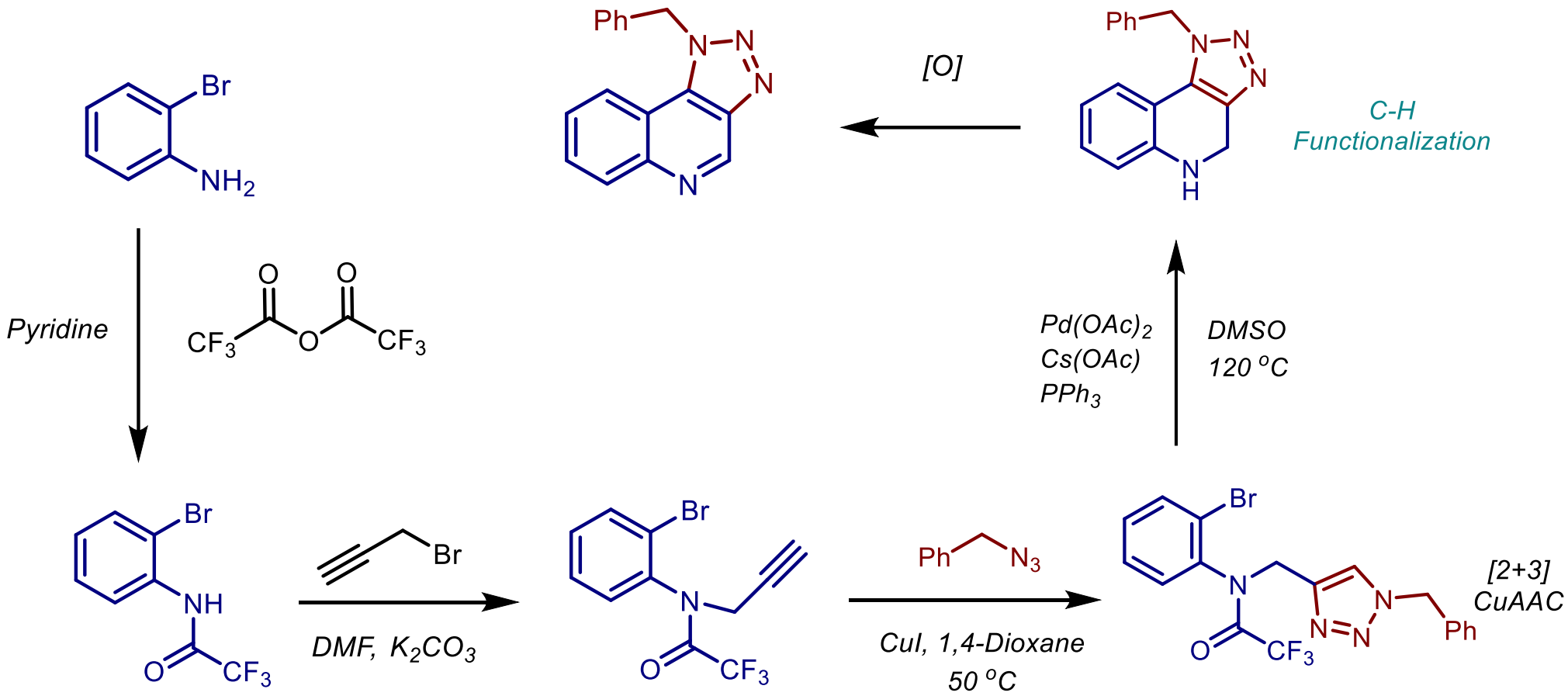

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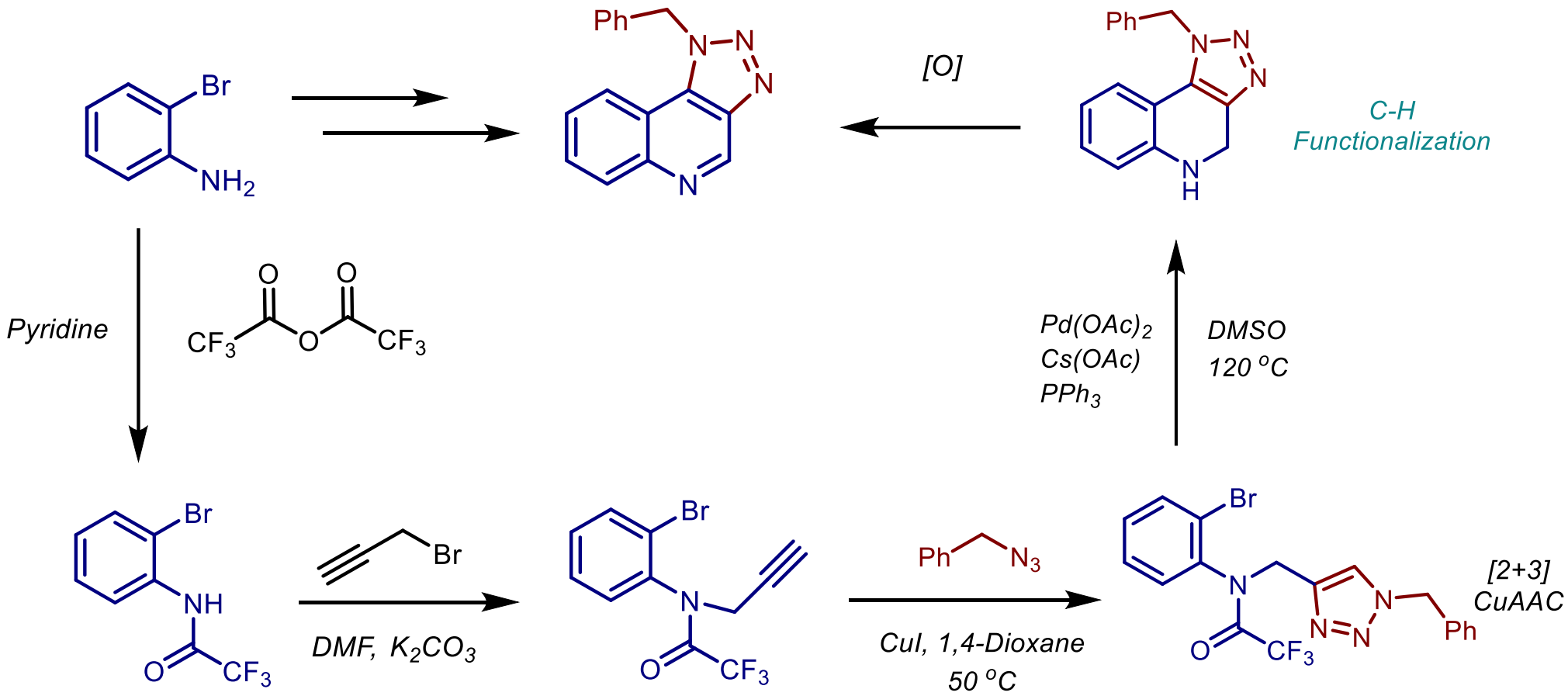
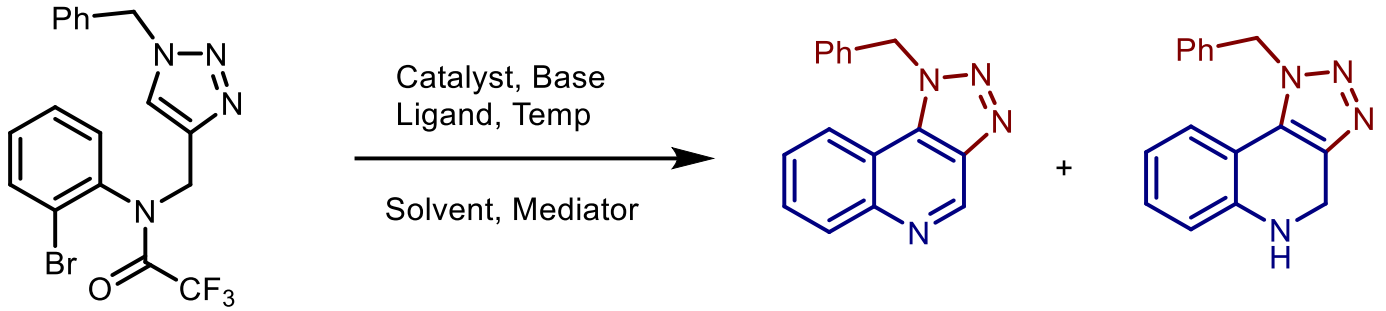


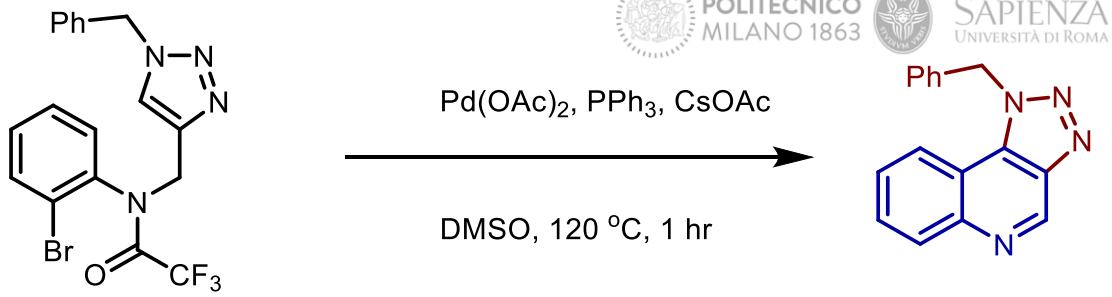
# Optimization of the reaction conditions for C-H activation



