Literature Report 4

Palladium-Catalyzed Difluorocarbene Transfer Enabled Divergent Synthesis of *γ*-Butenolides and Ynones from Iodobenzene and Terminal Alkynes

Reporter: Hao-Dong Chen
Checker: Yan-Jiang Yu
Date: 2024-01-29

Sheng, H.; Chen, Z.; Song, Q. *J. Am. Chem. Soc.* **2024**, *146,* 1722

CV of Prof. Qiuling Song

Background:

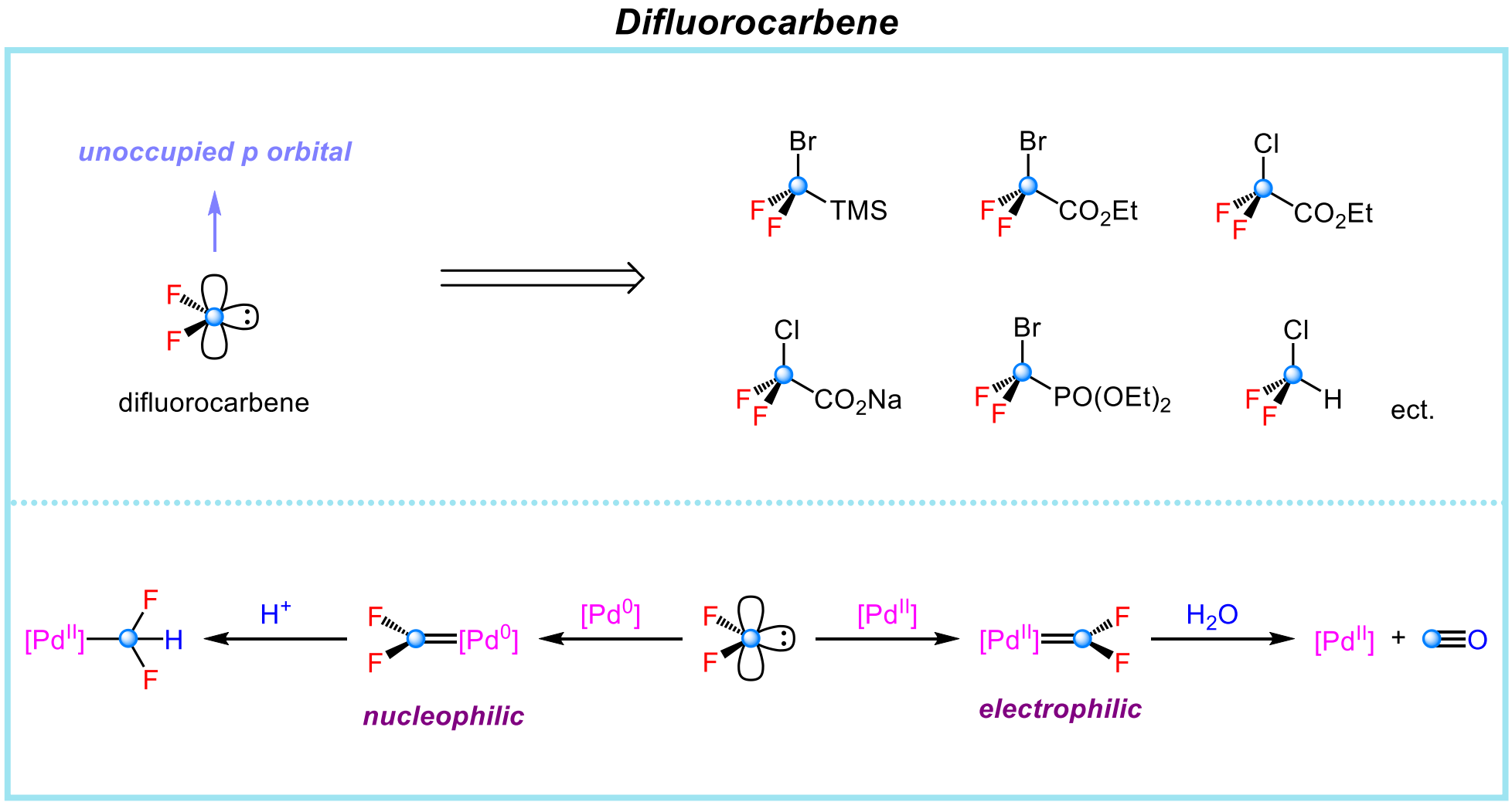
- **1994-1998** B.S., Zhengzhou University
- **1998-2001** M.S., Peking University
- **2002-2006** Ph.D., Princeton University
- **2007-2011** Researcher/Project Director, U.S. Pharmaceutical Company
- **2012-2023** Associate Professor/Professor, Huaqiao University
- **2023-now** Professor, Fuzhou University

Research:

- **Organoboron Chemistry**
- **Organic Fluorine Chemistry**
- **Radical Chemistry and Bioactive Molecular Synthetic Chemistry**

Contents

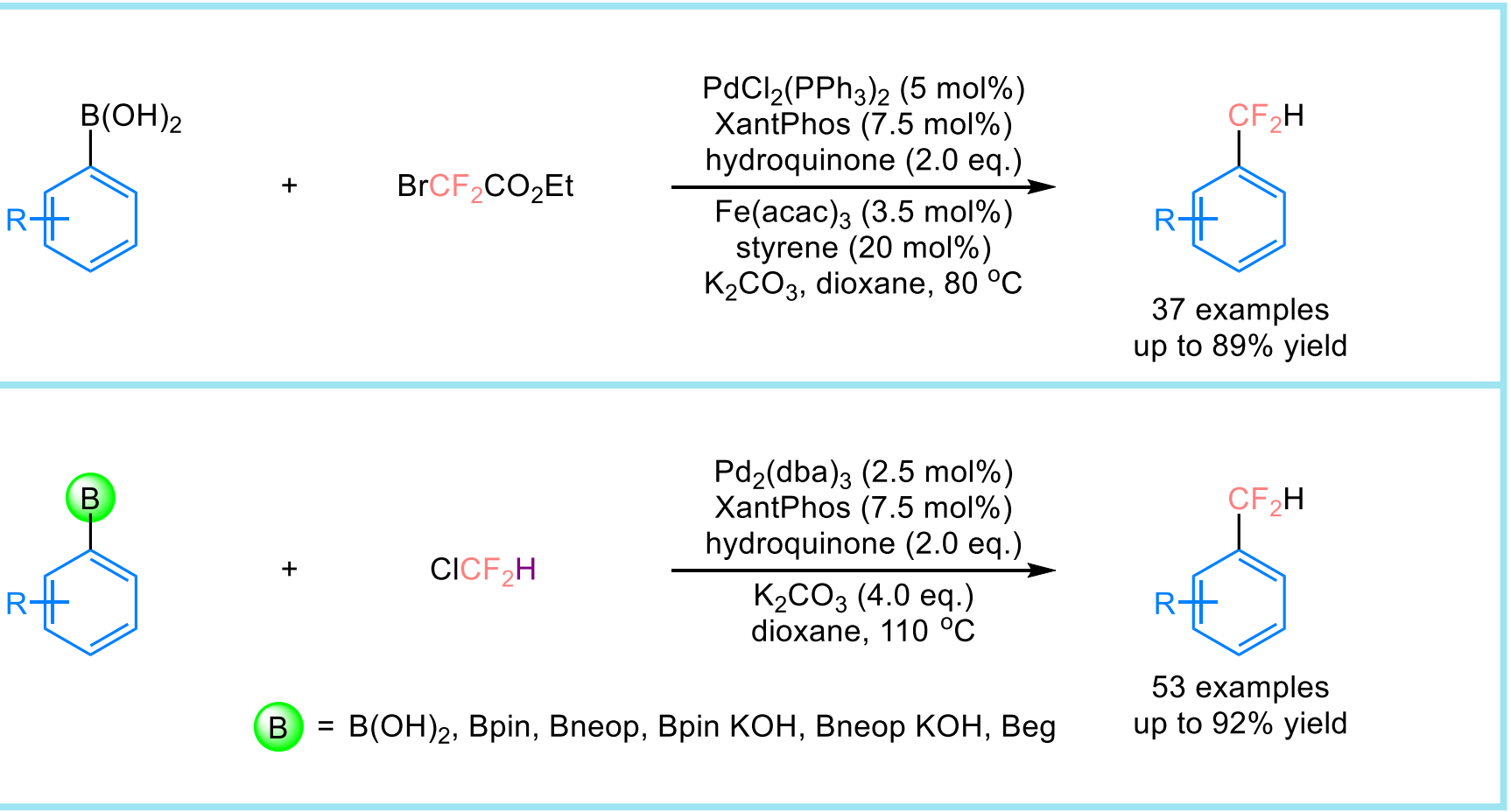
Introduction



Zhang, X.-Y.; Fu, X.- P.; Zhang, X. *CCS. Chem.* **2020**, *2*, 293; Ma, X.; Su, J.; Song, Q. *Acc. Chem. Res.* **2023**, *56*, 592

Introduction

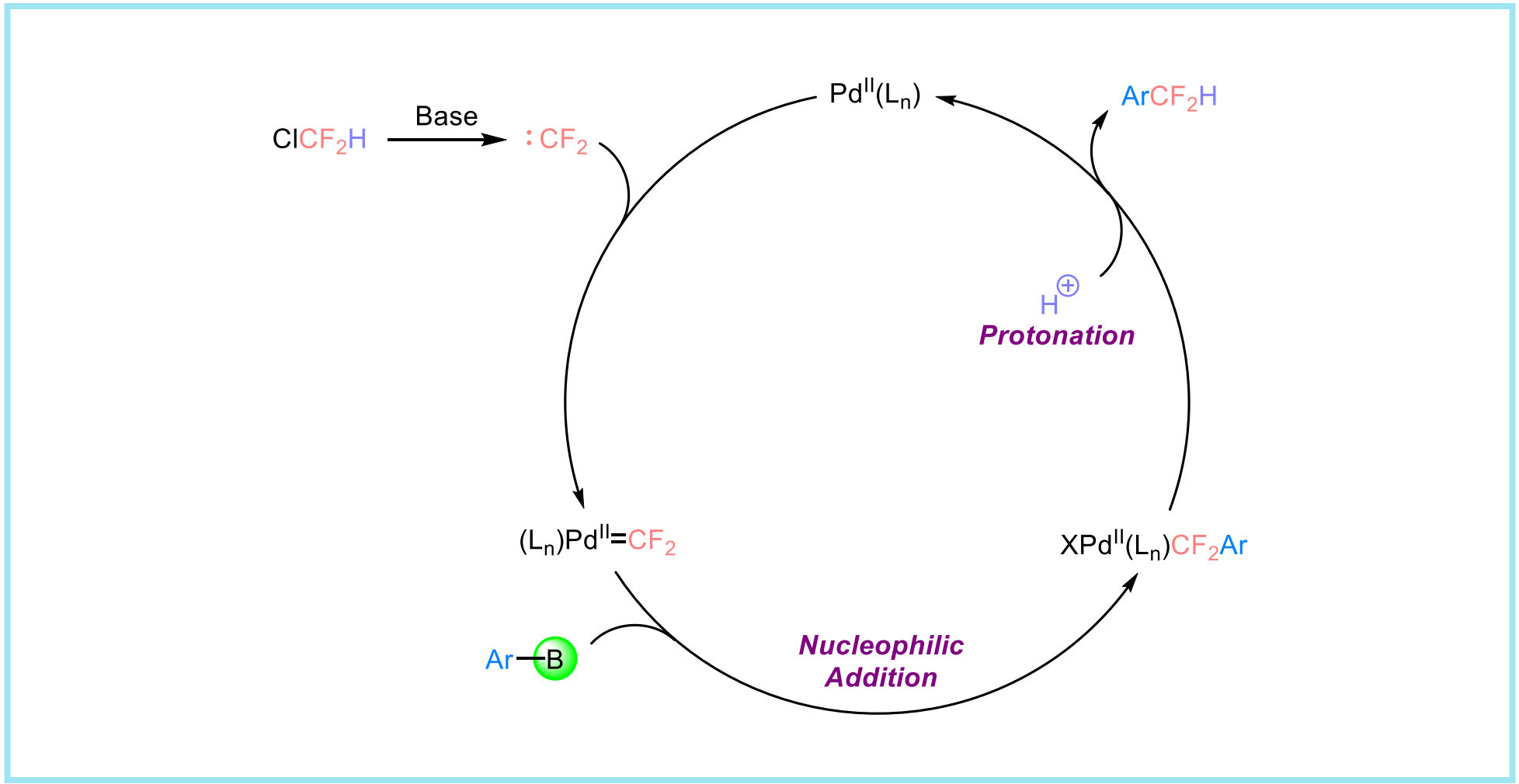
Palladium Difluorocarbene Involved Catalytic Coupling



