

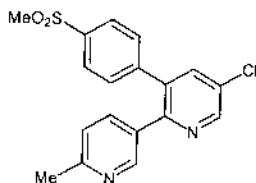
Mechanistic and synthetic studies inspired by novel
pharmaceutical agents

Ian Davies
Department of Process Research
Merck & Co., Inc.

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1

Cox-2 Specific Inhibitor etoricoxib (Arcoxia™)

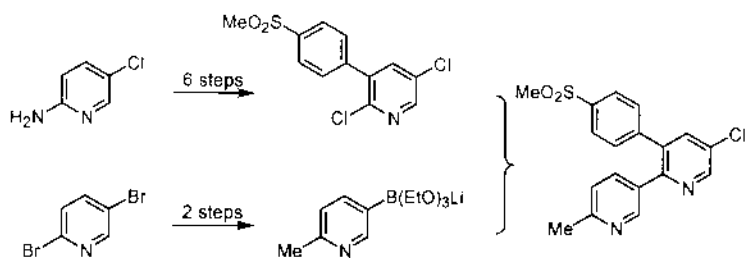


- Inhibition: COX-1 (IC₅₀ μM): 116, COX-2 (IC₅₀ μM): 1.09
(Human whole blood assay)

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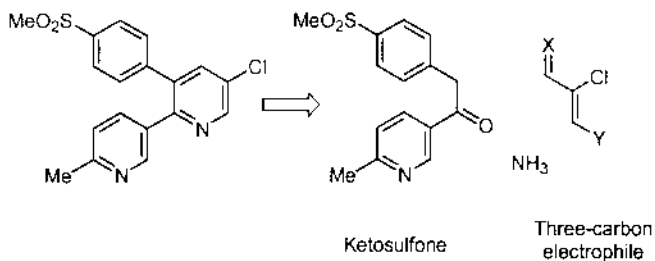
Medicinal Chemistry Approach



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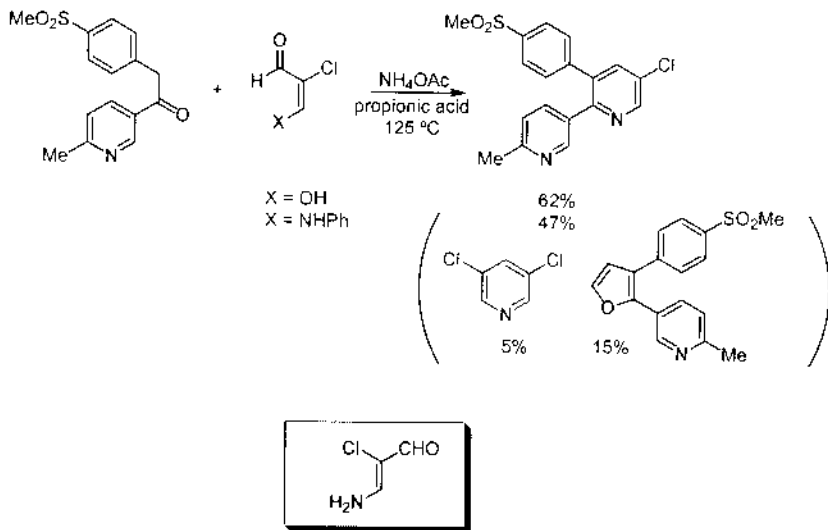
Process Research Approach



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J. Org. Chem. 2000, 65, 8445

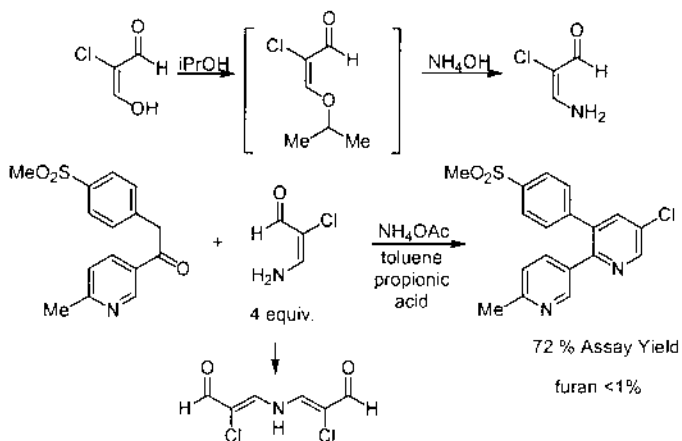
Annulation of Ketosulfone: Friedlander Condensation



