RCC

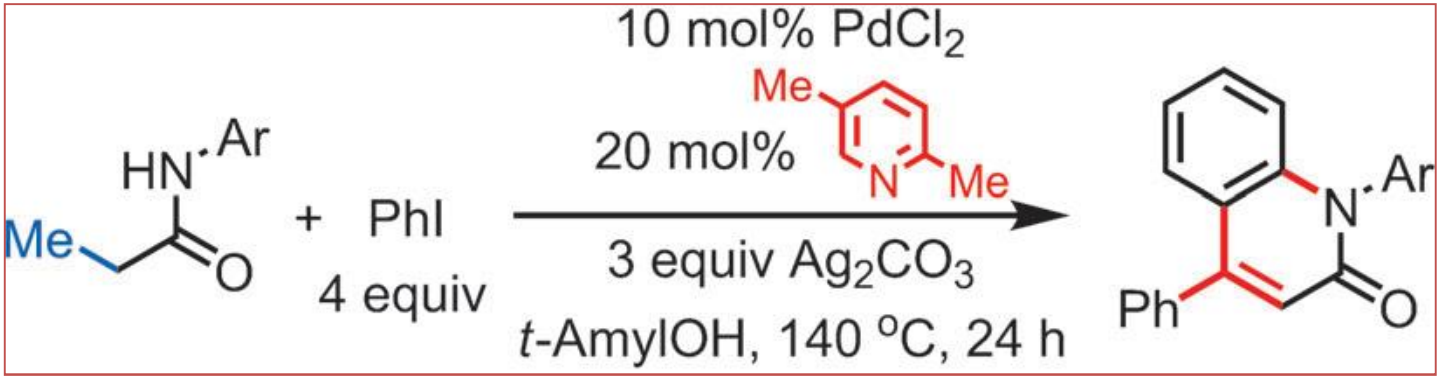
by

Prashant Borkar

(16th *June 2014*)

Title: **"Ligand-Enabled Triple C-H Activation Reactions: One-Pot Synthesis of Diverse 4-Aryl-2-quinolinones from Propionamides"**

Authors: **Youqian Deng, Wei Gong, Jian He, and Jin-Quan Yu***

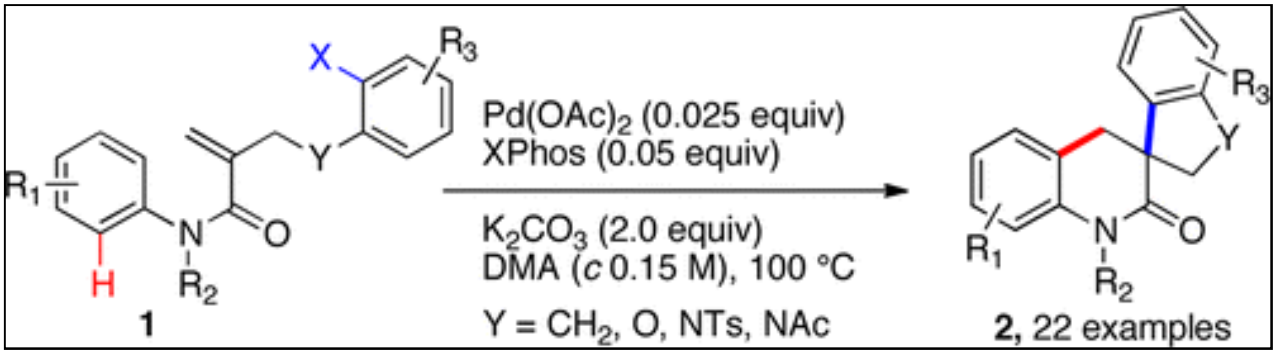


Angew. Chem. Int. Ed. 2014, DOI: 10.1002/anie.201403878

Introduction

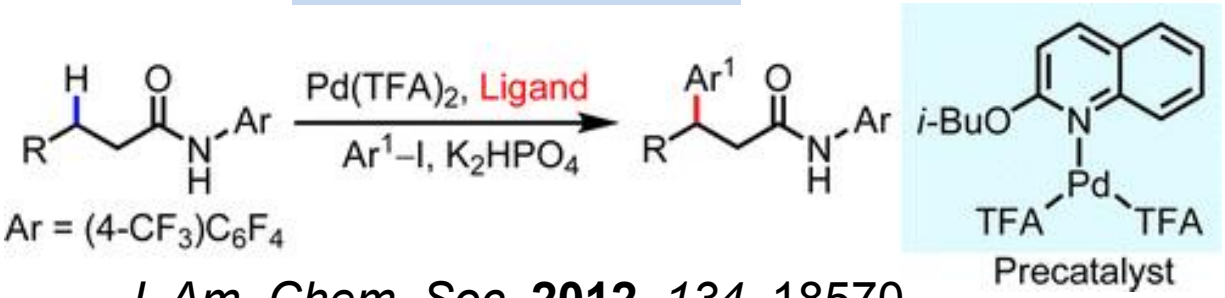
- **Ligand-controlled / ligand-accelerated C(sp3)-H activation with Pd^{II} catalysts has recently emerged as a promising strategy for developing new catalytic transformations.**
- **The compatibility of these ligands with C(sp3)-H activation and subsequent functionalization steps offers unprecedented opportunities to discover new catalytic reaction pathways by influencing the reactivity of various potential organopalladium intermediates.**
- **In particular, if a common ligand can be identified to promote cascade C-H activation reactions, molecular complexity and diversity can be readily generated from simple starting materials by sequential and diverse C-H functionalizations.**
- **Indeed cascade reactions involving a Heck reaction and a subsequent C-H activation step provide an elegant route for the synthesis of spirodihydro-quinolin-2-ones.**

Org. Lett. **2012**, *14*, 3760.

