中国科学技术大学
University of Science and Technology of China

N-Heterocyclic Carbenes (NHC) in Organic Synthesis

徐航勋

Email: hxu@ustc.edu.cn https://staff.ustc.edu.cn/~hxu

中国科学技术大学高分子科学与工程系

REVIEW

Nature 2014, 510, 485.

doi:10.1038/nature13384

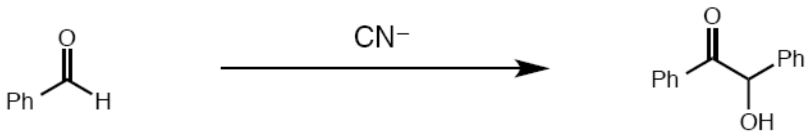
An overview of N-heterocyclic carbenes

Matthew N. Hopkinson[1], Christian Richter[1], Michael Schedler[1] & Frank Glorius[1]

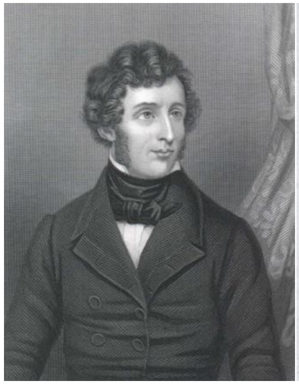
The successful isolation and characterization of an N-heterocyclic carbene in 1991 opened up a new class of organic compounds for investigation. From these beginnings as academic curiosities, N-heterocyclic carbenes today rank among the most powerful tools in organic chemistry, with numerous applications in commercially important processes. Here we provide a concise overview of N-heterocyclic carbenes in modern chemistry, summarizing their general properties and uses and highlighting how these features are being exploited in a selection of pioneering recent studies.

Early Development

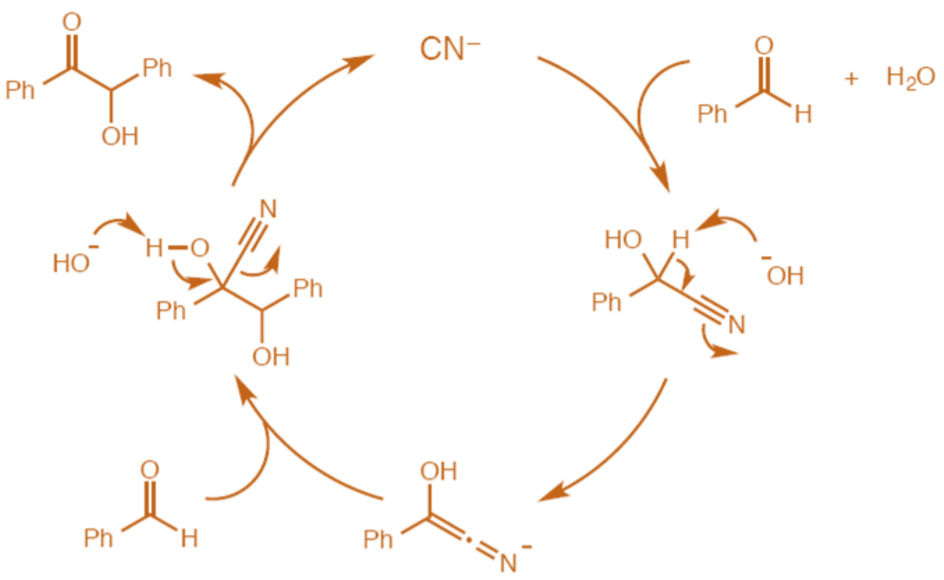
- **First report of benzoin condensation by Wohler and Liebig in 1832**



benzoin

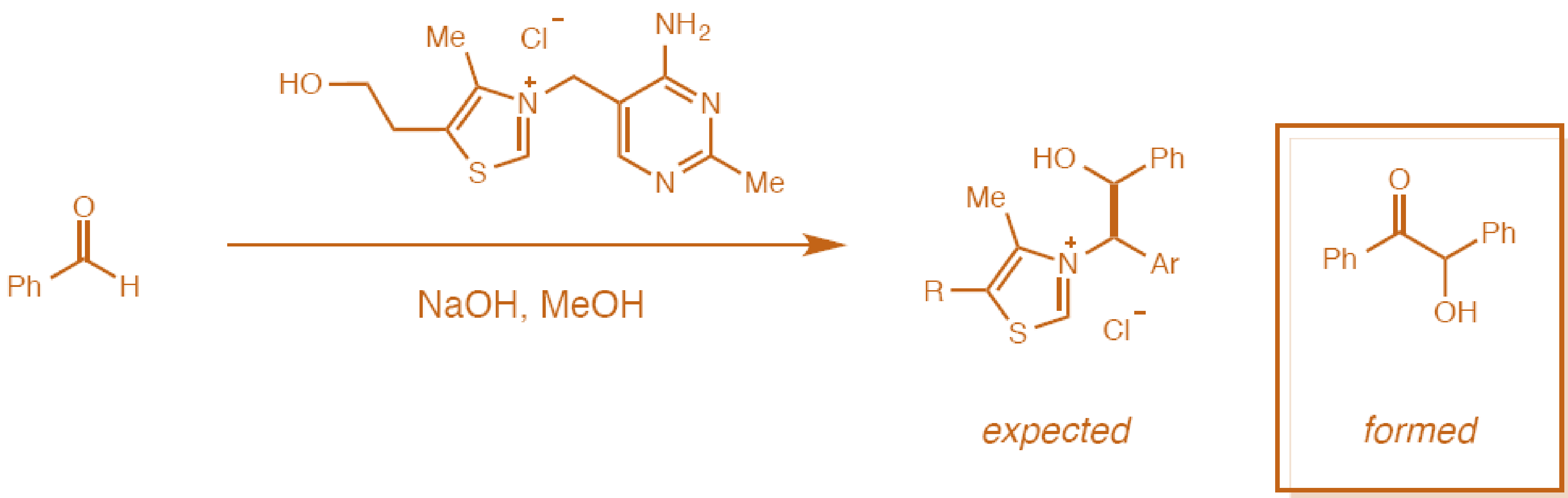


- **Mechanism proposed by Lapworth in 1903**

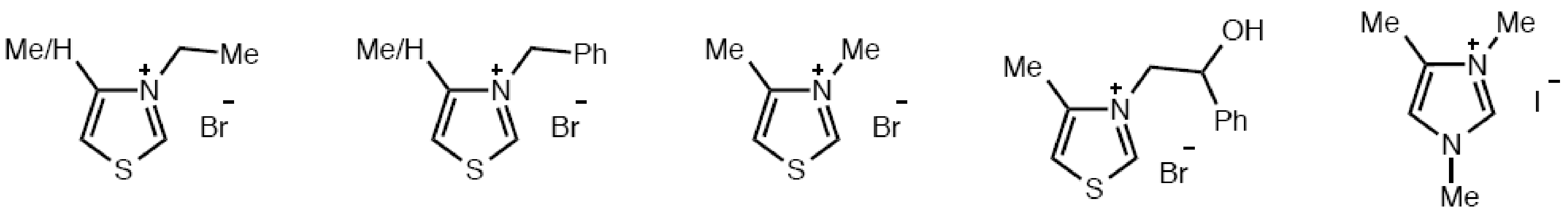


Early Development

◆ **1943: Ugai discovered that thiazolium salts could replace CN^- in benzoin condensations**

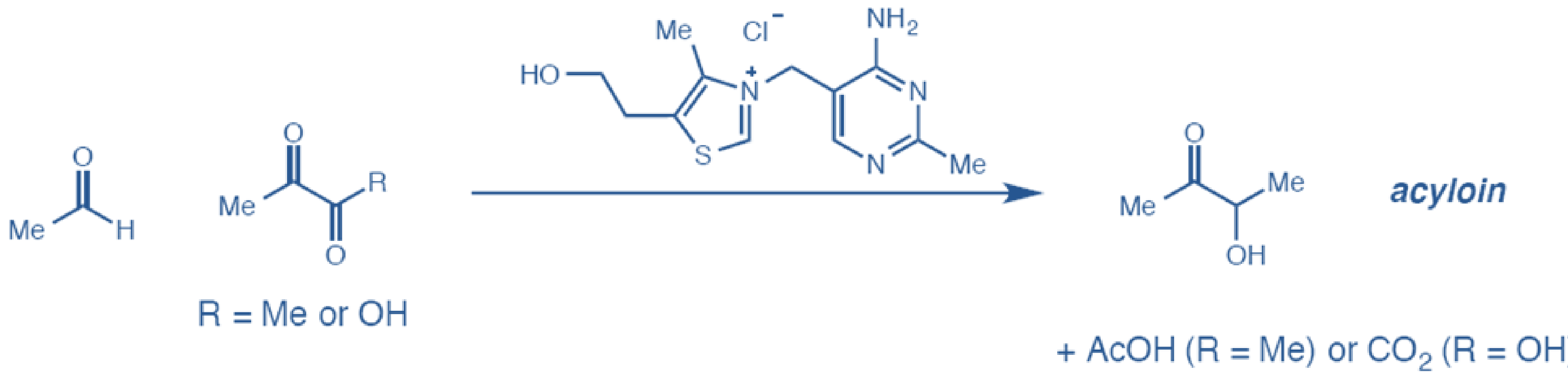


A variety of other thiazolium compounds were also found to be effective catalysts

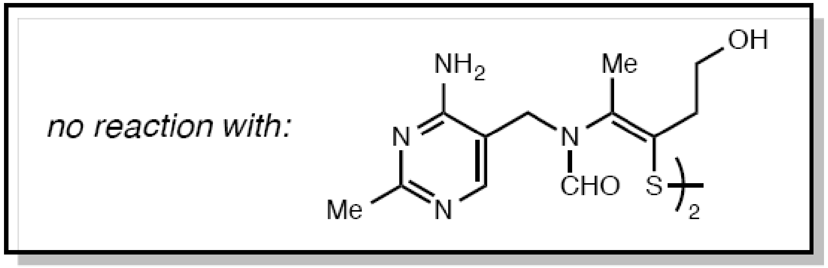


Early Development

◆ **1954: Mizuhara discovered that thiamine could catalyze many reactions that also been observed in biological systems**

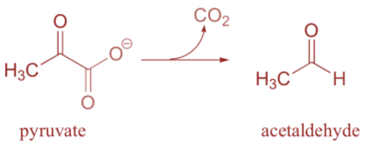


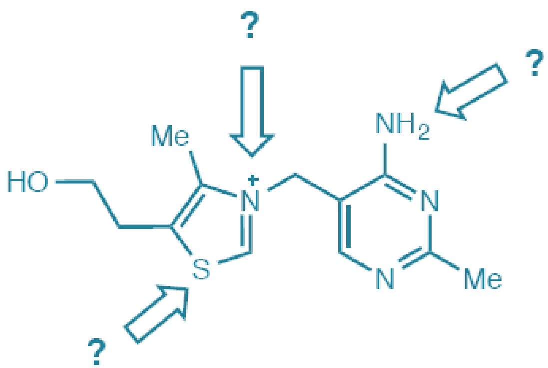
◆ **The thiazolium moiety of thamine is responsible for the catalytic activity**



Early Development

◆ Reactions catalyzed by thiamine (Vitamin B1) enzymes such as pyruvate decarboxylation and benzoin condensations were considered as the most "mysterious" chemical transformations.

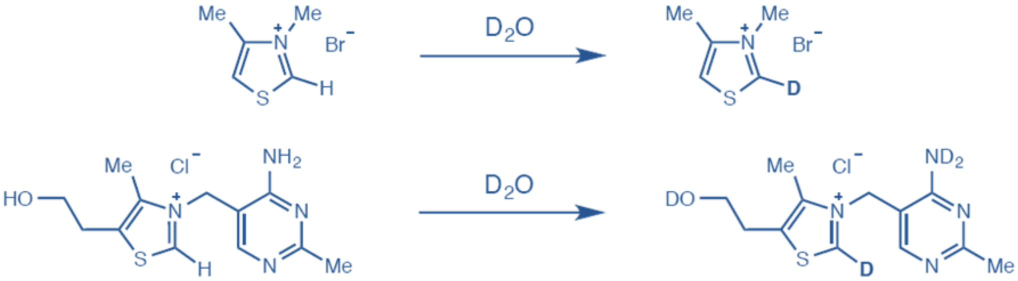




Robert H. Grubbs

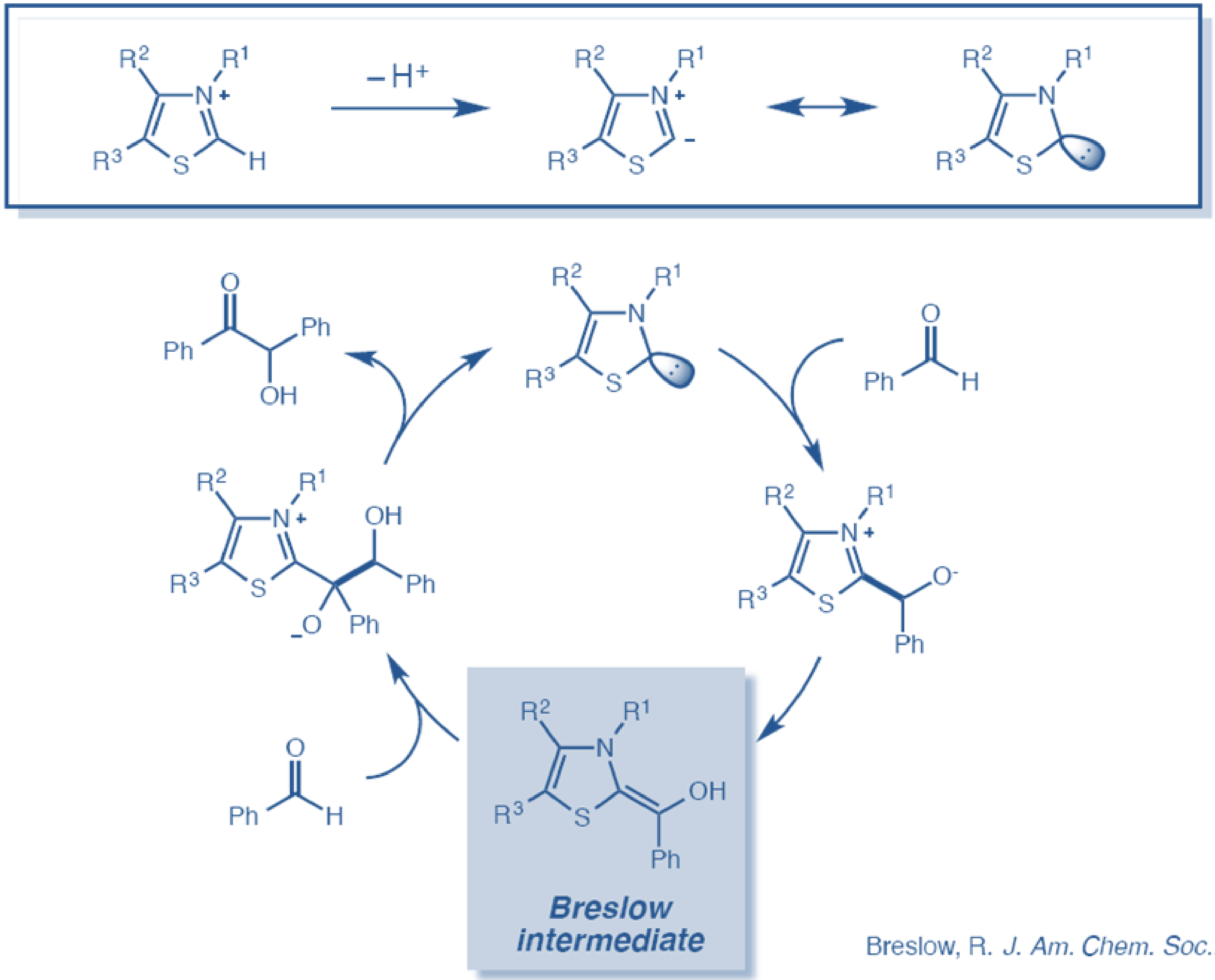
Steven C. Zimmerman

◆ Breslow discovered that the C-2 proton of the thiazoliums exchanges rapidly with deuterium



Early Development

1958: Breslow proposed the mechanism for the thiazolium catalyzed benzoin condensation



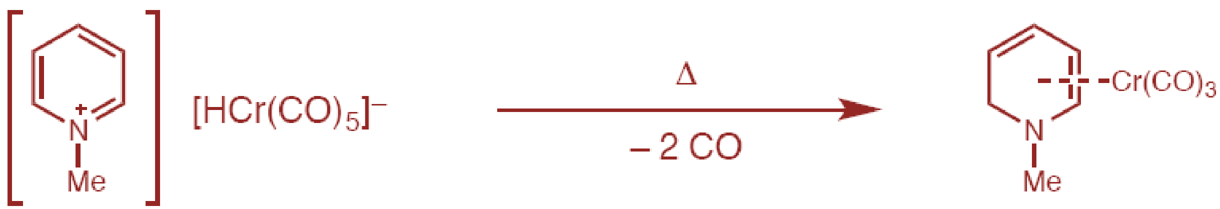
Breslow, R. *J. Am. Chem. Soc.*. **1958**, *80*, 3719.

