C-H Activation: Fundamentals and Recent Developments

ISOC
11th INTERNATIONAL SCHOOL OF ORGANOMETALLIC CHEMISTRY

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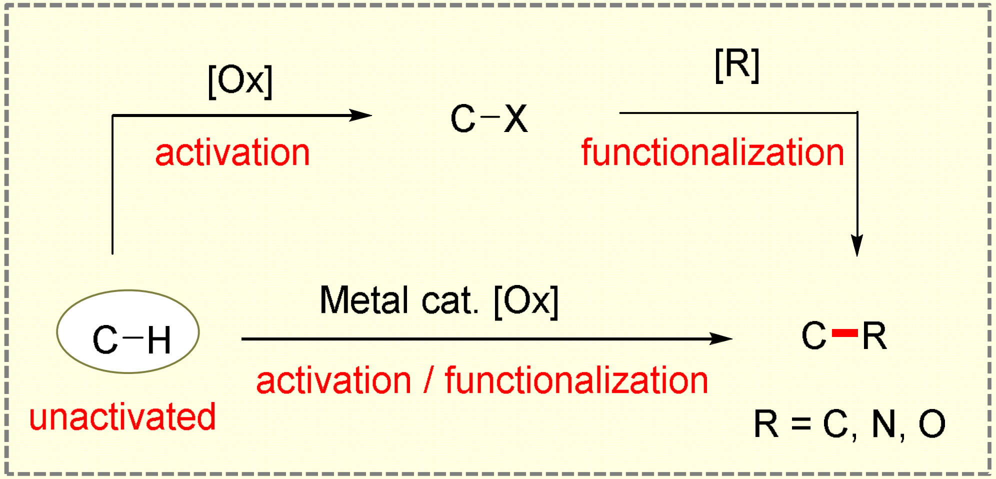
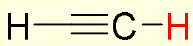
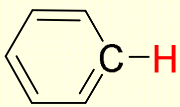
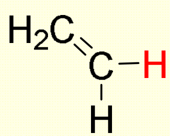
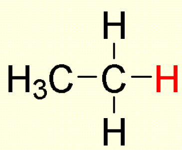
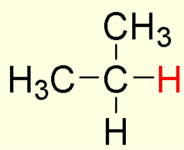
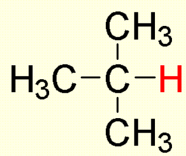
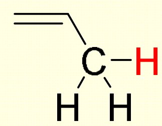
Plan: Focus on the Transformation

omium	manganese	iron	cobalt	nickel	copper	zi
24	25	26	27	28	29	3
Cr	Mn	Fe	Co	Ni	Cu	Z
.9961	54.93805	55.845	58.9332	58.6934	63.546	65.4
ybdenum	technetium	ruthenium	rhodium	palladium	silver	cadm
42	43	44	45	46	47	4
Mo	Tc	Ru	Rh	Pd	Ag	C
5.94	[98]	101.07	102.9055	106.42	107.8682	112.
ngsten	rhenium	osmium	iridium	platinum	gold	merc
74	75	76	77	78	79	8
W	Re	Os	Ir	Pt	Au	H
83.84	186.207	190.23	192.217	195.078	196.96655	200
oorgium	bohrium	hassium	meitnerium	darmstadtium	roentgenium	unun
106	107	108	109	110	111	11

- **Focus on the Transformation**
- Historical Background
- Overview of Mechanisms
- Selection of Specific Examples

Focus on the Transformations



type of C-H	C(sp)	$C(sp^2)_{arom}$	$C(sp^2)_{vinyl}$	$C(sp^3)_{1°}$	$C(sp^3)_{2°}$	$C(sp^3)_{3°}$	$C(sp^3)_{allylic}$
structure							
BDE (kJ/mol)	552.2	473.0	460.2	410.8	397.9	389.9	361.1
pK_a	~25	43	44	~50	~50	~50	43

The Holy Grail of Chemistry

ACS Symposium Series 885, *Activation and Functionalization of C-H Bonds*, 2004, 1-43

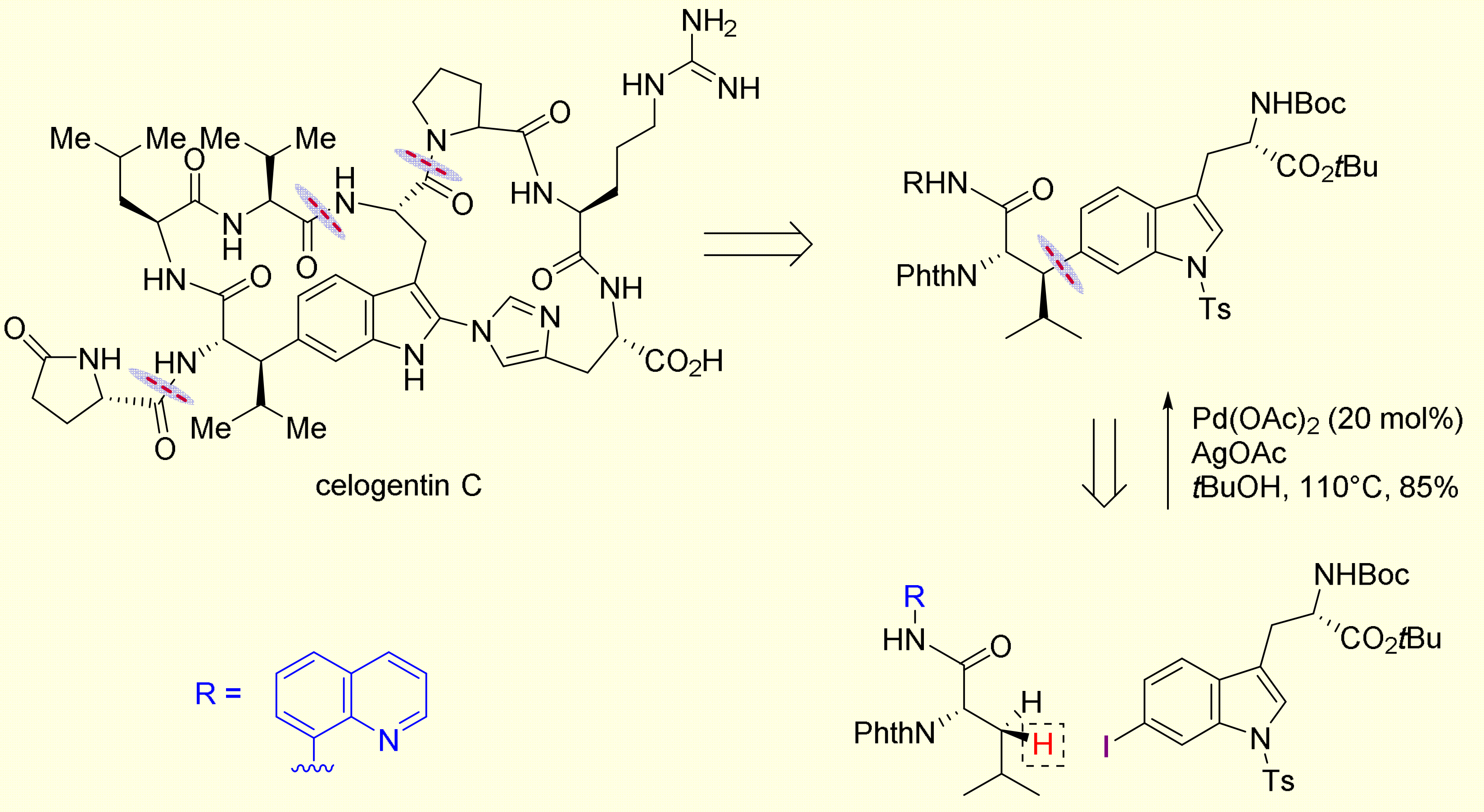
Organometallic C-H Bond Activation: An Introduction

Alan S. Goldman[1] and Karen I. Goldberg[2]

The carbon-hydrogen bond is the un-functional group. Its unique position in organic chemistry is well illustrated by the standard representation of organic molecules: the presence of C-H bonds is indicated simply by the absence of any other bond. This "invisibility" of C-H bonds reflects both their ubiquitous nature and their lack of reactivity. With these characteristics in mind it is clear that if the ability to selectively functionalize C-H bonds were well developed, it could potentially constitute the most broadly applicable and powerful class of transformations in organic synthesis. Realization of such potential could revolutionize the synthesis of organic molecules ranging in complexity from methanol to the most elaborate natural or unnatural products.

Multi-step Syntheses and C-H Activation /Functionalization

"Liberating chemistry from the tyranny of functional groups"… Of course, reactive groups have to be tolerated



Feng, Y.; Chen, G. *Angew. Chem., Int. Ed.*, **2010**, *49*, 958
Breslow, R.; Yang, J.; Yan, J. *Tetrahedron* **2002**, 58, 653

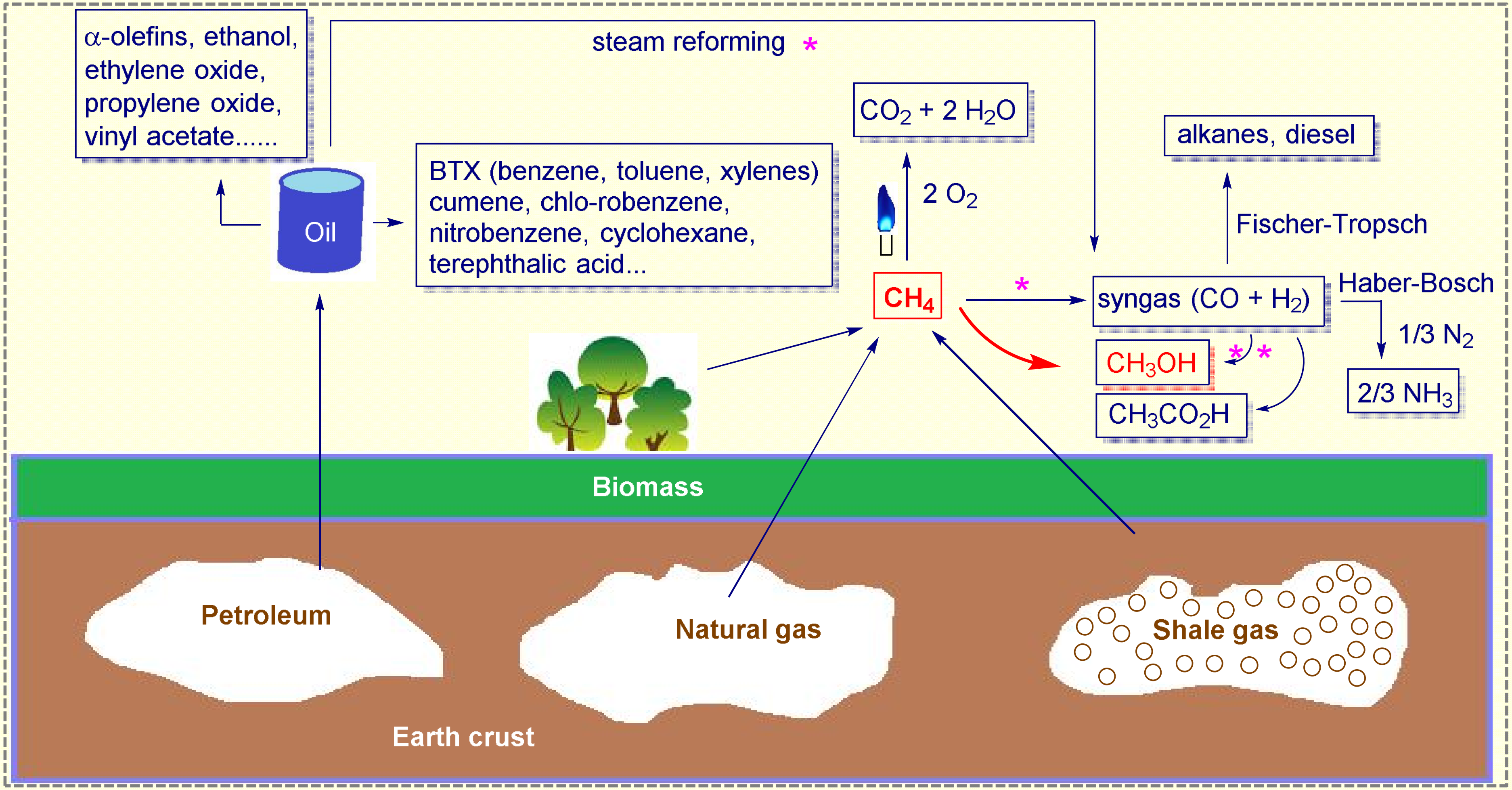
Feedstock Use and C–H Activation / Functionalization

Steam reforming *

$$CH_4 + H_2O \xrightarrow{Ni / Al_2O_3,\ 800\ °C} \underset{syngas}{CO + 3H_2} \qquad \Delta_rH° = +206\ kJ/mol$$

Synthesis **

$$\underset{syngas}{2H_2 + CO} \xrightarrow[50\text{-}100\ bar]{Cu/ZnO/Al_2O_3\ cat.\ 270\ °C} CH_3OH \qquad \Delta_rH° = -92\ kJ/mol$$



Adapted from: Caballero, A.; Perez, P. J. *Chem. Soc. Rev.* **2013**, *42*, 8809

Plan: Historical Background

omium 24 Cr .9961	manganese 25 Mn 54.93805	iron 26 Fe 55.845	cobalt 27 Co 58.9332	nickel 28 Ni 58.6934	copper 29 Cu 63.546	zir 3 Z 65.
ybdenum 42 Mo 95.94	technetium 43 Tc [98]	ruthenium 44 Ru 101.07	rhodium 45 Rh 102.9055	palladium 46 Pd 106.42	silver 47 Ag 107.8682	cadm 4 C 112.
ngsten 74 W 33.84	rhenium 75 Re 186.207	osmium 76 Os 190.23	iridium 77 Ir 192.217	platinum 78 Pt 195.078	gold 79 Au 196.96655	merc 8 H 200
oorgium 106	bohrium 107	hassium 108	meitnerium 109	darmstadtium 110	roentgenium 111	ununl 11

- Focus on the Transformation
- **Historical Background**
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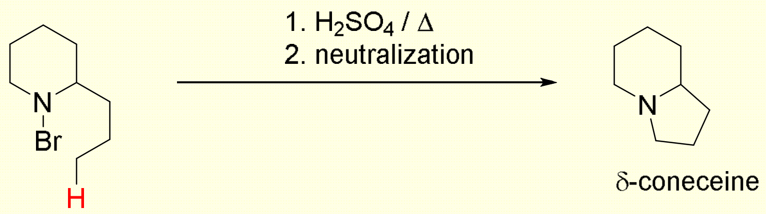
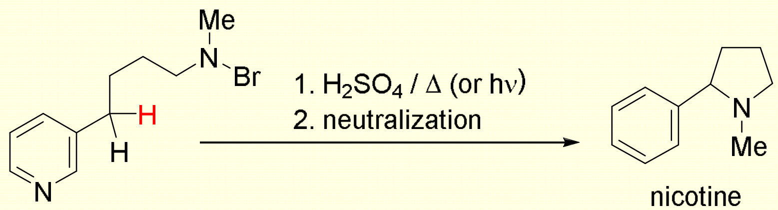
Hofmann-Löffler-Freytag (HLF) Reaction

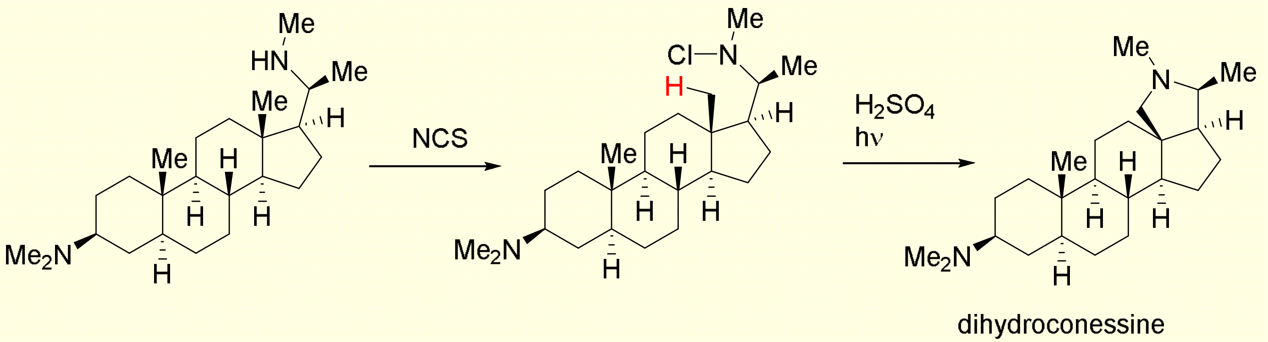
highly reactive intermediates……and structural proximity



photochemical decomposition of *N*-haloamines

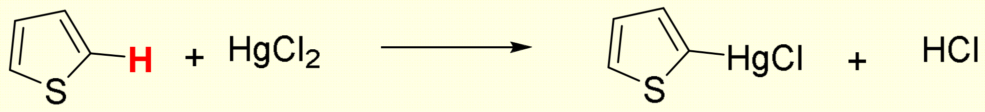
August Wilhelm von Hofmann



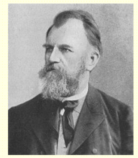


(a) Hofmann, A. W. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 558; Hofmann, A. W. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 5.
(b) Löffler, K.; Freytag, C. *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 3427.
(c) Corey, E. J.; Hertler, W. R. *J. Am. Chem. Soc.* **1958**, *80,* 2903.
(d) Buchschacher, P.; Kalvoda, J.; Arigoni, D.; Jeger, O. *J. Am. Chem. Soc.* **1958**, *80,* 2905**.**
(e) Corey, E. J.; Hertler, W. R. *J. Am. Chem. Soc.* **1959**, *81*, 5209.

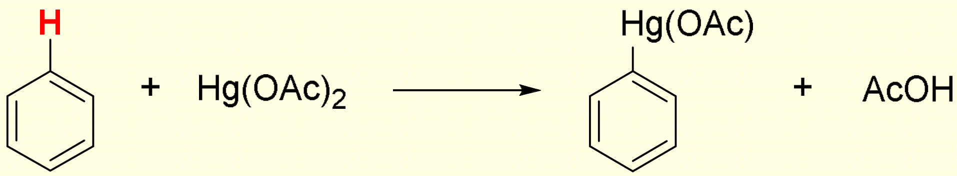
Pioneering Electrophilic C-H Metalations of Arenes



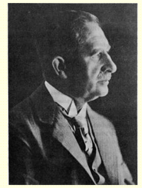
Volhard, J. *Justus Liebigs Ann Chem* . **1892**, 267, 172.



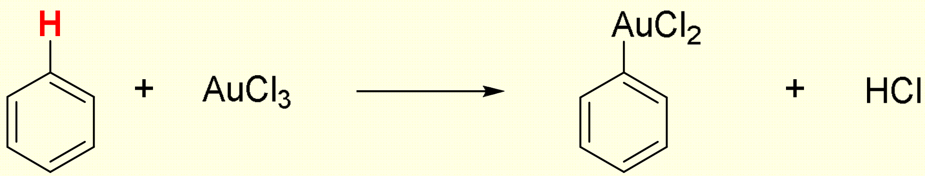
Jacob Volhard



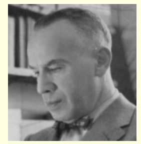
Dimroth, O. *Ber. Dtsch. Chem. Ges.* **1898,** *31*, 2154; **1899**, *32*, 758; **1902**, *35*, 2032 and 2853.



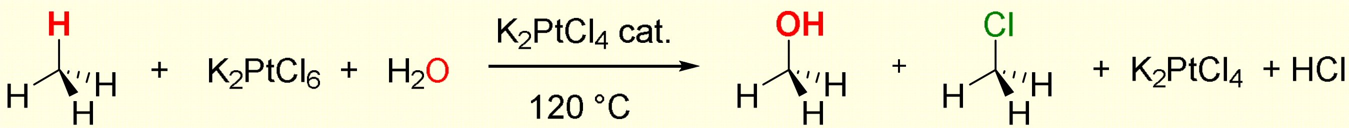
Otto Dimroth



Kharasch, M. S.; Isbell, H. S. *J.Am. Chem. Soc.* **1931**, *53*, 3053.



Morris Kharasch



Goldshleger, N. F.; Eskova, V. V.; Shilov, A. E.; Shteinman, A. A. *Russ. J. Phys. Chem.* **1972**, *46*, 785.

Alexander Shilov

Pioneering Nucleophilic Metalations of Arenes

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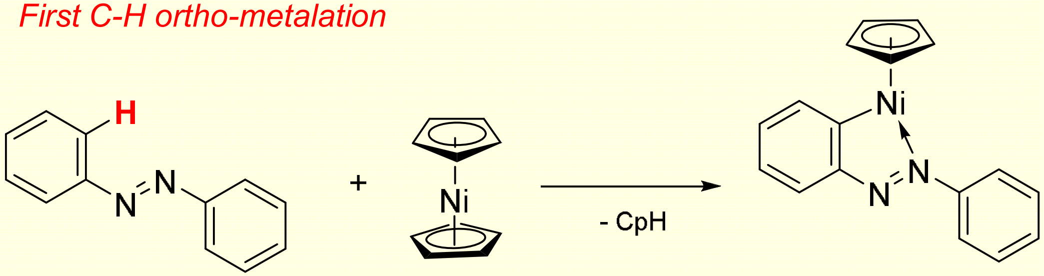
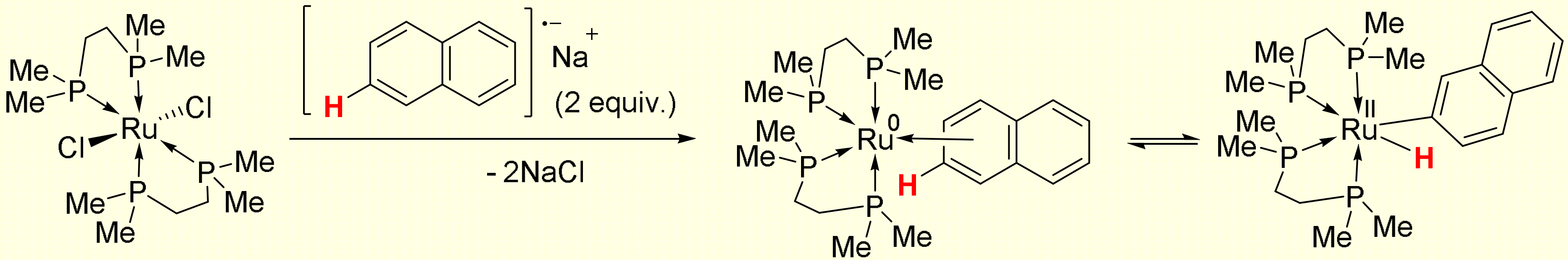
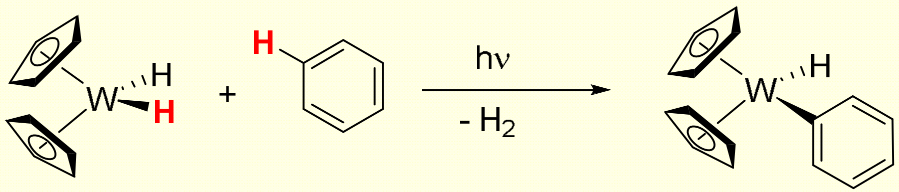
First C-H ortho-metalation



Kleiman, J. P.; Dubeck, M. *J. Am. Chem. Soc.* **1963**, *85*, 1544



Chatt, J.; Davidson, J. M.; J. Chem. Soc. (A) **1965**, 843.

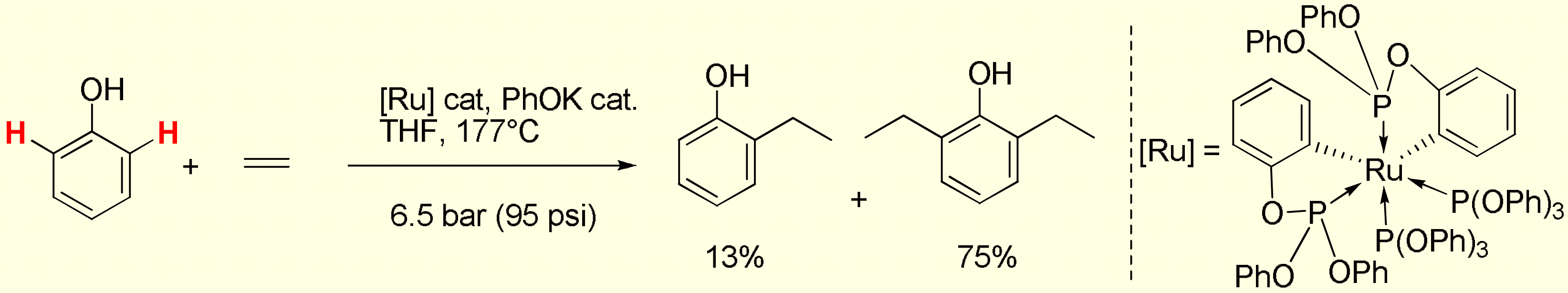


Green, M. L. H.; Knowles, P. J. *J. Chem. Soc., Chem. Comm.* **1970,** 1677.

Other Important Pioneering Steps Forward

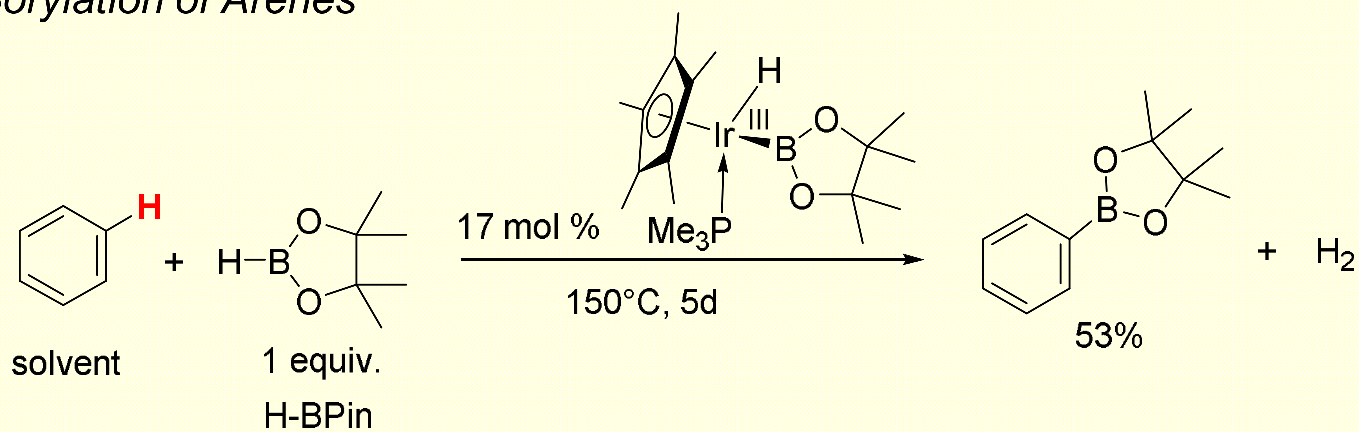
Catalytic aromatic ortho C-H activation

First catalytic C-H activation / functionalization



Lewis, L. N.; Smith, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 2728.

Borylation of Arenes



Iverson, C. N.; Smith III, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 7696

Plan: Overview of Mechanisms

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borgium 106	bohrium 107	hassium 108	meitnerium 109	darmstadtium 110	roentgenium 111	unun 11

- Focus on the Transformation
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- **Overview of Mechanisms**
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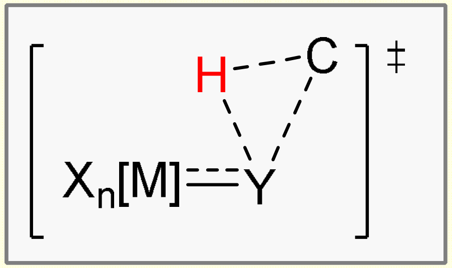
Overview of Mechanisms

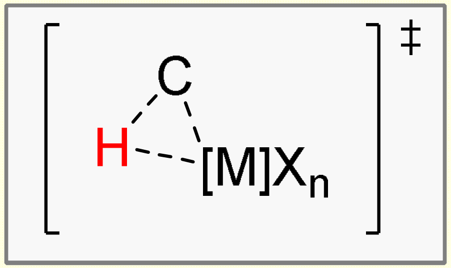
We can mechanistically classify the metal-catalyzed C-H activation / functionalization processes into **two main classes**.

1. Insertion of a C-H bond into the ligand of a transition metal (TM) complex



outer sphere

2. Coordination of the C-H bond to a metal vacant site to create an organometallic complex. The hydrocarbyl species stays in the inner-sphere during the C-H cleavage event.

