Literature Report

Catalytic Enantioselective Minisci-type Addition to Heteroarenes

Reporter：Hong-Qiang Shen
Checker：Fan-Jie Meng
Date：2018-05-21

Proctor, R. S. J.; Davis, H. J.; **Phipps, R. J.**
Science **2018**, *360*, 419-422.

Contents

CV of Robert J Phipps

Education:

200x-2006 M.S., Imperial College London.

2006-2010 Ph. D., University of Cambridge.

2010-2013 Postdoctoral, University of California, Berkeley.

2013-Now Research Fellow, University of Cambridge.

Research:

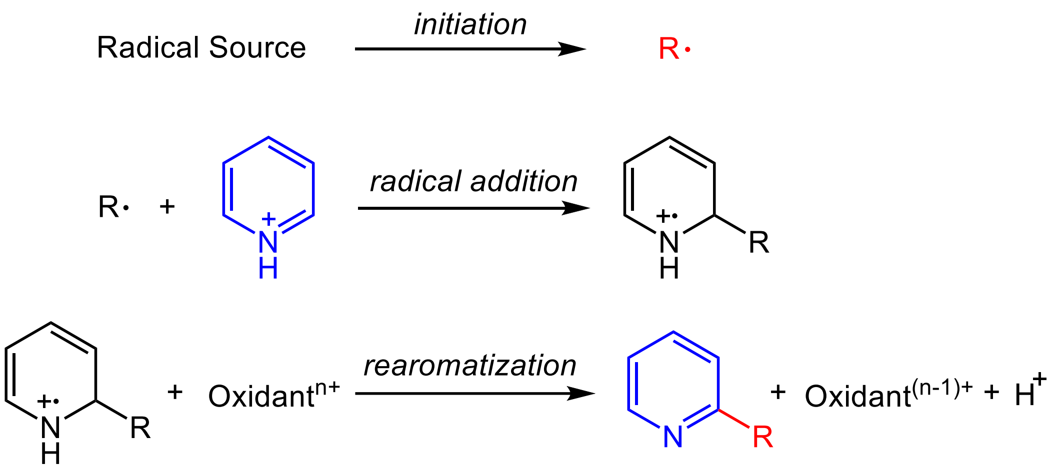
- Exploring new designs of multifunctional catalysts.
- Exploring the non-covalent interactions for catalysis.

Minisci-type Addition

First step:

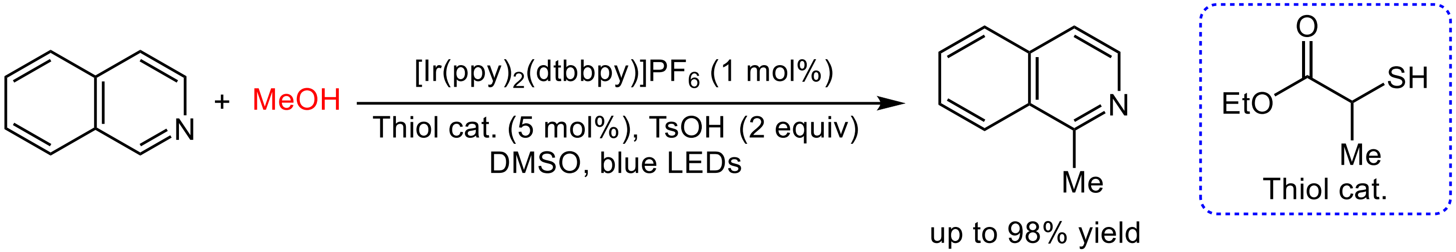
Second step:

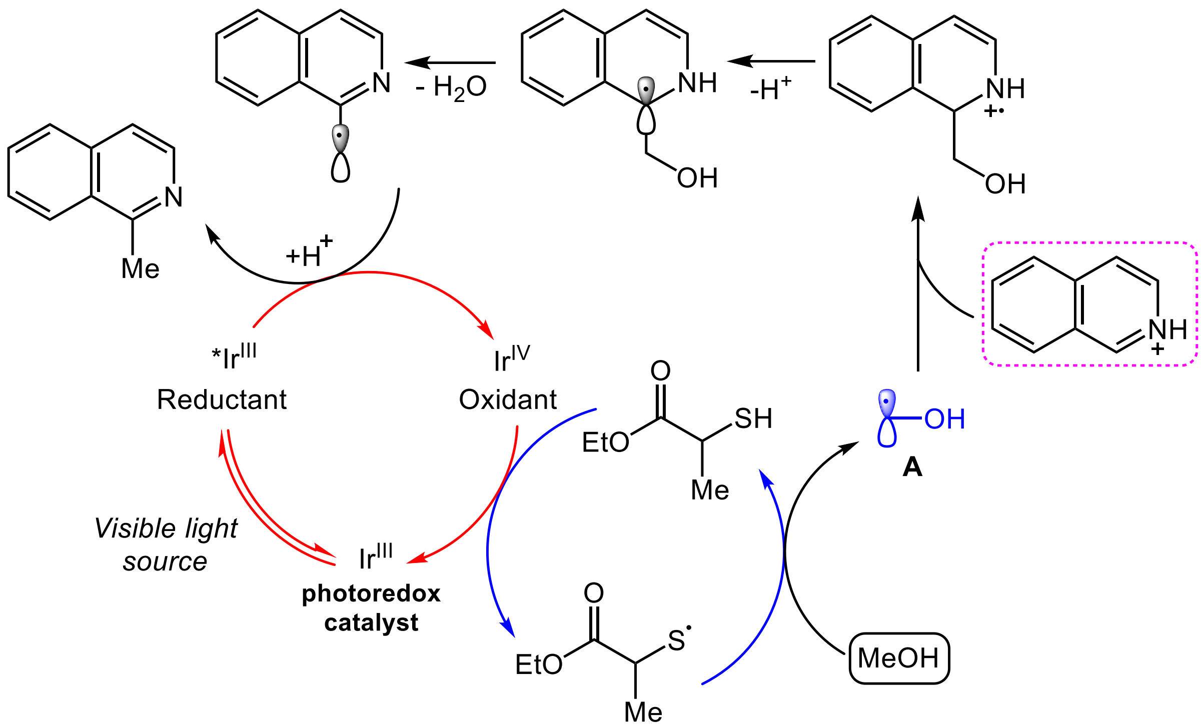
Third step:



Minisci, F. *et al. Tetrahedron* **1971**, *27*, 3575.