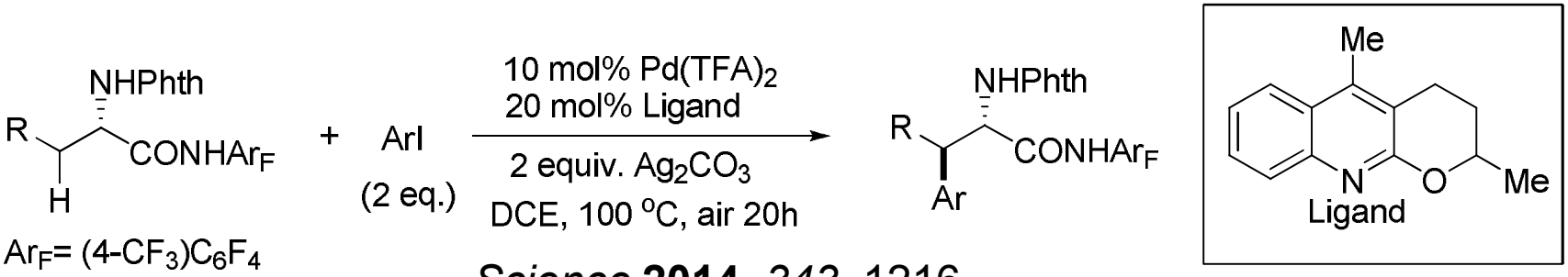


Introduction

Author's previous work

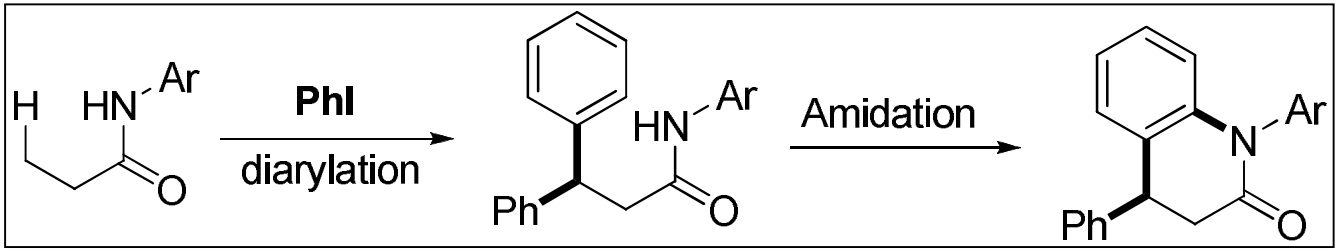


J. Am. Chem. Soc. **2012**, *134*, 18570.



Science **2014**, *343*, 1216

Proposed transformation



Observed transformation

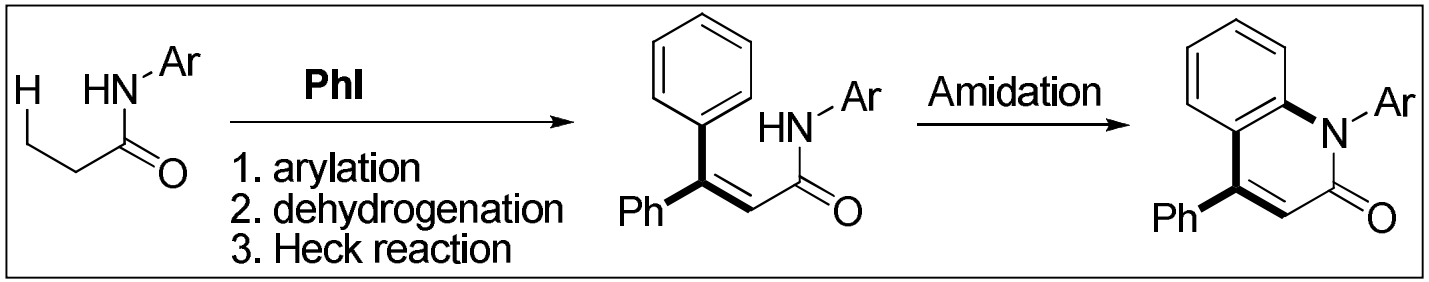
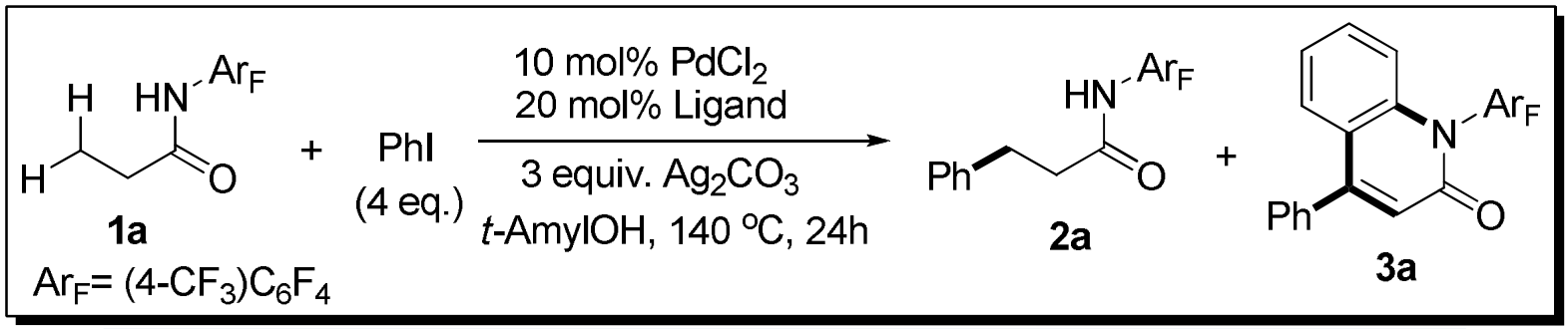