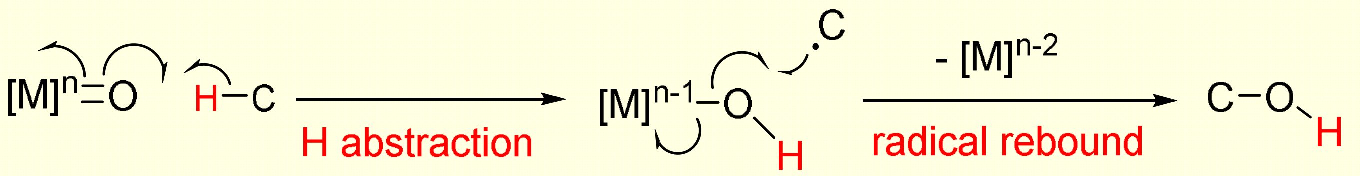


inner sphere

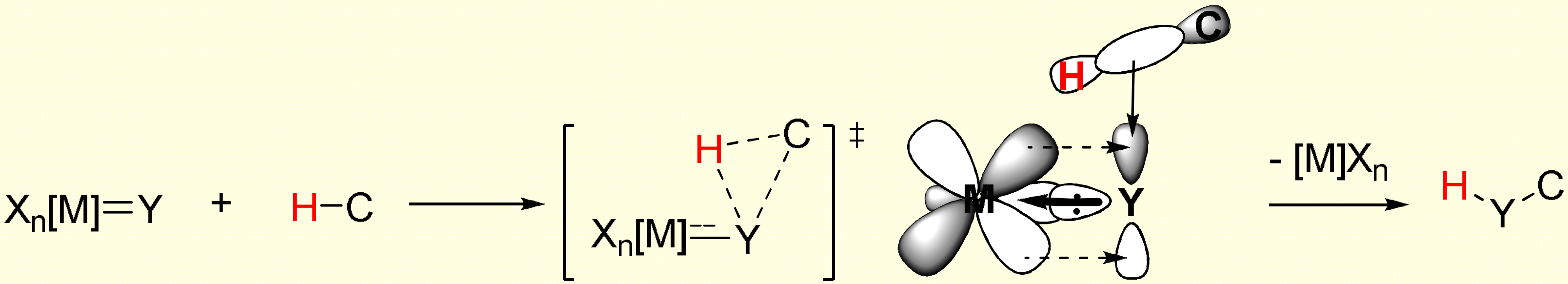
Outer Sphere

Metalloradical pathway (metal oxene)

Nature does it very well

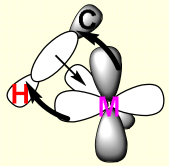


Metal carbenes (or nitrenes)

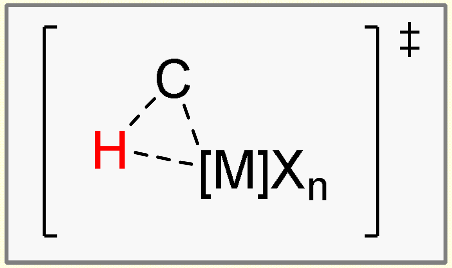


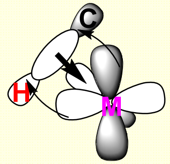
Y = CR_2, RN (metal carbene or nitrene)

Inner Sphere: Nucleophilic vs Electrophilic Character



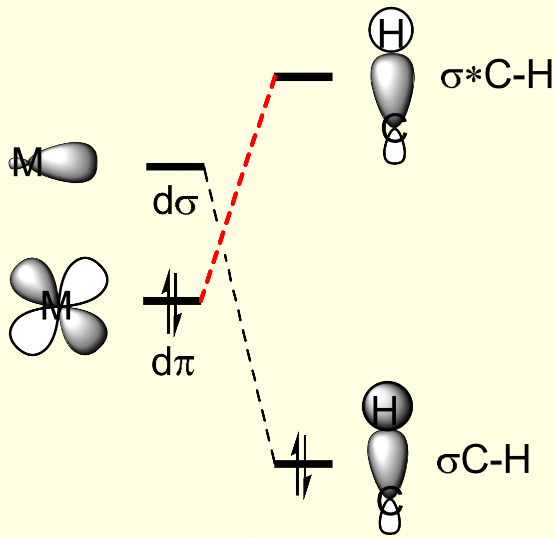
π-back-bonding >>
σ-donation





σ-donation >>
π-back-bonding

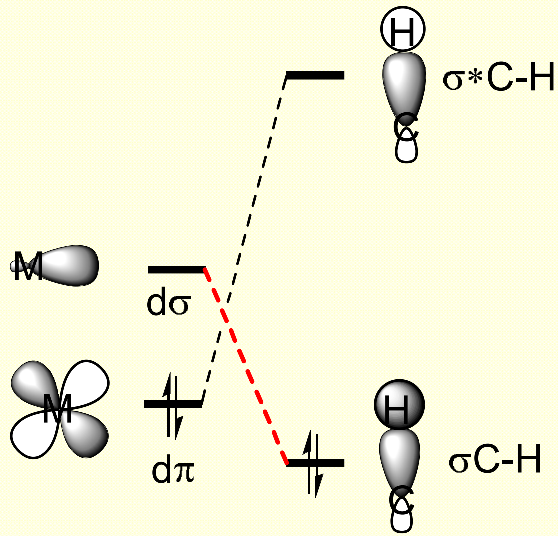
Nucleophilic C-H activation



Reverse CT (E_{CT1})
M → CH

Forward CT (E_{CT2})
M ← CH

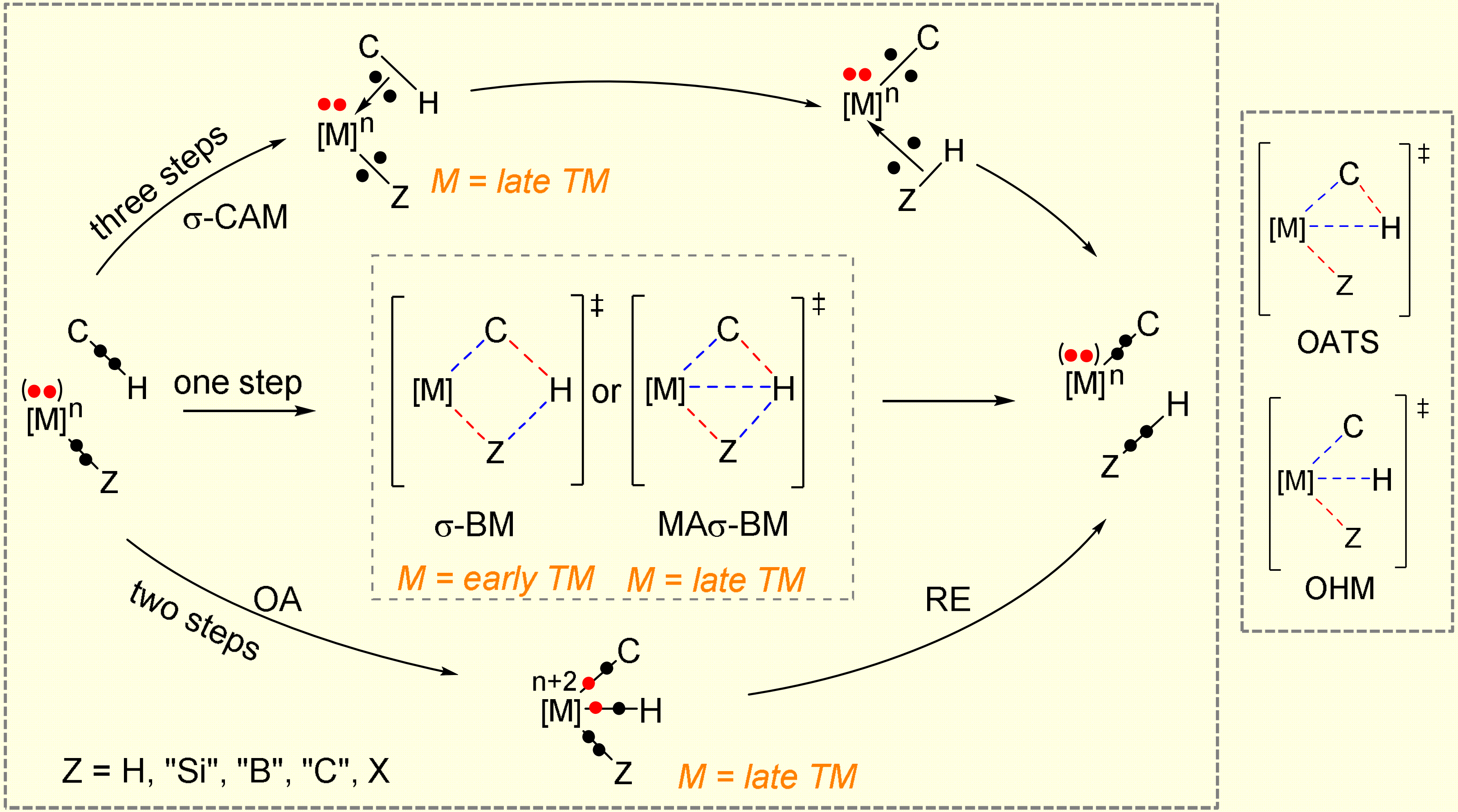
Electrophilic C-H activation



Reverse CT (E_{CT1})
M → CH

Forward CT (E_{CT2})
M ← CH

Oxidative Addition vs Sigma-bond Metathesis



σ-Bond metathesis (σ-BM)
Metal assisted σ-bond metathesis (MAσ-BM),
Oxidatively added transition state (OATS)

σ-Complex assisted metathesis (σ-CAM),
Oxidative hydrogen migration (OHM)

The Isohypsic Electrophilic Mechanisms

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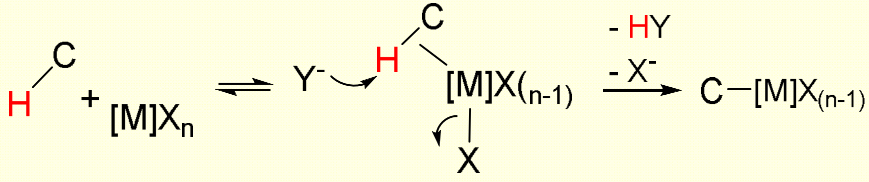
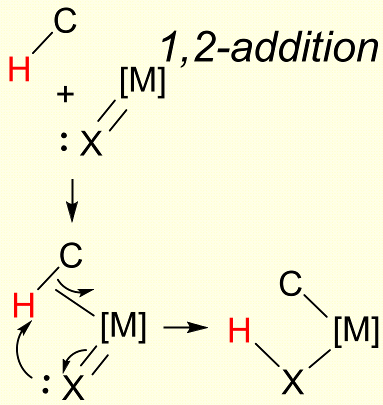
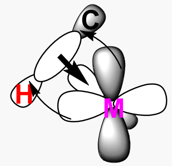
External heterolytic cleavage



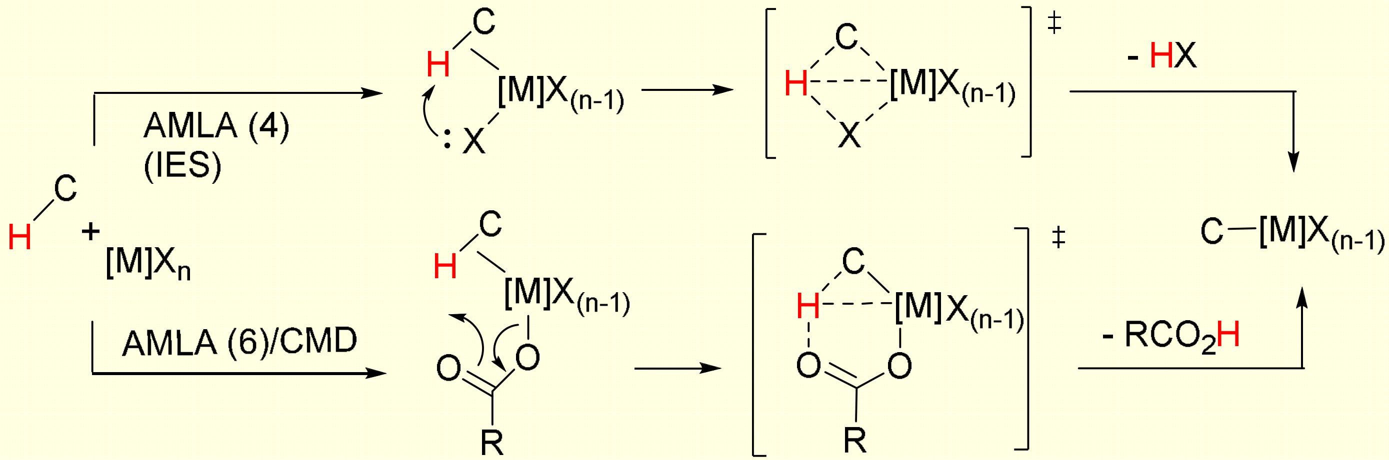
1,2-addition





σ-donation >>
π-back-bonding

Intramolecular concerted mechanisms (AMLA / CMD)



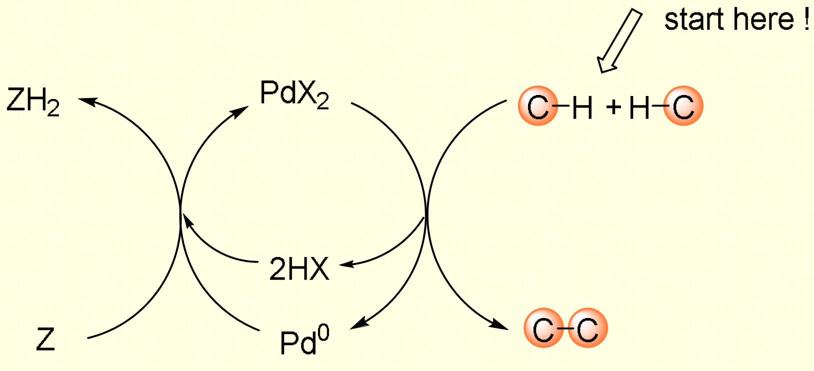
Ambiphilic metal-ligand activation (AMLA)
Concerted metalation deprotonation (CMD)
Internal electrophilic substitution (IES)

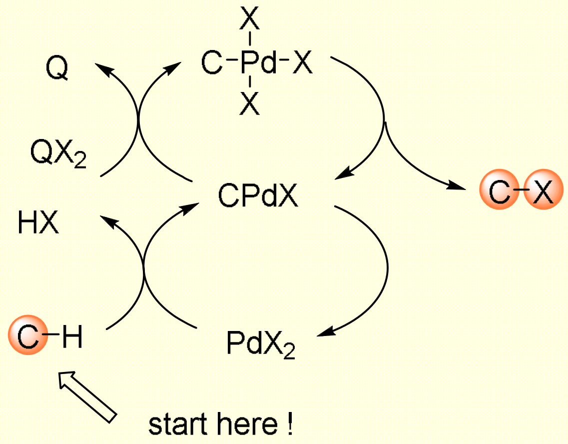
(a) Fagnou, K. *et al. J. Am. Chem. Soc.* **2008**, *130*, 10848; (b) *J. Org. Chem.* **2012**, *77*, 658; (c) *Chem. Lett.* **2010**, *39*, 1118.
(b) Davies, D. L.; Macgregor, S. *et al. Dalton Trans.* **2009**, 5820.
(c) Oxgaard, J.; Goddard III, W. A. *Organometallics* **2007**, *26*, 1565.

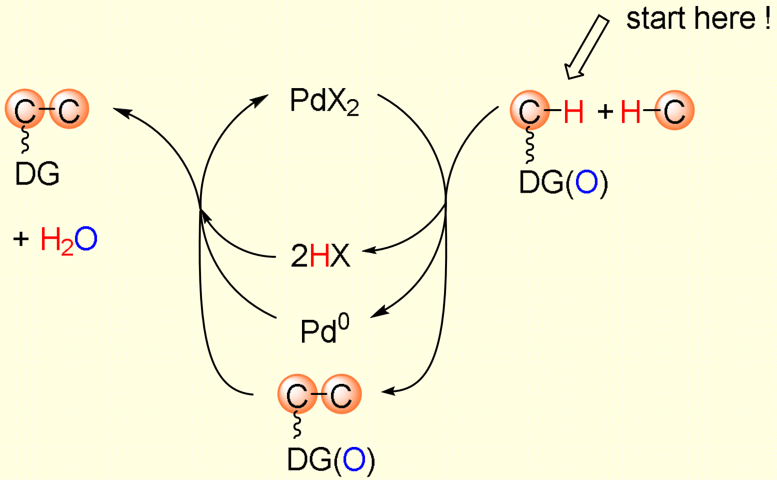
Redox Concepts in C-H Cross Couplings

	coupling type	redox	reaction type, typical example
a)	C–X + X–C $\xrightarrow{-X_2}$ C–C	reductive	Ulmann type coupling
b)	C–M + X–C $\xrightarrow{-MX}$ C–C	isohypsic	classical cross couplings
c)	C–H + X–C $\xrightarrow{-HX}$ C–C	isohypsic	Sonogashira, Mizoroki-Heck, Ohta
d)	C–H + H–C $\xrightarrow{-H_2}$ C–C	oxidative	cross dehydrogenative coupling (dual C-H)
e)	C–H + Nu-H $\xrightarrow{-H_2}$ Nu–C	oxidative	C-H nucleofunctionalization
f)	C=C–H + 2 Nu-H $\xrightarrow{-H_2}$ Nu–C–C–Nu	oxidative	alkene 1,2-nucleofunctionalization

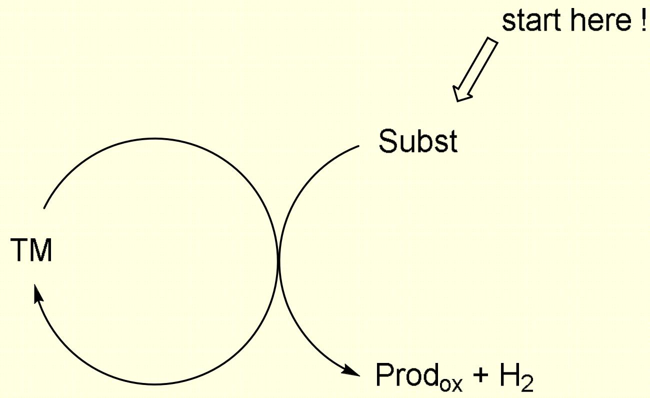
PdX_2-cat. Oxidative Transformations





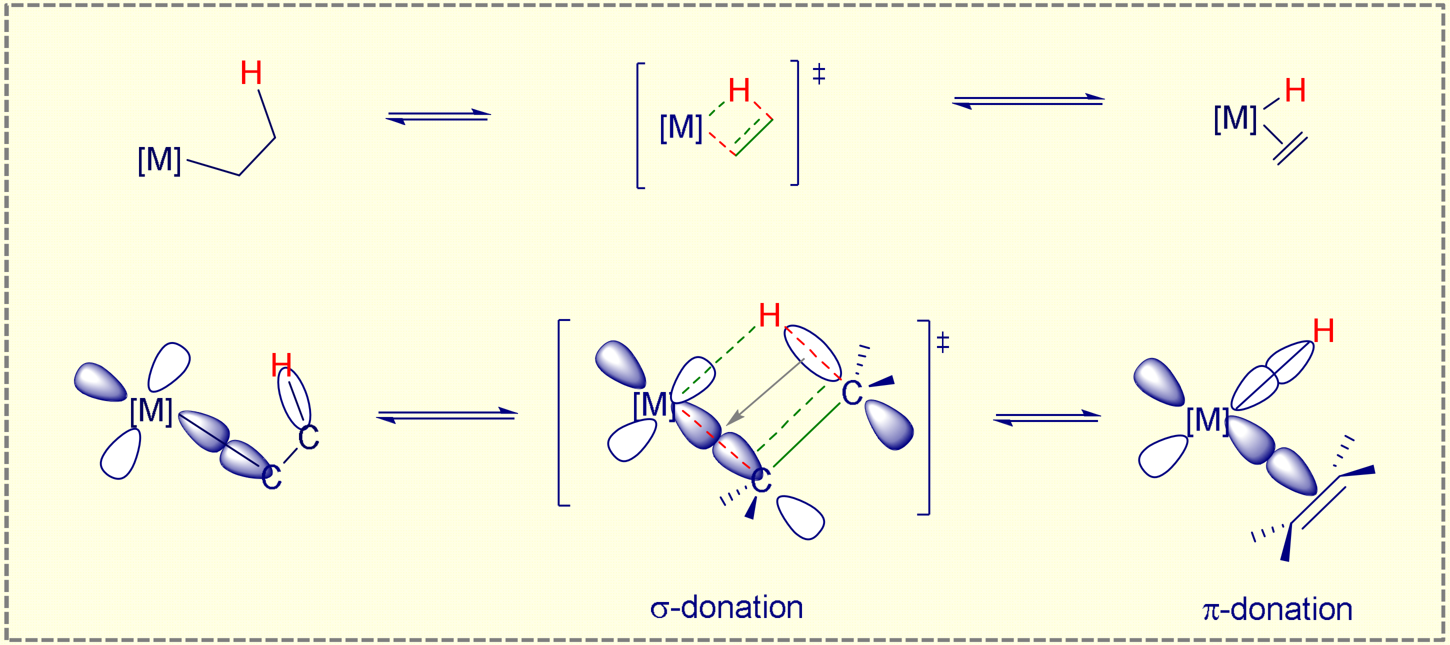


Acceptorless oxidation



Z and QX_2: $2e^-$ sacrificial oxidants; DG: directing group

Dehydrometalation / Hydrometalation

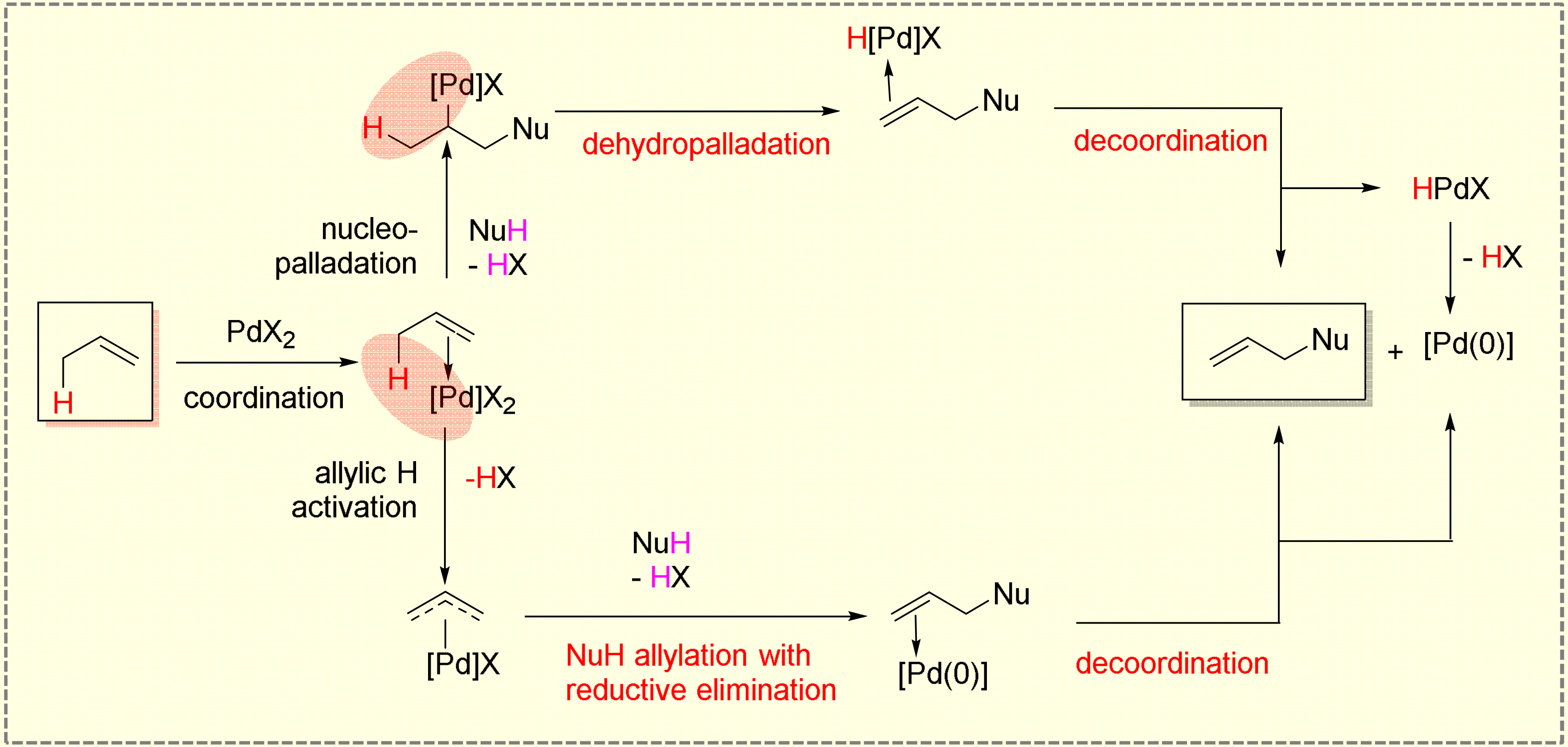


Thorn, D. L. Hoffmann, R. *J. Am. Chem. Soc.* **1978**, *100*, 2079

Transition metal alkyl complexes bearing a β-H atom that can adopt syncoplanar position with respect to the metal undergo easily β-hydride elimination (dehydrometalation).
The metal must have a vacant coordination site (empty orbital) that can interact with the H atom of the alkyl ligand. So, *a dehydrometalation step can be regarded as a special case of inner-sphere intramolecular C-H activation*.
d^0 metal complexes (*i.e.* Ag^+, Hg^{2+}) lacking the possibility to participate in d-orbital bonding are normally stable to β-hydride elimination:

The Case of the PdX_2 Catalyzed allylation of a NuH

e) C–H + H–X $\xrightarrow{-H_2}$ C–X   C-H nucleofunctionalization



Liron, F.; Oble, J.; Lorion, M. M.; Poli, G. *Eur. J. Org. Chem.* **2014**, 5863 **Microreview**

Lorion, M. M.; Nahra, F.; Ly, V.-L.; Mealli, C.; Messaoudi, A.; Liron, F. ; Oble, J.; Poli, G. *Chem Today* **2014**, 32, 30

Lorion, M. M.; Oble, J.; Poli, G. *Pure Appl. Chem.* **2016**, *88*, 381.