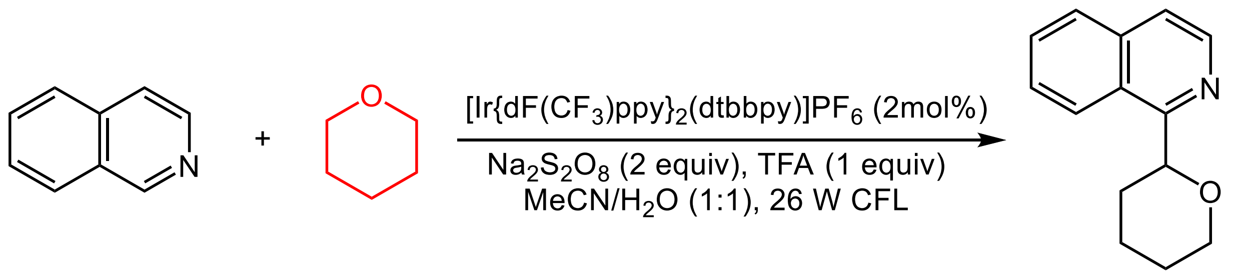
Introduction





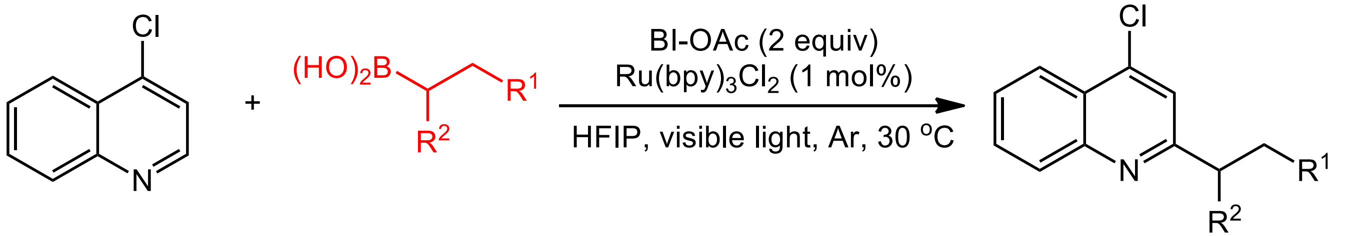
MacMillan, D. W. C. *et al. Nature* **2015**, *525*, 87.

Introduction



up to 93% yield

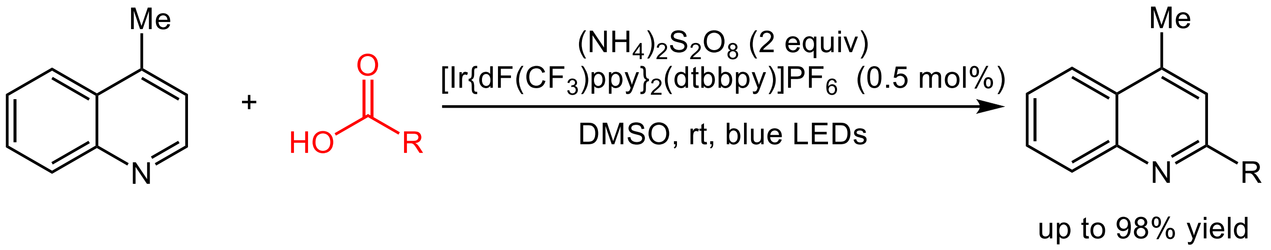
MacMillan, D. W. C. *et al. Angew. Chem. Int. Ed*. **2015**, *54*, 1565.



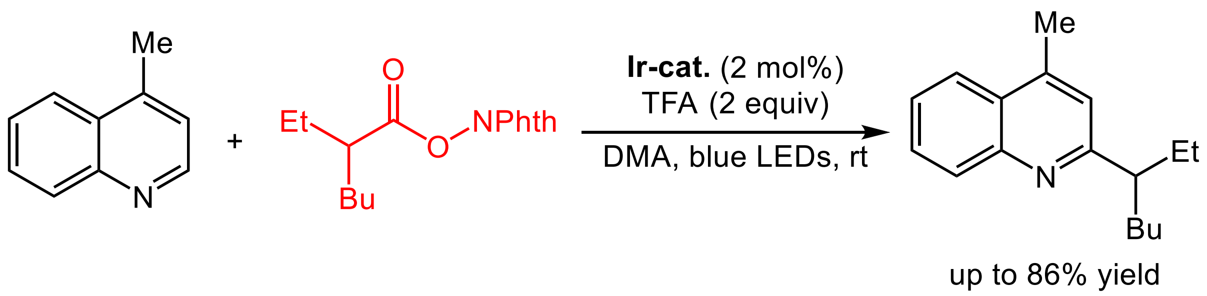
up to 96% yield

Chen, G.; Liu, P. *et al. Chem. Sci.* **2016**, *7,* 6407.

Introduction

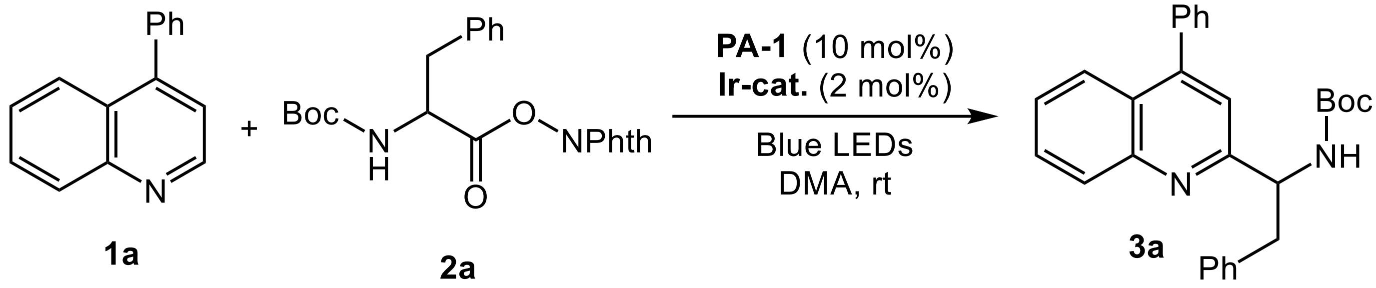


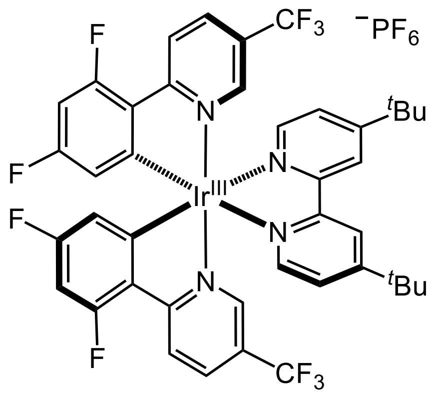
Glorius, F. *et al. ACS Catal*. **2017**, *7*, 4057.



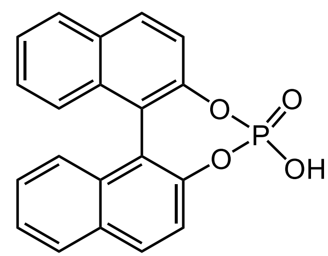
Fu, Y.; Shang, R. *et al. Chem. Eur. J.* **2017**, *23*, 2537.

Introduction

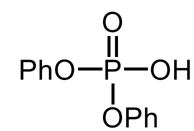




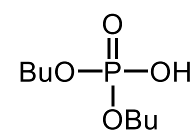
Ir-cat.: [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$