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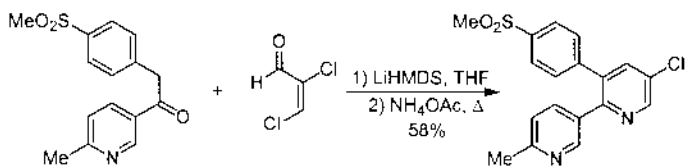
Use of Isolated Aminoacrolein



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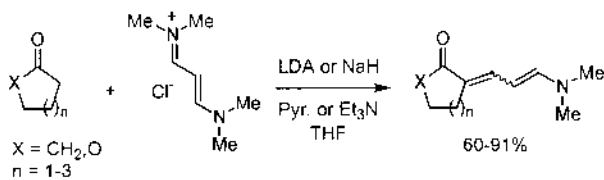
Base-Promoted Annulation



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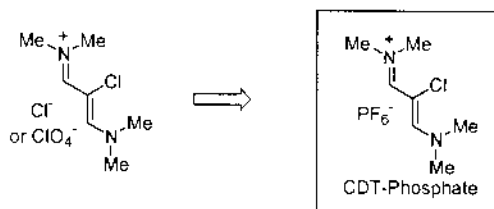
Vinamidinium Salts as Three-Carbon Synthons



Nair, V.; Cooper, C. S. *J. Org. Chem.* **1981**, *46*, 4759
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Vinamidinium Hexafluorophosphate Salts

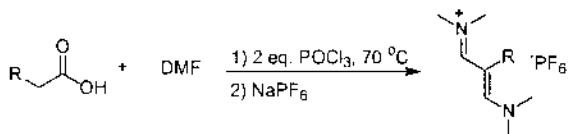


J. Org. Chem. **2000**, *65*, 4571

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Preparation of 2-Substituted Vinamidinium Salts

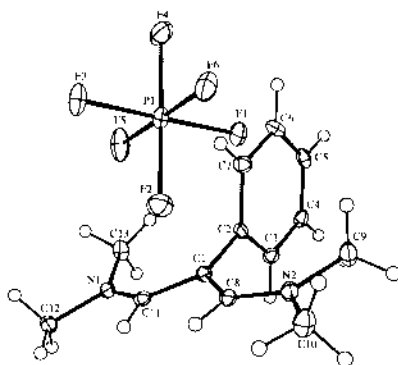


Entry	R =	Isolated Yield
1	Cl	79
2	Br	78
3	I	60
4	CF ₃	68
5	Ph	90
6	4-NO ₂ -C ₆ H ₄	80
7	4-OMe-C ₆ H ₄	75
8	Phthalimidyl	68
9	Me	28
10	Benzyl	33

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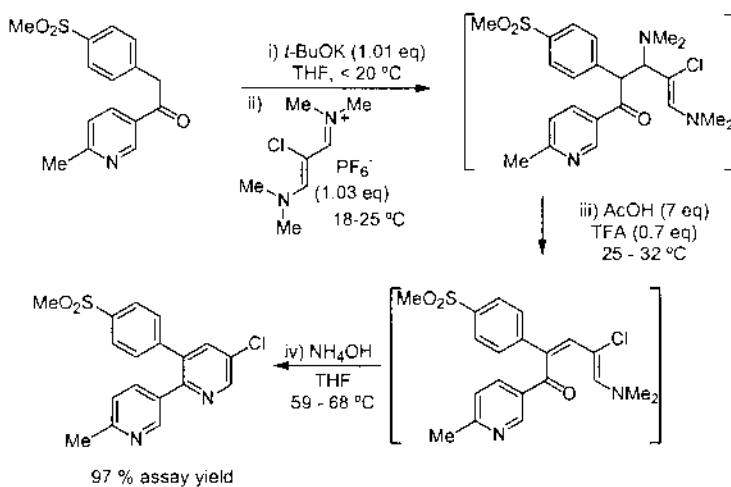
X-Ray Structure Determination of 2-Phenyl Analog