Feng, Z.; Min, Q.-Q.; Zhang, X. *Org. Lett.* **2016**, *18*, 44; Feng, Z.; Min, Q.-Q.; Fu, X.-P.; An, L.; Zhang, X. *Nat. Chem.* **2017**, *9*, 918

Introduction

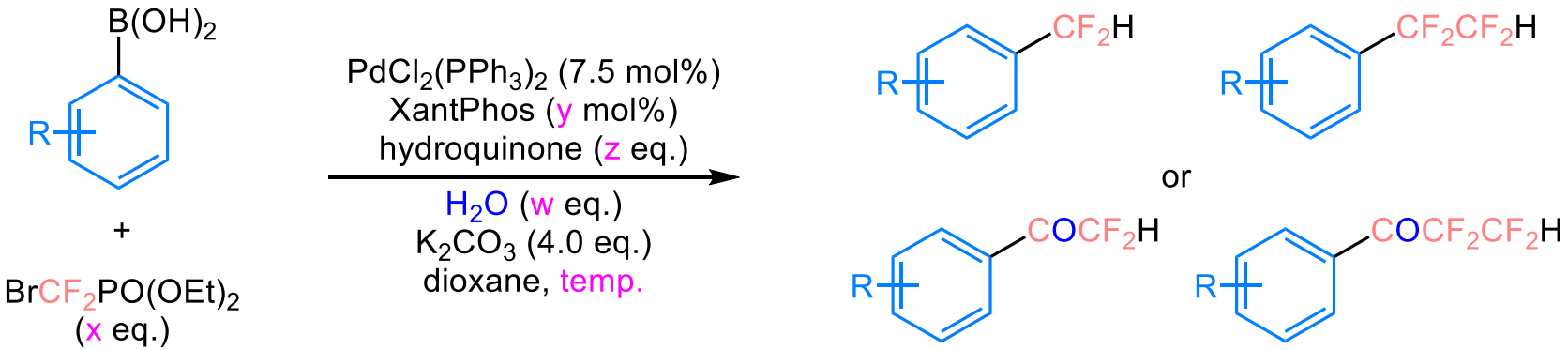
Palladium Difluorocarbene Involved Catalytic Coupling

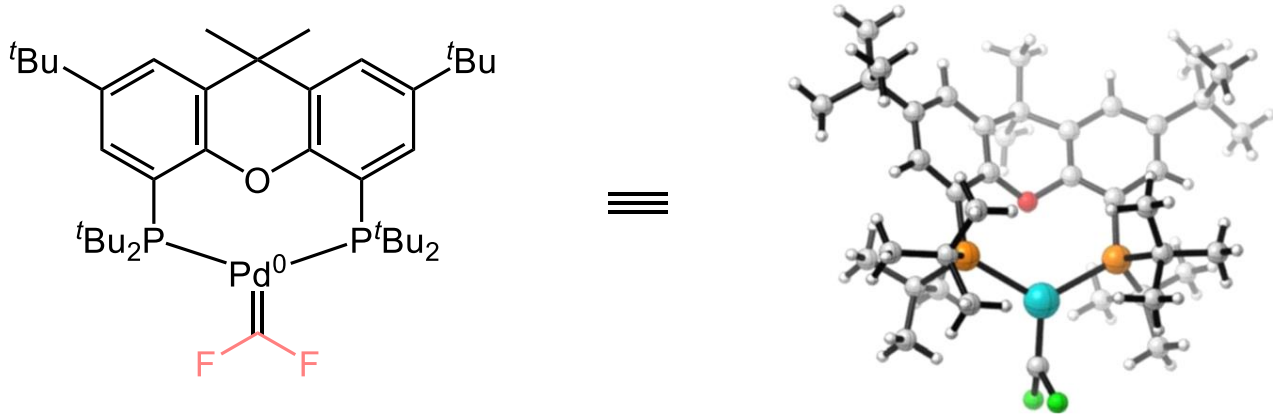


Feng, Z.; Min, Q.-Q.; Zhang, X. *Org. Lett.* **2016**, *18*, 44; Feng, Z.; Min, Q.-Q.; Fu, X.-P.; An, L.; Zhang, X. *Nat. Chem.* **2017**, *9*, 918

Introduction

Palladium-Catalyzed Difluorocarbene Transfer Reaction

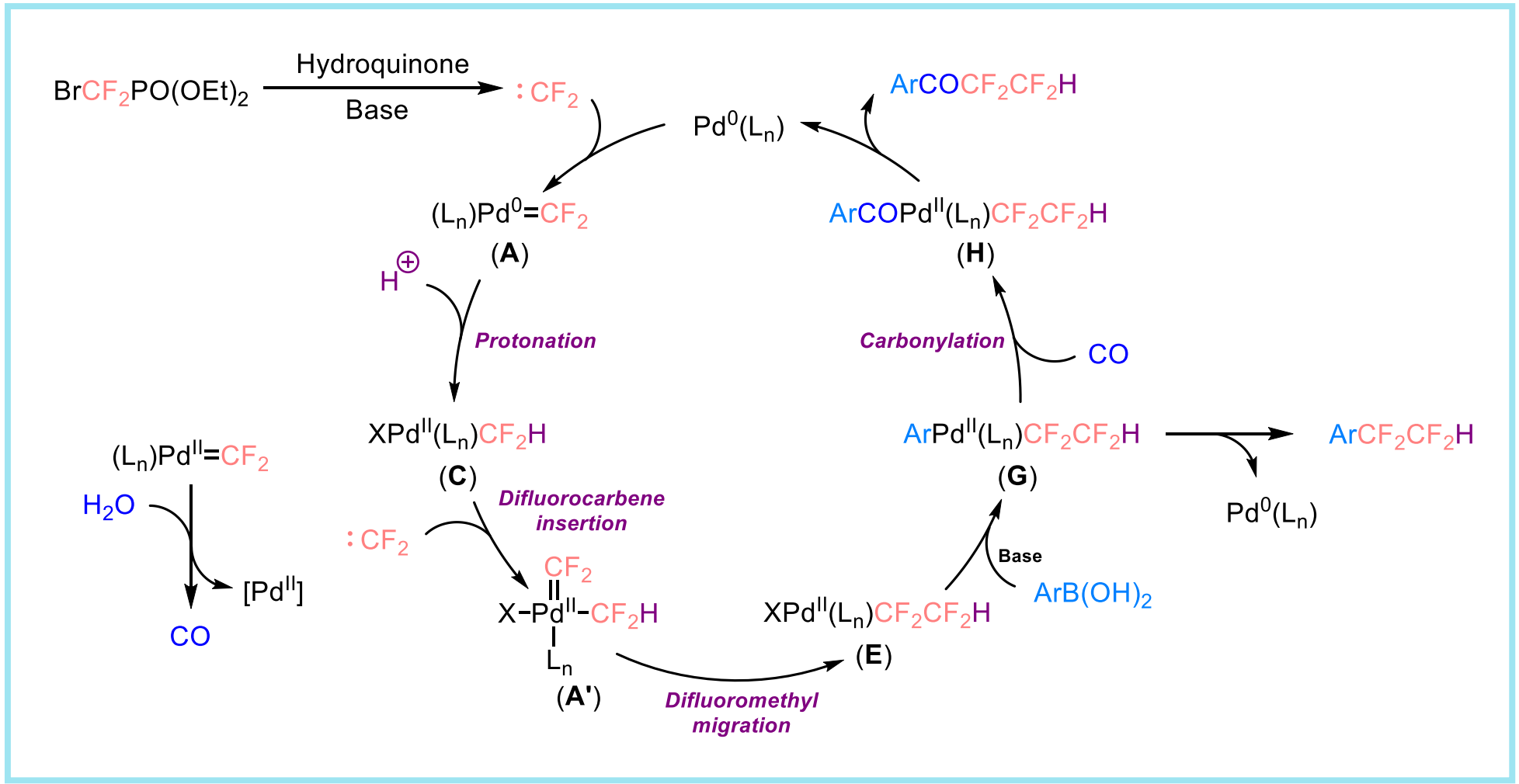




Fu, X.-P.; Xue, X.-S.; Zhang, X.-Y.; Xiao, Y.-L.; Zhang, S.; Guo, Y.-L.; Leng, X.; Houk, K. N.; Zhang, X. *Nat. Chem.* **2019**, *11*, 948

Introduction

Palladium-Catalyzed Difluorocarbene Transfer Reaction



Fu, X.-P.; Xue, X.-S.; Zhang, X.-Y.; Xiao, Y.-L.; Zhang, S.; Guo, Y.-L.; Leng, X.; Houk, K. N.; Zhang, X. *Nat. Chem.* **2019**, *11*, 948

