Tuning Reactivity and Site Selectivity of Simple Arenes in C-H Activation: Ortho-Arylation of Anisoles *via* Arene-Metal π–Complexation

Ricci, P.; Kramer, K.; Larrosa, I. *J. Am. Chem. Soc.* **2014**, *136*, 18082–18086.

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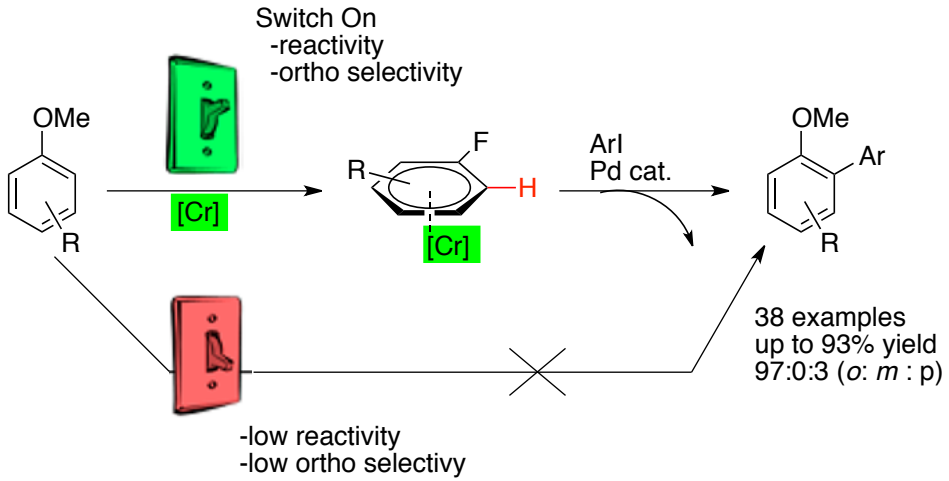
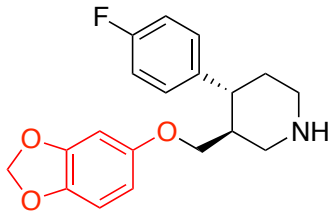
Abstract

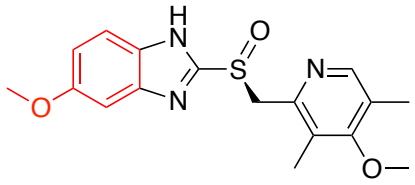


- Directing group free C-H activation
- Unprecedented *ortho*-selectivity
- Mild methodology
- Useful for late stage functionalization of bioactive compounds

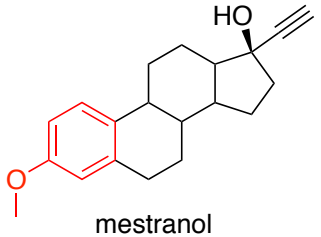
Examples of Anisole Containing Bioactive Compounds



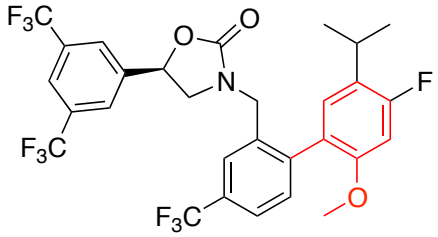
paroxetine
-antidepressant (trade name Paxil)



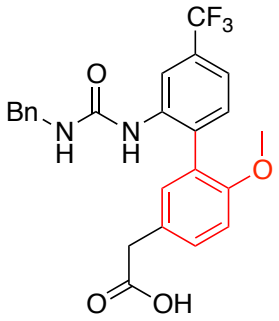
esomeprazole (brand name Nexium)
-proton pump inhibitor
-reduces stomach acid



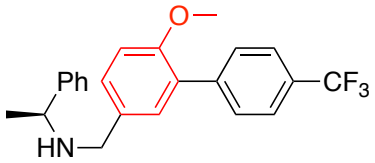
mestranol
-an oral contraceptive



anacetrapib
- for hypercholesterolemia

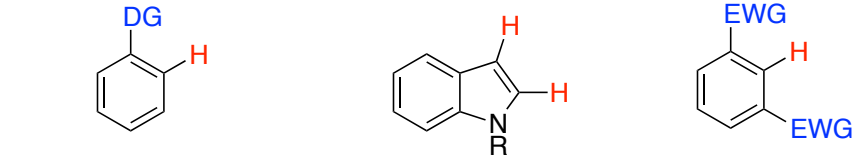


AM211 (DP2 antagonist)



AMG 641 (calcimimetic)

Direct C-H Arylation of Arenes: Requirements and Challenges



use of directing groups | electron rich | electron poor

- Low reactivity requiring larger amounts of arenes
- Useful regioselectivity was not obtained
- Requirements of directing groups