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Annulation of Ketosulfone: Optimized Conditions



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Pyridines from *l*-Aryl Ketones

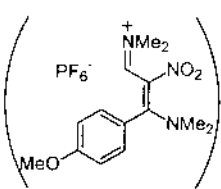
Ketone/Aldehyde	Product	Isolated Yield (%)
		R = SO ₂ Me 94 R = H 92 R = SMe 87
		R = SO ₂ Me 77 R = H 65 R = OMe 38
		73
		68
		80

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Organic Letters 2000, 31, 2339

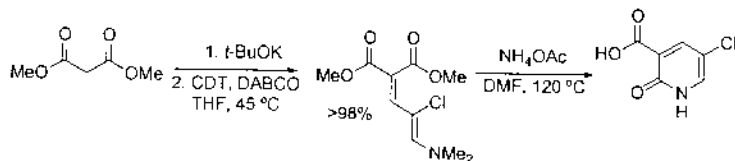
Scope of the Annulation

Ketone	Product	Yield (%)
		R=Cl 85 R=Ph 63
		R=NO ₂ 80
		89
		82
		65



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Preparation of Pyridones from Activated Esters



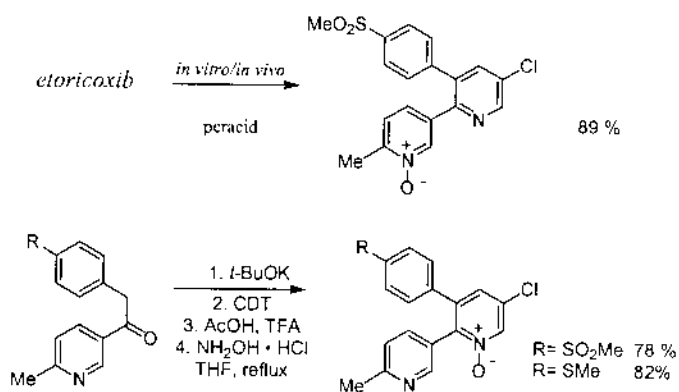
Starting Material	Product	Yield (%)
		76
		78
		82
		28

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J. Org. Chem. 2001, 66, 4194

A [3+2+1] Approach to Pyridine N-Oxides

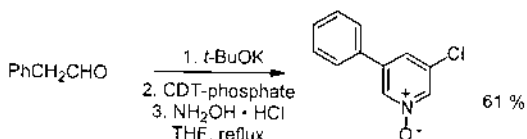
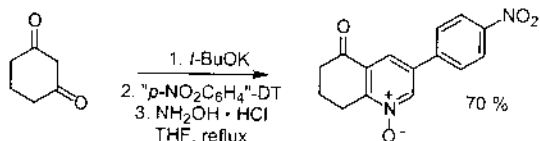
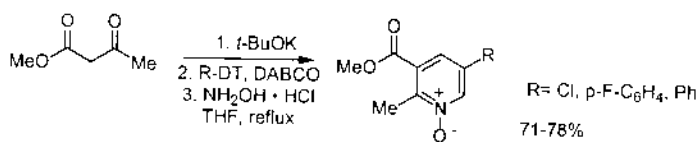


Organic Letters 2001, 3, 209

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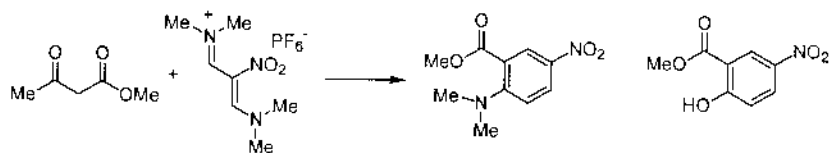
Preparation of Pyridine N-Oxides



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De Novo Approach to Anilines