Table 1- Reaction discovery and ligand screening



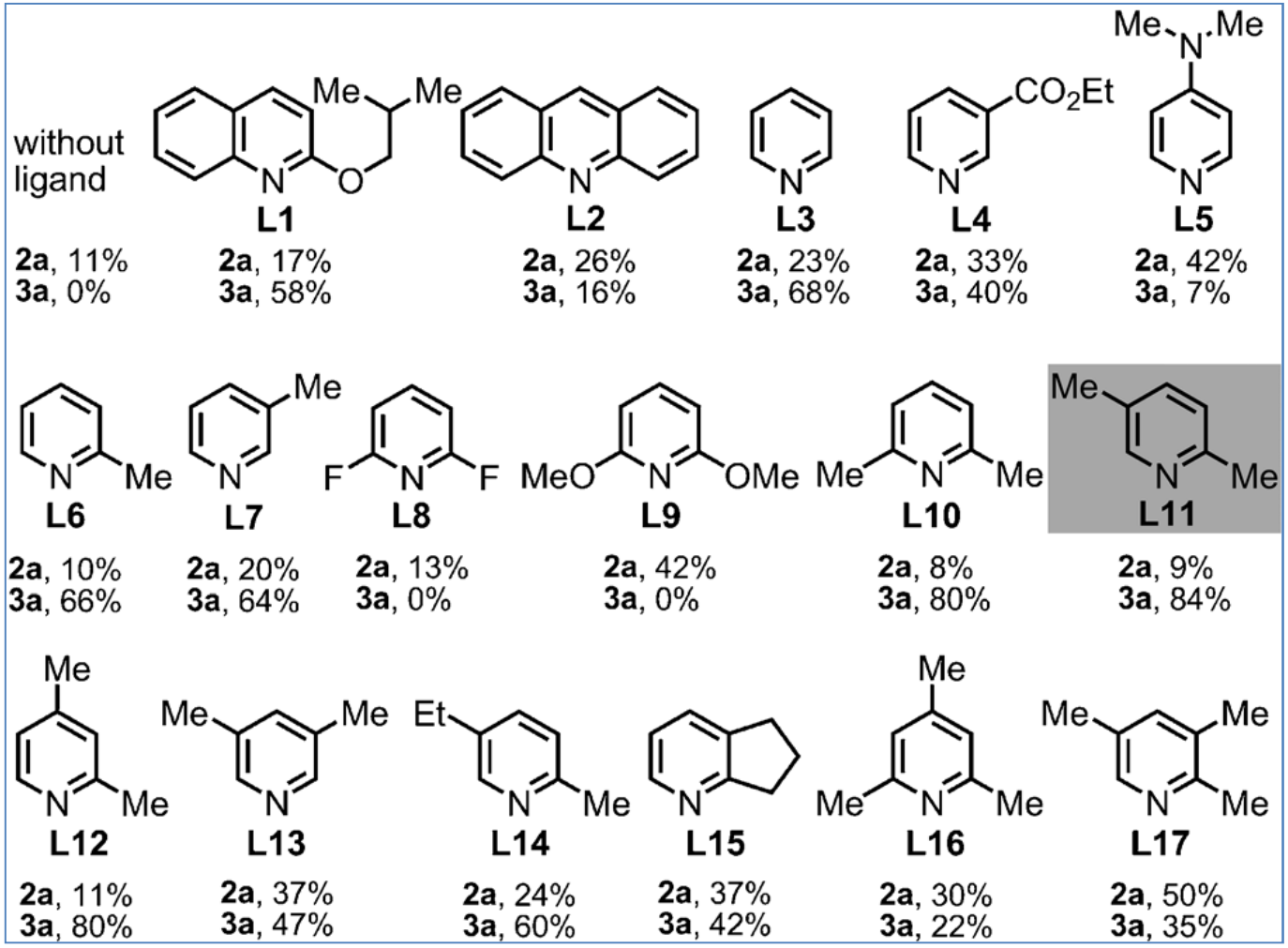
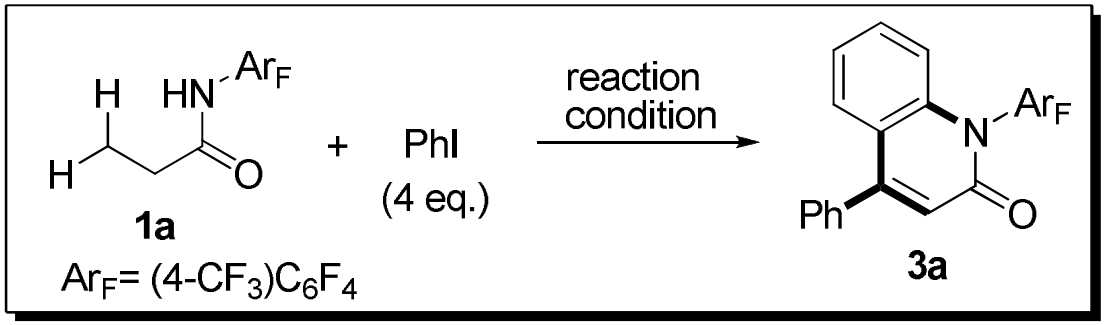
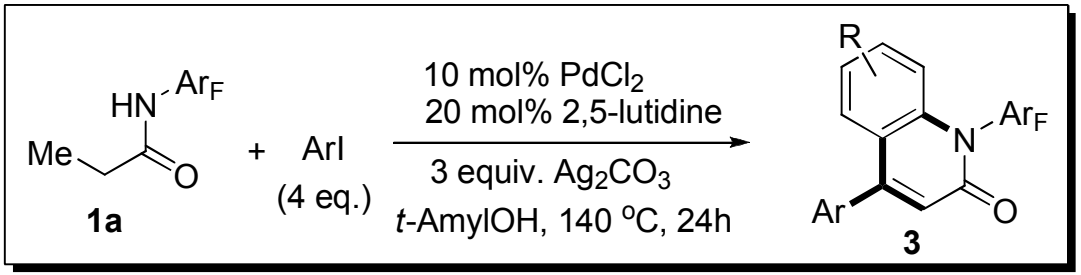