PA-1



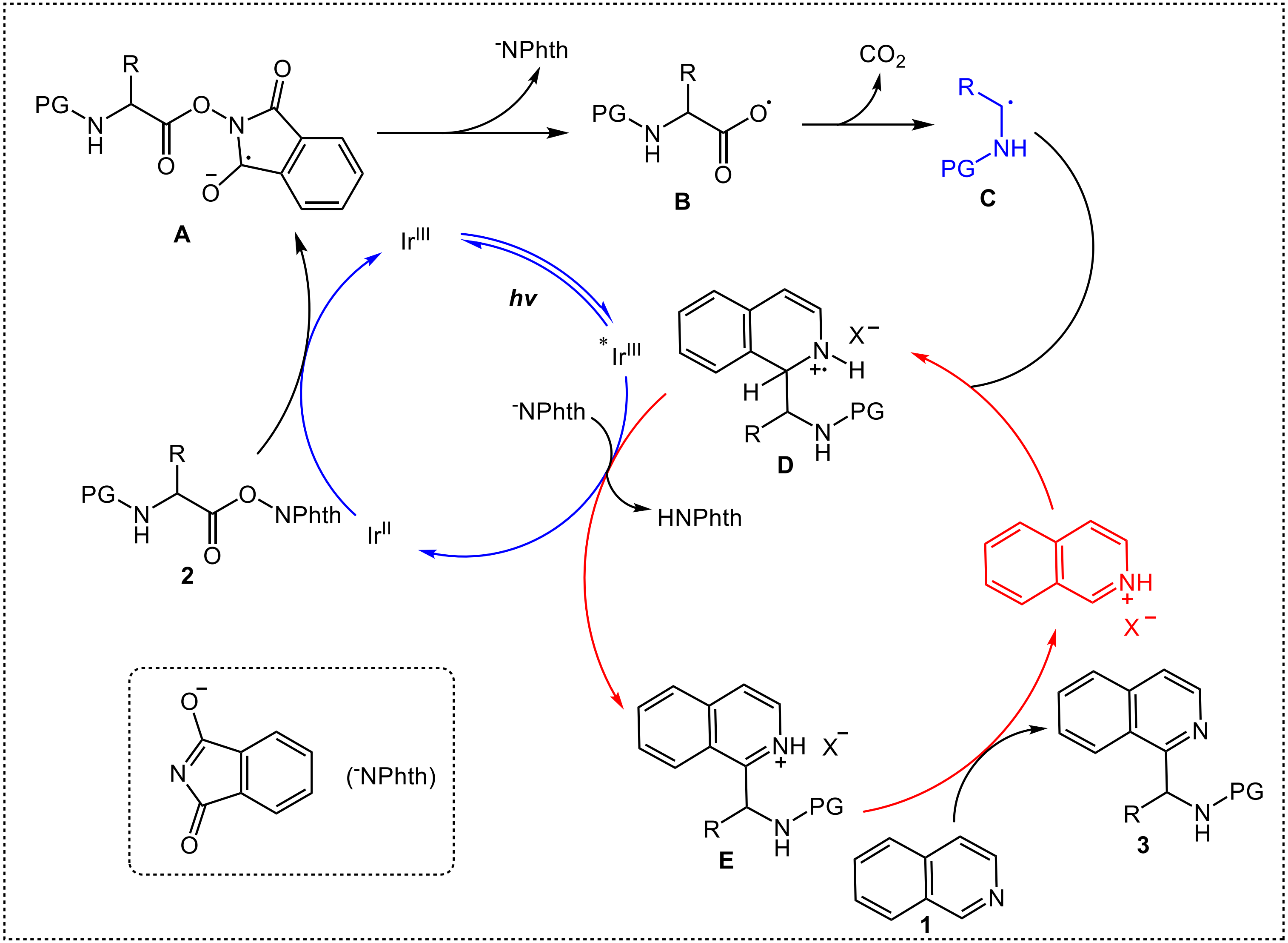
PA-2



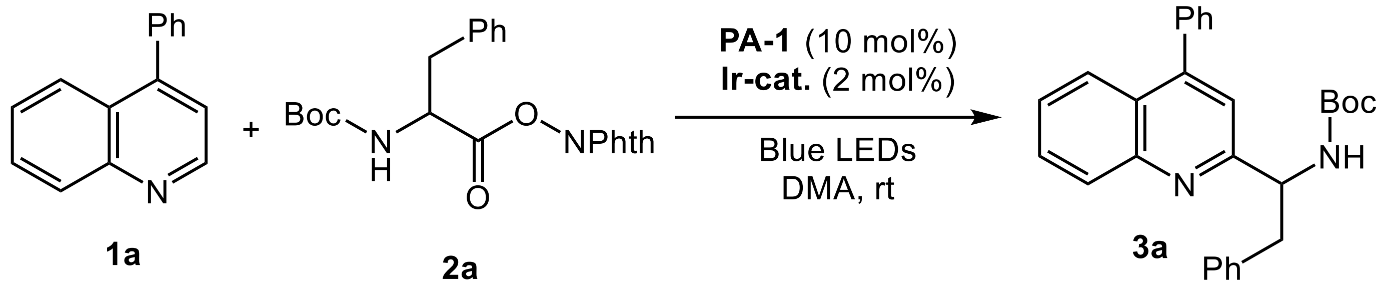
PA-3

Fu, Y.; Shang, R. *et al. ACS Catal*. **2017**, *7*, 907.

Proposed Mechanism



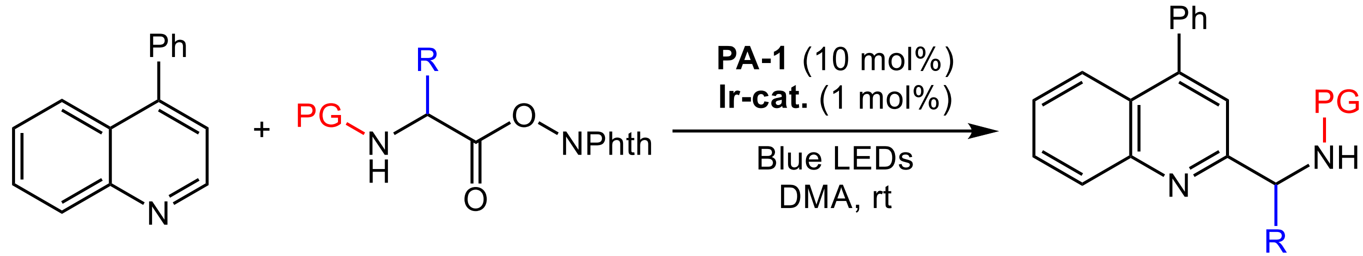
Optimization of the Reaction Parameters



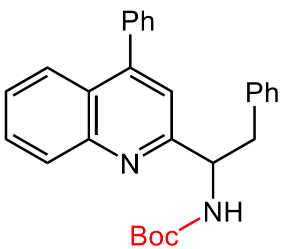
Entry	Variations of conditions[a]	Yield **3a** (%)[b]
1	None	85
2	$Ru(bpy)_3(PF_6)_2$ instead of **Ir-cat.**	<5
3	Without photocatalyst	N.D.
4	$Al(OTf)_3$ instead of **PA-1**	62
5	**PA-2** instead of **PA-1**	60
6	**PA-3** instead of **PA-1**	27
7	Without **PA-1**	15
8	Without light	<5
9	Using 1 mol% **Ir-cat.**	84

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.30 mmol%), photocatalyst (2 mol%), acid catalyst (2 mol%), DMA (2 mL). [b] Isolated yields.

