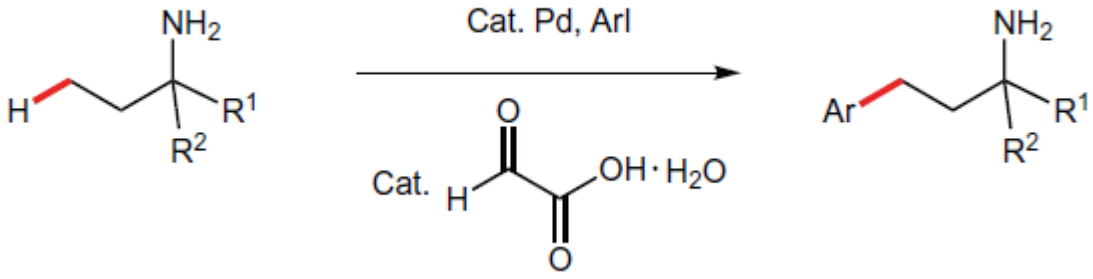
nature chemistry

ARTICLES

PUBLISHED ONLINE: 12 SEPTEMBER 2016 | DOI: 10.1038/NCHEM.2606

Site-selective C–H arylation of primary aliphatic amines enabled by a catalytic transient directing group

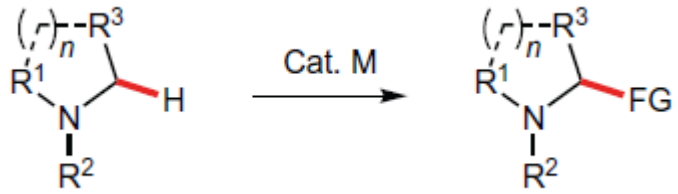
Yongbing Liu and Haibo Ge*

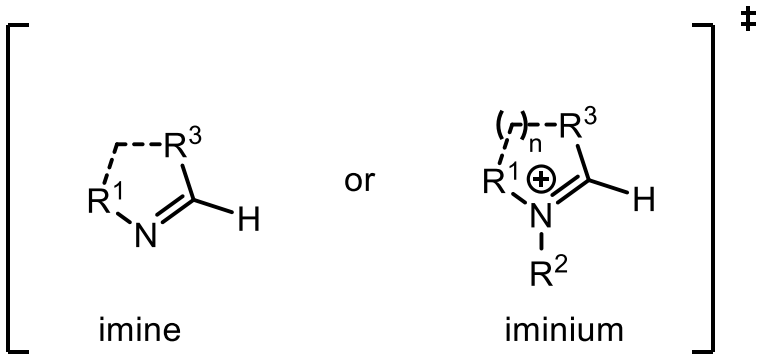


Reporter: Zhen Wang
Supervisor: Yong Huang
Date: 2016-09-26

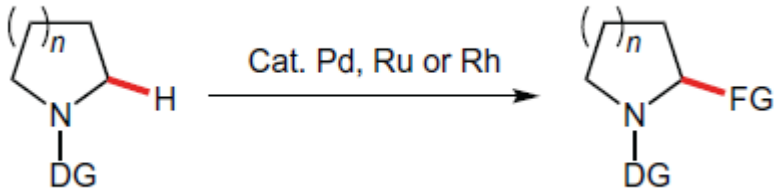
α-selective Functionalization

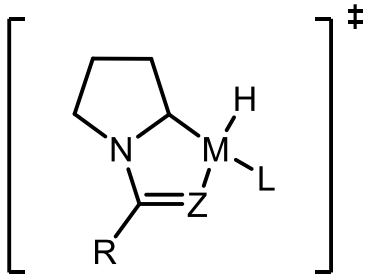
(i)



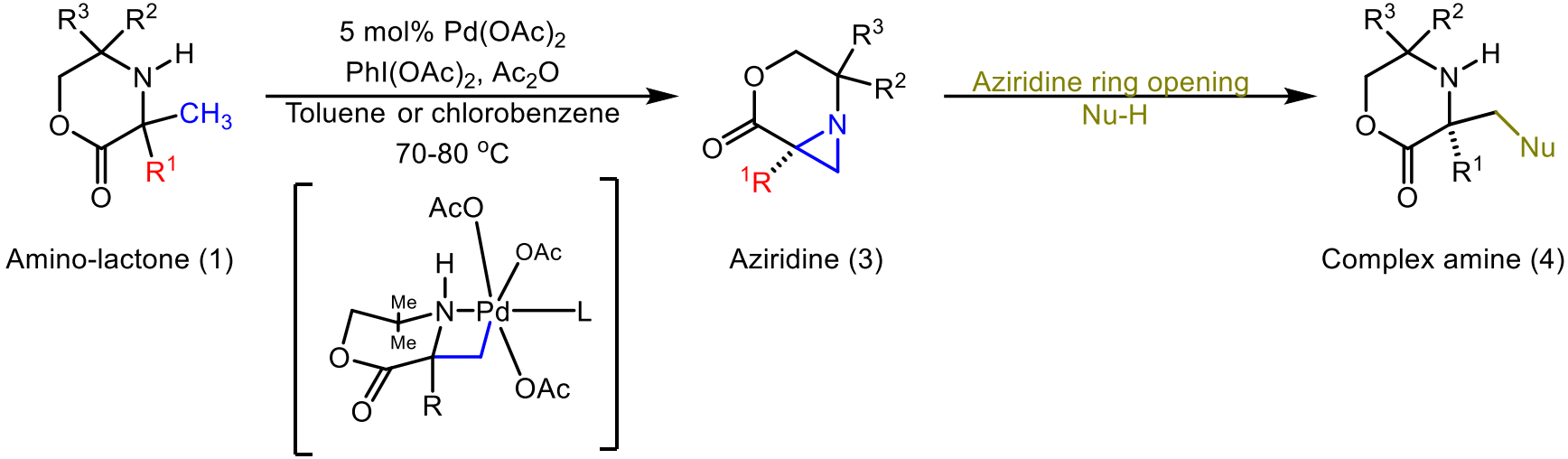


(ii)



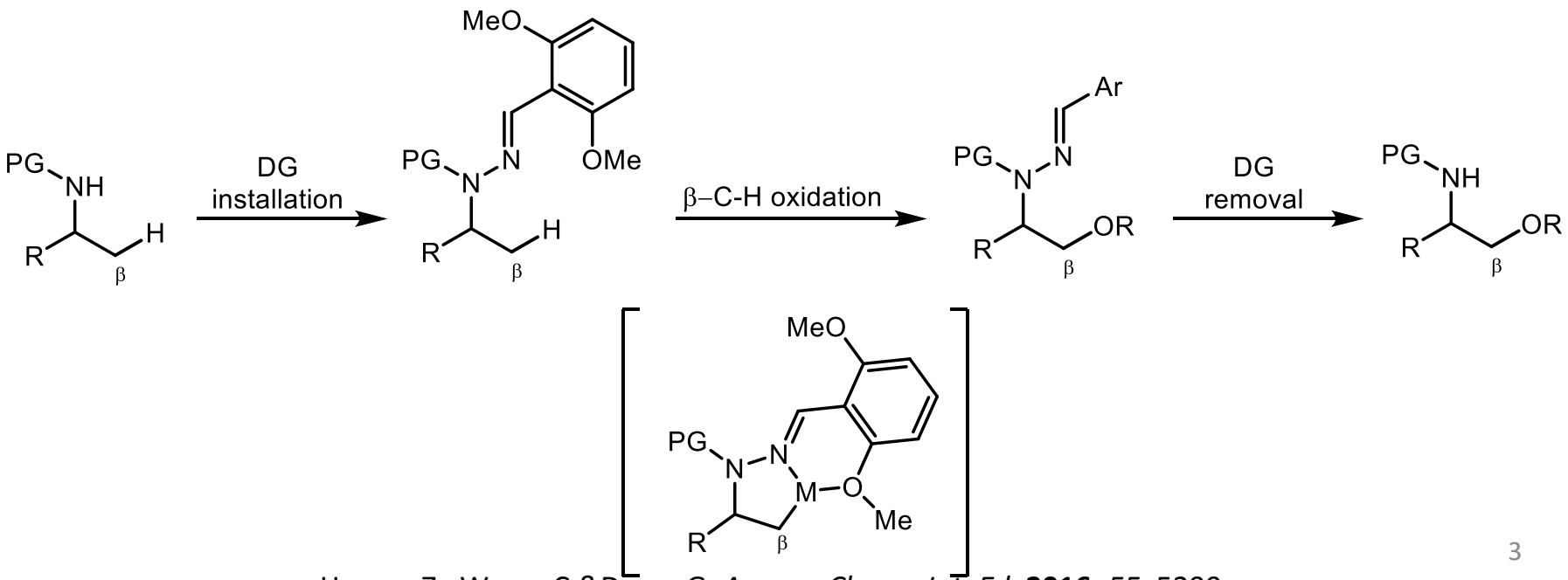


β-selective Functionalization



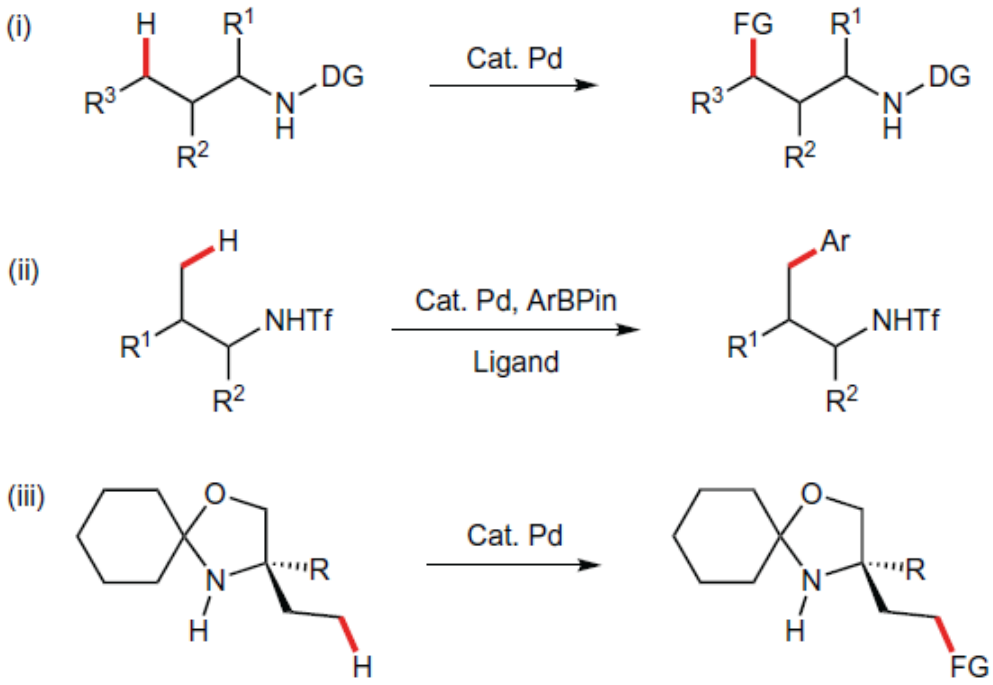
Amino-lactone (1) | Aziridine (3) | Complex amine (4)

McNally, A., Haffemayer, B., Collins, B. S. L. & Gaunt, M. J. *Nature* **2014**, *510*, 129.