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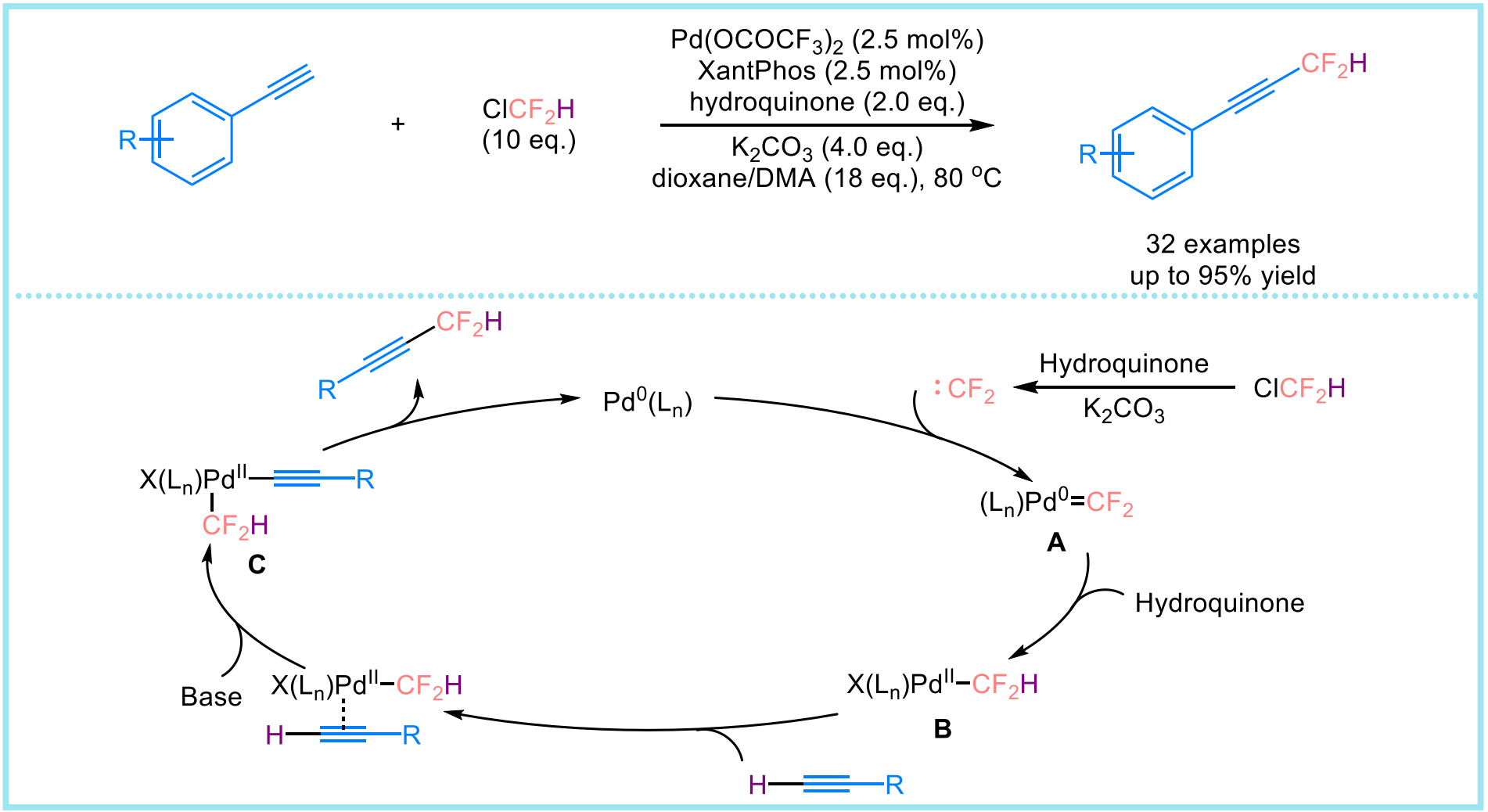
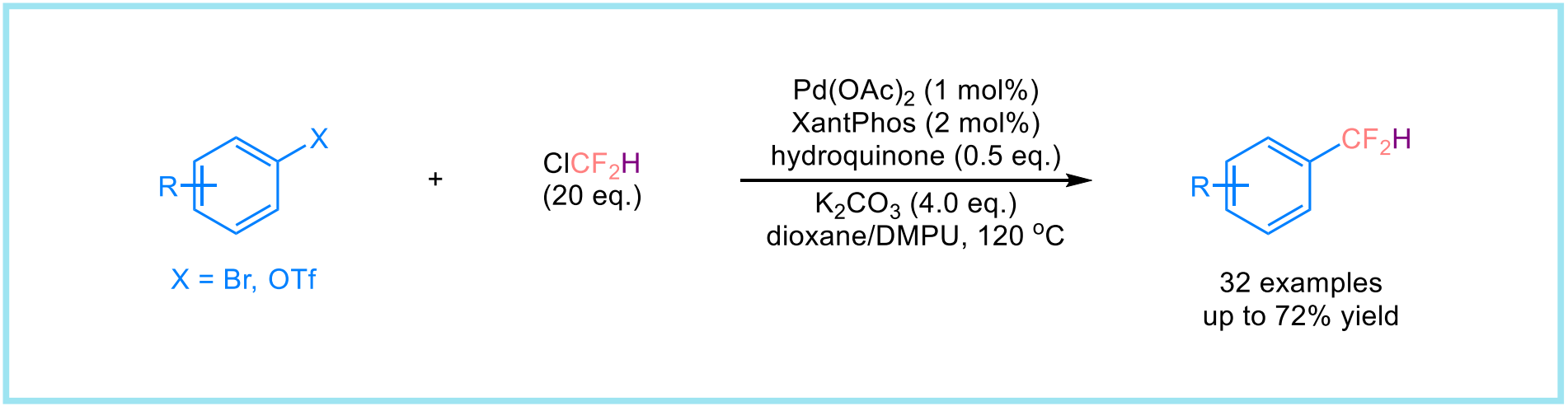
Palladium Difluorocarbene Involved Catalytic Coupling



Zhang, X.-Y.; Fu, X.-P.; Zhang, S.; Zhang, X. *CCS. Chem.* **2020**, *2*, 293

Introduction

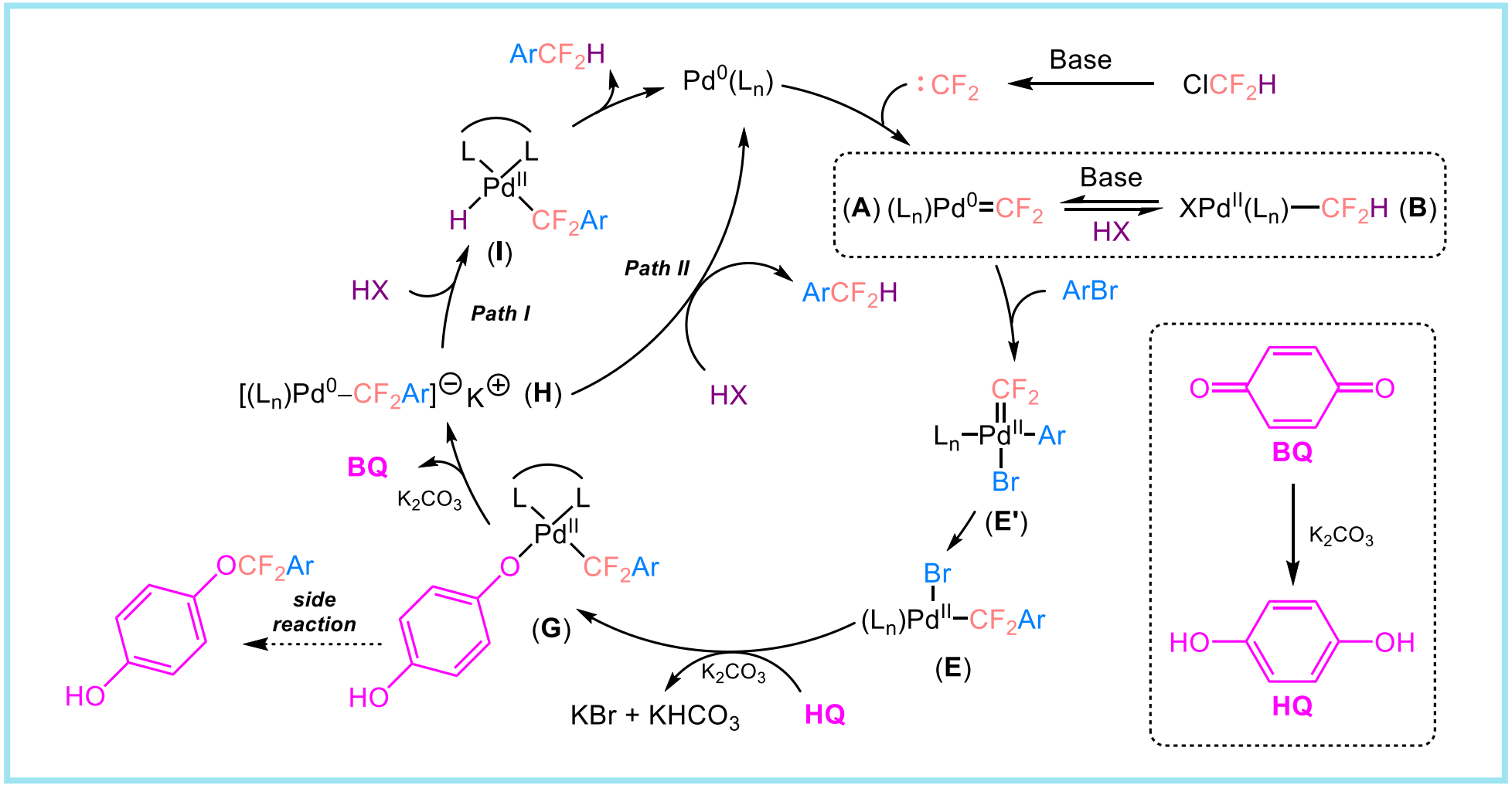
Palladium-Catalyzed Reductive Difluorocarbene Transfer



Zhang, X.-Y.; Sun, S.-P.; Sang, Y.-Q.; Xue, X.-S.; Min, Q.-Q.; Zhang, X. *Angew Chem. Int. Ed.* **2023**, *63*, e202306501

Introduction

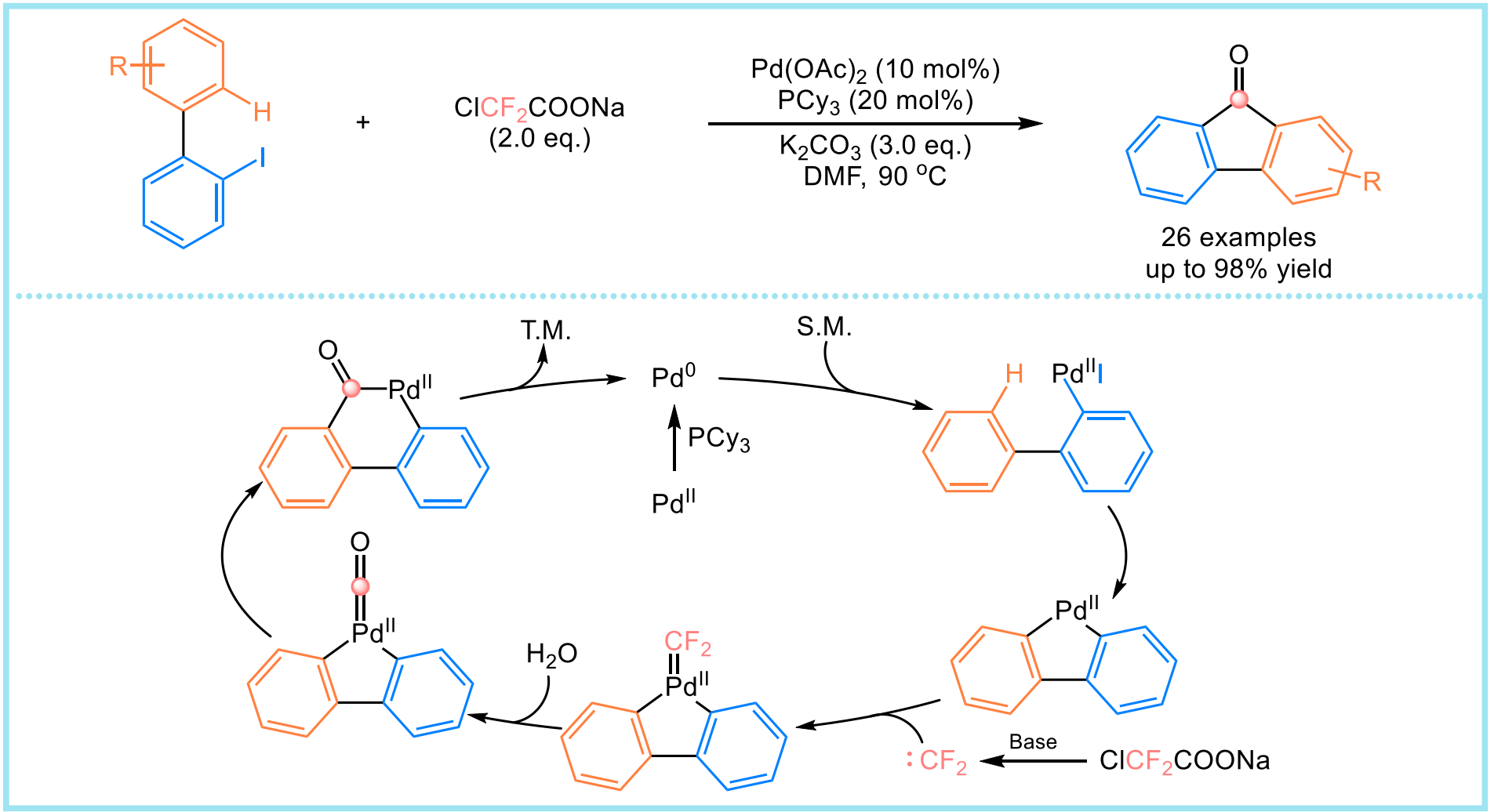
Pd-Catalyzed Reductive Difluorocarbene Transfer



Zhang, X.-Y.; Sun, S.-P.; Sang, Y.-Q.; Xue, X.-S.; Min, Q.-Q.; Zhang, X. *Angew Chem. Int. Ed.* **2023**, *63*, e202306501