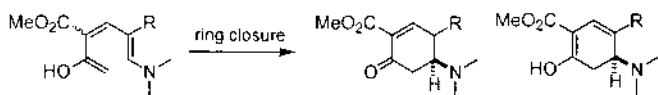
Organic Letters 2002, 4, 439
Organic Letters 2002, 4, 3017

Cat. t-BuOK, NaOAc, DMAP

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Ring Closure

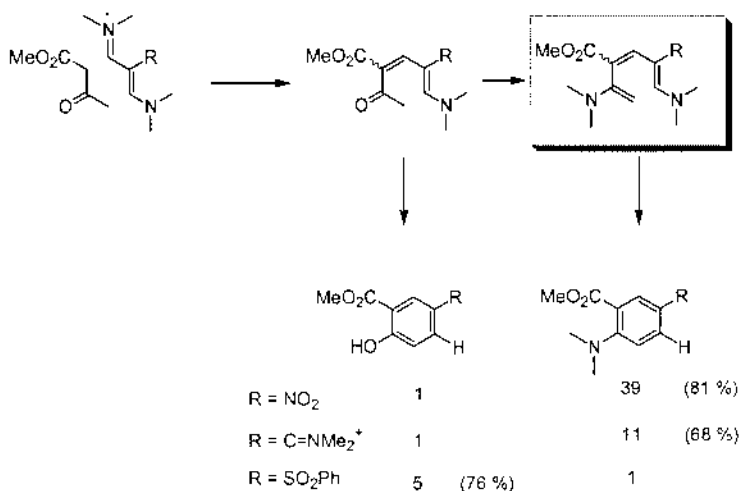


Entry	Dienone	RCH ₂ -H pKa (DMSO)	
pKa (water)			
1	a , R = H	56	
2	b , R = Ph	43	
3	c , R = Cl	41	
4	d , R = F	41	
5	e , R = CF ₃	n.a.	
6	f , R = CN	31	
7	g , R = SO ₂ Ph	29	
8	i , R = NO ₂	17	11
9	h , R = C=NMe ₂ ⁺	-	11

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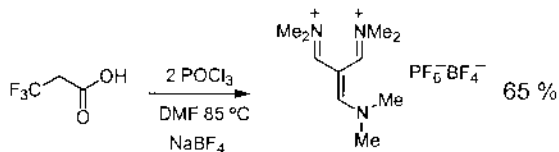
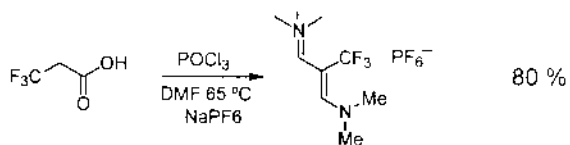
Vinamidinium Scope



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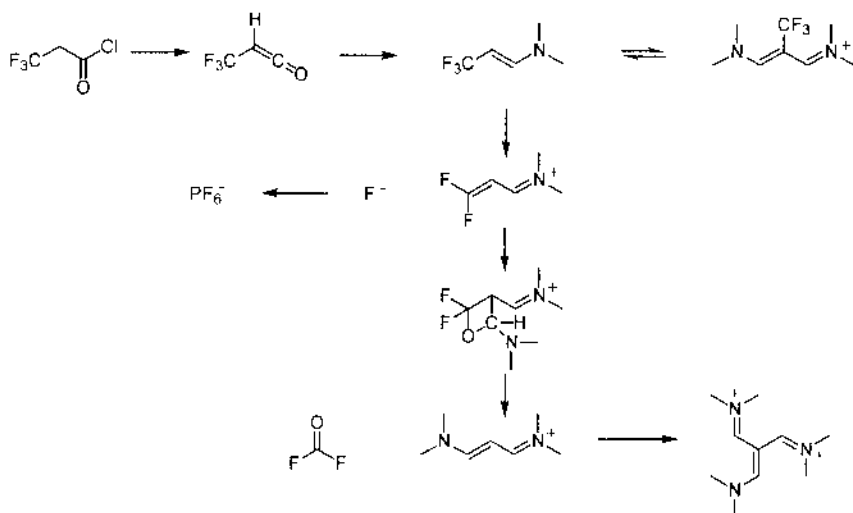
Preparation of trimethinium salts



