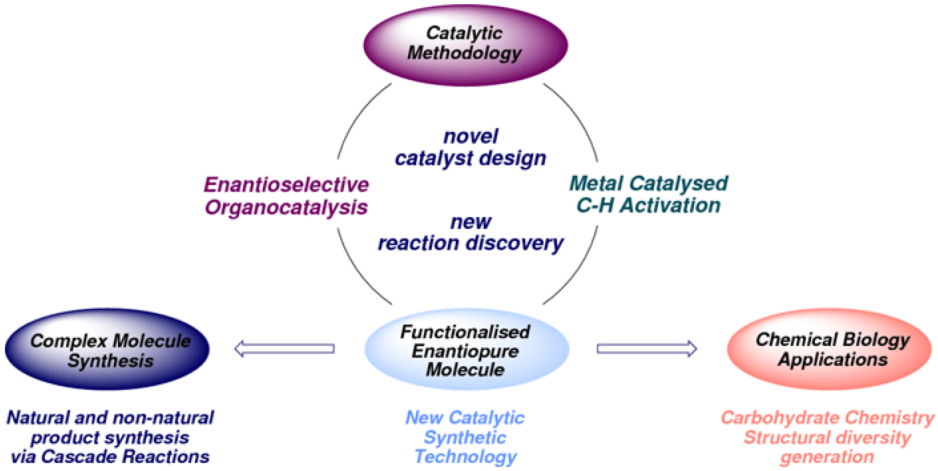
Matthew J. Gaunt Research Group

2012. 9. 24 (Mon.)
Keiichi KANEKO (M2)

0. Introduction

Biography

1995 graduated from the University of Birmingham.
1999 moved to the University of Cambridge to carry out his graduate studies, and finished.
he was awarded a prestigious GlaxoWellcome Postdoctoral Fellowship.
2001 returned to the UK to work with Professer Steven Ley as a Junior Research Fellow at Magdalene College.
2003 began his independent research career in October at the University of Cambridge.
2004 and awarded a Royal Society University Research Fellow in October.
2006 he was appointed Lecturer in Organic Chemistry, and a Philip & Patricia Brown Next Generation Fellow.



They are actively pursuing research programmes in the following areas

- **Enantioselective Organocatalysis**
- **Transition Metal Catalysed C-H Activation**
- **Cascade Reactions for Complex Natural Product Synthesis**
- **Chemical Biology**

Contents

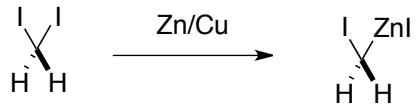
1.1 An Organocatalytic Cyclopropanation Reaction

[Background]

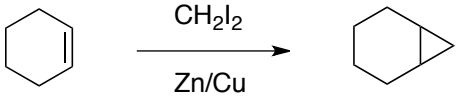
The cyclopropane motif is a common feature in the synthesis of complex molecules and in medicinal chemistry owing to a unique combination of reactivity and structural properties

1958

The formation of Simmons-Smith reagent

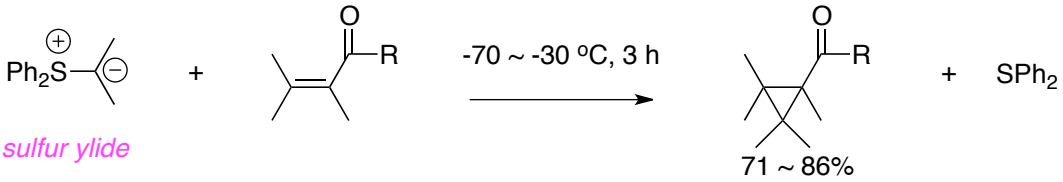


Simmons-Smith reaction



1967

E. J. Corey, *JACS*, **1967**, *89*, 3912.



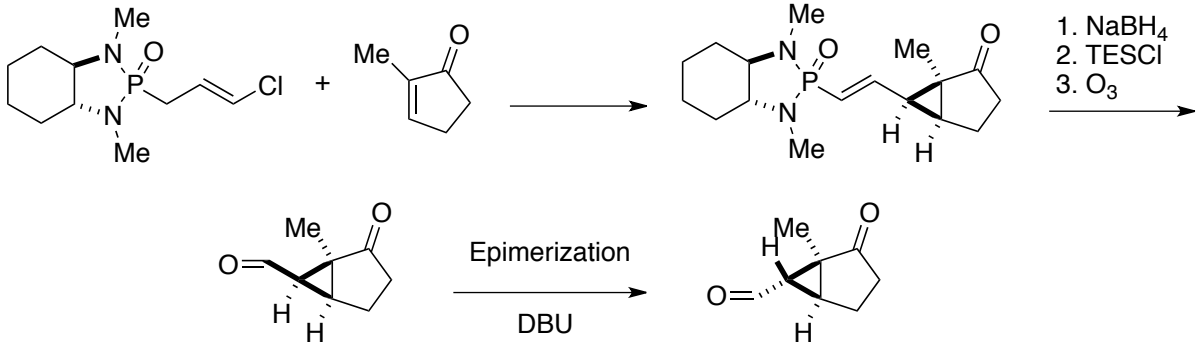
sulfur ylide

71 ~ 86%

⇨ There are comparatively few methods for synthesis of enantiomerically pure tri- and tetrasubstituted cyclopropanes.

1995

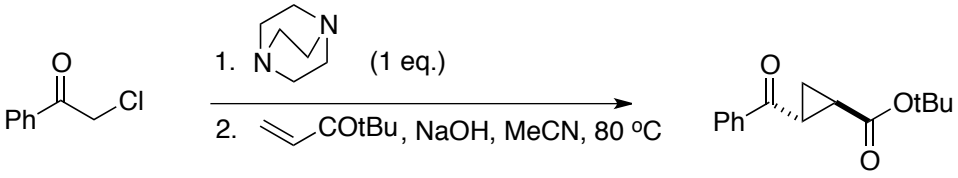
S. Hanessian, *JACS*, **1995**, *117*, 10393.



M. J. Gaunt's works

2003 Stoichiometric "one-pot" ammonium ylide based cyclopropanation

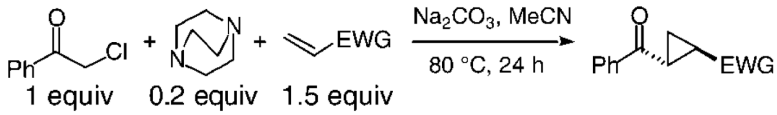
M. J. Gaunt, *ACIE*, **2003**, *42*, 828.



single diastereoisomer

The reaction proceeds without the formation of byproducts, and simple aqueous workup affords pure cyclopropane that does not neessarily require further purification.

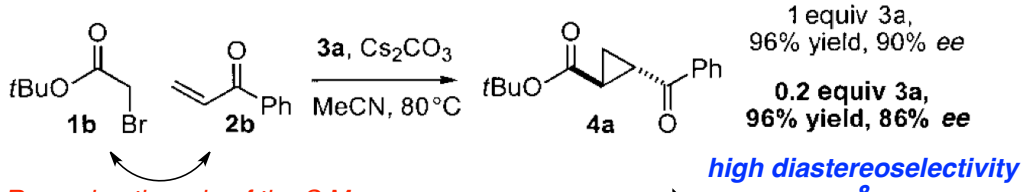
Catalytic cyclopropanation

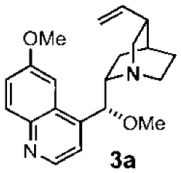


high diastereoselectivity

Enantioselective Organocatalytic Cyclopropanation

M. J. Gaunt, *ACIE*, **2004**, *43*, 4641.





Reversing the role of the S.M

high diastereoselectivity
&
high enantioselectivity

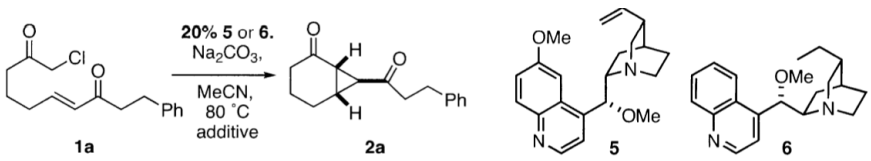
This enantioselective catalytic cyclopropanation process via ammonium ylides has a number of advantages.