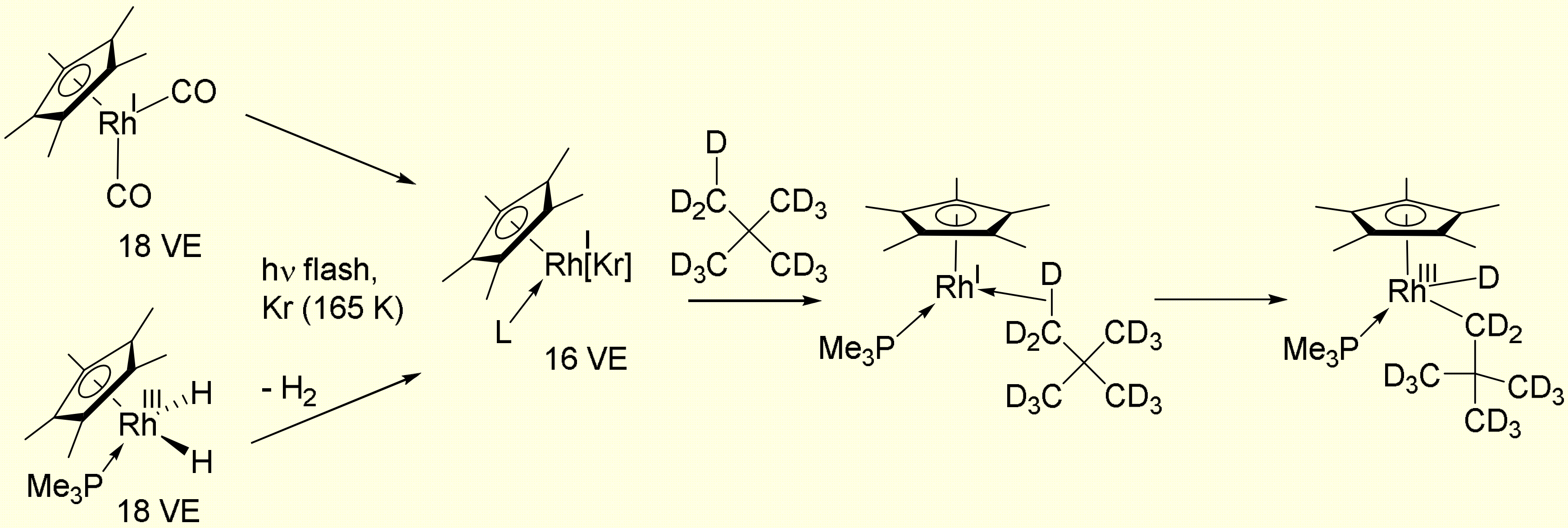
Plan: Selection of Specific Examples

omium 24 **Cr** .9961	manganese 25 **Mn** 54.93805	iron 26 **Fe** 55.845	cobalt 27 **Co** 58.9332	nickel 28 **Ni** 58.6934	copper 29 **Cu** 63.546	zin 3 **Z** 65.
bdenum 42 **Mo** 5.94	technetium 43 **Tc** [98]	ruthenium 44 **Ru** 101.07	rhodium 45 **Rh** 102.9055	palladium 46 **Pd** 106.42	silver 47 **Ag** 107.8682	cadm 4 **C** 112.
ngsten 74 **W** 33.84	rhenium 75 **Re** 186.207	osmium 76 **Os** 190.23	iridium 77 **Ir** 192.217	platinum 78 **Pt** 195.078	gold 79 **Au** 196.96655	mer 8 **H** 200
borgium 106	bohrium 107	hassium 108	meitnerium 109	darmstadtium 110	roentgenium 111	ununl 11

- Focus on the Transformation
- Historical Background
- Overview of Mechanisms
- **Selection of Specific Examples**

Inner Sphere: C-H Functionalization *(nucleophilic reactivity)*

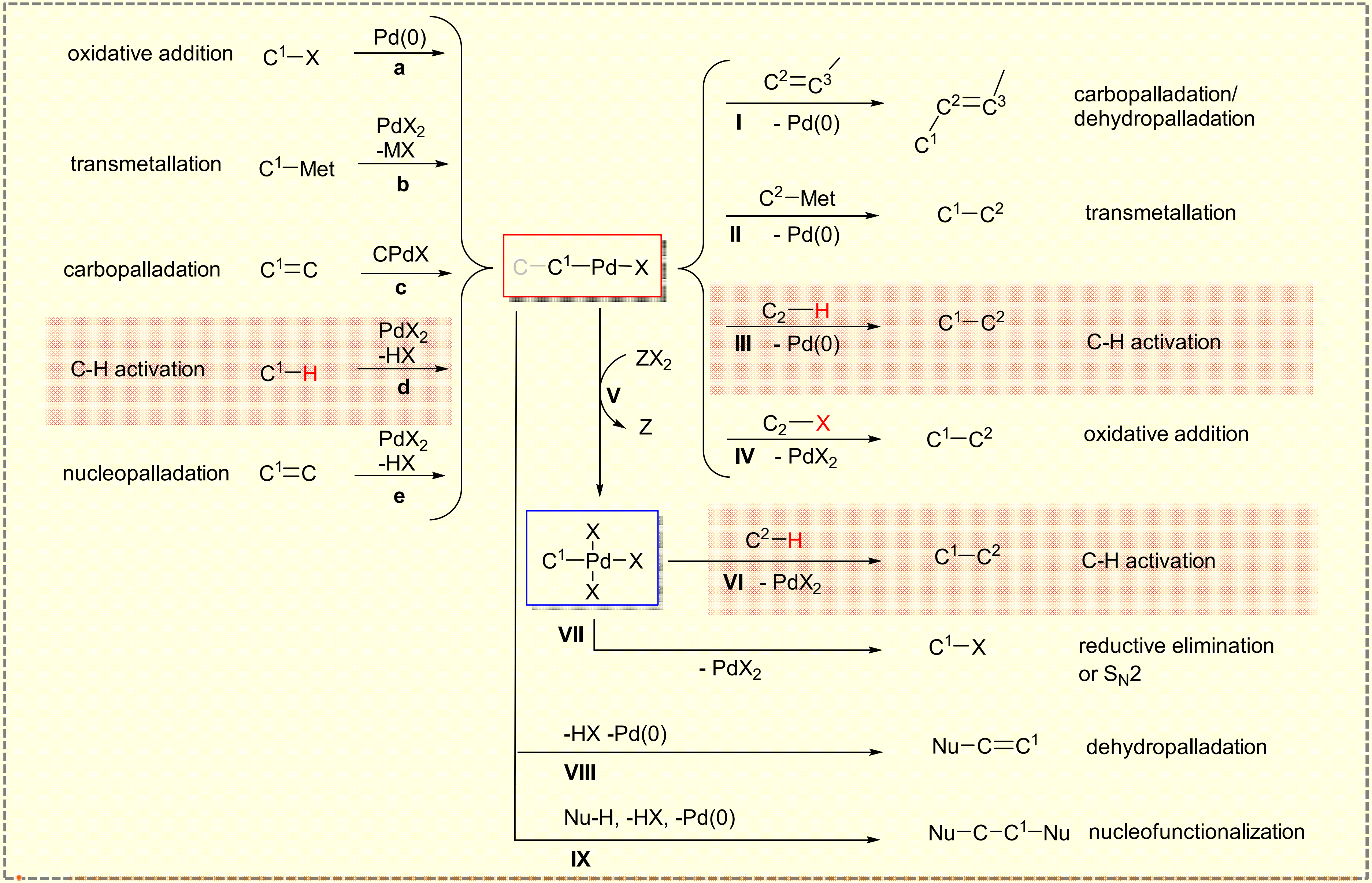
The Bergman Breakthrough



- Low temperature IR flash kinetic spectroscopy
- C-H selectivity: $sp^2 > 1^o\ sp^3$ (Rh easier than Ir)
- The hydrido(alkyl)metal complex is unproductive
- The oxidative addition is thermodynamically favored.
- Rh: thermodynamic control. Ir: kinetic control

(a) Janowicz, A. H.; Bergman, R. G. *J. Am. Chem. Soc.* **1982**, *104,* 352
(b) Hoyano, J. K.; Graham, W. A. G. *J. Am. Chem. Soc.* **1982**, *104*, 3723
(c) Jones, W. D.; Feher, F. J. *Organometallics* **1983**, *2*, 562

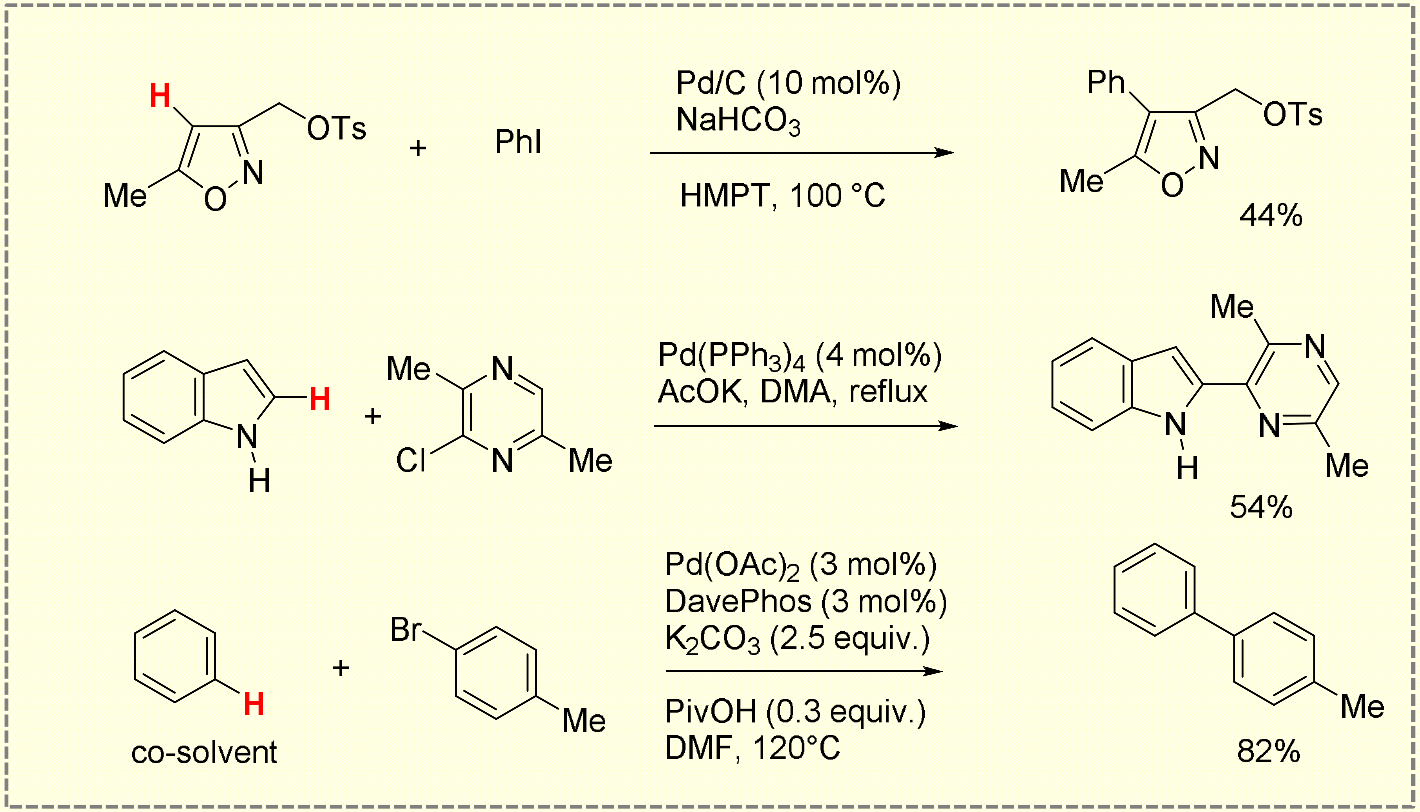
Electrophilic Paths: The Pivotal Role of C-Pd-X

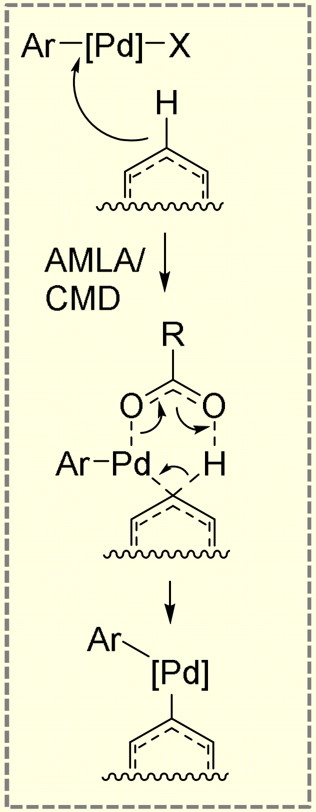


Oxidative Addition Triggered Arylations

coupling type c, path (a + III) — Electrophilic reactivity

aryl/aryl





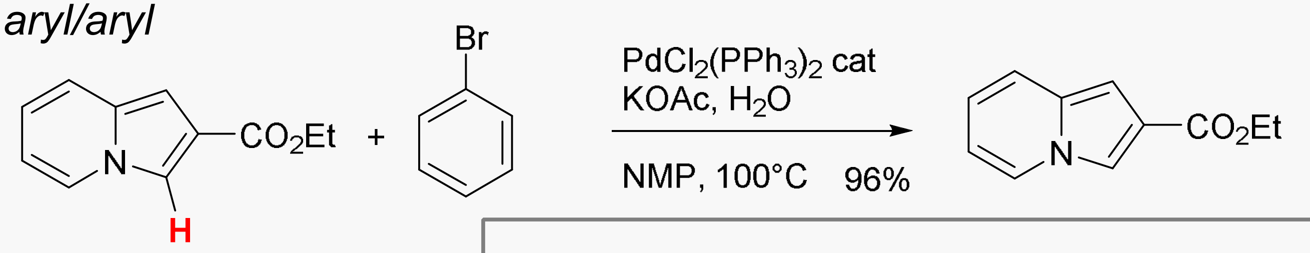
(a) Nakamura, N.; Tajima, Y.; Sakai, K. *Heterocycles* **1982**, *17*, 235
(b) Akita, Y. Ohta, A. *Heterocycles* **1982**, *19*, 329
(c) Fagnou, K. *et al. J. Am. Chem. Soc.* **2006**, *128*, 16496

Oxidative Addition Triggered Arylations

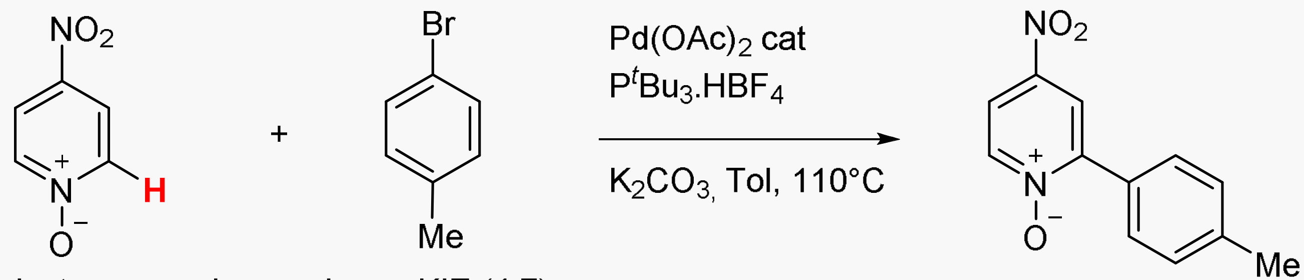
coupling type c, path (a + III)

Electrophilic reactivity

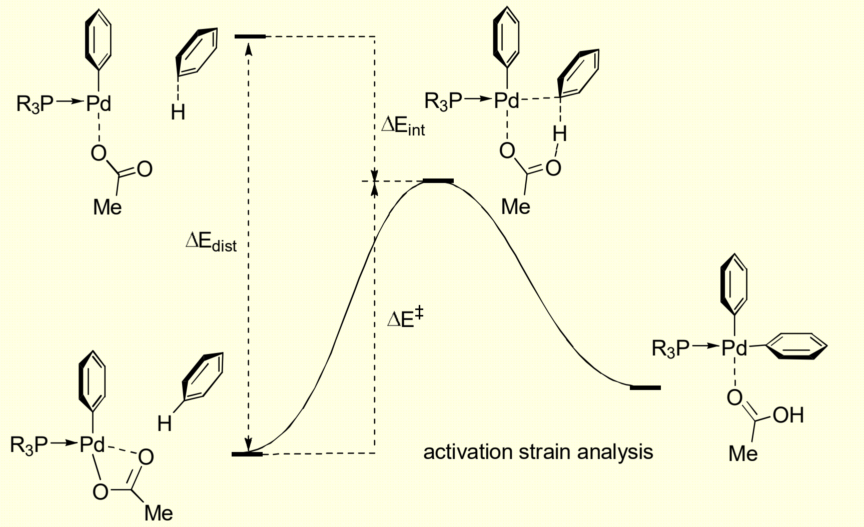
aryl/aryl



electron rich, no primary KIE



electron poor, large primary KIE (4.7)



(a) Park, C-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 115

(b) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020

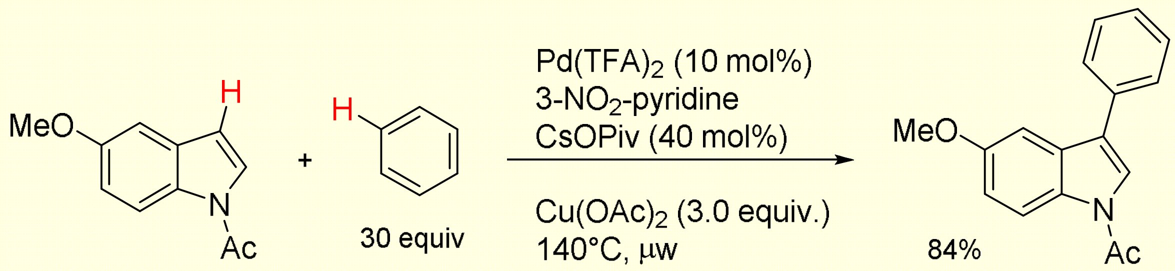
Cross Dehydrogenative Couplings (CDC)

coupling type d, path (d + III)

Electrophilic reactivity

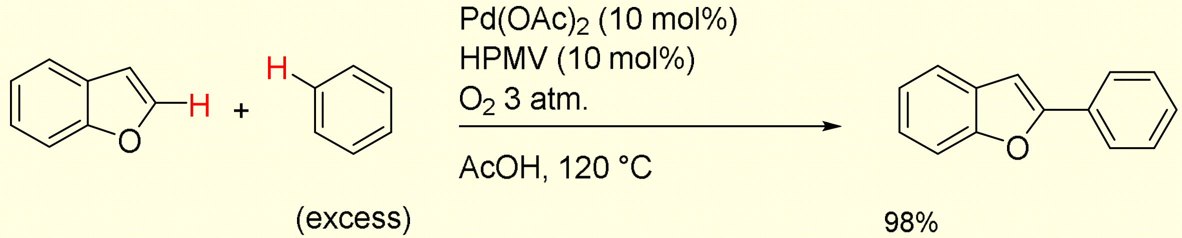
aryl/aryl

(a)

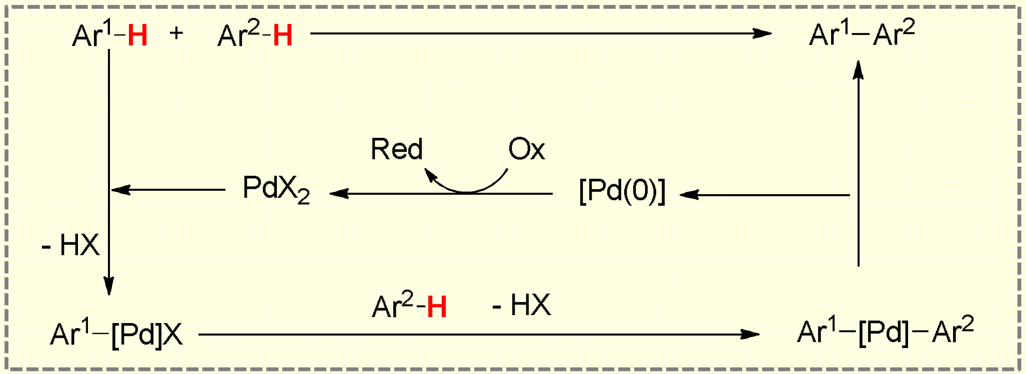


Stuart, D. R. Fagnou, K. *Science*, **2007**, *316*, 1172

(b)



Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett. 2007, 16*, 3137-3139

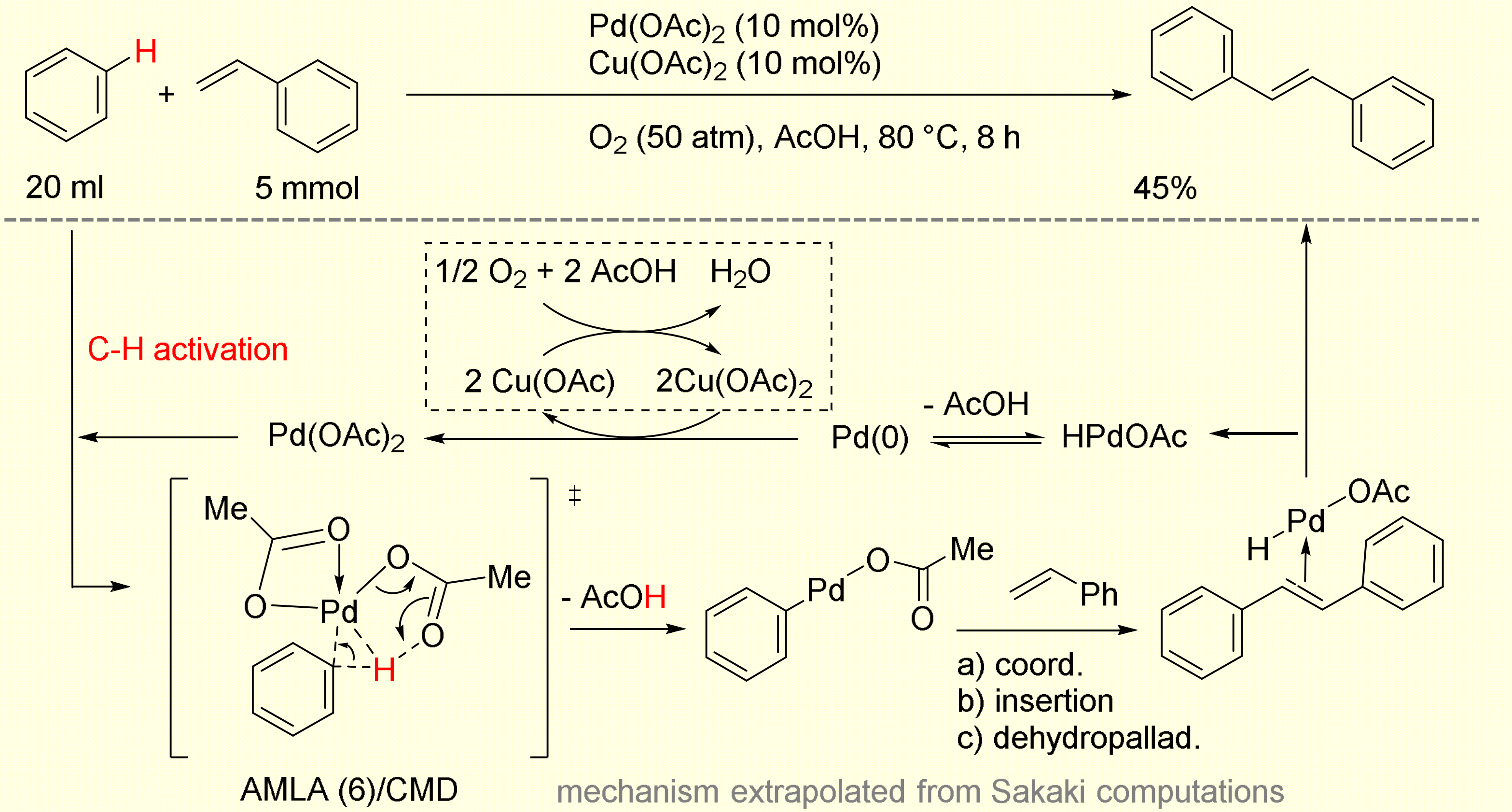


Fujiwara–Moritani reaction

aryl/vinyl, coupling type d, path (d + l)

Electrophilic reactivity

aryl/vinyl

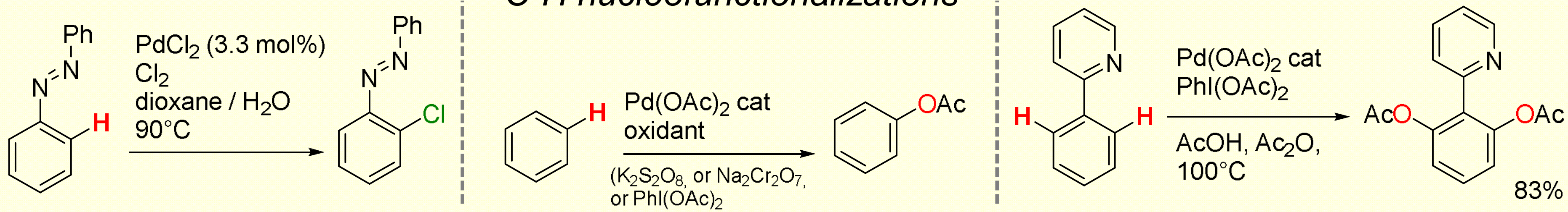


Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *8*, 1119

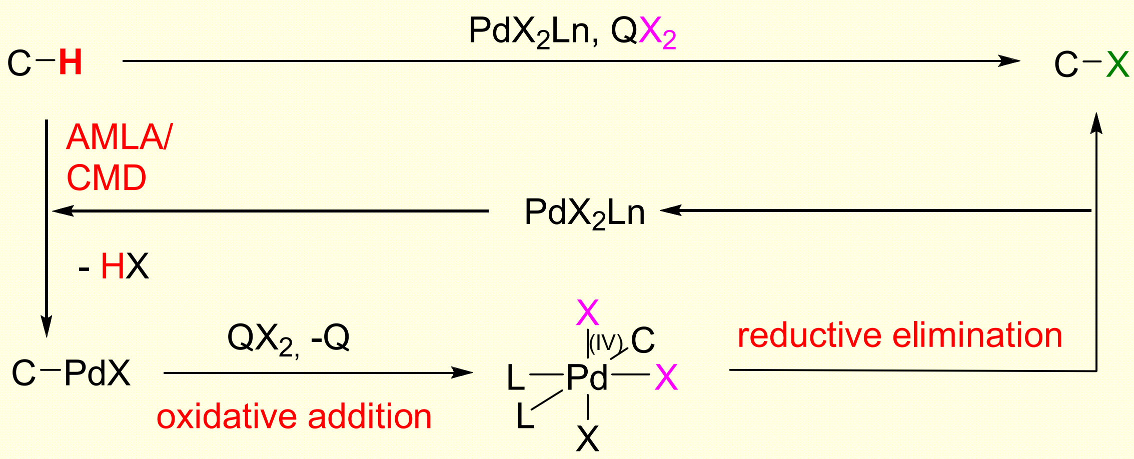
Oxidative Pd(II)/Pd(IV) Sequences

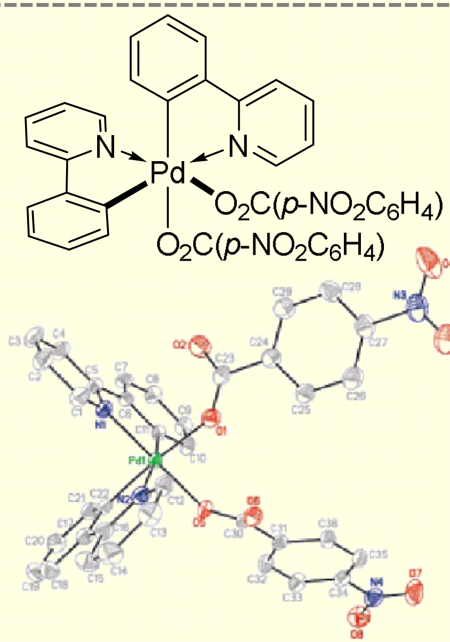
coupling type e, path (d + V + VII)

C-H nucleofunctionalizations



(a) Fahey, D. R. *J. Organometal. Chem.* **1971,** *27*, 283.
(b) Eberson, L. J. *et al. Liebigs Ann. Chem*. **1977,** 233; Stock, L. M. et al. *J. Org. Chem.* **1981**, *46*, 1759. Crabtree R. H. *et al. J. Mol. Catal. A: Chem.* **1996**, *108*, 35
(c) Sanford, M. S. *et al. J. Am. Chem. Soc.* **2004**, *126*, 2300.



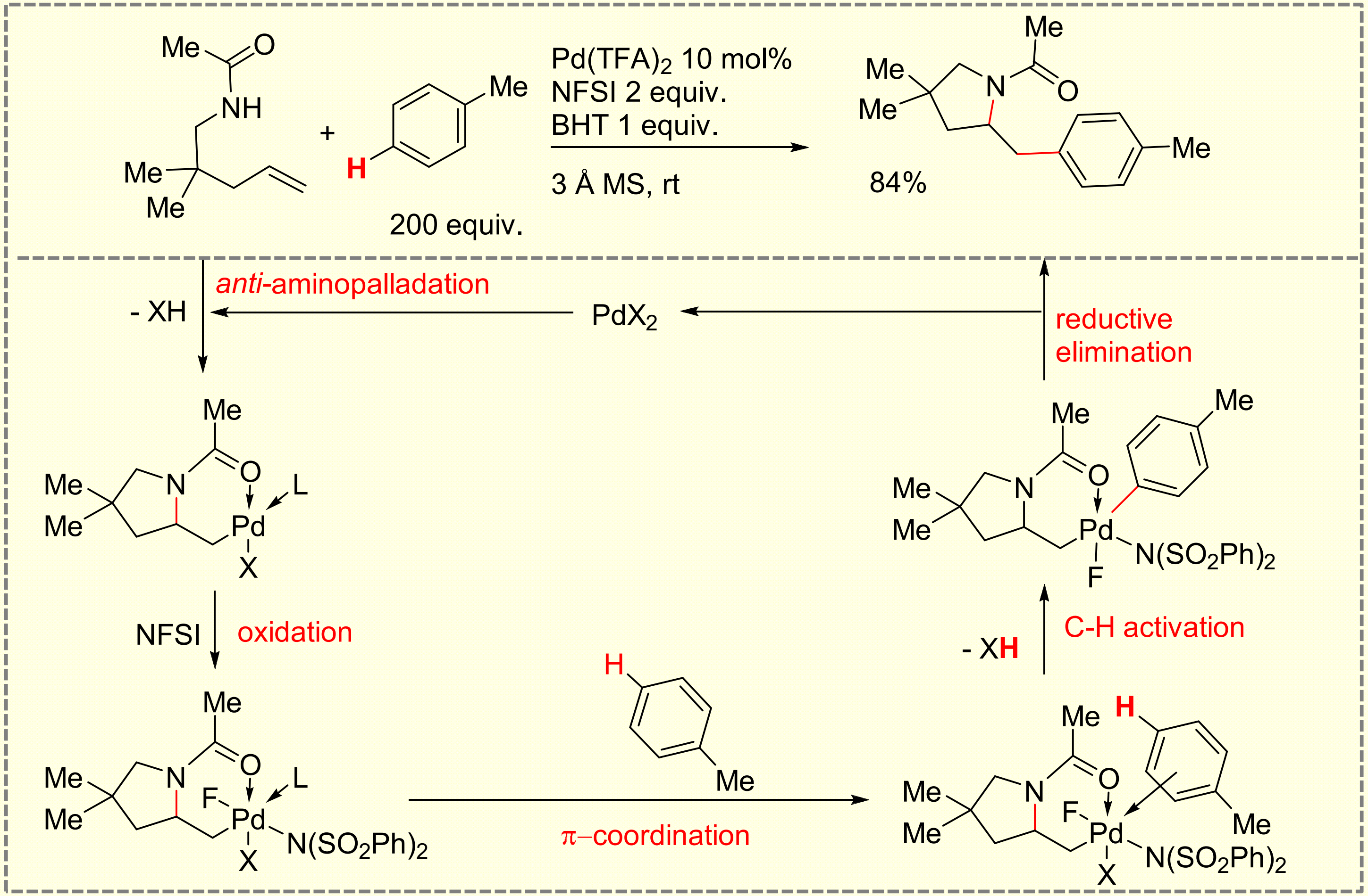


Sanford, M. *et al. J. Am. Chem. Soc.* **2005**, *127*, 12790

C–H activation at Pd(II) vs Pd(IV)

coupling type g, path (e + V + VI)

alkene 1,2-aminoalkylation



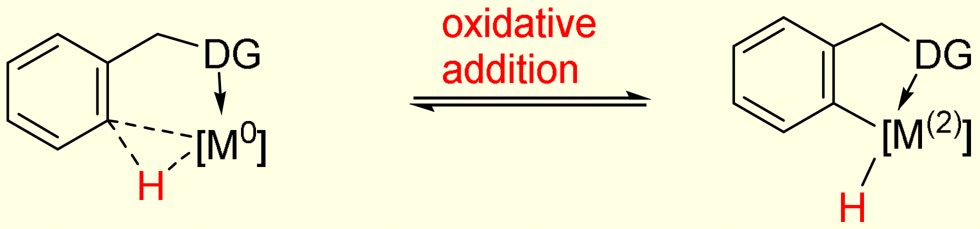
(a) Sibbald, P. A.; Rosewall, C. F.; Swartz, R. D.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 15945.

(b) Rosewall, C. F.; Sibbald, P. A.; Liskin, D. V.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, 131, 9488.