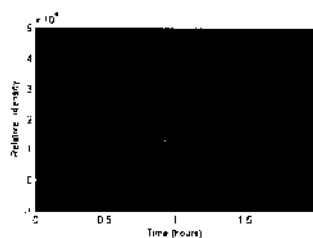
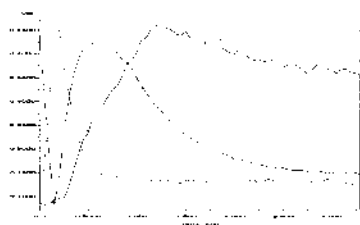
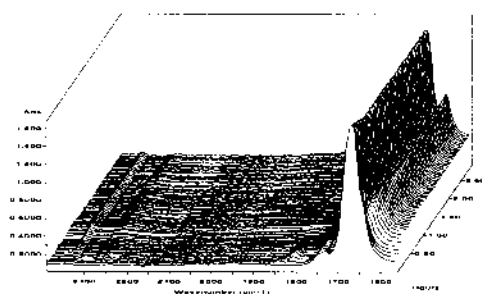
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A cycloaddition route to trimethinium salts



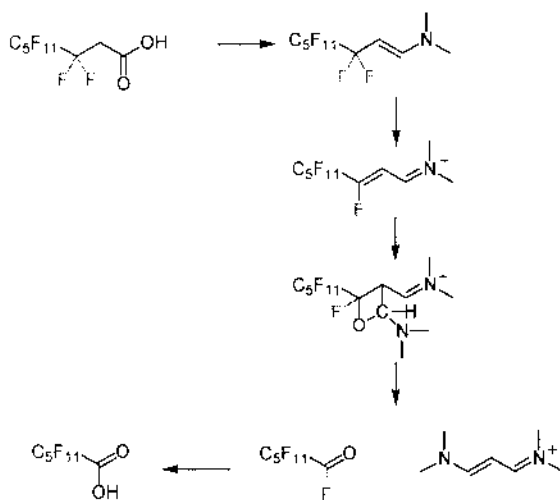
ReactIR and in situ Raman Spectroscopy



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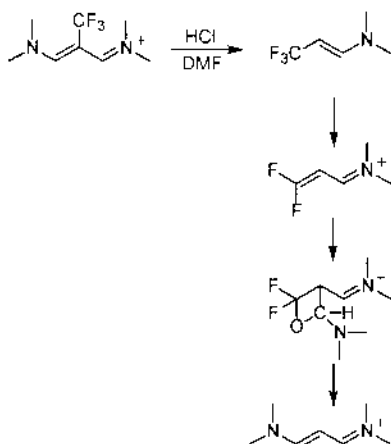
What is the fate of CF₃?



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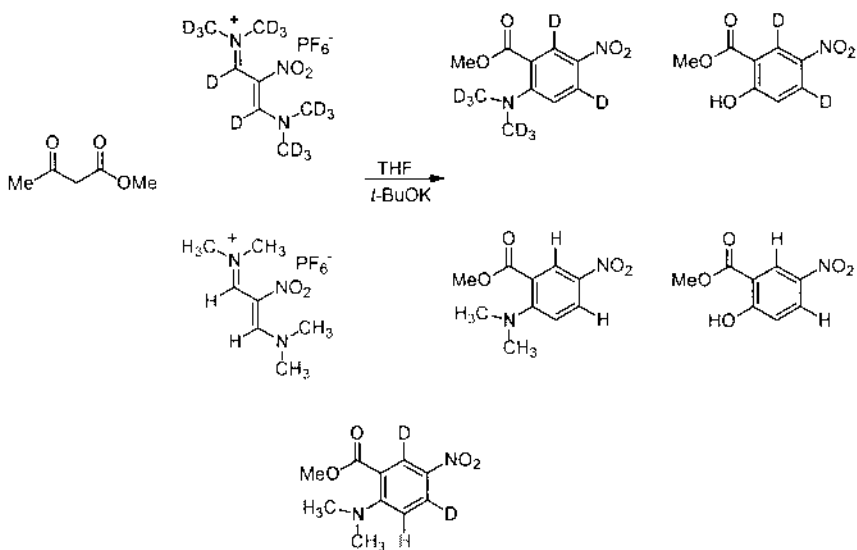
Competing retro-reaction