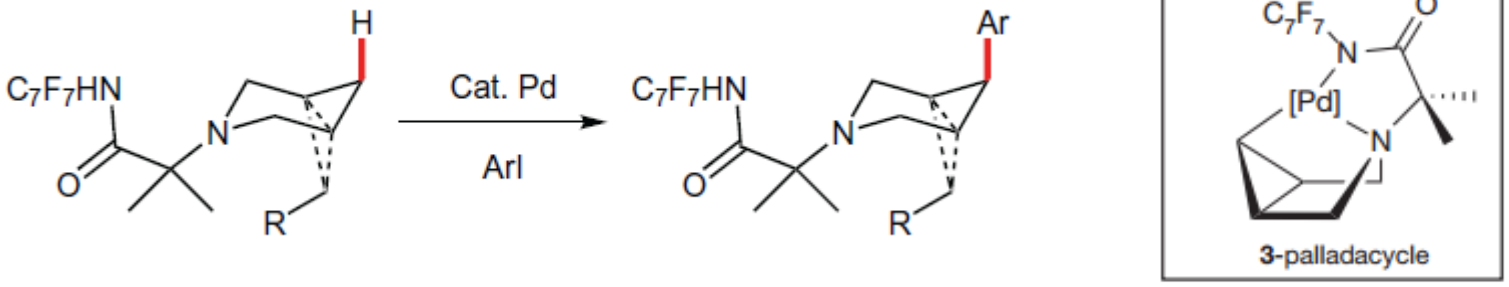


Huang, Z., Wang, C.&Dong, G. *Angew. Chem., Int. Ed*. **2016**, *55*, 5299.

γ-selective Functionalization

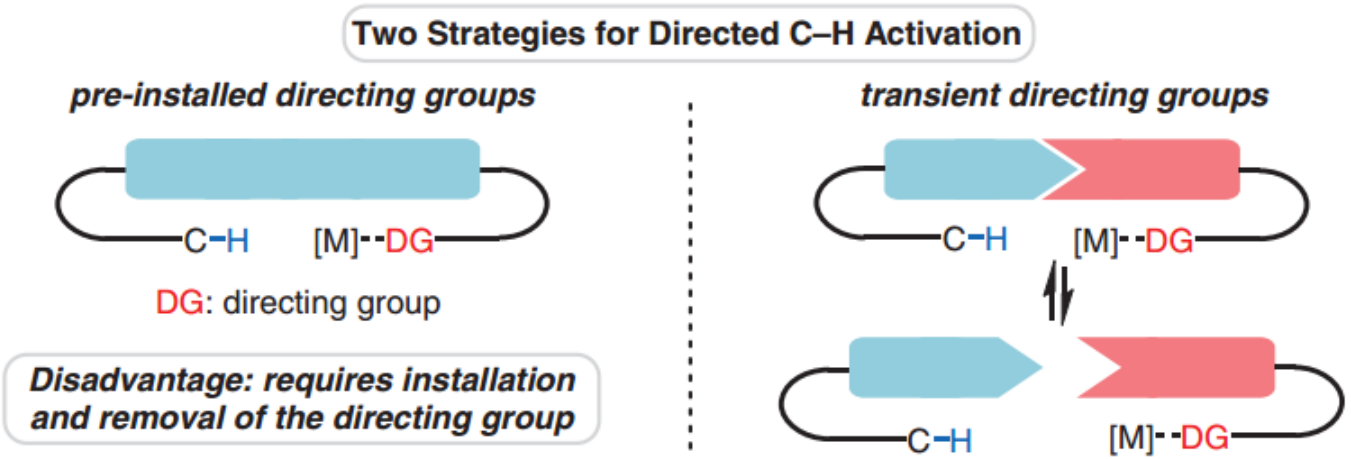


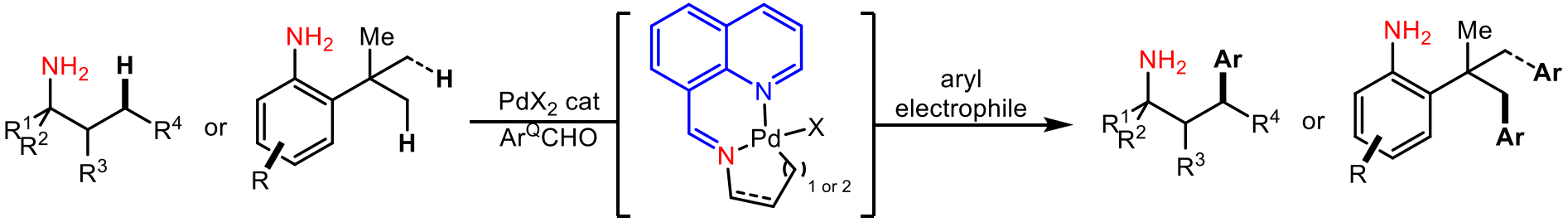
Calleja, J., Pla, D., Collins, B. S. L. & Gaunt, M. J. *Nat. Chem*. **2015**, *7*, 1009.



Topczewski, J. J., Cabrera, P. J., Saper, N. I. & Sanford, M. S. *Nature* **2016**, *531*, 220.

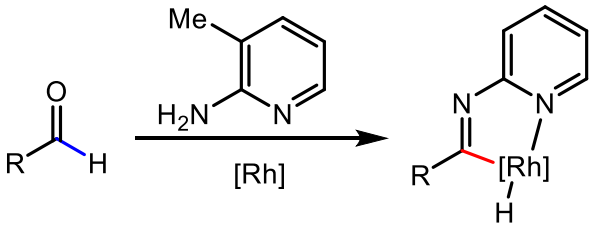
Transient Directing Group



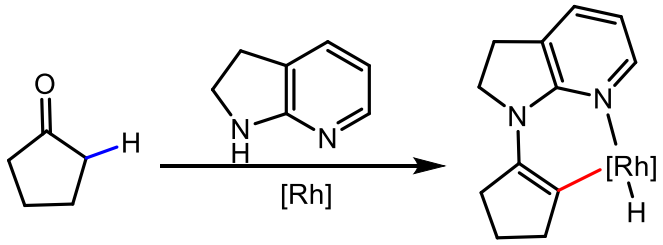


Xu, Y. Yong, M. C. Dong, G. *Angew. Chem., Int. Ed*. **2016**, *55*, 9084.

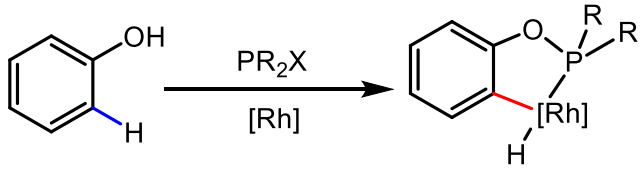
Catalytic Amount of Transient Directing Group



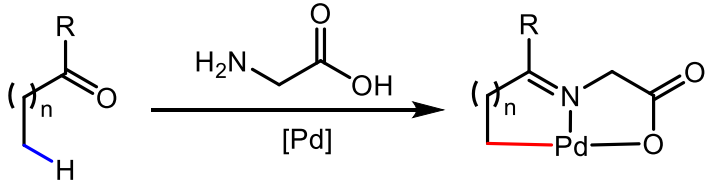
Jun(1997)



Dong(2014)



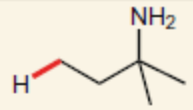
Beford(2003)



Yu(2016)

i) Jun, C.-H., Lee, H. & Hong, J.-B. *J. Org. Chem.* **1997**, *62*, 1200. ii) Mo, F., Dong, D. *Science* **2014,** *345*, 68.
iii) Bedford, R. B. *Angew. Chem., Int. Ed*. **2003**, *42*, 112. iv) Zhang, F.-L., Park, H. & Yu, J.-Q. Science **2016**, *351*, 252.