Substrate Control: Directed Aromatic ortho Activations

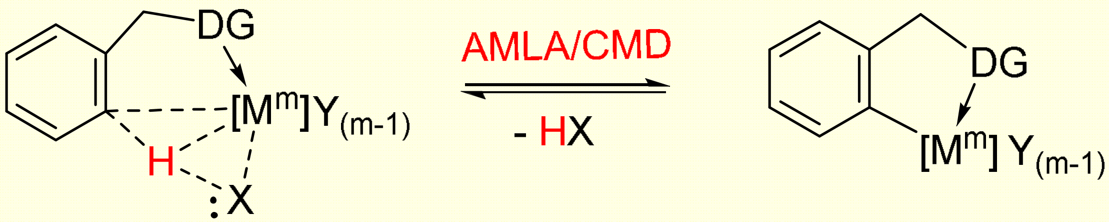
Two mechanistically different strategies

Nucleophilic



Ru(0) (Murai)

Electrophilic



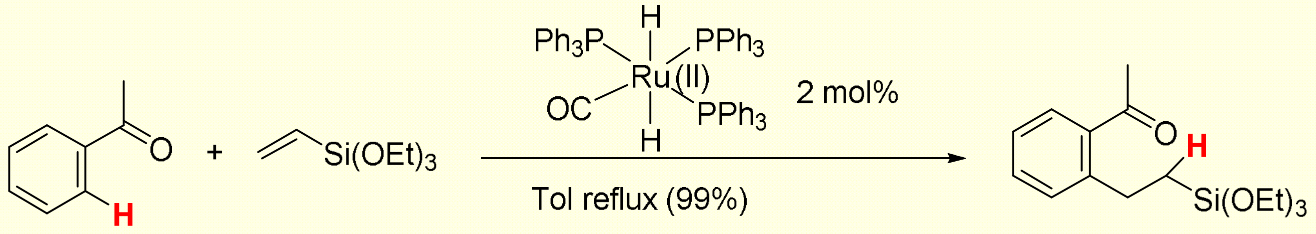
Pd(II), Ru(II)...
(Directed Fujiwara)

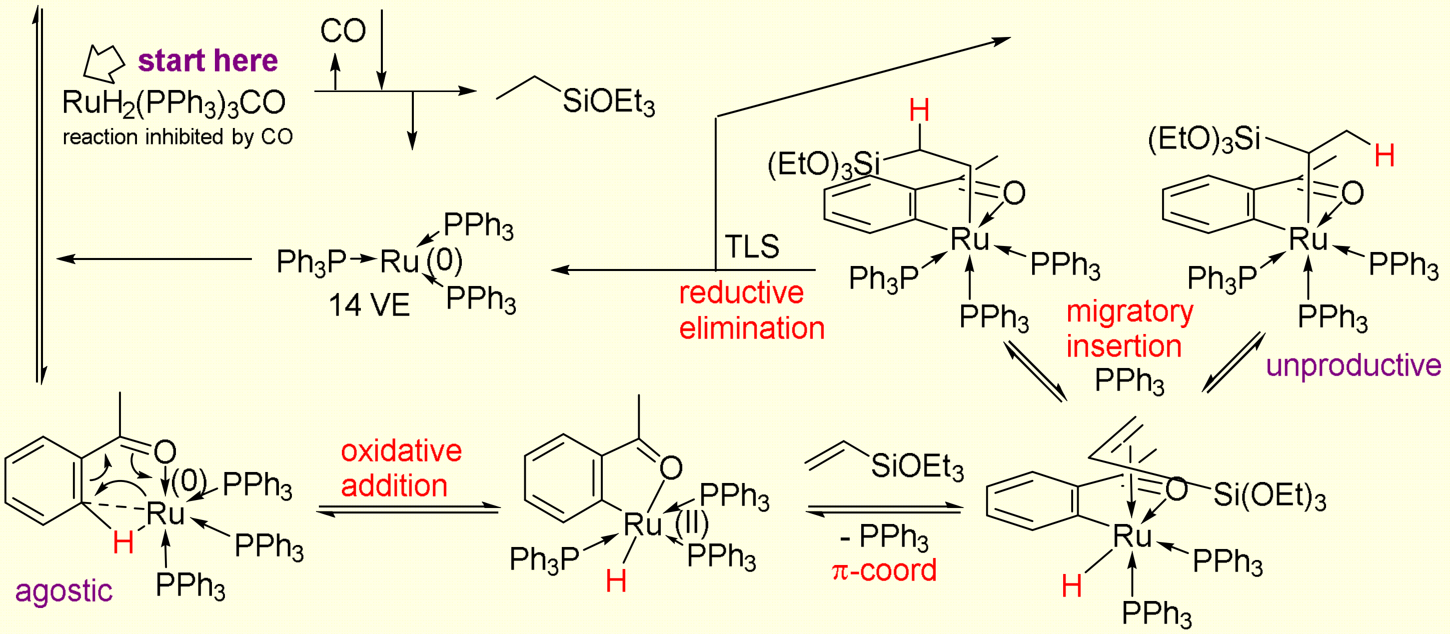
Seminal papers on directed *ortho* activation: (a) S. Murahashi *J. Am. Chem. Soc.* **1955**, *77* (1955) 6403-6404; (b) J. P. Kleiman, M. Dubeck, *J. Am. Chem. Soc.* **1963**, *85*, 1544-1545.

Nucleophilic Directed C-H Activation: The Murai Reaction

Aromatic ortho C-H activation, the Murai-Chatani-Kakiuchi reaction

Nucleophilic reactivity



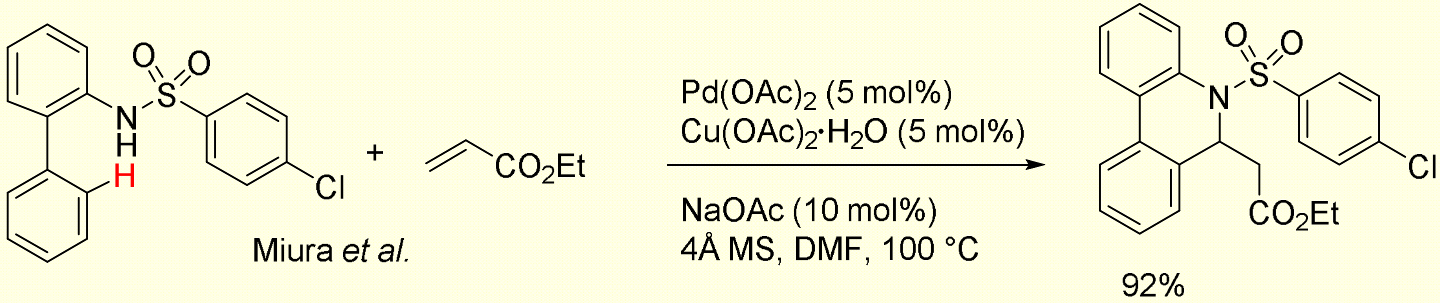


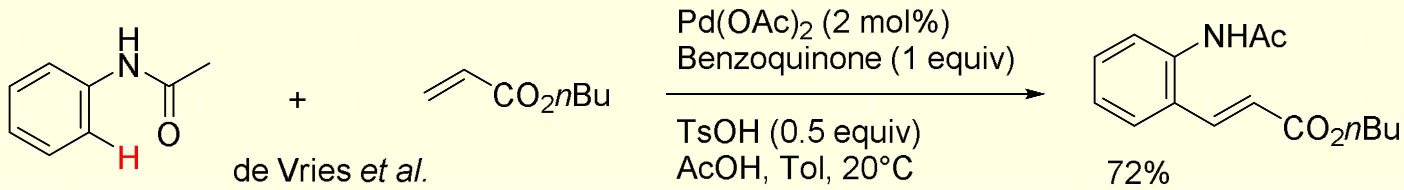
Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529.

Directed Fujiwara-Moritani

Ortho-metalation Pd(II)

Electrophilic reactivity





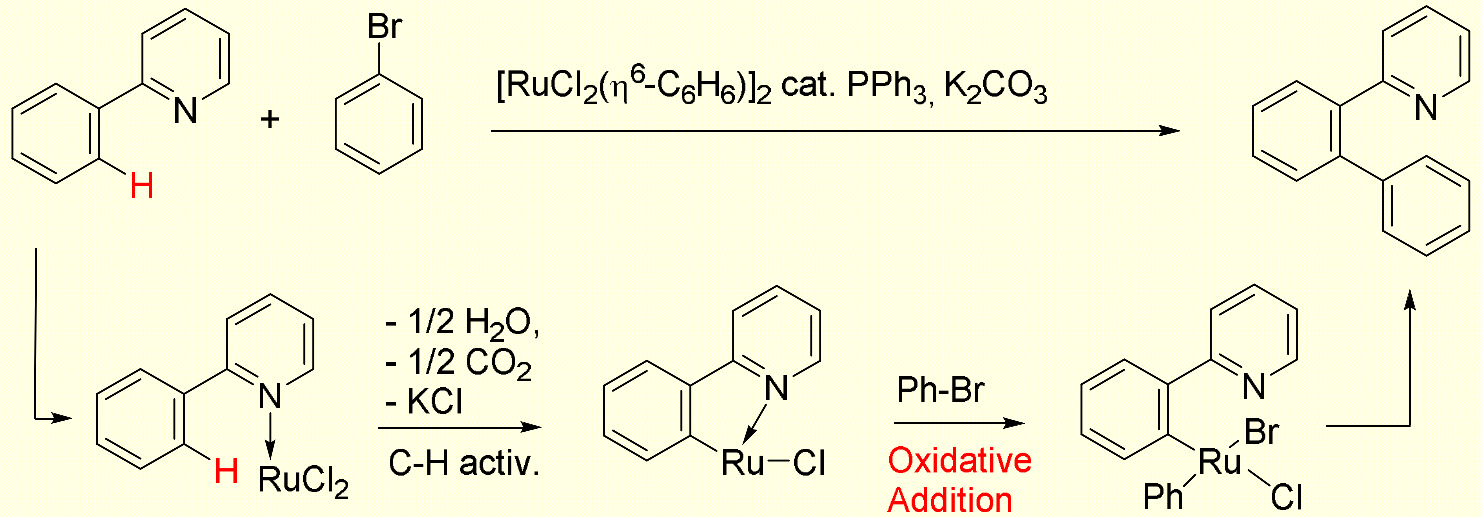
(a) Miura, M.; Tsuda, T.; Satoh, T.; Pivsa-Art, S.; Nomura, M. *J. Org. Chem.* **1998**, *63*, 5211

(b) Boele, M. D. K.; van Strijdonck, G. T. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586

Directed Aromatic C-H Activation

Ortho-metalation Ru(II)

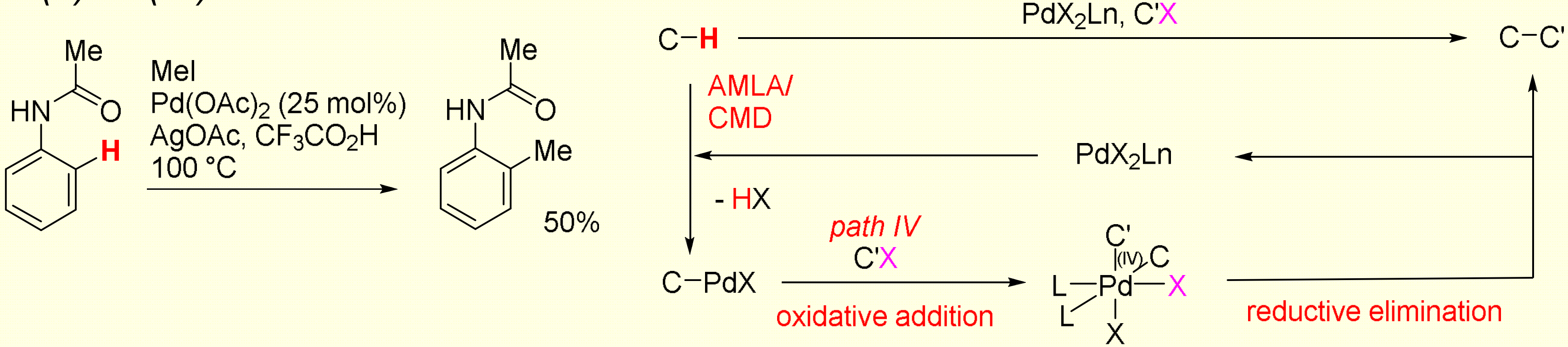
Electrophilic reactivity



Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y. *Org. Lett.* **2001**, *3*, 2579

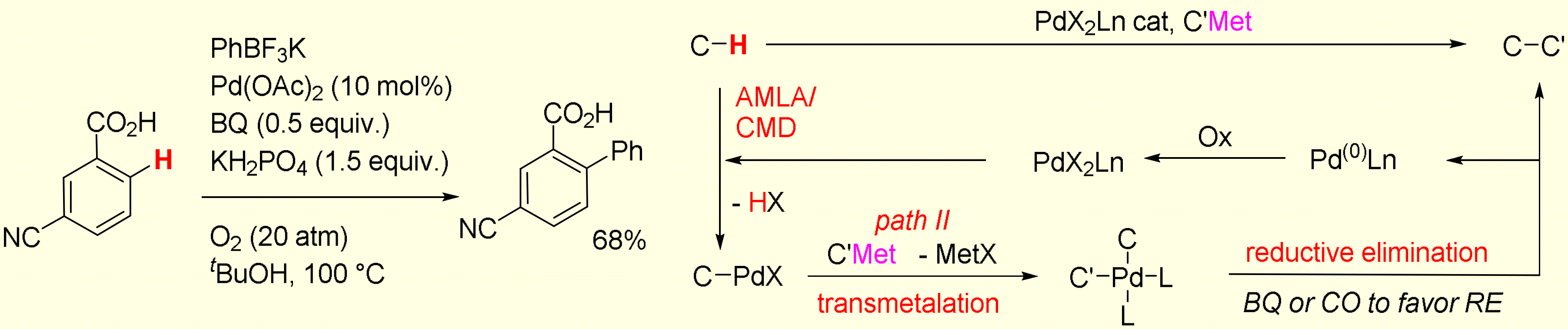
Different directed Pd-catalyzed ortho functionalization

Pd(II)/Pd(IV)



Daugulis, O. *et al. Angew. Chem., Int. Ed.* **2005**, *44*, 4046.

Pd(II)/Pd(0)



Yu. *et al. J. Am. Chem. Soc.* **2008**, *130*, 17676

Selectivity 1° > 2°

ΔBDE - 54 kJ/mol

$$H_3C{-}\mathbf{H} + (RO)_2B{-}B(OR)_2 \longrightarrow H_3C{-}B(OR)_2 + H{-}B(OR)_2$$

435 kJ/mol | 435 kJ/mol | 464 kJ/mol | 460 kJ/mol

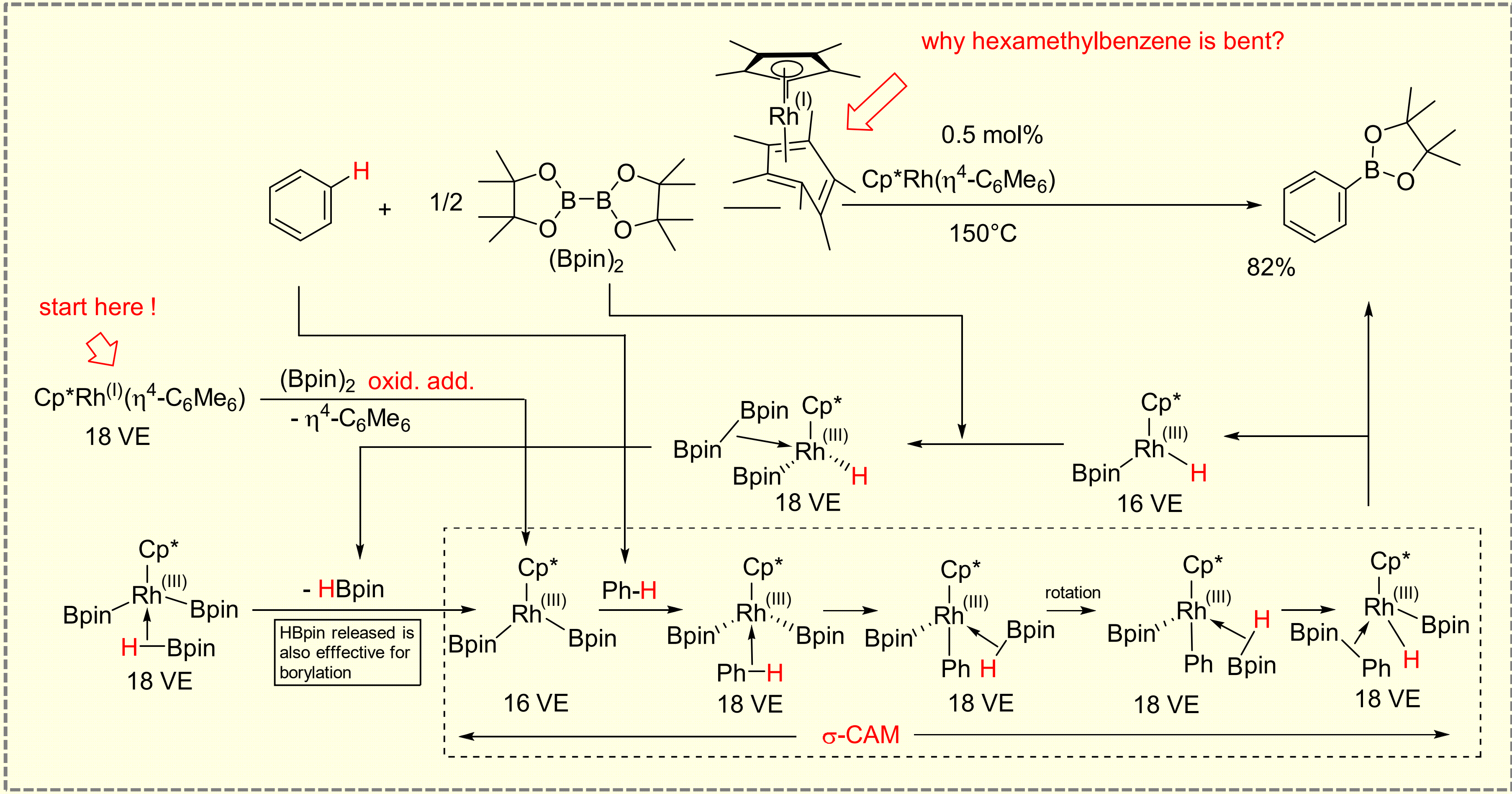
ΔBDE - 4 kJ/mol

$$H_3C{-}\mathbf{H} + H{-}B(OR)_2 \longrightarrow H_3C{-}B(OR)_2 + H{-}H$$

435 kJ/mol | 460 kJ/mol | 464 kJ/mol | 435 kJ/mol

Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890

C-H Borylation



Iverson, C. N.; Smith III, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 7696.
Chen, H.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **1999**, *38*, 3391.
Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.

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Metal-catalyzed C—H activation/functionalization: The fundamentals

CrossMark

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Dedicated to Professor Georgiy B. Shul'pin on the occasion of his 70th birthday.

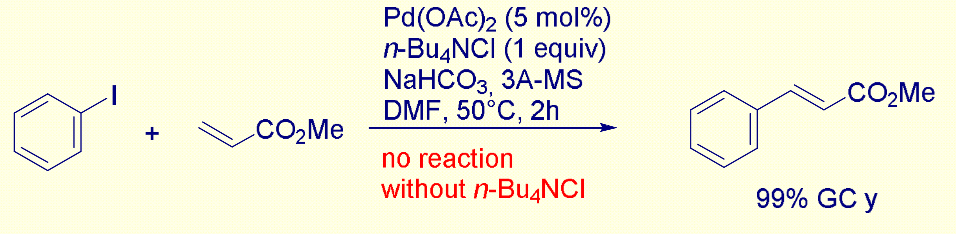
Keywords:
C—H activation
C—H functionalization
C—C bond formation
C-heteroatom bond formation
Mechanistic study

A B S T R A C T

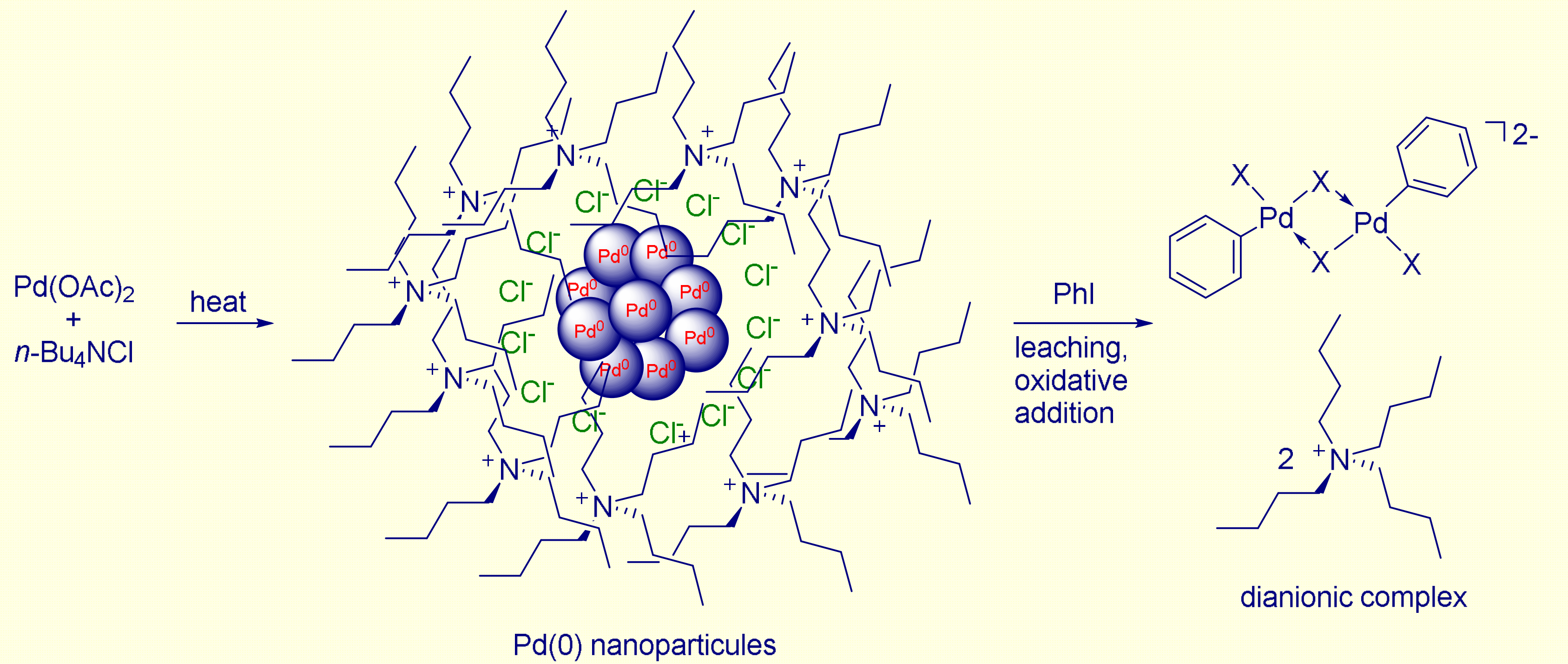
An isolated C—H bond in a molecule has a very low reactivity owing to the large kinetic barrier associated to the C—H bond cleavage and the apolar nature of this bond. For this reason, the selective reactivity of such a non-functional group is under active study since several decades and is still regarded as the Holy Grail in chemistry. Metal-catalyzed C—H activation/functionalization chemistry allows the step-economical and original construction of C—C as well as C—O and C—N bonds starting from hydrocarbons (or hydrocarbon fragments) without the need of prior non catalytic oxidation steps. Furthermore, it can be of utmost importance in the domain of multistep syntheses, and also in transformations of societal significance such as the conversion of methane into methanol. This tutorial review addresses to students and researchers who would like to become acquainted with this fascinating topic. After a brief historical introduction, the main mechanistic fundaments of metal-catalyzed C—H activation are exposed. Then, a selection of seminal advances and conceptual breakthroughs are presented.

Roudesly, F; Oble, J; Poli, G. *J. Mol. Cat. A. Chem.* **2017**, *426*, 275

The Jeffery ligandless conditions



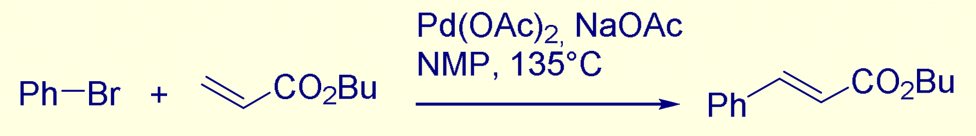
Jeffery, T. J. *Chem. Soc., Chem. Commun.* **1984**, 1287
Jeffery, T. *Tetrahedron*, **1996**, 52, 10113.

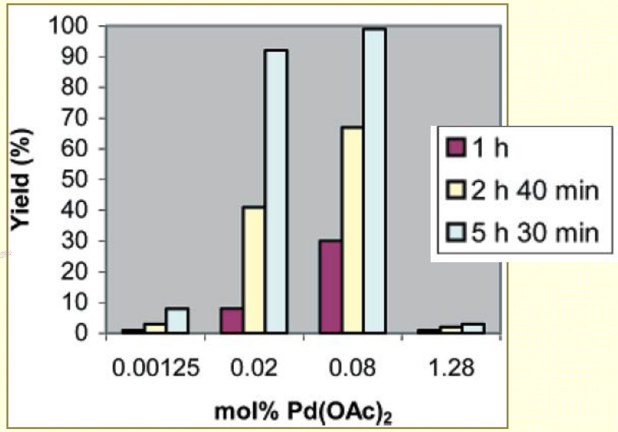


Gittins, D. I.; Caruso, F. *Angew. Chem. Int. Ed.*, **2001**, *40*, 3001
Astruc, D. *Inorg. Chem.*, **2007**, *46*, 1884

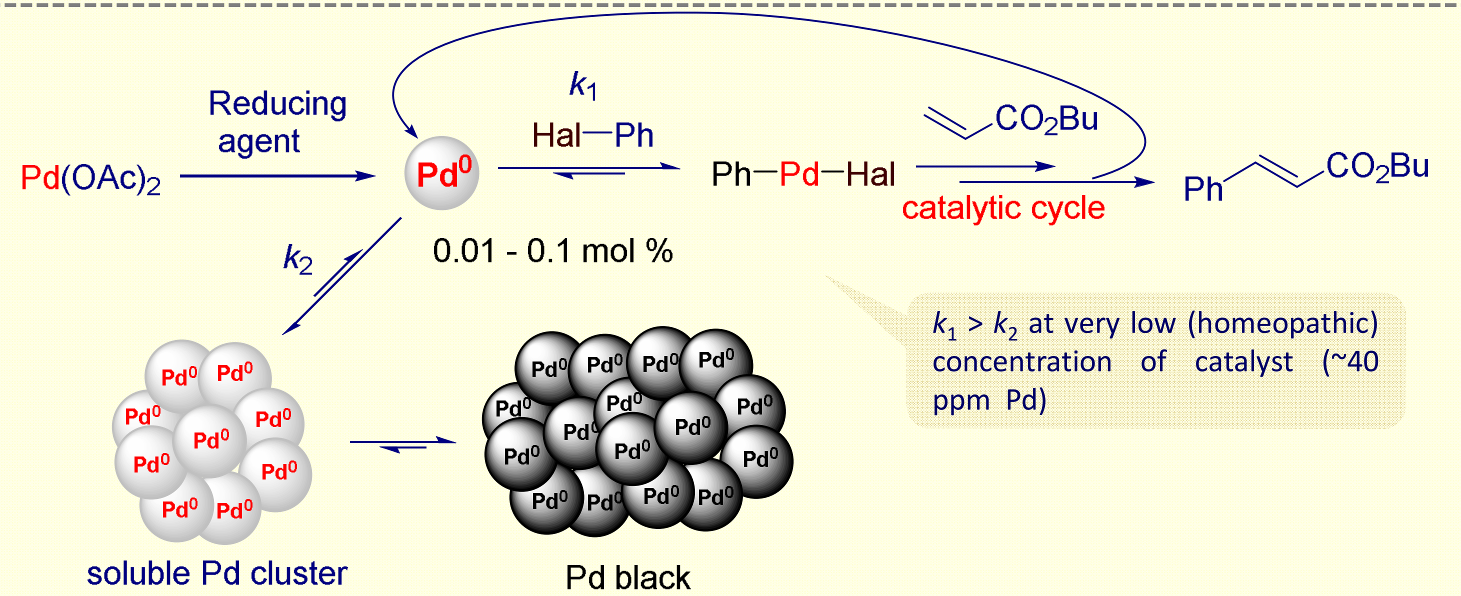
Cookson, *Platinum Metals Rev.*, **2012**, *56*, 83
Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 79

Homeopathic amounts of catalyst





Effect of palladium/substrate ratio on the yield of the Mizoroki-Heck reaction between PhBr and *n*-butyl acrylate at 135 °C

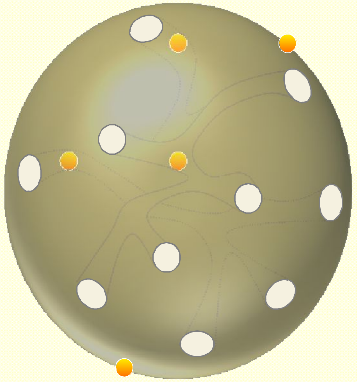


$k_1 > k_2$ at very low (homeopathic) concentration of catalyst (~40 ppm Pd)

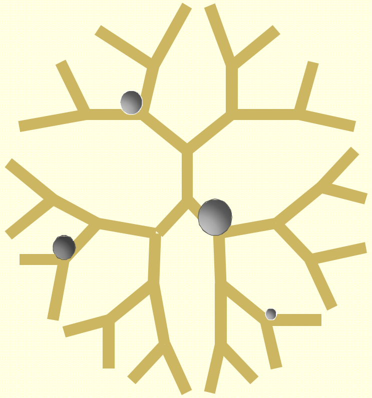
de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M. ; Henderickx, H. J. W. ; de Vries, J. G. *Org. Lett.*, **2003**, *5*, 3285.
Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F.; Sánchez, G.; López, G.; Serrano, J. L.; García L.; Pérez, E. *Dalton Trans.*, **2004**, 3970.