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Organic Letters 2002, 4, 2969₅

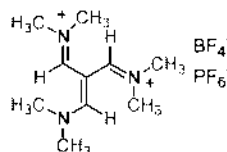
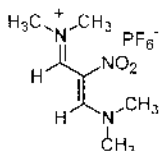
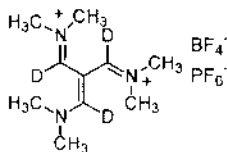
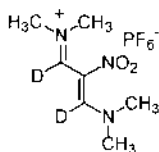
Competition Experiments



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Isotope effect



Inverse secondary $k_{H/D}$ 0.75

Inverse secondary $k_{H/D}$ 0.93

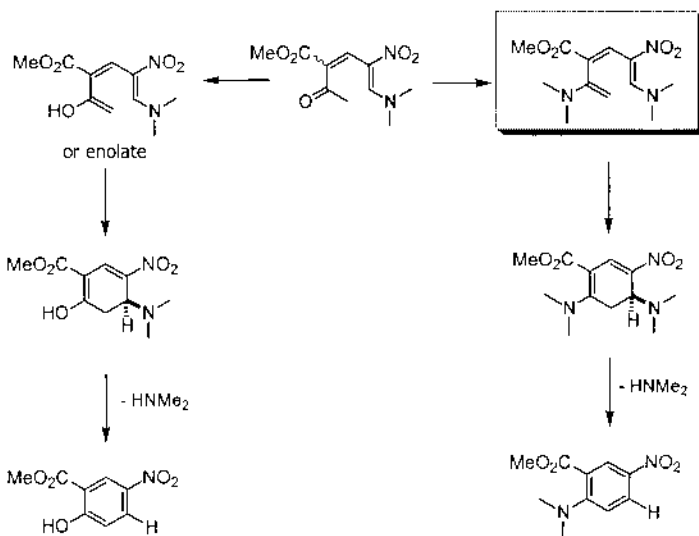
Product isotope effect 1.20

Product isotope 1.25

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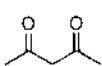
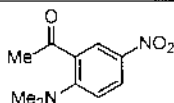
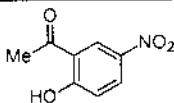
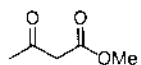
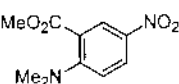
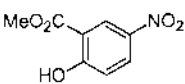
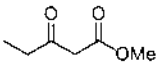
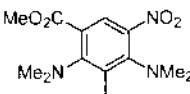
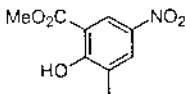

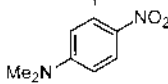
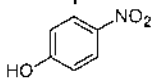
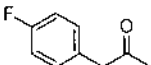
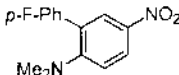
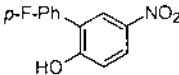
Proposed Mechanism



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Substrate Scope

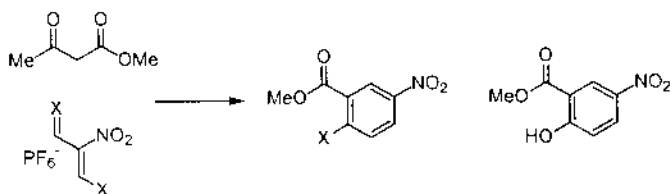
Substrate	Products		
			15:1
			39:1
			17:1
			20:1
			1:3




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Acetonitrile

Preparation of Anilines or Phenols

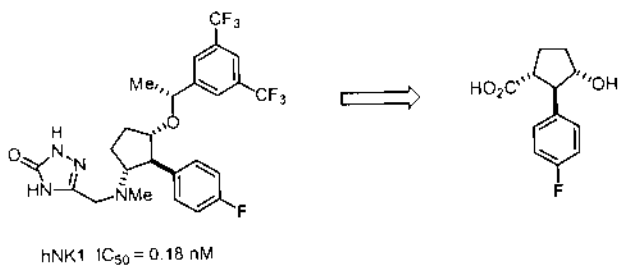


X =	Yield Aniline	Yield Phenol	Ratio Aniline/Phenol
	91	7	13 : 1
	89	11	8 : 1
	---	63	1 : >25