1) There are no transtion metals involved in the reaction.
2) The starting materials are readily available and conveniently handled.

This is the first general intermolecular enantioselective organocatalytic cyclopropanation reaction.

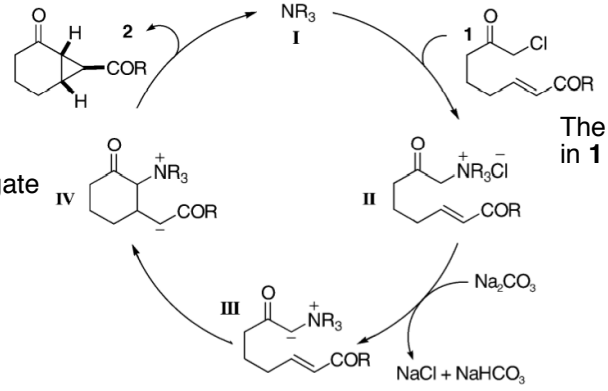
• *Intramolecular Cyclization*

M. J. Gaunt, *ACIE*, **2004**, *43*, 2681.



[Catalytic cycle]

Finally the bicycloalkane **2** is generated through displacement of the ammonium group, concurrently regenerating catalyst **I**.



The amine catalyst **I** displaces the chloride in **1** to give the quaternary ammonium salt **II**.

Intramolecular conjugate addition forms **IV**.

Deprotonation forms the ammonium ylide **III**.

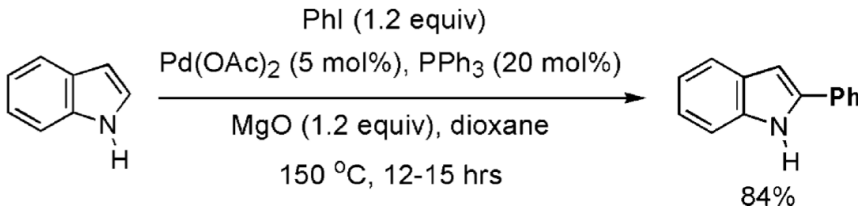
Small Summary

They have developed an organocatalytic inter- and intramolecular cyclopropanation reaction as single diastereoisomers. This powerful catalytic process effects the controlled formation of stereocenters in single transformation.

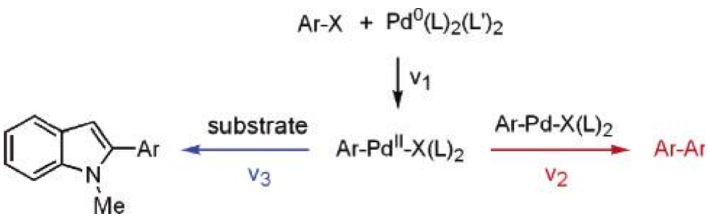
2.1 Palladium-Catalyzed Intermolecular Arylation of Indoles

Selective C-2 Arylation of (NH)-Indole

D. Sames, *JACS*, **2005**, *127*, 8050.
D. Sames, *OL*, **2004**, *6*, 2897.



i) The Key Reaction Pathway in the C-2 Arylation of 1-Methylindole



The first step proceeds to an aryl-palladium halide intermediate, which may then undergo two competing pathway:

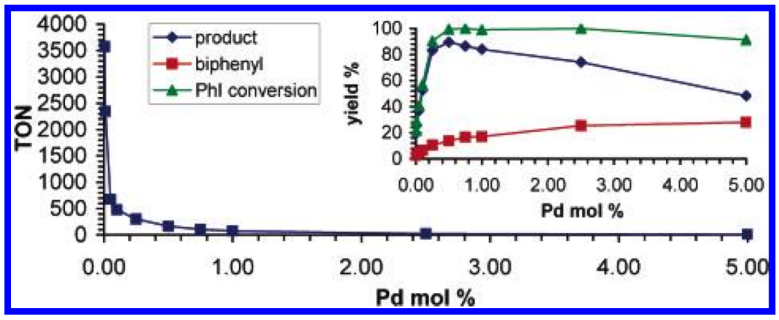
(1) cross-coupling with the substrate to furnish the disered product

or

(2) formation of byproduct biphenyl.

key issues: 1) the choice of base
2) formation of the biphenyl side product

biphenyl formation required a bimolecular transmetalation of the allyl-palladium species.



[Hypothesis]

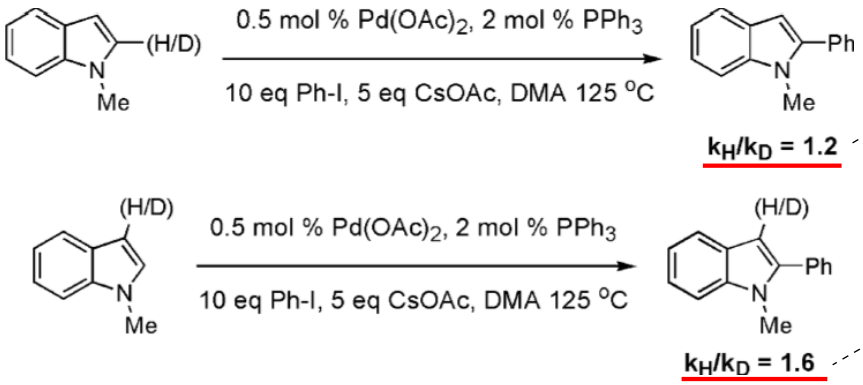
Decrasing the catalyst loading should increase the rate ratio v_3/v_2 and thus favor production of the desired product.

Figure 2. Chemical yield and TON as a function of catalyst loading in reaction of *N*-methylindole and Ph-I: $Pd(OAc)_2/PPh_3$ (1:4), 2.54 M in substrate, CsOAc, DMA, 125 °C, 24 h.

> 0.5 mol%: biphenyl formation
< 0.5 mol%: led to a sharp decline in yeild, which was accompanied by a dramatic increase in the catalyst turnover number.

⇨ At such low concentrations, catalyst decomposition processes, including biphenyl formation were suppressed.
Good functional group tolerance was demonstrated.

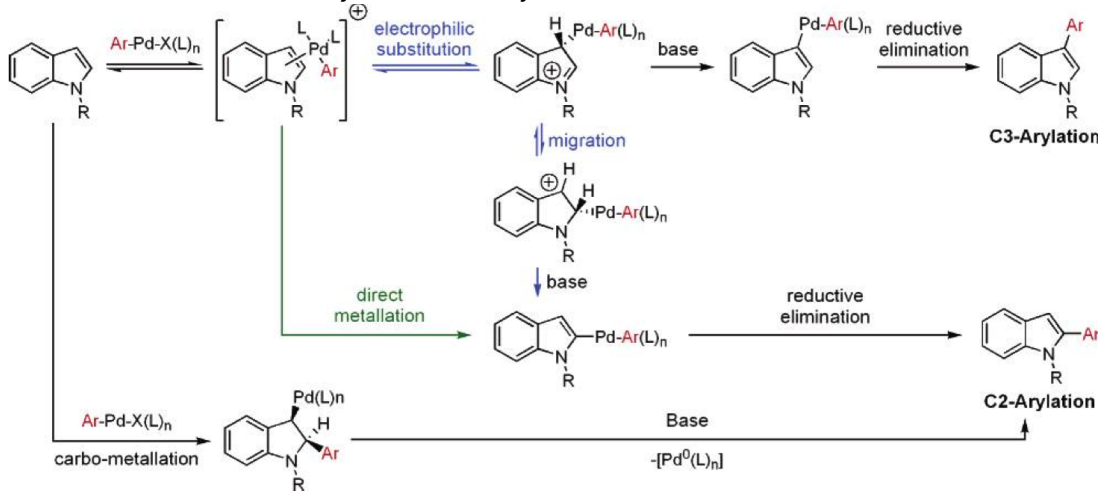
ii) Mechanistic Study



a value too small for the cleavage of this bond to be involved in the rate-limiting step.

the large KIE value was obtained for the 3-position where the substitution does not occur.