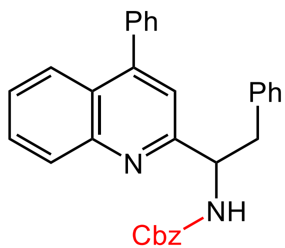
Substrate Scope



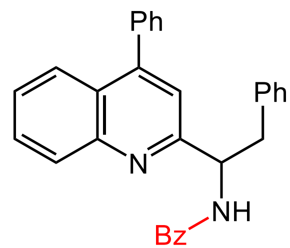
1a **2** **3**



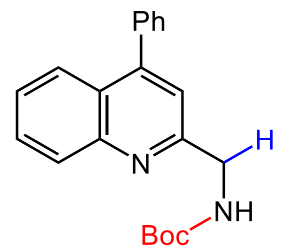
3aa: 84% yield



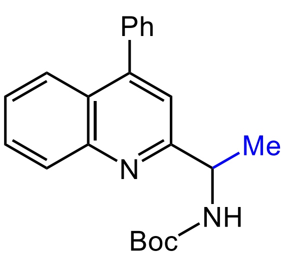
3ab: 81% yield



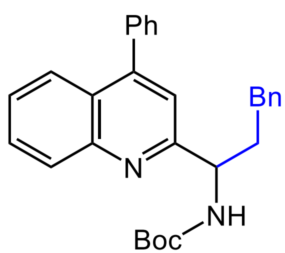
3ac: 83% yield



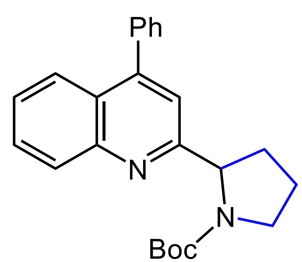
3ad: 80% yield



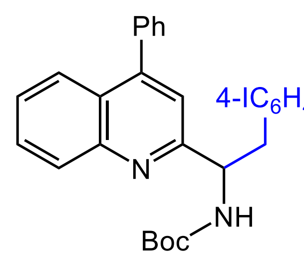
3ae: 78% yield



3af: 79% yield

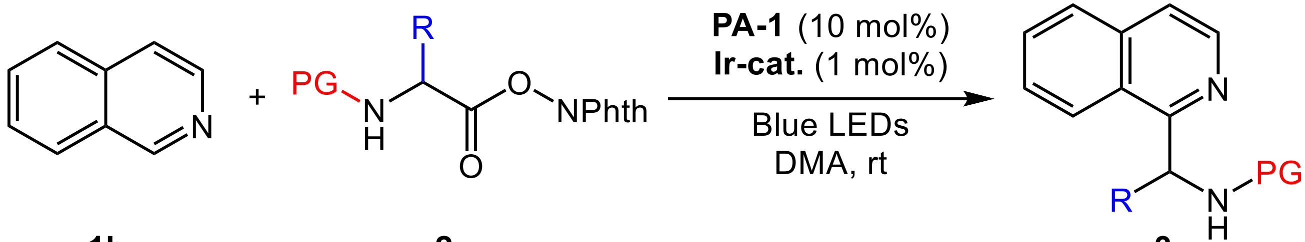


3ag: 92% yield

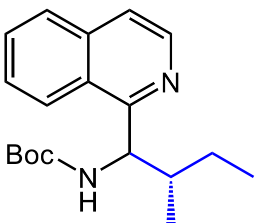


3ah: 95% yield

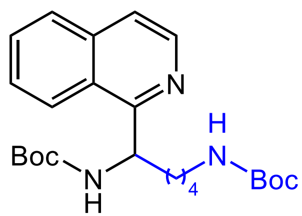
Substrate Scope



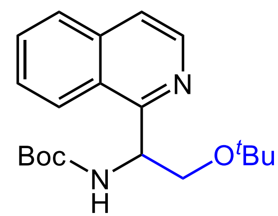
1b **2** **3**



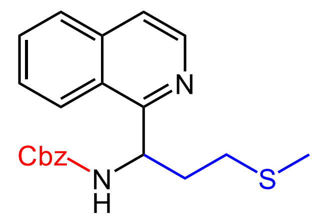
3bi: 80% yield
(d.r. = 1:1)