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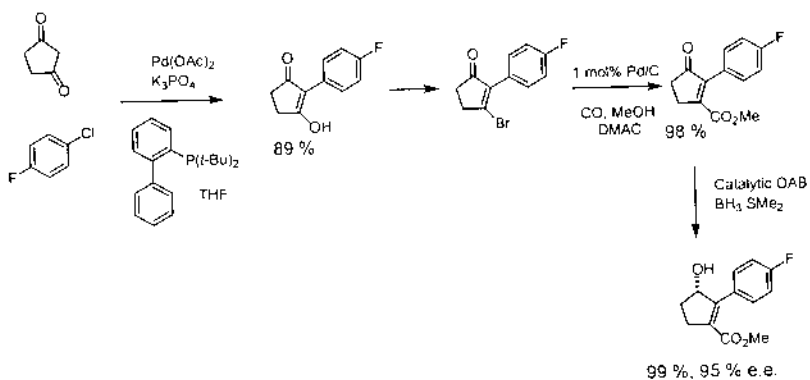
Palladium-catalyzed coupling



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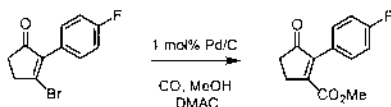
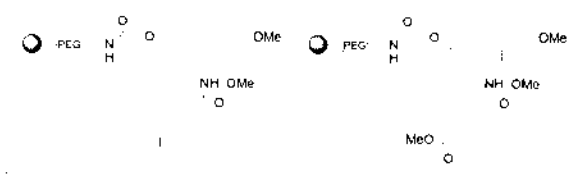
Palladium-catalyzed coupling



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J. Org. Chem. - 2002, 67, 5993
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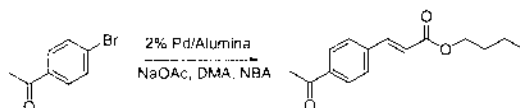
Palladium-catalyzed Carbonylation