Polymer supports in catalysis

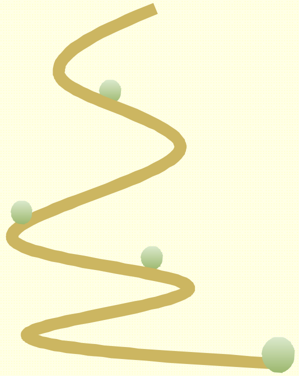
From heterogeneous to quasi homogeneous catalysis



Merrifield resins, aerogels



Dendrimers



Polymer Chains

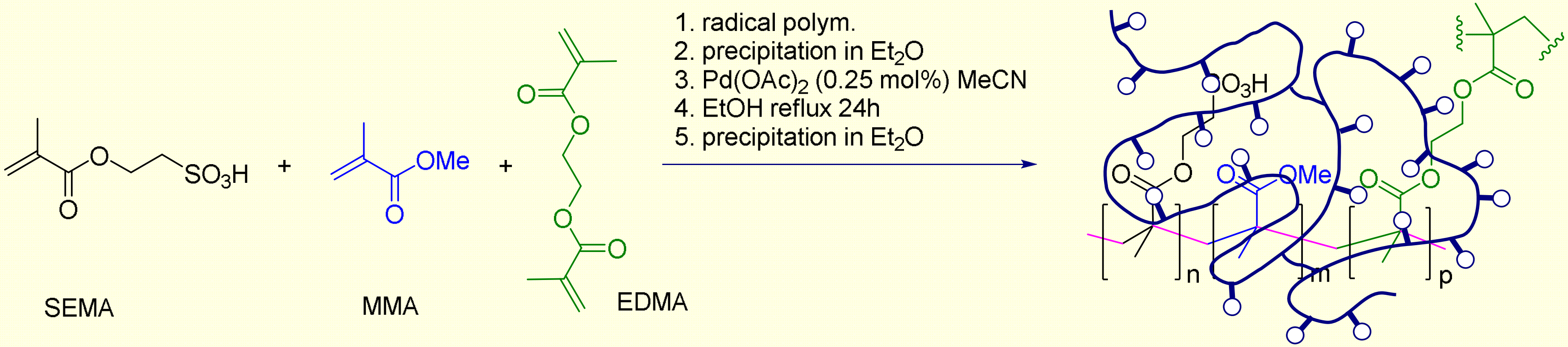
quasi-homogeneous catalysis

Insoluble | **Soluble**

- nonlinear kinetic behavior
- unequal distribution and/or access to the chemical reaction
- solvation problems associated with the nature of the support
- synthetic difficulties in transferring standard organic reactions to the solid phase

Chem. Rev. **2009**, *109*, 302.; *ACS Macro Lett.* **2014**, *3*, 260.

Functionalised microgels to stabilise metal colloids

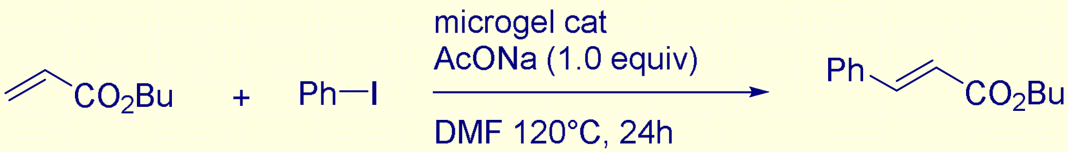


20% w/w | 60% w/w | 20% w/w

Clear colloidal suspension

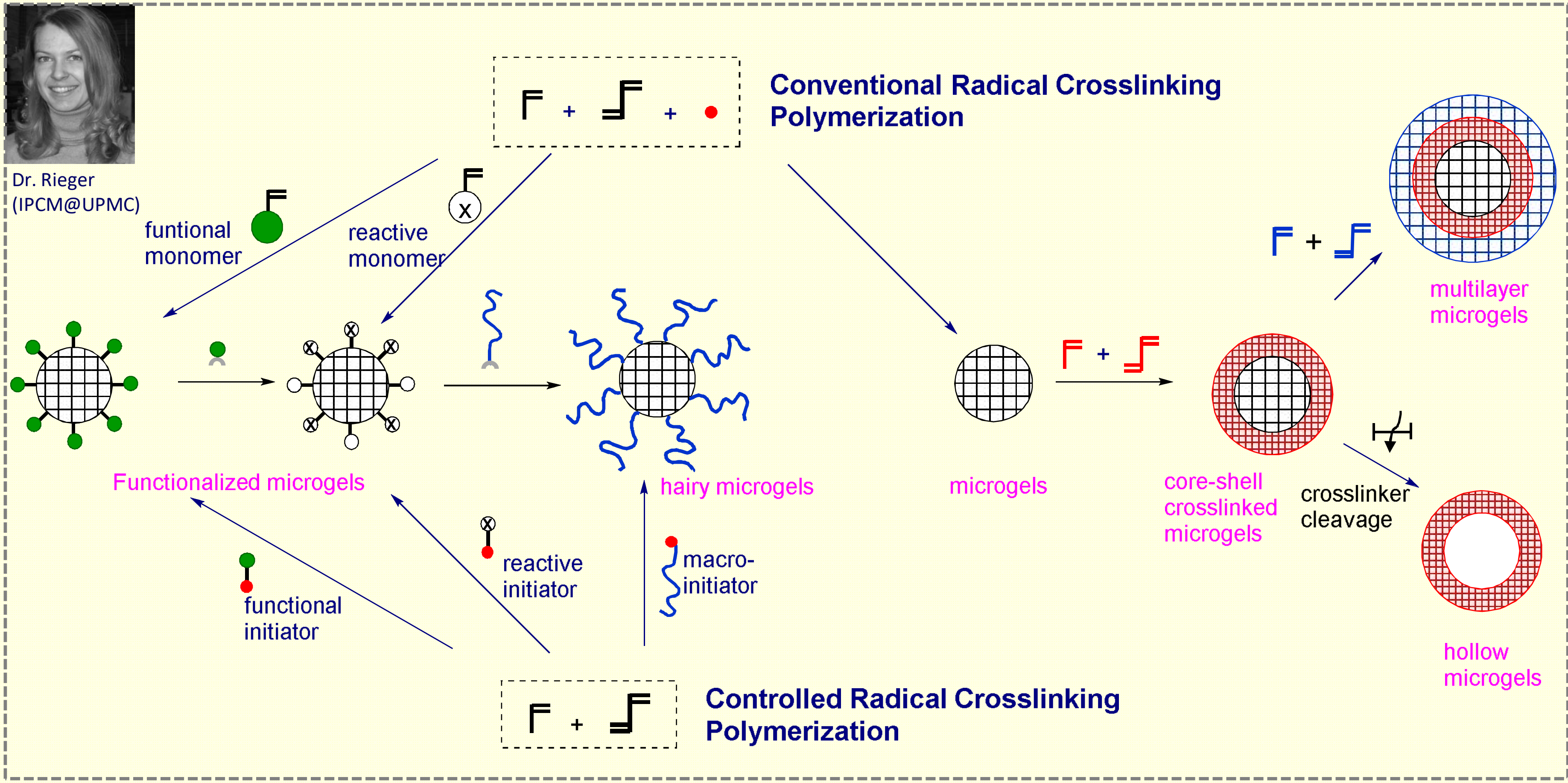
10-20 nm particle size

100 nm



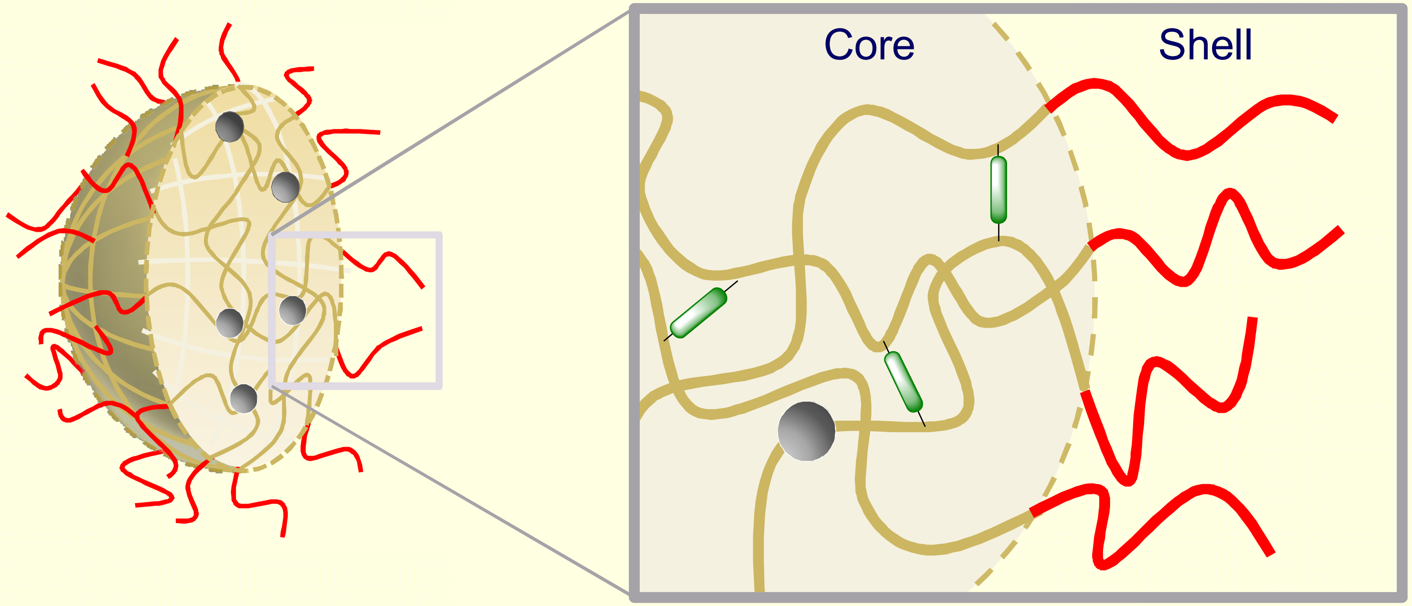
A. Biffis, *J. Mol. Catal. A : Chem.* **2001**, *165*, 303-307

Smart well-defined catalytic nanoreactors



Sanson, N. ; Rieger, J. *Polym. Chem.*, **2010**, *1*, 965–977

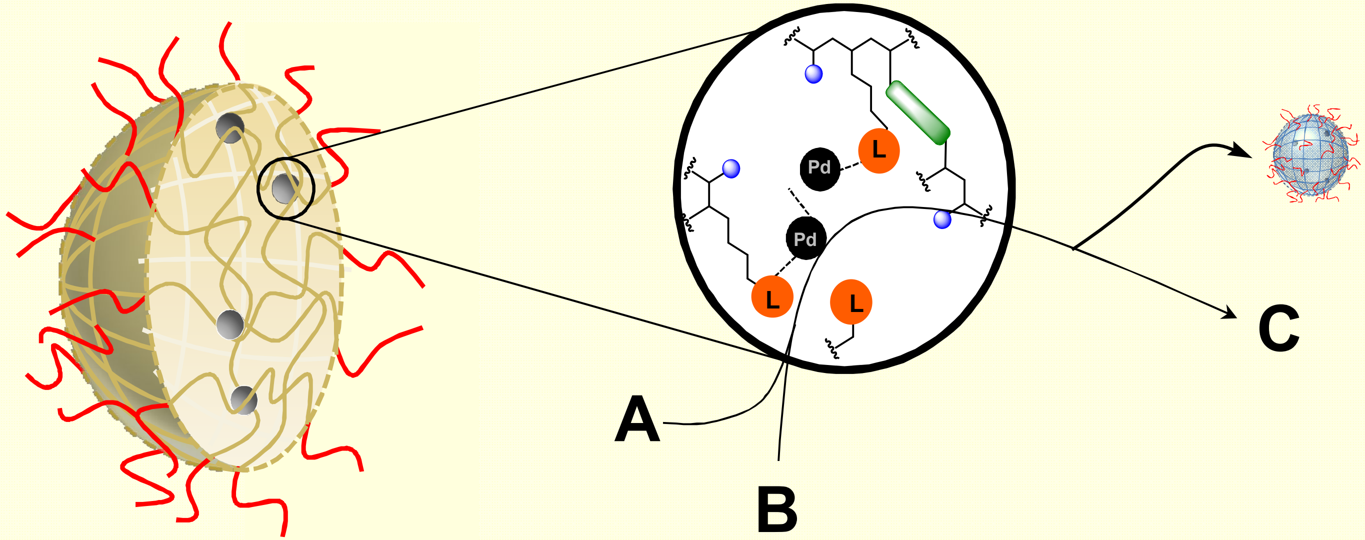
Hybrid core-shell nanogels



- Globular shaped cross-linked polymers in the range of 10-500 nm
- Different polymers in the shell and the core
- Swell in the presence of good solvents
- Confine metallic species (recycling, nanoreactors)

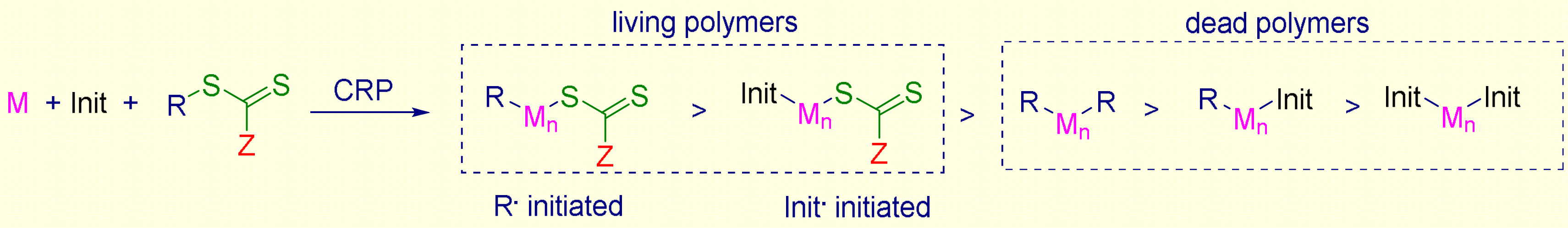
Macromol. Rapid Commun. **2008**, *29*, 1965.
Macromol. Rapid Commun. **2015**, *36*, 1458.
Chem. Rev. **2015**, *115*, 9745.

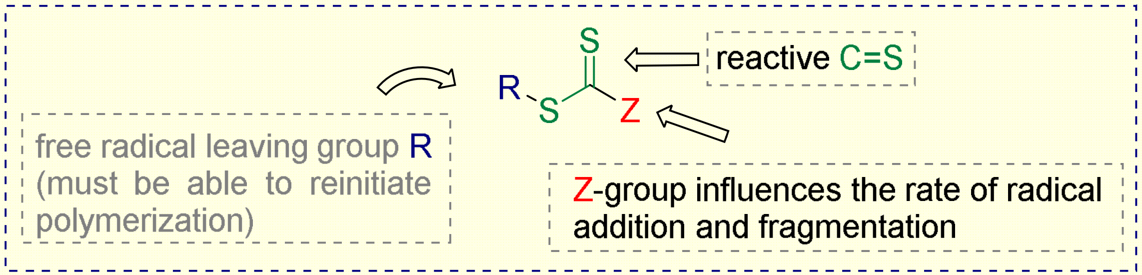
Objectives



- Synthesize Core-Shell nanogels with metal coordinating monomers
- Functionalisation with metallic species
- Study the catalytic properties of the hybrid materials
- Understanding system robustness and recyclability

Reversible addition-fragmentation chain-transfer polym

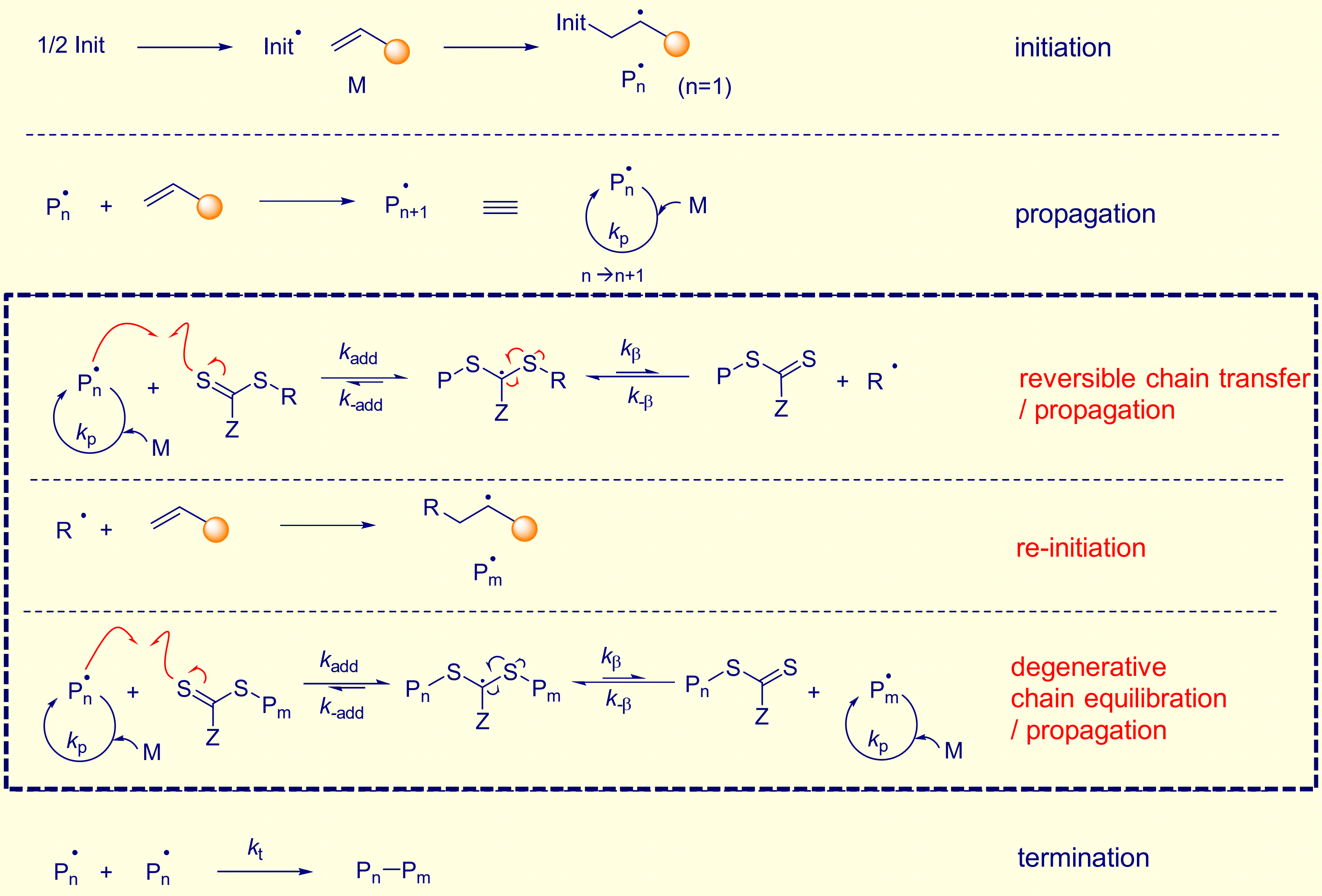




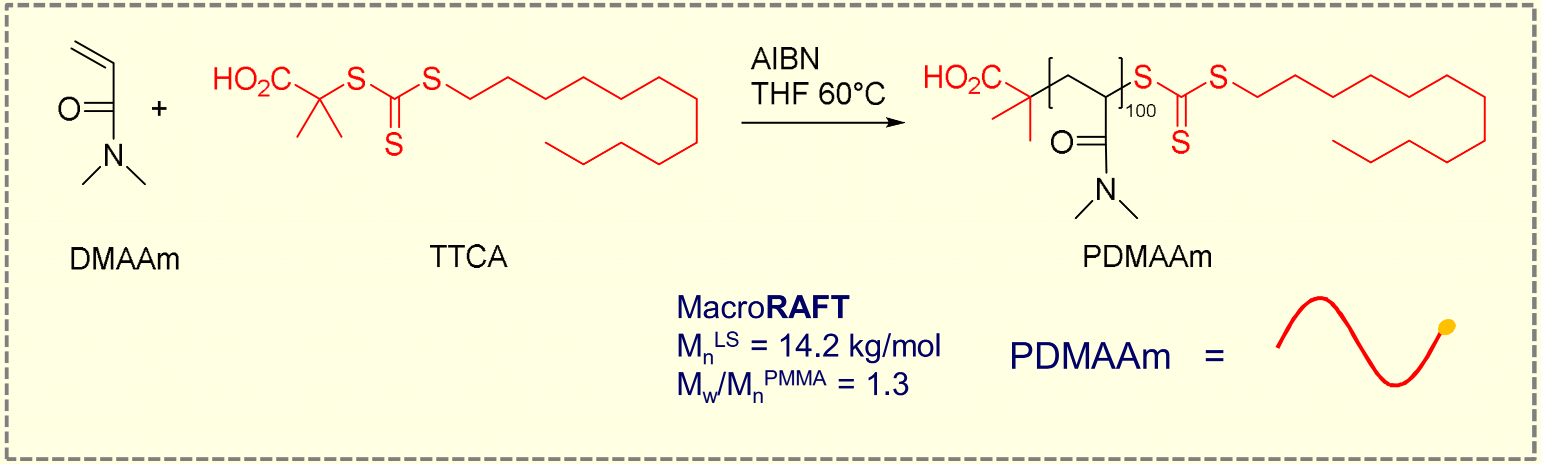
- Mechanism superimposed on a conventional free radical polymerization
- Predictable size and narrow M_n distribution (chain length and molar mass distribution depend directly on the monomer/control agent ratio).
- Large range of monomers: (meth)acrylates, (meth)acrylamides, vinyl, …
- Fast initiation, absence of termination…
- Polymer architecture (alternate or gradient copolymers; one or more blocks; ...)

Rizzardo, E. Thang, S. H. *Macromolecules*, **1998**, *31*, 5559.
Matyjaszewski K. et al. *Materialstoday* **2005**, *8*, 26; *Prog. Polym. Sci.* **2007**, *32*, 93.

Reversible addition-fragmentation chain-transfer polym.

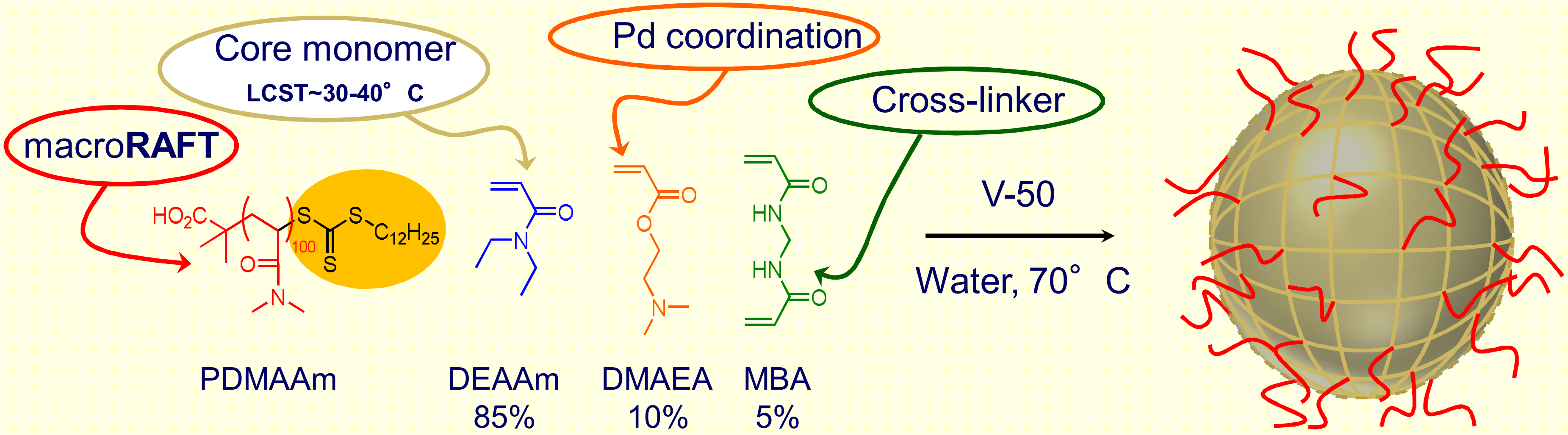


Reversible addition-fragmentation chain-transfer polym.

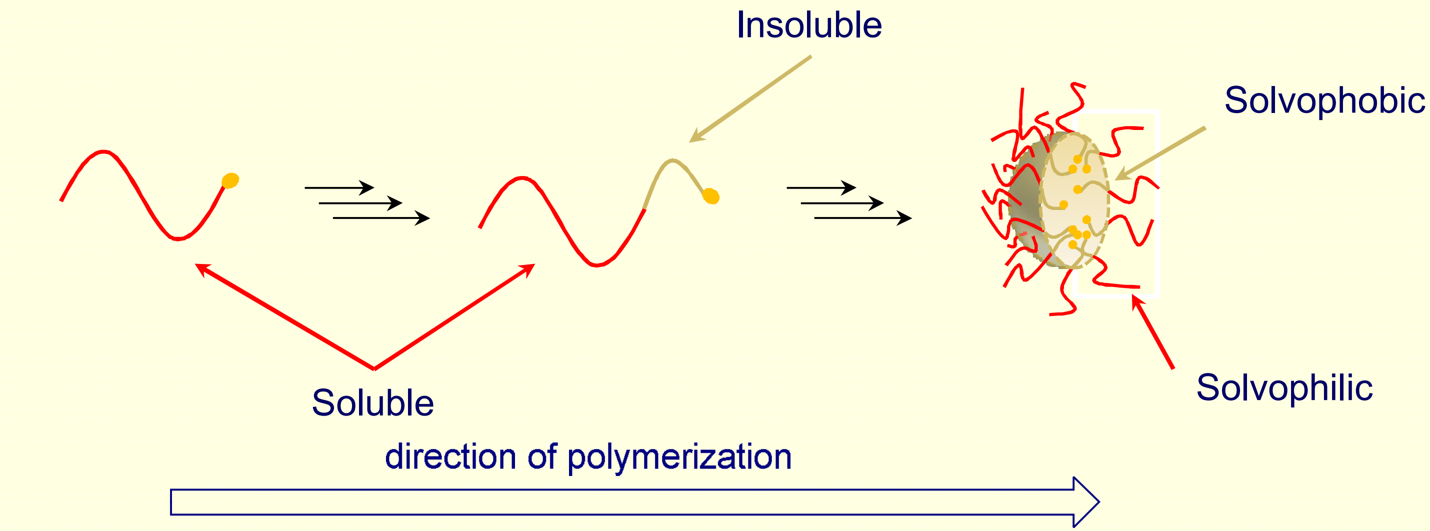


Hawker, C. J.; et al. *J. Am. Chem. Soc* **2007**, *129*, 14493

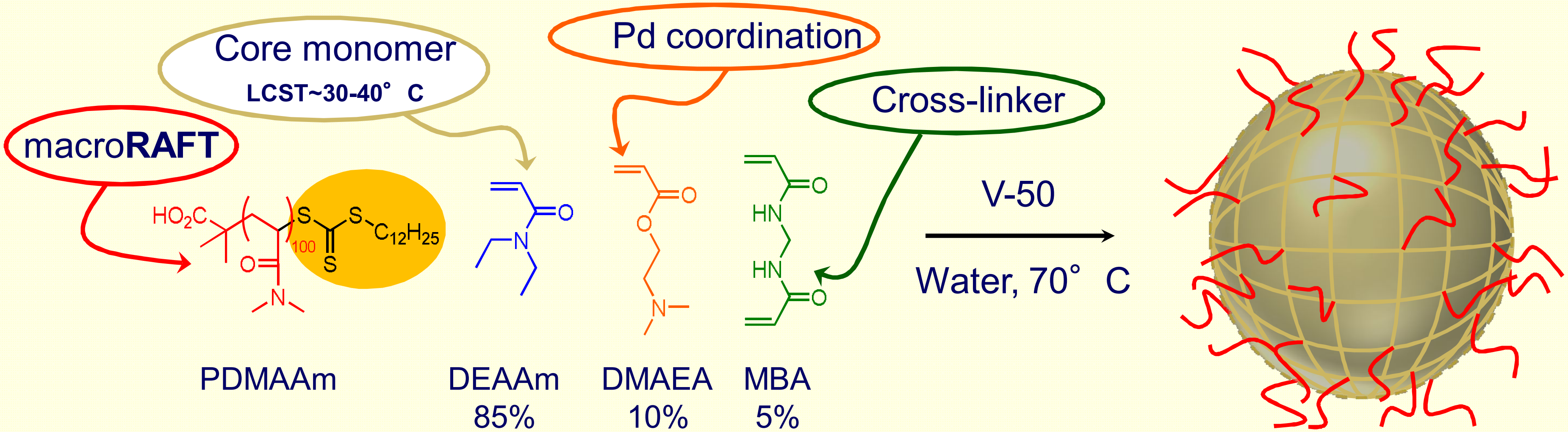
Nanogel synthesis



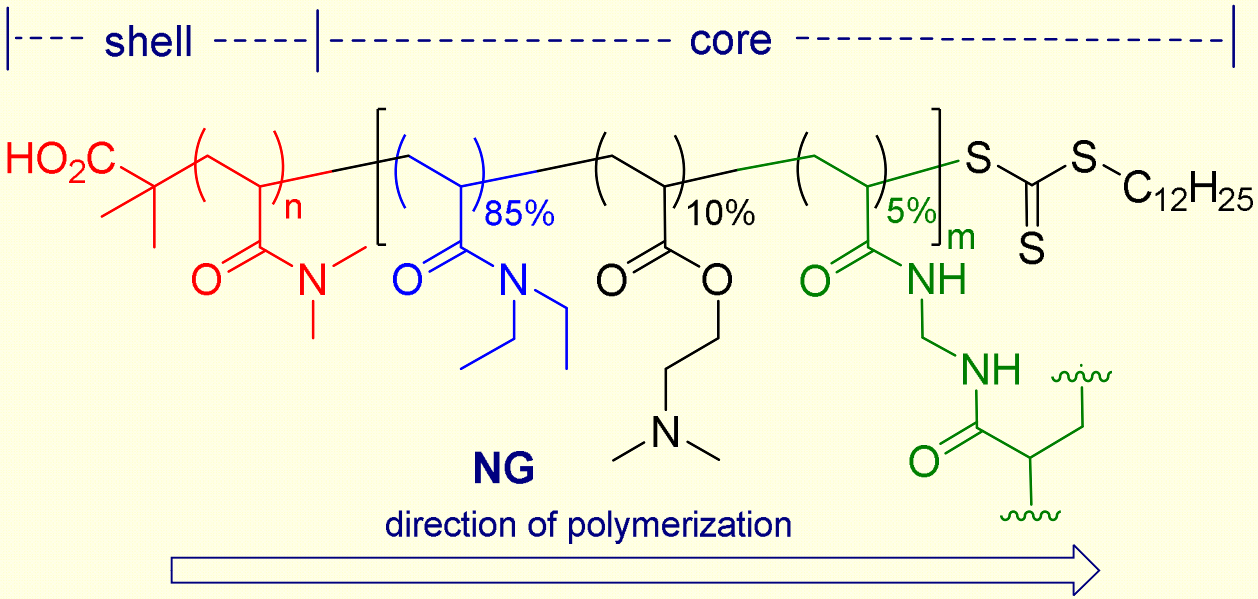
PDMAAm-*b*-P(DEAAm-*co*-DMAEA-*co*-MBA) **NG**