Possible Reaction Mechanisms in the Arylation of N-Alkylindole



There are three reaction mechanisms that may rationalize the strong preference for C-2 arylation.

(1) Electrophilic metalation-migration
(2) δ-Bond metathesis
(3) Carbometalation, that is, Heck-type reaction

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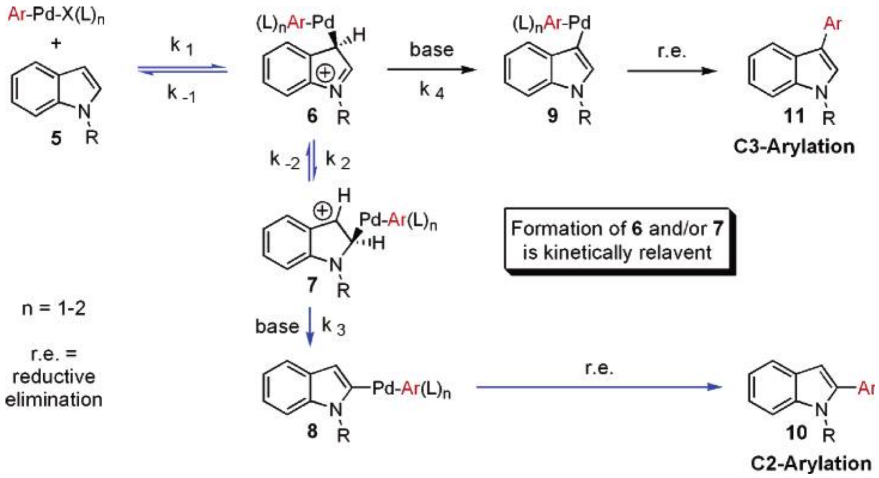
(2) This is primarily due to the large KIE at C-3.
(3) Carbopalladation of indole, following by isomerization and syn-β-hydride elimination, should also be considered. A plausible mechanism for the isomerizaiton step is a reversible α-hydride elimination, proceeding via a palladium hydride-carbene intermediate.
(1) The most likely candidate seems to be the electrophilic palladation pathway, supported by the kinetic studies.

Electrophilic Pathway for Arylation of Indole



The first step involves the formation of intermediate **6** by electrophilic addition of an aryl-palladium(II) species to the 3-position of indole. If the reverse step (k_1) and the migration (k_2), then the formation of 6 and the migration may become kinetically relevant.

⇒ In such instance, k_3 must be faster than k_2, and k_4 must be slower than k_2.

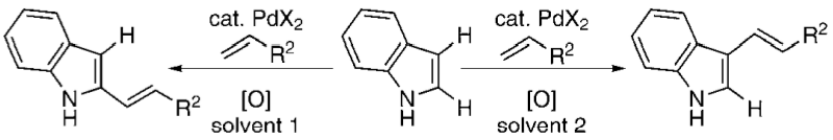
The driving force for this migration is related to stabilizaiton of the carbon-palladium bond by the adjacent nitrogen atom.

M. J. Gaunt's works

iii) Intermolecular Alkenylation of Indoles by Solvent-Controlled Regioselective C-H Functionalization

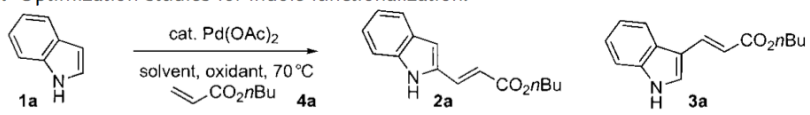
New swichable solvent-controlled regioselective palladium-catalyzed indole alkenylation by C-H functionalization.

M. J. Gaunt, *ACIE*, **2005**, *44*, 3125.



The natural reactivity of indole suggested that palladation and Heck coupling would take place preferentially at the 3-position.

Table 1: Optimization studies for indole functionalization.[a]



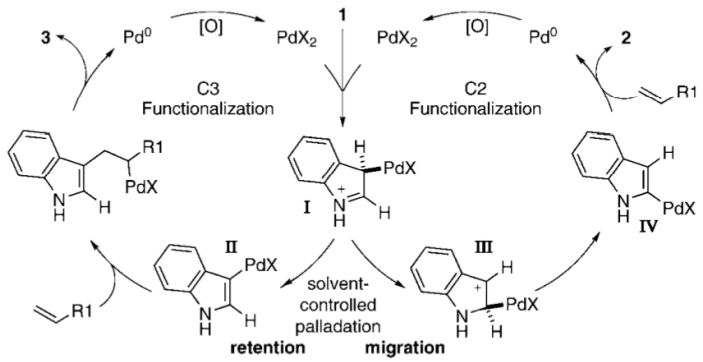
Entry	Catalyst loading [%]	Oxidant (equiv)	Solvent (*v*/*v*)	Yield of **2**+**3** [%][b]	**3a**/**2a**
1	10	$Cu(OAc)_2$ (1.8)	DMF	54	>95:5
2	10	$Cu(OAc)_2$ (1.8)	DMSO	66	>95:5
3	10	$Cu(OAc)_2$ (1.8)	1,4-dioxane	n.r.	–
4	10	*t*BuOOBz (0.9)	1,4-dioxane	48	1:2
5	10	$Cu(OAc)_2$ (1.8)	DMF/AcOH (3:1)	54	1:1
6	20	*t*BuOOBz (0.9)	1,4-dioxane/AcOH (3:1)	58	1:7
7	10	$Cu(OAc)_2$ (1.8)	DMF/DMSO (10:1)	79	>95:5
8	10	*t*BuOOBz (0.9)	MeCN/AcOH (3:1)	65	>95:5
9	10	*t*BuOOBz (0.9)	1,4-dioxane/AcOH/DMSO (3:1:0.4)	66	>95:5

reversal of selectivity

acid effect

improve the yield

[a] For all reactions the mixture (0.4 M) was stirred for 18 h. [b] Yields after isolation and purification by flash silica-gel chromatography. n.r. = no reaction. Bz = benzoyl, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide.



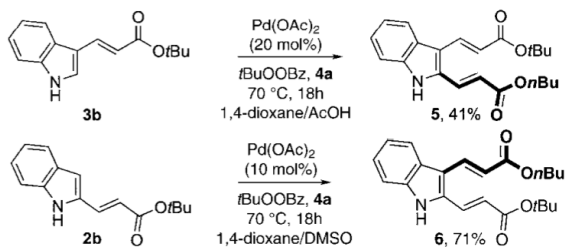
Scheme 2. Proposed mechanism of C–H functionalization.

They propsed plausible pathways for the two reactions in Scheme 2. Palladation at C3 is thought to occur via intermediate **I**, and following rearomatization to **II** a Heck-type reaction forms the C3-functionalized indole **3**.

Under neutral conditions, the acetate ion formed from the attack of indole on $Pd(OAc)_2$ will readily remove a proton from **I** to form the C3-palladated species **II**.

Under acidic condition they propose that this deprotonation would be slow, which could allow a migration of the C3-PdX bond in **I** to the highly activated 2-position of the iminium intermediate to give intermediate **III** and ultimately **IV**.

The effect of the cosolvent is also important since the results in Table 1 suggest that strongly coordinating solvents (DMSO, MeCN) override any effect that the presence of acid may have, thus leading to C3 selectivity.



Scheme 3. Formation of bis(alkenyl)indoles.

This strategy thus allows the selective installation of substituents at either position in any order and provides access to highly functionalized indoles by catalytic methods.

iv) Cu(II)-Catalyzed Direct and Site-Selective Arylation of Indoles

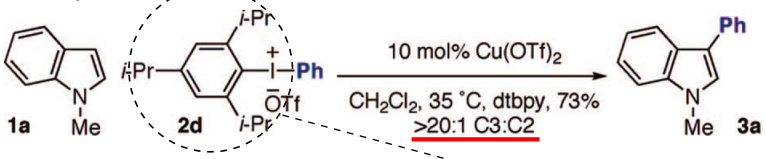
M. J. Gaunt, *JACS*, **2008**, *130*, 8172.