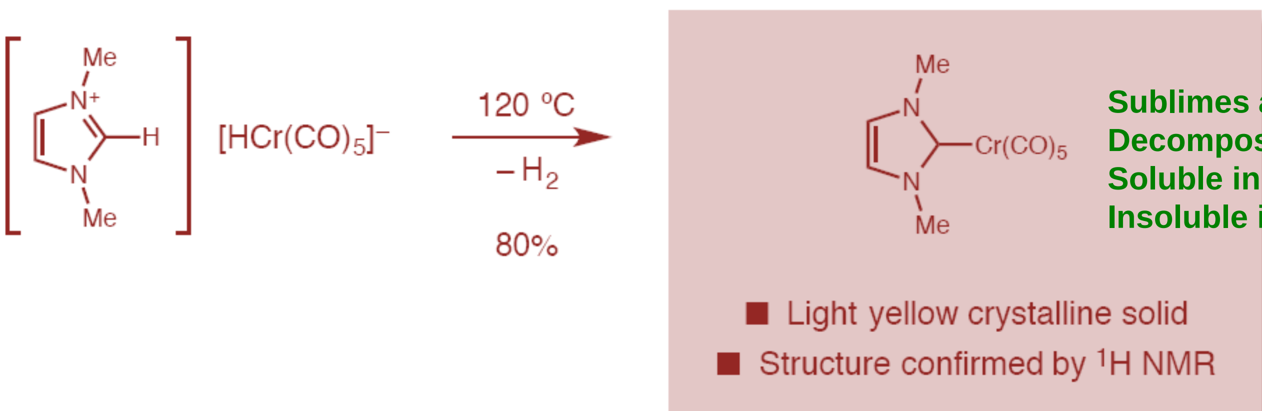
Early Development

Prior to 1960, chemists thought that carbenes were too reactive to be isolated in a stable form, which thwarted widespread efforts to investigate carbene chemistry.

Perhaps true for many carbenes, but proved to be inaccurate for N-heterocyclic carbenes.

Ofele isolated a chromium NHC complex in 1968



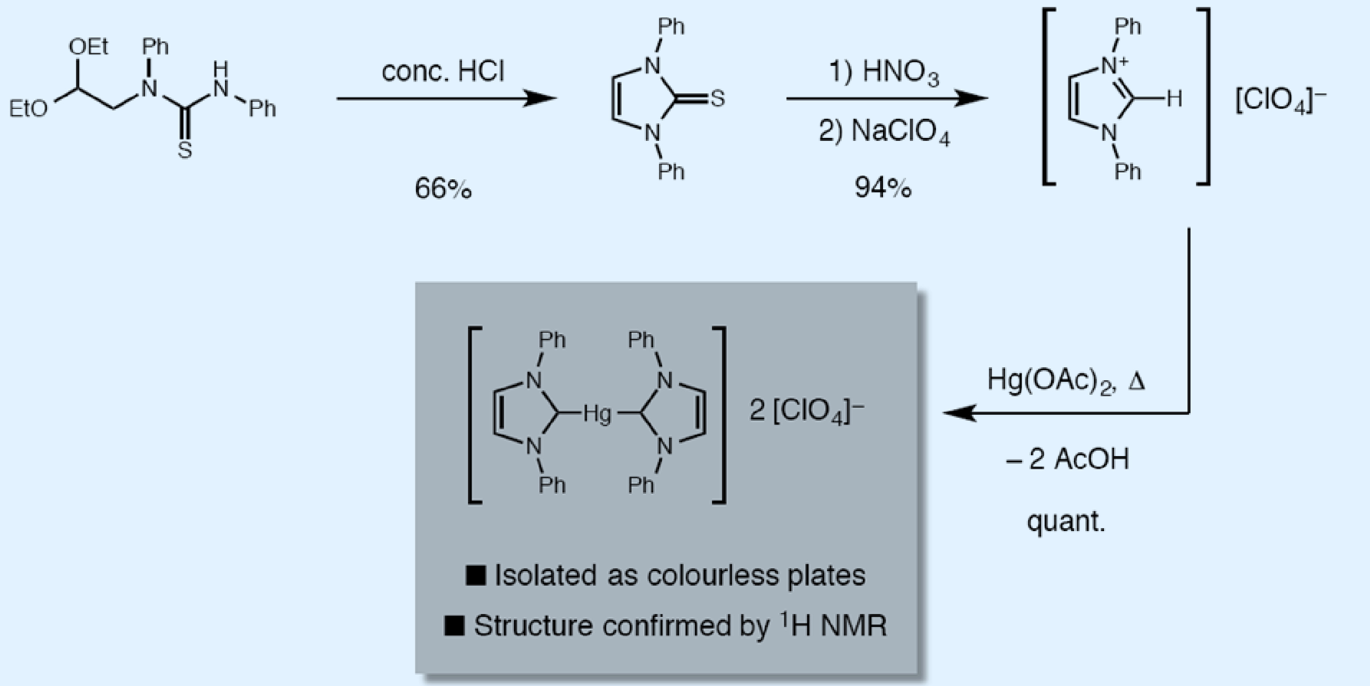


Sublimes at 80 °C
Decomposes to $Cr(CO)_6$ over 175 °C
Soluble in alcohol, CCl_4, petroleum ether
Insoluble in H_2O

J. Organomet. Chem. 1968, 42.

Early Development

Wanzlick isolated a mercury NHC complex in 1968, 550 km away from Ofele



Angew. Chem. Int. Ed. 1968, 7, 141.

Advancing the NHC ligand in Organometallic Chemistry remained inactive for more than 23 years until...!!!

Early Development

In 1991 Arduengo isolated the first stable, crystalline carbene

A Stable Crystalline Carbene

Anthony J. Arduengo, III,* Richard L. Harlow, and Michael Kline

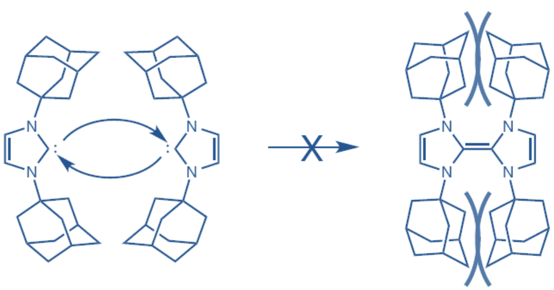
Contribution No. 5671
Central Research and Development Department
E. I. du Pont de Nemours & Company
Experimental Station
Wilmington, Delaware 19880-0328

Received September 26, 1990

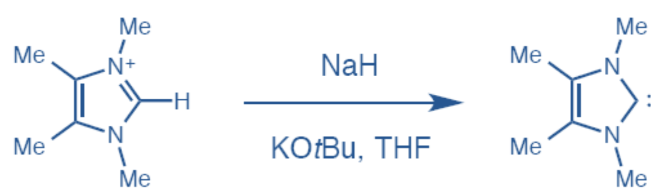
We report the synthesis, structure, and characterization of the first crystalline carbene. Carbene **1**, 1,3-di-1-adamantylimidazol-2-ylidene, forms colorless crystals with sufficient kinetic and thermodynamic stability to be easily isolated and characterized. The deprotonation of 1,3-di-1-adamantylimidazolium chloride (**2**) in THF at room temperature with catalytic dimsyl anion ($^{-}CH_2S(O)CH_3$) in the presence of 1 equiv of sodium hydride produces carbene **1** (eq 1). This deprotonation can also be accomplished with potassium *tert*-butoxide in THF to give a 96% yield of **1**.

The miracles of science™

Thermally stable carbene form due to steric and electronic effects



steric effect

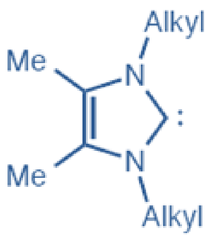


electronic effect

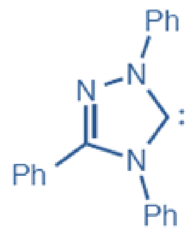
Stability of the carbenes can be attributed more to electronic factors than sterics!

Early Development

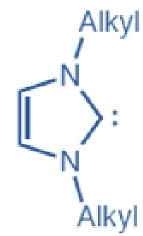
Other stable carbenes isolated following the Arduengo's work



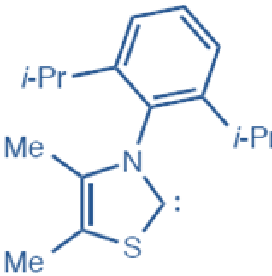
Arduengo et al
1992



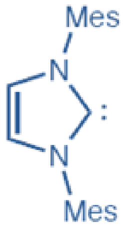
Enders et al
1995
(first commercially available carbene)



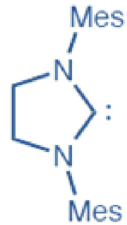
Herrmann et al
1996



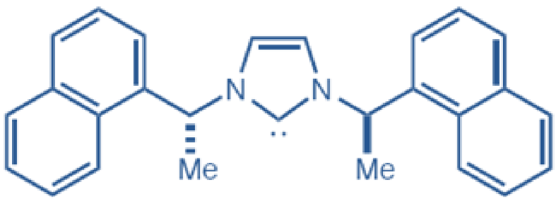
Arduengo et al
1997



Arduengo et al
1992



Arduengo et al
1995



Herrmann et al
1996

Magic Power of NHCs

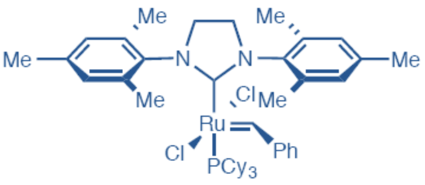
NHCs are exceptionally good δ-donors to form strong metal–carbon bonds, they behave like classical 2e$^-$ donor ligands.

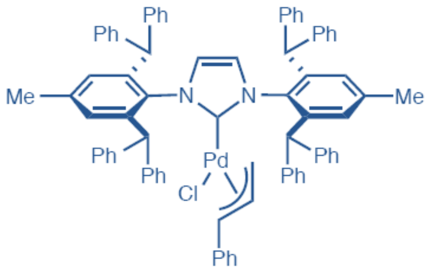
M-NHC bonds are longer (>210 pm) than Fisher- and Schrock- type carbenes (<200 pm)

Compared to phosphines, NHCs form complexes that:

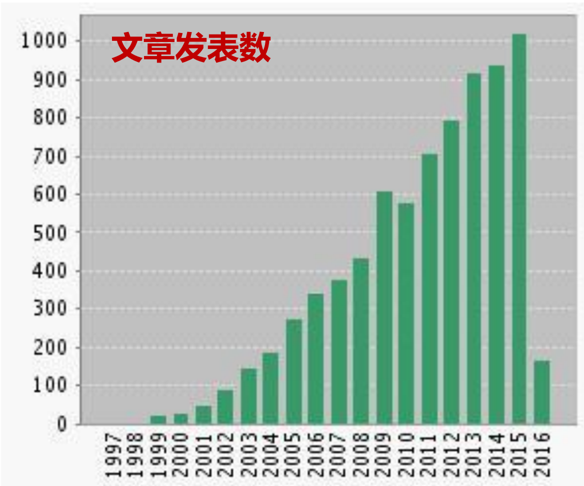
- **Easy to prepare (in situ formation of NHCs)**
- **Show better air and thermal stability**
- **More catalytically active (100~1000 times)**
- **Various synthetic methods for ligand design**

"...in general [NHCs] behave as better donors than the best phosphane donor ligands with the exception of the sterically demanding (adamantyl) carbene." - S. P. Nolan





Magic Power of NHCs



Top Cited Articles

选择记录前面的复选框，从 "引文报告" 中删除记录

或者限定在以下时间范围内出版的记录，从 1900 至 2016 转至

1. **N-heterocyclic carbenes: A new concept in organometallic catalysis**
   作者: Herrmann, WA
   ANGEWANDTE CHEMIE-INTERNATIONAL EDITION 卷: 41 期: 8 页: 1290-1309 出版年: 2002

2. **Ionic liquid (molten salt) phase organometallic catalysis**
   作者: Dupont, J; de Souza, RF; Suarez, PAZ
   CHEMICAL REVIEWS 卷: 102 期: 10 页: 3667-3691 出版年: OCT 2002

3. **The development of L2X2Ru = CHR olefin metathesis catalysts: An organometallic success story**
   作者: Trnka, TM; Grubbs, RH
   ACCOUNTS OF CHEMICAL RESEARCH 卷: 34 期: 1 页: 18-29 出版年: JAN 2001

4. **Heterocyclic carbenes: Synthesis and coordination chemistry**
   作者: Hahn, F. Ekkehardt; Jahnke, Mareike C.
   ANGEWANDTE CHEMIE-INTERNATIONAL EDITION 卷: 47 期: 17 页: 3122-3172 出版年: 2008

5. **Organocatalysis by N-heterocyclic, carbenes**
   作者: Enders, Dieter; Niemeier, Oliver; Henseler, Alexander
   CHEMICAL REVIEWS 卷: 107 期: 12 页: 5606-5655 出版年: DEC 2007

6. **Catalytic carbophilic activation: Catalysis by platinum and gold pi acids**
   作者: Fuerstner, Alois; Davies, Paul W.
   ANGEWANDTE CHEMIE-INTERNATIONAL EDITION 卷: 46 期: 19 页: 3410-3449 出版年: 2007

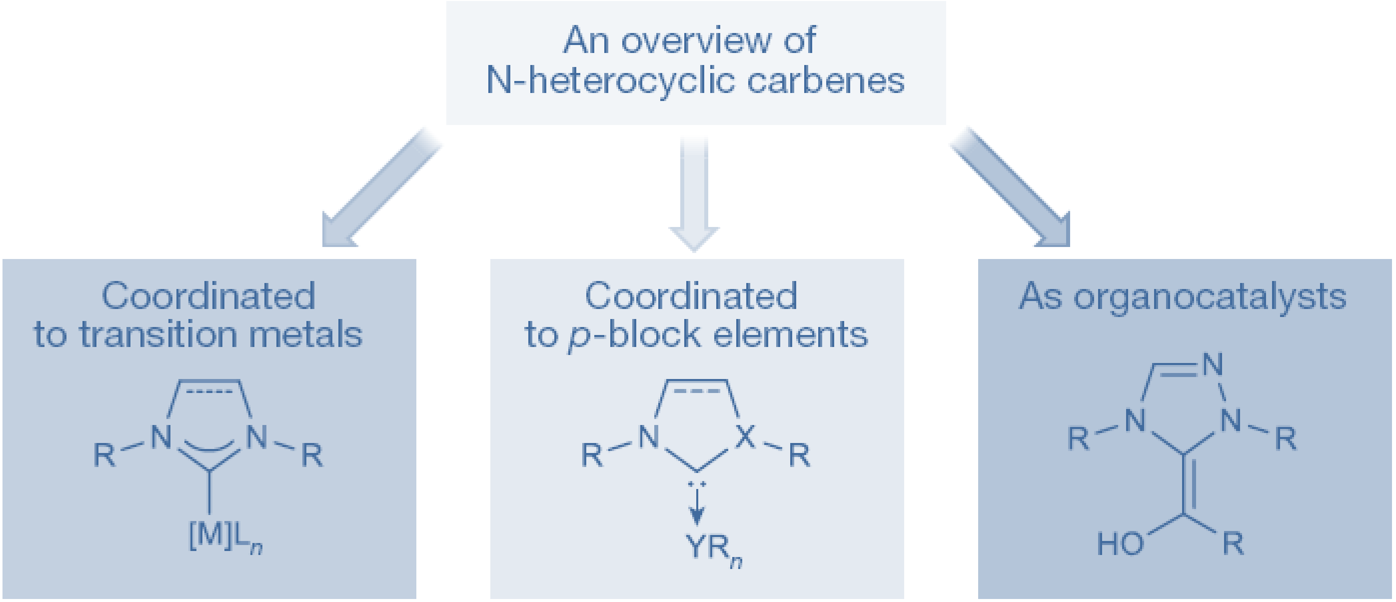
7. **On the nature of the active species in palladium catalyzed Mizoroki-Heck and Suzuki-Miyaura couplings - Homogeneous or heterogeneous catalysis, a critical review**
   作者: Phan, NTS; Van Der Sluys, M; Jones, CW
   ADVANCED SYNTHESIS & CATALYSIS 卷: 348 期: 6 页: 609-679 出版年: APR 2006

8. **Selected patented cross-coupling reaction technologies**
   作者: Corbet, Jean-Pierre; Mignani, Gerard
   CHEMICAL REVIEWS 卷: 106 期: 7 页: 2651-2710 出版年: JUL 12 2006