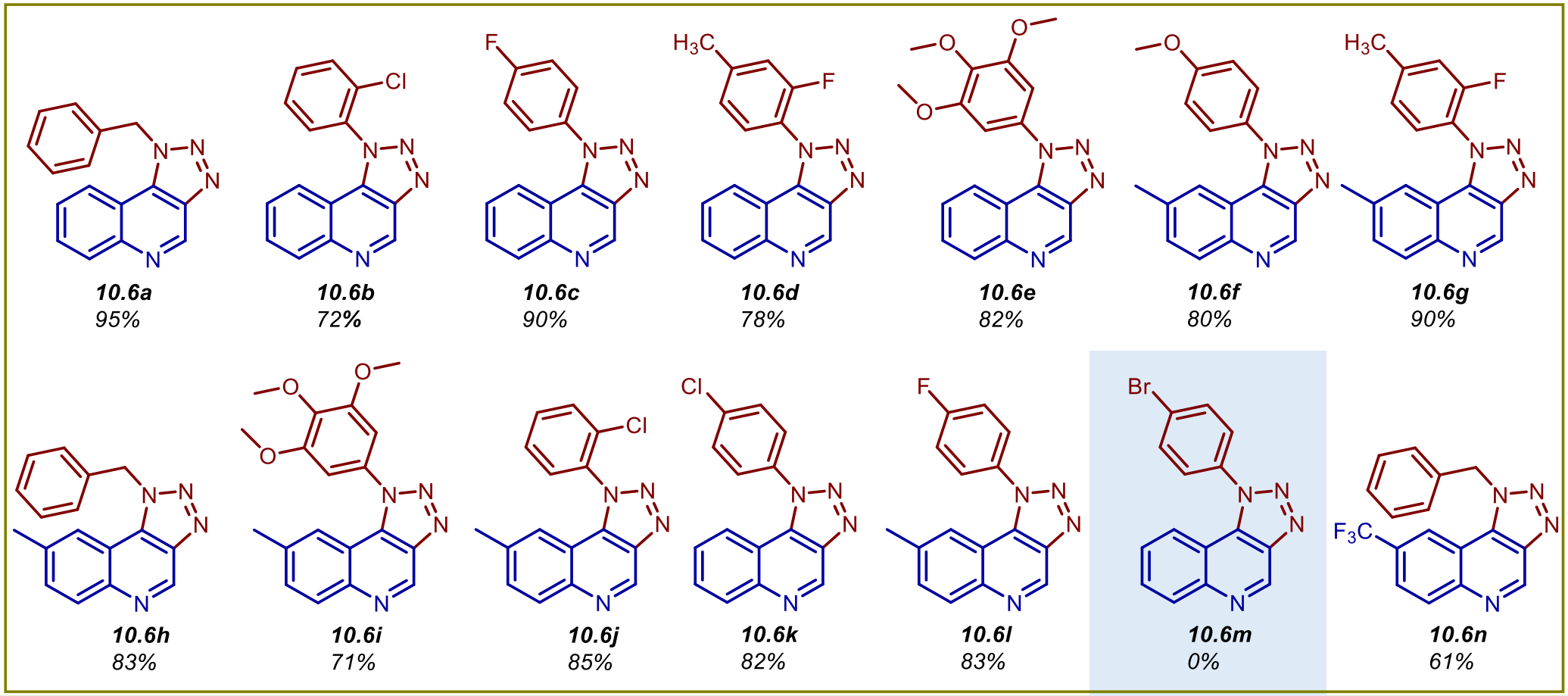

***10.4a*** ***10.6a*** ***10.5a***

| Entry | Catalyst | Ligand | Base | Mediator | Solvent | Temp °C | Time | Yield (%) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | **10.6a** | **10.5a** |
| 1 | $Pd_2(dba)_3$ | XPhos | $K_2CO_3$ | - | Dioxane | 120 | 12 h | - | - |
| 2 | $Pd(OAc)_2$ | $PPh_3$ | CsOAc | - | DMF | 120 | 0.5 h | 12 | 56 |
| 3 | $Pd(OAc)_2$ | $PPh_3$ | CsOAc | - | DMF | 100 | 1h | 45 | 18 |
| 4 | $Pd(OAc)_2$ | $PPh_3$ | CsOAc | - | DMF | 80 | 3 h | 38 | 15 |
| 5 | $Pd(OAc)_2$ | $PPh_3$ | CsOAc | - | DMF | 60 | 6 h | 25 | 26 |
| 6 | $Pd(OAc)_2$ | $PPh_3$ | CsOAc | - | MeCN | 80 | 12 h | 12 | 31 |
| 7 | $Pd(OAc)_2$ | $PPh_3$ | CsOAc | - | DMSO | 120 | 0.5 h | 24 | 61 |
| **8** | **$Pd(OAc)_2$** | **$PPh_3$** | **CsOAc** | **[O]** | **DMSO** | **120** | **1 h** | **95** | **-** |
| 9 | $Pd(OAc)_2$ | $PPh_3$ | CsOAc | [O] | DMF | 120 | 1 h | 65 | - |
| 10 | $Pd(OAc)_2$ | $PPh_3$ | CsOAc | [O] | Dioxane | 120 | 12 h | - | - |
| 11 | $Pd(OAc)_2$ | $PPh_3$ | CsOAc | [O] | MeCN | 120 | 1 h | 30 | - |

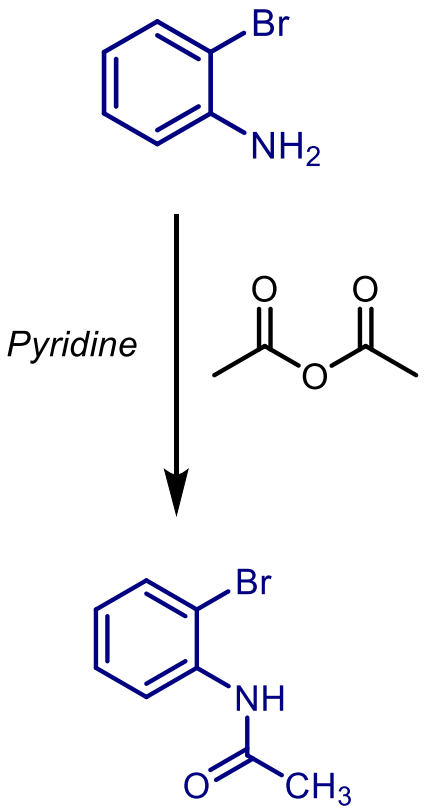
# Scope of the reaction

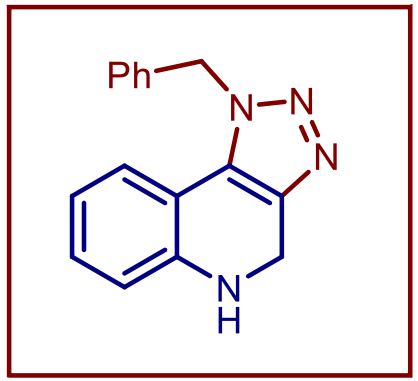



***10.4a*** ***10.6a***



# Synthetic Strategy for dihydroquinoline fused 1,2,3-Triazole



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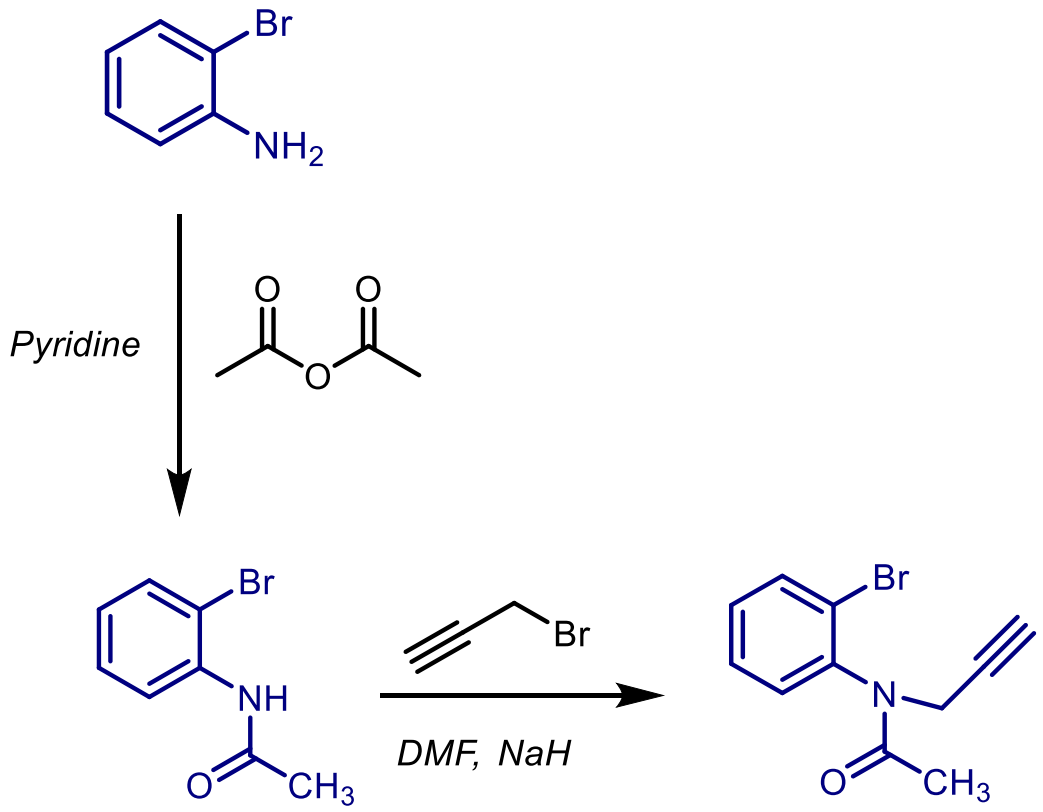