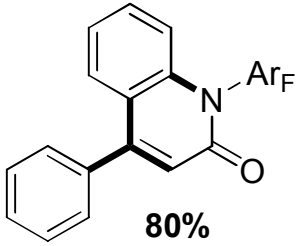
Table 2- Screening of Pd(II)-catalyst, solvent, temperature and oxidant using 2,5-lutidine as ligand.

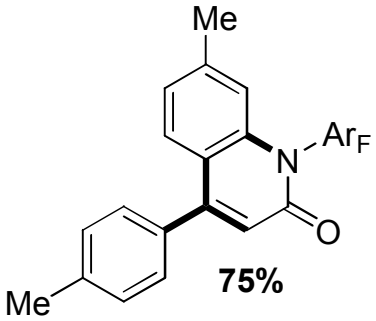


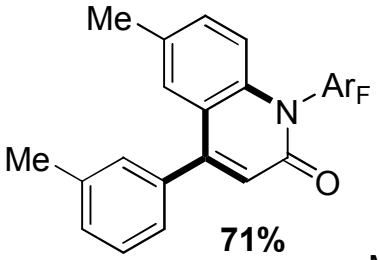
reaction condition: 10 mol% Pd(II), 20 mol% 2,5-lutidine, 3 equiv. Ag_2CO_3, *t*-AmylOH, 140 °C, 24h		reaction condition: 10 mol% $PdCl_2$, 20 mol% 2,5-lutidine, 3 equiv. Ag_2CO_3, solvent, 140 °C, 24h		reaction condition: 10 mol% $PdCl_2$, 20 mol% 2,5-lutidine, 3 equiv. Ag_2CO_3, *t*-AmylOH, Temp, 24h		reaction condition: 10 mol% $PdCl_2$, 20 mol% 2,5-lutidine, Oxidant, *t*-AmylOH, 140 °C, 24h	
Pd(II) catalyst	**3a%**	**Solvent**	**3a%**	**Temp.** (°C)	**3a%**	**Oxidant** (eq.)	**3a%**
$Pd(OAc)_2$	77	*t*-AmylOH	84	100	23	Ag_2CO_3 (3)	84
$Pd(TFA)_2$	36	*t*-BuOH	35	120	48	AgOAc (6)	45
$Pd(BF_4)_2(CH_3CN)_4$	26	Hexane	57	140	84	AgOPiv (6)	15
$PdCl_2(CH_3CN)_2$	75	1,4-dioxane	68	160	82	Ag_2O (3)	10
$PdCl_4Na_2$	67	DCE	81			$Cu(OAc)_2$ (3)	0
$PdCl_2$	84	Toluene	71			BQ (3)	0