Reaction Condition Optimization

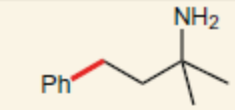


1a

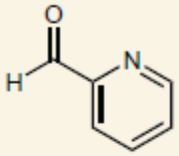
+ PhI

Pd (10 mol%), L (20 mol%)

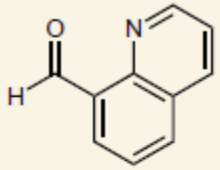
Additive (1.5 equiv.)
Solvent (0.15 M), air, 100 °C



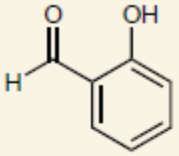
2a



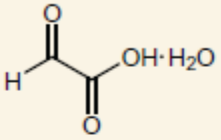
L1



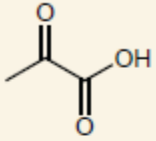
L2



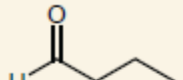
L3



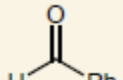
L4



L5



L6

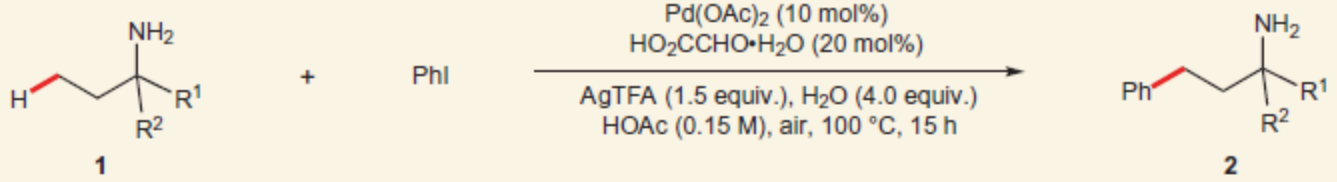


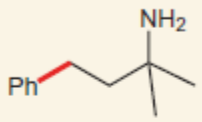
L7

Entry	Pd source	Ligand	Additive	Solvent	Yield (%)
1	$Pd(OAc)_2$	L1	AgTFA	HOAc	Trace
2	$Pd(OAc)_2$	L2	AgTFA	HOAc	Trace
3	$Pd(OAc)_2$	L3	AgTFA	HOAc	5
4	$Pd(OAc)_2$	L4	AgTFA	HOAc	72
5	$Pd(OAc)_2$	L5	AgTFA	HOAc	12
6	$Pd(OAc)_2$	L6	AgTFA	HOAc	Trace
7	$Pd(OAc)_2$	L7	AgTFA	HOAc	Trace
8	$Pd(OAc)_2$	-	AgTFA	HOAc	10
9	$Pd(OAc)_2$	L4	AgTFA	TFE	5
10	$Pd(OAc)_2$	L4	AgTFA	HFIP	20
11	$Pd(OAc)_2$	L4	AgTFA	^{t}BuOH	Trace
12	$Pd(TFA)_2$	L4	AgTFA	HOAc	70
13	$Pd(OPiv)_2$	L4	AgTFA	HOAc	67
14	$Pd(acac)_2$	L4	AgTFA	HOAc	62
15	$PdCl_2$	L4	AgTFA	HOAc	55
16	$Pd(OAc)_2$	L4	AgOAc	HOAc	46
17	$Pd(OAc)_2$	L4	Ag_2CO_3	HOAc	50
18	$Pd(OAc)_2$	L4	Ag_2O	HOAc	47
19	$Pd(OAc)_2$	L4	-	HOAc	0
20*	$Pd(OAc)_2$	L4	AgTFA	HOAc	80(74)†
21*,‡	$Pd(OAc)_2$	L4	AgTFA	HOAc	78

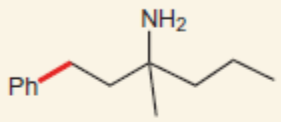
Reaction conditions: 1a (0.30 mmol), iodobenzene (0.45 mmol), Pd source (0.03 mmol), ligand (0.06 mmol), additive (0.45 mmol), solvent (2 ml), 100 °C, air, 15 h. Yields are based on 1a, determined by ^{1}H-NMR using dibromomethane as internal standard. *Reaction performed with H_2O (1.2 mmol); †Isolated yield; ‡Reaction carried out under N_2; Ph, phenyl; Ac, acetyl; TFA, trifluoroacetate; Piv, pivaloy; acac, acetylacetonate; TFE, 2,2,2-trifluoroethanol; HFIP, hexafluoroisopropanol; ^{t}Bu, *tert*-butyl.

Substrate Scope of Alkylamines

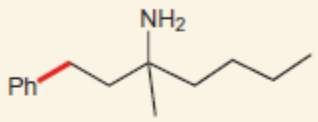




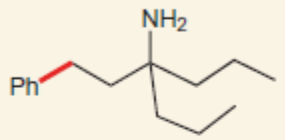
2a, 74%



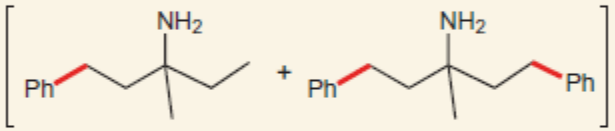
2b, 63%



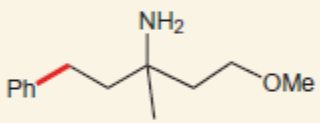
2c, 66%



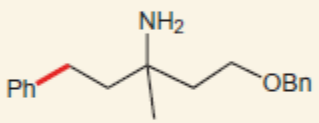
2d, 60%



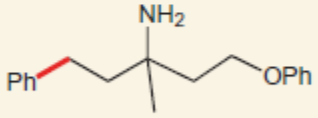
2e, 72% (mono: **2e1**, di: **2e2**, **2e1**/**2e2** = 1/0.43)



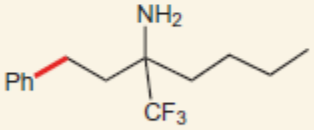
2f, 64%



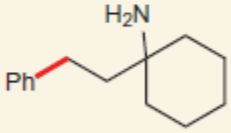
2g, 62%*



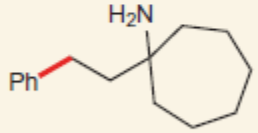
2h, 71%*



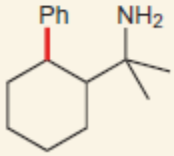
2i, 61%



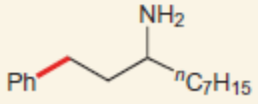
2j, 55%



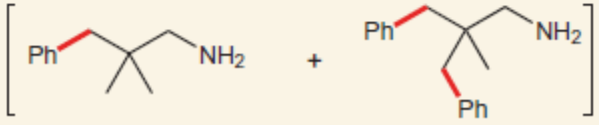
2k, 62%



2l, 23%†
cis isomer, d.r. > 20/1



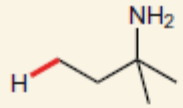
2m, trace‡



2n, 48% (mono: **2n1**, di: **2n2**, **2n1**/**2n2** = 1/0.65)§

Reaction conditions: amine **1** (0.30 mmol), iodobenzene (0.45 mmol), $Pd(OAc)_2$ (0.03 mmol), ligand (0.06 mmol), AgTFA (0.45 mmol), HOAc (2 ml), 100 °C, air, 15 h. Isolated yields based on **1**; *^{1}H-NMR yield of **2** in a mixture with starting material (see Supplementary section 'Analytical data of products'); †Unreacted substrate (60%) was determined by crude ^{1}H-NMR; ‡Unreacted substrate (76%) and 3-decanone (14%) were determined by crude ^{1}H-NMR; §Yield and selectivity were determined by crude ^{1}H-NMR. Bn, benzyl; ^{n}C_7H_{15}, heptyl.

Substrate Scope of Aryl Iodides

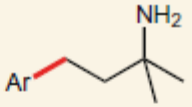


1a

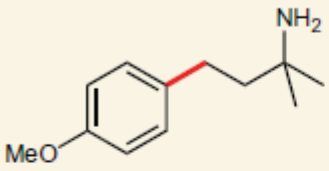
\+ ArI

$Pd(OAc)_2$ (10 mol%)
$HO_2CCHO \cdot H_2O$ (20 mol%)

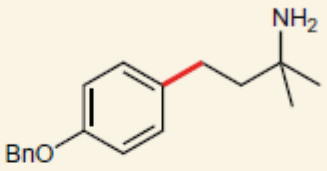
AgTFA (1.5 equiv.), H_2O (4.0 equiv.)
HOAc (0.15 M), air, 100 °C, 15 h