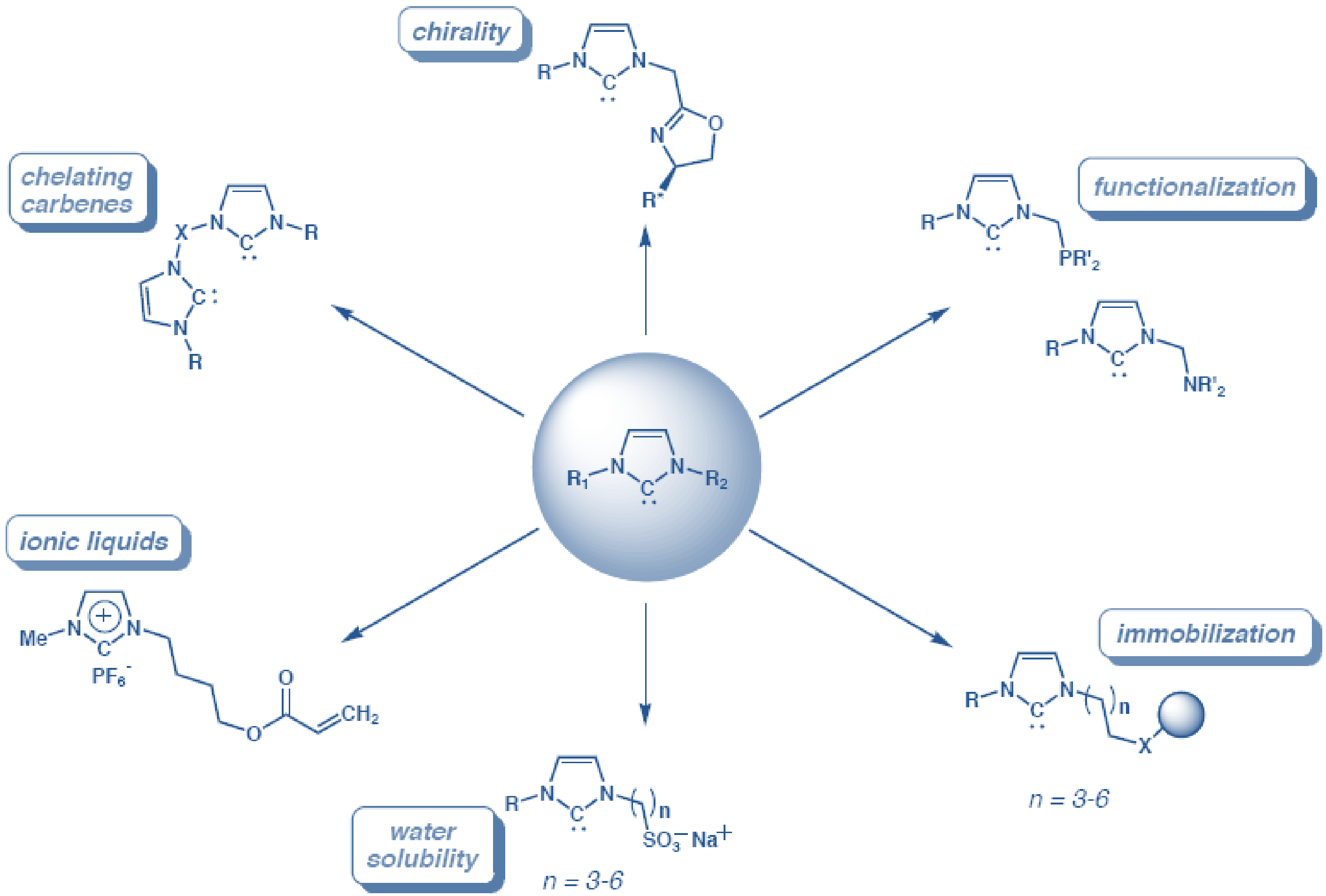
9. **Palladium complexes of N-heterocyclic carbenes as catalysts for cross-coupling reactions - A synthetic chemist's perspective**
   作者: Kantchev, Eric Assen B.; O'Brien, Christopher J.; Organ, Michael G.
   ANGEWANDTE CHEMIE-INTERNATIONAL EDITION 卷: 46 期: 16 页: 2768-2813 出版年: 2007

10. **Recent homogeneous catalytic applications of chelate and pincer N-heterocyclic carbenes**
    作者: Peris, E; Crabtree, RH
    COORDINATION CHEMISTRY REVIEWS 卷: 248 期: 21-24 页: 2239-2246 出版年: DEC 2004

Magic Power of NHCs



Structure Versatility of NHCs



Important Catalytic Processes by NHCs

Suzuki Couplings

Furan Synthesis

Hydrosilylation

Sonagashira Couplings

Cyclopropanation

Aryl Aminations

Polymerizations

Olefin Metathesis

Stille Couplings

Hydrogenation

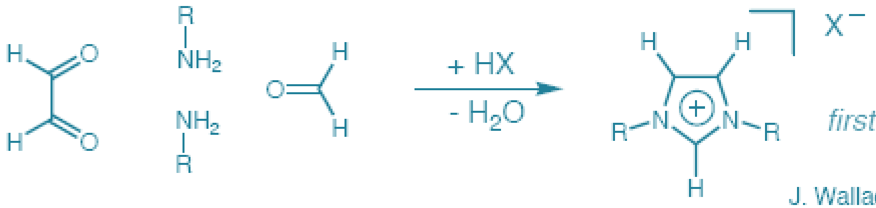
Heck Reactions

Kumada Couplings

Transesterification

Synthesis of NHCs

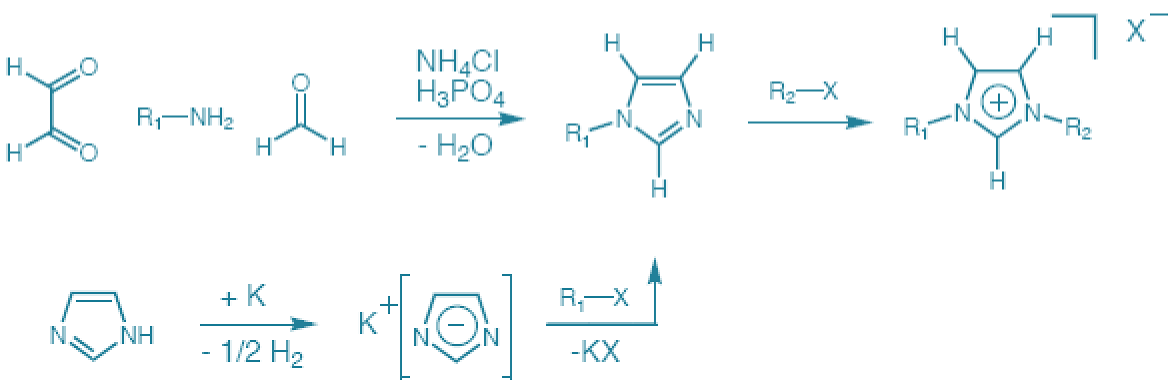
Symmetric N-Substitution



first reported synthesis in 1925!

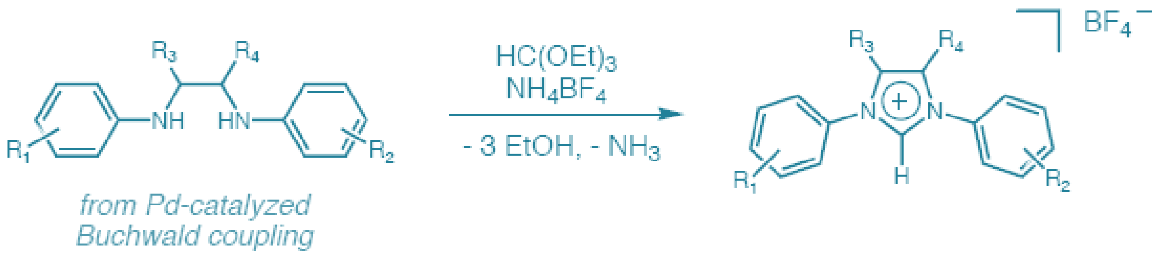
J. Wallach. *Ber. Dtsch. Chem. Ges.* **1925**, *15*, 645.

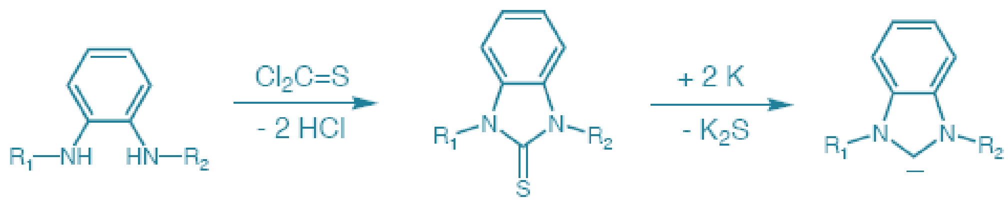
Unsymmetric N-Substitution



Synthesis of NHCs

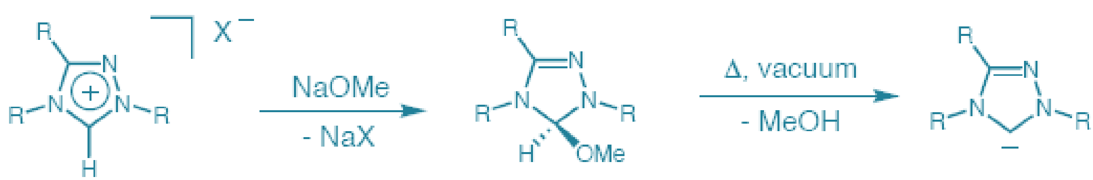
Unsymmetric N-Substitution





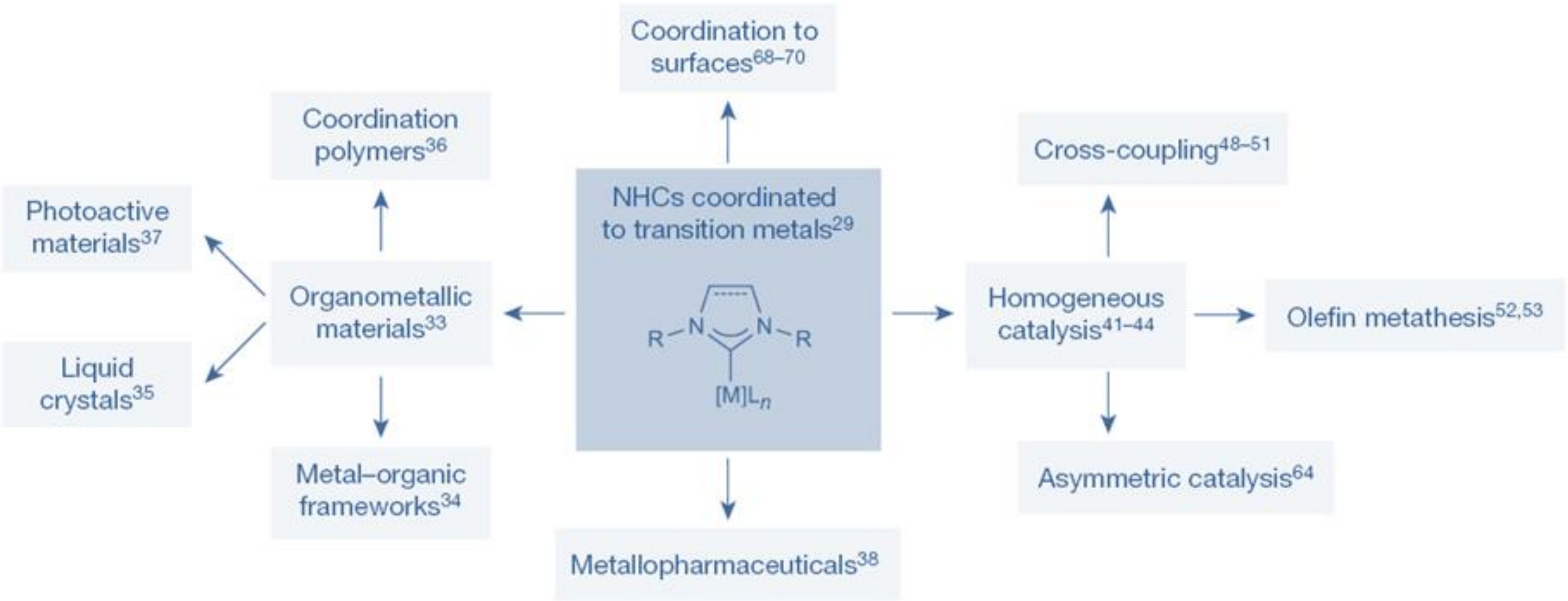
relatively drastic conditions, but works well for some substrates

F. E. Hahn, L. Wittenbacher, D. L. Van, R. Frolich. *Angew. Chem. Int. Ed.* **2000**, *39*, 541.



D. Enders, et al. *Angew. Chem. Int. Ed.* **1995**, *107*, 1119.

NHC-M Complex for Catalysis



NHC-M Complex for Catalysis

Metal Complexes of N-Heterocyclic Carbenes—A New Structural Principle for Catalysts in Homogeneous Catalysis**

Wolfgang A. Herrmann,* Martina Elison, Jakob Fischer, Christian Köcher, and Georg R. J. Artus

A basic functional principle in homogeneous complex catalysis is based on the fact that phosphane and phosphite ligands not only protect low-valent metal centers from aggregation (stabilization effect), but also create coordination sites in dissociation equilibria at which the catalytic elementary steps proceed (activation effect).[1] Examples of industrial importance are hydrocyanation ($Ni^0/P(OR)_3$) and hydroformylation (Co^I/PR_3, Rh^I/PR_3). Generally, as a result of the notorious phosphane degradation by P–C bond cleavage,[2] an excess of the ligand—often 100 times more than the metal—is required to control the equilibrium in the activation and propagation steps in homogeneous catalysis. This excess increases the running costs of technical plants.[3] Phosphane and phosphite complexes are also often water- and air-sensitive. Using the Heck coupling as example,[1c, 4] we now describe a new catalyst principle that does not have these disadvantages. It relies on the special ligand properties of N-heterocyclic carbenes and stands out because of its simplicity and efficiency.

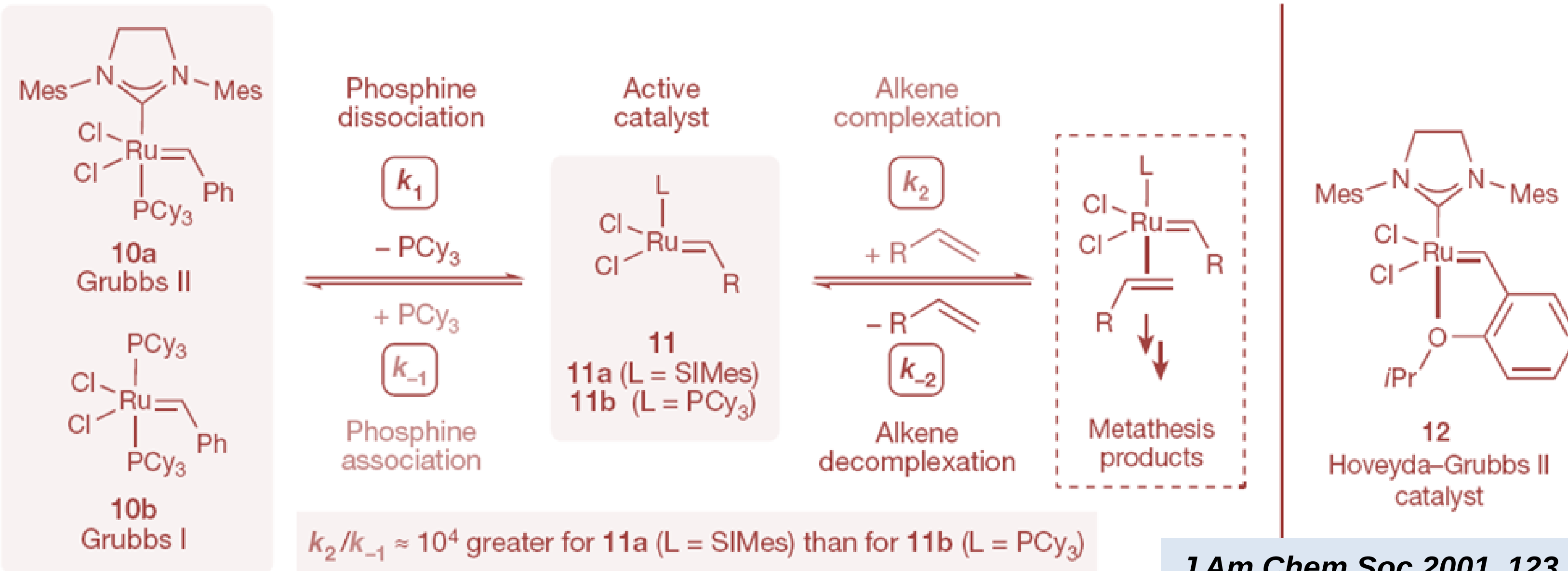
Angew Chem Int Ed 1995, 34, 2371.

X	Br	Br, Cl	Br	Cl
R	CH_3O	C(=O)H	$C(=O)CH_3$	NO_2

Substrate	Catalyst	Amount of catalyst [mol%]	t [h]	Turnover [%]
$4\text{-}BrC_6H_4CHO$	**1**	0.5	10	>99
$4\text{-}BrC_6H_4CHO$	**2**	0.5	10	>99
$4\text{-}BrC_6H_4CHO$	**3**	0.1	3	>99
$4\text{-}BrC_6H_4C(=O)CH_3$	**1**	0.5	10	>99
$4\text{-}BrC_6H_4C(=O)CH_3$	**2**	0.5	10	>99
$4\text{-}BrC_6H_4C(=O)CH_3$	**3**	0.1	3	>99
$4\text{-}BrC_6H_4C(=O)CH_3$	**3**	2×10^{-3}	19	>99
$4\text{-}BrC_6H_4C(=O)CH_3$	**3**	4×10^{-4}	43	>99
$4\text{-}BrC_6H_4C(=O)CH_3$	**3**	2×10^{-4}	96	66
$4\text{-}BrC_6H_4OCH_3$	**1**	0.67	50	60
$4\text{-}BrC_6H_4OCH_3$	**2**	0.67	50	20
$4\text{-}BrC_6H_4OCH_3$	**3**	2×10^{-3}	8	78
$4\text{-}ClC_6H_4CHO$	**1**	1	24	12
$4\text{-}ClC_6H_4CHO$	**1** [b]	1	24	>99
$4\text{-}ClC_6H_4NO_2$	**1** [b]	0.1	36	>99

First work using metal-NHC complexes in homogeneous catalysis.