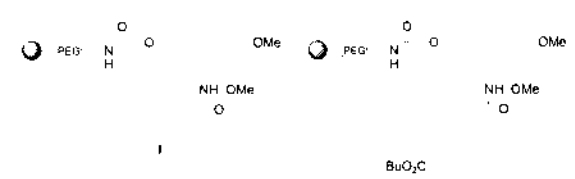
Minimum ton 850
Minimum tof 250/h

Merck & Co., Inc. *J. Am. Chem. Soc.* **2001**, *123*, 10139³³

Palladium-catalyzed coupling: Heck Reaction

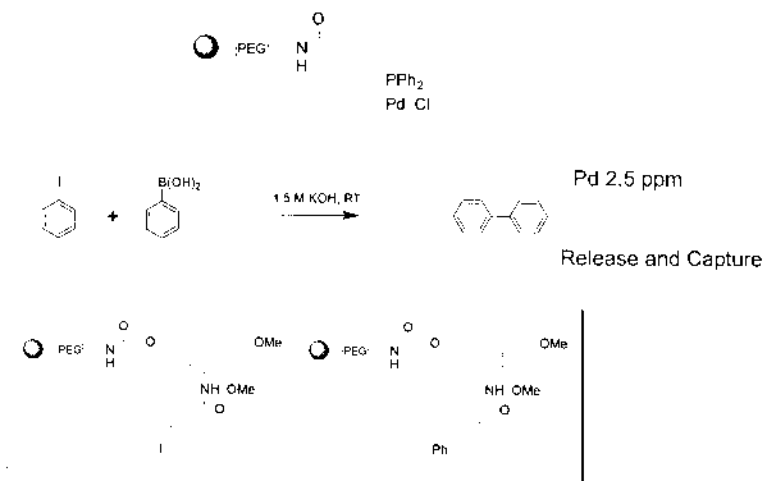


Bromide and acetate act cooperatively
 $\text{ArPdBr}(\text{OAc})_n$



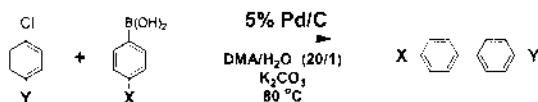
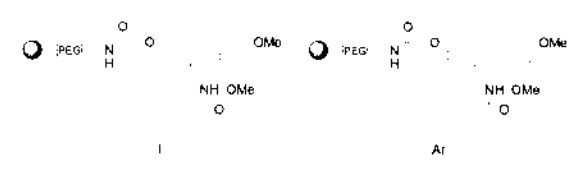
Merck & Co., Inc. *J. Am. Chem. Soc.* **2001**, *123*, 10139³⁴

Suzuki-Miyaura Coupling

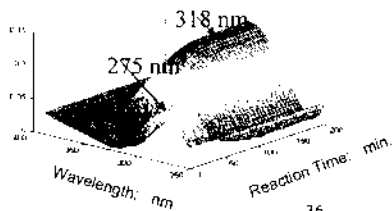
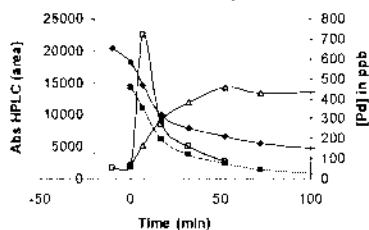


Merck & Co., Inc. *J. Am. Chem. Soc.* **2001**, *123*, 10139³⁵

Suzuki-Miyaura Coupling



Suzuki Coupling of MeOPhBr and PhB(OH)₂ at 50 °C.

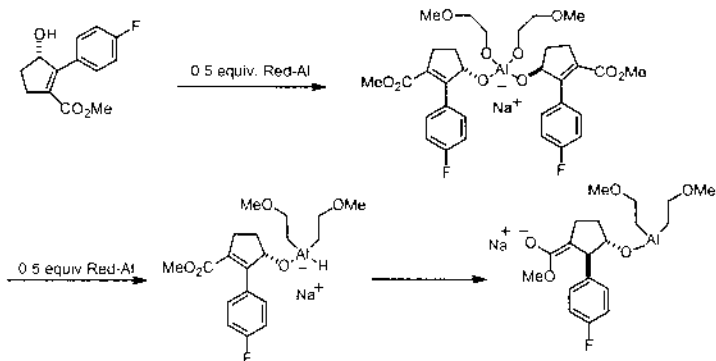


X = H; Y = NO₂

.. Inc.

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Diastereoselective RedAl Reduction

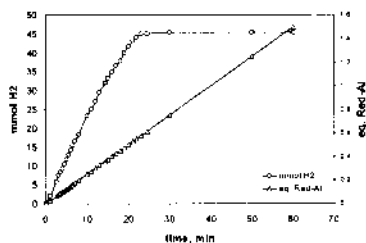
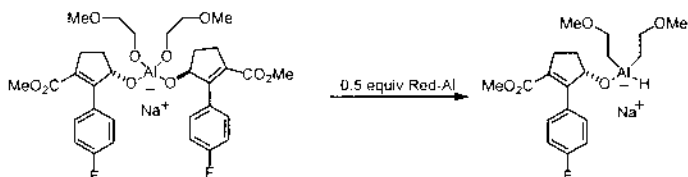


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RedAl Reduction - Hydrogen Uptake



J. Org. Chem. - 2002, 67, 5993

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Acknowledgements

- Ed Corley
- Peter Dormer
- Fred Fleitz
- David Hughes
- Ken Houk (UCLA)
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- Jeff Marcoux
- Lou Matty
- Paul Reider (Amgen)
- Nancy Tsou
- Jeremy Taylor (Oxford)
- Mark Taylor (Harvard)
- David Tellers
- Scott Schultz
- John Sowa
- Yongkui Sun
- Audrey Wong
- Jimmy Wu (Harvard)
- Tiebang Wang
- Dalian Zhao