Introduction

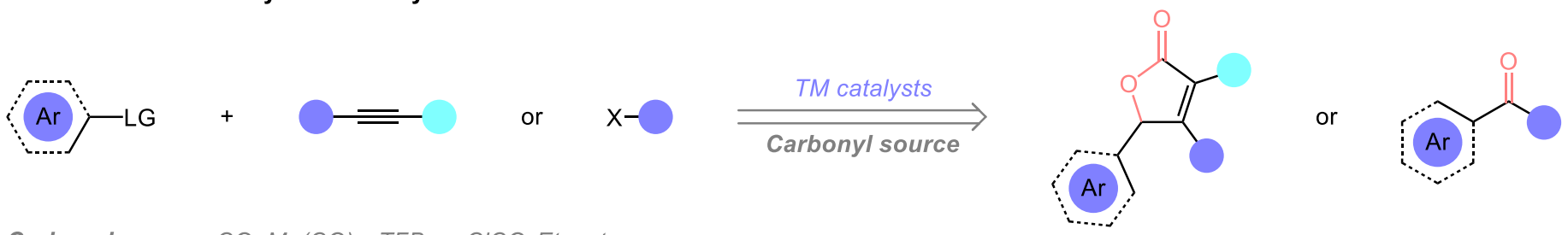
Pd-Catalyzed Difluorocarbene Transfer Reaction by Combining C-H Activation



Liu, X.; Sheng, H.; Zhou, Y.; Song, Q. *Org. Lett.* **2021**, *23*, 2543

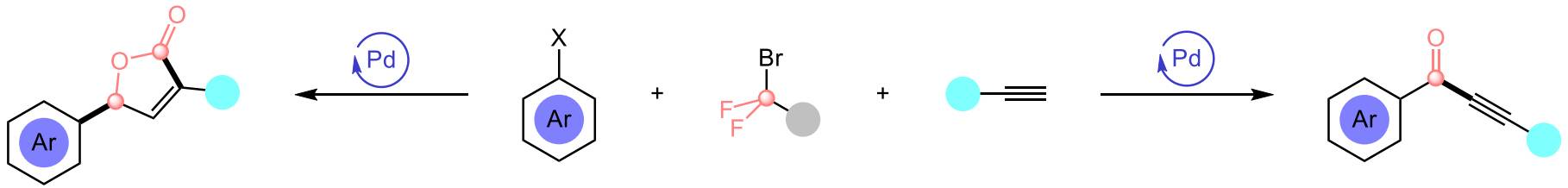
Project Synopsis

Transition Metal-Catalyzed Carbonylation/Esterification Reactions



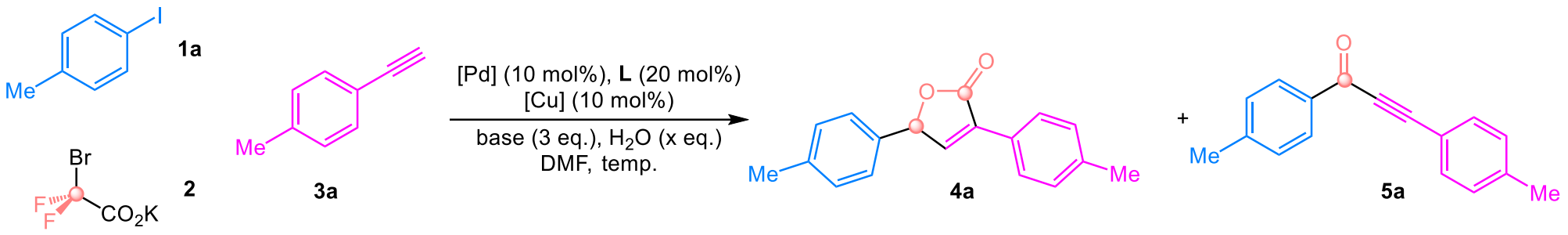
Carbonyl source: *CO, $Mo(CO)_6$, TFBen, $ClCO_2Et$, ect.*

Palladium-Catalyzed Difluorocarbene Transfer Enables Access to γ-Butenolides and Ynones



Optimization of the Reaction Conditions

Optimization of the Reaction Conditions



Entry[a]	[Pd]	[Cu]	**L**	H_2O (x eq.)	Base	**4a** yield (%)	**5a** yield (%)
1	$Pd(MeCN)_2Cl_2$	-	PCy_3	5	HCO_2Na	70	nd
2	$Pd(PPh_3)_2Cl_2$	-	PCy_3	5	HCO_2Na	11	15
3	$Pd(OAc)_2$	-	PCy_3	5	HCO_2Na	64	nd
4	$Pd(MeCN)_2Cl_2$	-	S-Phos	5	HCO_2Na	48	7
5	$Pd(MeCN)_2Cl_2$	-	PPh_3	5	HCO_2Na	9	21
6	$Pd(MeCN)_2Cl_2$	-	$PPhCy_2$	5	HCO_2Na	58	nd
7	$Pd(MeCN)_2Cl_2$	-	BINAP	5	HCO_2Na	12	14
8	$Pd(MeCN)_2Cl_2$	-	PCy_3	5	Na_2CO_3	66	17

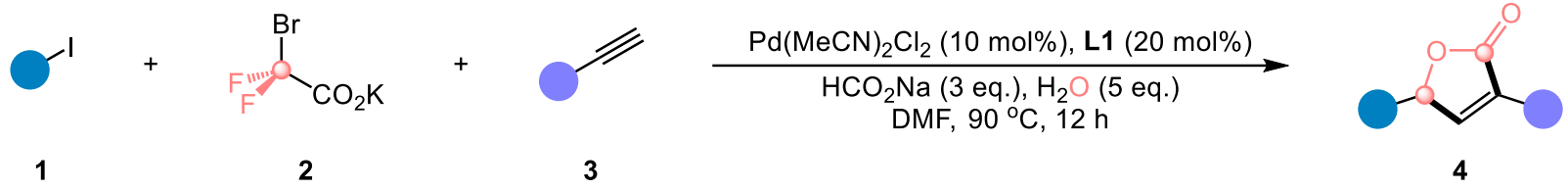
[a]**1a** (0.2 mmol), **2** (0.6 mmol, 3.0 eq.), **3a** (0.3 mmol,1.5 eq.), [Pd] (10 mol %), L (20 mol %), [Cu] (x mol%), base (0.6 mmol, 3.0 eq.), H_2O (y eq.), DMF (2 mL), 90 °C, 12 h, isolated yields.

Optimization of the Reaction Conditions

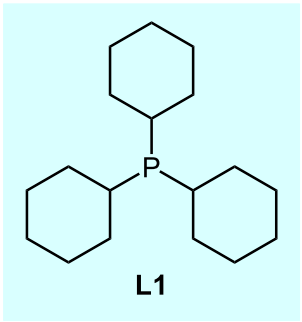
Entry[a]	[Pd]	[Cu]	**L**	H_2O (x eq.)	Base	**4a** yield (%)	**5a** yield (%)
9	$Pd(MeCN)_2Cl_2$	-	PCy_3	5	K_2CO_3	nd	11
10[b]	$Pd(MeCN)_2Cl_2$	CuI	PCy_3	5	HCO_2Na	65	nd
11[b]	$Pd(MeCN)_2Cl_2$	CuI	PPh_3	5	HCO_2Na	nd	48
12[b]	$Pd(MeCN)_2Cl_2$	CuI	PPh_3	5	Na_2CO_3	nd	54
13[b]	$Pd(MeCN)_2Cl_2$	CuI	4-F-PPh_3	5	Na_2CO_3	nd	64
14[b]	$Pd(MeCN)_2Cl_2$	CuI	4-F-PPh_3	3	Na_2CO_3	nd	70
15[b]	$Pd(MeCN)_2Cl_2$	CuI	4-F-PPh_3	1	Na_2CO_3	nd	87
16[b,c]	$Pd(MeCN)_2Cl_2$	CuI	4-F-PPh_3	1	Na_2CO_3	nd	73
17[b,d]	$Pd(MeCN)_2Cl_2$	CuI	4-F-PPh_3	1	Na_2CO_3	nd	61
18[b,e]	$Pd(MeCN)_2Cl_2$	CuI	4-F-PPh_3	1	Na_2CO_3	nd	86

[a]**1a** (0.2 mmol), **2** (0.6 mmol, 3.0 eq.),**3a** (0.3 mmol,1.5 eq.), [Pd] (10 mol %), L (20 mol %), [Cu] (x mol%), base (0.6 mmol, 3.0 eq.), H_2O (y eq.), DMF (2 mL), 90 ^oC, 12 h, isolated yields; [b]CuI (10 mol%), 100 ^oC; [c]8 h; [d]dioxane instead of DMF; [e]$Pd(MeCN)_2Cl_2$ (5 mol%).

Synthesis of γ-Butenolides

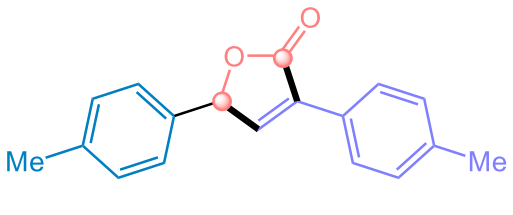


1 **2** **3** **4**

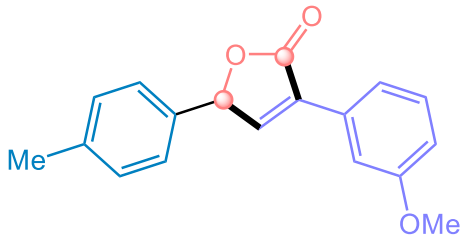


L1

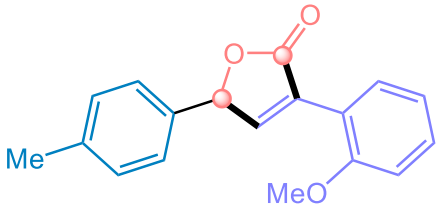
Substrate Scope



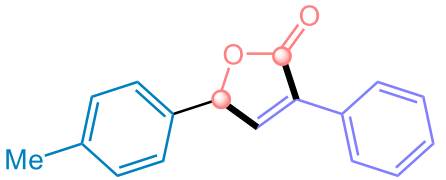
4a, 70%



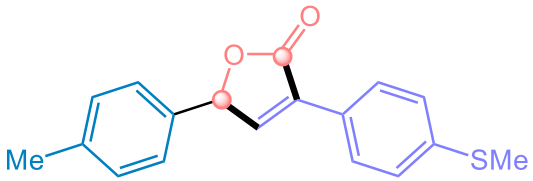
4b, 66%



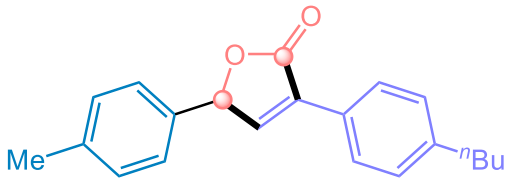
4c, 41%



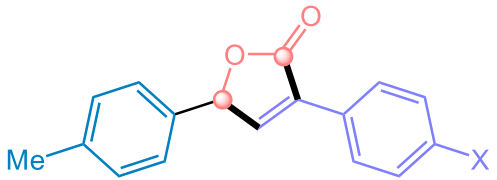
4d, 73%



4e, 53%



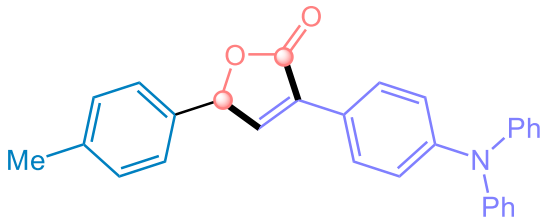
4f, 68%



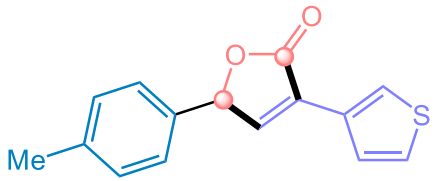
4g, X = F, 72%
4h, X = Cl, 71%
4i, X = Br, 42%