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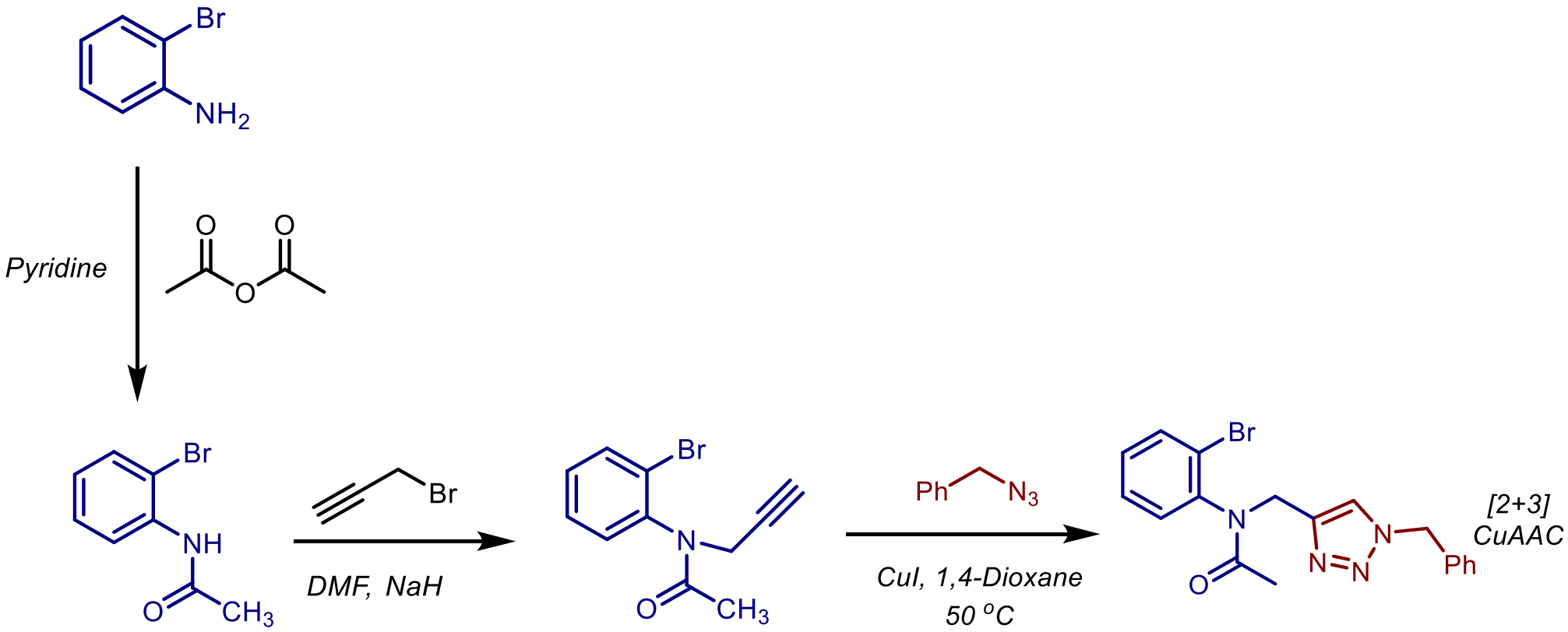

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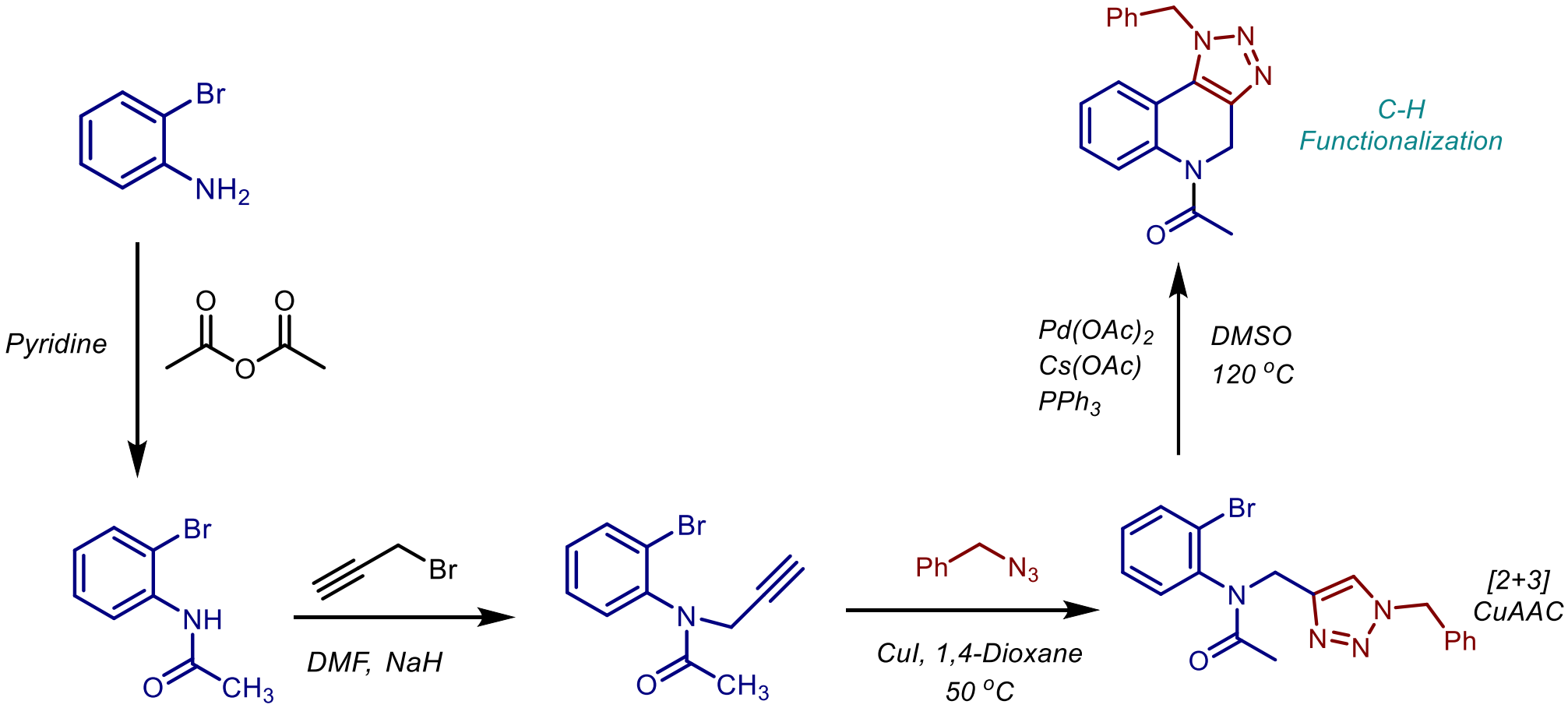