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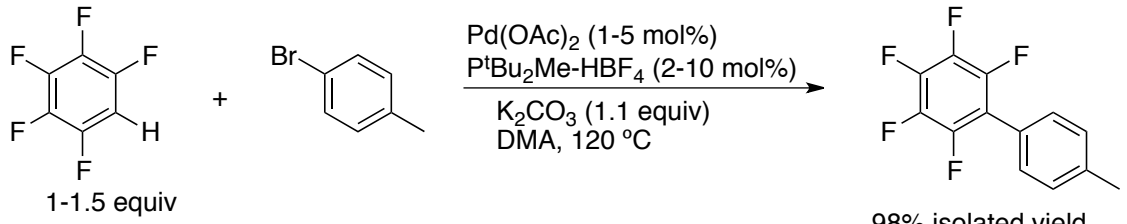
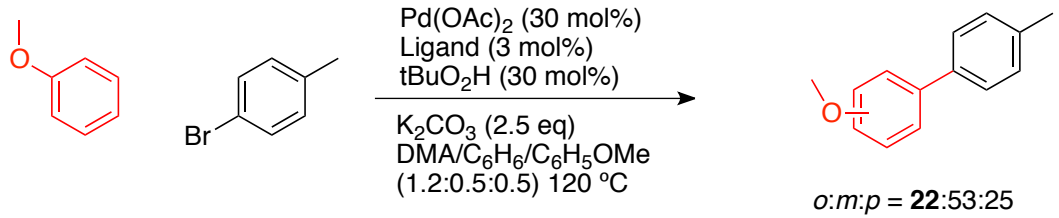
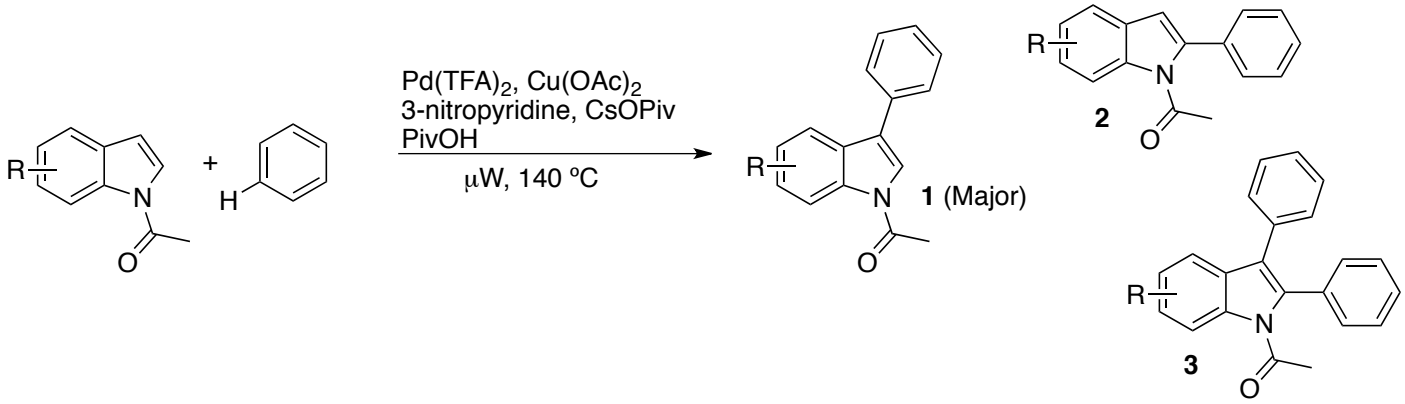
Direct C-H Arylation: Keith Fagnou



Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754.

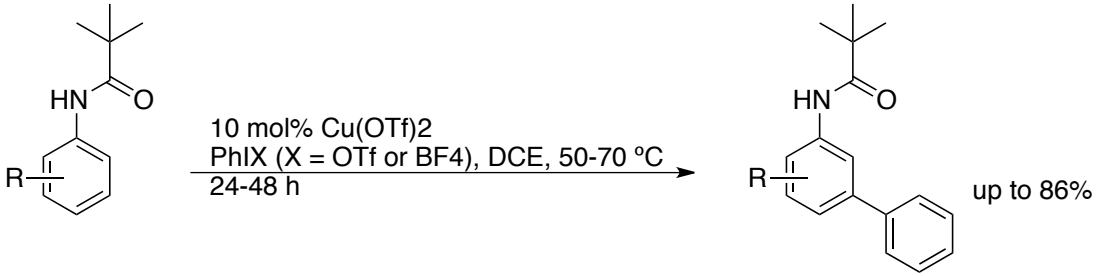


Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**. *128*, 16496-16497.