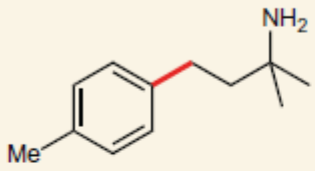
3



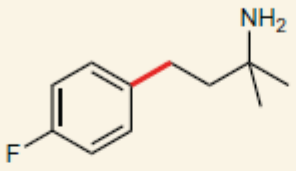
3a, 61%



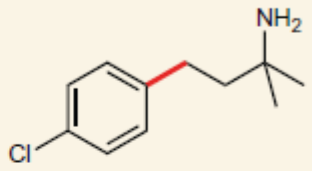
3b, 57%



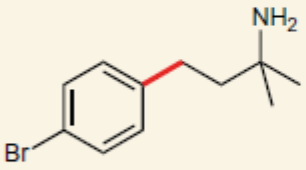
3c, 68%



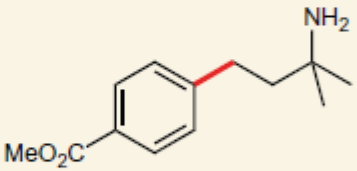
3d, 66%



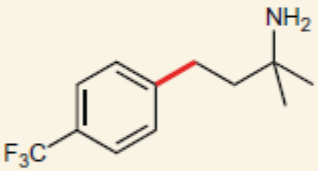
3e, 70%



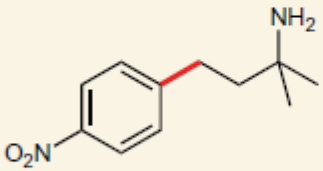
3f, 70%



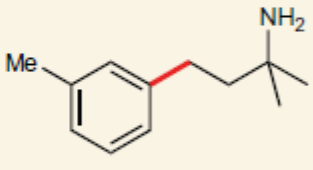
3g, 60%*



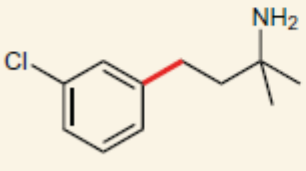
3h, 73%



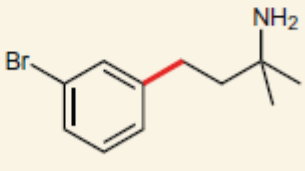
3i, 56%*



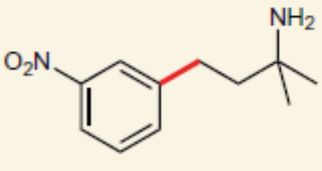
3j, 71%



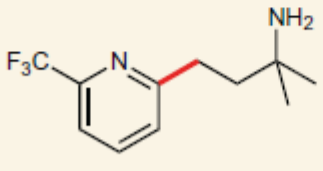
3k, 64%



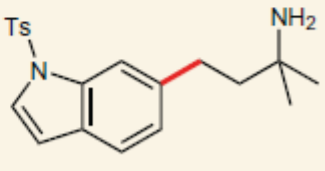
3l, 66%



3m, 64%



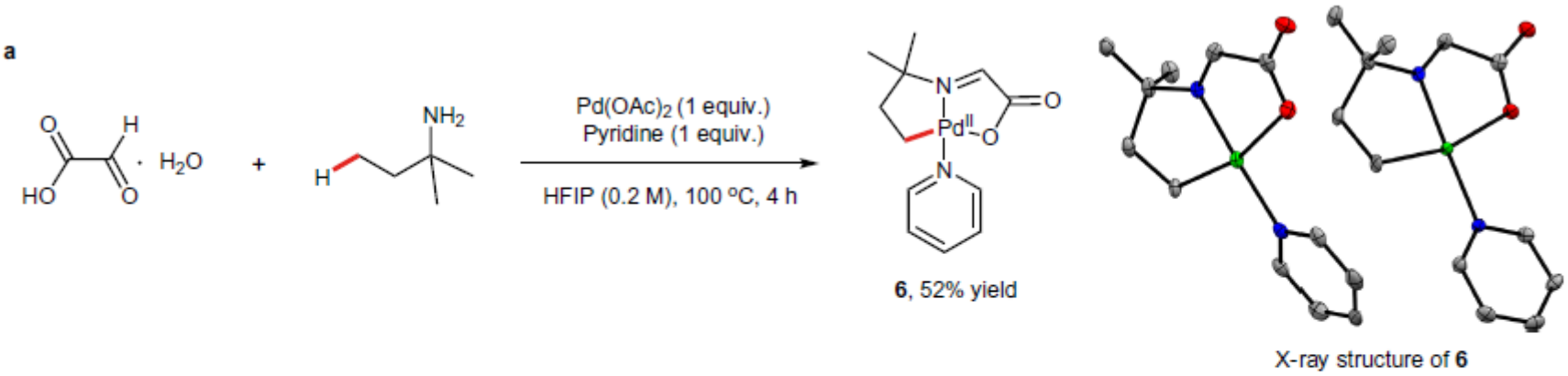
3n, 72%



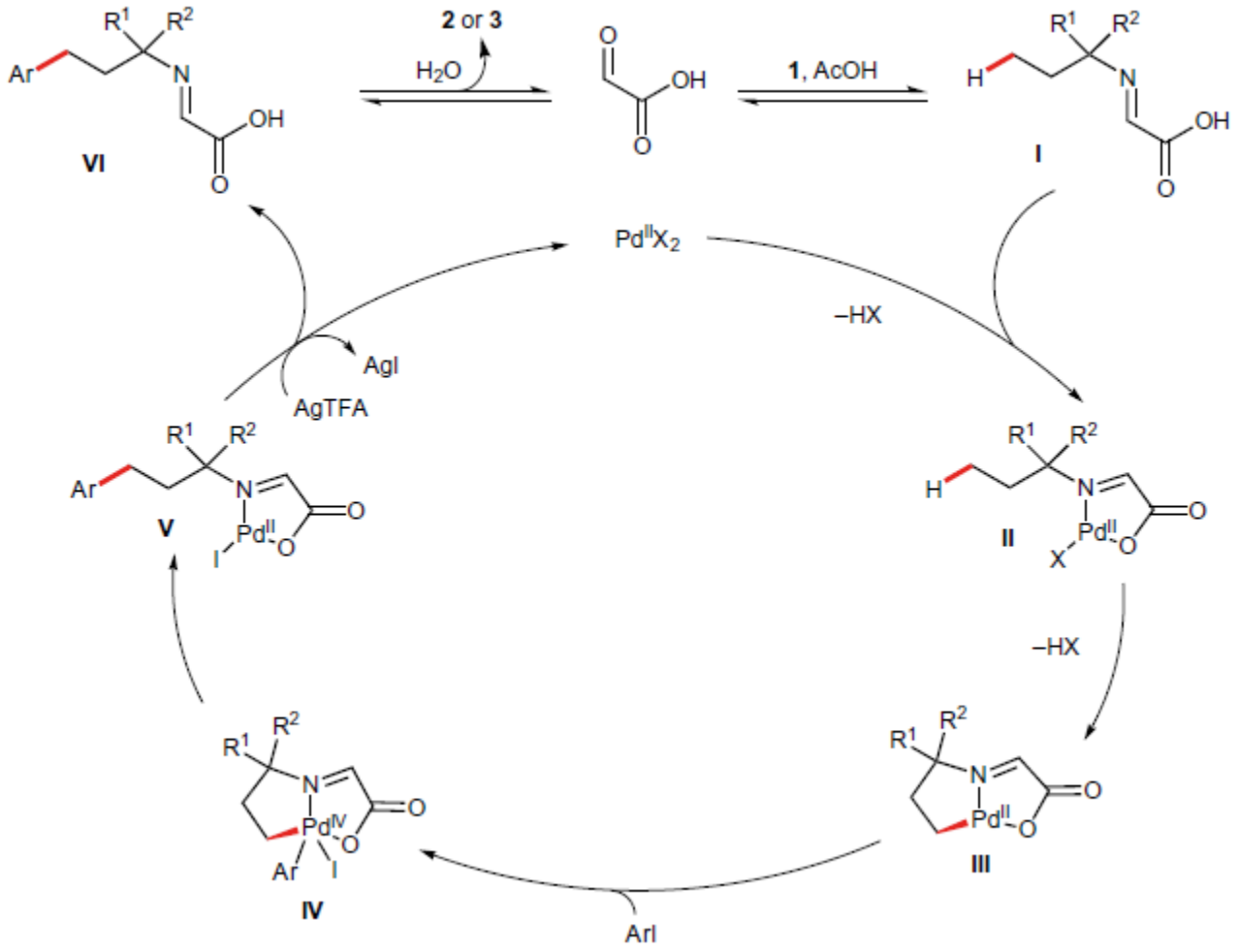
3o, 42%

Reaction conditions: amine 1a (0.30 mmol), ArI (0.45 mmol), $Pd(OAc)_2$ (0.03 mmol), ligand (0.06 mmol), AgTFA (0.45 mmol), HOAc (2 ml), 100 °C, air, 15 h. Isolated yields based on 1a. *Reaction carried out without H_2O.

Insights into the Reaction Mechanism



Plausible Catalytic Cycle



Synthetic Applications

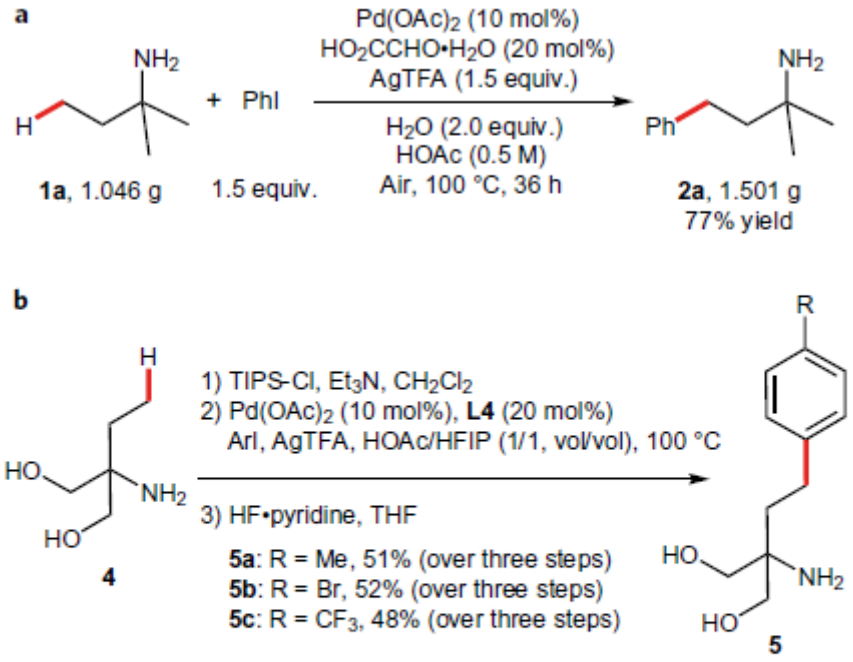


Figure 2 | Synthetic applications of palladium-catalysed arylation of alkylamines. a, Gram-scale synthesis of 2-methyl-4-phenylbutan-2-amine (2a). **b**, Synthesis of fingolimod analogues. The synthesis of analogues to fingolimod, a drug for treating multiple sclerosis, can be achieved in three steps from commercial reagents. TIPS, triisopropylsilyl; Et, ethyl.