Synthesis of *γ*-Butenolides

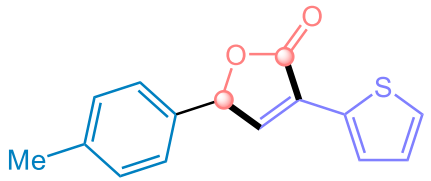
Substrate Scope



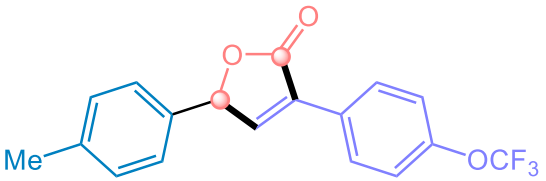
4j, 59%



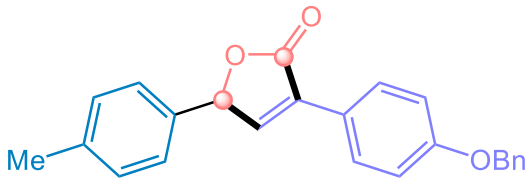
4k, 70%



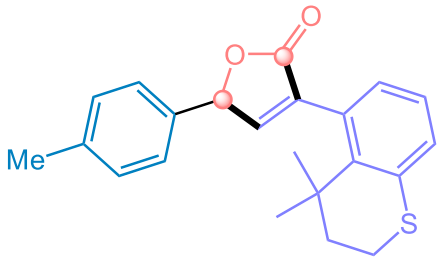
4l, 43%



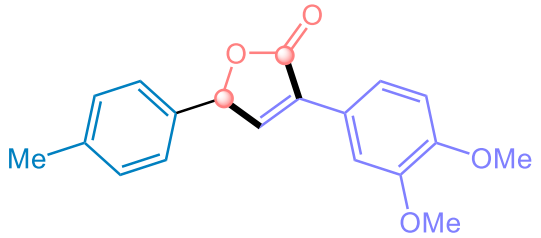
4m, 59%



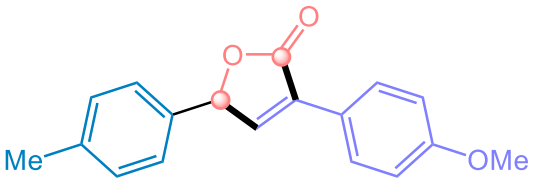
4n, 41%



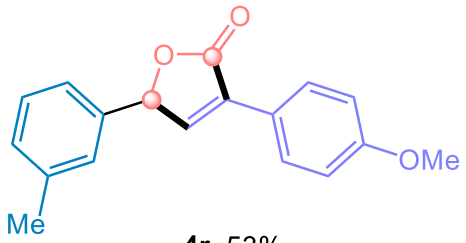
4o, 68%



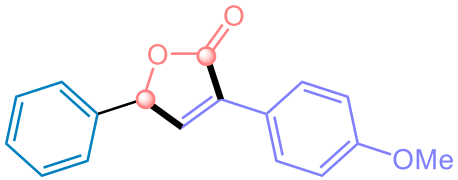
4p, 67%



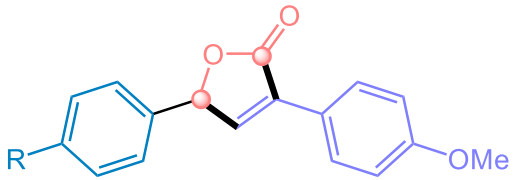
4q, 66%



4r, 53%



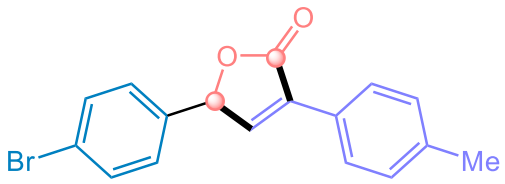
4s, 65%



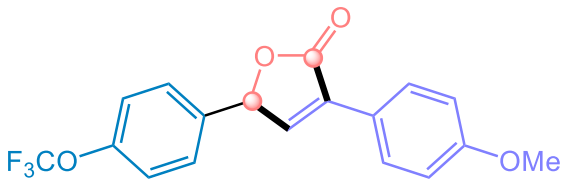
4t, R = ^{i}Pr, 69%
4u, R = F, 41%
4v, R = Cl, 46%

Synthesis of *γ*-Butenolides

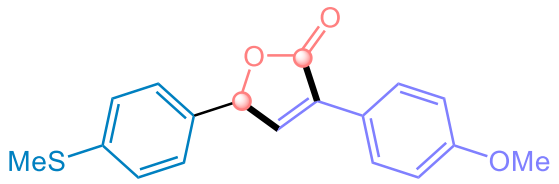
Substrate Scope



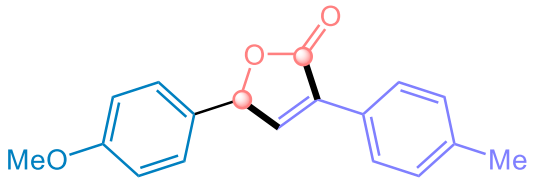
4w, 45%



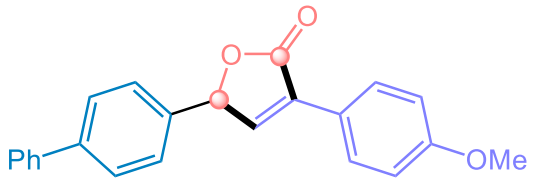
4x, 42%



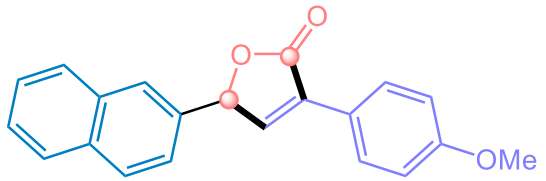
4y, 61%



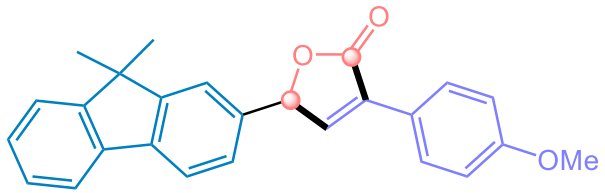
4z, 54%



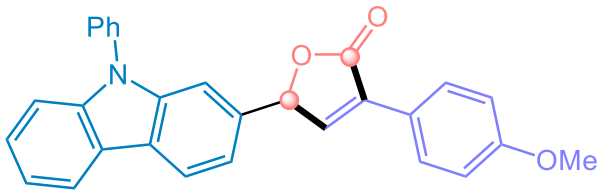
4aa, 66%



4ab, 64%

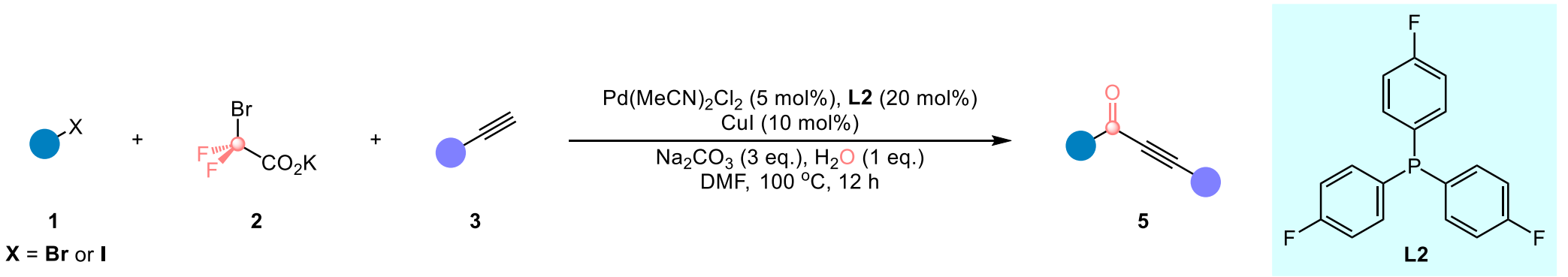


4ac, 52%



4ad, 58%

Synthesis of Ynones



1
X = **Br** or **I**

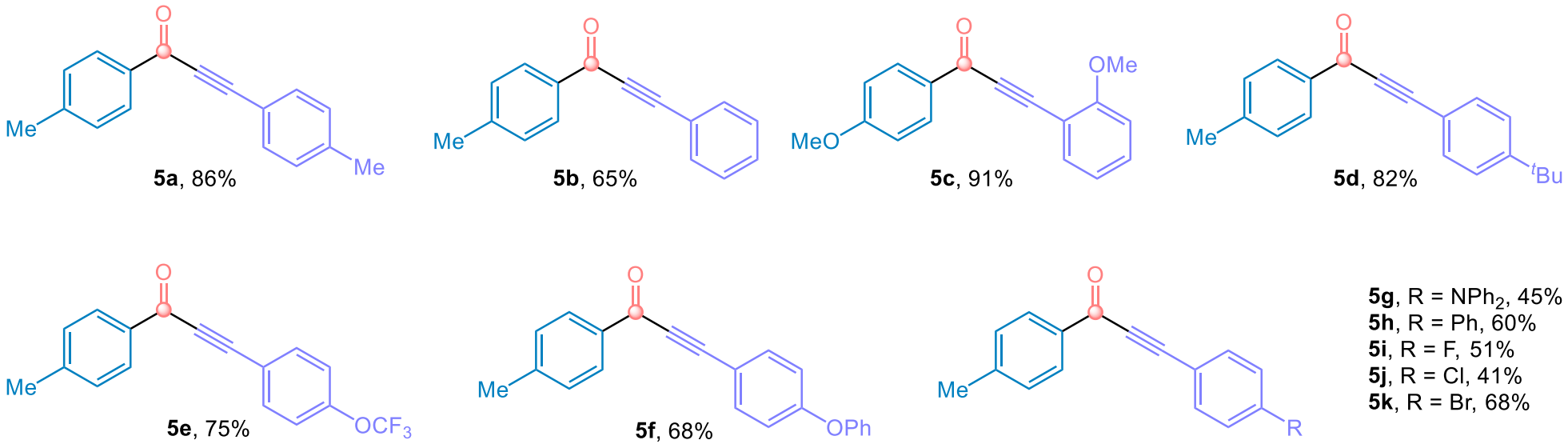
2

3

5

L2

Substrate Scope



5a, 86%

5b, 65%

5c, 91%

5d, 82%

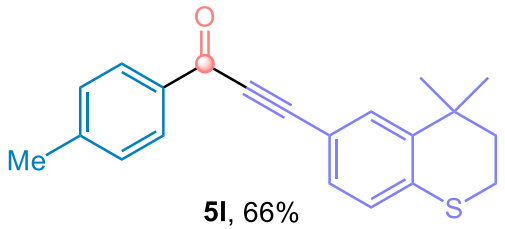
5e, 75%

5f, 68%

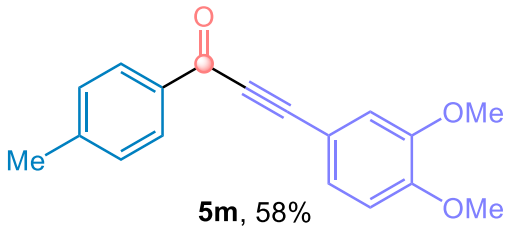
5g, R = NPh_2, 45%
5h, R = Ph, 60%
5i, R = F, 51%
5j, R = Cl, 41%
5k, R = Br, 68%