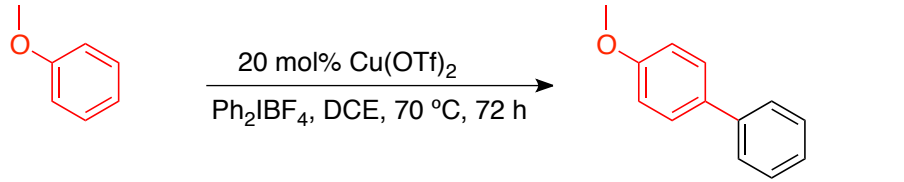


Stuart, D. R.; Fagnou, K. *Science*, **2007**, *316*, 1172.

Direct C-H Arylation: M. J. Guant



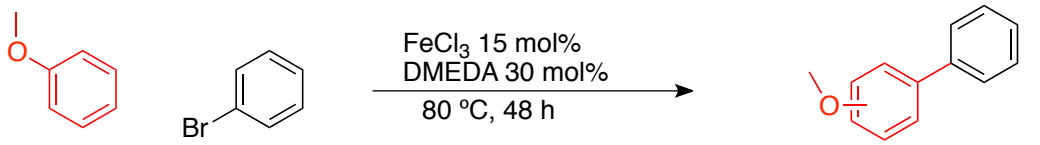
Phipps, R. J.; Gaunt, M. J. *Science*, **2009**, *323*, 1593.



only the *para* isomer formed

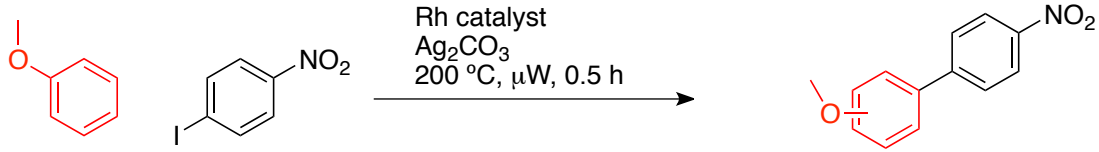
Ciana, C-L.; Phipps, R. J.; Brandt, J. R.; Meyer, F-M.; Gaunt, M. J. *Angew. Chem. Int. Et.* **2011,** *50,* 458-462.

Direct C-H Arylation: Others



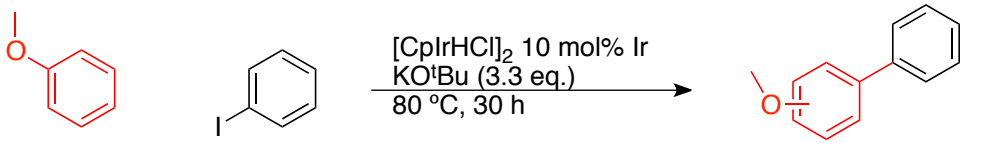
o:*m*:*p* = **64**:24:12

Liu, W.; Cao, H.; Lei, A. *Angew. Chem. Int. Ed.* **2010**. *49*, 2004-2008.



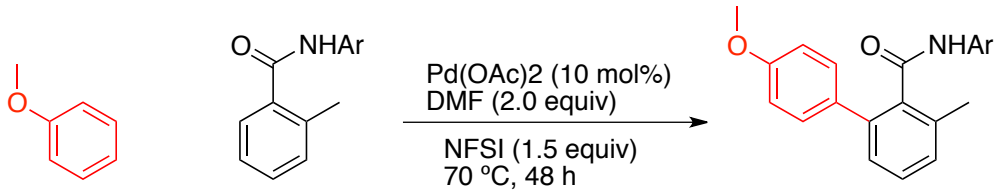
o:*m*:*p* = **29**:0:71

Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *Tetrahedron*, **2008**, *64*, 6073-6081.