Pd(II) → d^8 ≡ Cu(III) ------ *highly electrophilic aryl-Cu(III) intermediate*

⇩

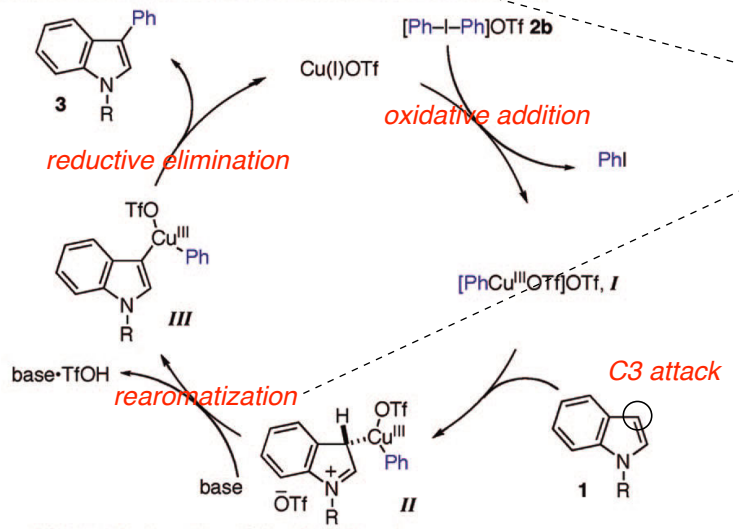
enable a mild arylation process

C3 Arylation



In order to improve the conversion, 10 mol% of the Cu catalyst was required, prusumably because the pyridine base binds to the Cu center and reduces its activity.

a. Proposed catalytic cycle for the Cu(II) catalyzed C–H arylation



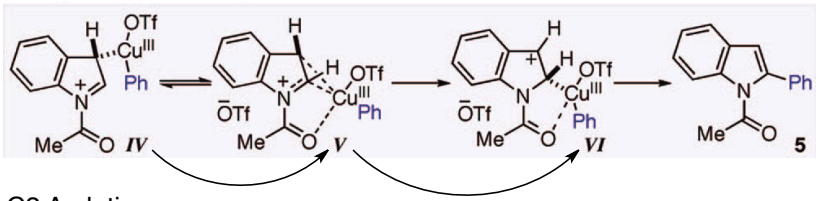
poor aryl transfer of a large group

Cu(III)-arylintermideate ***I*** would react initially through the C3 position before migration to C2.

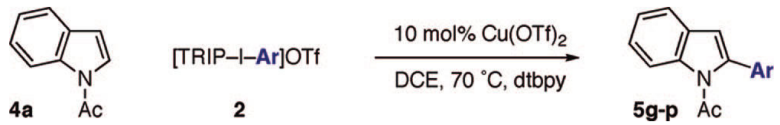
⇩

They reasoned that the use of an *N*-acetyl group might render the intermediate iminium ion ***IV*** more likely to accept the migrating C-Cu bond at the C2 position.

b. Proposed C3 to C2 migration of the C–Cu bond



C2 Arylation



C2:C3 = 2.6:1 ~ 6.5:1

49 ~ 82% yield

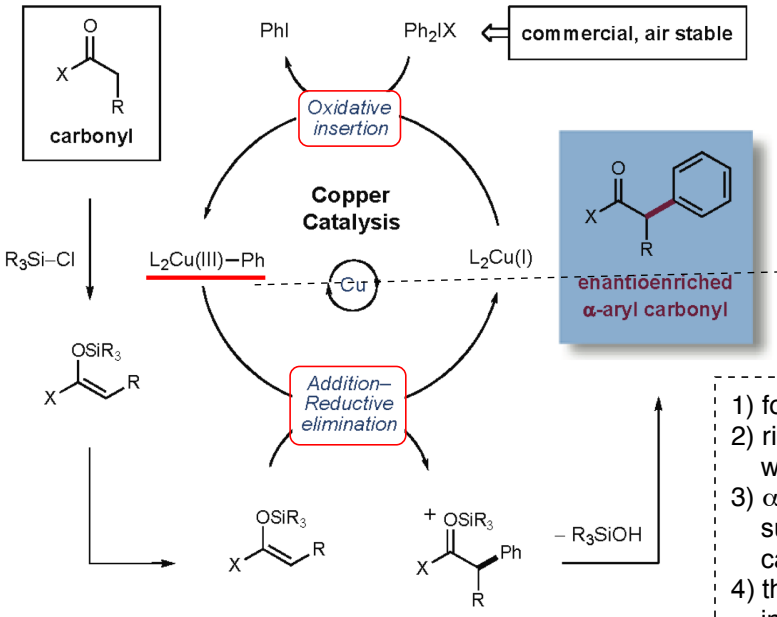
Small Summary

Free(NH)- and *N*-alkylindoles → C3-arylated product
N-acetylindoles → C2-arylated product

2.2 Arylation with Diaryliodonium Salts

i) Copper-Catalyzed Alkene Arylation with Diaryliodonium Salts

W. C. MacMillan, *JACS*, **2011**, *133*, 13782.
M. J. Gaunt, *JACS*, **2011**, *133*, 13778.

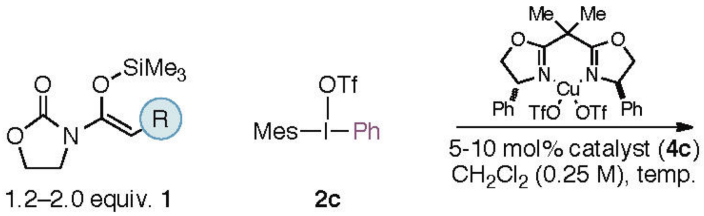


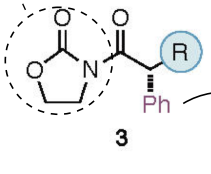
A broadly expanded array of carbonyl systems might be readily accessible using **chiral copper catalysts** in the presence of **iodonium salts** with silyketene acetals.

high electrophilic chiral copper(III) species

1) formed as single (*Z*)-isomers,
2) rigidify a transition state via stabilizing interaction with a chral copper complex,
3) α-functionalized *N*-acyloxaxolidinones are less susceptible to postreaction racemization than other carbonyl compounds,
4) the products can be transformed into useful intermediates.

Catalytic Enantioselective Arylation

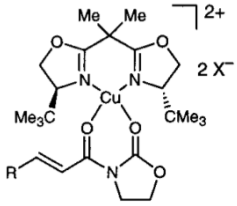




75 ~ 96% yield
90 ~ 95% ee

electron-deficient arenes
electron-rich arenes
meta- and para-substituted aryl rings
heteroaromatic systems

Appendix

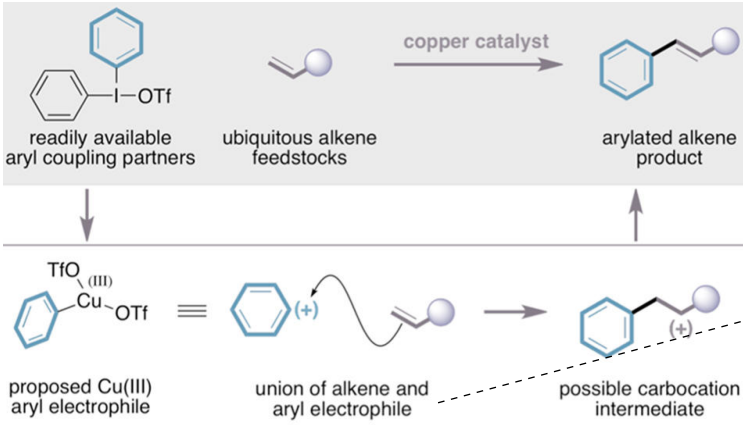


The order for divalent ions in the first transition series indicates that Cu(II) forms the most stable ligand-metal complex and dissociation of the chelating chiral ligand in derived complexs apparently not a complication.