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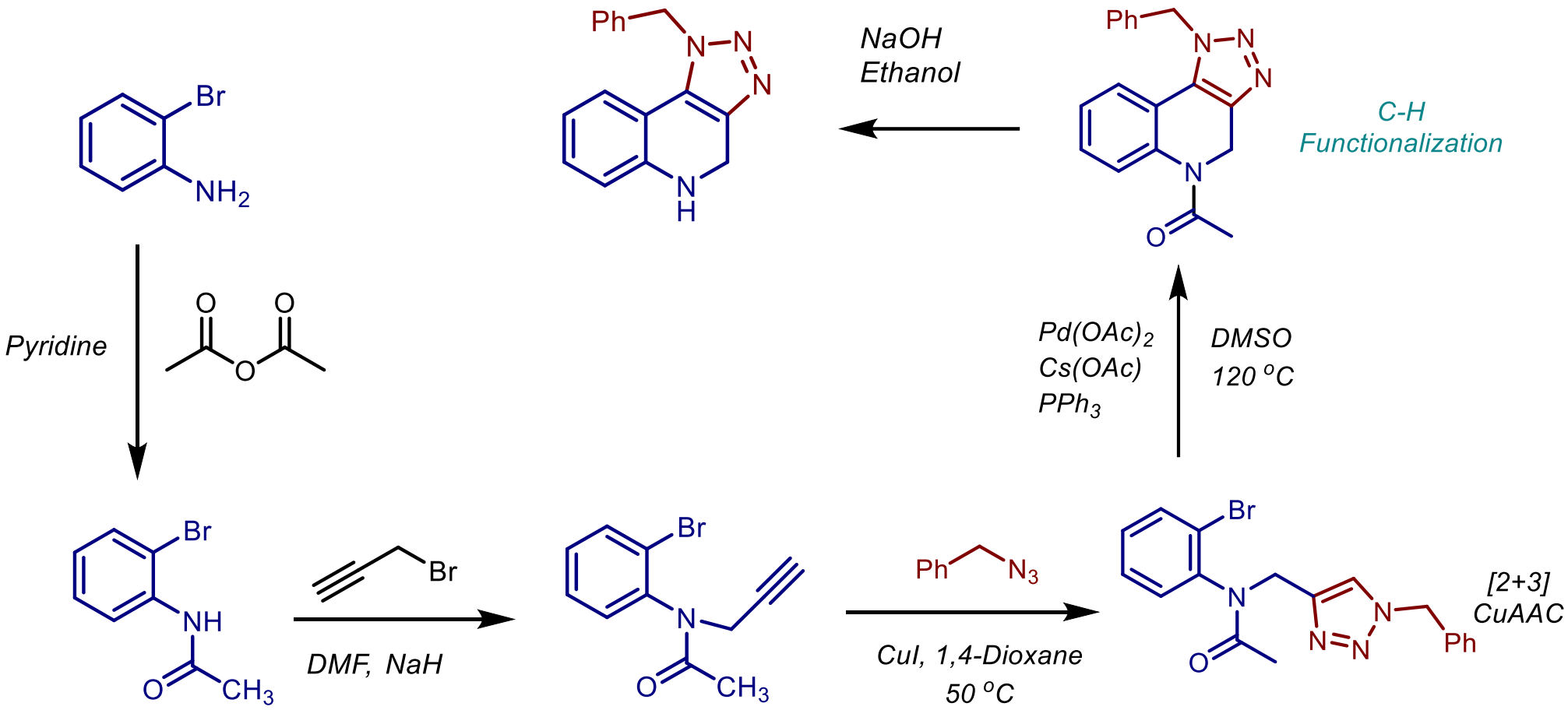

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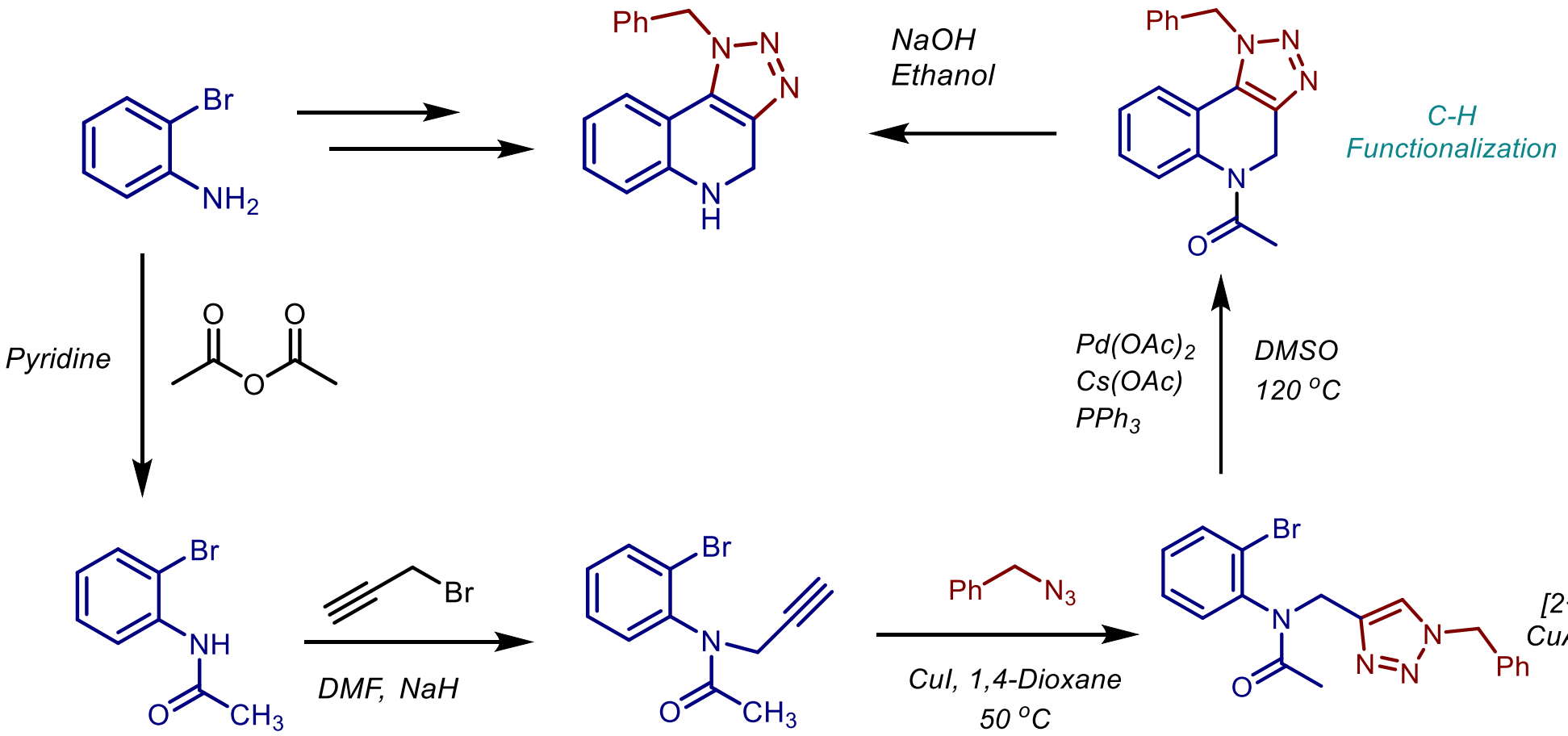
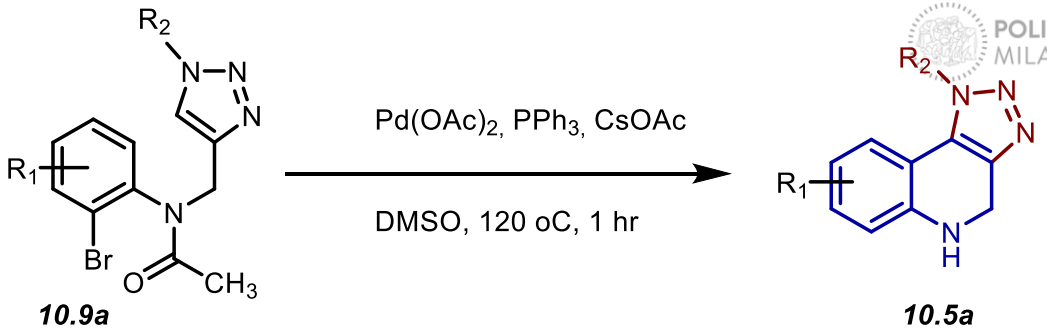
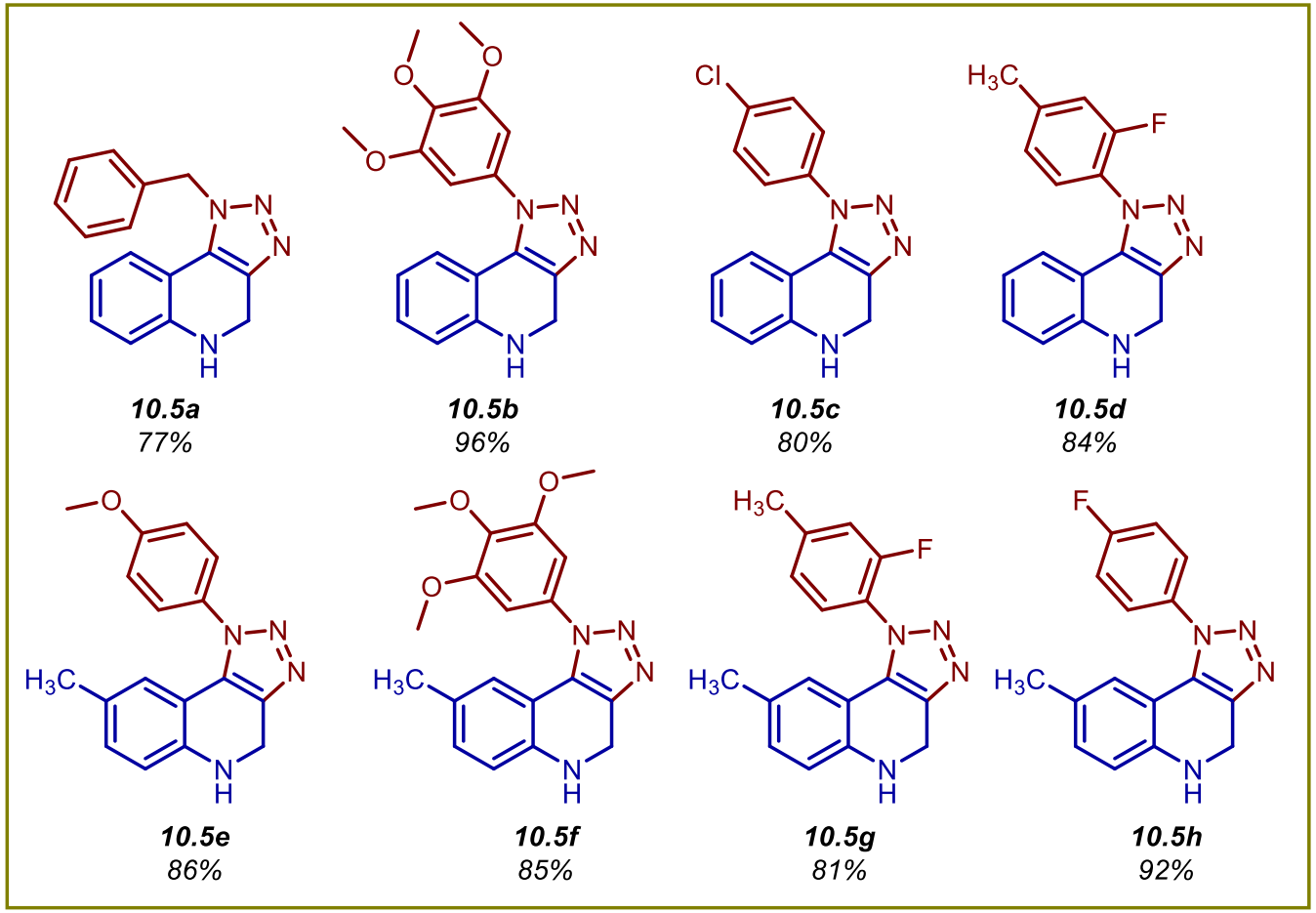