o:*m*:*p* = 72:16:12

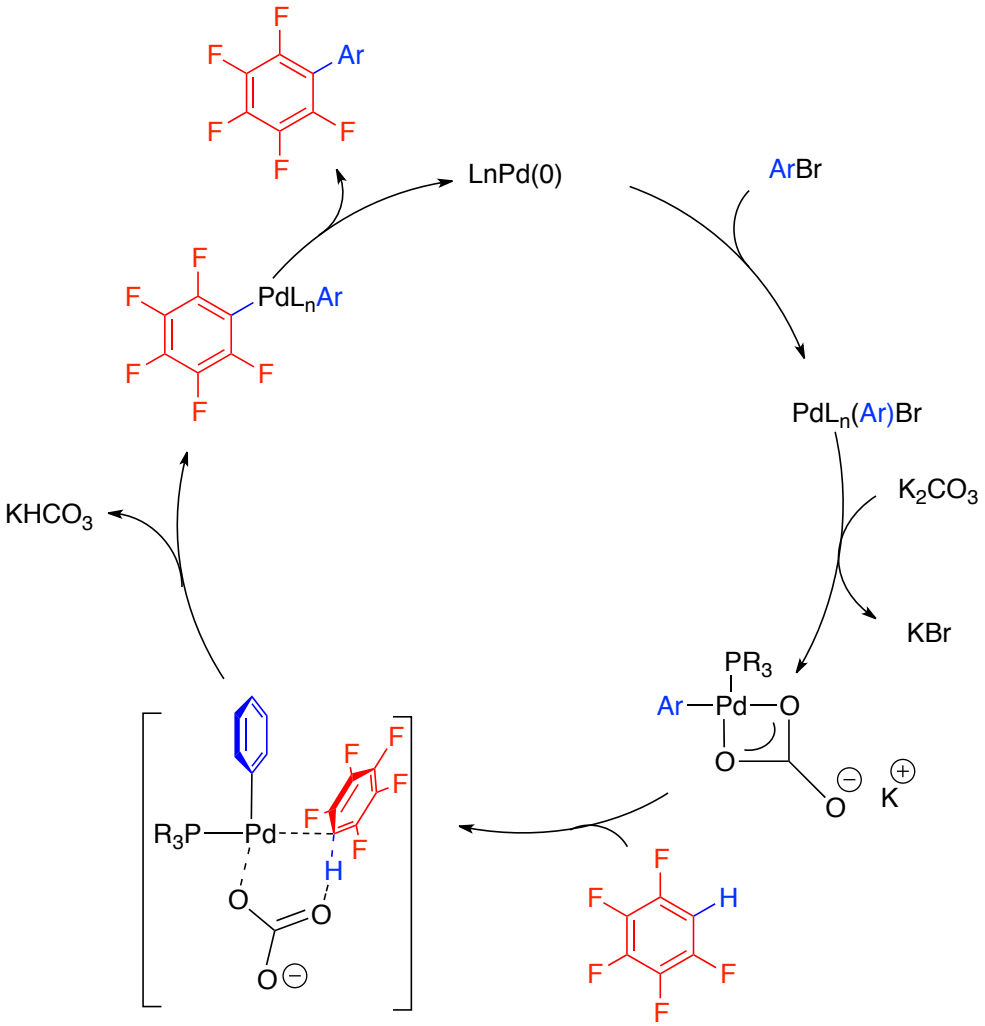
Fujita, K-i.; Nonogawa, M.; Yamaguchi, R. *Chem. Commun.* **2004**, 1926.



Wang, X.; Leow, D.; Yu, J-Q. *J. Am. Chem. Soc.* **2011**, *133*, 13864-13867.

Mechanistic Studies: Keith Fagnou

Concerted Metalation and Deprotonation (CMD) path way

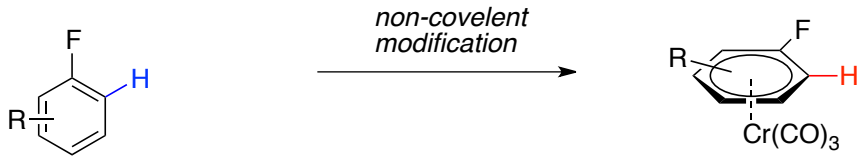


Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754.

Keith Fagnou
1971-2009
University of Ottawa, Canada

Chem. Lett. **2010**, *39*, 1118.

Previous Work by Igor Larossa Group: Enhancing Reactivity *via* π-Complexation



unreactive
- 50 equiv required to facilitate
- C-H arylation
- mixture of isomers forms

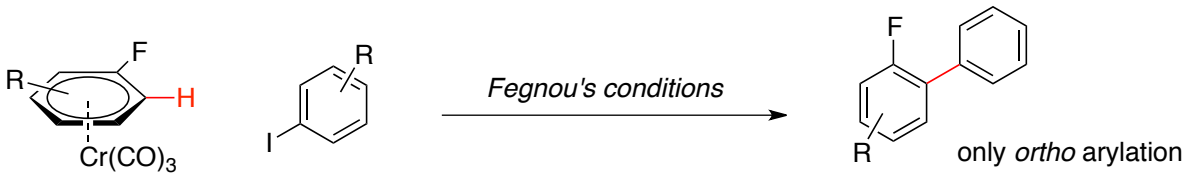
Stable η^6 complex with arene
- decrease electron density
- increse arene C-H acity
  e.g. $Cr(CO)_3$ drops pKa of C-H by 7 units
  (similar effect to a *ortho* NO_2 group)

***Hypothesis*:**

- **$Cr(CO)_3$ complexes** of simple arenes **enhances the reactivity** under **CMD type arylation**

[CMD: Concerted Metallation Deprotonation]