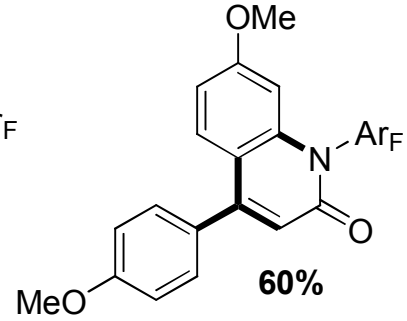
Table 3- Scope of aryl iodides

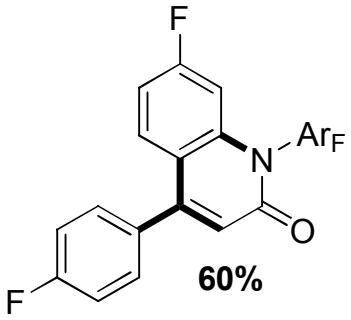


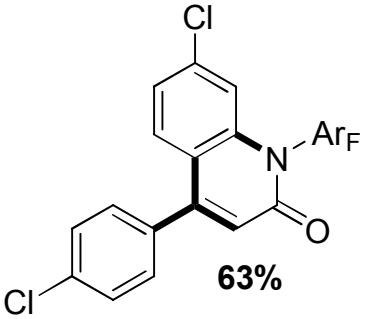


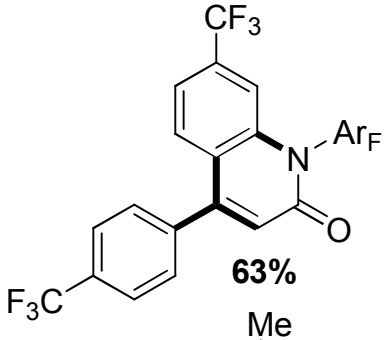


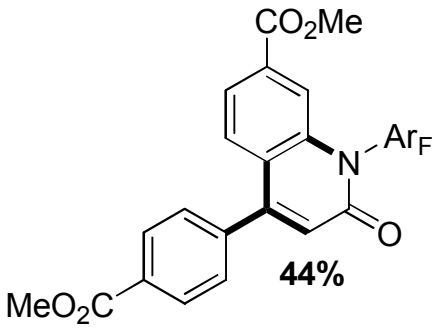


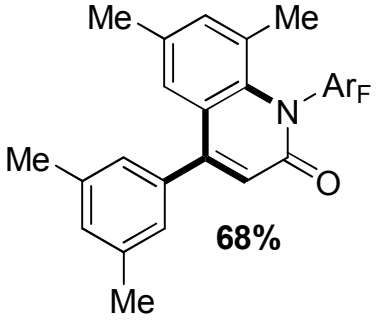












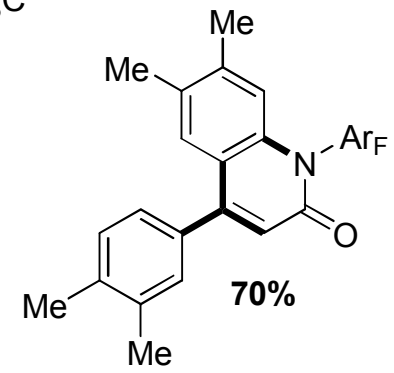
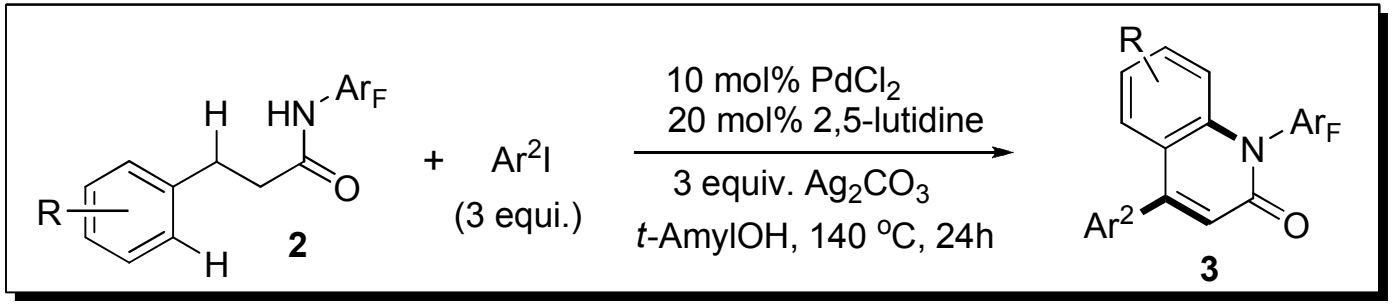
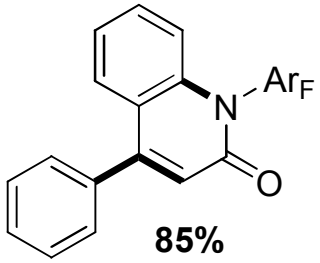


Table 4: Incorporation of two different aryl groups





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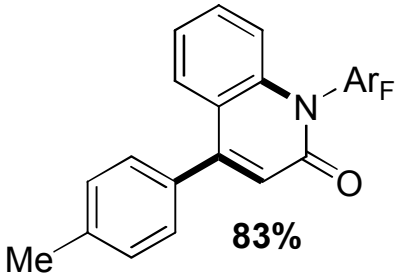

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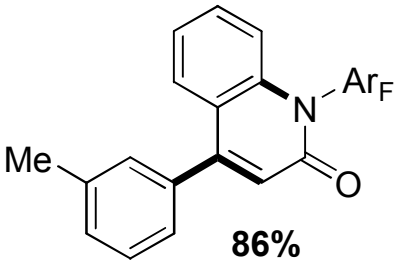

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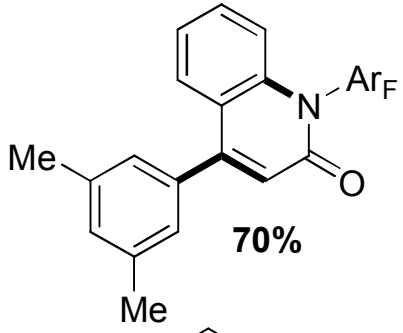

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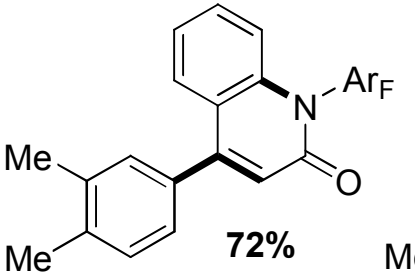