# Scope of the reaction




***10.9a*** ***10.5a***




***10.5a*** *77%*

***10.5b*** *96%*

***10.5c*** *80%*

***10.5d*** *84%*

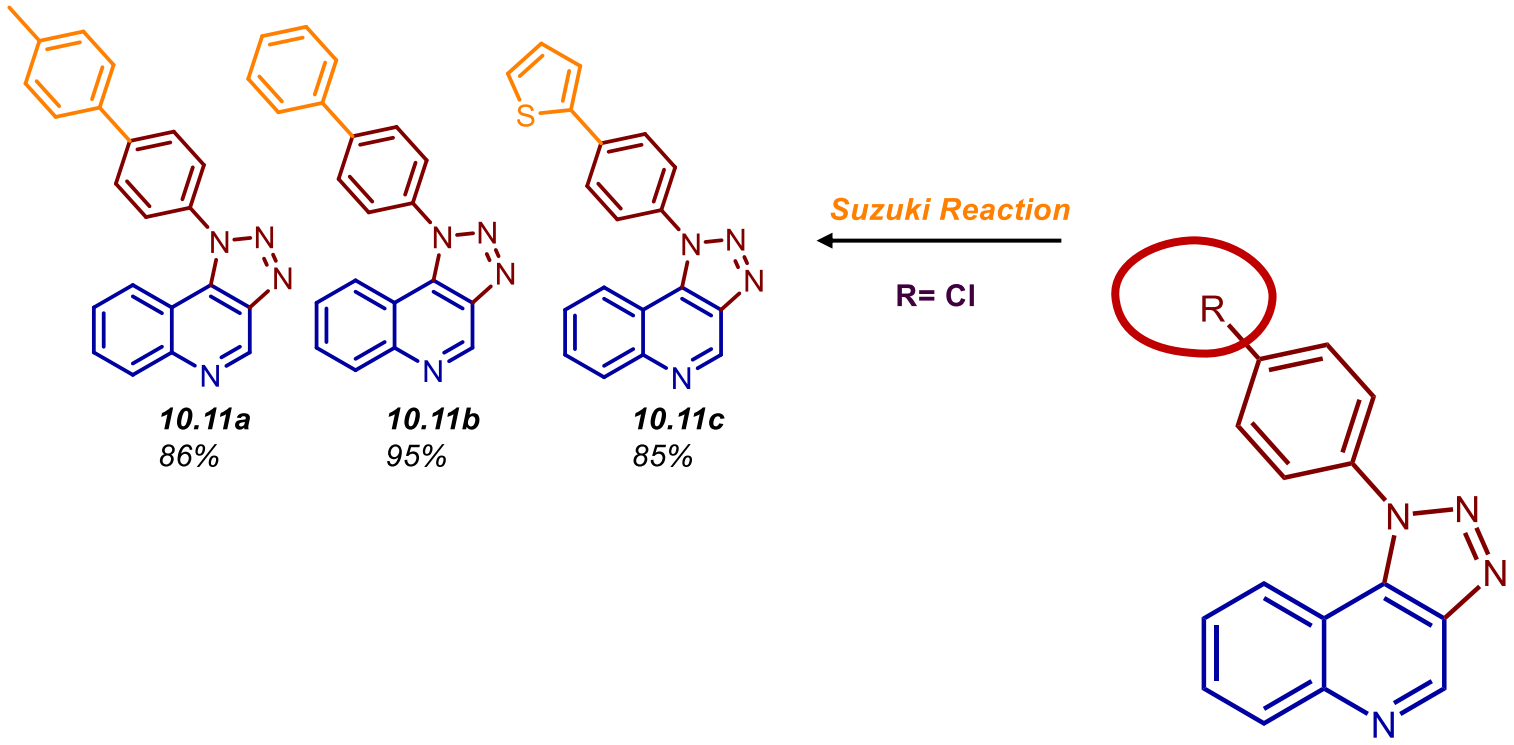
***10.5e*** *86%*

***10.5f*** *85%*

***10.5g*** *81%*

***10.5h*** *92%*

# Post-synthetic modification



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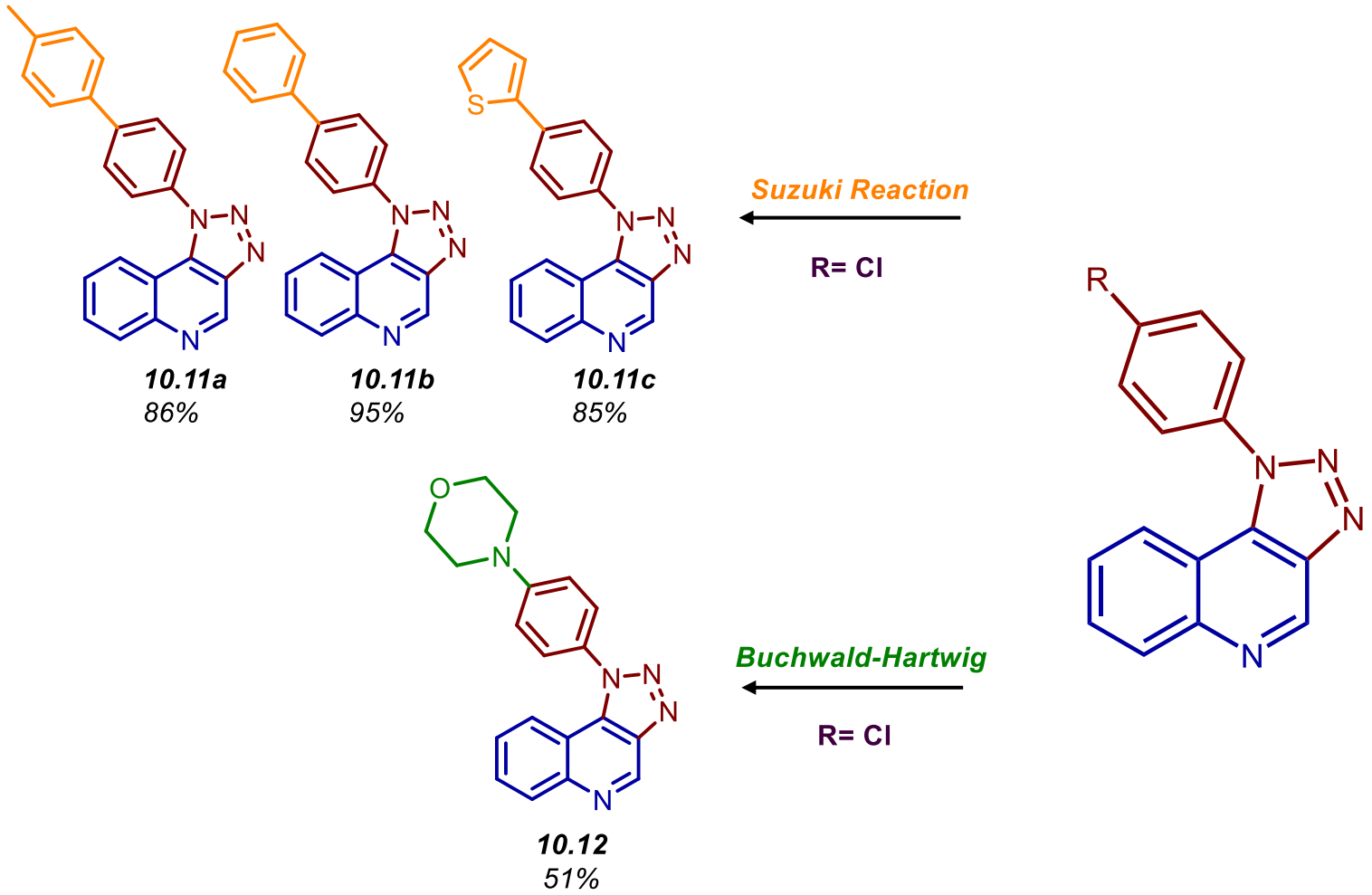