***Testing the Hypothesis*:**



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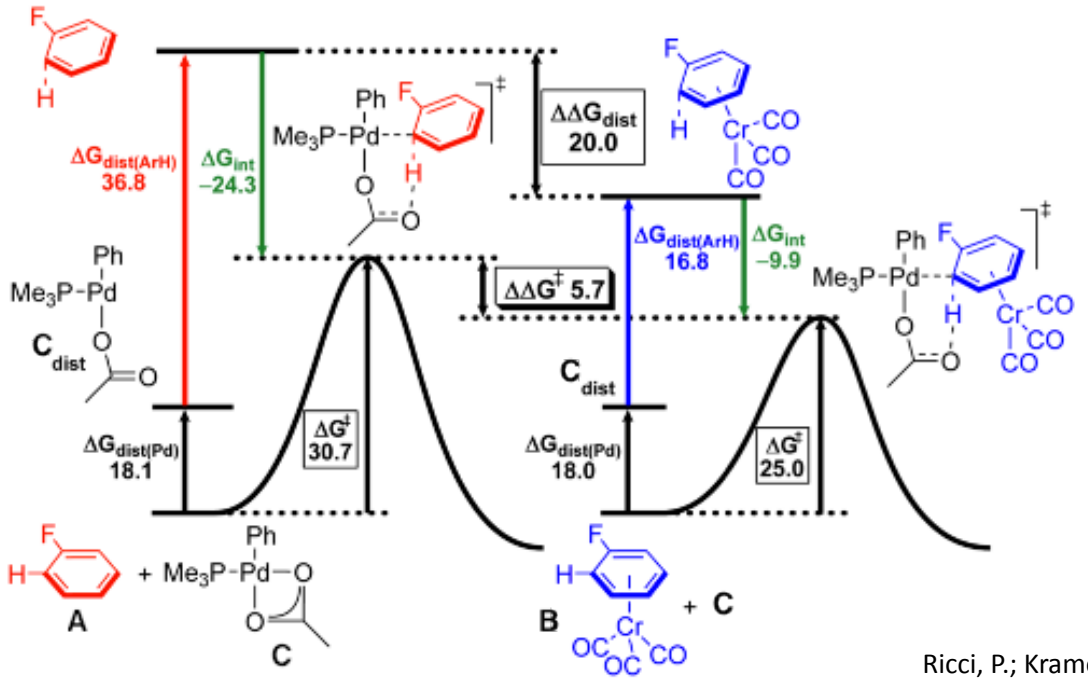
DFT Calculations: Probing the Origin of Enhanced Reactivity



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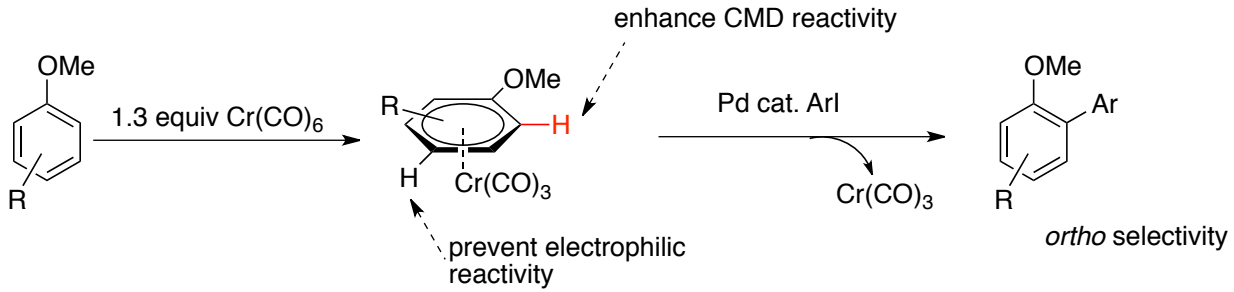
Calculated [TS] **B** < [TS] **A** by 5.7 kcal/mol

- $\Delta G_{interaction}$**B** - $\Delta G_{interaction}$**A** = -9.9 kcal/mol - (-24.3 kcal/mol) = 14.4 kcal/mol
- ΔG_{dist}**B** - ΔG_{dist}**A** = 16.8 kcal/mol - 36.8 kcal/mol = -20.0 kcal/mol
  - Much lower distortion energy cost for B

C-H activation

- $\Delta G_{elongation}$ **B** - $\Delta G_{elongation}$ **A** = 1.0 kcal/mol
- $\Delta G_{bending}$ **B** - $\Delta G_{bending}$ **A** = 19.1 kcal/mol
  - $Cr(CO)_3$ facilitate the C-H bending in the TS leading to CMD

Arylation of Anisole Type Arenes: Highly *ortho* Selective Pd Catalysed Direct Arylation (*Chosen paper*)



Hypothesis:

$Cr(CO)_3$ activation can operate on electron rich arenes

1. Enhance reactivity toward a CMD process (avoid large excess of arene)
2. Eleminate S_EAr type reactivity (*para* reactivity)
3. Afford CMD prefferd *ortho* siomer