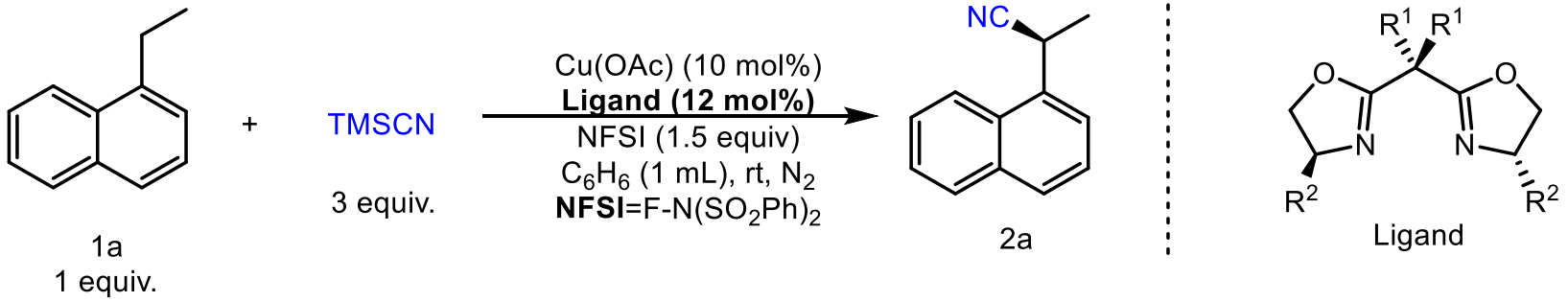
Summary

- Palladium-catalyzed direct arylation of primary aliphatic amines was achieved via an sp^3 C-H bond functionalization process with assistance of a catalytic directing group.
- This reaction has high site selectivity of γ-C-H bond of the methyl group
- This reaction has good functional group compatibility
- This reaction avoids the pro-installation and subsequent removal of a directing group.
- This reaction has broad applications in drug development and discovery processes

Science AAAS

Enantioselective cyanation of benzylic C–H bonds via copper-catalyzed radical relay

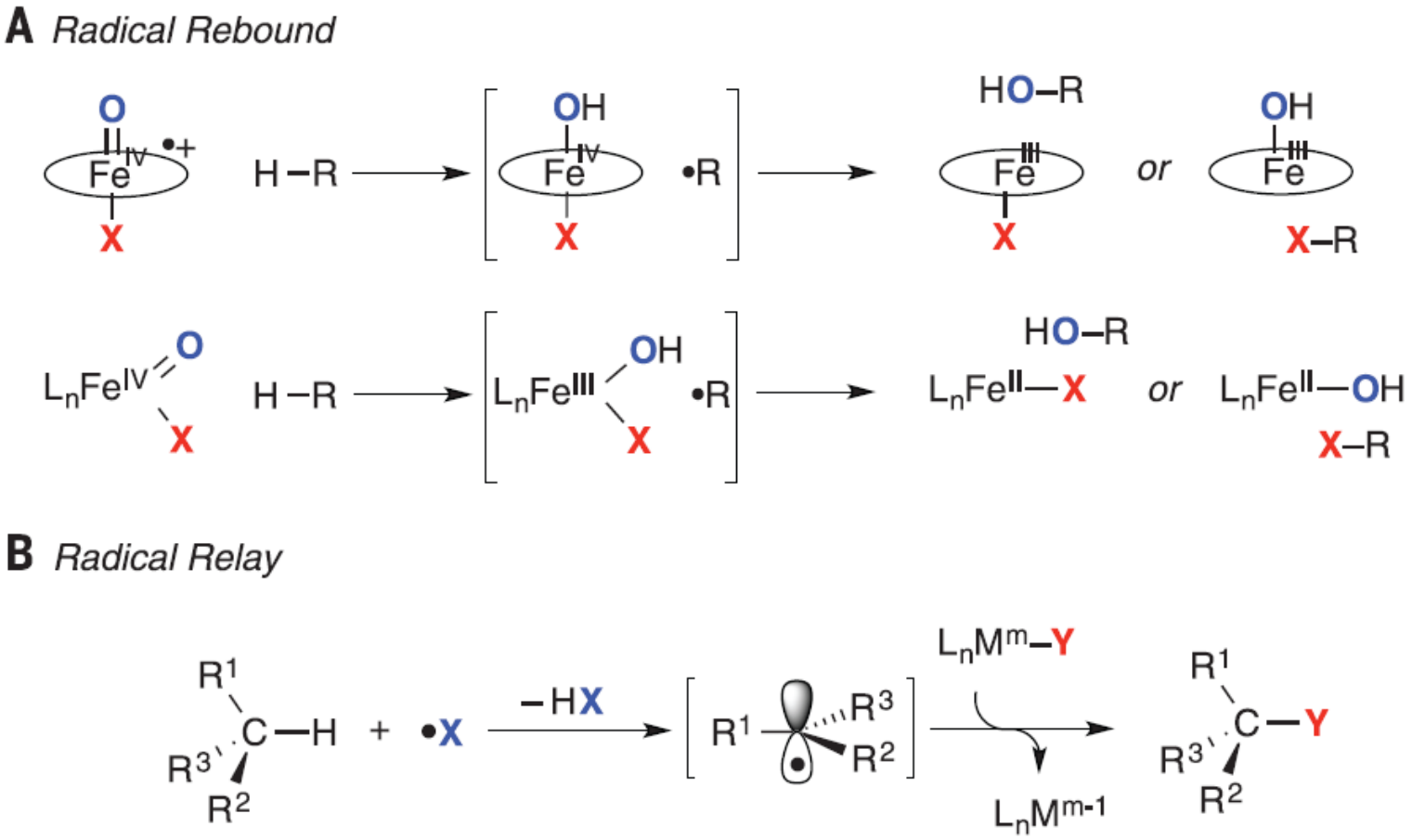
Wen Zhang,[1*] Fei Wang,[1*] Scott D. McCann,[2] Dinghai Wang,[1] Pinhong Chen,[1] Shannon S. Stahl,[2†] Guosheng Liu[1†]



Reporter: Zhen Wang
Supervisor: Yong Huang
Date: 2016-09-26

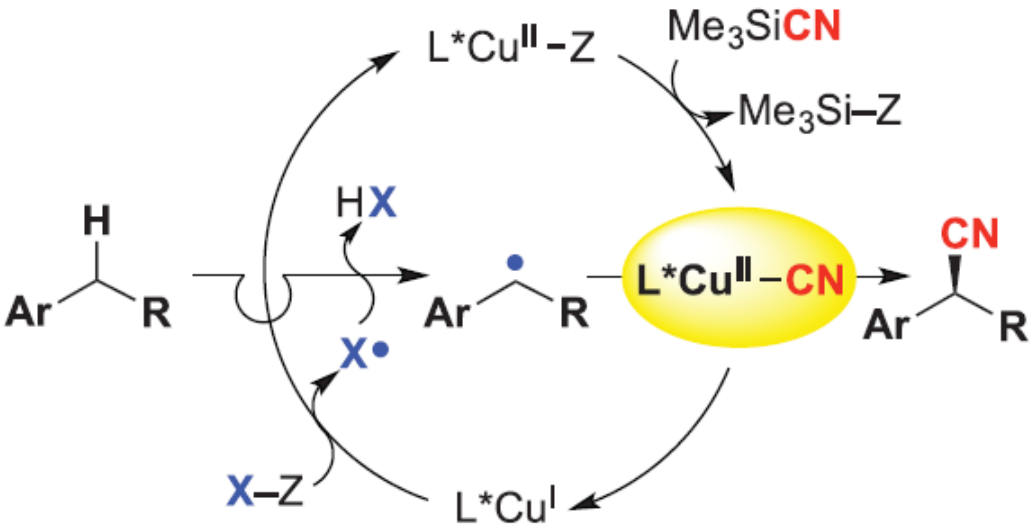
W. Zhang, F. Wang, S. S. Stahl & G. Liu, *Science* **353**, 1014-1018 (2016).

Strategies for Hydrogen-atom-transfer-mediated C-H Oxidation

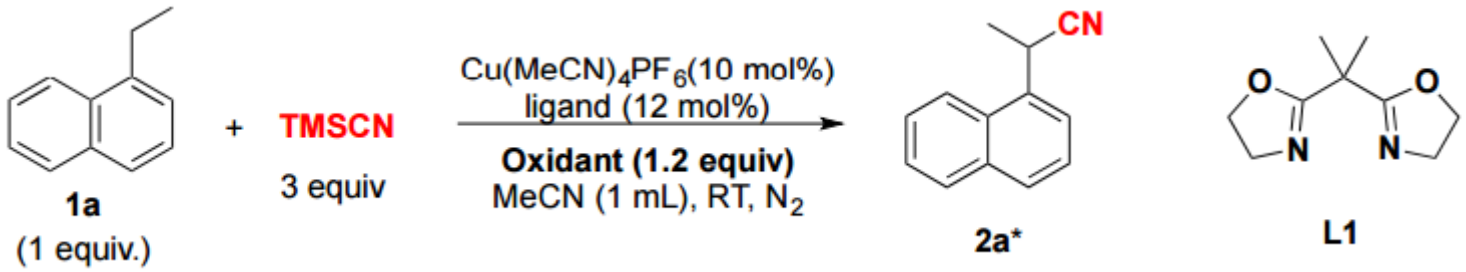


Radical Relay Pathway

C ***Cu-Catalyzed Enantioselective C–H Cyanation via Radical Relay***

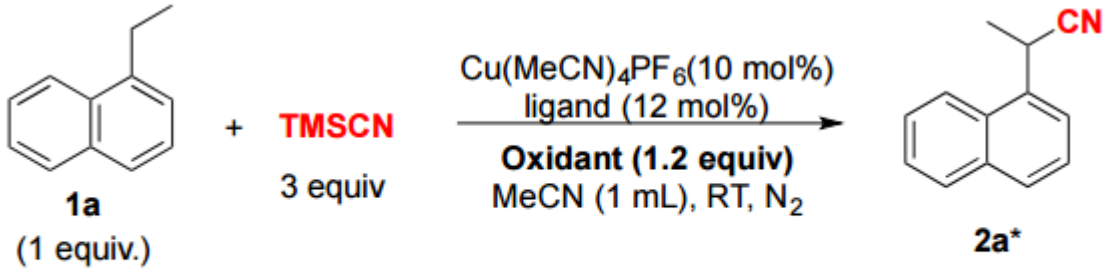


Screen Oxidants "X-Z"