Mn < Fe < Co < Ni < Cu > Zn

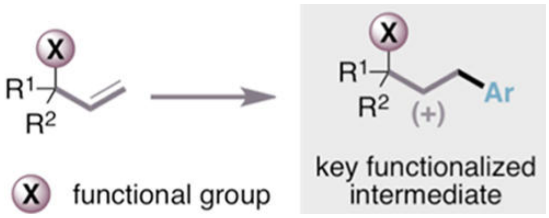
ii) Copper-Catalyzed Alkene Arylation with Diaryliodonium Salts

M. J. Gaunt, *JACS*, **2012**, *134*, 10773.



This combination of a Cu catalyst and a diaryliodonium salt appears to behave as an activated aromatic electrophile, paralleling the **Friedel-Crafts type** reactivity.

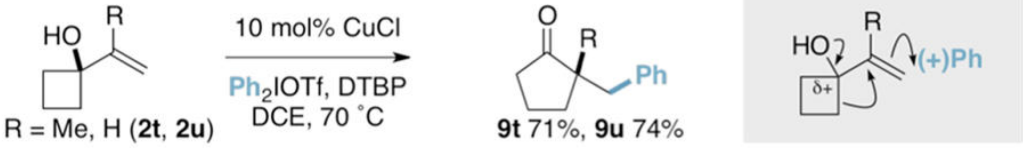
Exploiting the diverse reactivity of a possible carbocation intermediate



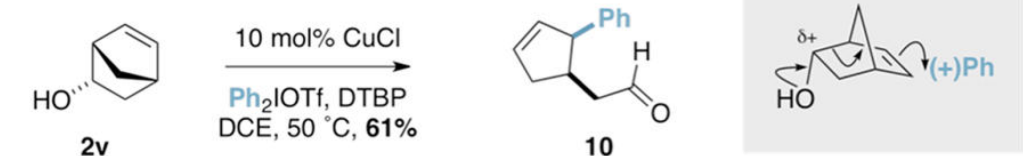
- **Pinacol rearrangements**
- **Grob fragmentations**
- **Cascade reactions**

This new Cu-Catalyzed arylation may proceed by a reaction pathway displaying **carbocation-like character**, allowing the development of a number of novel tandem and cascade reactions that could expedite the synthesis of complex molecules.

(c) Arylation – semi-Pinacol reaction



(d) Arylation – Grob-type fragmentation



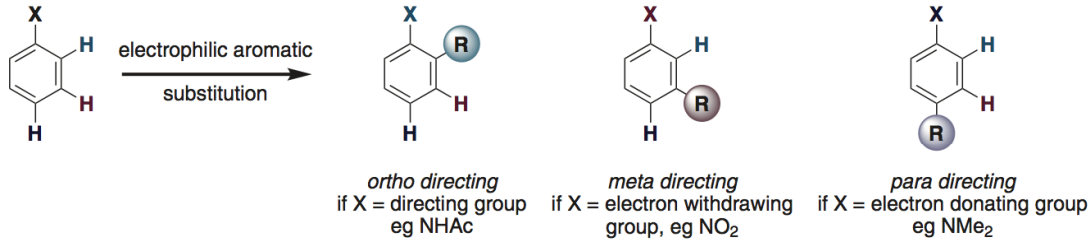
Small summary

They have shown that the product out comes differ significantly from these commonly obtained by the Heck reaction. Preliminary studies have shown that a carbocation-type mechanism may be involeved in these reactions.

3.1 *Meta*-Selective C-H Bond Activation

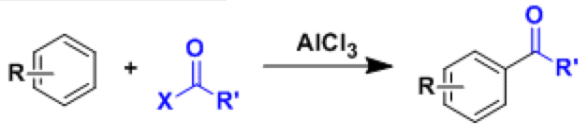
Introduction

Chemical transformations of benzene derivatives have been guided by the high selectivity for electrrophilic attack at the ortho/para positions in electron-rich substrates and at the meta position in electron-deficient molecules.



Pioneerting Work

Friedel-Crafts Reaction

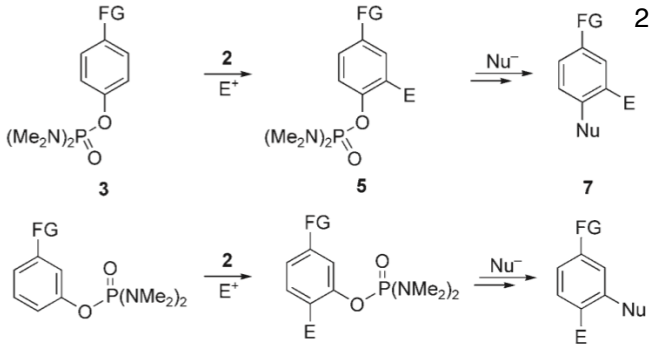


electron-donating substituents → **ortho and para**
electron-withdrawing substituents → **meta**

Precedent & Other Works

meta and para Functionalization of Arenes

P. Knochel, *ACIE*, **2008**, *47*, 1503.

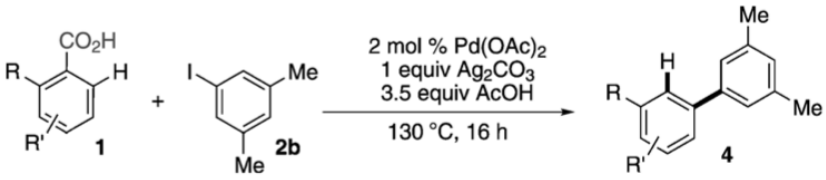


2: TMP_2Mg•2 LiCl

not completely selective meta functionalization

Carboxylic Acid as Traceless Directing Groups for meta Selective Direct Arylation

I. Larrosa, *ACIE*, **2011**, *50*, 9429.



58 ~ 83% yield

harch condition and long reaction time
$Pd(OAc)_2$ were needed.

Why was meta-selective C-H bond activation difficult and elusive ?

The several mechanisms that usually rationalize the majority of selective metal-catalyzed C-H bond activation.

a) oxidative addition (OA) at electron-rich low-valent transition metal centers
b) σ-bond metathesis (SBM) at electrophilic early transitionmetal centers
c) electrophilic activation (EA) at electron-deficient late transitionmetal centers
d) concerted metalation-deprotonation (CMD)

⇨ These mechanistic pathways most commonly form the ortho-substitution product.

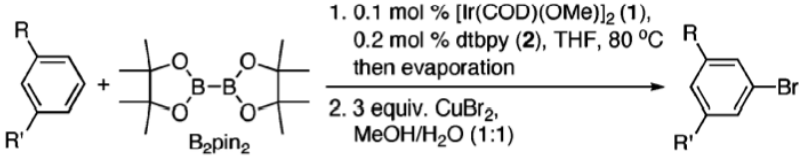
⇣

But there is a paucity of methods for metal-catalyzed C-H bond activation at the meta position.

Meta-Selective C-H borylation

i) Meta Halogenation of 1,3-Disubstituted Arenes via Iridium-Catalyzed Arene Borylation

J. F. Hartwing, *JACS*, **2007**, *129*, 15434.



They reported the development of such a **one-pot** method for synthesis of bromo- and chloroarene.

but.....

The regiochemstry of the products results more from steric than electroic control.
Regioselectivity was low.
Substrate scope was narrow.

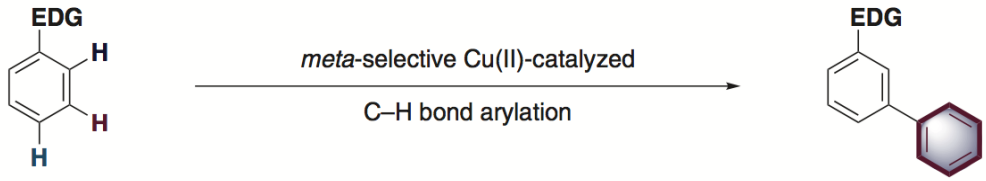
1. iridium-catalyzed borylation of arenes
2. halogenation of the resulting aryl boronate esters with copper(II) bromide or copper(II) chloride

M. J. Gaunt's works

M. J. Gaunt, *Science*, **2009**, *323*, 159.

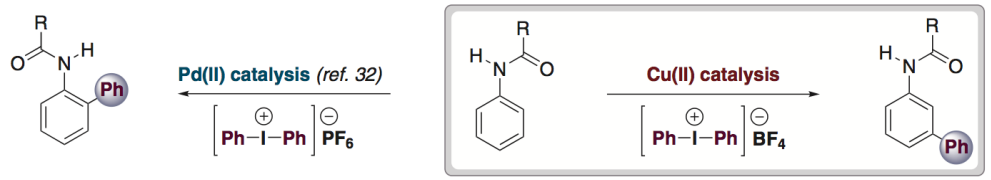
M. J. Gaunt, *ACIE*, **2011**, *50*, 463.