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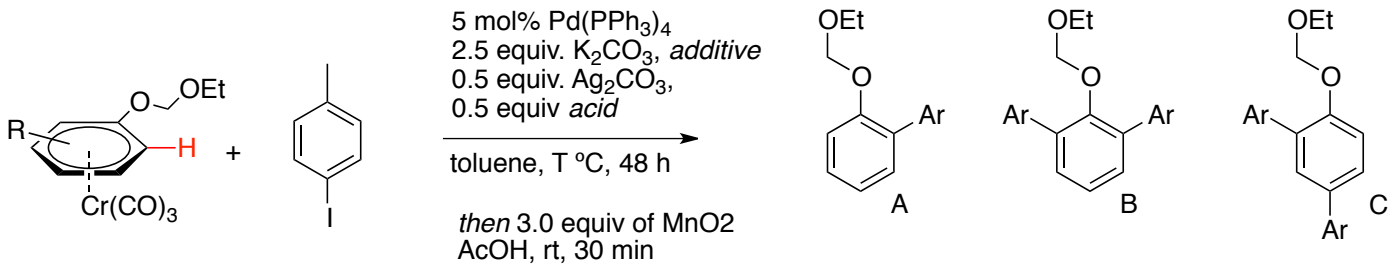
Optimization of the Conditions



Entry	R-CO_2H	additive (2 equiv)	T (°C)	**A** : **B** : **C** (yield%)
1	1-AdCO_2H	-	60	58:3:1
2	PhCO_2H	-	60	34:1:1
3	*p*-NO_2-C_6H_4-CO_2H	-	60	0:0:0
4	*p*-NH_2-C_6H_4-CO_2H	-	60	52:3:5
5	1-AdCO_2H	piperidine	60	0:0:0
6	1-AdCO_2H	Et_3N	60	57:3:3
7	**1-AdCO_2H**	**TMP**	**60**	**78:3:5 (95:0:5 *o*:*m*:*p* selectivity)**
8	1-AdCO_2H	TMP	50	69:3:5
9	1-AdCO_2H	TMP	60	52:5:6
10	-	TMP	60	39:2:1
11	1-AdCO_2H	TMP	60	0:0:0*
13	1-AdCO_2H	TMP	60	0:0:0*

TMP: 2,2,6,6-tetramethylpiperidine, * No Ag_2CO_3 added

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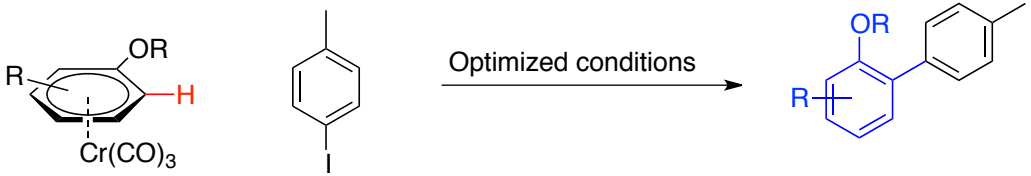
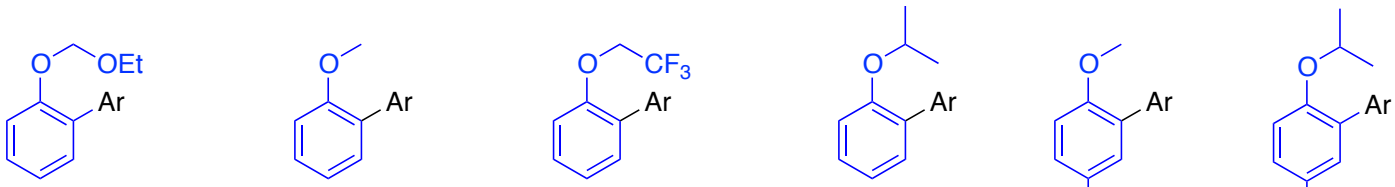
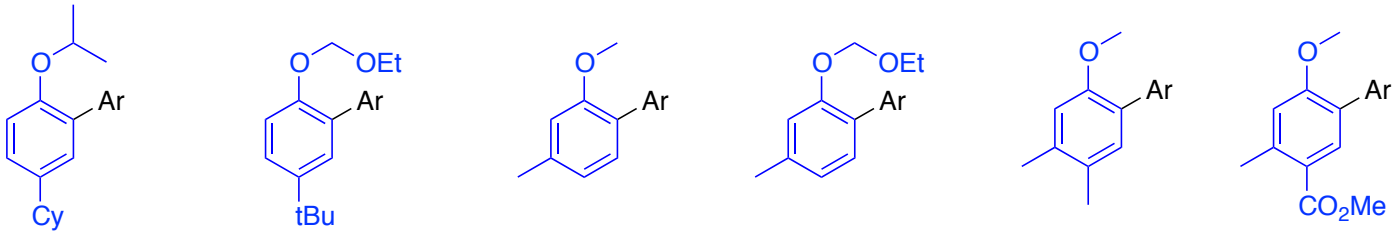
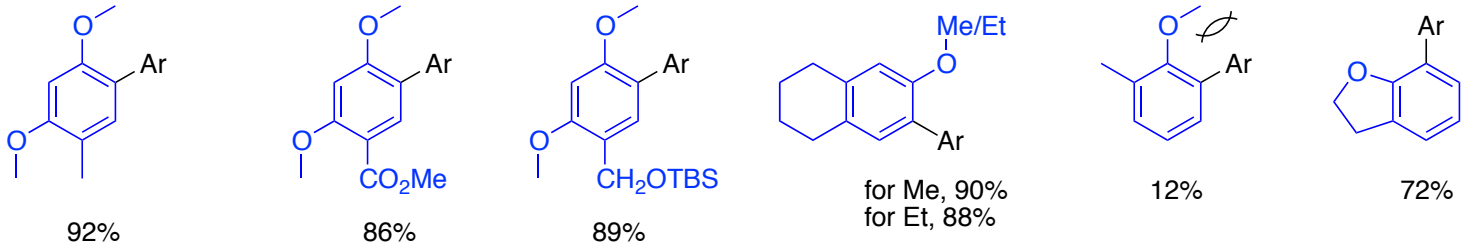
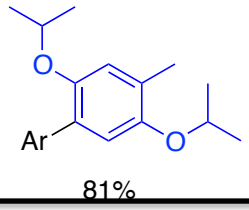
Substrate Scope: Different Anisoles