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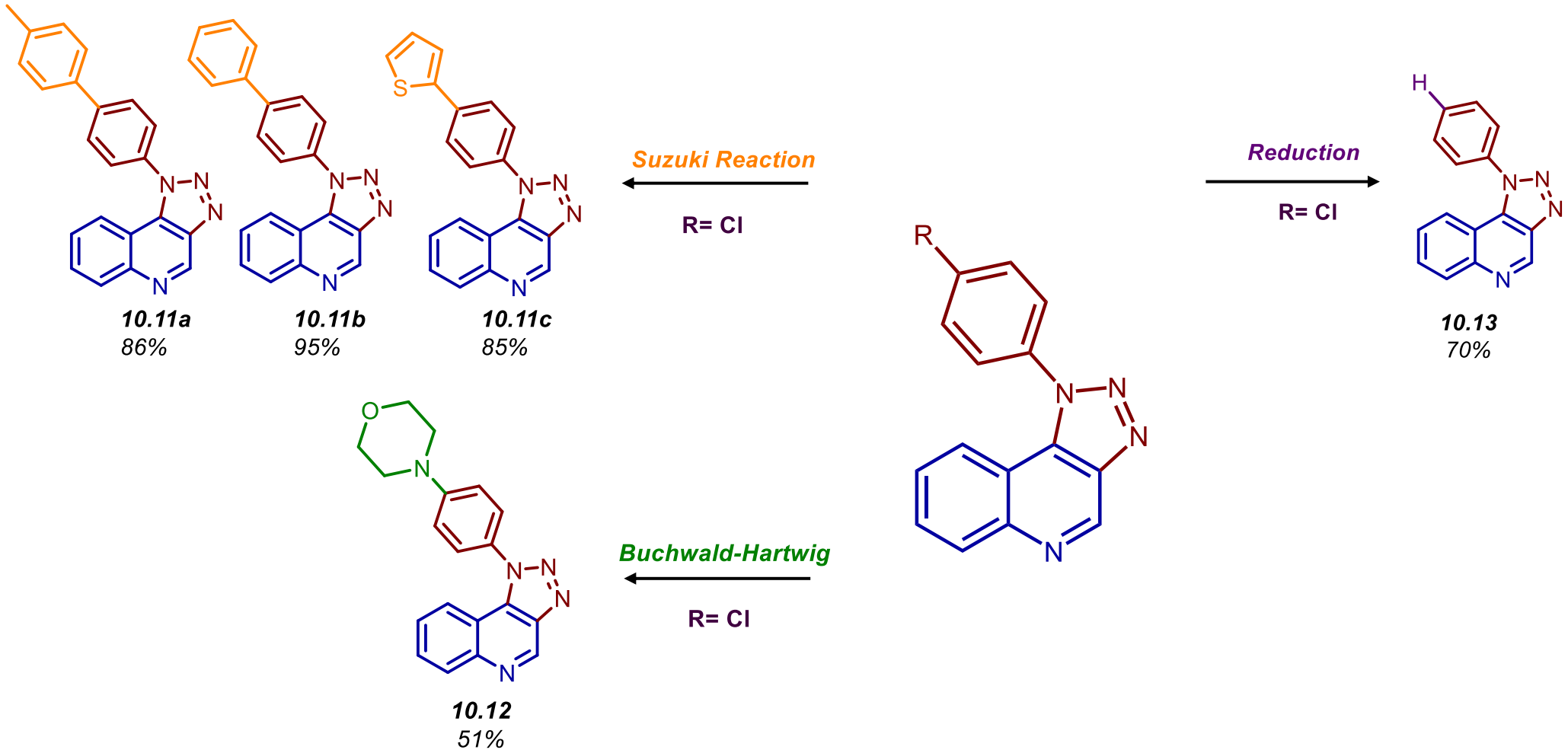

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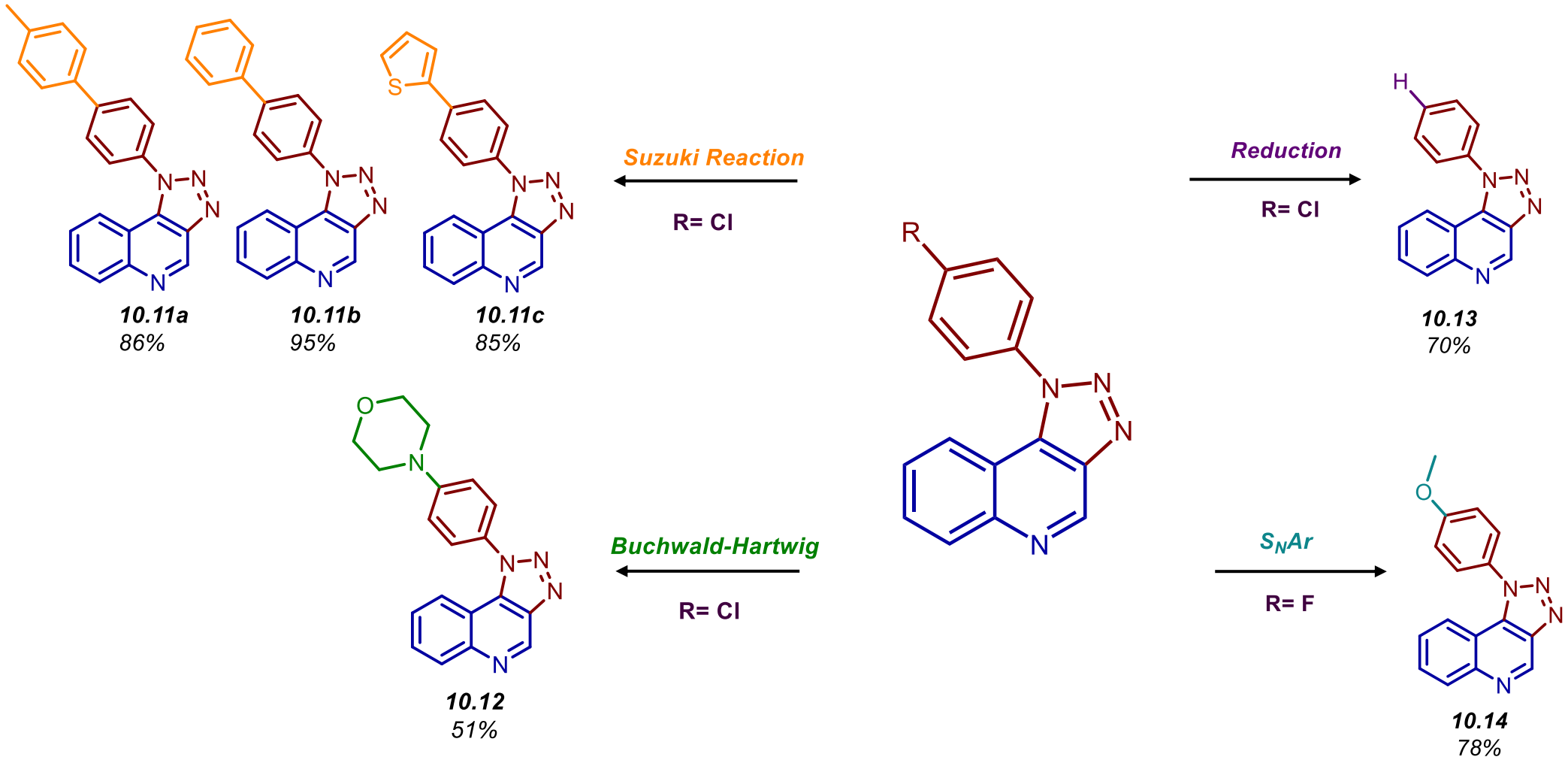
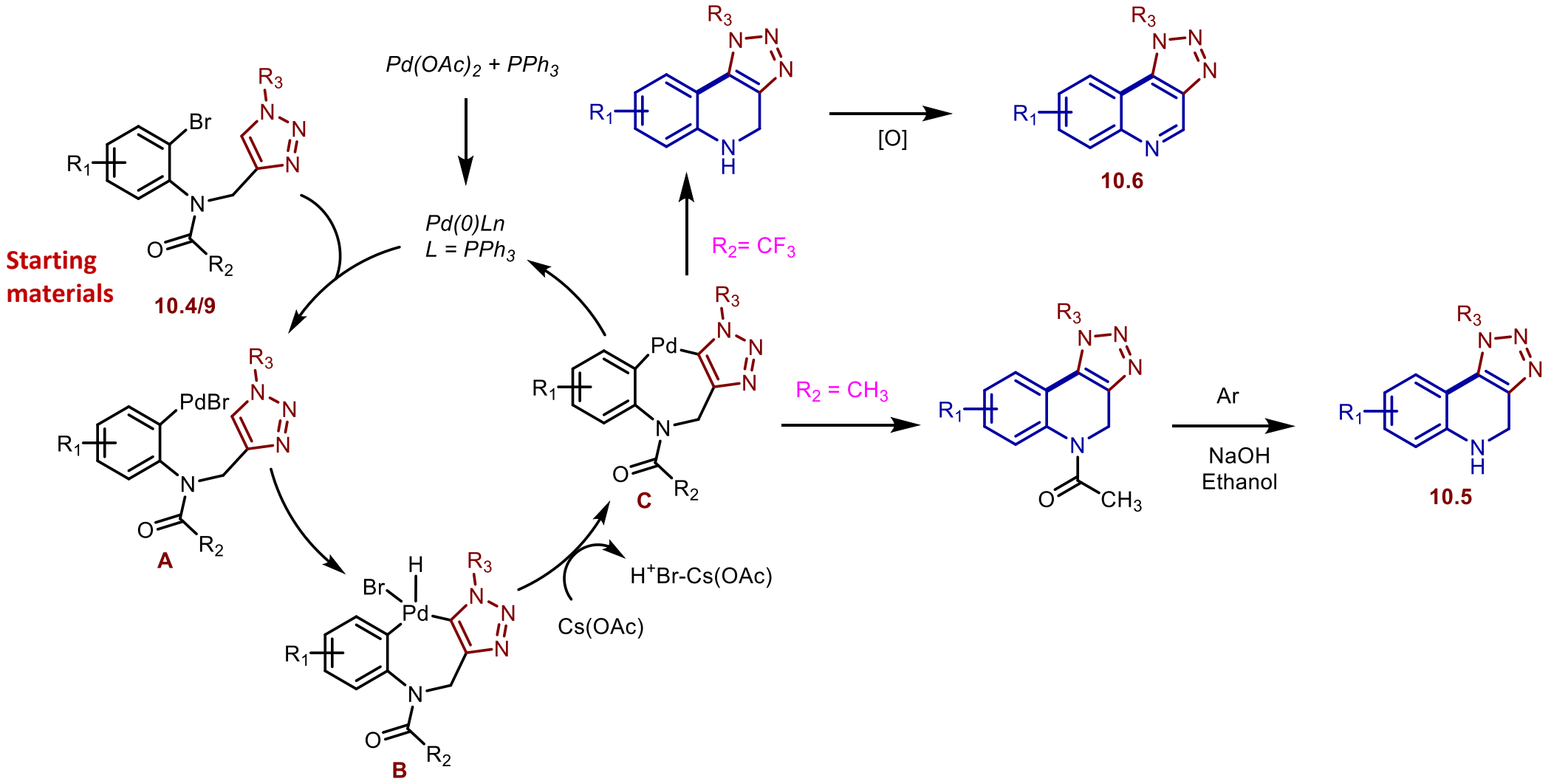