NHC-M Complex for Catalysis

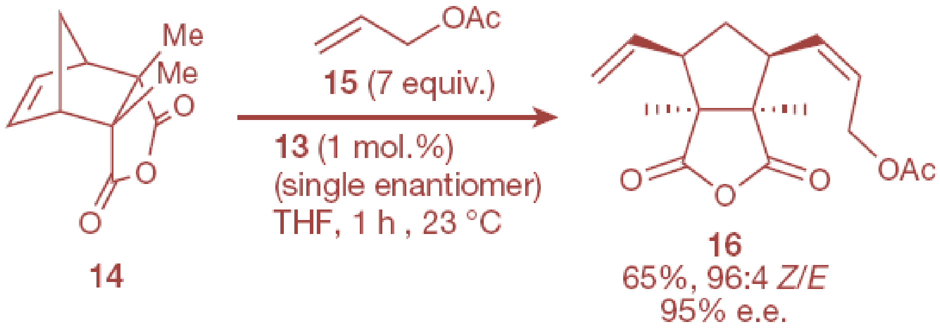


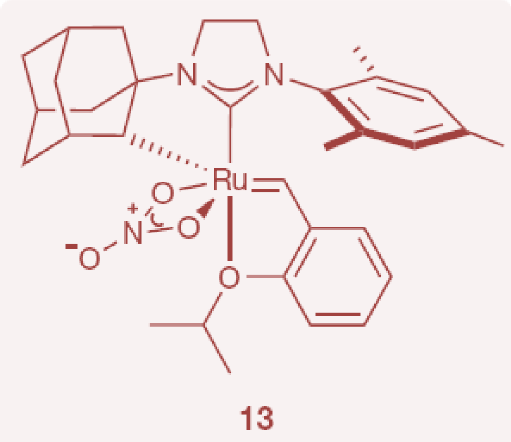
J Am Chem Soc 2001, 123, 6543.

NHC bearing Grubbs' 2nd generation catalyst has 1000 times greater affinity for the alkene substrates, resulting in higher activity than phosphine coordinated 1st generation catalyst.

NHC-M Complex for Catalysis

J Am Chem Soc 2013, 135, 10183.

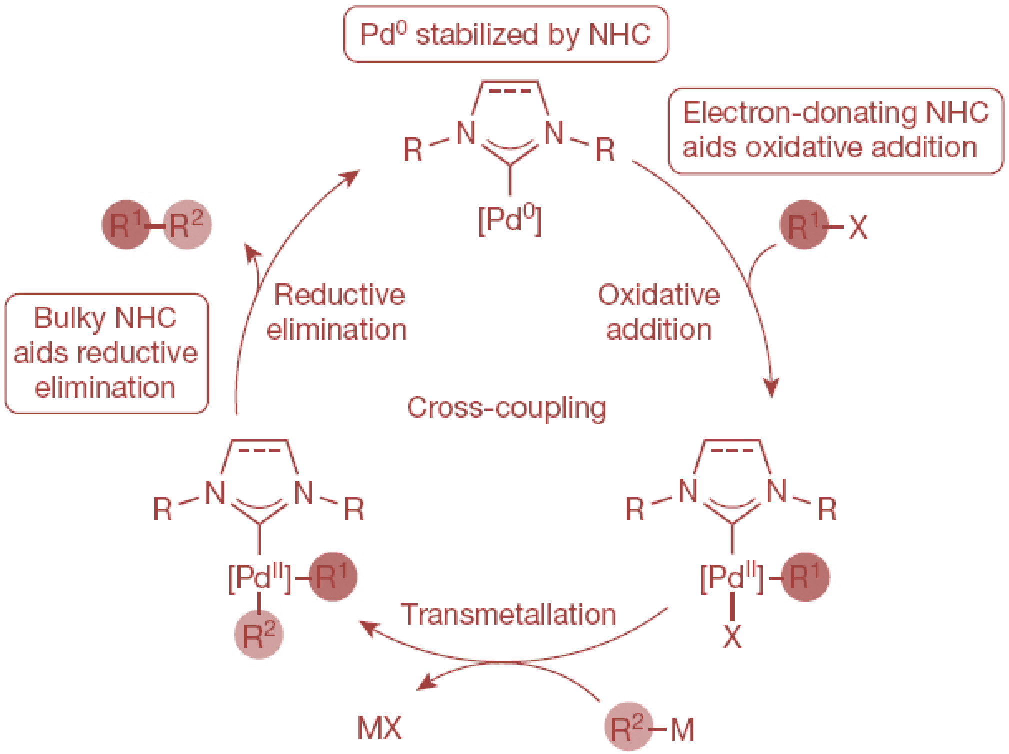




The steric environment in this catalyst is fixed by a key *sp*³- C-H activation at the adamantyl group, which leads to the high Z-selectivity.

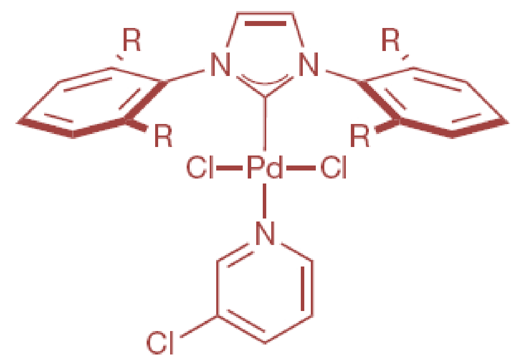
Ru complexes with unsymmetrical N-admantyl substituted ligand show high Z-selectivity in cross-metathesis reactions, while previous reports only get E-seletivity.

NHC-M Complex for Catalysis



R^1, R^2 = aryl, heteroaryl, alkyl
X = halide, pseudohalide
M = $B(OR)_2$ (Suzuki–Miyaura), SnR_3 (Stille), ZnR (Negishi) and also heteroatom coupling partners such as HNR_2 (Buchwald–Hartwig)

The electron richness of NHCs can lead to improved oxidative addition while reductive elimination can benefit from the steric bulkiness of the NHC.



17

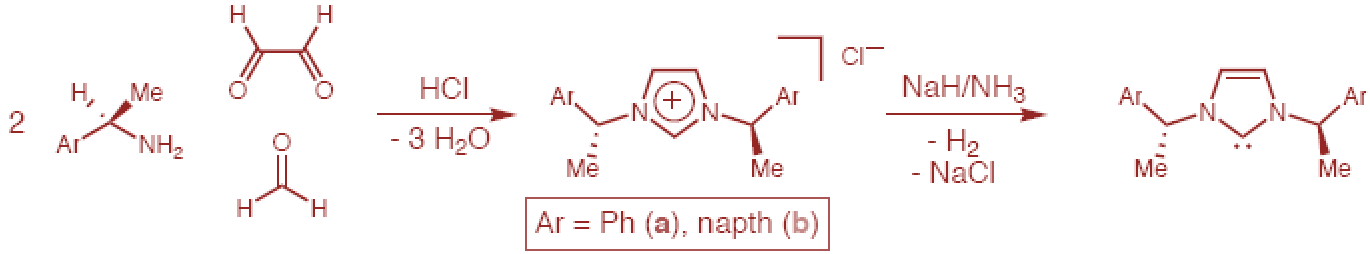
17a R = *i*Pr Pd-PEPPSI-IPr
17b R = *i*Pent Pd-PEPPSI-IPent

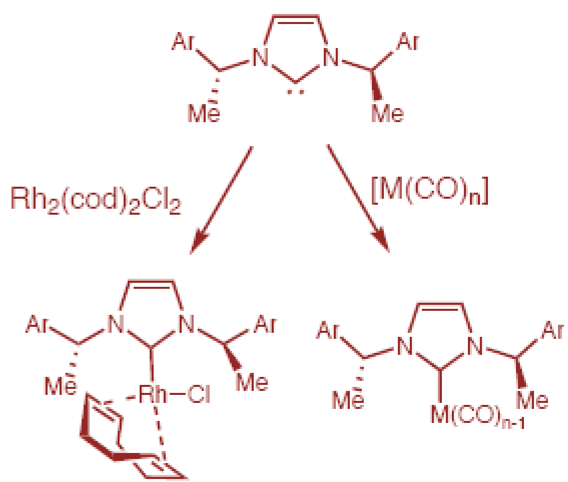
Easy to make catalysts

NHC-M Complex for Catalysis

Chiral NHCs for Enantioselective Catalysts

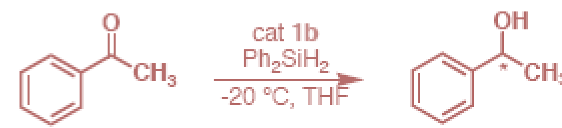
Adding Chirality on the N of the NHC





1a: Ar = Ph
1b: Ar = napth

2a: M = Ni, n = 4
3a: M = W, n = 6
3b: M = W, n = 6



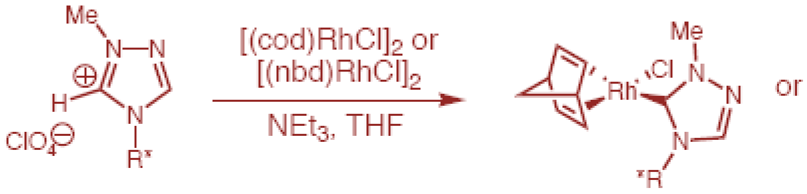
Cat (%)	T(°C)	time	Conv (%)	ee (%)	TON
1	-20	1 d	90	26	90
0.2	-20	6 d	90	26	450
0.1	-20	12 d	90	26	900
1	**-34**	**2 d**	**90**	**32**	**90**
1	0	4 h	90	12	90
1	20	1 h	90	<5	90
1 [a]	-20	1 d	90	26	90
0.1 [b]	-20	6 d	90	24	900
1	-20	7 d	60	26	60
1 [c]	-20	1 d	60	27	60

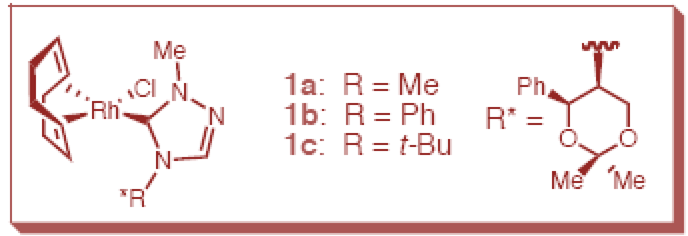
[a] Addition of 3 equiv carbene. [b] Containing 5% $Rh_2(cod)_2Cl_2$.
[c] Methyl napthyl ketone instead of acetophenone

Herrmann, W. A. et al. *Angew. Chem. Int. Ed.* **1996**, *35*, 2805.

NHC-M Complex for Catalysis

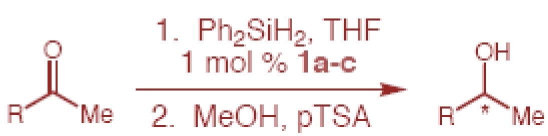
Preparation of Rhodium(cod) and -(nbd) complexes

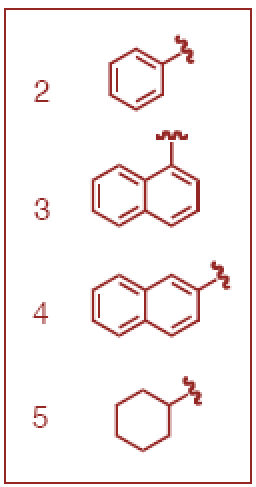




- COD complexes give better e.e.'s than NBD because COD is bigger and restricts rotation around the Rh - carbene bond

Hydrosilylation with Cataysts **1**

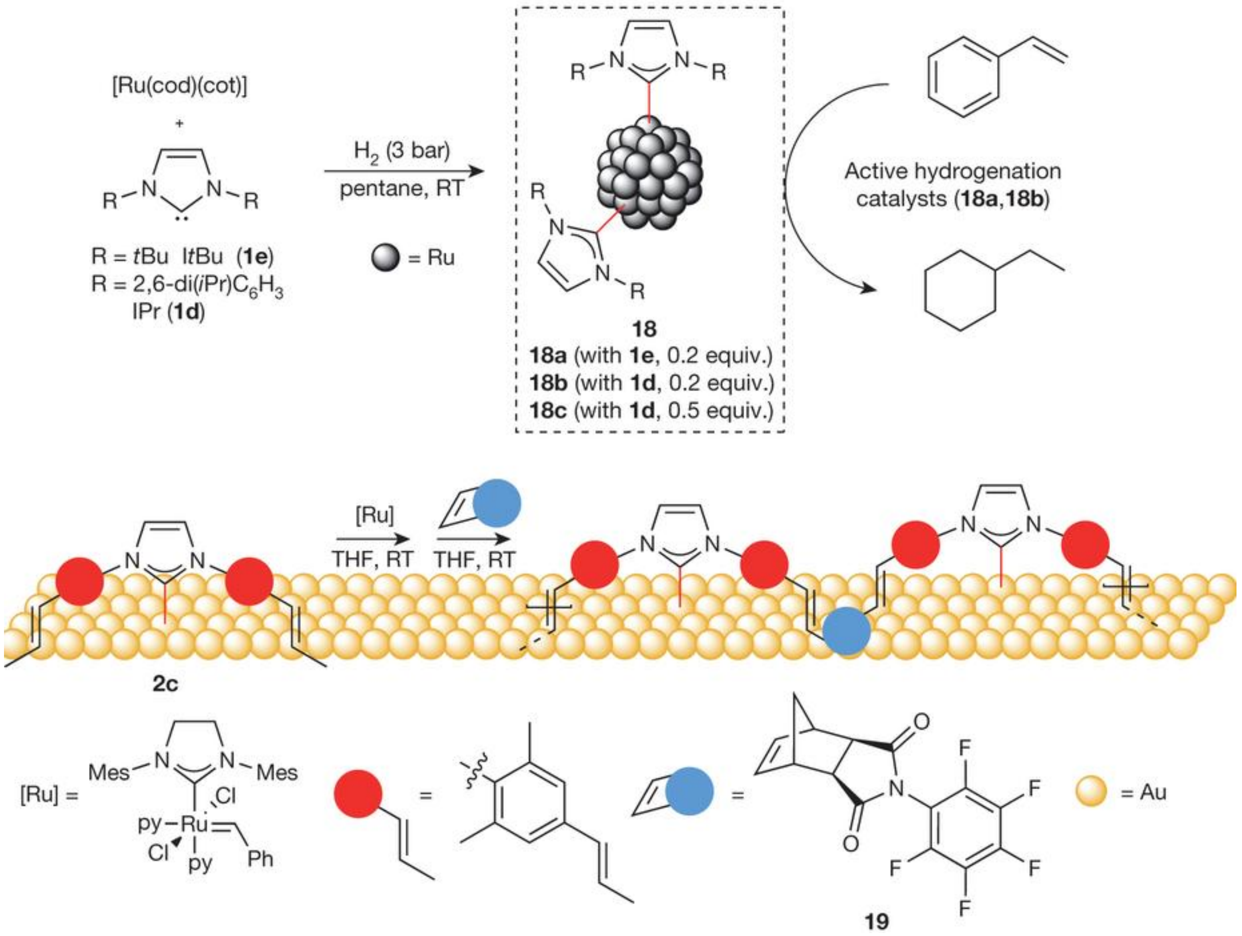




Catalyst	Ketone	T (°C)	Time	Yield (%)	*ee* (%)
4a	9	22	4 h	90	20 (*S*)
4c	9	11	6 d	60	40 (*R*)
4a	10	42	4 h	80	37 (*R*)
4b	10	2	10 d	40	32 (*R*)
4a	11	2	5 d	90	19 (*S*)
4c	11	22	16 h	40	24 (*R*)
4a	12	-10	6 d	75	44 (*S*)
4b	12	2	4 d	80	43 (*S*)
4c	12	22	3 d	70	43 (*R*)

Enders, D. A.; Gielen, H.; Breuer, K. *Tetrahedron: Asymmetry.* **1997**, *21*, 3571.
Enders, D. A. et al. *Eur. J. Inorg. Chem.* **1998**, 913.