ACIE, **2009**, *48*, 9052.



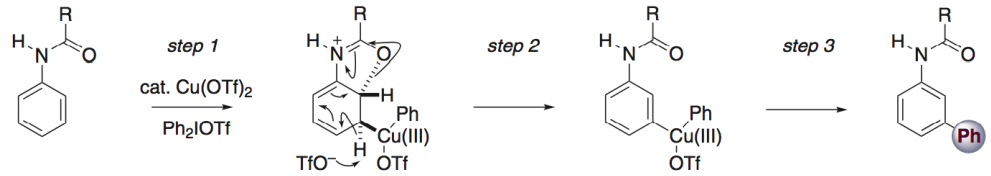
Circumventing the inherent ortho/para-selectivity of electron-rich aromatic systems to generate the meta product remains a largely elusive and unmet goal for chemical synthesis.

(C) This study – *meta*-C–H arylation of acetanilides with Cu(II) catalysis



***ortho*-arylation** ← complementary reactivity → ***meta*-arylation**

(D) Proposed mechanistic hypothesis



meta-C–H bond cupration via dearomatizing 'oxy-cupration'

Step 1:

A possible rationalization could involve the highly **electrophilic Cu(III)-aryl species** activating the aromatic ring sufficiently to permit an anti-oxy-cupration of the carbonyl group of an acetamide across the 2,3-positions on the arene ring.

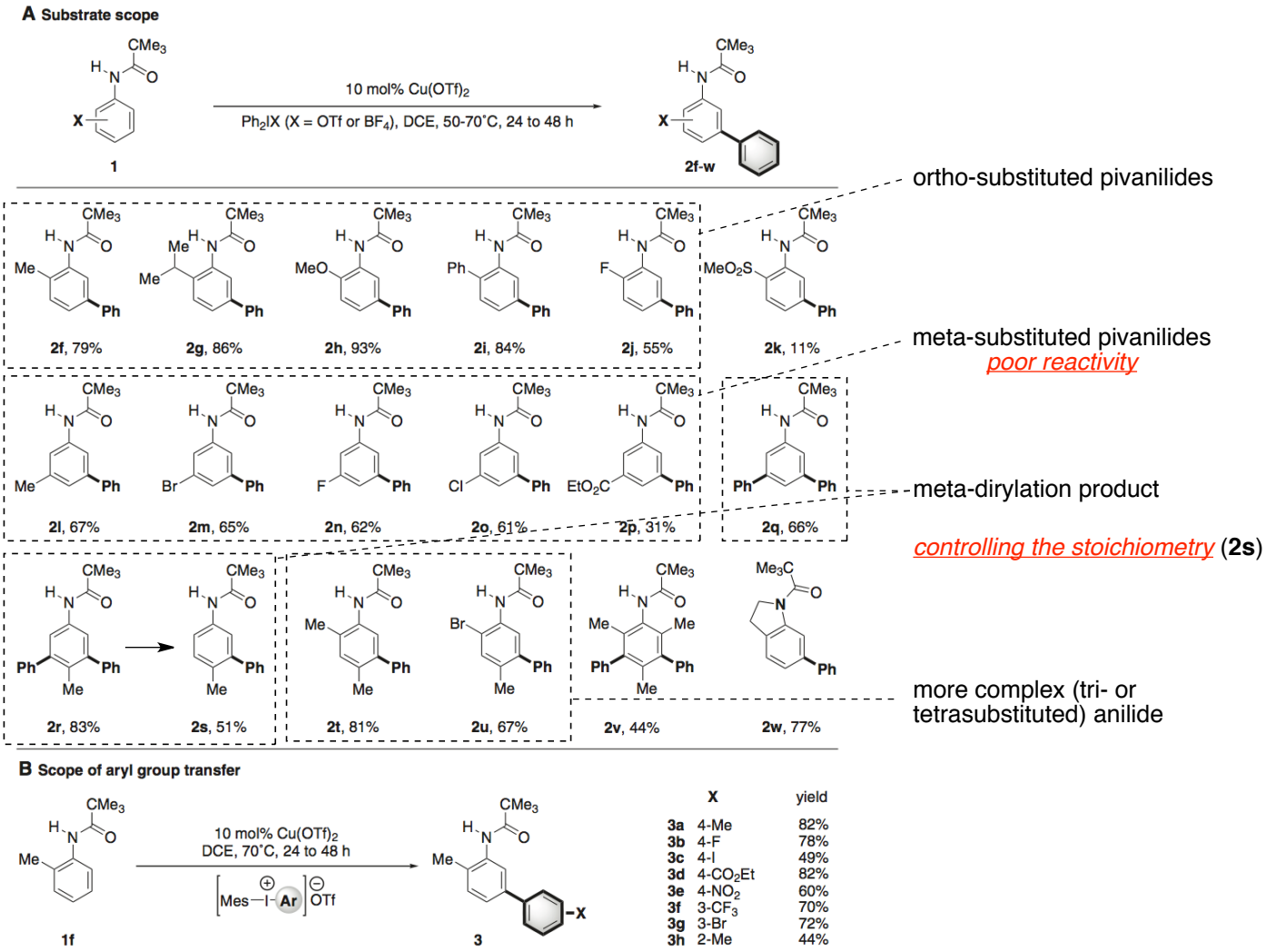
Step 2:

The dearomatizing transformation would place the **Cu(III)-aryl species** at the meta position, and rearomatizing deprotonation.

Step 3:

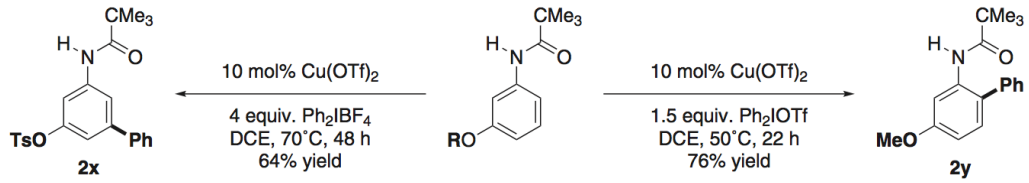
Reductive elimination

ii) Meta-Selective Copper-Catalyzed C-H Bond Arylation



	X	yield
3a	4-Me	82%
3b	4-F	78%
3c	4-I	49%
3d	4-CO_2Et	82%
3e	4-NO_2	60%
3f	3-CF_3	70%
3g	3-Br	72%
3h	2-Me	44%

Controlling the site selectivity of the C-H arylation



controllable swich in regioselectivity

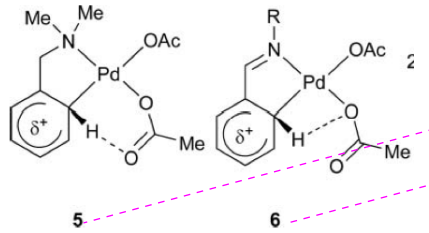
3-OTs group → 1,3,5-trisubstitute arene product
3-OMe group → 1,3,6-trisubstitute arene product

In certain cases the meta-selectivity can be overridden by strongly electron-donating substiruents.

iii) Concerted Metalation deprotonation (CMD)

Dalton Trans, **2009**, *30*, 5820.

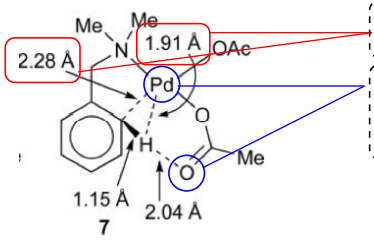
Proposed transition states and calculated agostic intermediate



an electrophilic substitution *via* a **Wheland intermediate** with subsequent intramolecular deprotonation by coordianted acetate *via* a **6-membered transition state** (**5**).