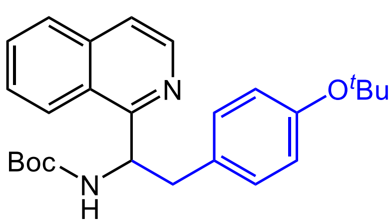
3bj: 93% yield



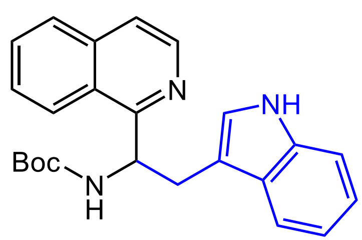
3bk: 89% yield



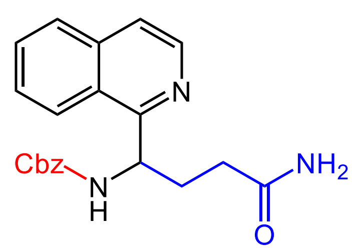
3bl: 92% yield



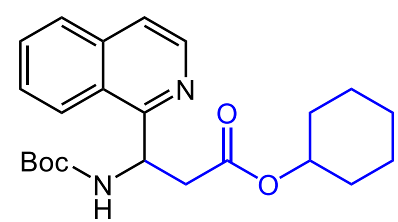
3bm: 96% yield



3bn: 91% yield

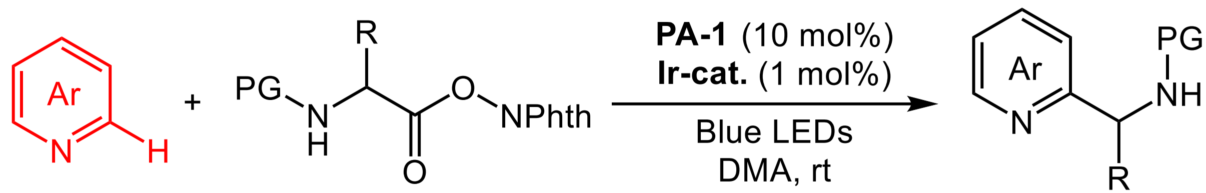


3bo: 82% yield

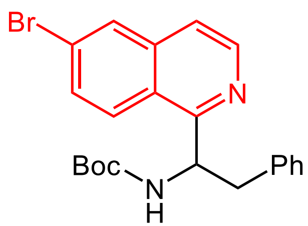


3bp: 92% yield

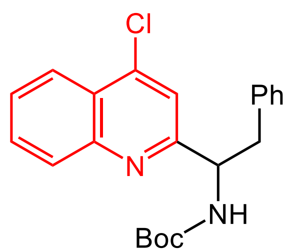
Substrate Scope



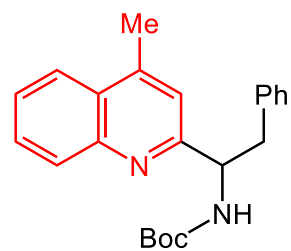
1 **2** **3**



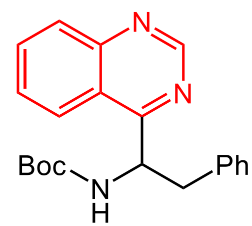
3ca: 90% yield



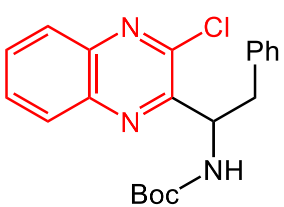
3da: 51% yield



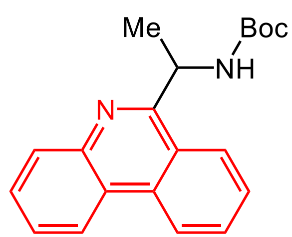
3ea: 88% yield



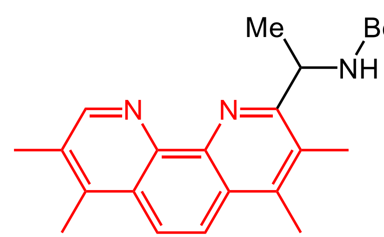
3fa: 50% yield



3ga: 53% yield

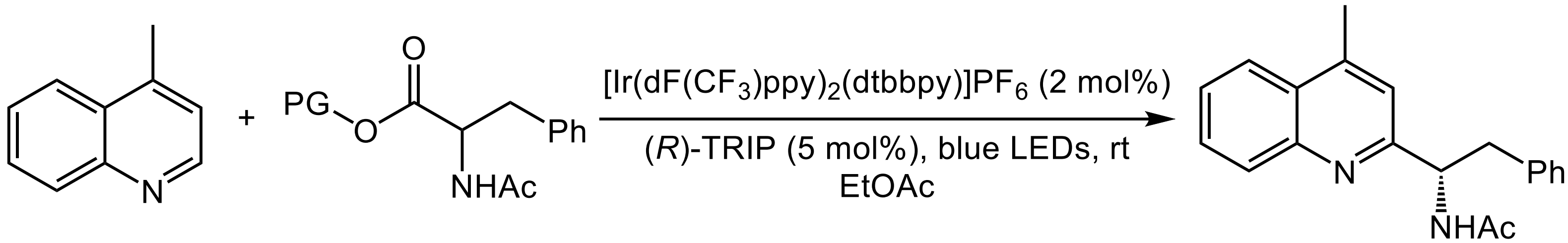


3he: 89% yield

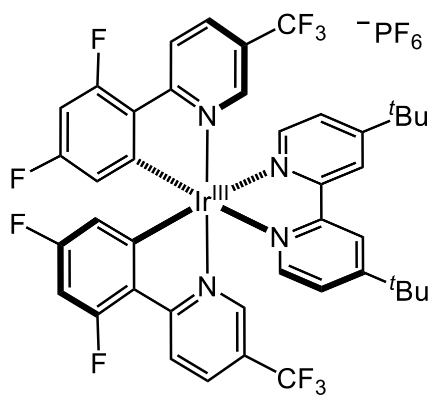


3ie: 72% yield

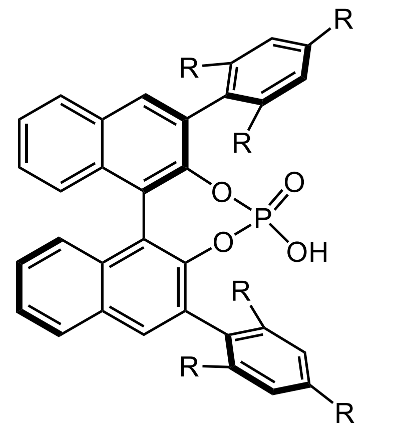
Enantioselective Minisci-type Addition



4 **5** **6**



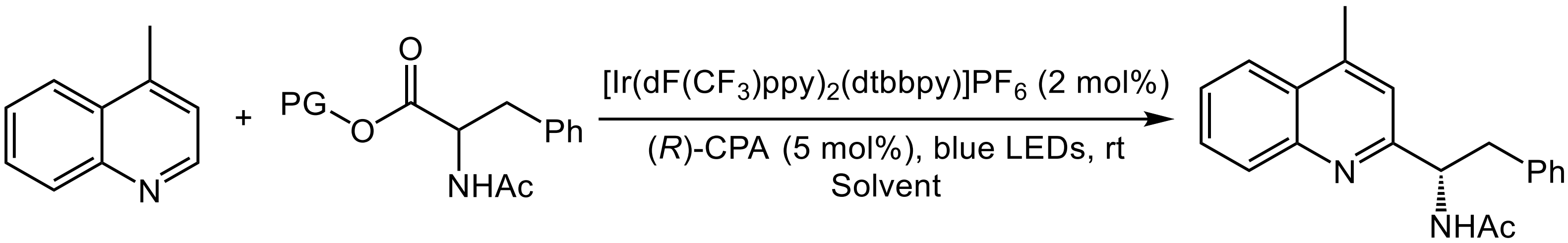
[Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$



R = ^{i}Pr, (*R*)-TRIP; R = Cy, (*R*)-TCYP