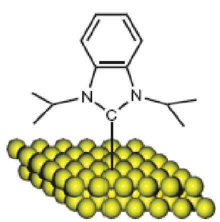
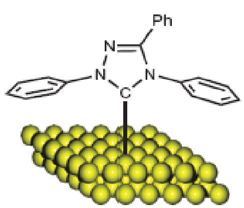
NHC-M Complex on Heterogeneous Surfaces

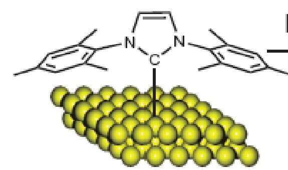
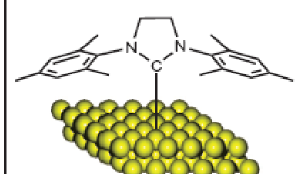
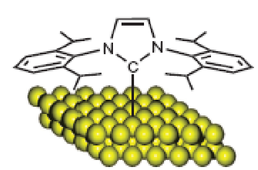


NHC-M Complex on Heterogeneous Surfaces

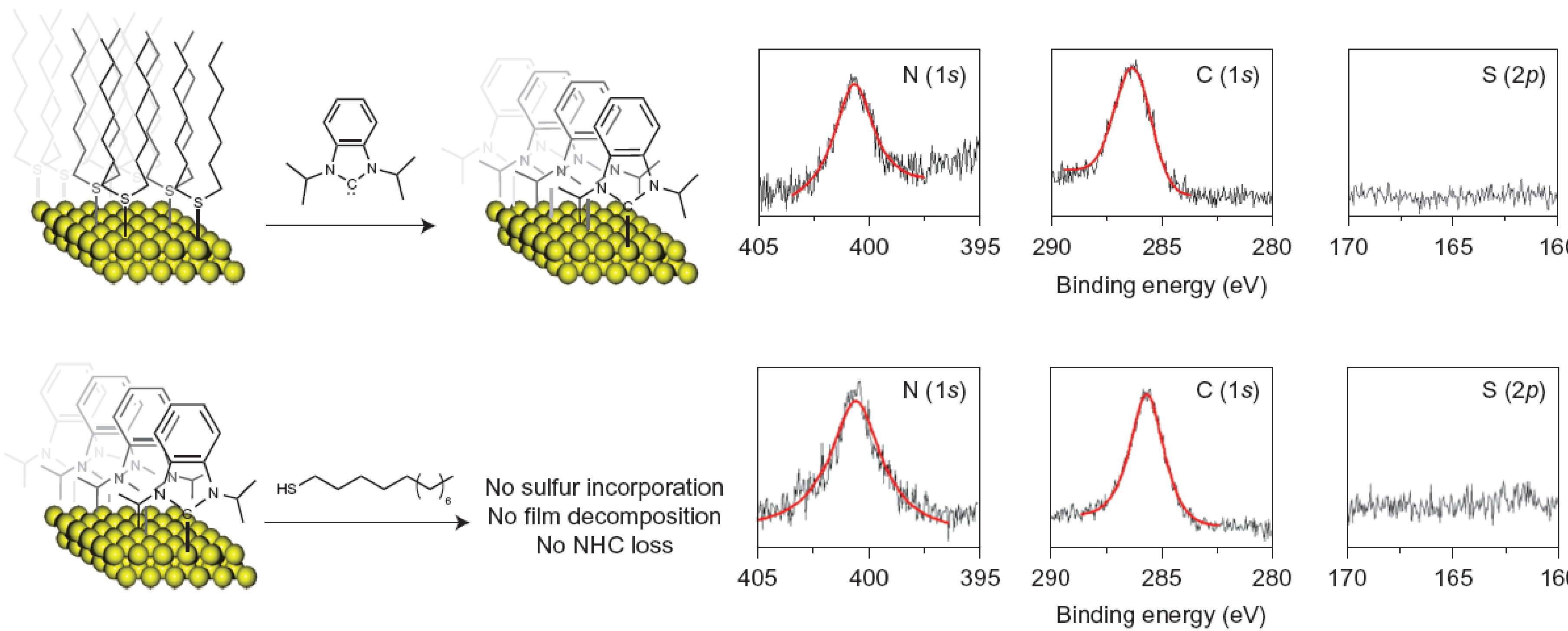
nature chemistry | ARTICLES
PUBLISHED ONLINE: 23 MARCH 2014 | DOI: 10.1038/NCHEM.1891

Ultra stable self-assembled monolayers of N-heterocyclic carbenes on gold

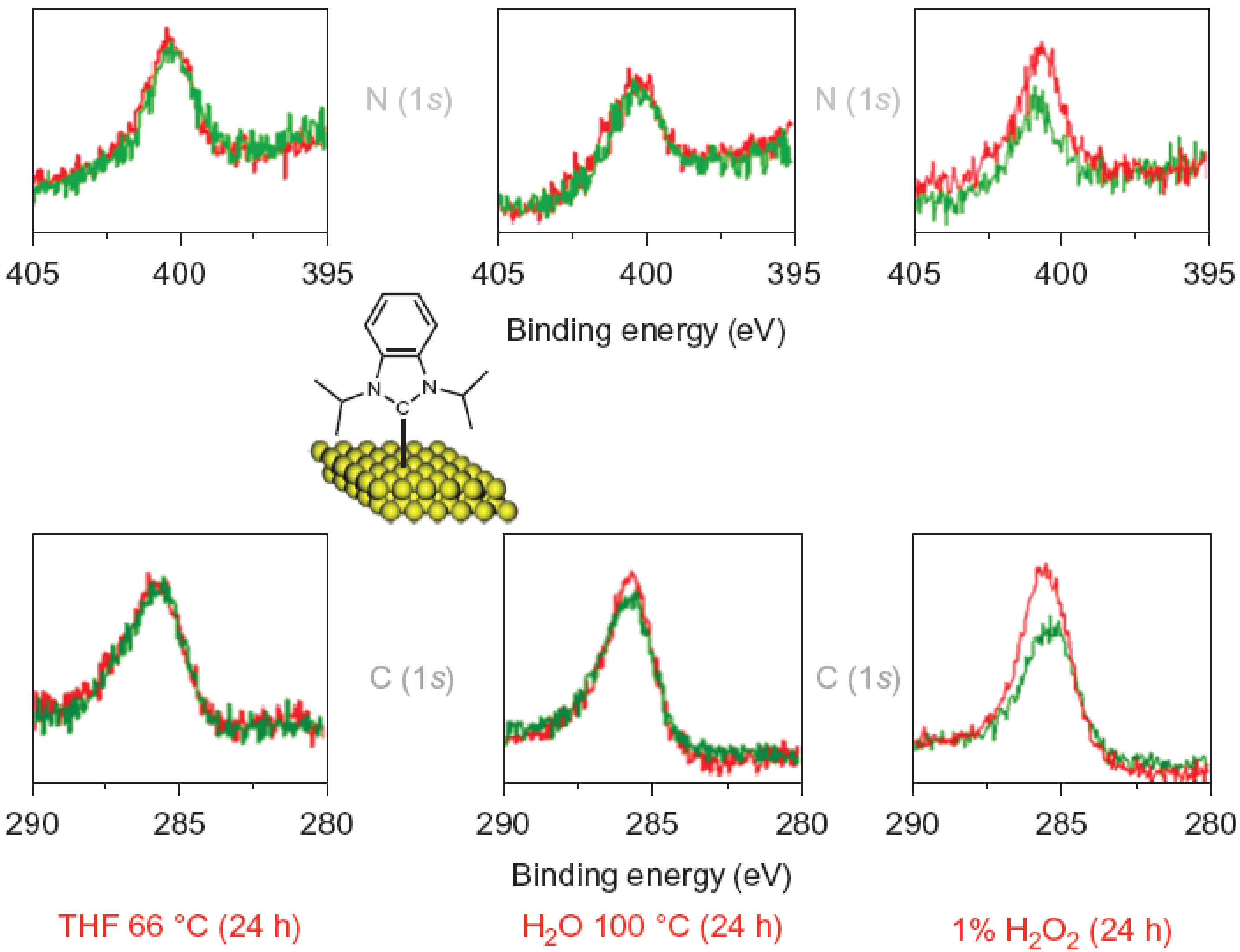
Carbene	C/N ratios (XPS)		
	Molecule	Au(111)	Au_{np}
 1–Au(111)	13/2	14/2	13/2
 2–Au(111)	20/3	21/3	22/3

Carbene	C/N ratios (XPS)		
	Molecule	Au(111)	Au_{np}
 3–Au(111)	21/2	21/2	23/2
 4–Au(111)	21/2	22/2	22/2
 5–Au(111)	27/2	29/2	27/2

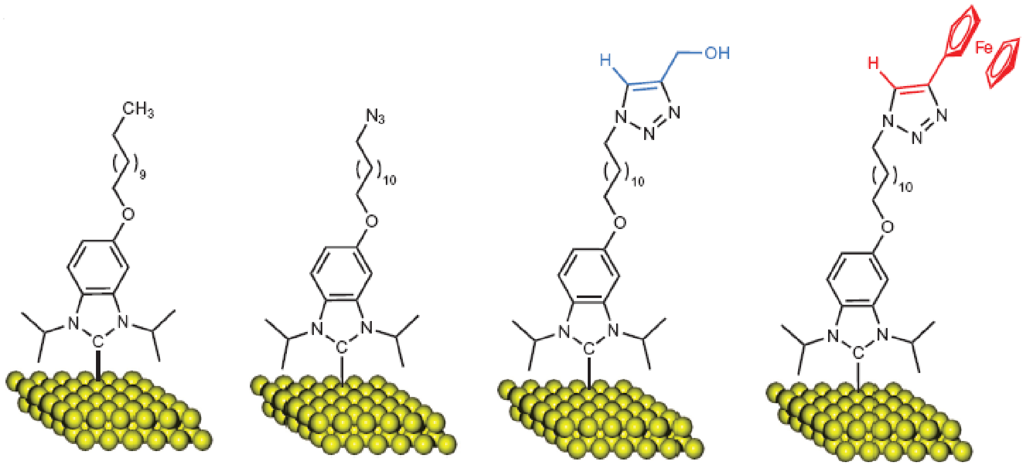
NHC-M Complex on Heterogeneous Surfaces



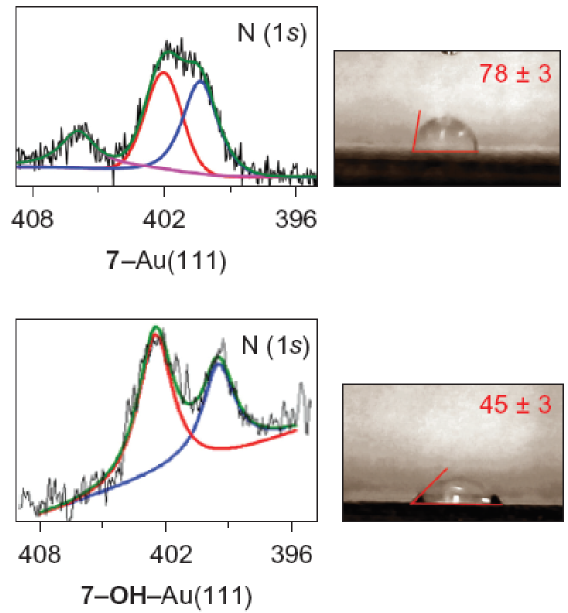
NHC-M Complex on Heterogeneous Surfaces



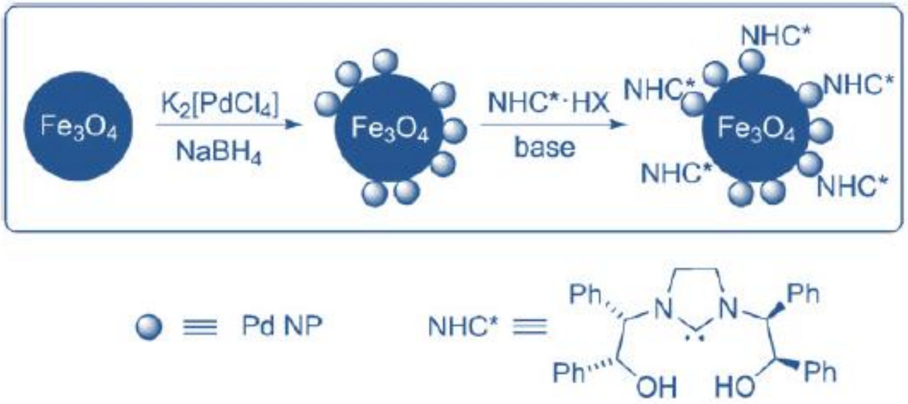
NHC-M Complex on Heterogeneous Surfaces

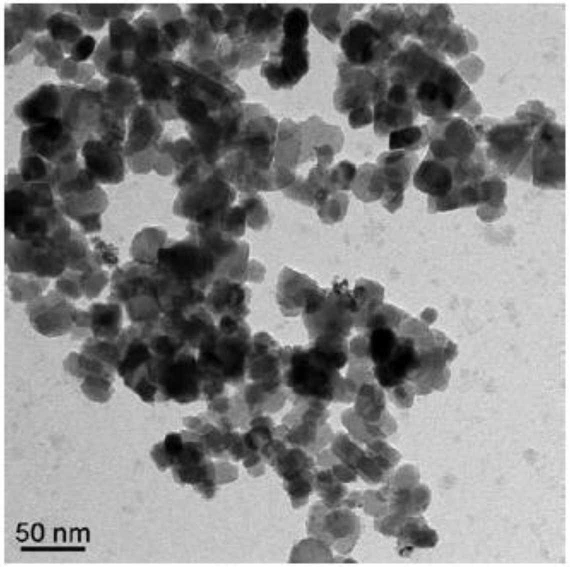


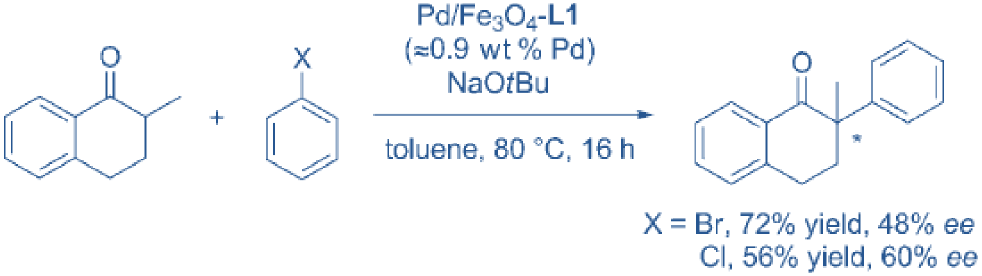
6–Au(111) **7**–Au(111) **7–OH**–Au(111) **7–Fc**–Au(111)