# Proposed mechanism



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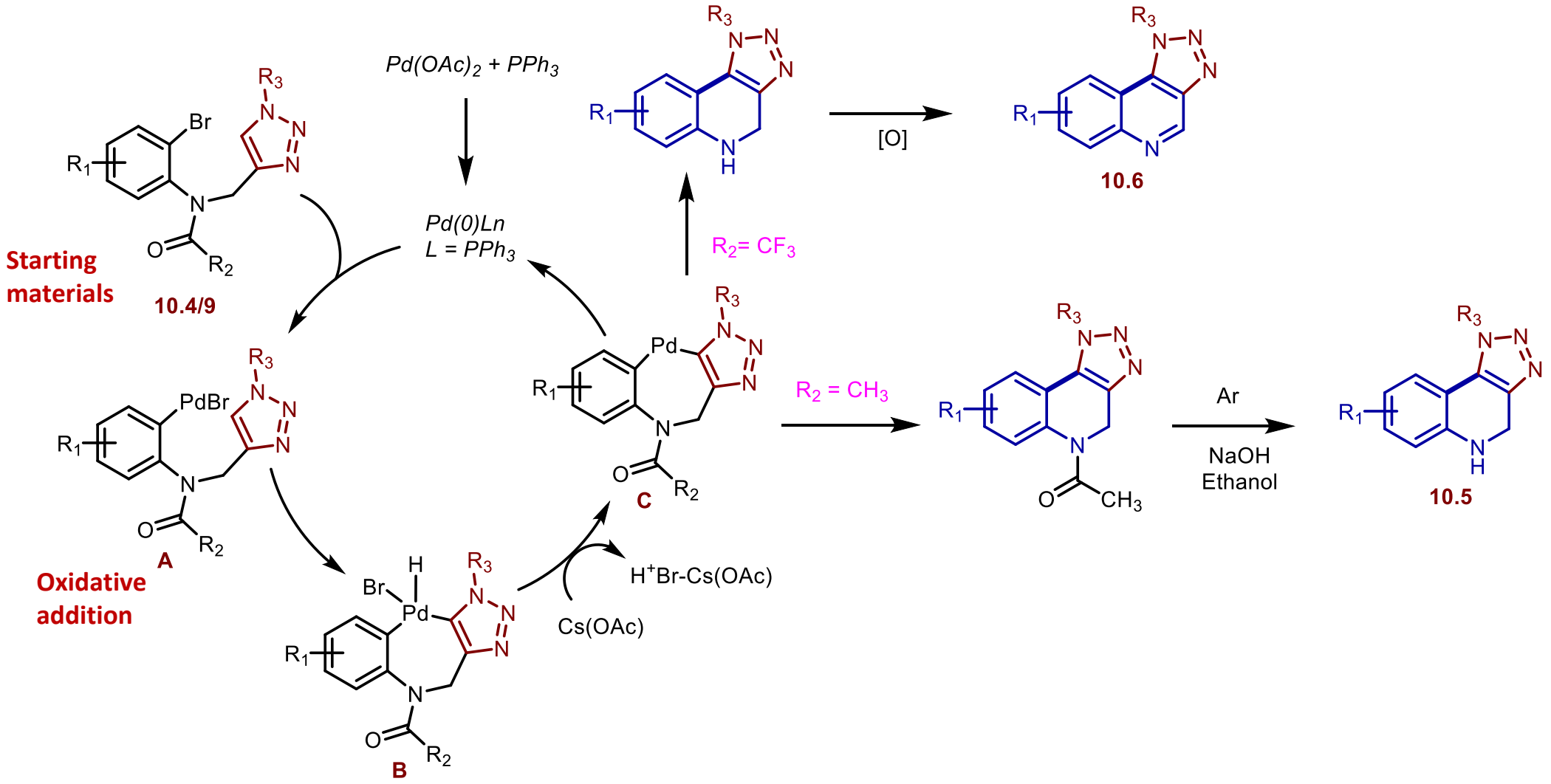

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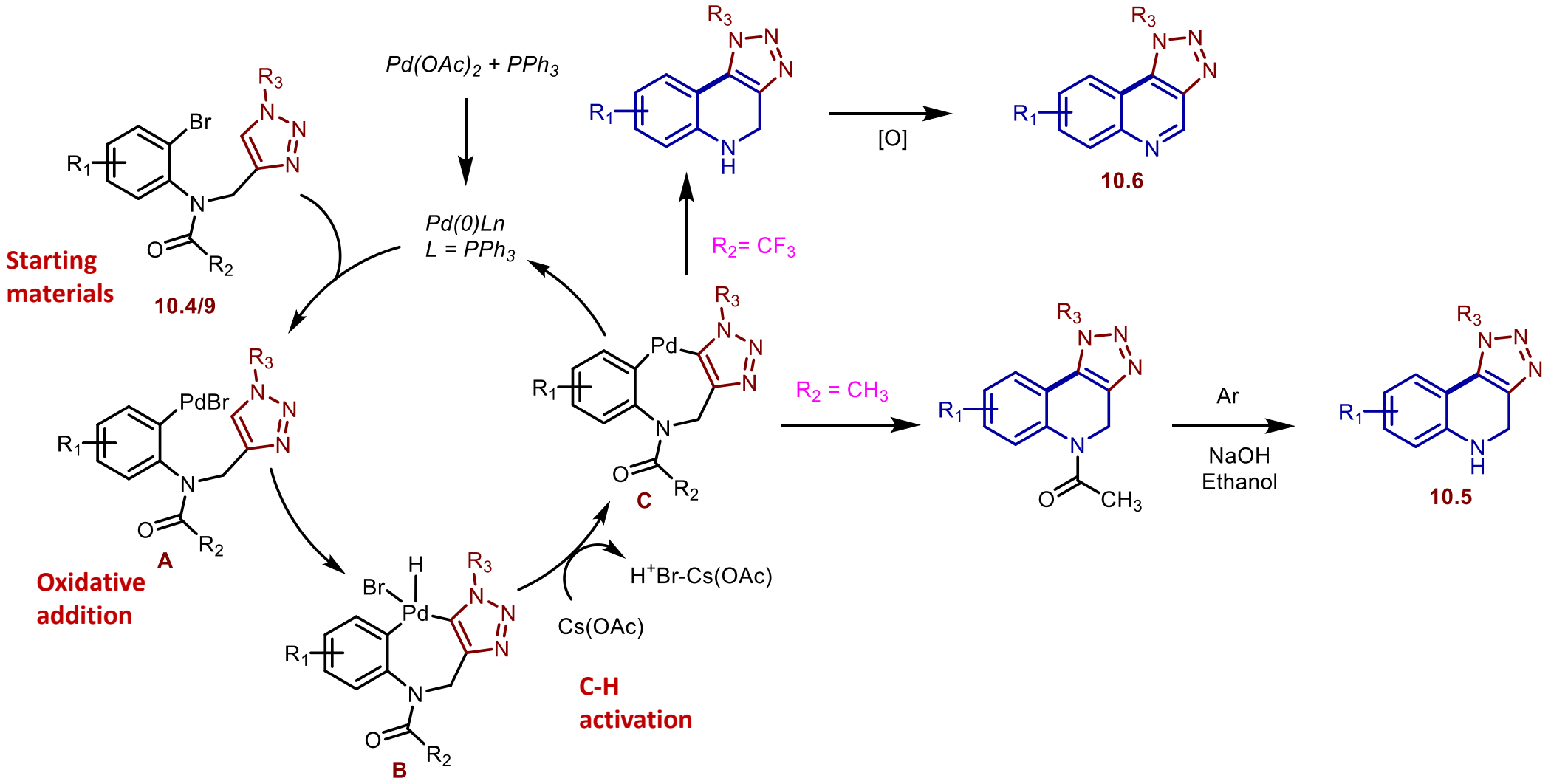