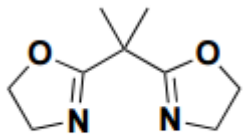
Entry	Oxidant	Ligand	Conversion of **1a**	Yield of **2a**
1	$(^tBuO)_2$	**L1**	2%	0
2	^tBuONO	**L1**	3%	0
3	^tBuOOH	**L1**	5%	0
4	$(BzO)_2$	**L1**	12%	0
5	$PhCO_3{}^tBu$	**L1**	1%	0
6	$K_2S_2O_8$	**L1**	2%	0
7	Oxone	**L1**	11%	0
8	$PhI(OAc)_2$	**L1**	1%	0
9	PhIO	**L1**	9%	0
10	SelectFluor	**L1**	3%	0
11	NFSI	**L1**	9%	7%

Screen Ligands and Solvents

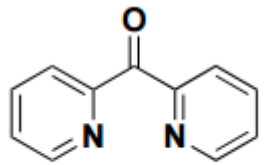


Entry	Oxidant	Ligand	Conversion of **1a**	Yield of **2a**
12	NFSI	**dpk**	21%	4%
13	NFSI	**Bpy**	1%	0
14	NFSI	**Phen**	2%	0
15	NFSI	**4,4-^{t}BuBpy**	9%	0
16	NFSI	**dpck**	15%	2%
17	NFSI	**TerPy**	1%	0
18†	NFSI	**dpk**	5%	3%
19‡	NFSI	**dpk**	7%	6%
20‡	NFSI	**L1**	14%	10%
21§	NFSI	**dpk**	19%	12%
22‖	NFSI	**dpk**	41%	23%
23§,‖	NFSI	**L1**	63%	40%
24‡,¶	NFSI	**L1**	29%	25%
25§,¶	NFSI	**L1**	62%	43%
26§,**	NFSI	**L1**	93%	73%

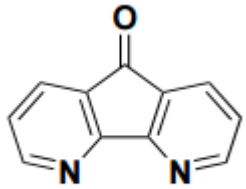
†dichloromethane (DCM) as solvent. ‡PhCl as solvent.
§benzene as solvent. ‖reaction at 40 °C. ¶CuOAc as catalyst. **CuF_2 as catalyst.



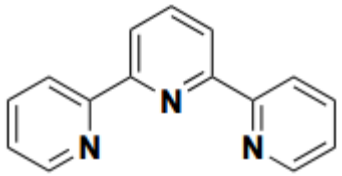
L1



dpk

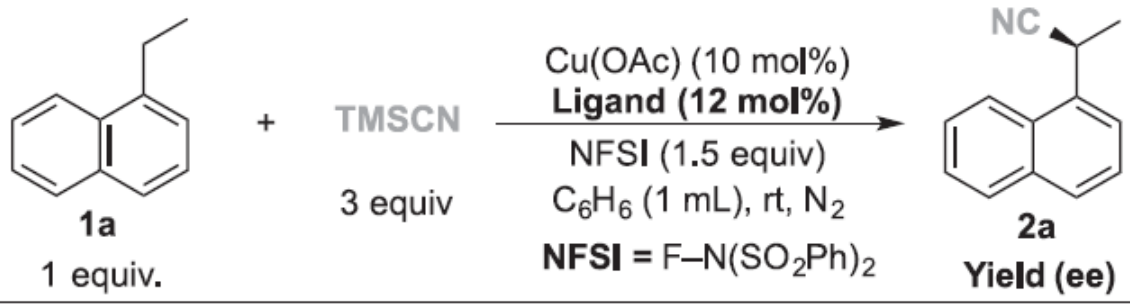


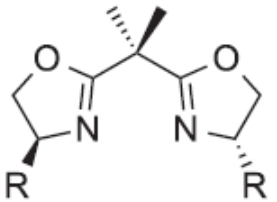
dpck



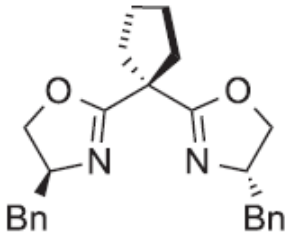
TerPy

Chiral Ligands

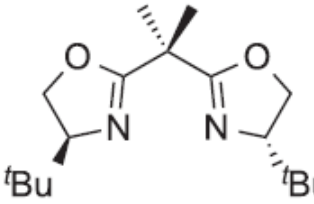




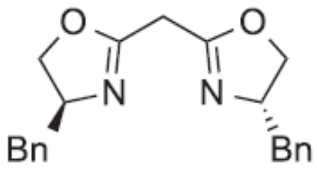
L1 R = H: 25% (N/A)*
L2 R= Bn: 91% (96% ee)



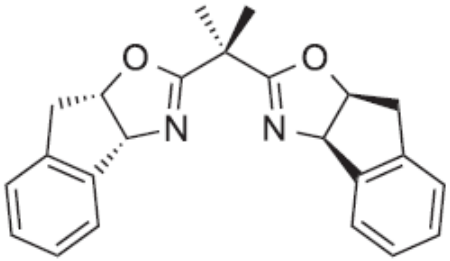
L3: 84% (95% ee)



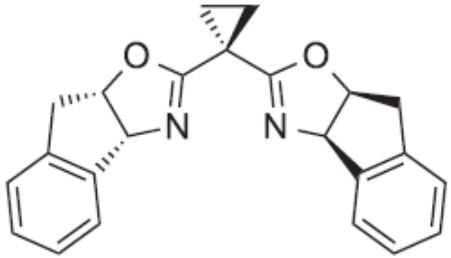
L4: 6% (15% ee)*



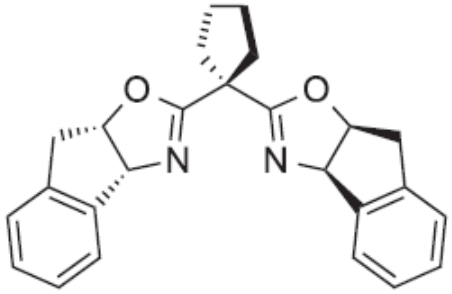
L5: trace*



L6: 53% (-97% ee)*



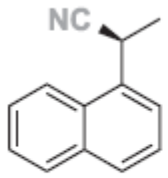
L7: 37% (-88% ee)*



L8: 71% (-97% ee)

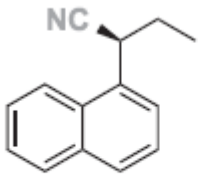
Substrate Scope: Alkyl Naphthalenes

(i) alkyl naphthalenes



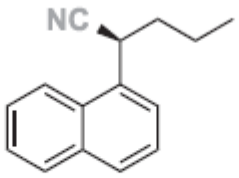
2a

71%, -97% ee (**L8**)
91%, 96% ee (**L2**)



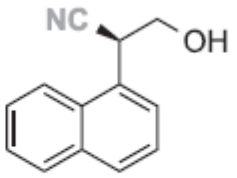
2b

72%, 97% ee (**L3**)



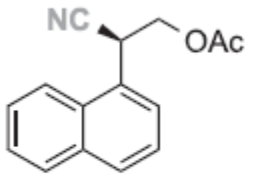
2c

81%, 96% ee (**L2**)
80% (1.34 g), 96% ee (L2)†



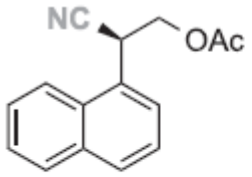
2d

42%, 95% ee **(L3)**



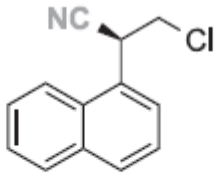
2e

87%, -99% ee (**L8**)
83%, 92% ee (**L2**)†



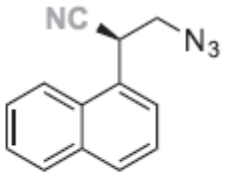
2e

87%, -99% ee (**L8**)
83%, 92% ee (**L2**)†



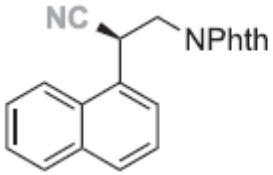
2f

72%, 98% ee (**L2**)†



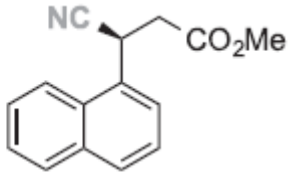
2g

73%, 97% ee (**L2**)



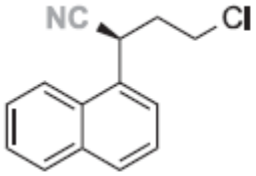
2h

60%, -98% ee (**L8**)
71% (4.62 g), -94% ee (L8)†



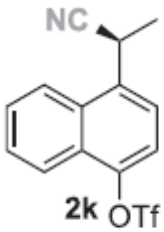
2i

67%, -99% ee (**L8**)
85%, 96% ee (**L3**)

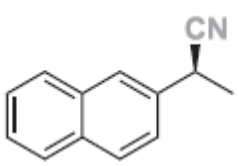


2j

65%, 98% ee (**L3**)

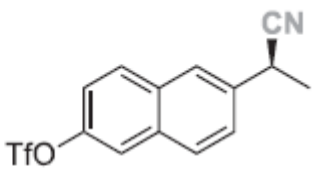


91%, -99% ee (**L8**)



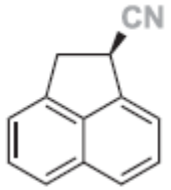
2l

65%,-95% ee (**L8**)



2m

80%, -91% ee (**L8**)