Phipps, R. J. *et al. Science* **2018**, *360*, 419.

Optimization of the Reaction Parameters

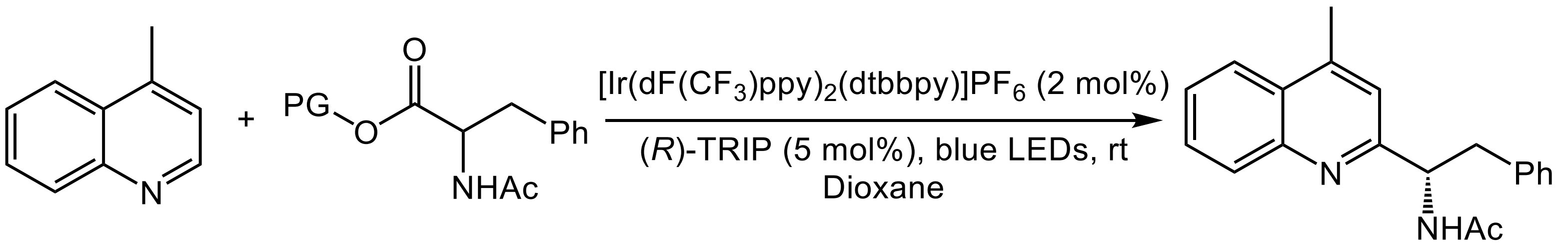


4a **5a** **6aa**

Entry	Solvent	CPA	Yield (%)[b]	Ee (%)[c]
1	Dioxane	(*R*)-TRIP	94	94
2	THF	(*R*)-TRIP	83	93
3	Toluene	(*R*)-TRIP	95	90
4	MeCN	(*R*)-TRIP	34	70
5	DMA	(*R*)-TRIP	39	65
6	DCM	(*R*)-TRIP	85	73
7	EtOAc	(*R*)-TRIP	93	84
8	Dioxane	(*R*)-TCYP	98	84

[a] Reaction conditions: **4a** (0.10 mmol), **5a** (0.15 mmol), Photocatalyst (2 mol%), acid catalyst (5 mol%), Solvent (2 mL). [b] Isolated yields [c] Determined by HPLC.

Optimization of the Reaction Parameters

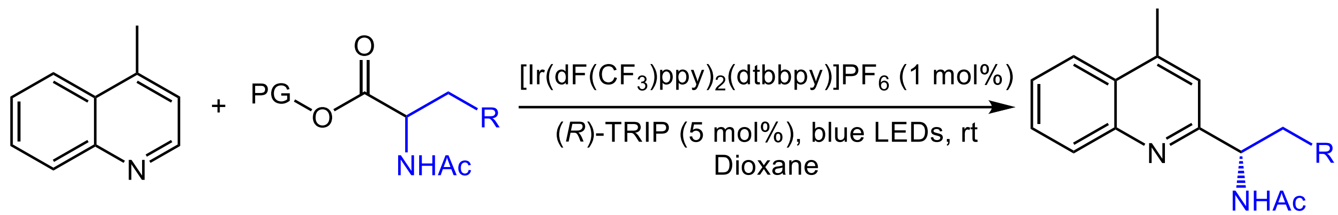


4a **5a** **6aa**

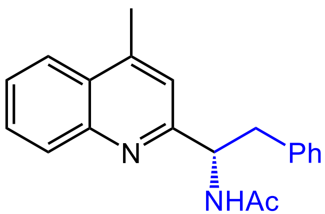
Entry	Variations of conditions[a]	Yield (%)[b]	Ee (%)[c]
1	None	94	94
2	Without Photocatalyst	0	0
3	Without (*R*)-TRIP	0	0
4	Without light	0	0
5	1 mol% Photocatalyst	87	94
6	1.1 equiv **5a**	89	93
7	**4a** (0.25 mmol), **5a** (1.1 equiv)	93	96

[a] Reaction conditions: **4a** (0.10 mmol), **5a** (0.15 mmol), Photocatalyst (2 mol%), acid catalyst (5 mol%), Solvent (2 mL). [b] Isolated yields [c] Determined by HPLC.