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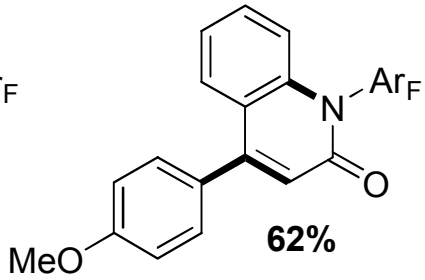

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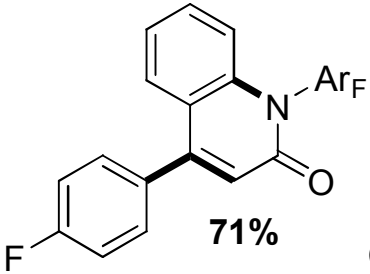

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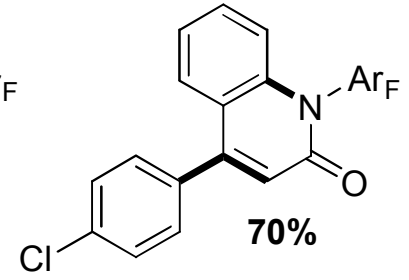

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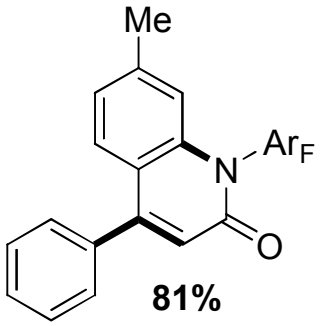

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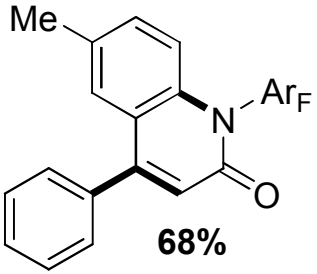

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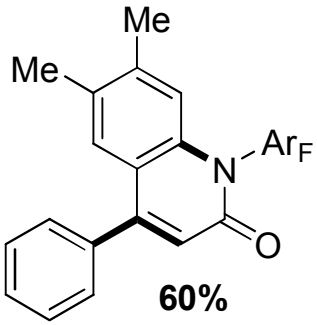

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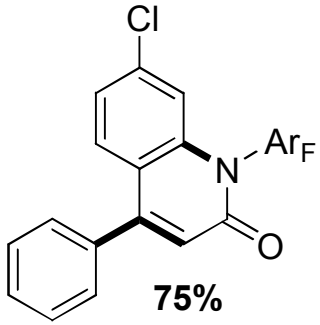

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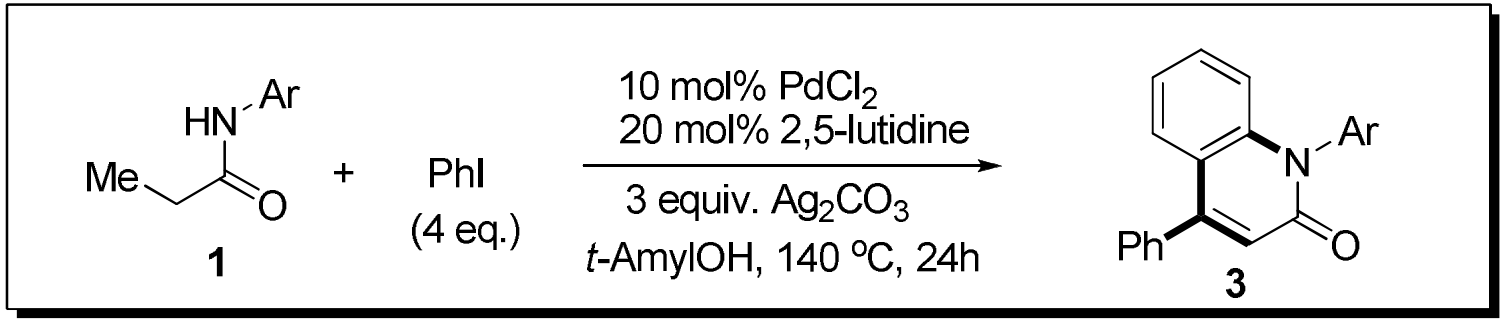
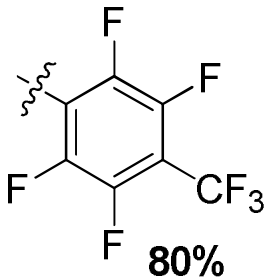
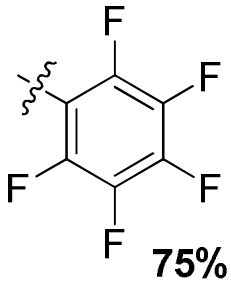
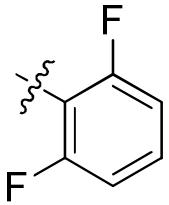
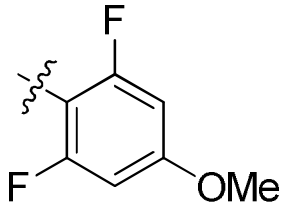
Table 5: The scope of the N-aryl group