Synthesis of Ynones

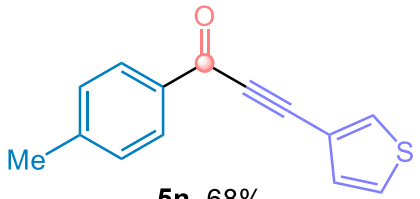
Substrate Scope



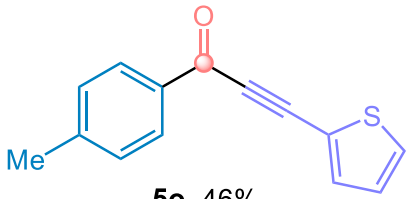
5l, 66%



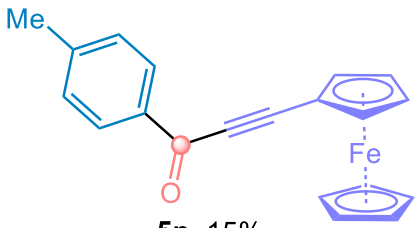
5m, 58%



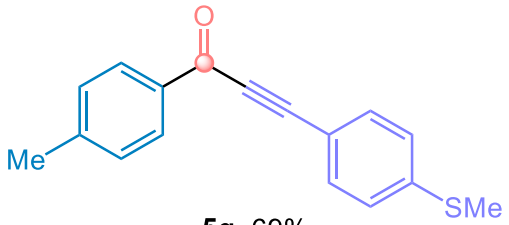
5n, 68%



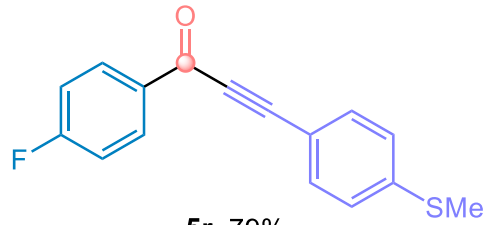
5o, 46%



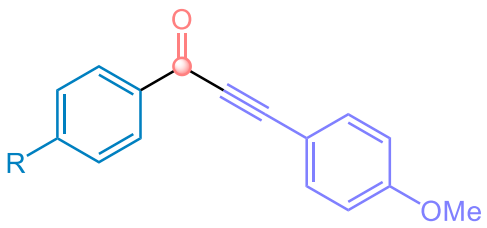
5p, 15%



5q, 69%

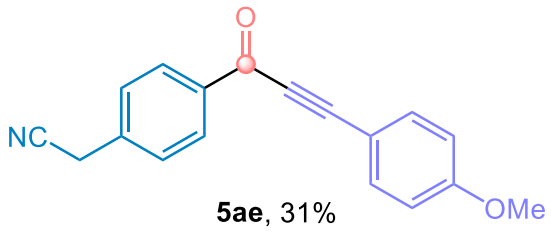


5r, 79%



5s, R = Me, 83%
5t, R = F, 66%
5u, R = Cl, 83%
5v, R = Br, 76%
5w, R = OMe, 83%
5x, R = ^{i}Pr, 90%

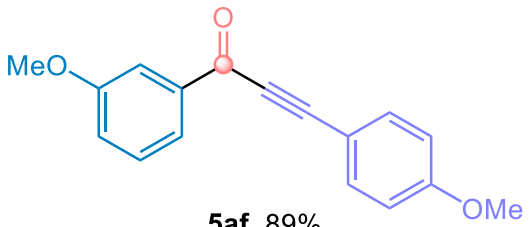
5y, R = ^{t}Bu, 80%
5z, R = H, 75%
5aa, R = SMe, 91%
5ab, R = CF_3, 76%
5ac, R = Ph, 43%
5ad, R = OCF_3, 58%