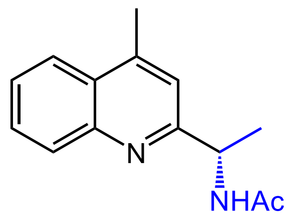
Substrate Scope



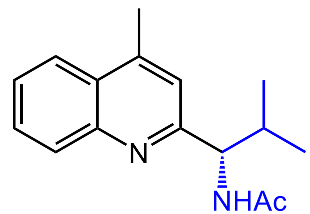
4a **5** **6**



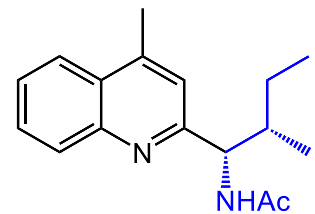
6aa: 93% yield, 96% ee



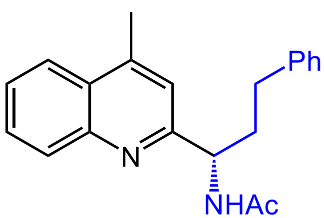
6ab: 91% yield, 94% ee



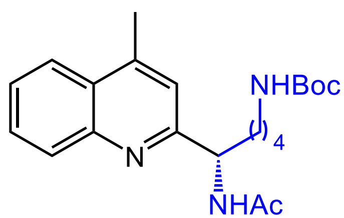
6ac: 89% yield, 97% ee



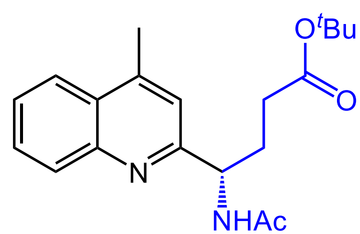
6ad: 76% yield, >20:1 dr



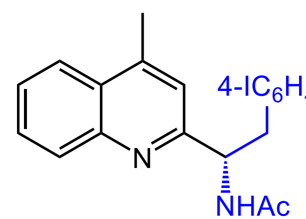
6ae: 82% yield, 90% ee



6af: 63% yield, 88% ee

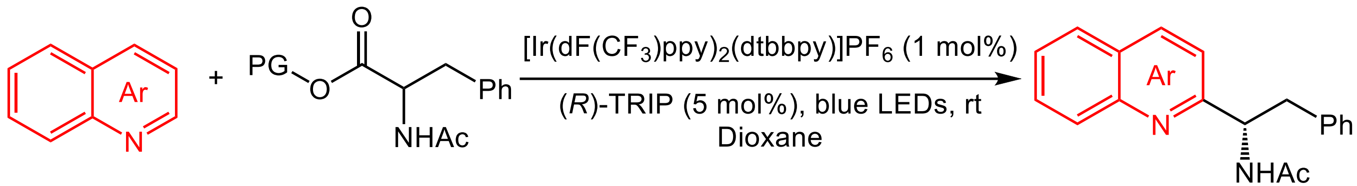


6ag: 70% yield, 91% ee

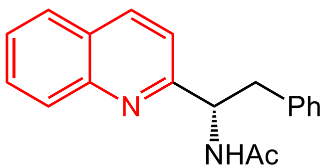


6ah: 94% yield, 90% ee

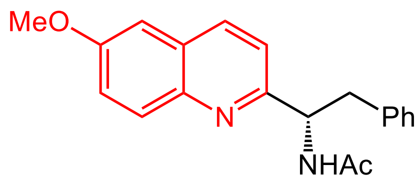
Substrate Scope



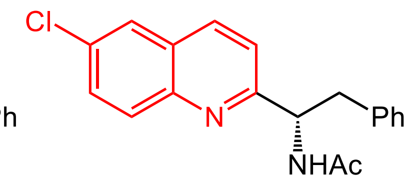
4 **5a** **6**



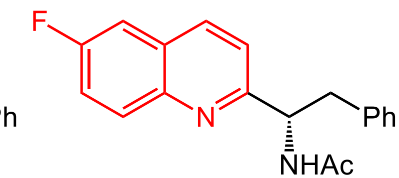
6ba: 89 yield, 96% ee



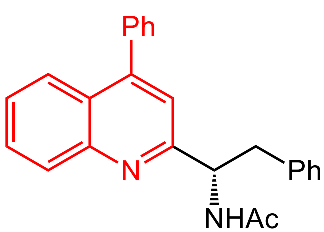
6ca: 82 yield, 94% ee



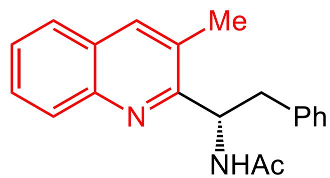
6da: 71 yield, 94% ee



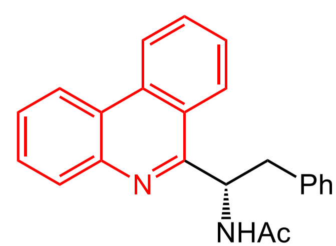
6ea: 82 yield, 95% ee



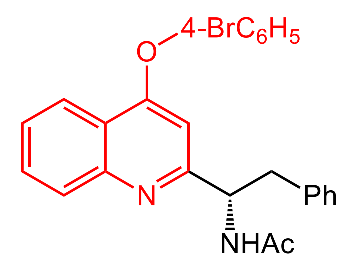
6fa: 95 yield, 95% ee



6ga: 87 yield, 97% ee

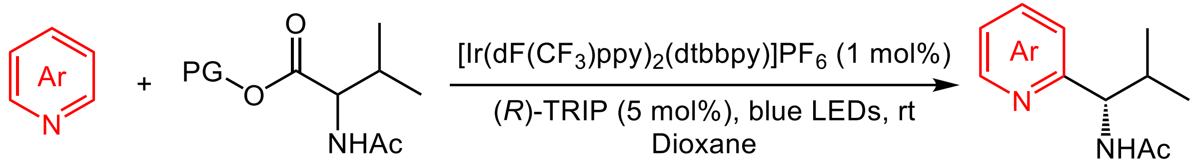


6ha: 92 yield, 92% ee

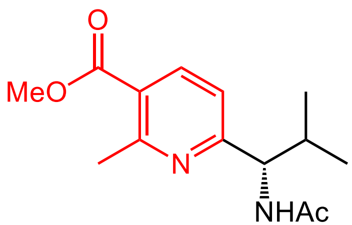


6ia: 89 yield, 97% ee

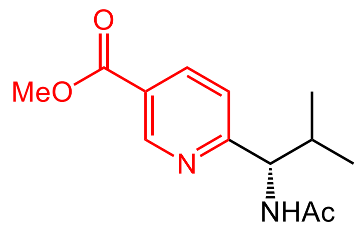
Substrate Scope



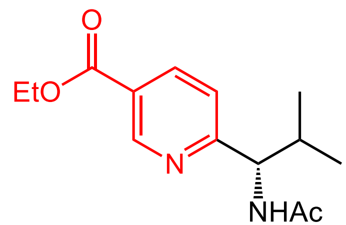
7 **5c** **8**



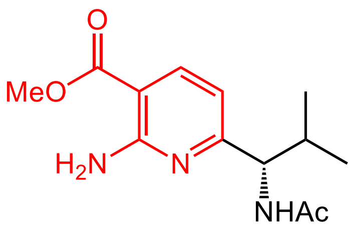
8a: 80% yield, 92% ee



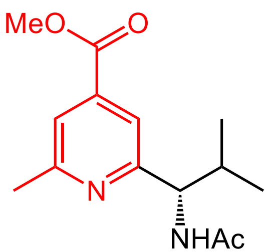
8b: 97% yield, 90% ee



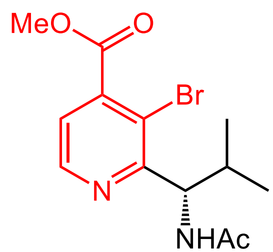
8c: 92% yield, 93% ee



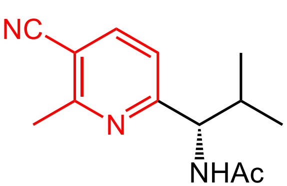
8d: 76% yield, 84% ee



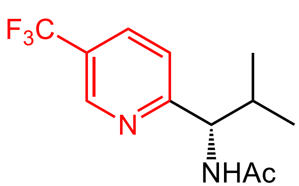
8e: 58% yield, 87% ee



8f: 60% yield, 85% ee



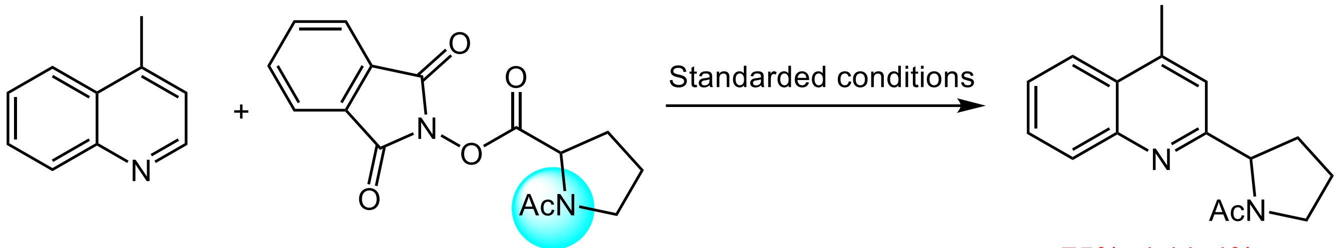
8g: 98% yield, 92% ee



8h: 60% yield, 93% ee

Control Experiments

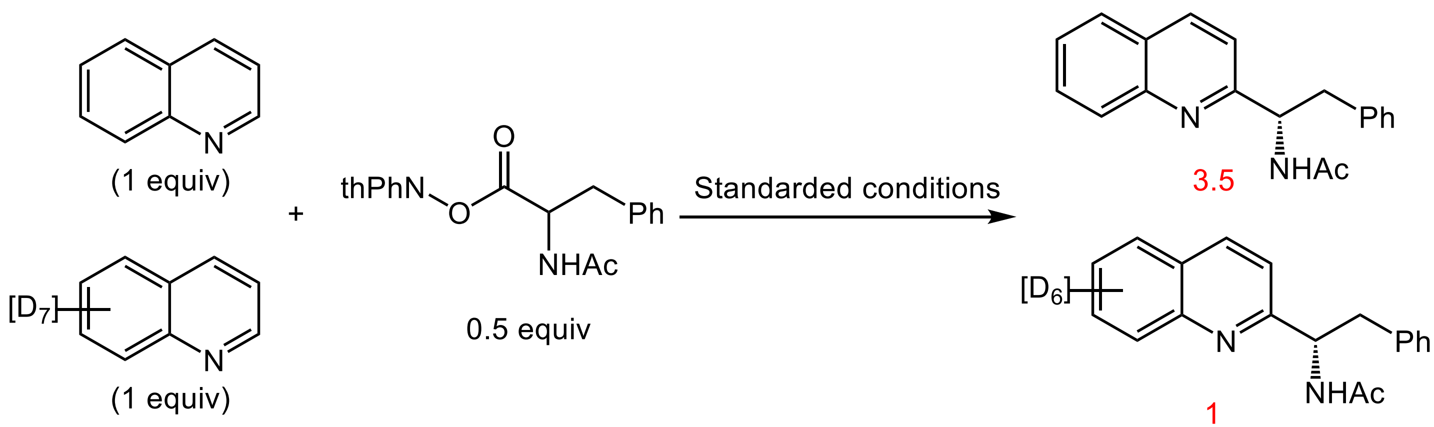
A: Investigation of a REA bearing no hydrogen bond donor