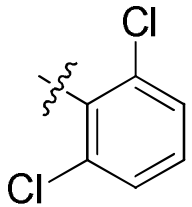


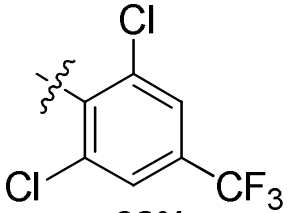
Ar =  **80%**

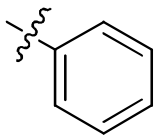
 **75%**

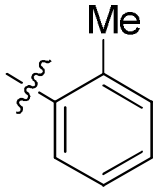
 **69%**

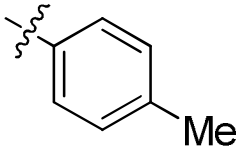
 **64%**

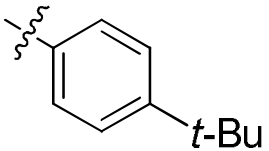
 **66%**

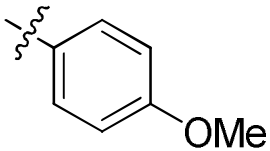
Ar =  **62%**

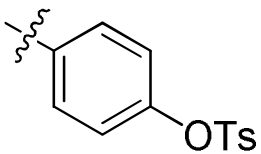
 **48%**

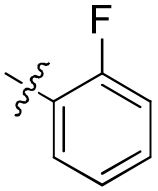
 **54%**

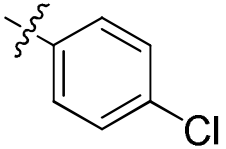
 **41%**

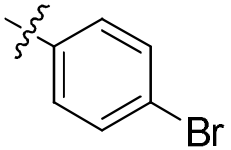
 **40%**

Ar =  **42%**

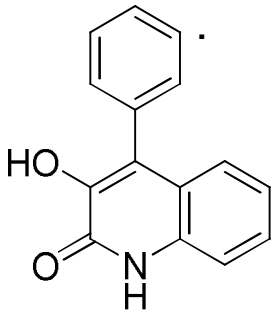
 **50%**

 **53%**

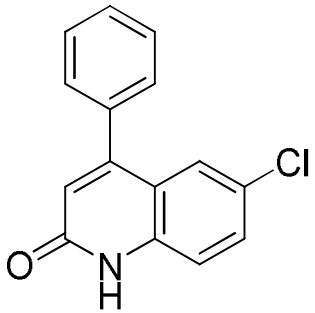
 **46%**

 **40%**

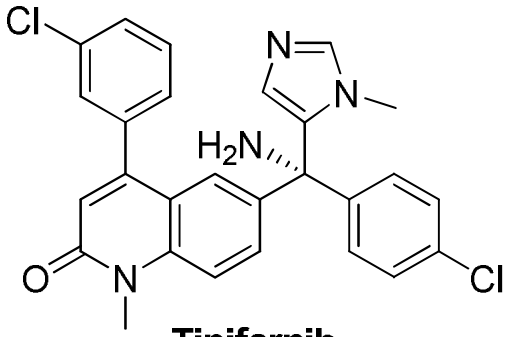
Biologically active 4-aryl-2-quinolinones