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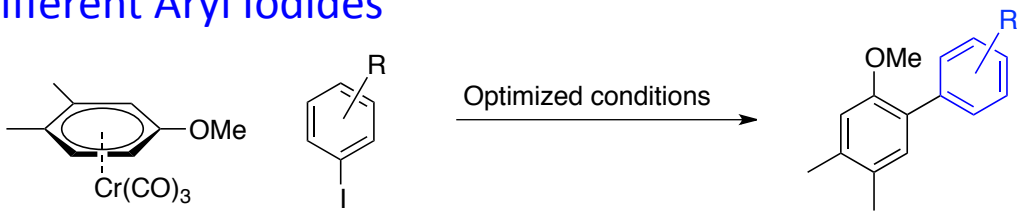
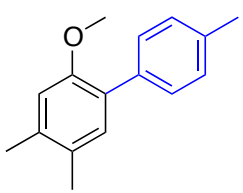
Substrate Scope: Different Aryl Iodides

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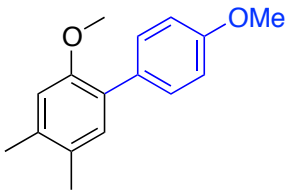

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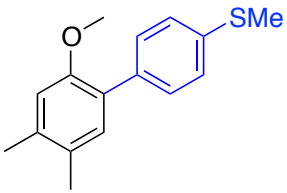

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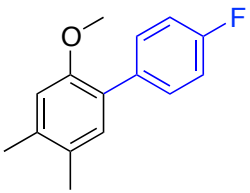

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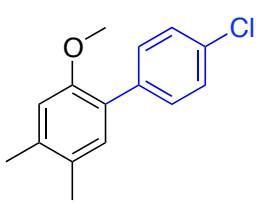

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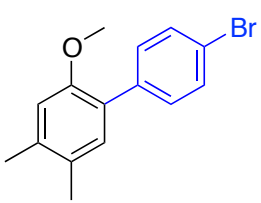

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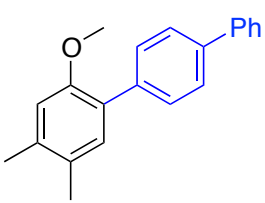

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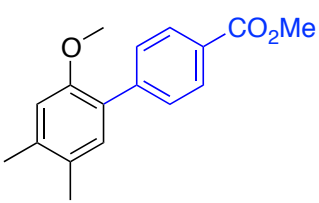

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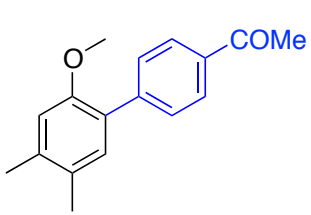

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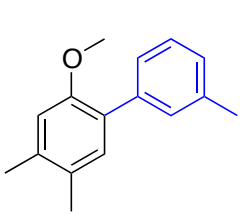
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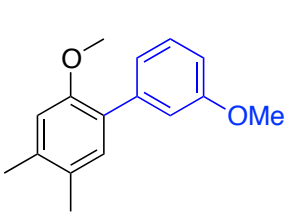

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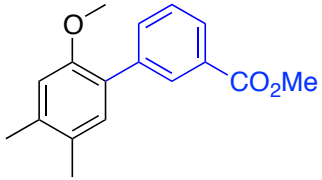

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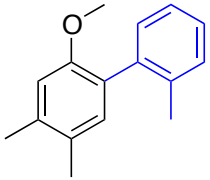
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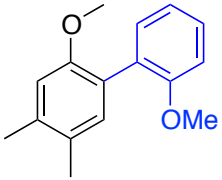