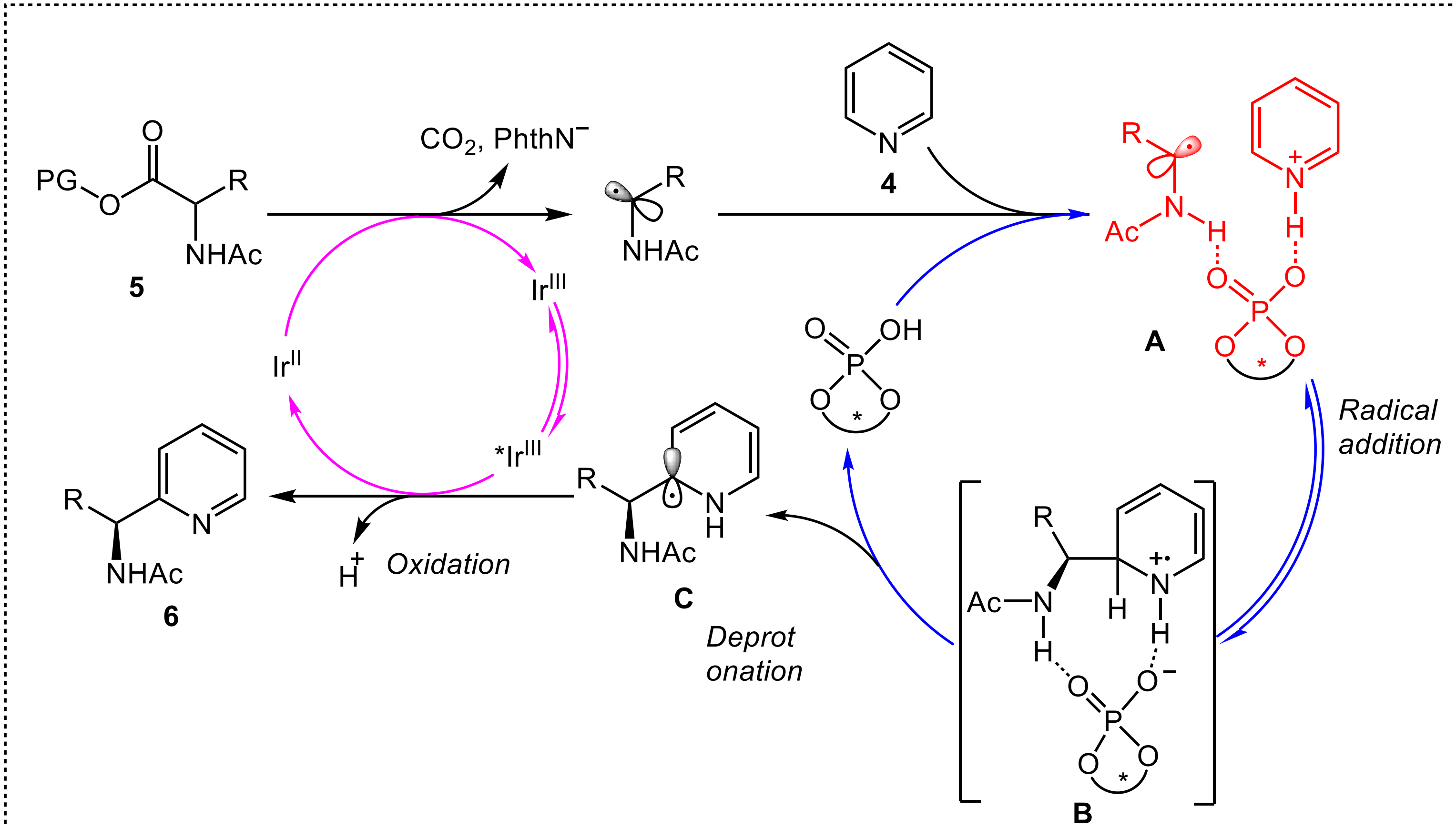
75% yield, 4% ee

5i

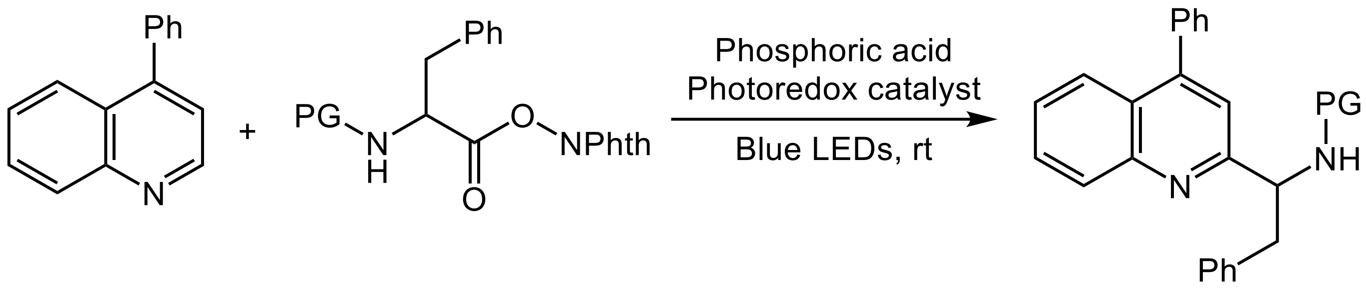
B: Kinetic effect experiment

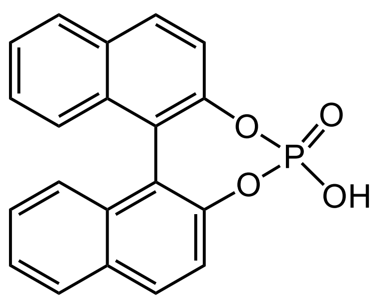


Proposed Mechanism



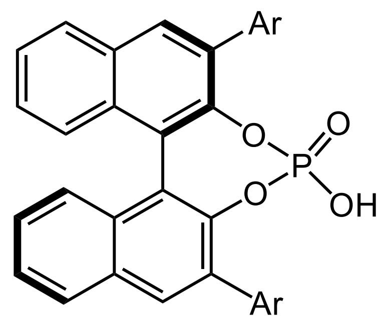
Summary





up to 96%yield

Fu and Shang



Ar = 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$

up to 98% yield, 97% ee

Phipps

The First Paragraph

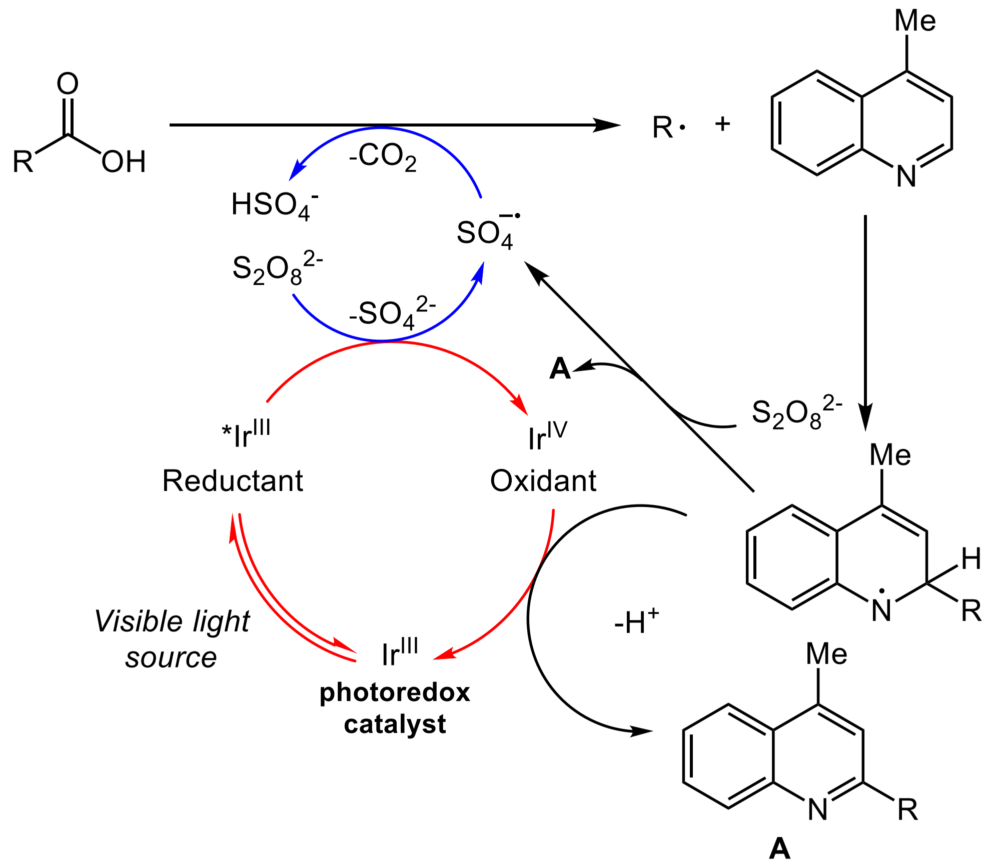
Heteroarenes with basic nitrogen centers, of which pyridines and quinolines are the most common classes, are ubiquitous in pharmaceuticals, agrochemicals, and small molecules of medicinal interest. The nitrogen's basicity precludes traditional electrophilic aromatic substitution pathways, necessitating alternative strategies for elaboration. One widely used protocol is the addition of free radicals to protonated heterocycles, pioneered by Minisci in the 1960s and 1970s and often referred to as "Minisci-type" chemistry. Recent renewed interest has led to numerous advances in radical generation, allowing for milder conditions and convenient radical precursors.

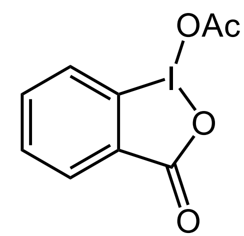
The First Paragraph

Furthermore, photoredox catalysis has provided exciting avenues for radical generation in Minisci-type additions with precursors that include alcohols, ethers , boronic acids, carboxylic acids, and redoxactive esters (RAEs). However, control over absolute stereochemistry in the addition of prochiral radicals has proven elusive, even though many of the aforementioned protocols result in the formation of a stereocenter at the benzylic position.

The Last Paragraph

Given the extraordinary pace of advancement of the field of photoredox catalysis and the range of molecules that are susceptible to Brønsted acid activation, we envisage that our successful merger of these strategies to address the challenge of enantioselective Minisci chemistry will have broad impact in both areas.


O
R
OH
R·
+
Me
N
-CO2
HSO4-
SO4-·
S2O82-
-SO42-
A
*IrIII
Reductant
IrIV
Oxidant
S2O82-
Me
H
N
R
-H+
Visible light
source
IrIII
photoredox
catalyst
Me
N
R
A


OAc
I
O
O

BI-OAc