Viridicatin

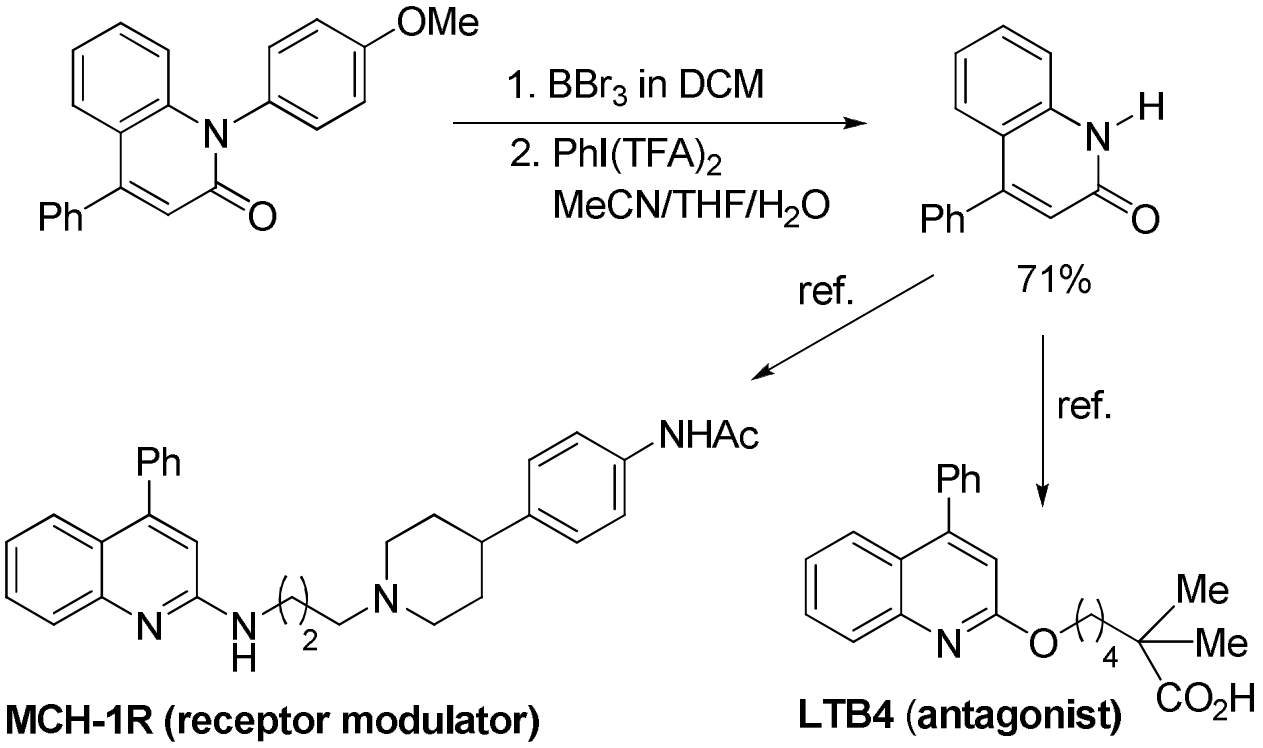


HBV Inhibitor



Tipifarnib

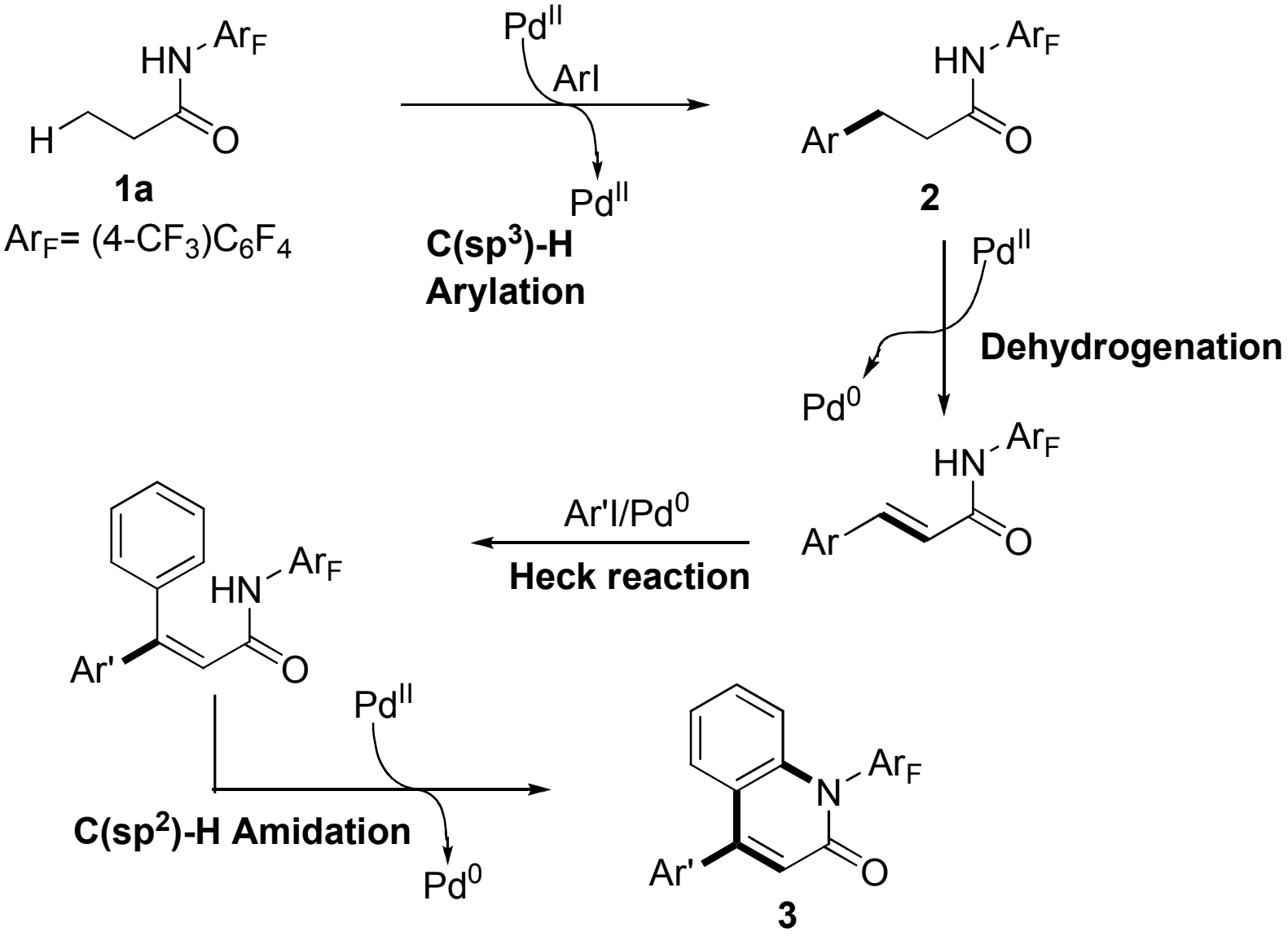
Synthetic applications:



MCH-1R (receptor modulator)

LTB4 (antagonist)

Proposed catalytic pathway



Conclusion

- Protocol provides molecular complexity from simple substrate in a single step operation.
- Development of an unprecedented pyridine ligand-promoted cascade C-H activation of propionamides under oxidative palladium catalysis.
- One-pot procedure for the preparation of diverse 4-aryl-2-quinolinones from simple propionic acid.
- This cascade reaction involves the cleavage of five C-H bonds, two C-I bonds, and one N-H bond, and the formation of three C-C bonds and one C-N bond via four different types of palladium catalytic cycles.

THANK YOU FOR YOUR KIND ATTENTION