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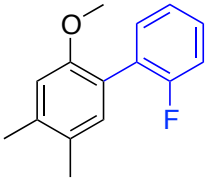

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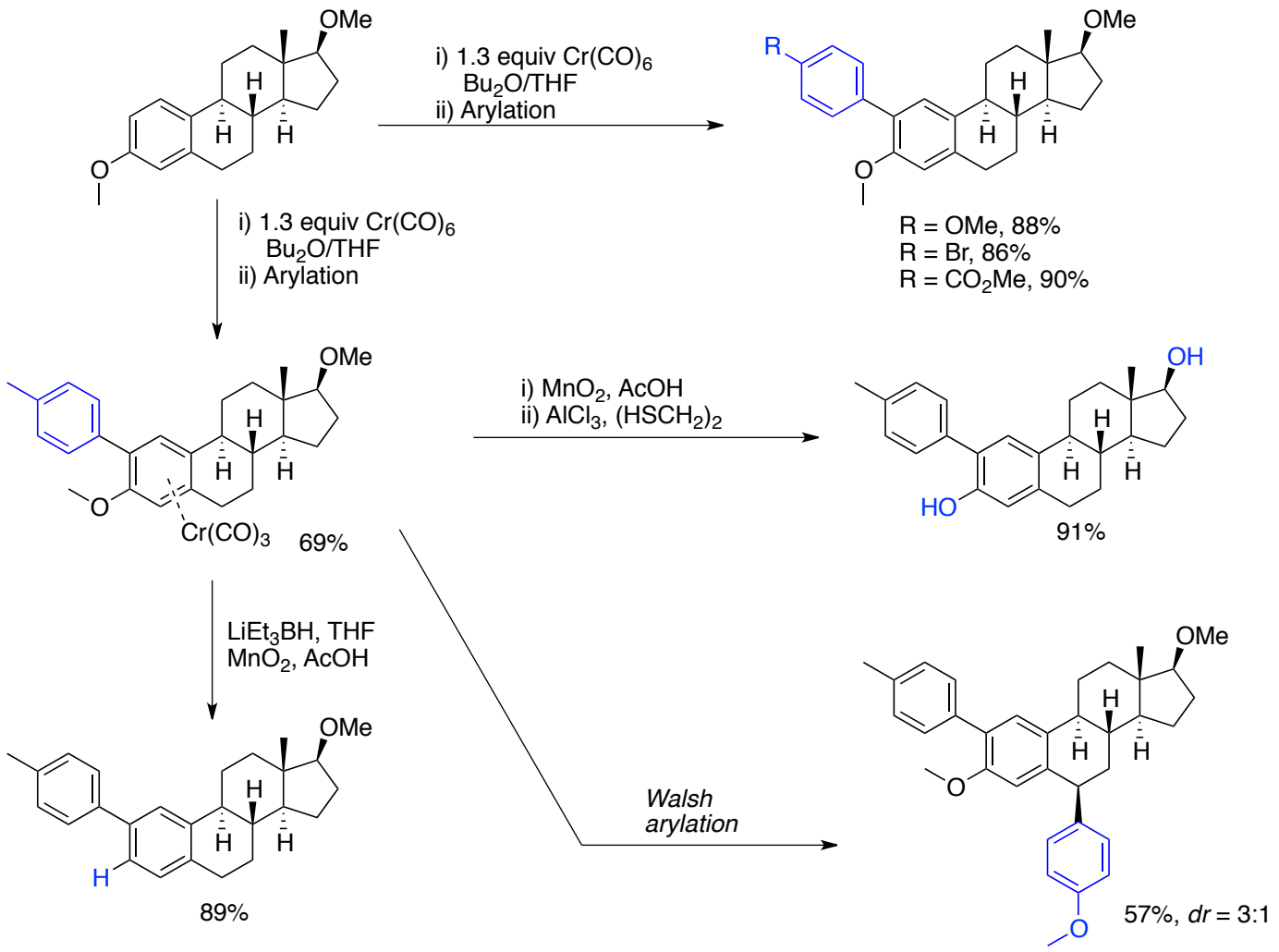
Late Stage Functionalization of Estradiol Derivatives



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Conclusions

- **π-Complexation of a $Cr(CO)_3$** unit to anisole-type arenes can **"switch on"** a highly **ortho-selective Pd-catalyzed direct arylation** process.
- Only **1 equiv** of the **arene** under **mild conditions** (no strong acids/ bases, 60 ° C)
- **Cr-unit** can be used as **a handle for further transformations** on and around the arene
- A **concerted metalation–deprotonation** type pathway, which **is normally not accessible to electron-rich arenes**
- Suitable for **the late-stage functionalization** of **anisole-containing bioactive compounds**

Acknowledgements

- Prof. Peter Wipf
- All Wipf group members

Thank you!