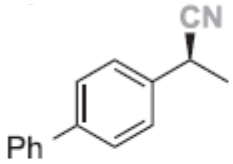


2n

55%, 79% ee (**L2**)

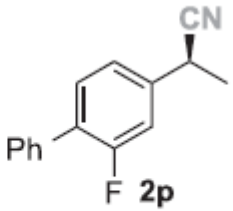
Substrate Scope: Alkyl Arenes

(ii) alkyl arenes



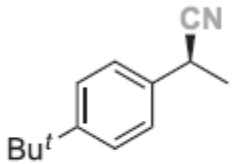
2o

61%, -93% ee (**L8**)
80%, 88% ee (**L3**)



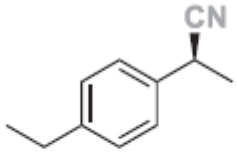
2p

67%, 90% ee (**L2**)
85%, 87% ee (**L2**)†



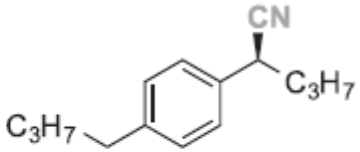
2q

60%, -91% ee (**L8**)
93%, 85% ee (**L2**)



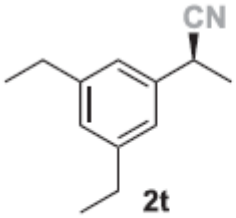
2r

76%, 84% ee (**L2**)†



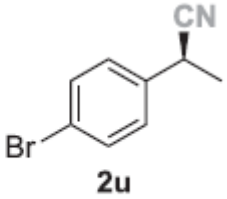
2s

72%, 84% ee (**L3**)



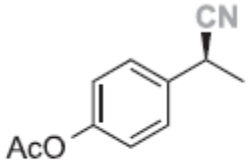
2t

70%, 84% ee (**L3**)



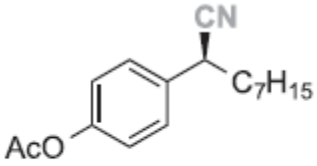
2u

46%, 90% ee (**L3**)



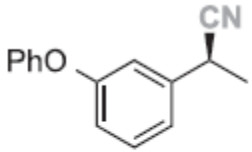
2v

62%, 90% ee (**L2**)
70%, 89% ee (**L2**)†



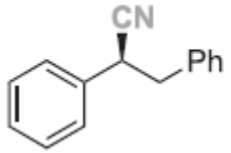
2w

42%, 91% ee (**L3**)



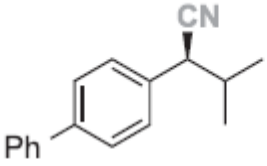
2x

52%, -90% ee (**L8**)



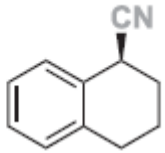
2y

62%, 94% ee (**L2**)



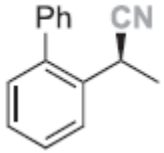
2z

85%, 96% ee (**L3**)†



3a

48%, -92% ee (**L8**)
61%, 86% ee (**L2**)

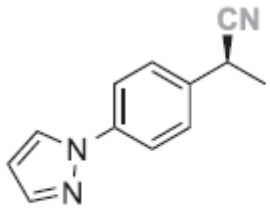


3b

39%, 95% ee (**L2**)

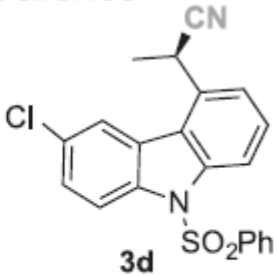
Substrate Scope: Heterocycle-containing Alkyl Arenes

(iii) heterocycle-containing alkyl arenes



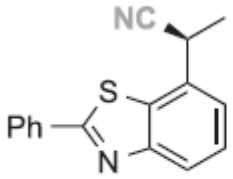
3c

59%, 90% ee (**L2**)
79%, 86% ee (**L2**)†



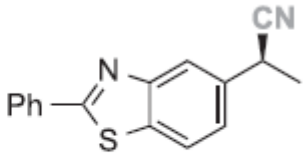
3d

76% (1.05 g), 98% ee (L2)



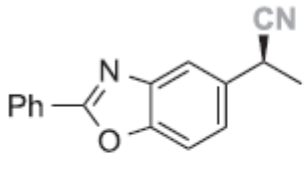
3e

80%, 96% ee (**L2**)



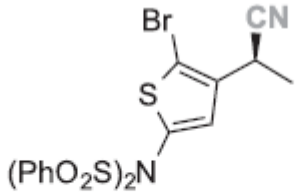
3f

89%, 83% ee,
92% ee‡ (**L2**)



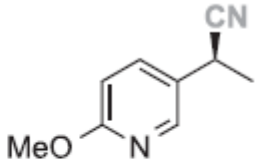
3g

50%, 75% ee (**L2**)



3h

79%, -94% ee (**L8**)
67% (5.16 g), -96% ee (L8)†



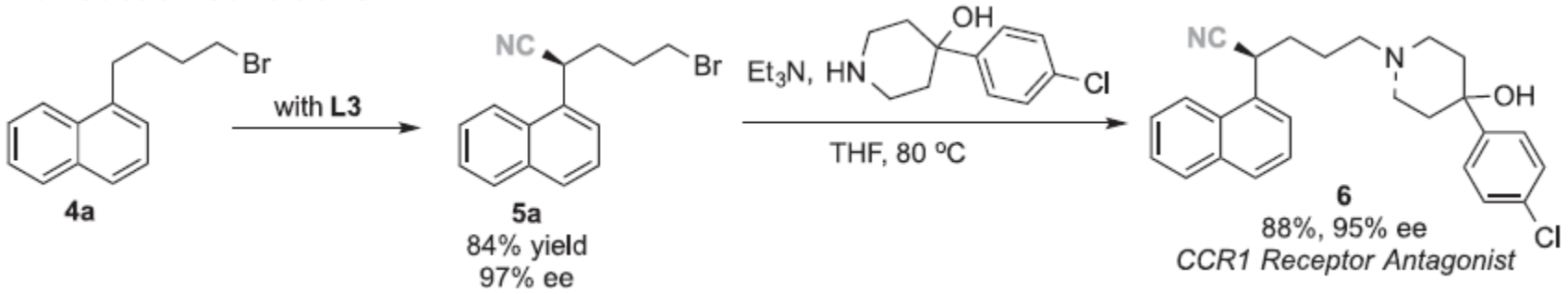
3i

39%, 80% ee (**L3**)

Synthetic Applications

B Synthetic Applications

(i) Mild reaction conditions

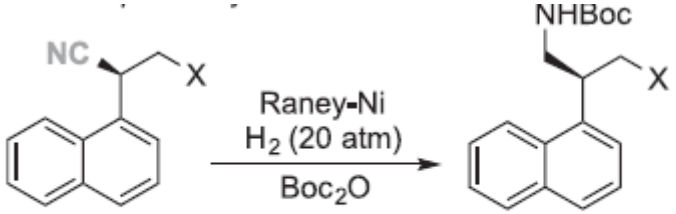


4a

5a
84% yield
97% ee

6
88%, 95% ee
CCR1 Receptor Antagonist

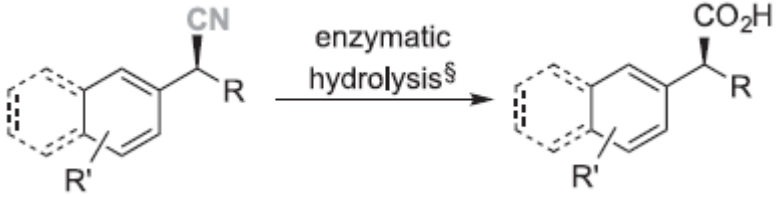
(ii) Nitrile hydrogenation: chiral phenethylamine derivatives



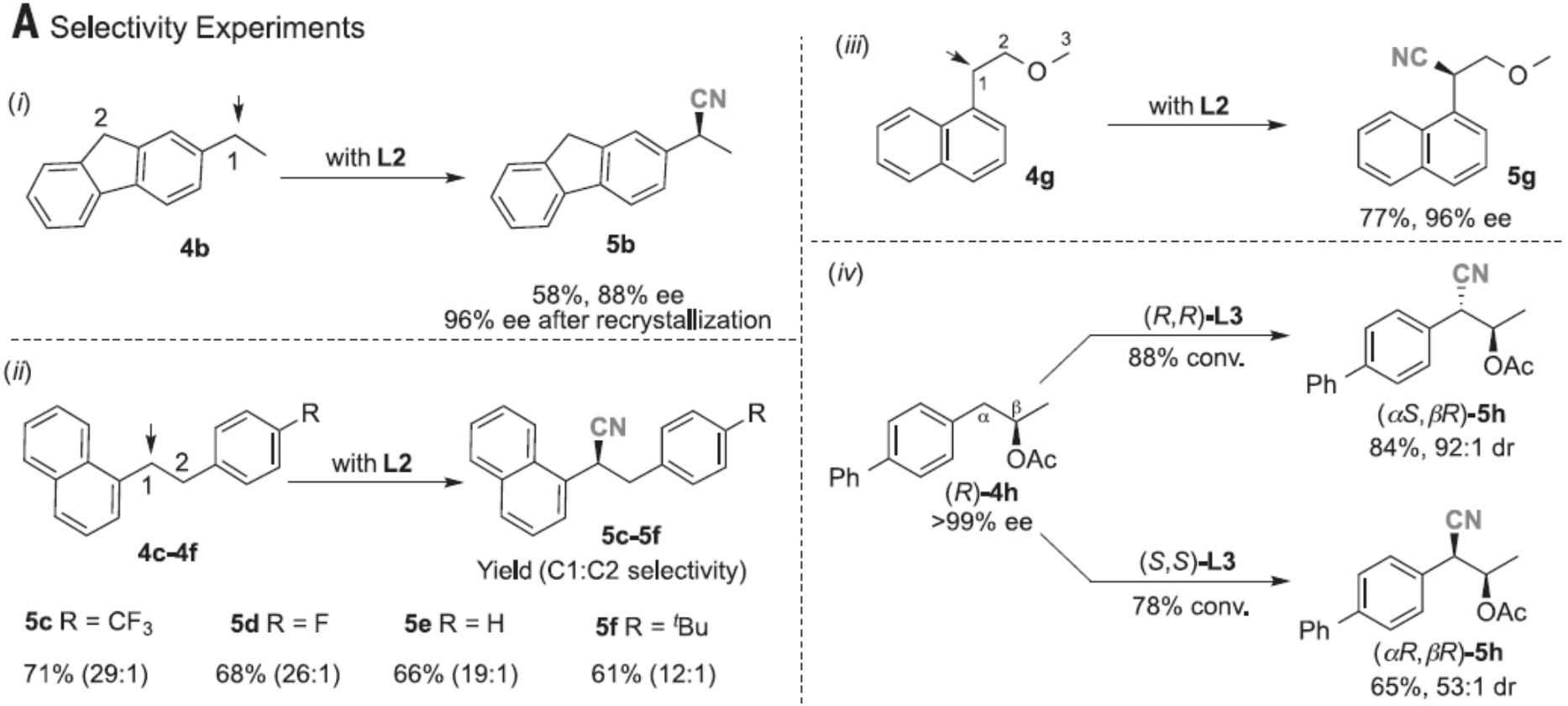
X = OH (**2d**) 95% ee
X = Nphth (**2h**) -98% ee