NHC-M Complex on Heterogeneous Surfaces

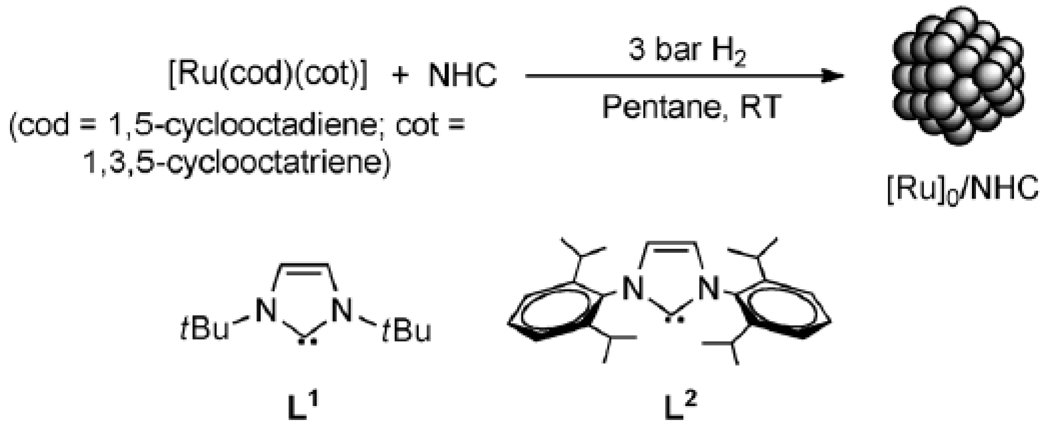


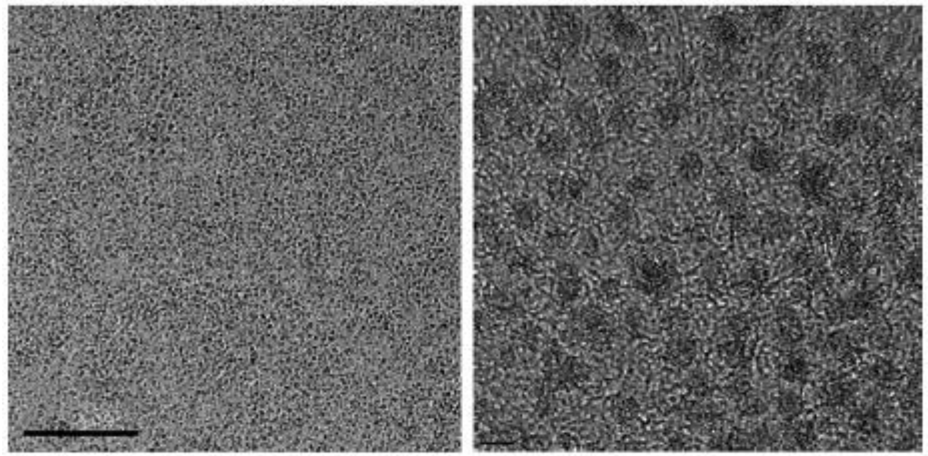




Angew Chem Int Ed 2010, 49, 7786

NHC-M Complex on Heterogeneous Surfaces

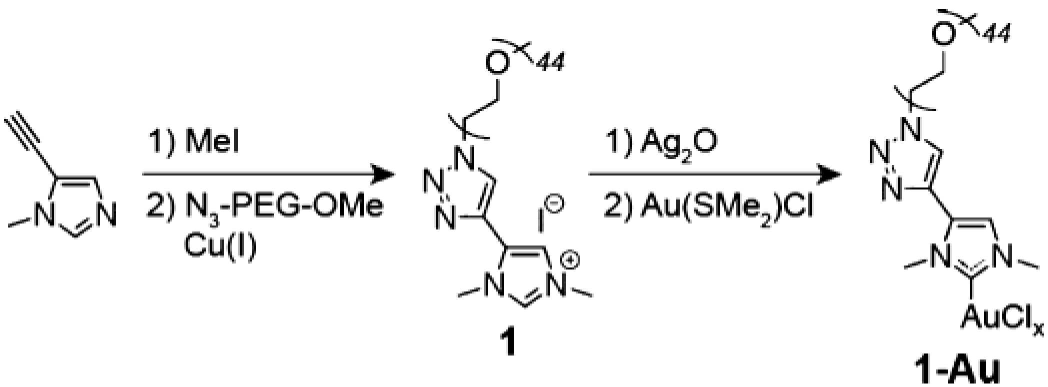




Angew Chem Int Ed 2011, 50, 12080

NHC-M Complex on Heterogeneous Surfaces

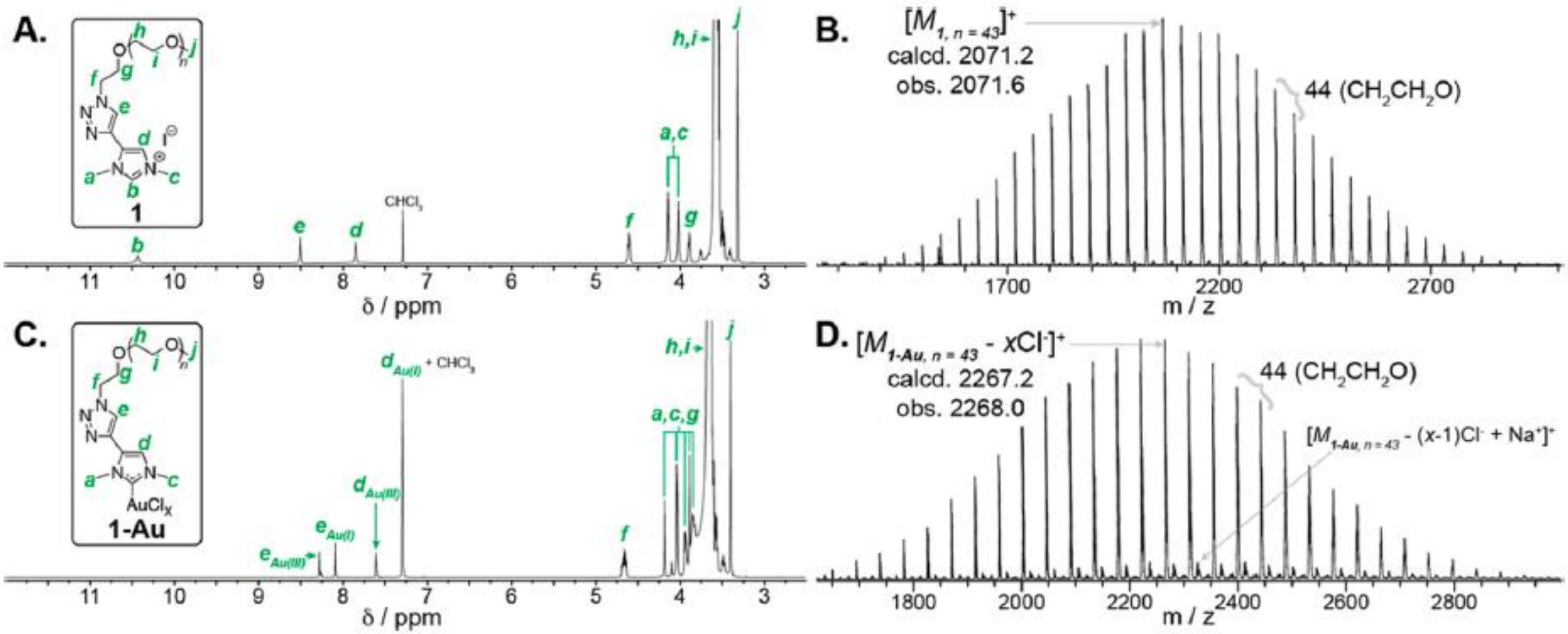
Scheme 1. Synthesis of PEGylated NHC Precursor 1 and Complex 1-Au[a]



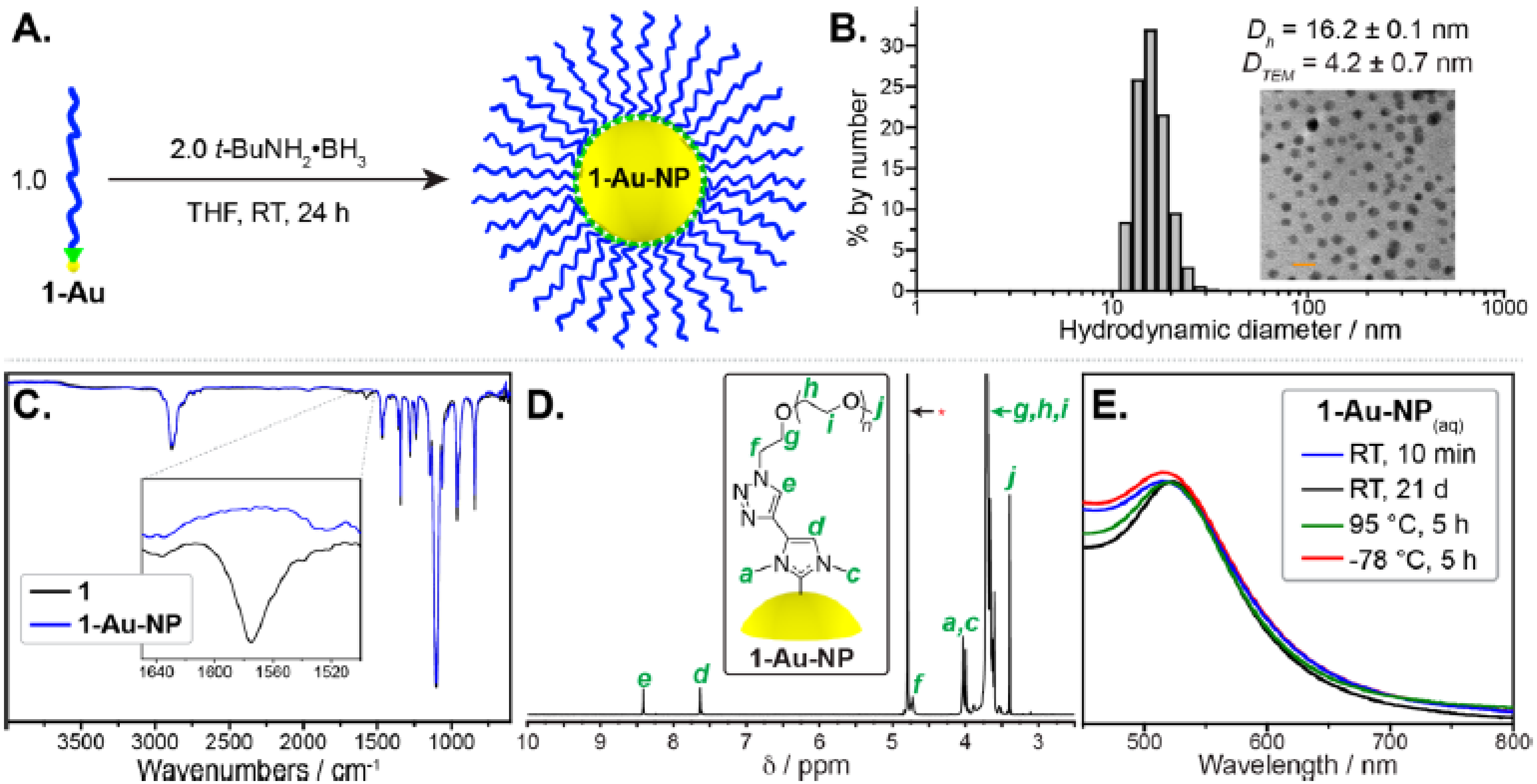
[a]A mixture of Au(I) and Au(III) species with $x = 1$ or 3, respectively.

JACS **2015**, *137*, 7974.

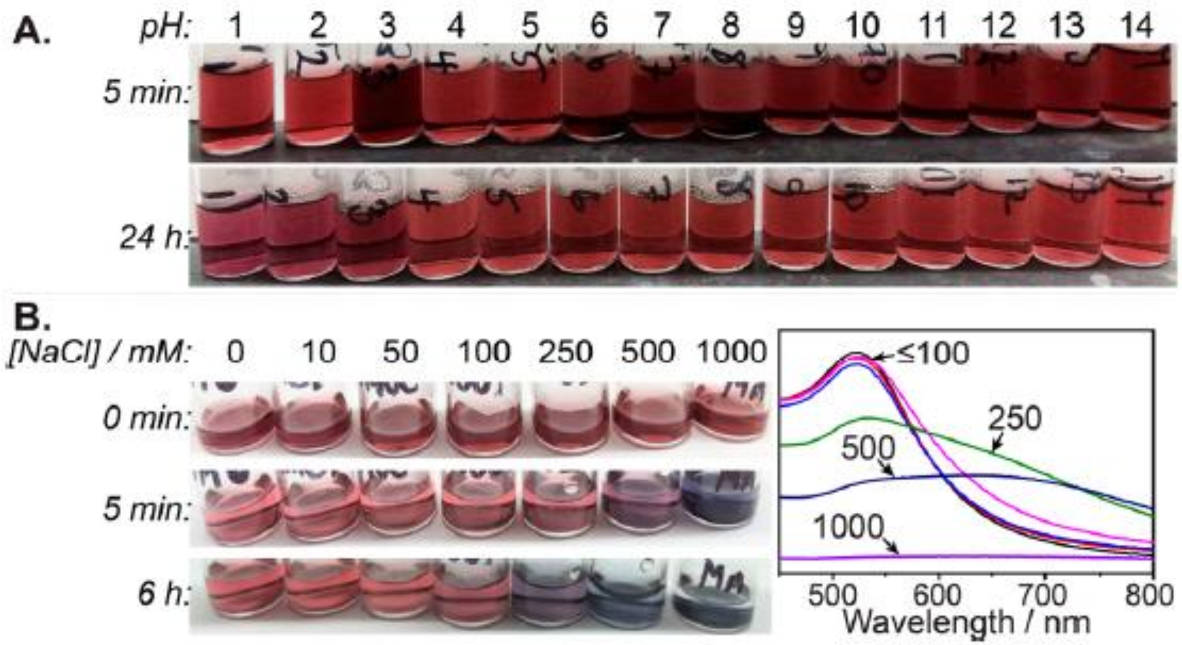
NHC-M Complex on Heterogeneous Surfaces



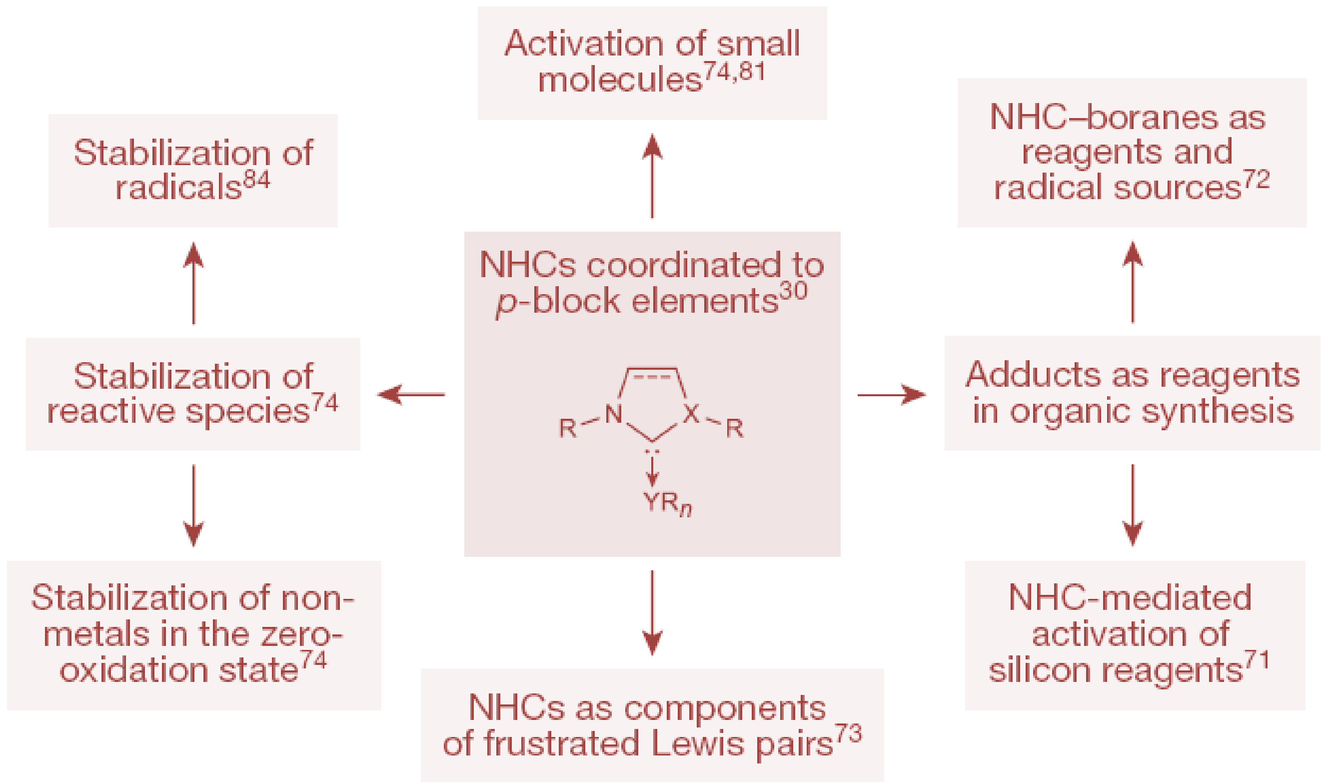
NHC-M Complex on Heterogeneous Surfaces



NHC-M Complex on Heterogeneous Surfaces

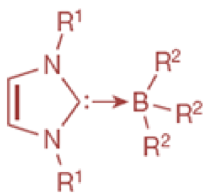


NHCs Coordinate to *p*-Block Elements

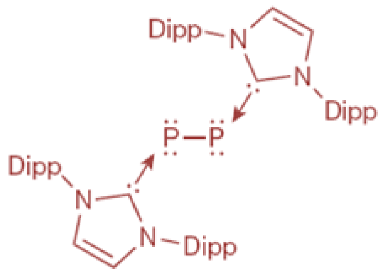


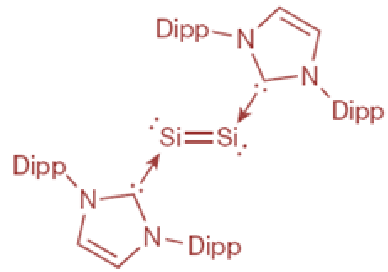
NHCs enable the preparation and characterization of various unknown species featuring *p*-block species in unconventional forms

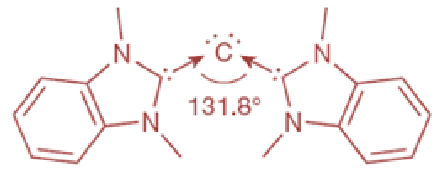
NHCs Coordinate to *p*-Block Elements



R^2 = H, alkyl, aryl





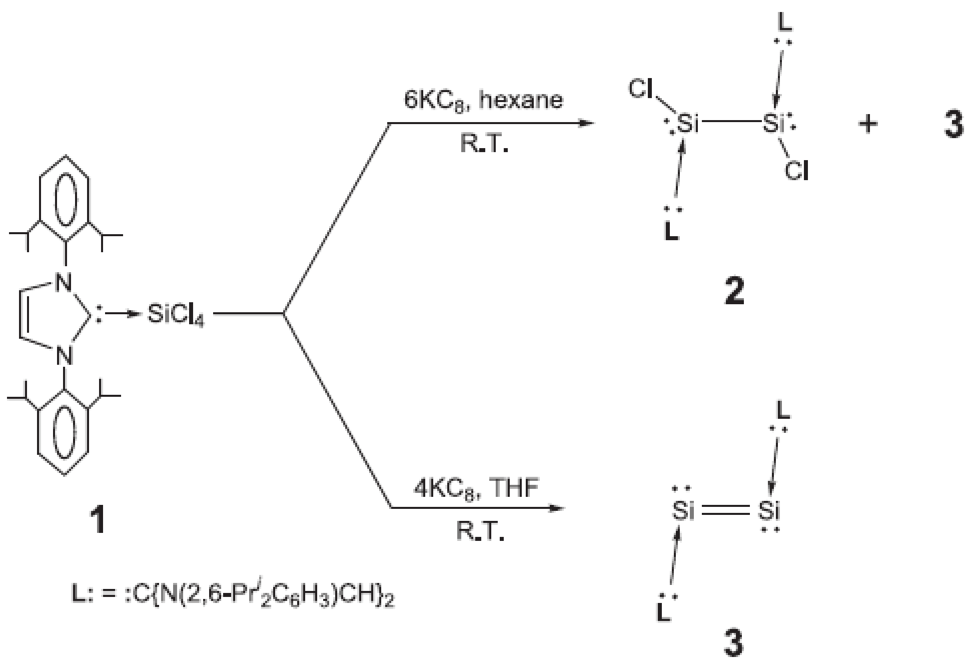


NHCs Coordinate to *p*-Block Elements

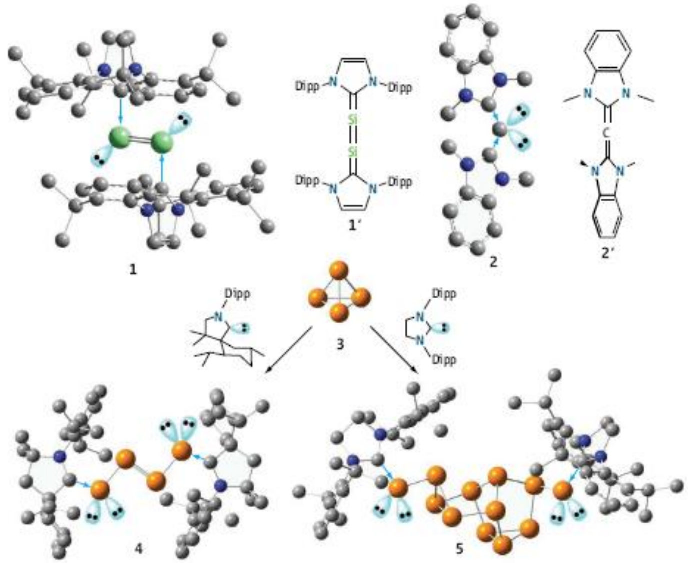
A Stable Silicon(0) Compound with a Si=Si Double Bond

Science 2008, 321, 1069.