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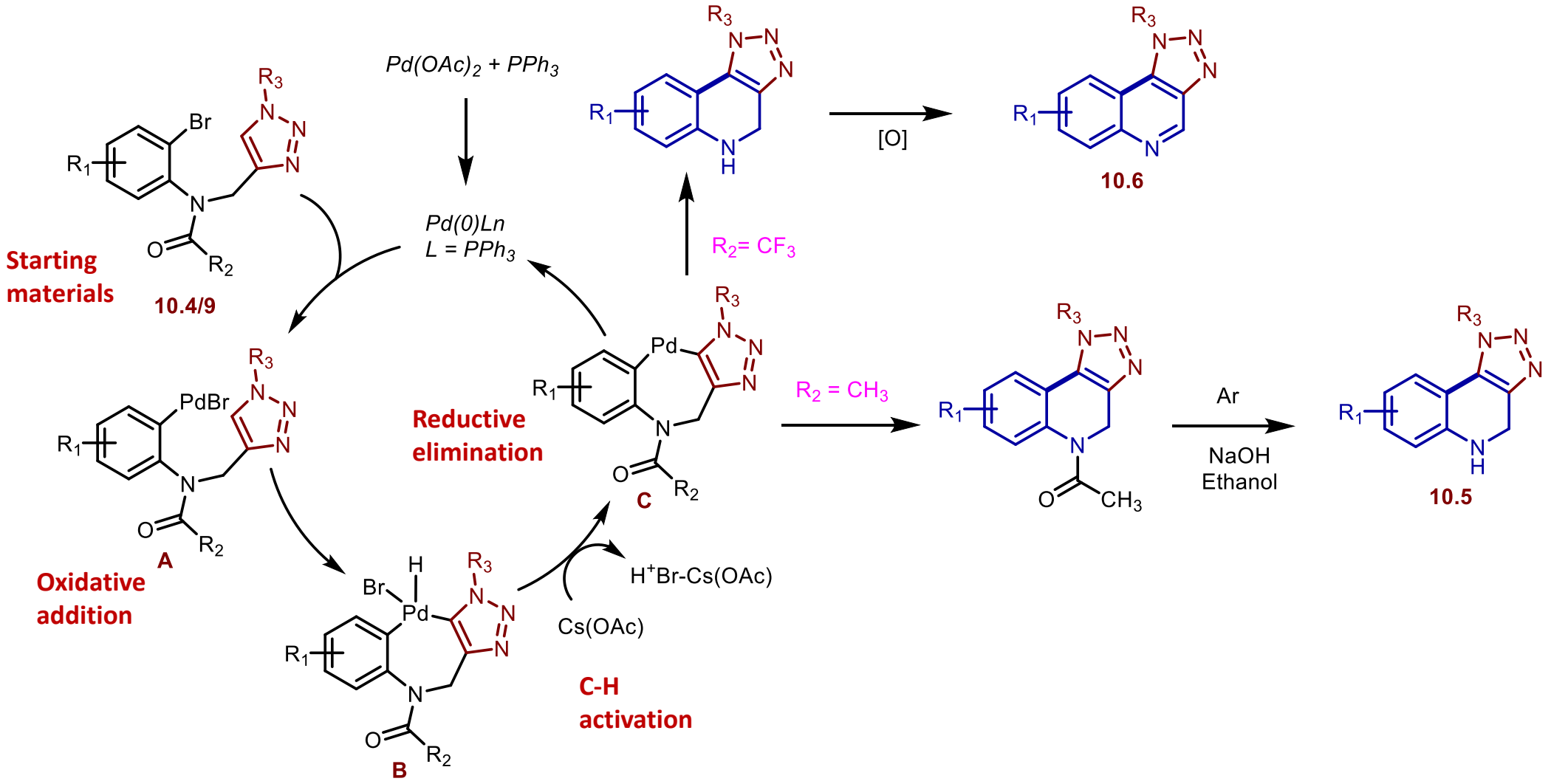

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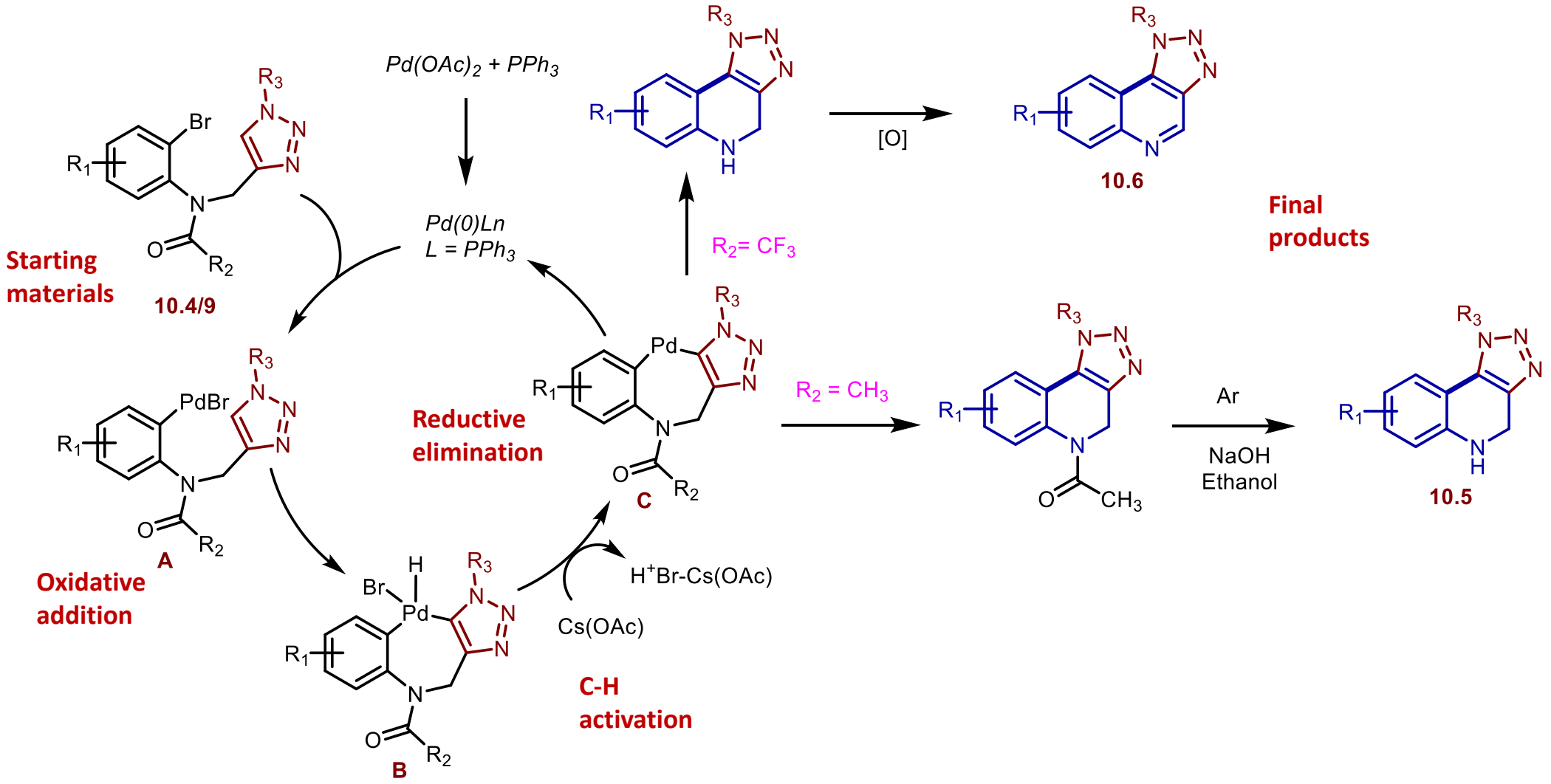

# Conclusion

- Palladium and, in general, metal catalyzed reactions, allows for **excellent atom economy**, reducing waste materials and temperature of reactions.
- New approach is proposed to perform the **intramolecular ring closure** of substituted *N*-((1*H*-1,2,3-triazol-4-yl)methyl)-2-bromo-*N*-protected anilines via Pd-catalyzed C–H annulation.
- This transformation gave **direct access to fused 1,2,3-triazole quinolines and dihydroquinolines** in yields ranging from good to excellent.
- Further **post-synthetic modifications** of polycyclic quinoline derivatives have been investigated.

# Acknowledgments


25 - 27 February 2026 | Catania, Italy

**Prof.ssa Vincenzina Barbera**
**Prof. Maurizio Galimberti**
**Dott. Davide Gentile**

**Prof. Giancarlo Fabrizi**
**Prof.ssa Antonella Goggiamani**
**Dott. Federico Marrone**
**Dott. Karim Ullah**

**Prof.ssa Antonia Iazzetti**


THANK YOU FOR THE KIND ATTENTION