Nanogel synthesis

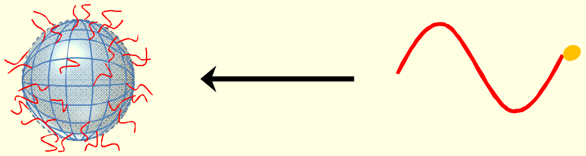


PDMAAm-*b*-P(DEAAm-*co*-DMAEA-*co*-MBA) **NG**



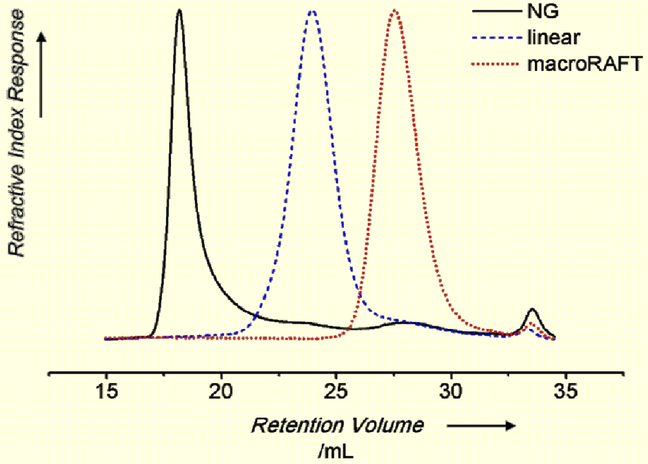
Nanogel characterization

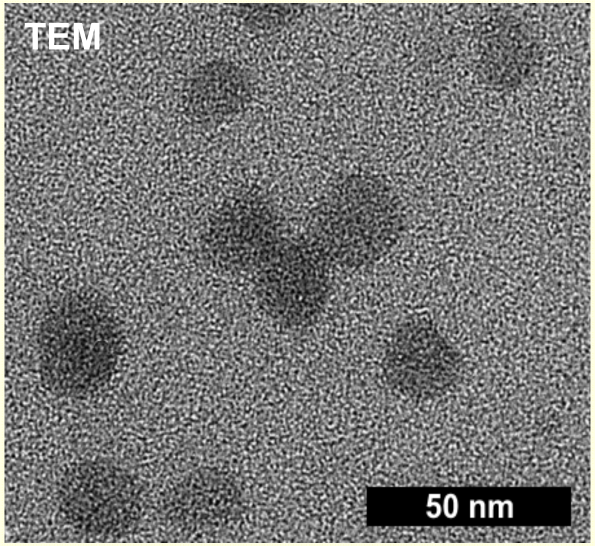
SEC



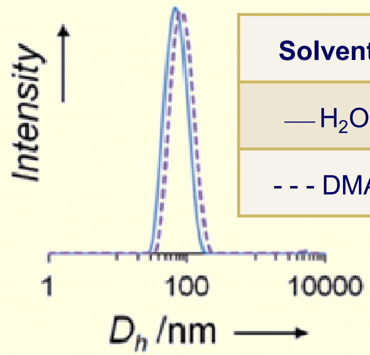
NG
M_n^{LS} = 13.4 x 10^3 kg/mol
M_w/M_n^{PMMA} = 1.8
N_{agg} = 240

Macro**RAFT**
M_n^{LS} = 14.2 kg/mol
M_w/M_n^{PMMA} = 1.3



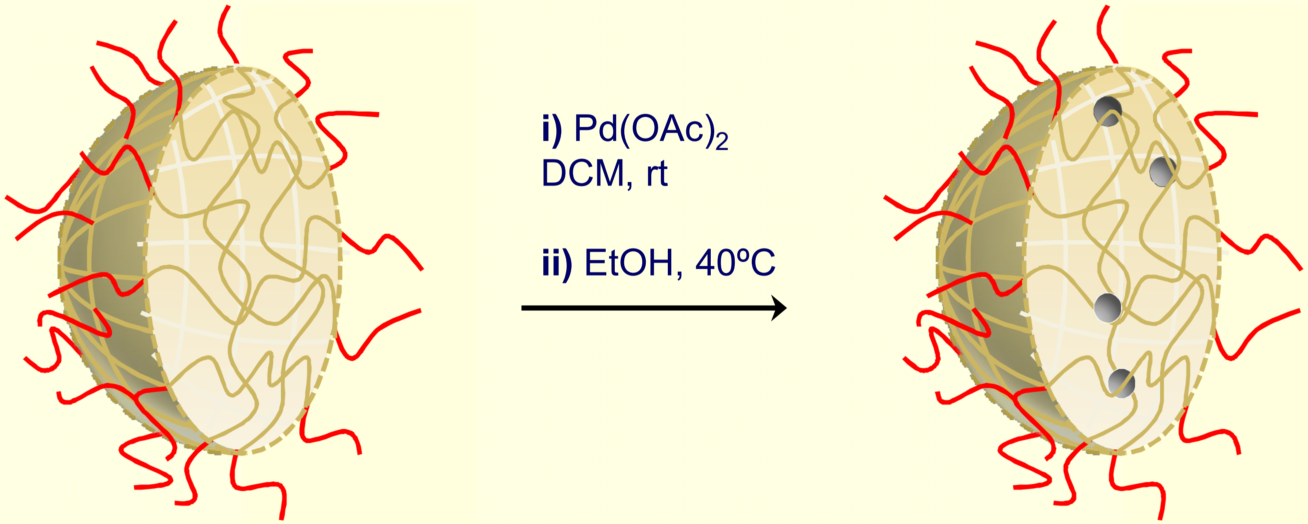


DLS @ 20° C



Solvent	D_Z(nm)	PDI
— H_2O	67	0.09
- - - DMAc	82	0.13

Functionalisation with Pd nanoparticles



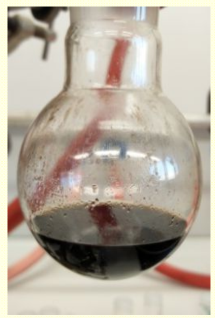
NG + $Pd(OAc)_2$

rt, 24h

precipitation
DCM + EtOH

40° C, 24h

dialysis
lyophilized

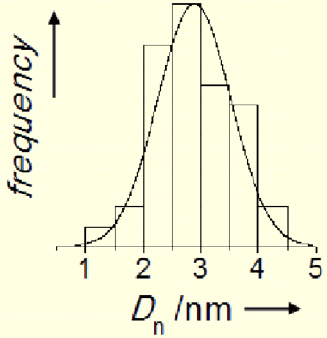


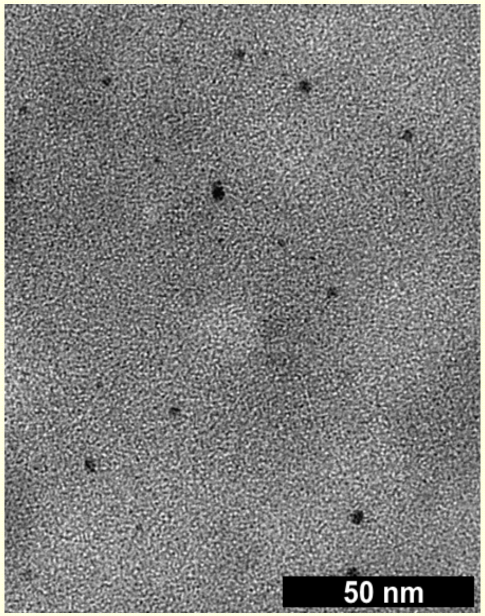
PdNP@NG

Characterization of PdNP@NG

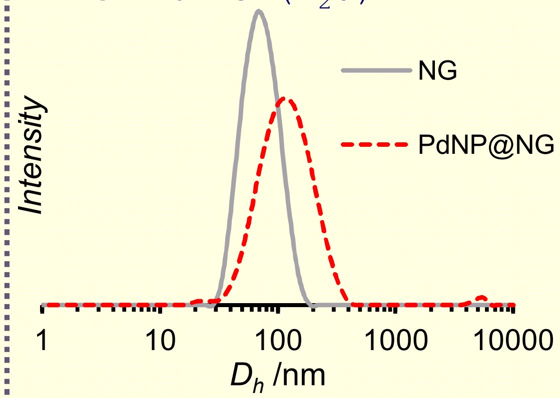
TEM

D_n = 2.9 ± 0.6 nm
~868 Pd atoms /NP





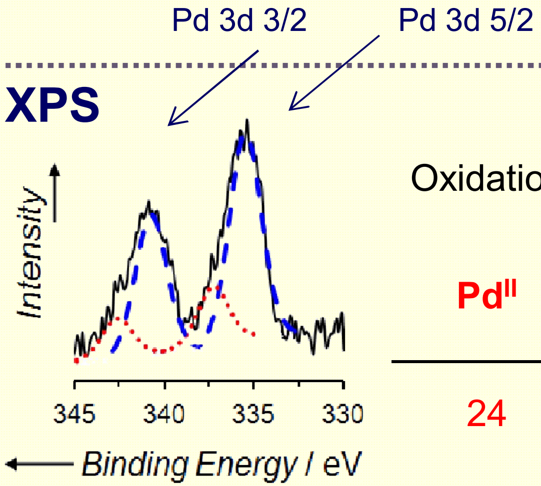
DLS 20° C (H_2O)



D_h = 104 nm

Pd content (wt%)		
ICP-MS	**XPS**	**TGA**
0.95	1.3	1.4

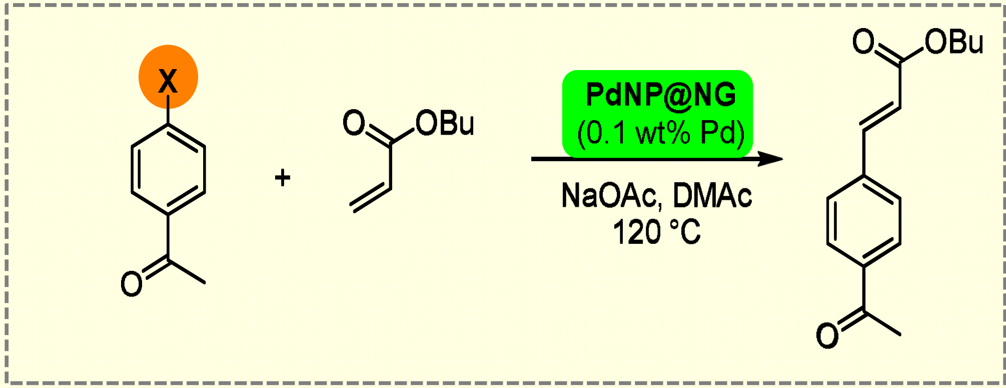
XPS

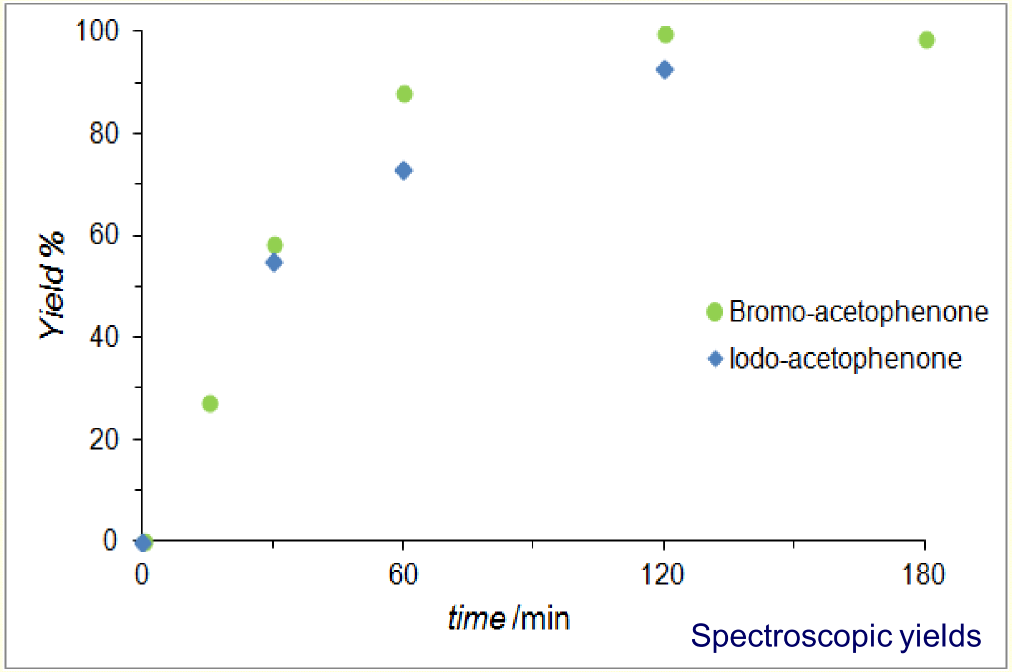


Oxidation state (%)