Yuzhong Wang, Yaoming Xie, Pingrong Wei, R. Bruce King, Henry F. Schaefer III, Paul von R. Schleyer,* Gregory H. Robinson*

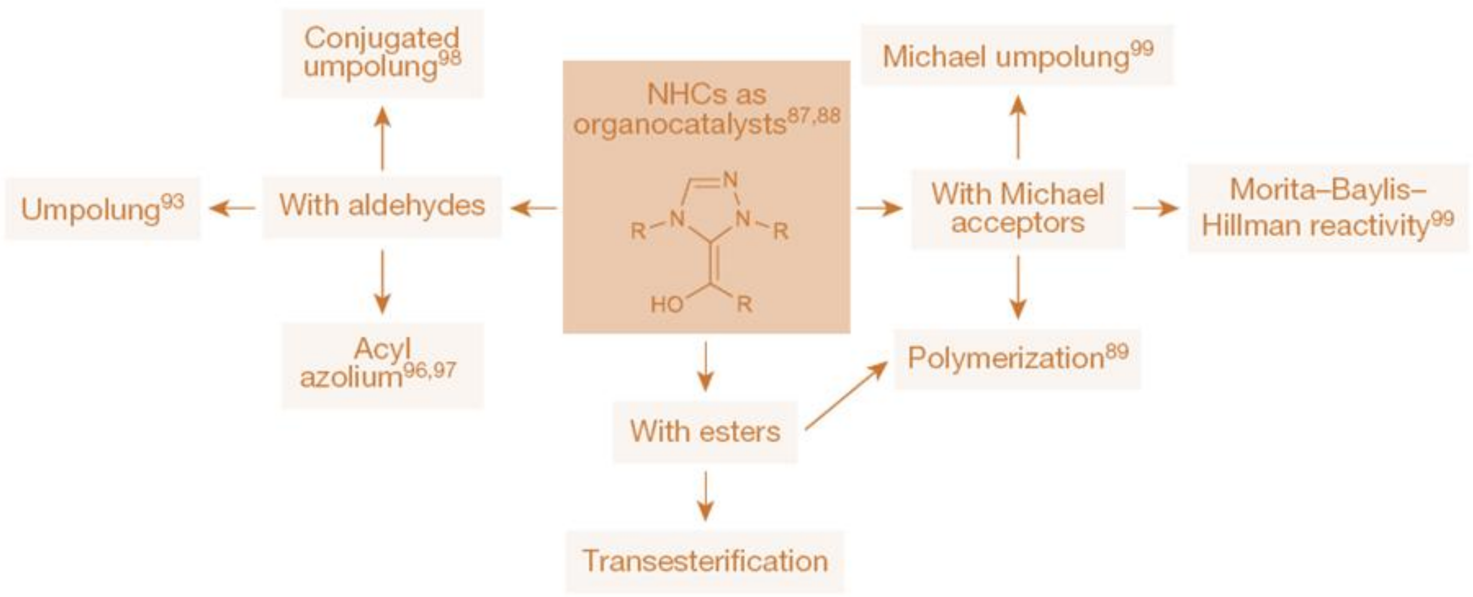


NHCs Coordinate to *p*-Block Elements



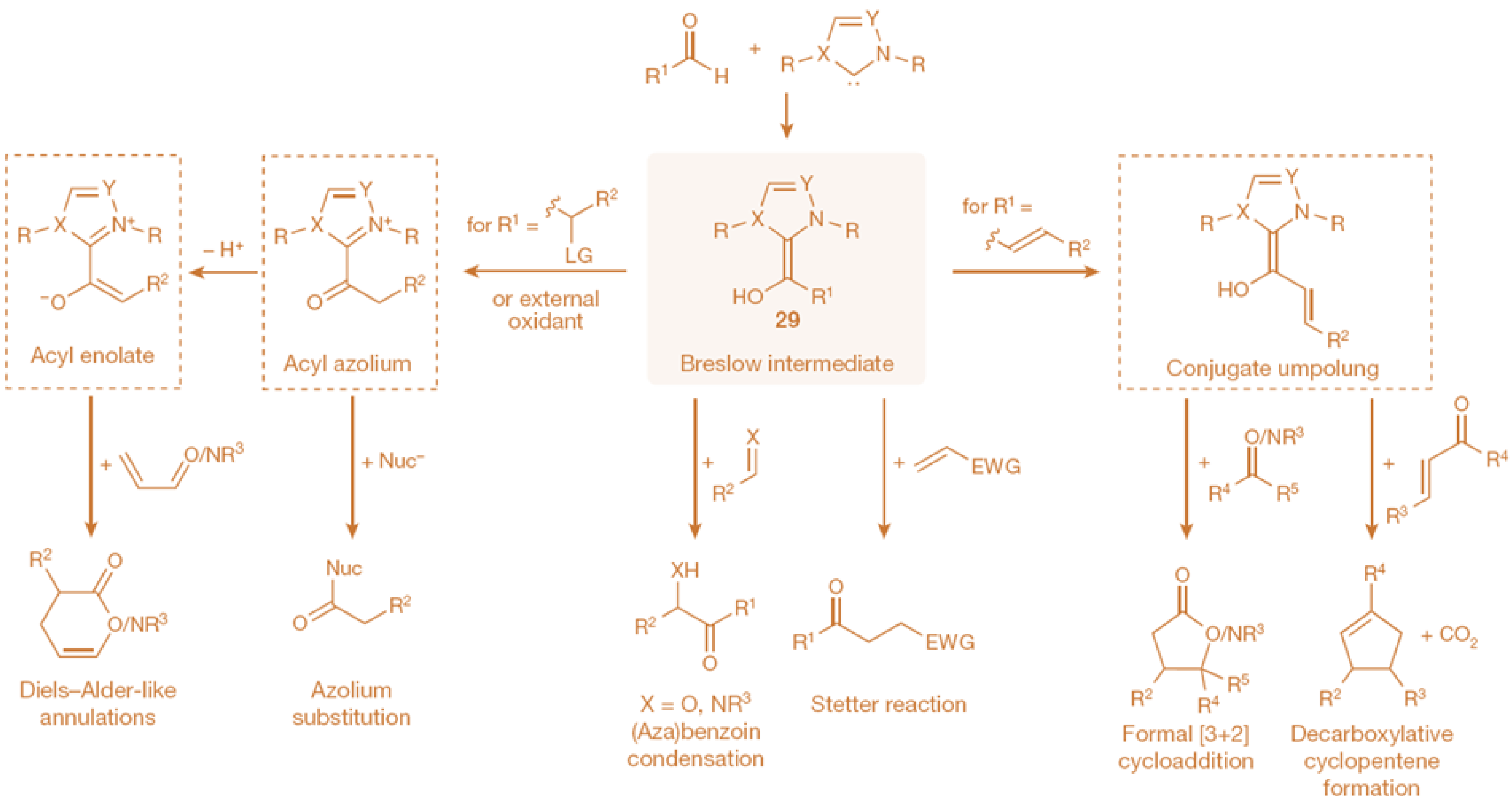
Stabilizing power. Carbenes with their nonbonding electrons in the same orbital (the spin-paired singlet state) act as nonoxidizing two-electron donors toward Si_2 and C_1 units, as indicated by the observed geometry of compounds 1 and 2, versus more classical Lewis structures 1' and 2', which are not observed. Both the silicon and central carbon centers of 1 and 2 possess one and two electron pairs, respectively, and are in the zero oxidation state. Carbene-induced transformations of white phosphorus (3) into novel P_4 (4) and P_{12} (5) clusters illustrate the broad applicability of carbenes in the stabilization of artificial main-group-element allotropes. (Dipp, 2,6-diisopropylphenyl; carbon, gray; silicon, green; nitrogen, blue; phosphorus, orange.)

NHCs as Organocatalysts



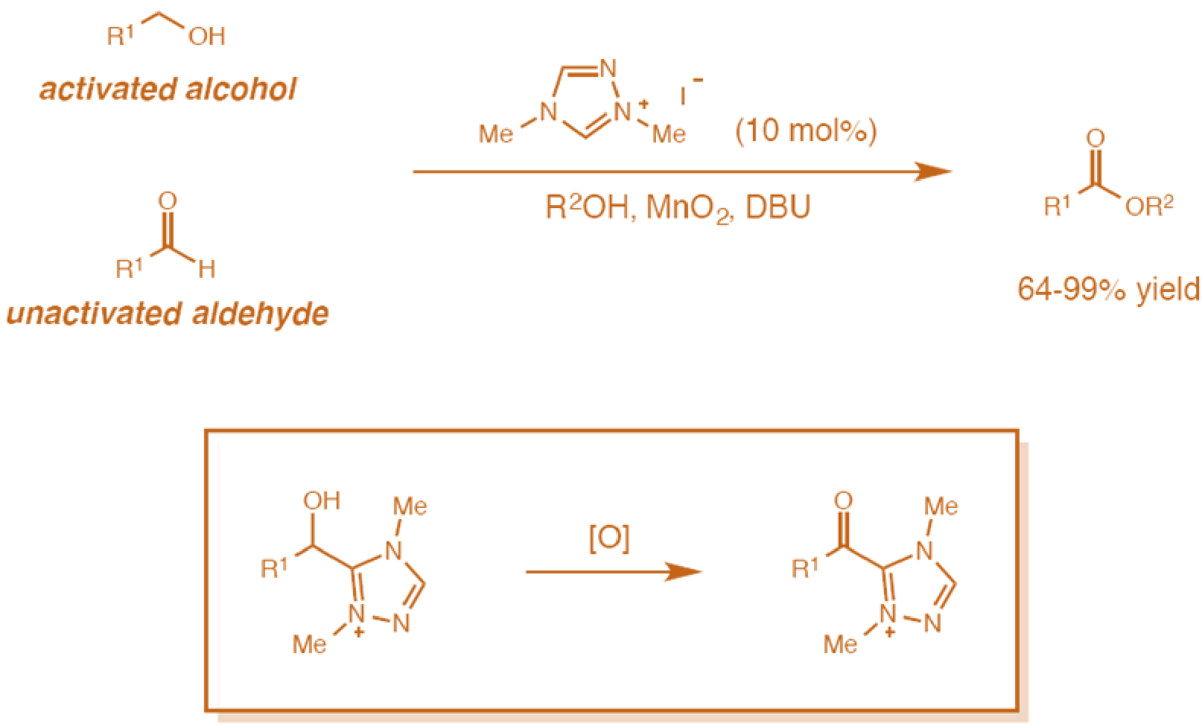
NHCs mediate a wide range of different organic transformations

NHCs as Organocatalysts



NHCs as Organocatalysts

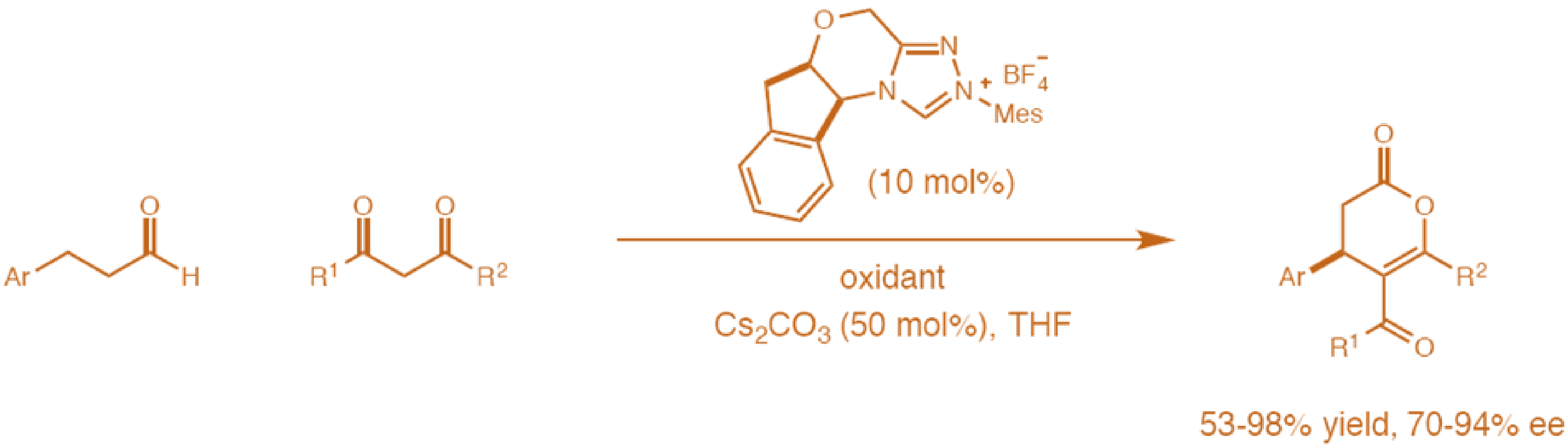
In 2007 & 2008, Scheidt demonstrated NHCs could catalyze the MnO_2 promoted oxidation of benzylic and vinylic alcohols, and unactivated aldehydes to esters.

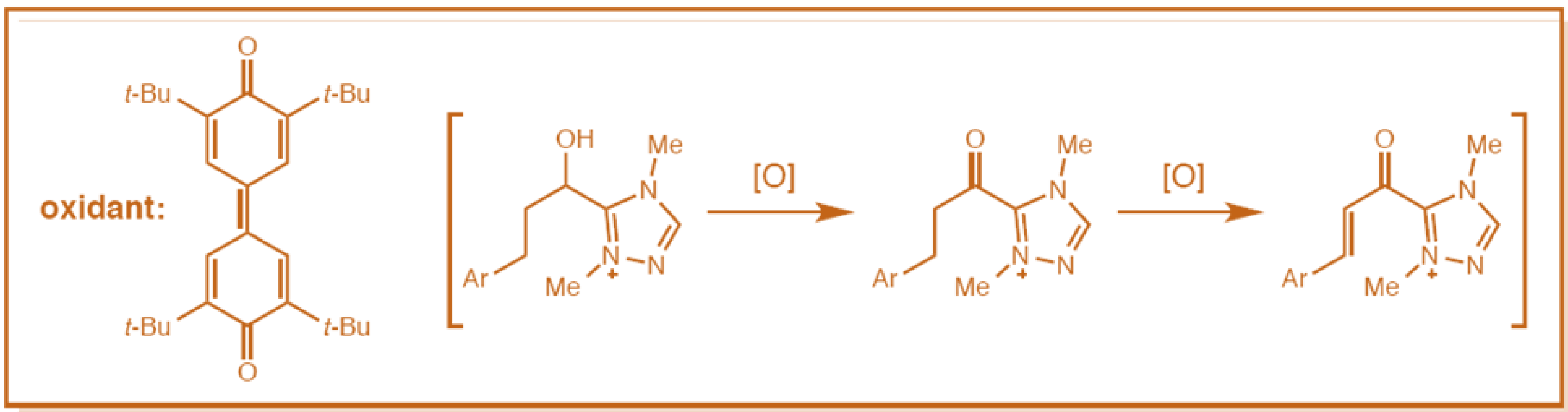


Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Org. Lett.* **2007**, *9*, 371.
Maki, B. E.; Scheidt, K. A. *Org. Lett.* **2008**, *10*, 4331.