4-membered transition state for intramolecular deprotonation (**6**).

agostic structure > Wheland intermediate



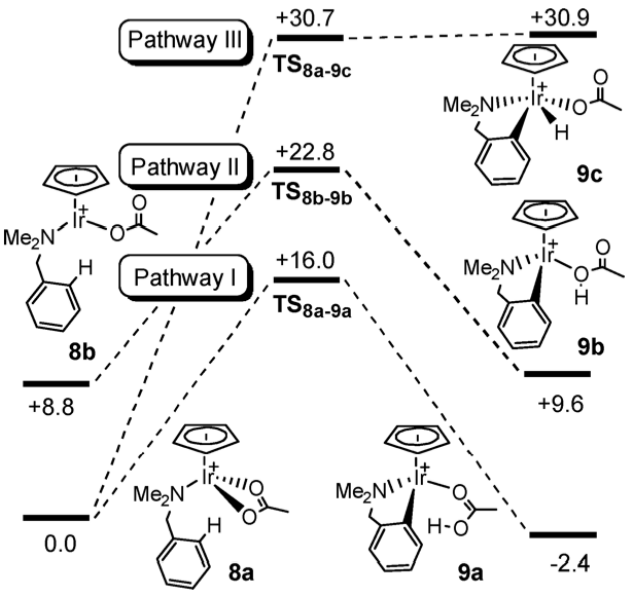
agostic interaction (weak)

ambiphilic activation — electrophilic metal center & intramolecular base

The rate-determining step is computed to be formation of the agostic intermediate via the κ^2-κ^1 displacement of acetate.

The agostic structure is sufficient to polarize the C-H bond and allow acetate to form an intramoleular hydrogen bond to the transferring hydrogen.

Computed reaction profiles for C-H activation [DMBA-H with ($Cp^*_2IrCl_2$)]



Pathway I: via a 6-membered transition state
Pathway II: via a 4-membered transition state
Pathway III: by oxidative addition

No intermediate agostic complex was obseved.

⇩

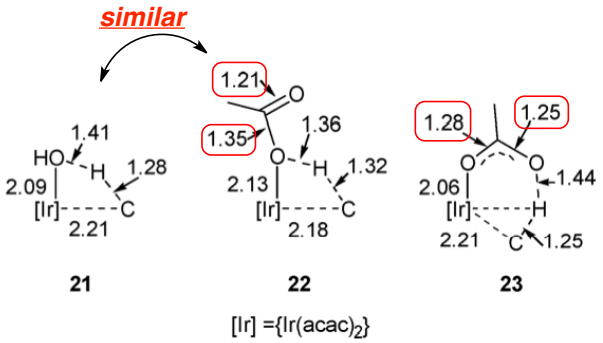
The main activation energy barrier seems to be related to converting a κ^2-acetate to κ^1.

[Small summary]

6-Membered transitionstate to give **9a** was favoured over a 4-membered process via **8b** to **9b** or oxidative addition to an Ir(V) species, **9c**.

Transition state energy decomposition study of C-H activation

similar



Hydroxide can only act as an intramolecular base with a 4-membered transitionstate (**21**).
but acetate can have a 4-membered or 6-membered transisiton state (**22, 23**).

The authors conclude the most significant contribution to the energy difference between **23** and **22** is the energy required to deform the reactants into their transition state geometries.

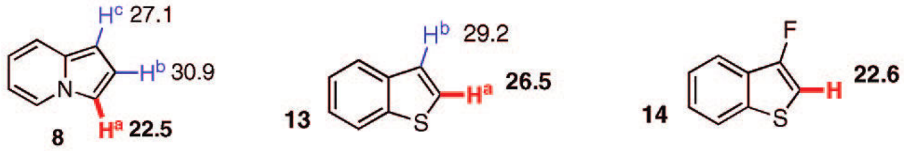
Analysis of the Concerted Metalation-Deprotonation Mechanism

K. Fagnou, *JACS*, **2008**, *130*, 10848.

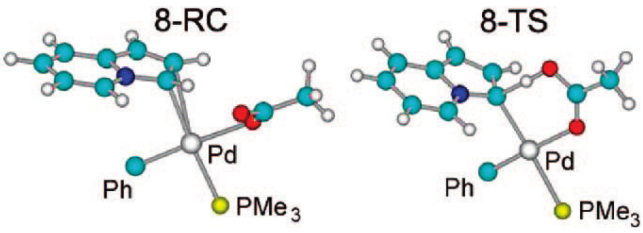
- ***Concerted Metalation-Deprotonation (CMD)***

[Feature] 1. Very little charge is present on the aromatic ring.
2. Retention of aromaticity is observed for all substrates at the CMD TS.

Free energy of activation for direct arylation via the CDM pathway



CDM TS (**8**)



η^1- and η^2–C-Pd coordination compleses, not Wheland intermediates

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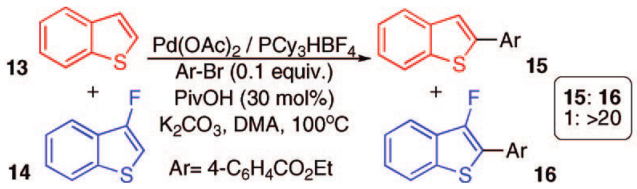
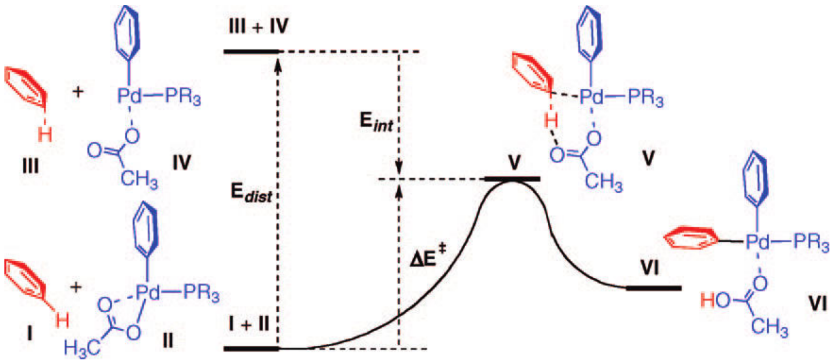


14 reacts preferentially over the more nucleophilic **13** in a competition reaction.

⇩

It conforms with CMD values.

Activation-Stain Analysis



distortion energy, E_{dist} : associated with distortion of the catalyst and arene from ground state ***I*** and ***II*** to TS geometries ***III*** and ***IV***.

electronic interaction energy E_{int} : arising from bringing ***III*** and ***IV*** together to form TS ***V***.

E_{int} = strength of the carboxylate-H_{Ar} and Pd-C_{Ar} interaction
E_{dist} = ongoing study

thiazole *N*-oxides
small E_{dist}
large E_{int}

electrondeficient arene
not large E_{int}
low E_{dist}

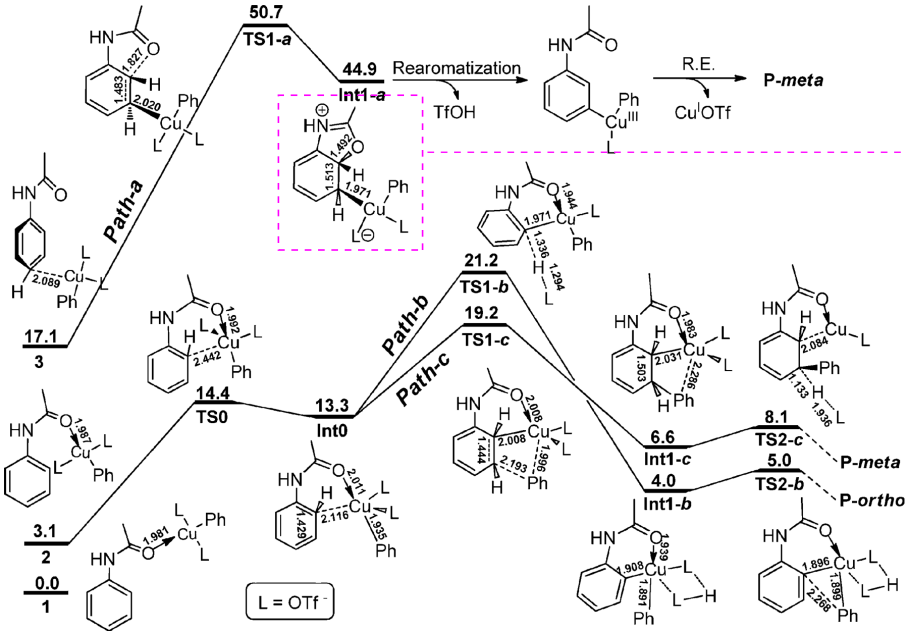
π-electron-rich arenes
large negative E_{int}
large E_{dist}