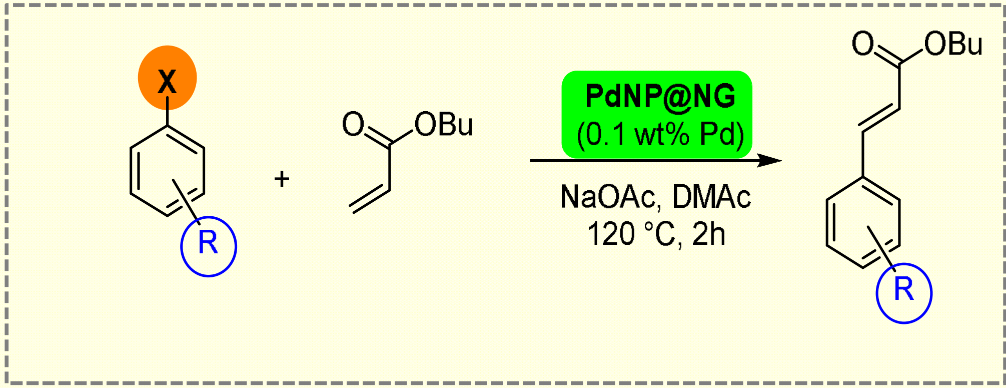
Pd^{II}	Pd^{0}
24	76

The Mizoroki-Heck reaction

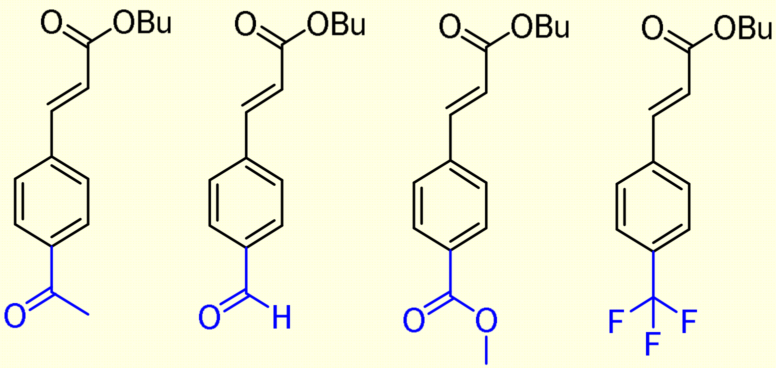




The Mizoroki-Heck reaction



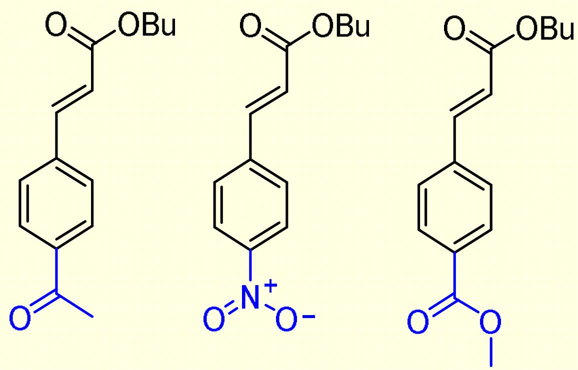
X = Br



92% 96% 70% 96%

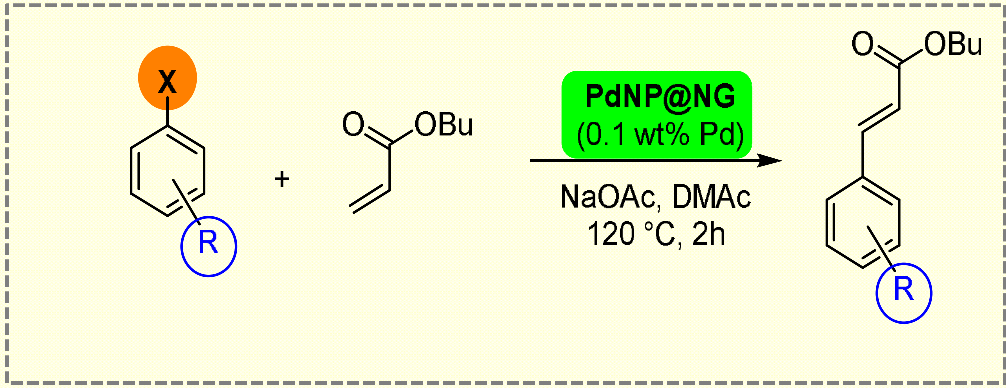
Isolated yields

X = I

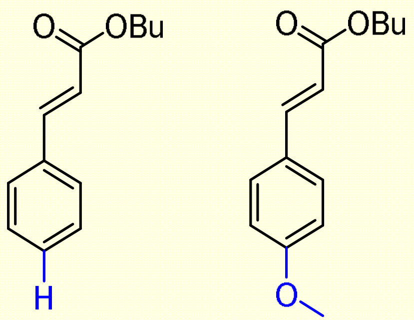


94% 69% 99%

The Mizoroki-Heck reaction



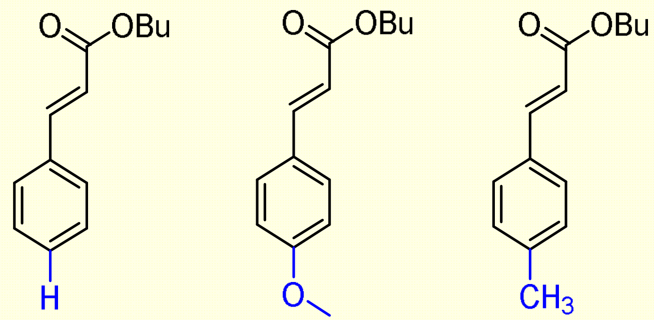
X = Br



NR

NR

X = I



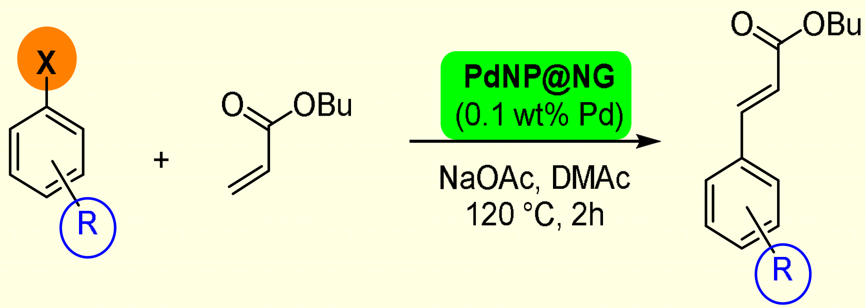
Isolated yields

68%

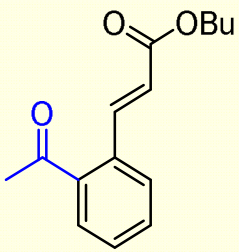
95%

84%

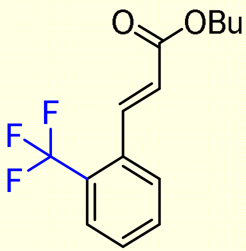
The Mizoroki-Heck reaction



X = Br



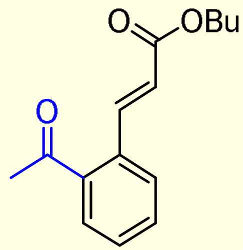
26%



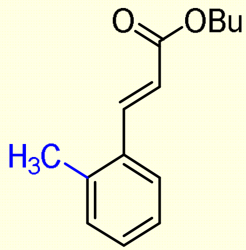
96%

Isolated yields

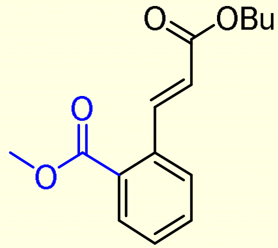
X = I



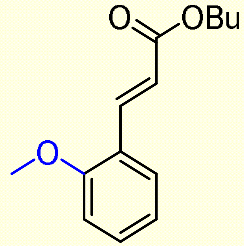
8%



98%

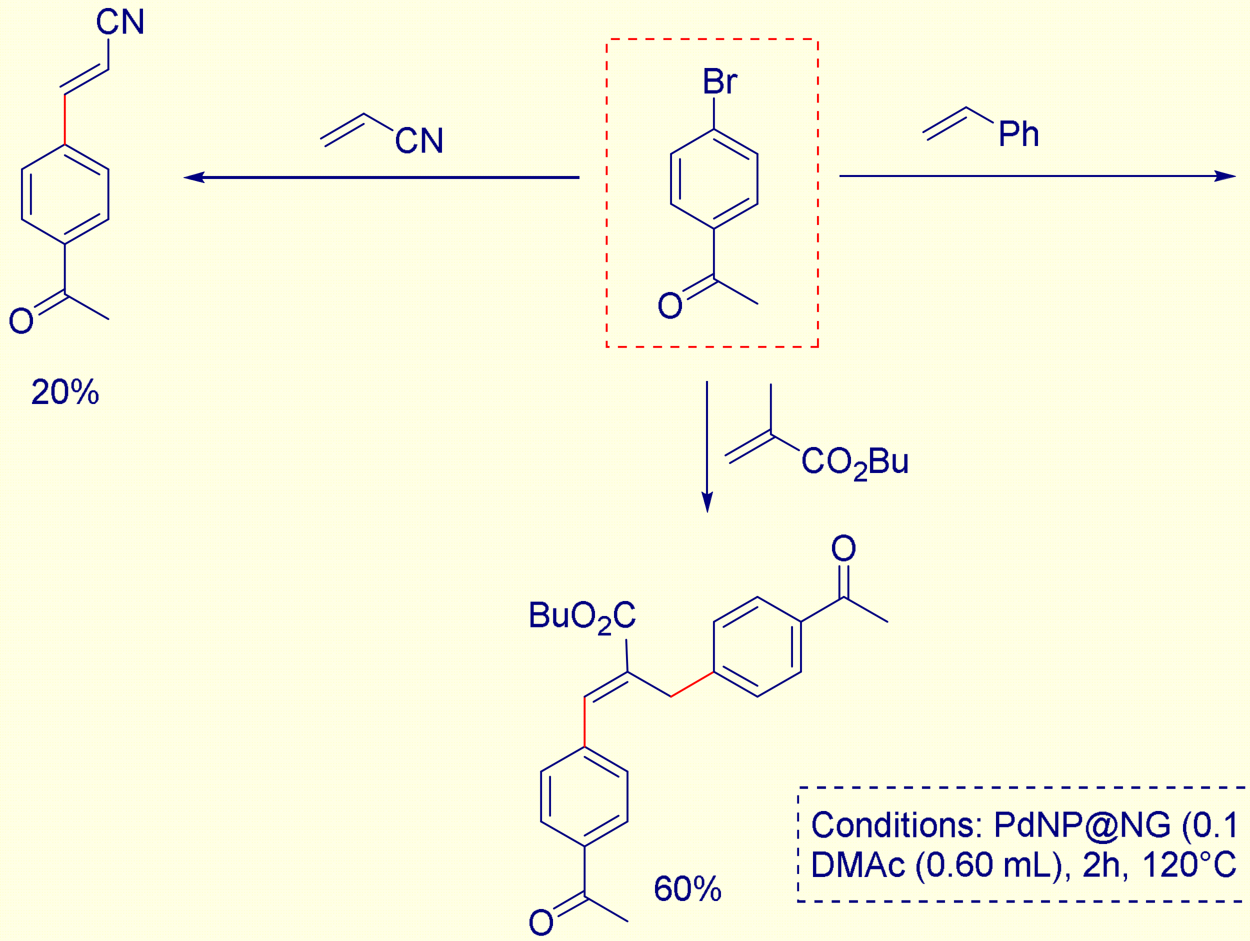


21%



97%

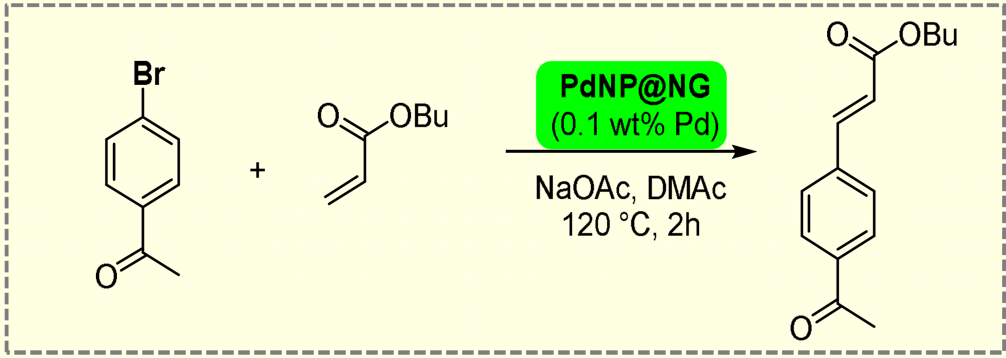
The Mizoroki-Heck reaction

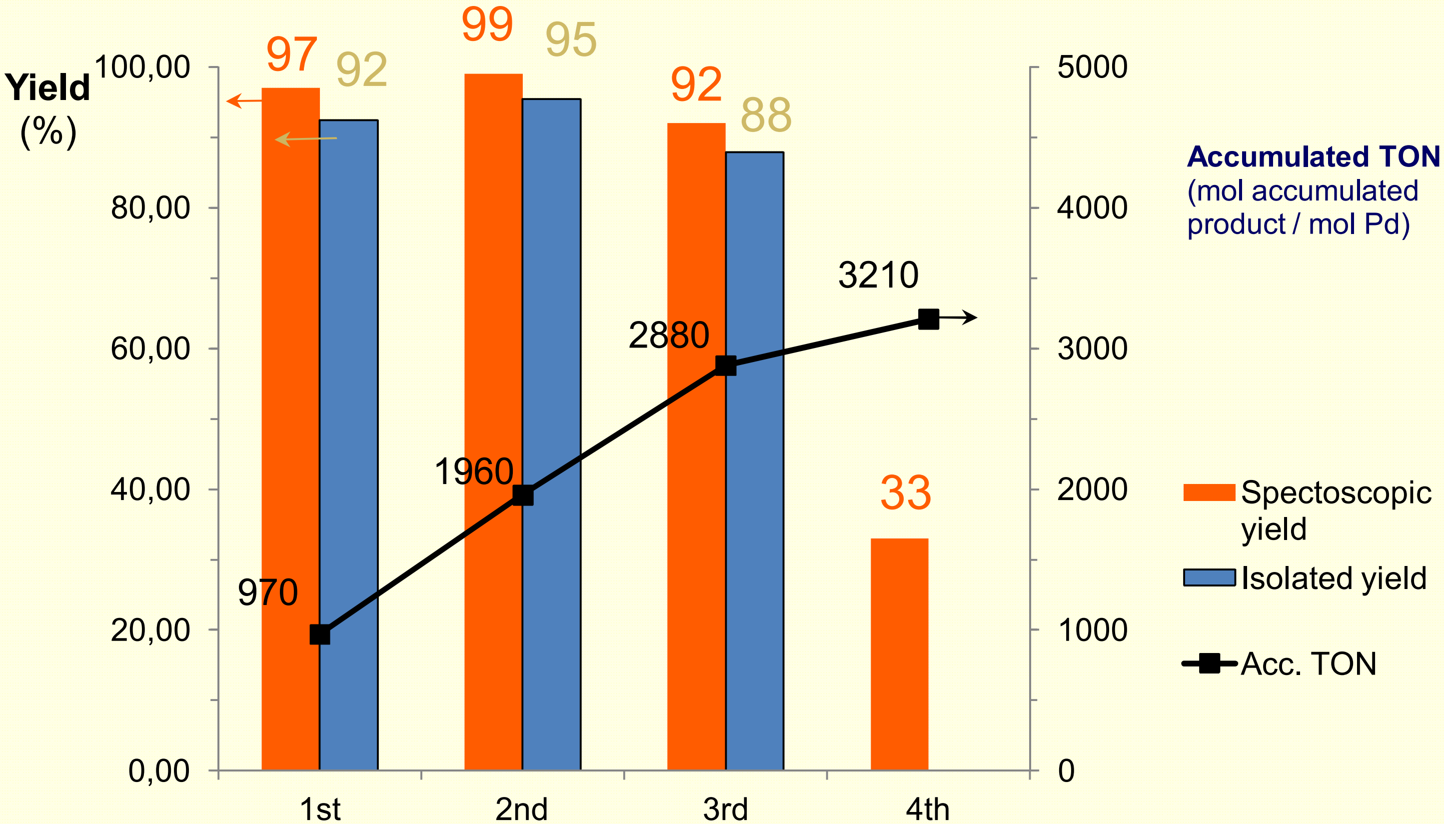


Conditions: PdNP@NG (0.1 mol% Pd), DMAc (0.60 mL), 2h, 120°C

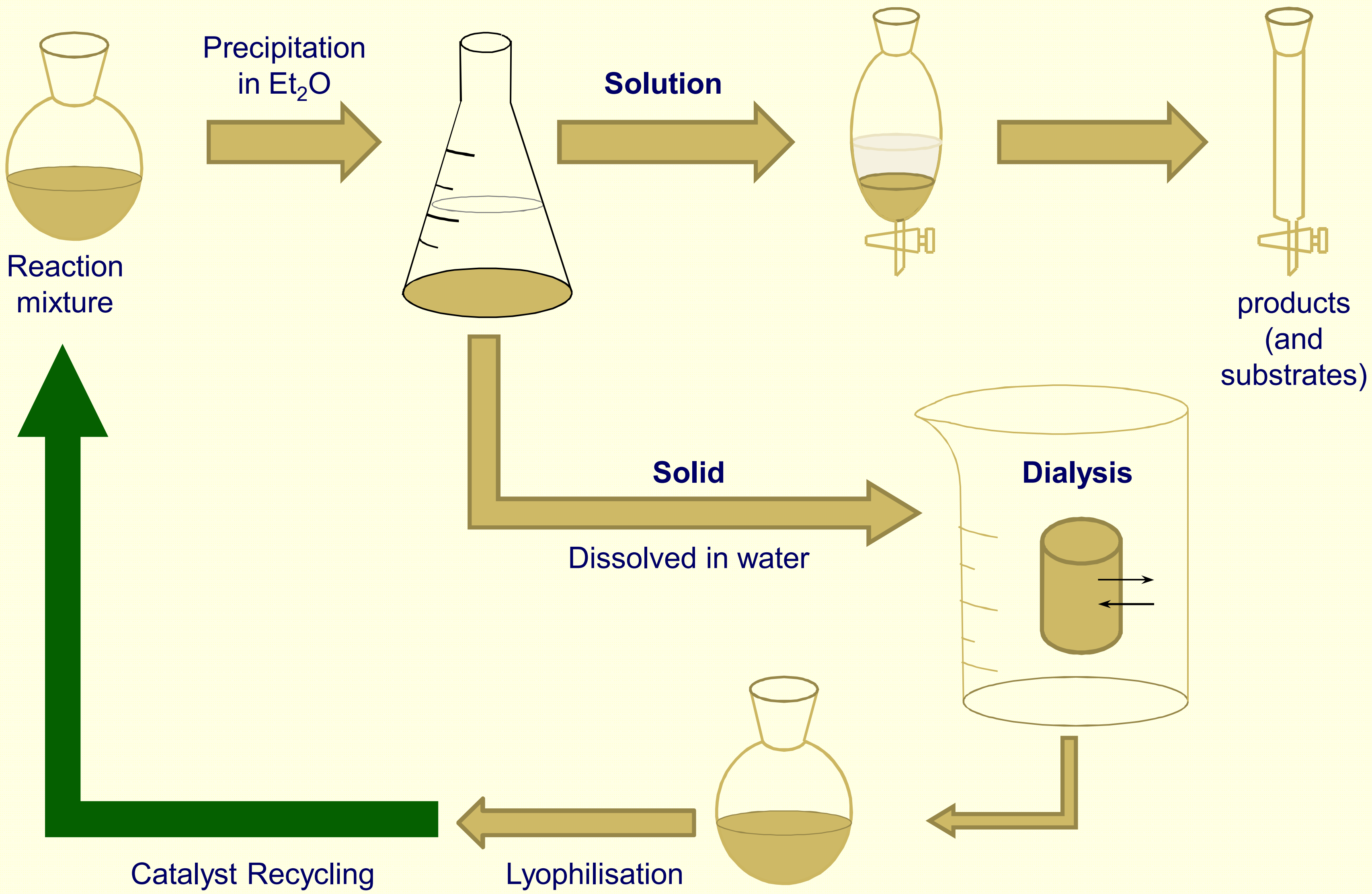
Hybrid Nanogel Recycling

tenfold scale up

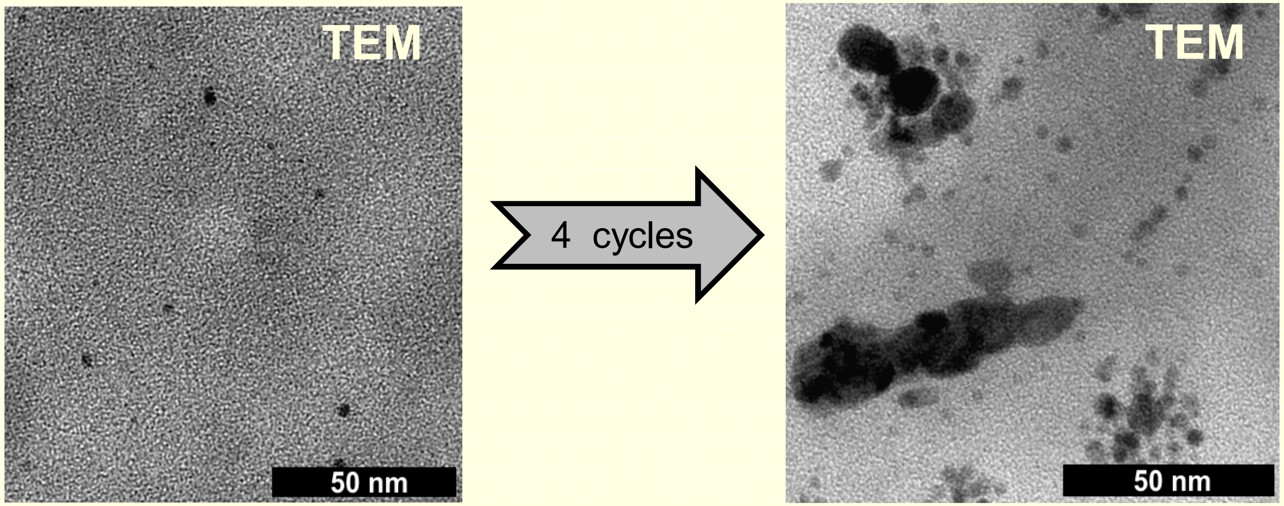




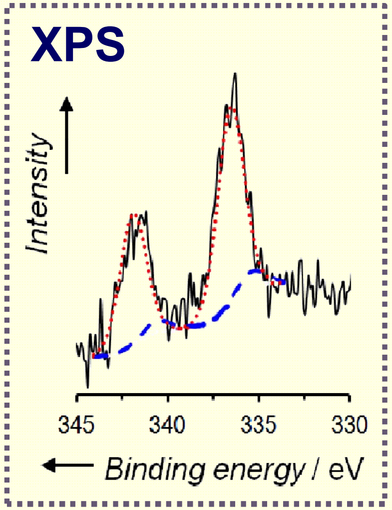
PdNP@NG Recycling



After 4 cycles of catalysis



Ostwald ripening

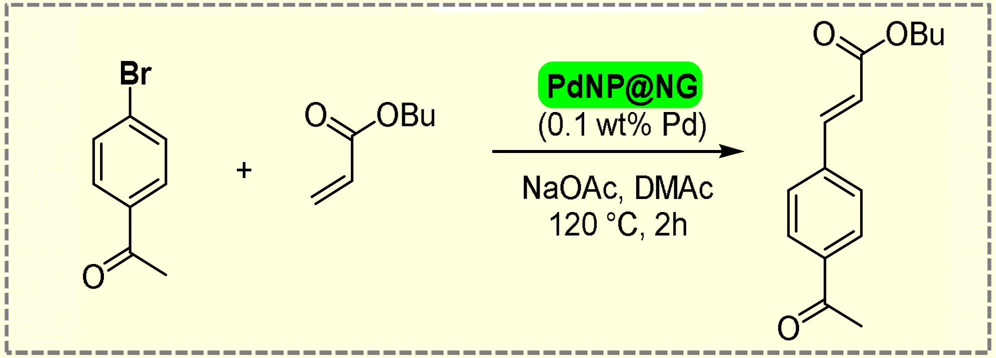


	ICP-MS	XPS	
PdNP@NG	Pd cont (wt%)	%Pd(II)	%Pd(0)
t_0	0.95	24	76
After 4 cycles	0.22	93	7

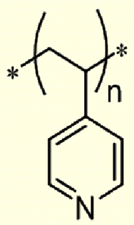
Pd leaching out of the NG		
	Pd content	
Phase	ppm	% total Pd
Organic	76.6	19
Aqueous	0.04	2

Pd leaching test #1

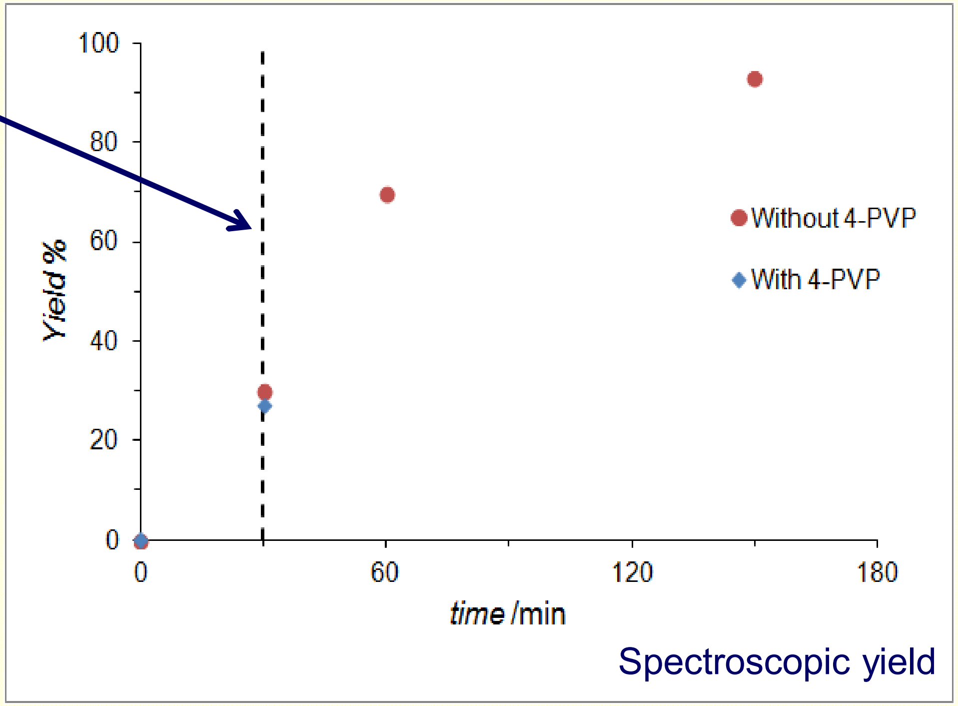
Macromolecular base



Addition of 4-PVP
(M_n = 50 kg/mol)

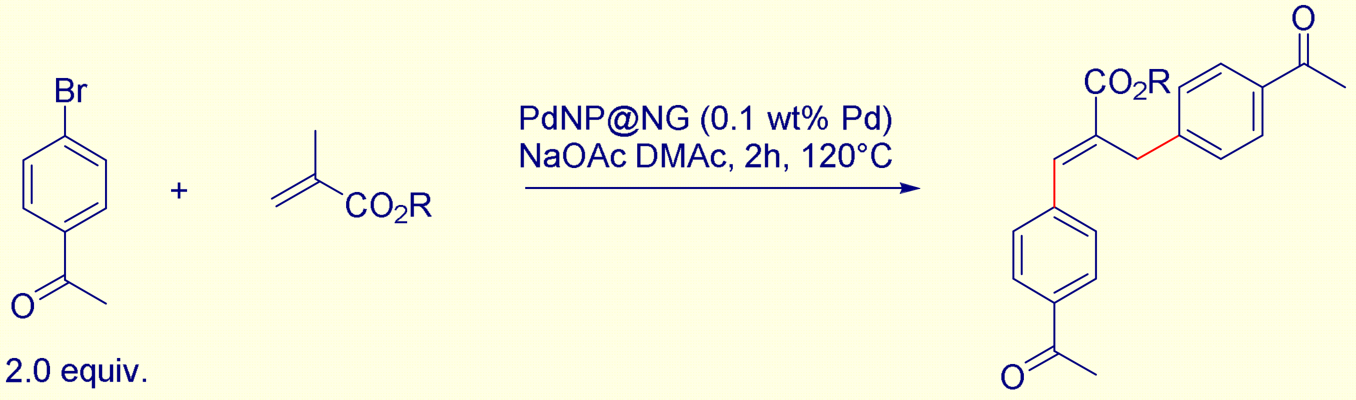


4-PVP



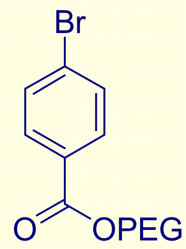
Pd leaching test #2

Macromolecular substrate

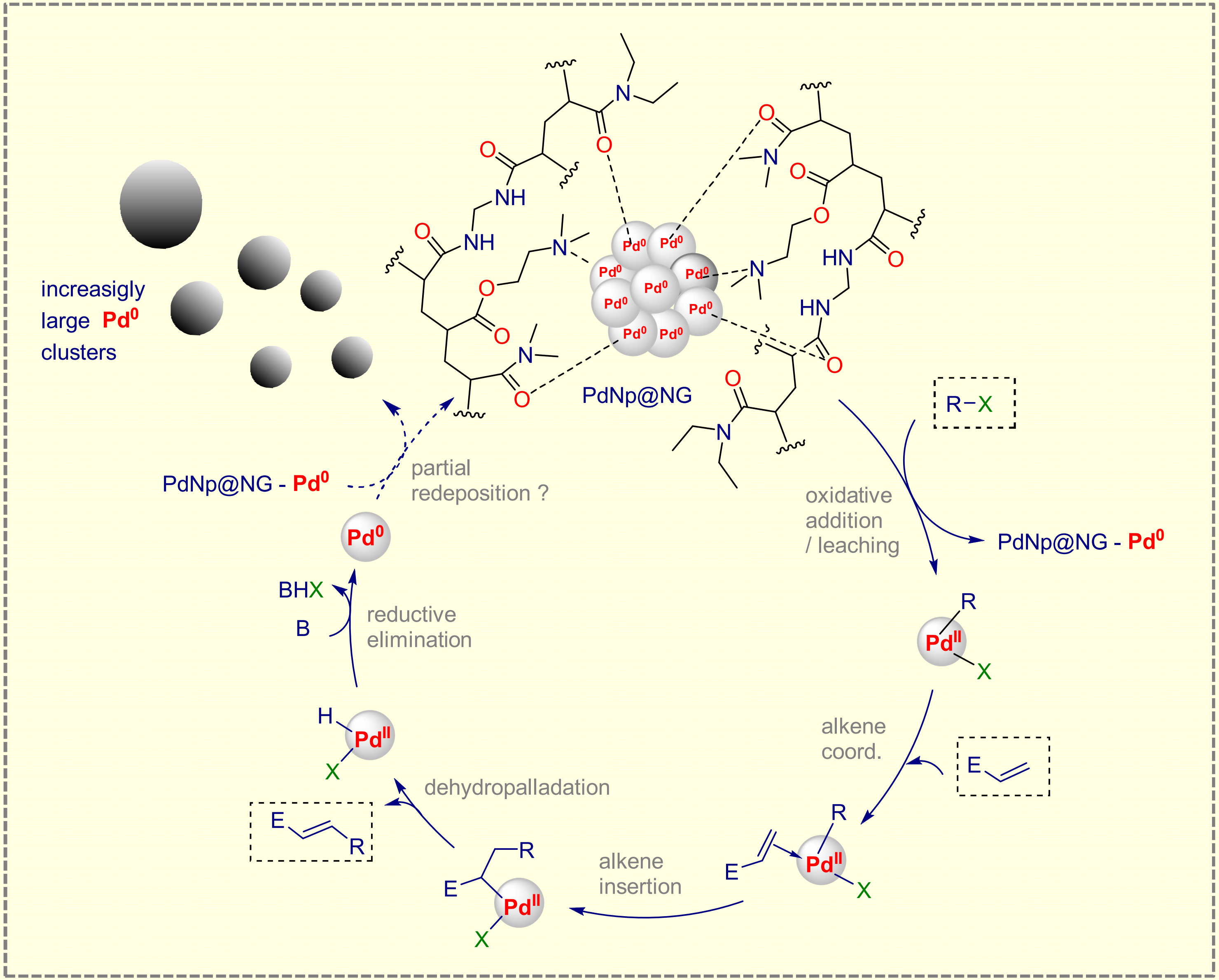


R	yield(%)
Bu-n	60
$[CH_2CH_2]_nOMe$	60

PEG-methacrylate: M_n=1.1 kg/mol



Proposed mechanism for the PdNP@NG cat Mizoroki-Heck rxn



Conclusion part I

- ✓ Well defined core-shell nanogels **NG** have been synthesised and characterised

  RAFT aqueous dispersion polymerisation process

- ✓ Pd^0 NP were incorporated (~1.3 wt%) **PdNP@NG**

  Long-term stability even under air and moisture

- ✓ Nanogel Pd is an active catalyst in the Mizoroki-Heck reaction in 0.1 wt%

  Substrates: bromo- and iodo-arenes (accumulated TOF: 2880)

- ✓ The hybrid materials can be recycled up to three cycles

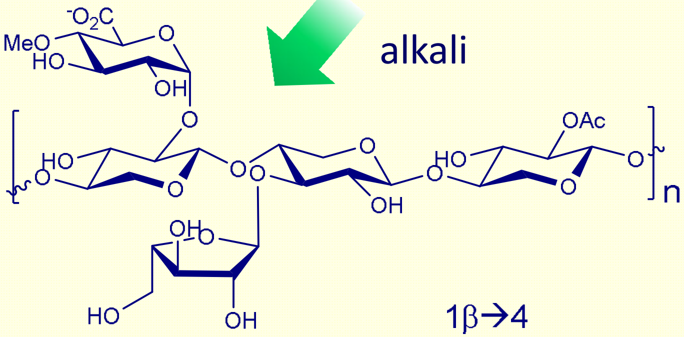
  Leaching of Pd lead to the formation of Pd(II)

Pontes da Costa, A.; Rosa Nunes, D.; Tharaud, M.; Oble, J.; Poli, G.; Rieger, J. *ChemCatChem*, **2017**, *9*, 2167 -2175

From agricultural waste to furfural

corn cobs oat hulls wood chips bagasse

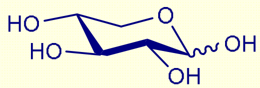
alkali



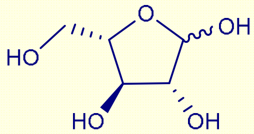
1β→4

O-acetyl-4-O-methylglucuronoxylan

acid

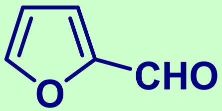


D-xylose



L-arabinose

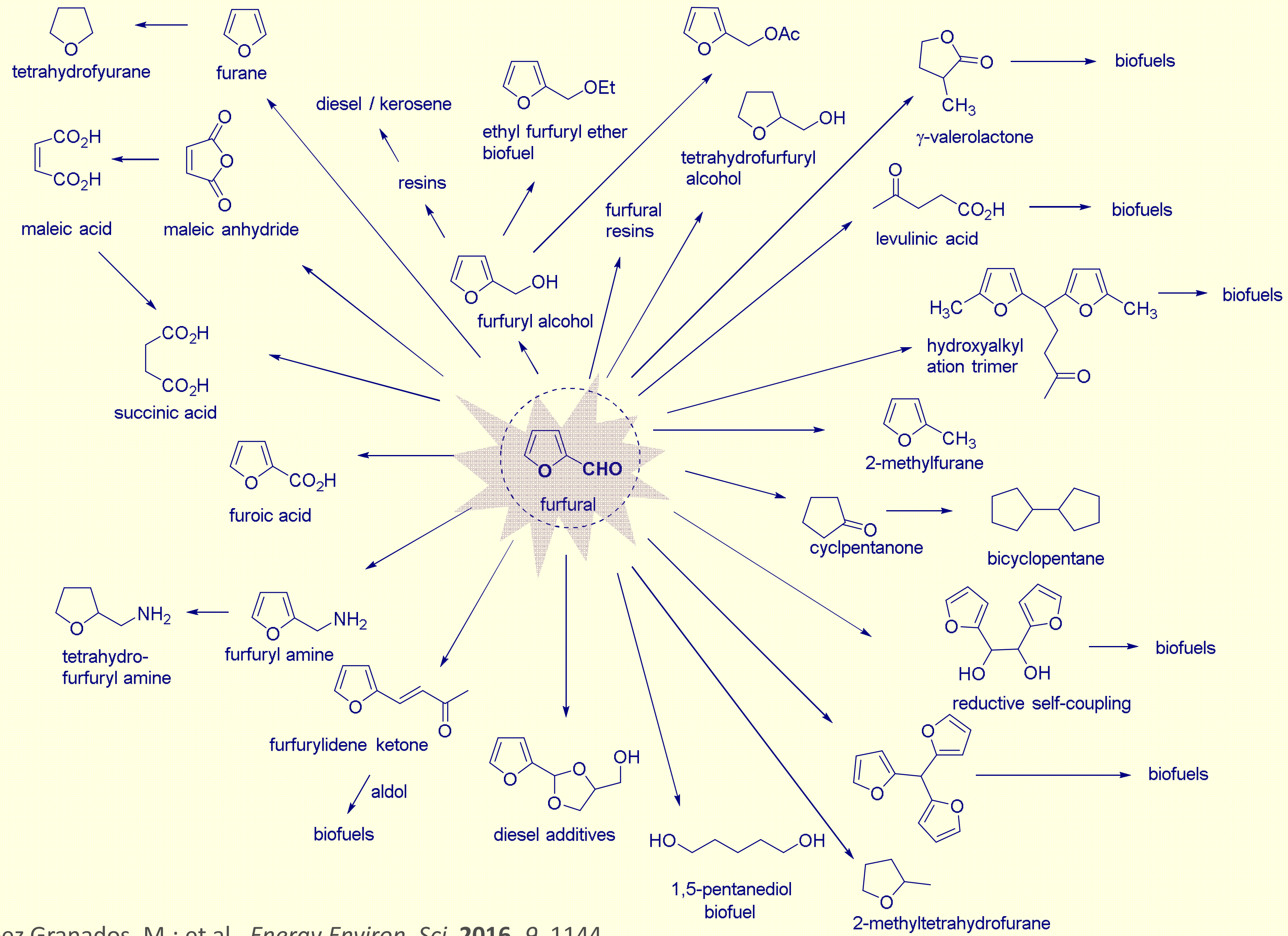
acid



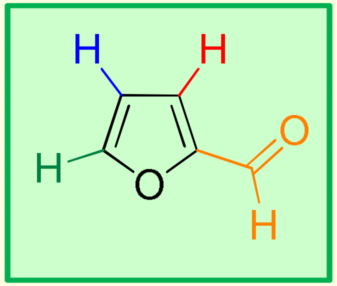
furfural

Furfural and Derivatives – Ullmann's Encyclopedia of Industrial Chemistry **2012**, Wiley-VCH
Zeitsch, K. J. *The chemistry* and *technology* of *furfural* and *its many* by-*products*, **2000** vol 13, Elsevier Lichtenthaler F. W. *Acc. Chem. Res.* **2002**, *3*, 201

From furfural to bulk chemicals

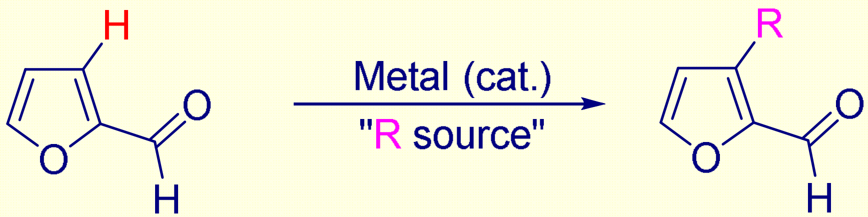


López Granados, M.; et al., *Energy Environ. Sci.* **2016**, *9*, 1144

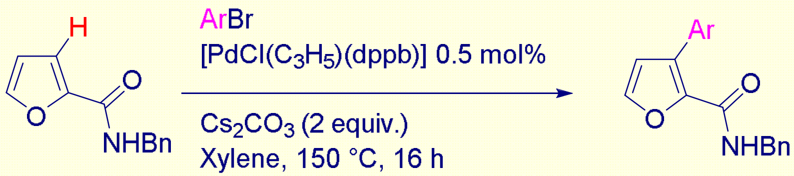


- ✓ Formyl function ☑
- ✓ Aromatic nucleus ☑
- ✓ Three different aromatic C-H bonds ☑ ☑ ☑

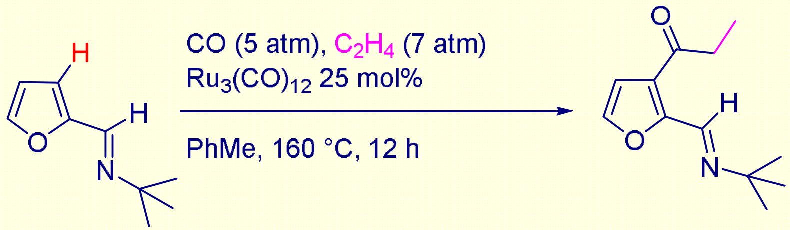
The challenge: C3 alkylation of furfural via catalytic directed C-H activation



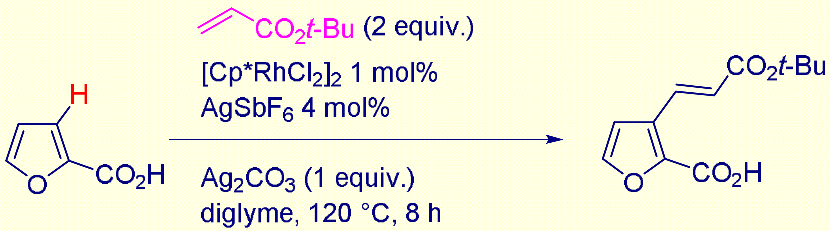
Related "cat C-H" activation precedents



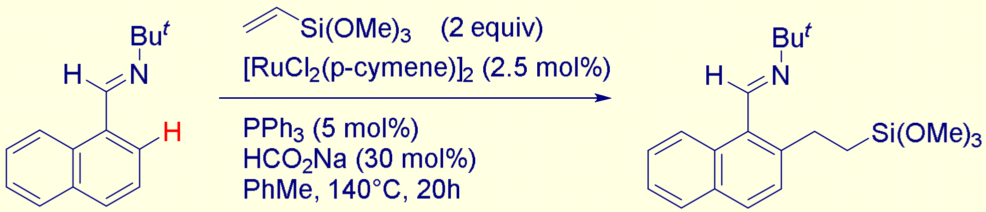
Doucet H. *et al. Chem. Cat. Chem.* **2012**, *4*, 815



Chatani, N.; Murai*, S. et al. J. Org. Chem.* **1997**, *62*, 5647.

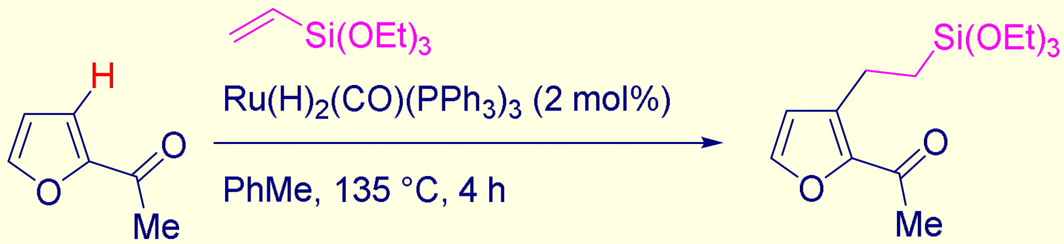


Miura M. J. *et al. J. Org. Chem.* **2013**, *78*, 7126

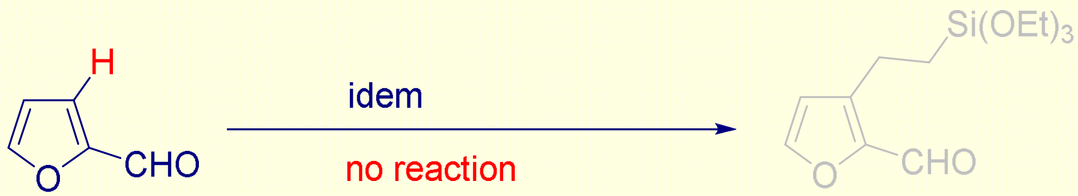


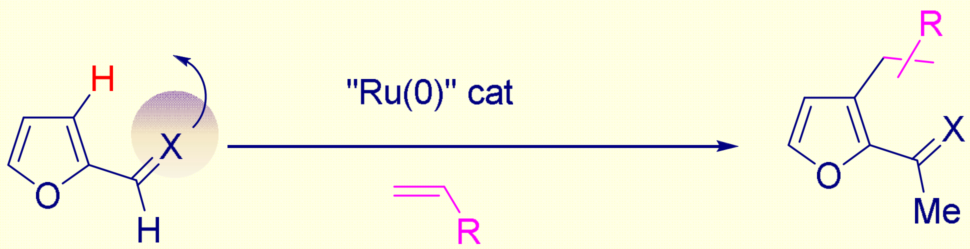
Darses, S.; Genet, J. P. *et al. Angew. Chem. Int. Ed.* **2006**, *45*, 8232 ;
J. Am. Chem. Soc. **2009**, 131, 7887.