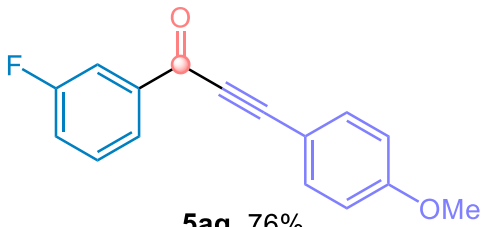
5ae, 31%

Synthesis of Ynones

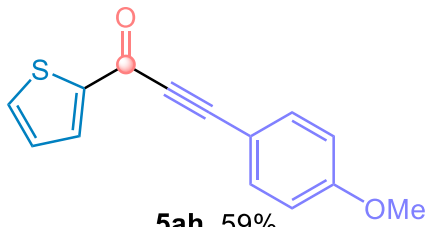
Substrate Scope



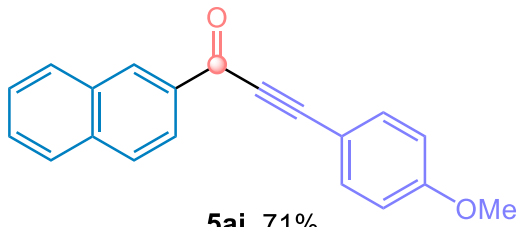
5af, 89%



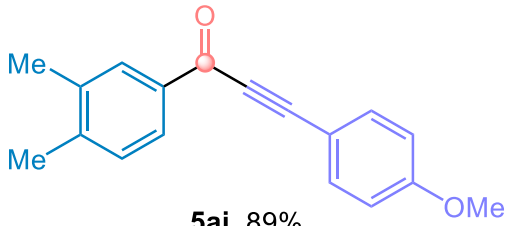
5ag, 76%



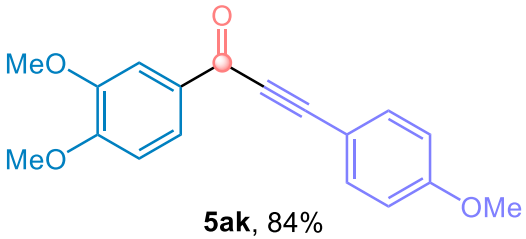
5ah, 59%



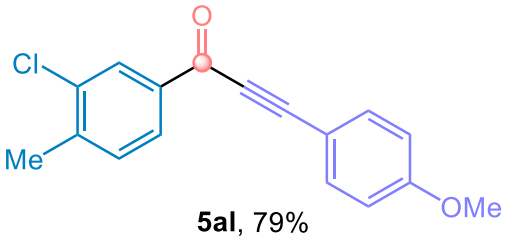
5ai, 71%



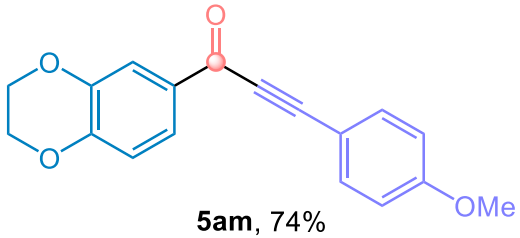
5aj, 89%



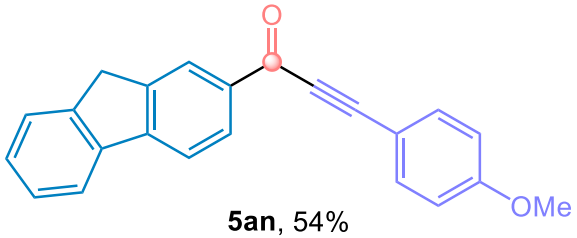
5ak, 84%



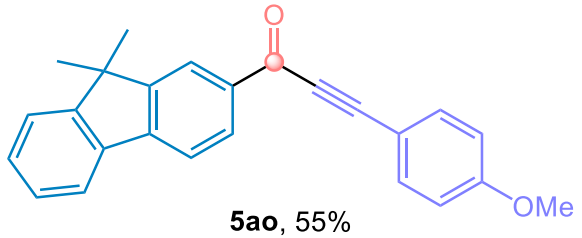
5al, 79%



5am, 74%

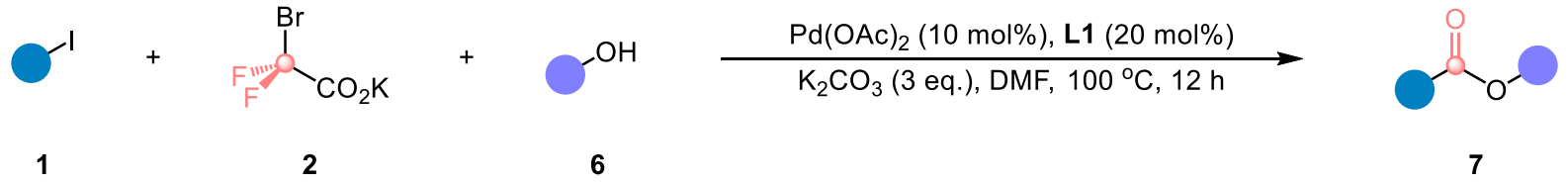


5an, 54%

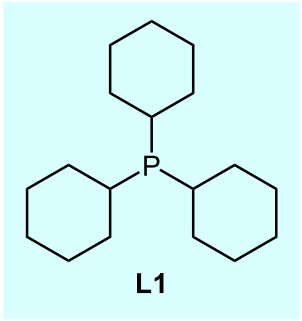


5ao, 55%

Synthesis of Esters

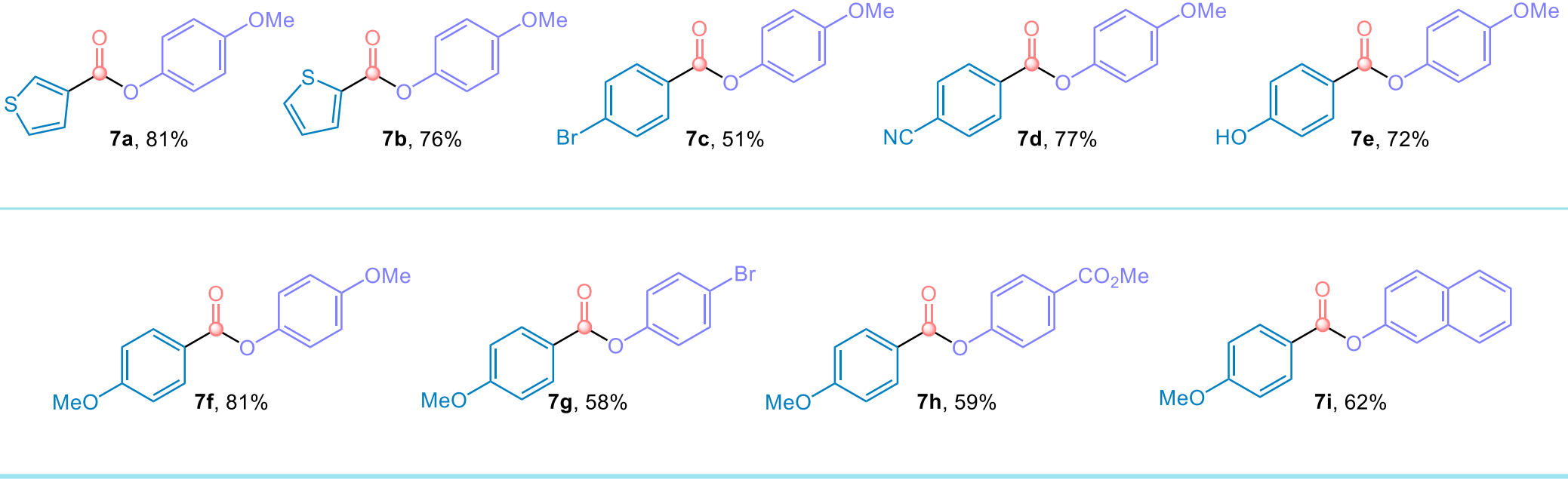


1 **2** **6** **7**



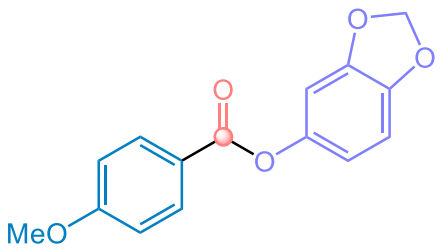
L1

Substrate Scope

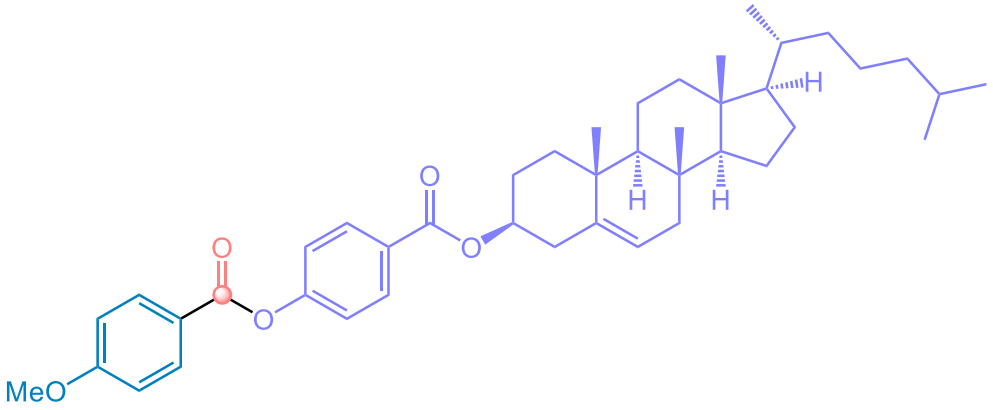


Synthesis of Esters

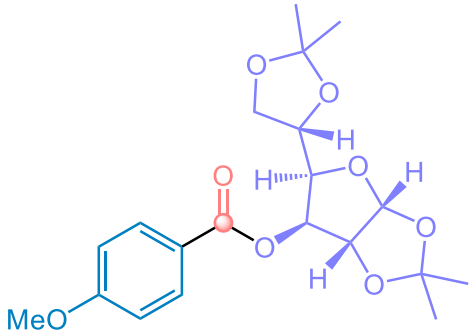
Substrate Scope



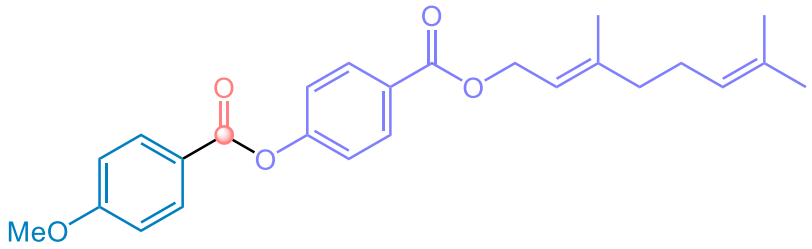
from Sesamol
7j, 88%



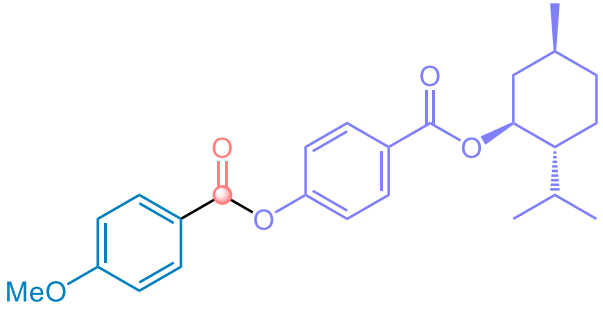
from Cholesterol
7K, 41%



from Diacetone-D-glucose
7l, 78%

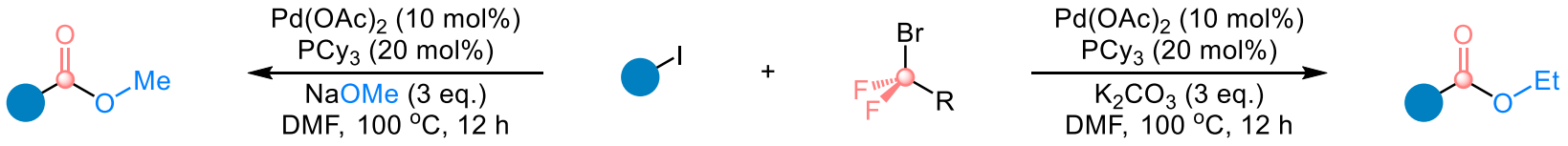


from Geraniol
7m, 37%



from DL-Menthol
7n, 69%

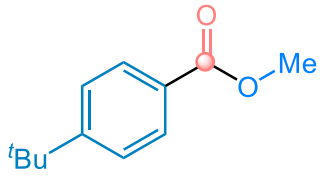
Scope of Other Nucleophilic Reagents



8 **1** **2'** **9**

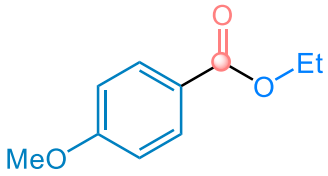
Substrate Scope

R = CO_2K

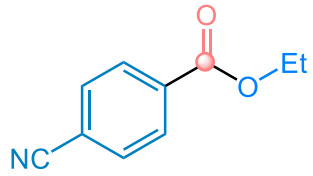


8a, 63%

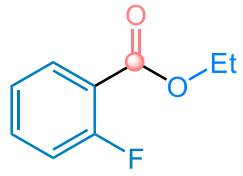
R = $OP(OEt)_2$



9a, 82%

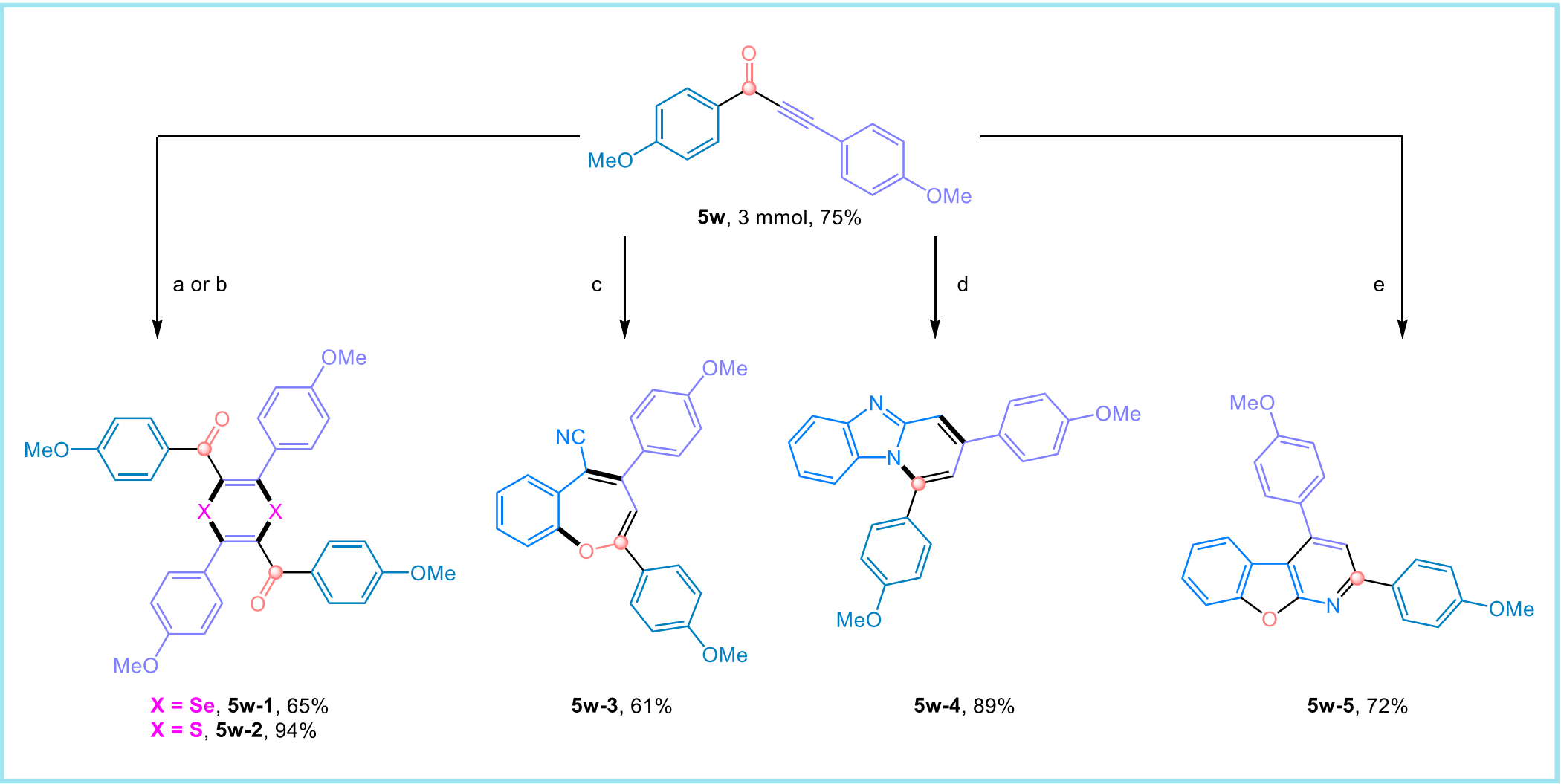


9b, 65%



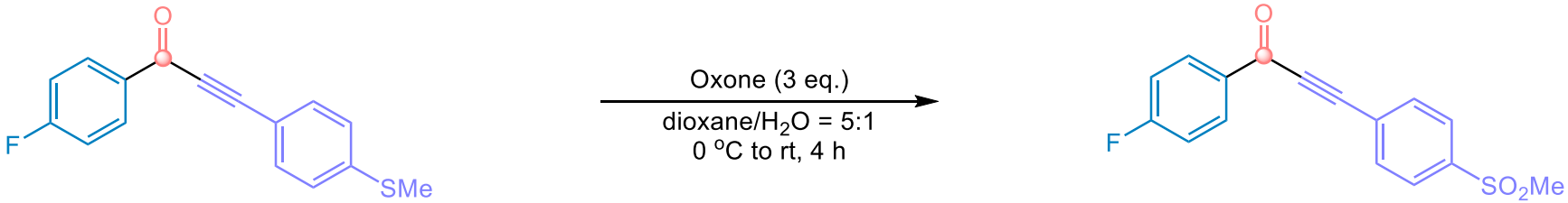
9c, 75%

Synthetic Applications



(a), S_8, K_2CO_3, DMF, 0 °C, 4 h. (b), Se, K_2CO_3, DMF, 80 °C, 4 h. (c), 2-Bromobenzyl cyanide, ^{t}BuOLi, NMP, 100 °C, 5 h. (d), 2-Methylbenz-imidazole, KOH, dioxane, 100 °C, 6 h. (e), 2-Bromobenzyl cyanide, DBU, DMSO, 100 °C, 12 h.