X = OH: 65%, 96% ee
X = Nphth: 71%, -98% ee

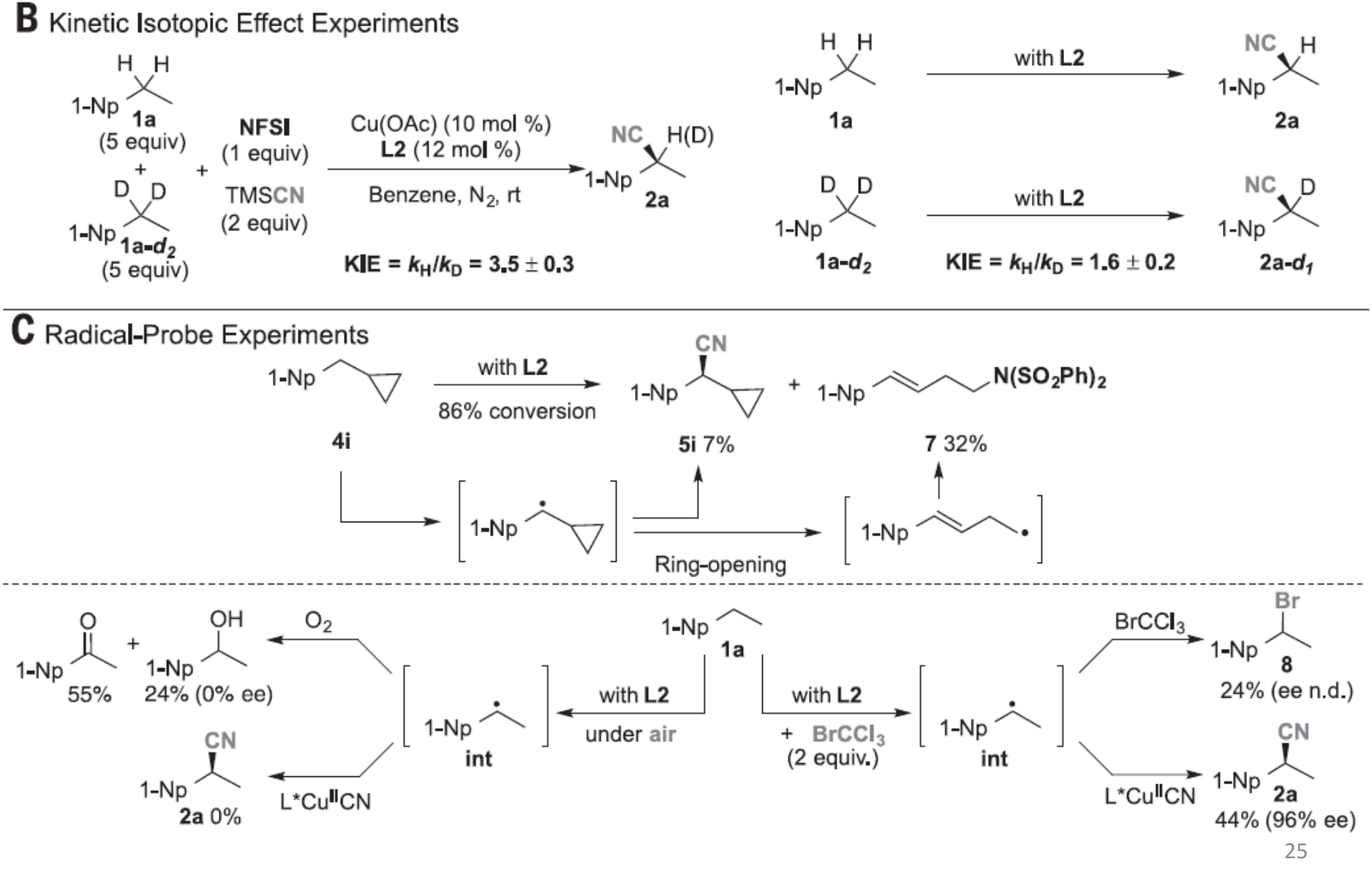
(iii) Nitrile hydrolysis: chiral arylacetic acid derivatives



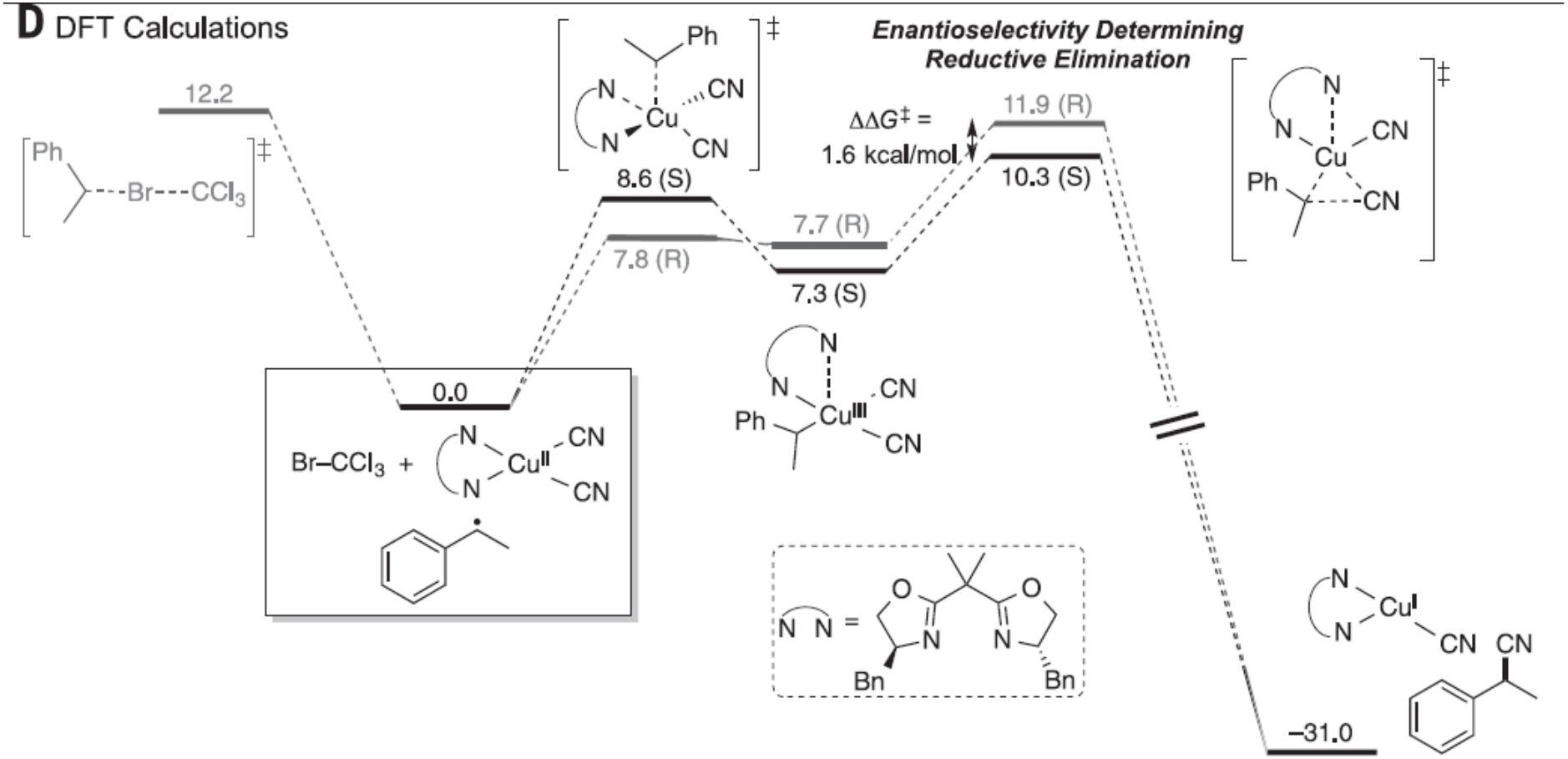
Selectivity Experiments



Kinetic Isotopic Effect and Radical-Probe



DFT Calculations



Summary

- This method represents a valuable demonstration of radical relay catalysis.
- This method has some advantages: mild reaction conditions, excellent enantio-selectivity, broad substrate scope and provide key foundations for other C-H oxidation reactions.
- The shortage of this method is the limiting C(sp^3)-H substrates.

Thank you for your attention!