Start of the project

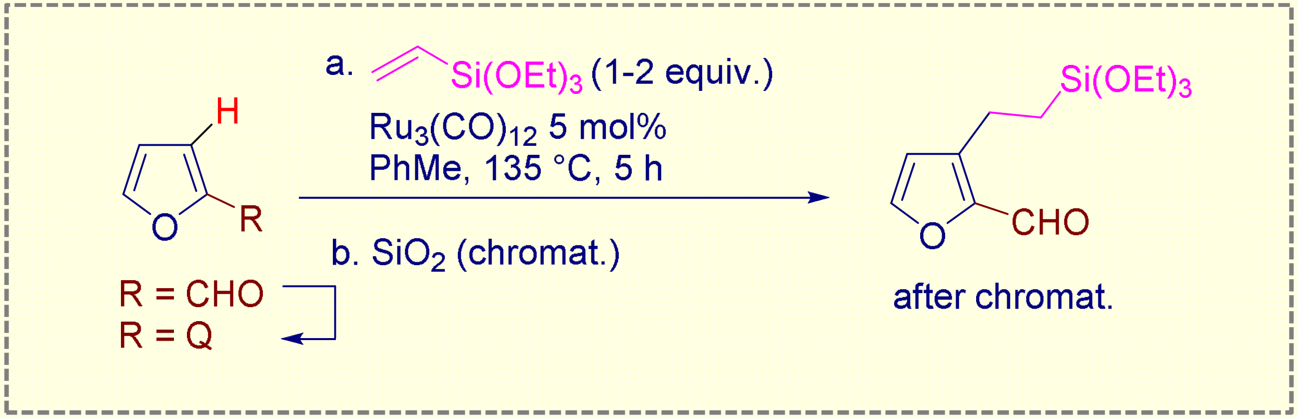


Murai, S.; Kakiuchi, F.; Chatani N. *et al. Nature* **1993**, *366*, 529

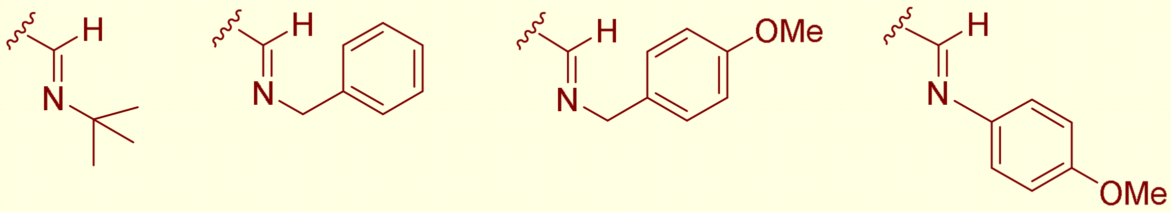




The first – disappointing – trials

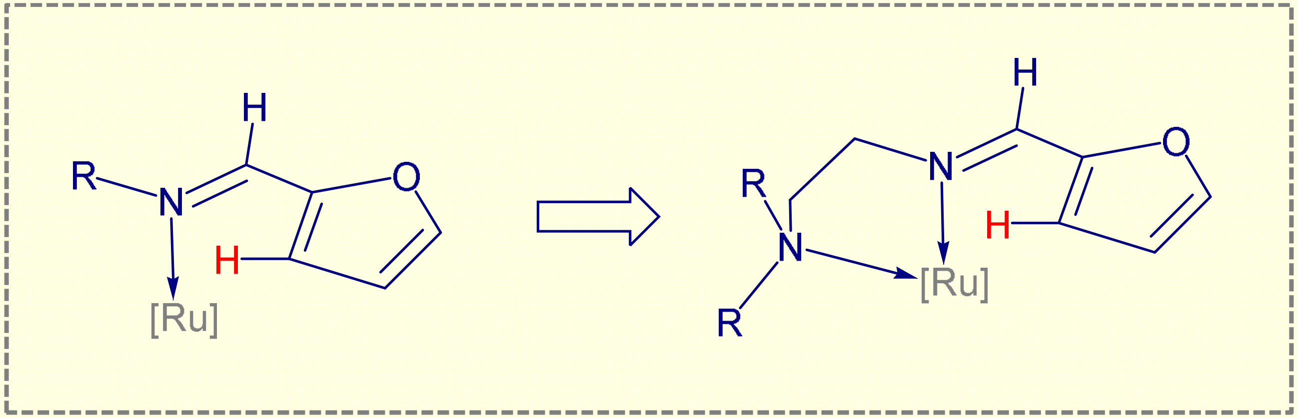


Q

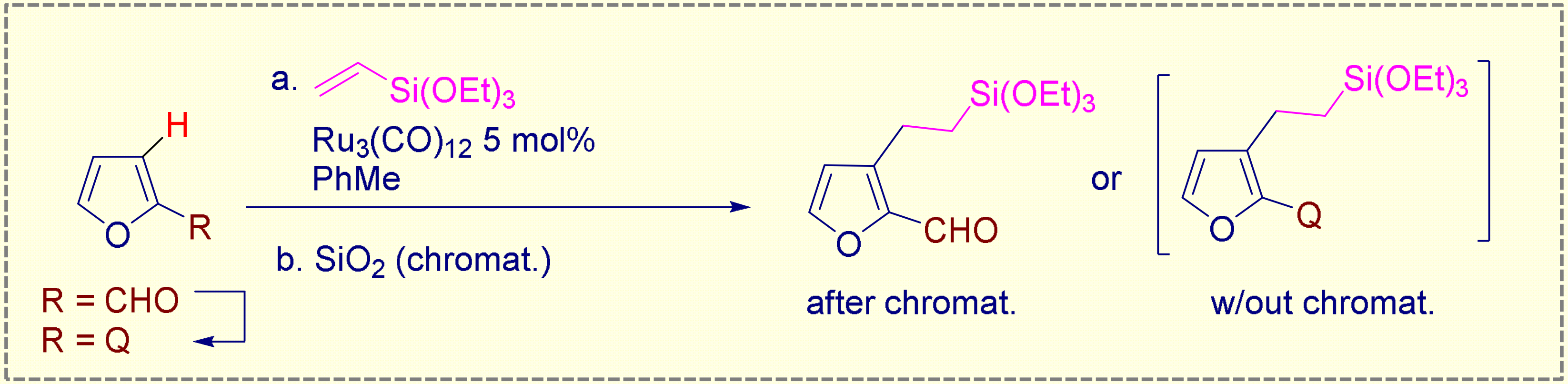


% yield	0	5	~8	~8

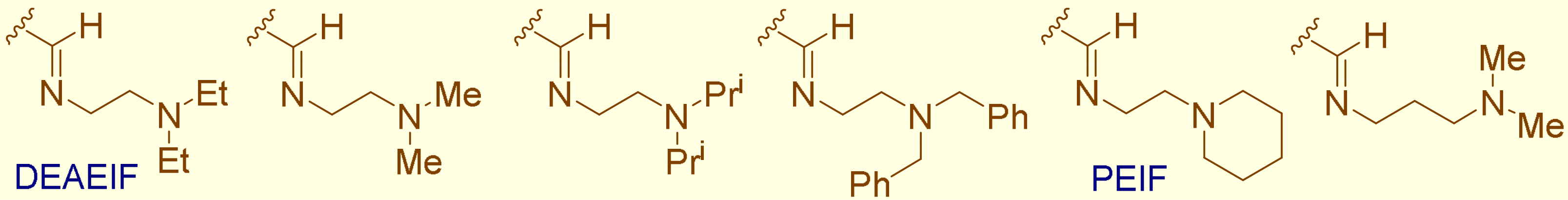
From imino coordination to amino-imino chelation



Amino-imines as chlelating groups

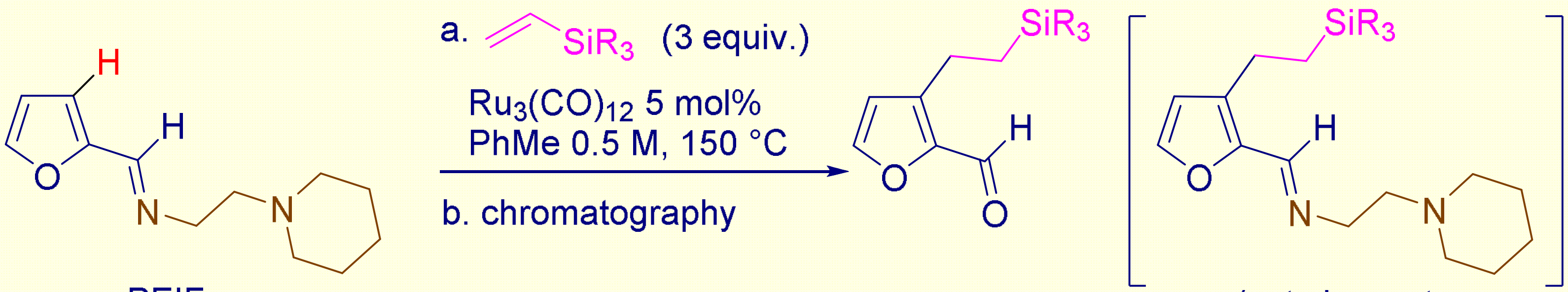


Q



	DEAEIF	DEAEIF				PEIF	PEIF	PEIF	
T (°C)	135	150	135	135	135	135	150	150	135
t (h)	18	5	18	18	18	18	5	5	18
equiv silane	2	2	2	2	2	2	2	3	2
yield %	47 [50]	[51]	[9]	5	0	49 [55]	[70]	62 [71]	0

Scope with vinylsilanes



PEIF

after chromat.

w/out chromat.

5h, 62%
(71%)

5h,
(62%)

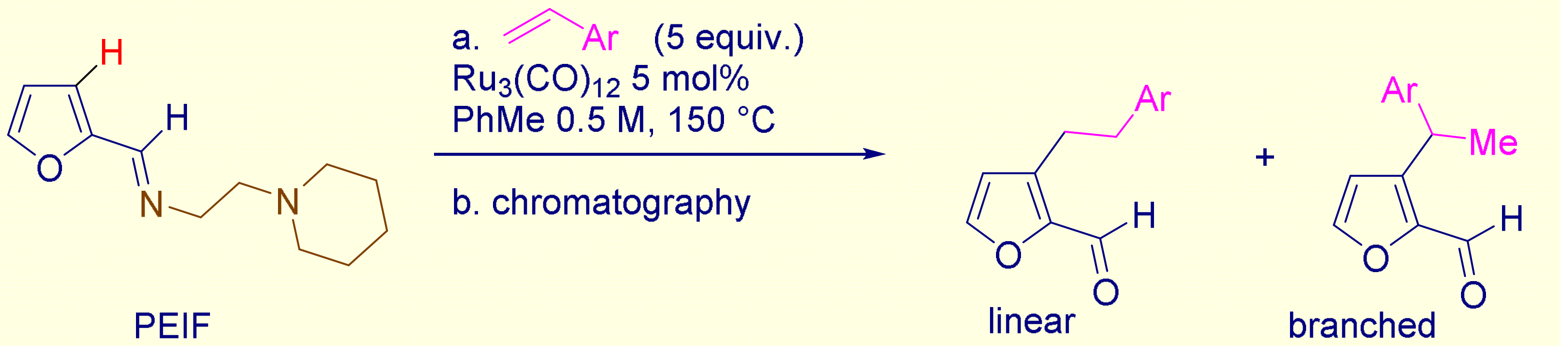
24h,
31% (33%)

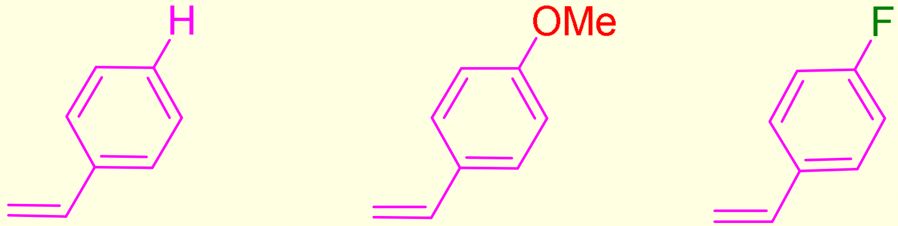
16 h
66% (68%)

5 h,
40% (63%)

16 h,
57%

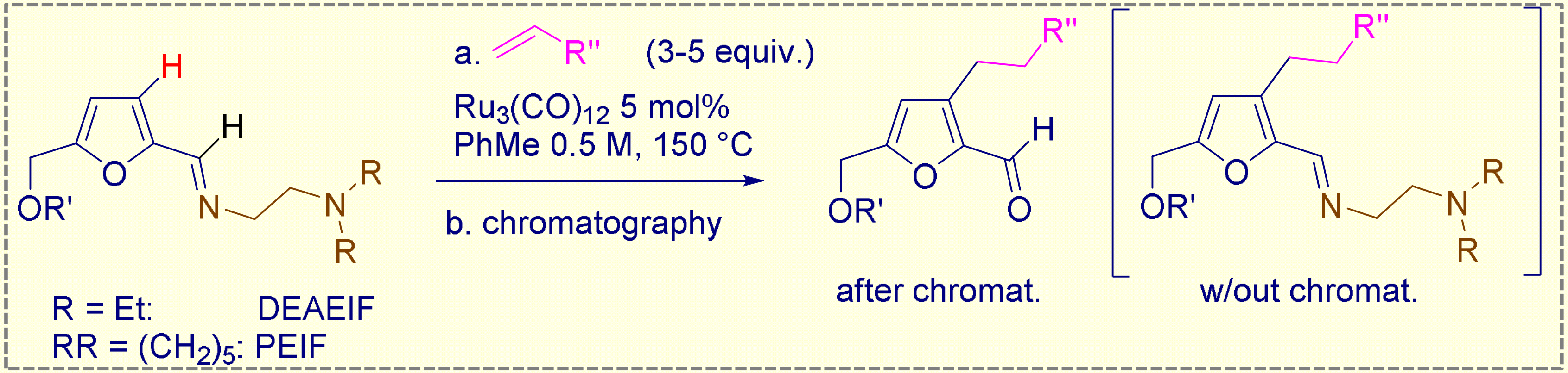
Scope with styrenes





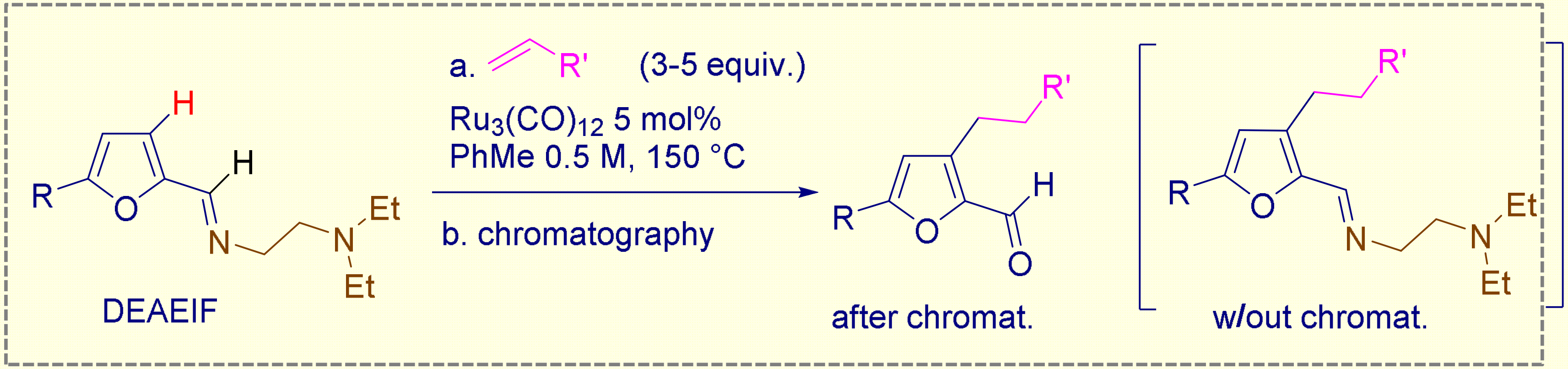
time, yield %	24 h, 26	16 h, 26	16 h, 31
linear : branched	85: 15	87: 13	87:13

Scope from HMF derived substrates



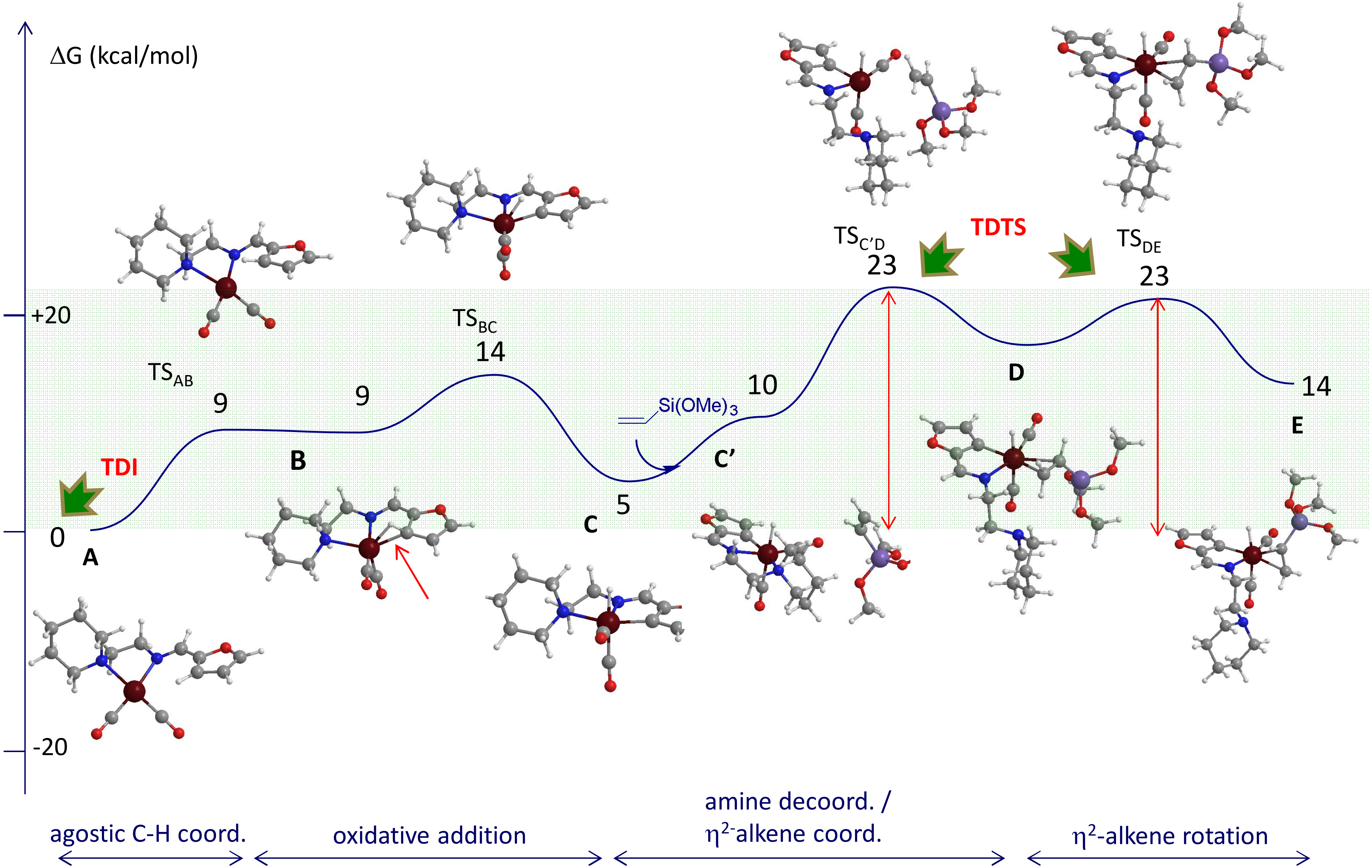
Entry	Imine	R'	R''	t(h)	Yield (%)	
					chromat.	w/t chromat
1	DEAEIF	TBDMS	$Si(OEt)_3$	5	57	
2	PEIF	TBDMS	$Si(OEt)_3$	5		44
3	DEAEIF	TBDMS	$Si(OMe)_3$	16		59
4	DEAEIF	TBDMS	$SiPh_3$	17	62	66
5	DEAEIF	Ac	$Si(OEt)_3$	5	NR	
6	DEAEIF	Bn	$Si(OEt)_3$	5	20	
7	DEAEIF	THP	$Si(OEt)_3$	5	NR	
8	DEAEIF	Tr	$Si(OEt)_3$	17	17	

Scope: C5 substituted furfurals



Entry	R	R'	t(h)	yield (%)	lin/br
9	CH_3	$Si(OEt)_3$	5	56 (64)	
10	CH_3	$SiMe_2(OEt)$	5	40 (65)	
11	CH_3	Ph	17	38	88:12
12	Ph	$Si(OEt)_3$	16	20	

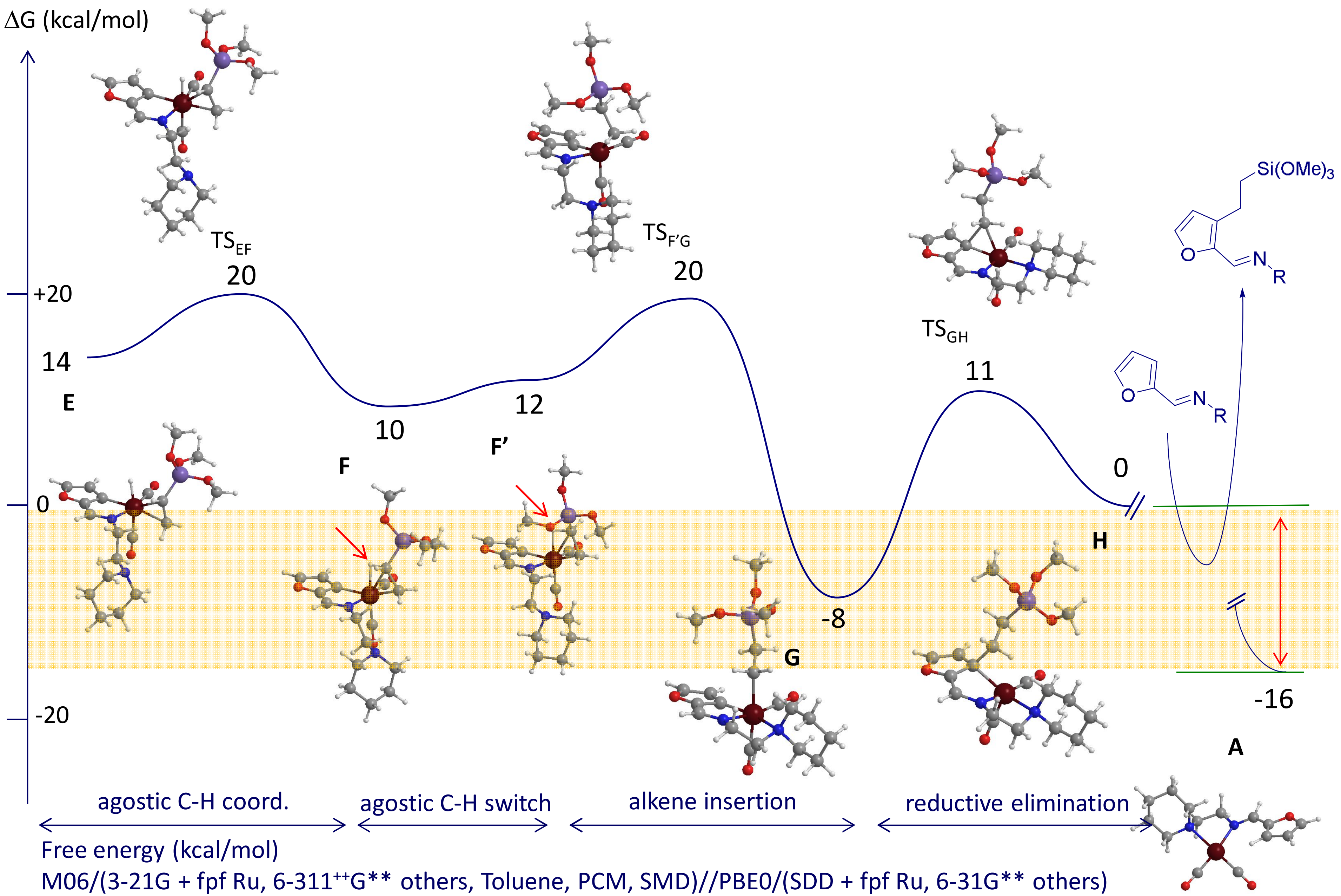
Energetic profile 1



Free energy (kcal/mol)

M06/(3-21G + fpf Ru, 6-311^{++}G** others, Toluene, PCM, SMD)//PBE0/(SDD + fpf Ru, 6-31G** others)

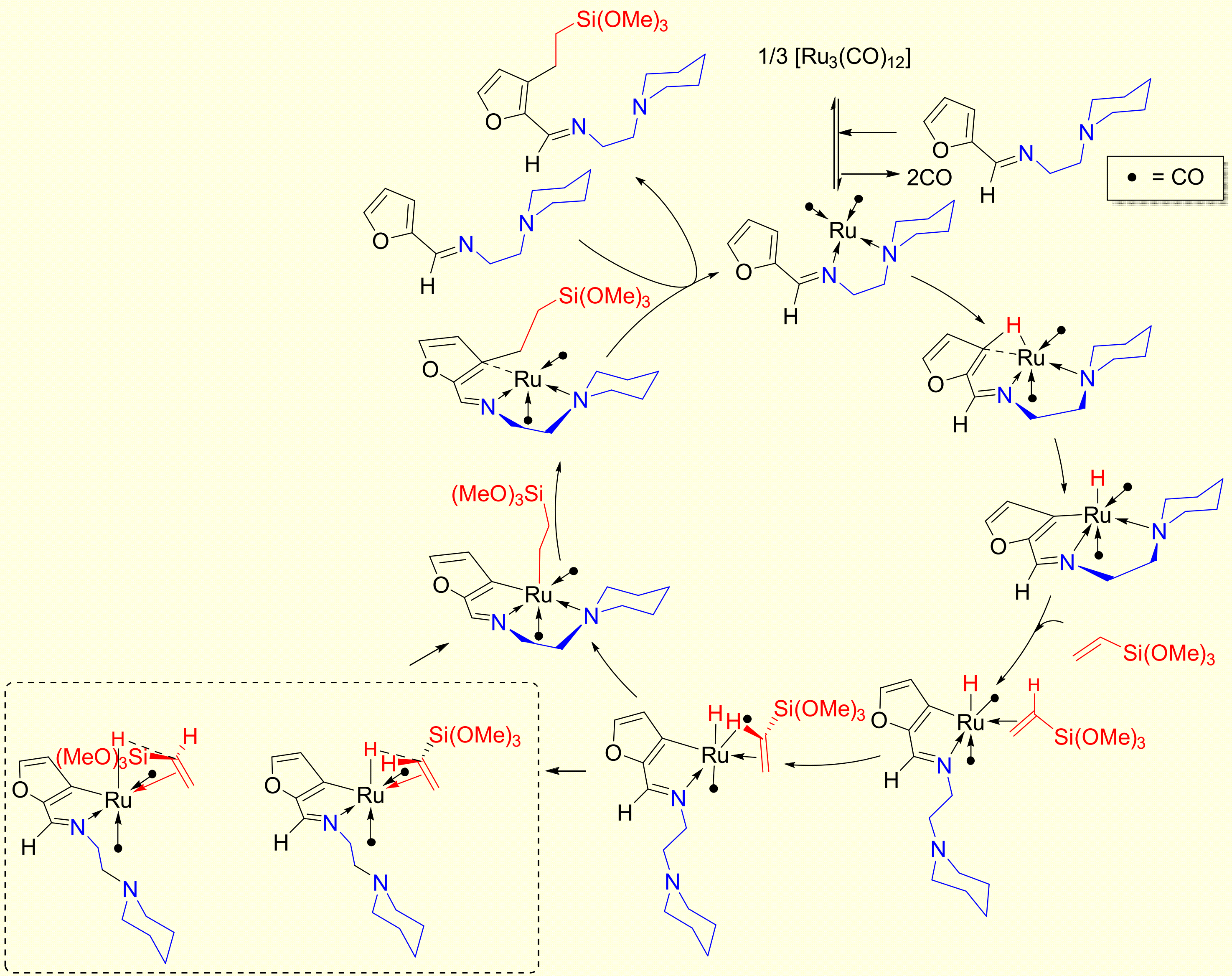
Energetic profile 2



Free energy (kcal/mol)

M06/(3-21G + fpf Ru, 6-311^{++}G** others, Toluene, PCM, SMD)//PBE0/(SDD + fpf Ru, 6-31G** others)

39/41Global mechanism



Conclusion part II

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- ✓ First example of directed olefin insertion at C3 of furfurals (Murai reaction)
- ✓ Use of a removable iminoamine N,N'-bidentate directing group is the key to success
- ✓ DFT calculations provided a plausible catalytic cycle to put forward.
- ✓ Breakthroughs in the valorization of lignocellulosic biomass substrates

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