Synthetic Applications

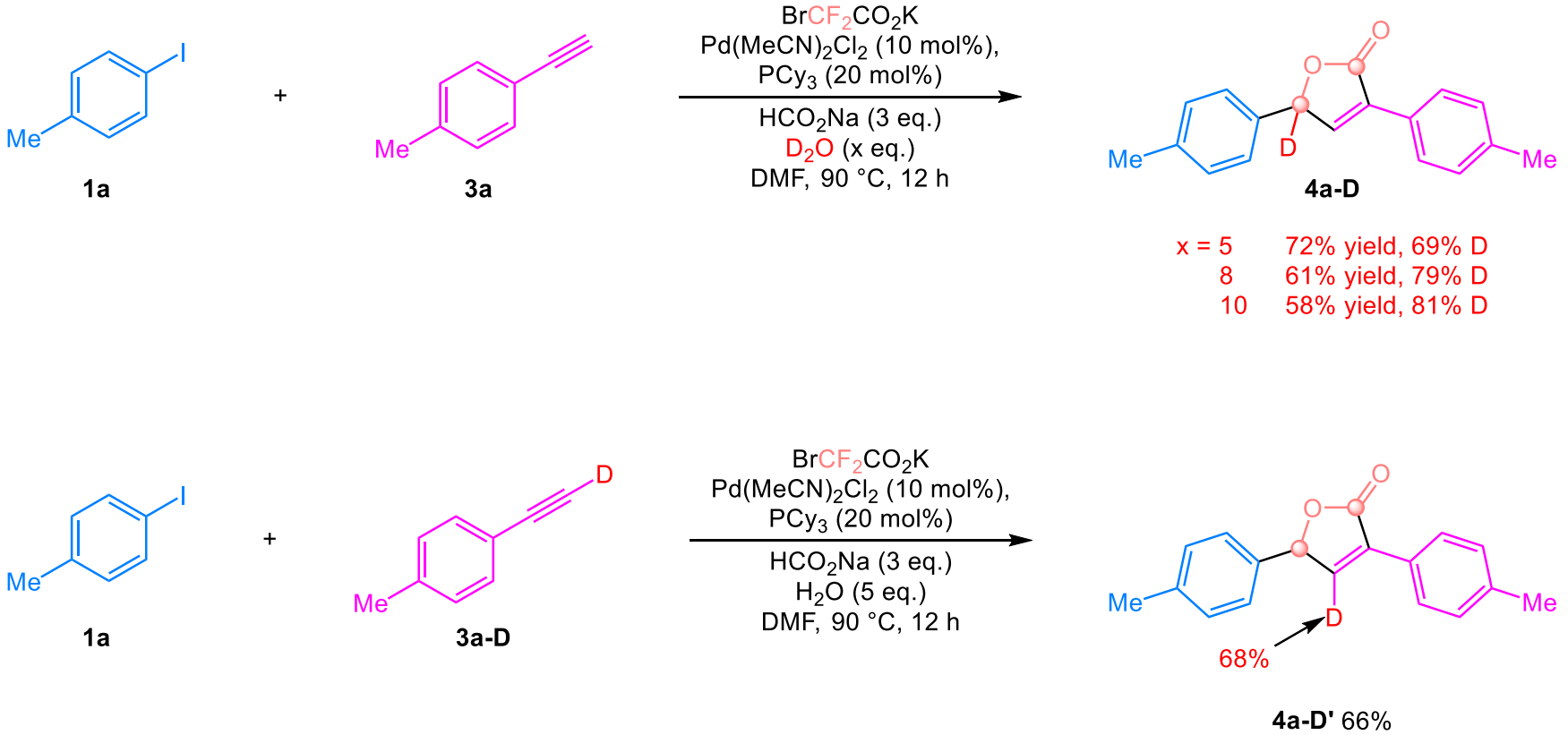


5r

5r-1, 95%
Anti-inflammatory analgesic

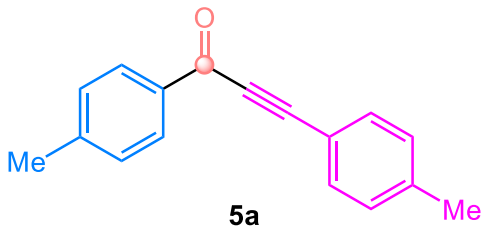
Mechanistic Investigation

Deuterium Labeling Experiment



Mechanistic Investigation

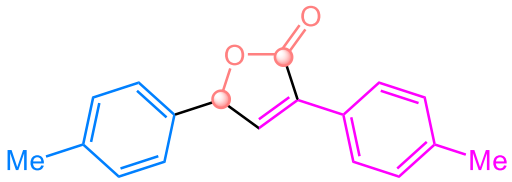
Controlled Experiments



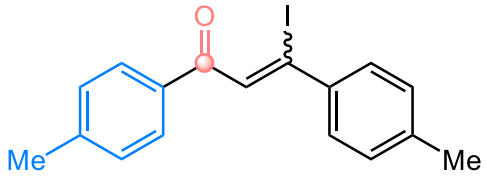
5a

$BrCF_2CO_2K$
$Pd(MeCN)_2Cl_2$ (10 mol%),
PCy_3 (20 mol%)

HCO_2Na (3 eq.)
H_2O (5 equiv)
DMF, 90 °C, 12 h



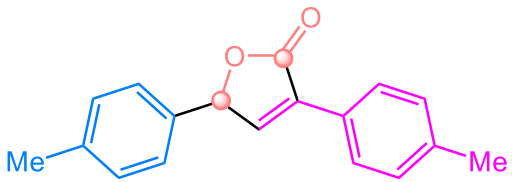
4a nd



10

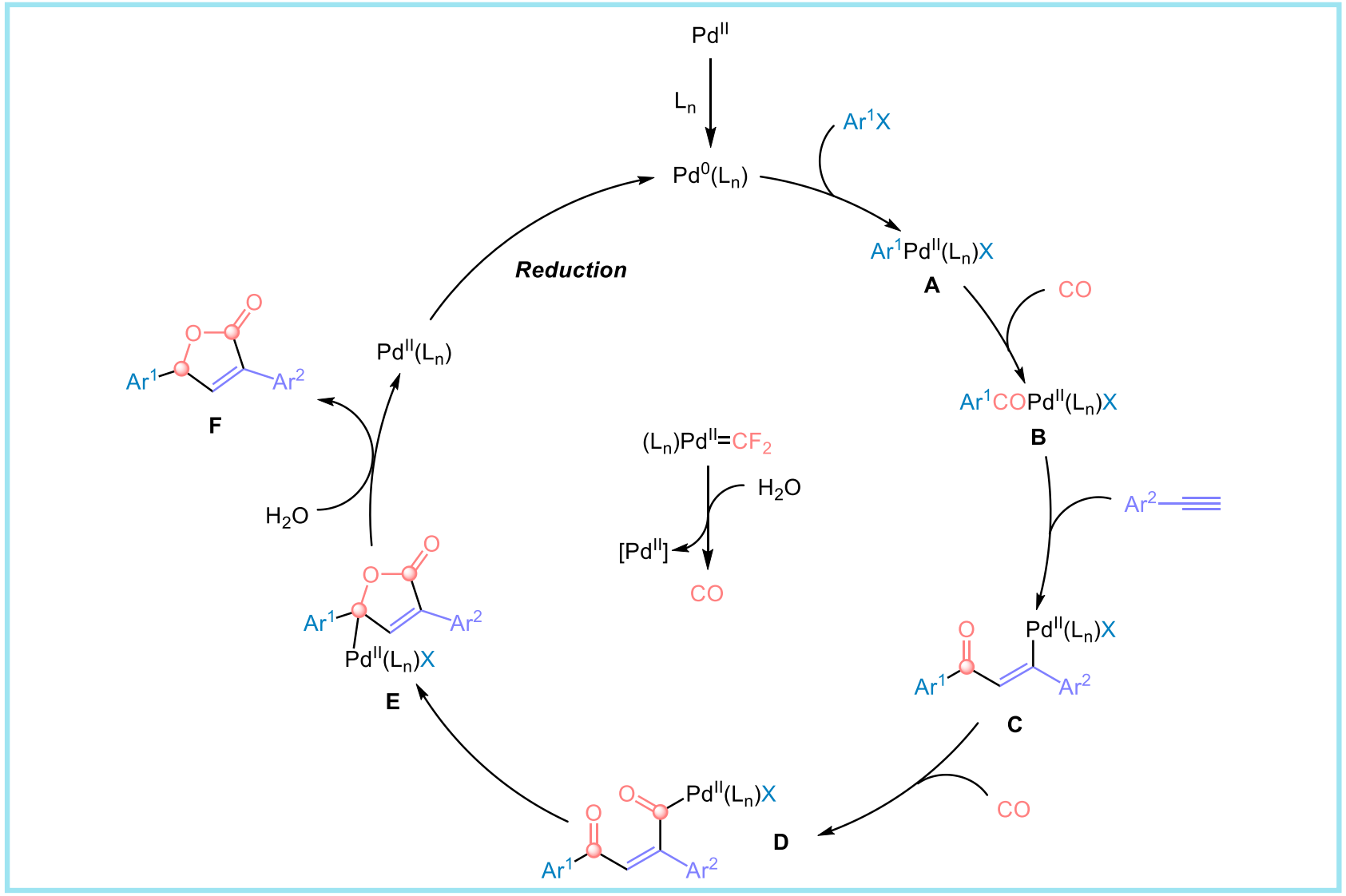
$BrCF_2CO_2K$
$Pd(MeCN)_2Cl_2$ (10 mol%),
PCy_3 (20 mol%)

HCO_2Na (3 eq.)
H_2O (5 eq.)
DMF, 90 °C, 12 h

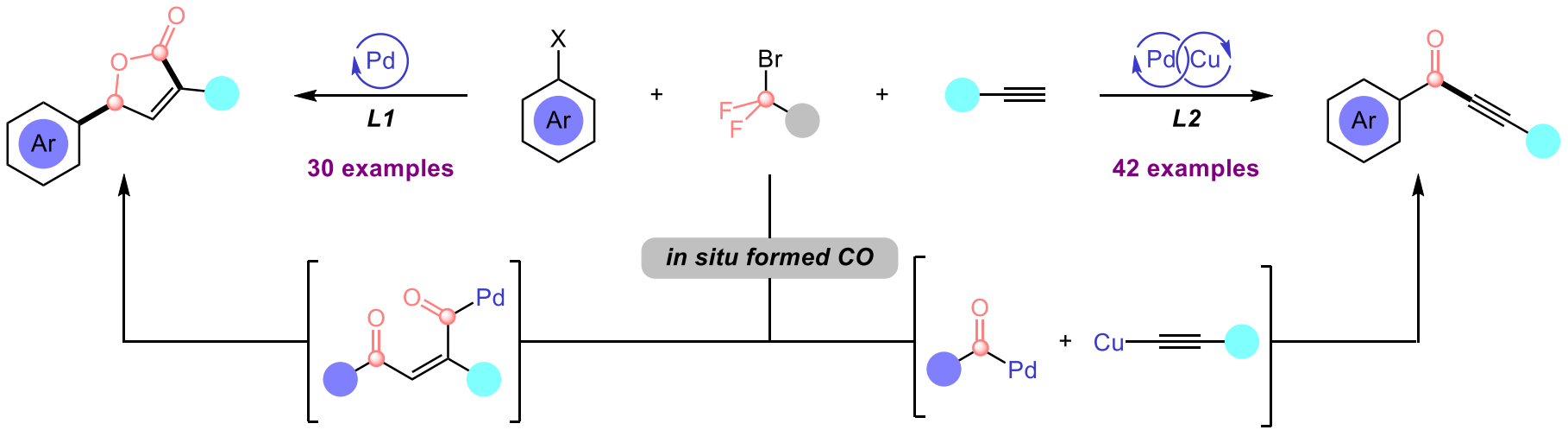


4a 86%

Proposed Mechanism



Summary



- *Readily available materials*
- *Excellent regioselectivity*
- *Multi-component reaction*
- *Broad substrate scope*
- *Cheap, mild and efficient CO generation from $BrCF_2CO_2K$*

Strategy for Writing The First Paragraph

介绍二氟卡宾以及二氟卡宾的转化

过去 γ−丁烯酸内酯和烯酮的合成方法

引出本文工作

- ✓ Difluorocarbene as a building block has been widely employed in organic synthesis, drug development, and medicinal chemistry, by leading to difluoromethyl ethers, *gem*-difluorocyclopropanes, and *gem*-difluoroalkenes from corresponding substrates.
- ✓ *γ*-Butenolides and ynones are prevalent structural scaffolds due to their comprehensive service ability as building blocks. Profound synthetic studies have been devoted to this field and most of them concentrate on the synthesis of *γ*-butenolides.
- ✓ Here, we report a multicomponent palladium-catalyzed method that enables the synthesis of ynones and *γ*-butenolides from arylacetylene and aryl iodides with difluorocarbene as the CO source by ligand control.

Strategy for Writing The Last Paragraph

总结工作

✓ In conclusion, we have developed a practical ligand-controlled palladium-catalyzed synthesis of ynones and *γ*-butyrolactones from aryl iodides and terminal alkynes using $BrCF_2CO_2K$ as the carbonyl source.

强调亮点

✓ The reaction portrays readily available starting materials, mild conditions, carbonyl constructions without using the toxic CO gas, and versatile and valuable products with tandem processes. Moreover, the practicality of this method has been validated through the synthesis of ester compounds and subsequent modification of drug-like molecules.

Representative Examples

- Therefore, we speculate that the ligand might have a significant impact on the reaction. (speculate，推测，猜测，可代替reason)
- The reaction portrays readily available starting materials, mild conditions, carbonyl constructions without using the toxic CO gas, and versatile and valuable products with tandem processes. (portray, 描绘，描画)
- Moreover, the practicality of this method has been validated through the synthesis of ester compounds and subsequent modification of drug-like molecules(通过…验证了…，validate，验证，确认)

Acknowledgement

Thanks for your attention