benzene
not favored either value

Arene	ΔE‡	E_{dist} (ArH)	E_{dist} (PdL)[a]	E_{int}	q_{NPA} (ArH)[b]	B_{Pd-C}[c]
1	5.8	29.3	16.6	-40.1	-0.039	0.45
2	12.4	33.8	16.7	-38.1	-0.079	0.44
3	16.5	36.8	15.4	-35.7	-0.065	0.43
4	14.5	36.8	16.9	-39.2	-0.041	0.51
5	15.9	39.9	17.4	-41.4	-0.014	0.52
6	15.6	42.5	17.9	-44.8	+0.009	0.56
7	11.1	42.2	18.3	-49.4	+0.017	0.58
8	13.1	48.1	19.9	-54.9	+0.065	0.62
9	12.5	50.1	20.4	-58.0	+0.078	0.59
10	12.8	40.0	18.6	-45.8	+0.003	0.51
11	11.9	28.8	15.3	-32.2	-0.092	0.44
12	25.1	44.6	15.8	-35.3	-0.010	0.51
13	16.7	37.5	16.8	-37.6	-0.035	0.50
14	12.3	32.4	17.2	-37.3	-0.041	0.48

iv) Mechanistic Understanding

The three calculated reaction pathways. Relative free energies including the solvent effect (ΔG_{sol}) are given in kcal/mol.



[Path a]

Antioxycupration mechanism
1. the highly electrophilic Cu(III)-aryl species activates the aromatic system as Lewis acid
2. the carbonyl oxygen attacks the ortho position, pushing electrons out to form a C-Cu bond at the expected meta position.

Path a is extremely unfavorable for the following reasons;

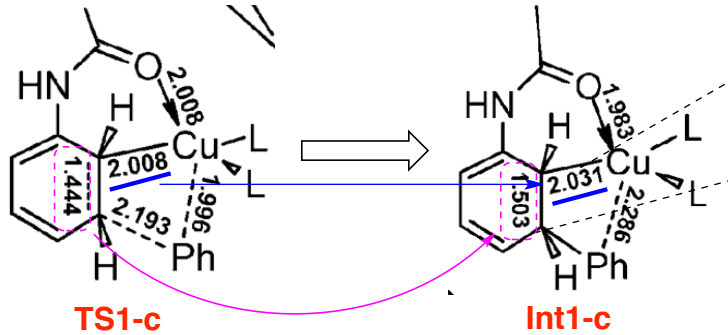
(a) the amide group is a weak π-electron donor, and the site being attacked is the unfavorable electron-rich ortho position.
(b) copper shifts from the preferred electron-rich para position to the unfavorable meta position.
(c) the aromaticity is brocken without adequate compensation.

[Path b]

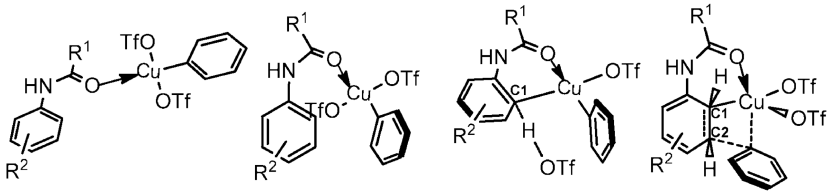
Starting Z-type carbonyl coordinated complex **2** with the copper, a intramolecular **Friedel-Crafts-type** electrophilic attack at C_{ortho} takes place. ⇨ The other four ligands roughly in a plane ⇨ The apical OTf^- anion disassociates from the copper and abstracts the proton from C_{ortho} in an intermolecular fashion. ⇨ **Reductive elimination**, which is easy because of the strong driving force for Cu(III) reduction, results in the ortho-arylated product.

[Path c]

path c shares with path b the electrophilic-attack step from **2** to **Int0**. ⇨ The phenyl group bonded to copper is transferred to the mata position via the **Heck-like four-membered-ring transition state TS1-c**, leading to intermediate **Int1-c**. ⇨ Free OTf^- anion abstracts the proton at the meta positon, recovering the aromaticity and resulting in the meta-arylated product.



The effects of the terminal R^1 proup and the aromatic substituent R^2 group — *JACS*, **2011**, *133*, 7668.



1 **2** **TS1-*b*** **TS1-*c***

entry	R^1	R^2	1	2	TS1-*b*	TS1-*c*
1	Me	H	0.0	3.1	21.2	19.2
2	CMe_3	H	0.0	0.2	18.0	16.1
3	Ph	H	0.0	2.5	20.9	18.0
4	*p*-MeC_6H_4	H	0.0	3.0	21.0	19.1
5	*p*-$OMeC_6H_4$	H	0.0	1.9	19.6	17.6
6	*p*-FC_6H_4	H	0.0	2.7	20.4	18.4
7	*p*-$CF_3C_6H_4$	H	0.0	3.0	21.6	18.6
8	CMe_3	*o*-OMe	0.6	0.0	19.2	13.7
9	CMe_3	*o*-Me	0.5	0.0	18.1	13.6
10	CMe_3	*o*-F	0.0	0.0	19.0	17.8
11	CMe_3	*m*-OMe	0.4	0.0	13.5	12.3
12	CMe_3	*m*-Me	0.1	0.0	16.7	14.3
13	CMe_3	*m*-F	0.0	0.1	17.8	16.8
14	CMe_3	*p*-OMe	0.6	0.0	18.6	13.9
15	CMe_3	*p*-Me	0.5	0.0	17.9	14.1
16	CMe_3	*p*-F	0.0	0.4	19.9	17.8

[a] The numerical values are relative free energies in solvent (ΔG_{sol}) in kcal/mol.

• A large R^1 group pushes copper to the trans position, facilitating the electrophilic attack at the ortho carbon. (**entry 2**)

• The electronic character of R^1 has a small effect on the reaction. (**entry 3~7**)

• All of the ortho, meta, and para EDGs lower the barrier for path c because they can increase the electron density at either C1 or C2.

• EWGs generally raise the berriers for both pathways.

R^1 → reflect the steric character of the Cu(III)-Ph species
R^2 → reflect the electrophilic character of the Cu(III)-Ph species

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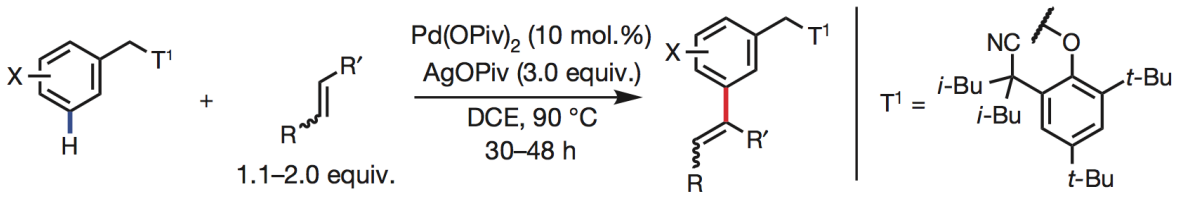
v) Activation of remote meta-C-H bonds

Jin-Quan Yu, *Nature*, **2012**, *486*, 518.



high meta-selectivity

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4. Summary

Meta-selective C-H activation chemistry has room to improve the range of substrates so on.

but I think.....