NHCs as Organocatalysts

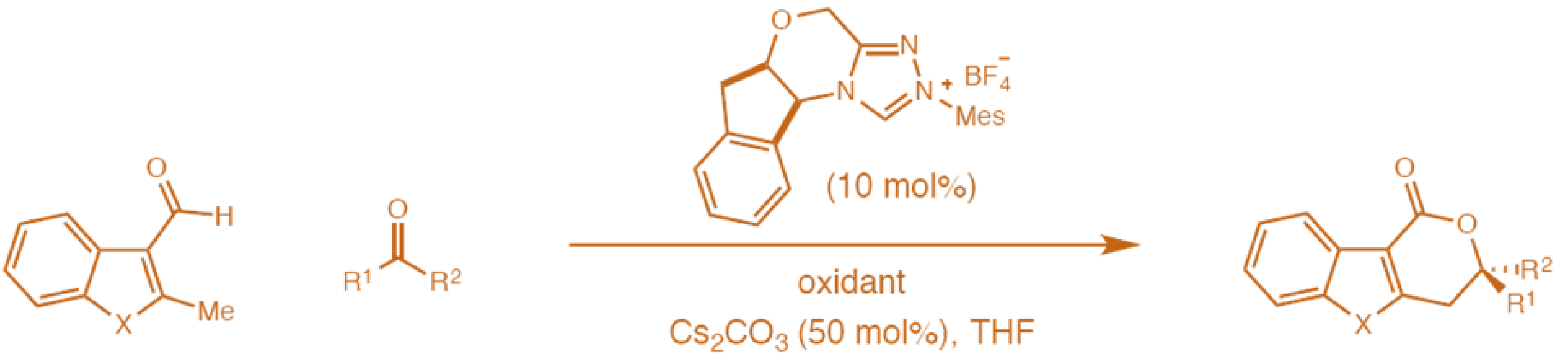
NHCs could be used in a number of highly enantioselective reactions



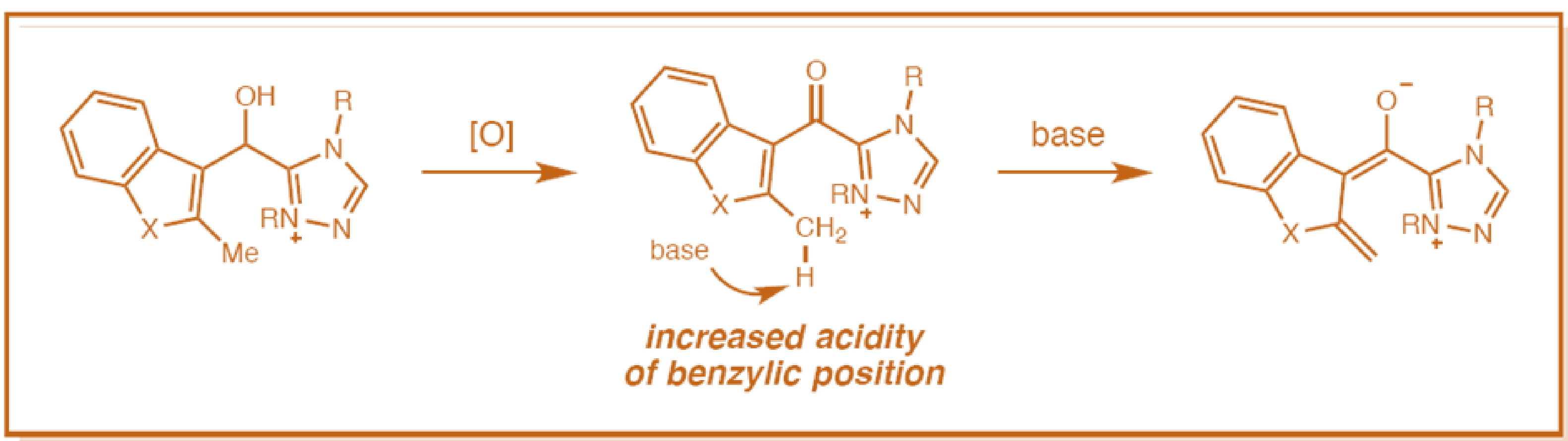


Mo, J.; Shen, L.; Chi, Y. R. *Angew. Chem. Int. Ed.* **2013**, *52*, 8588.

NHCs as Organocatalysts



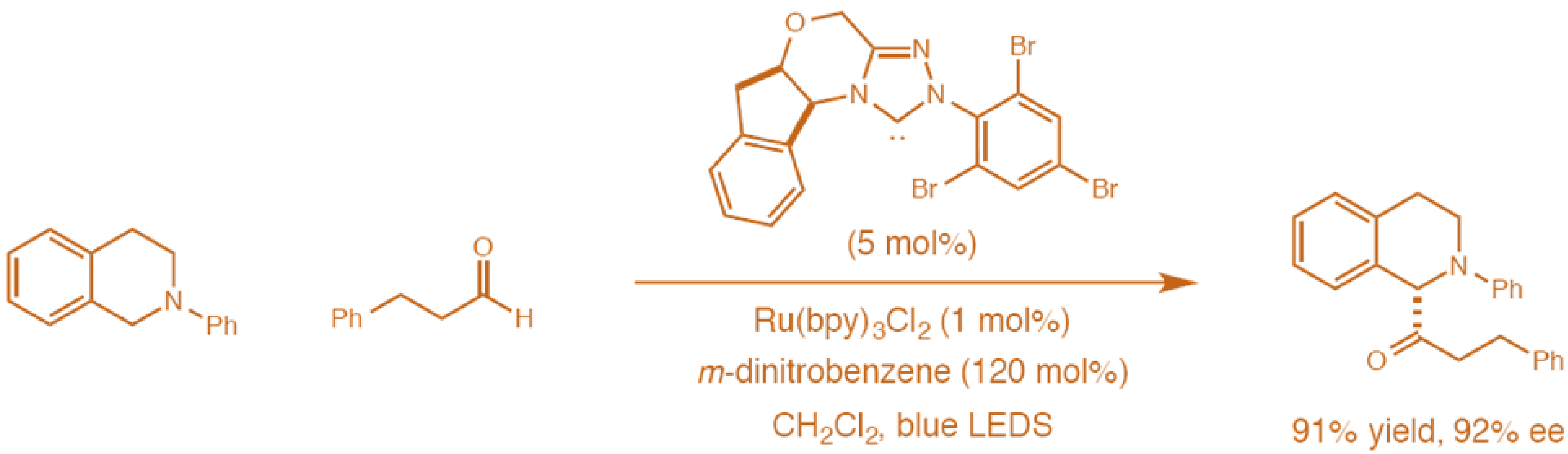
61-89% yield, 84-99% ee

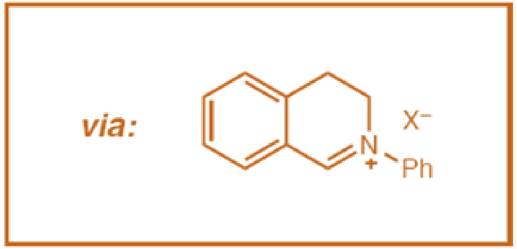


Chen, X.; Yang, S.; Song, B.-A.; Chi, Y. R. *Angew. Chem. Int. Ed.* **2013**, *52*, 11134.

NHCs as Organocatalysts

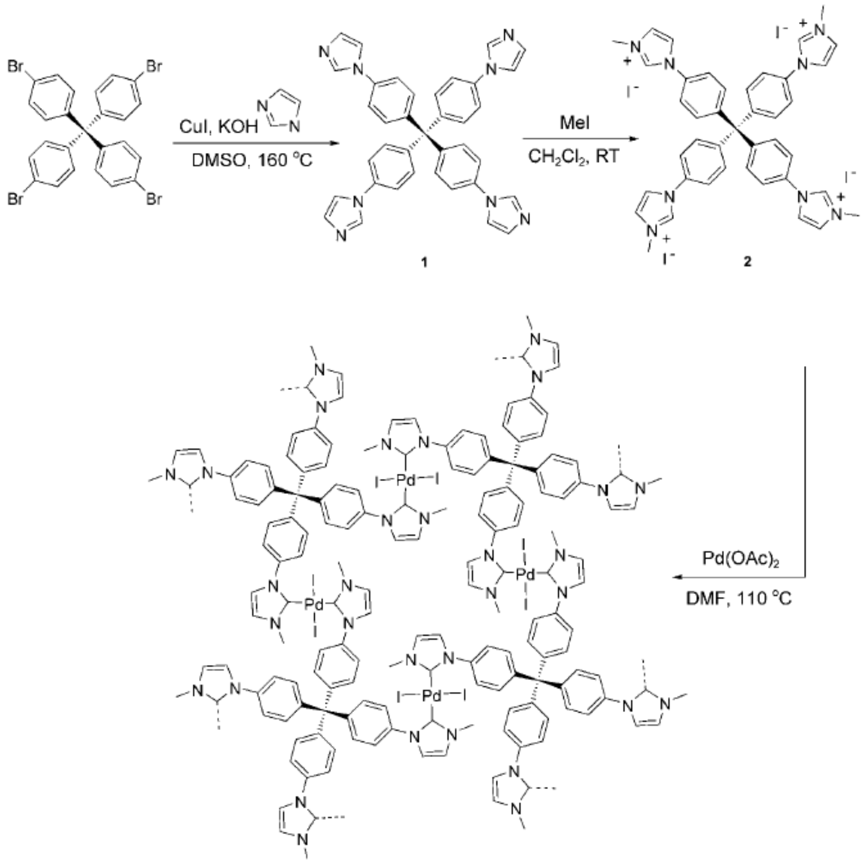
Combination of photoredox and NHC catalysis in organocatalysis



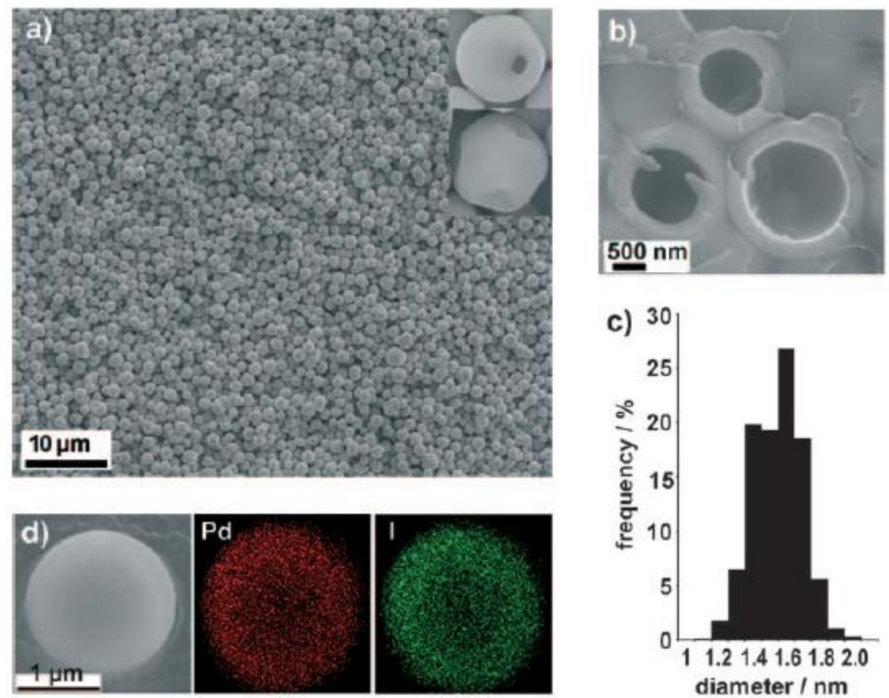


DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 8094.

NHCs in Polymer Science

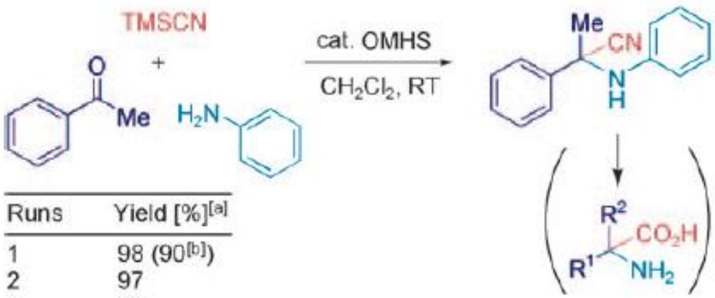


organometallic hollow sphere (OMHS)

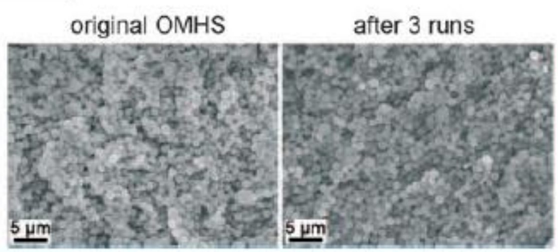


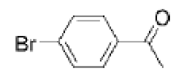
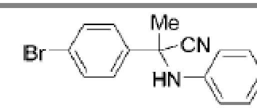
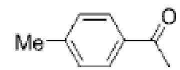
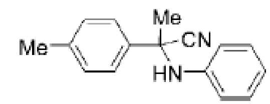
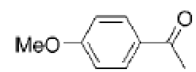
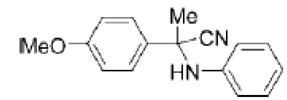
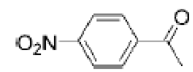
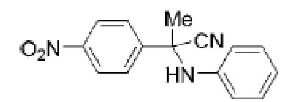
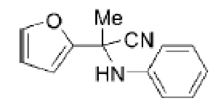
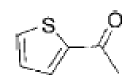
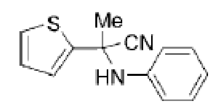
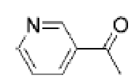
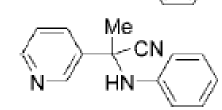
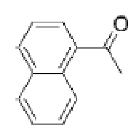
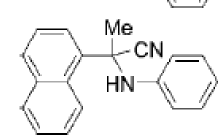
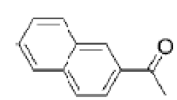
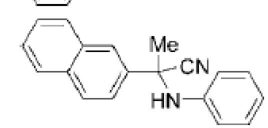
Angew Chem Int Ed 2010, 49, 7718

NHCs in Polymer Science



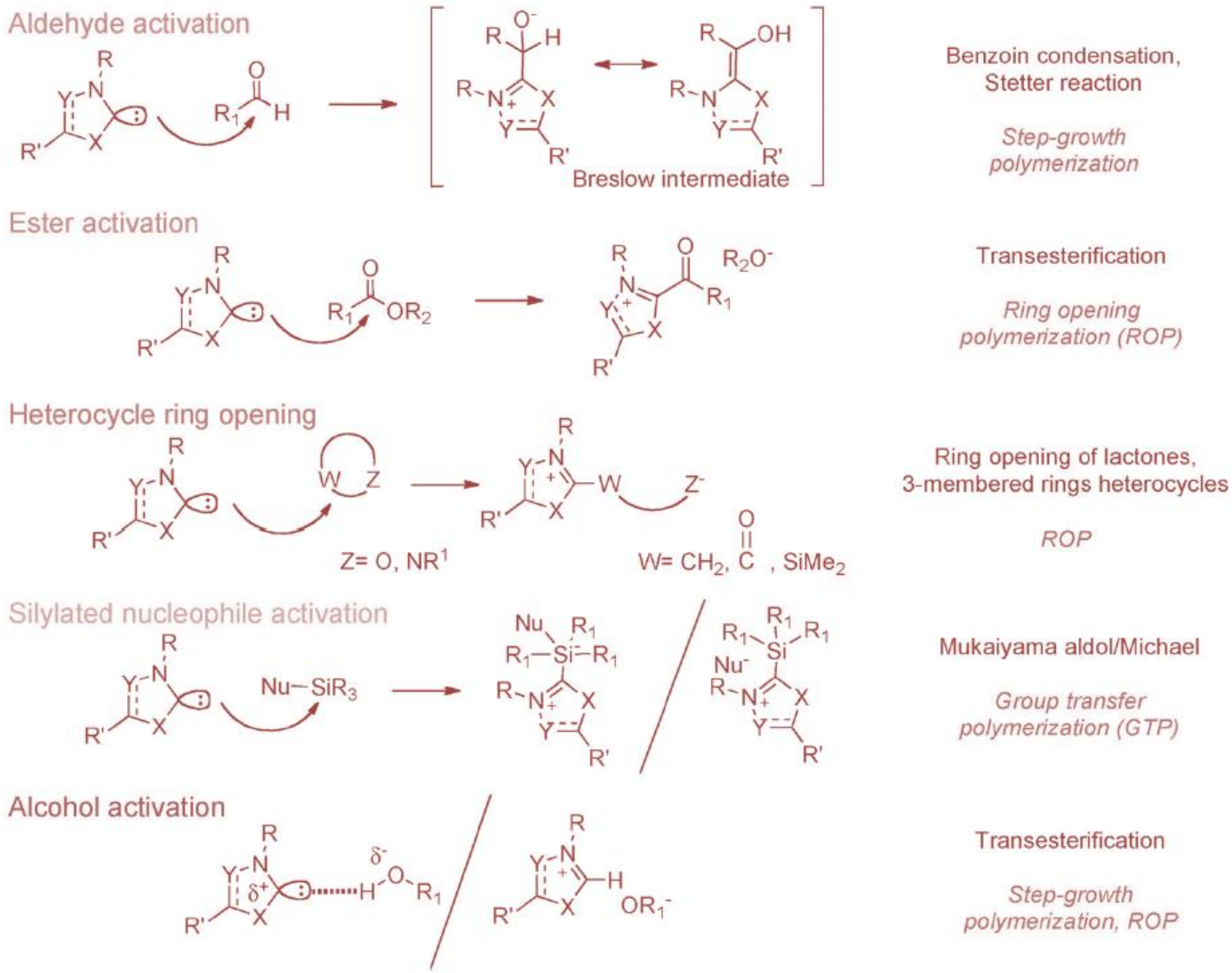
Runs	Yield [%][a]
1	98 (90[b])
2	97
3	99



Entry	Ketone	Product	Yield [%][b]
1			96 (85)
2			95 (91)
3			92 (83)
4			3 (–)[c]
5			95 (89)
6			56 (44)
7			51 (50)
8			68 (65)
9			91 (86)

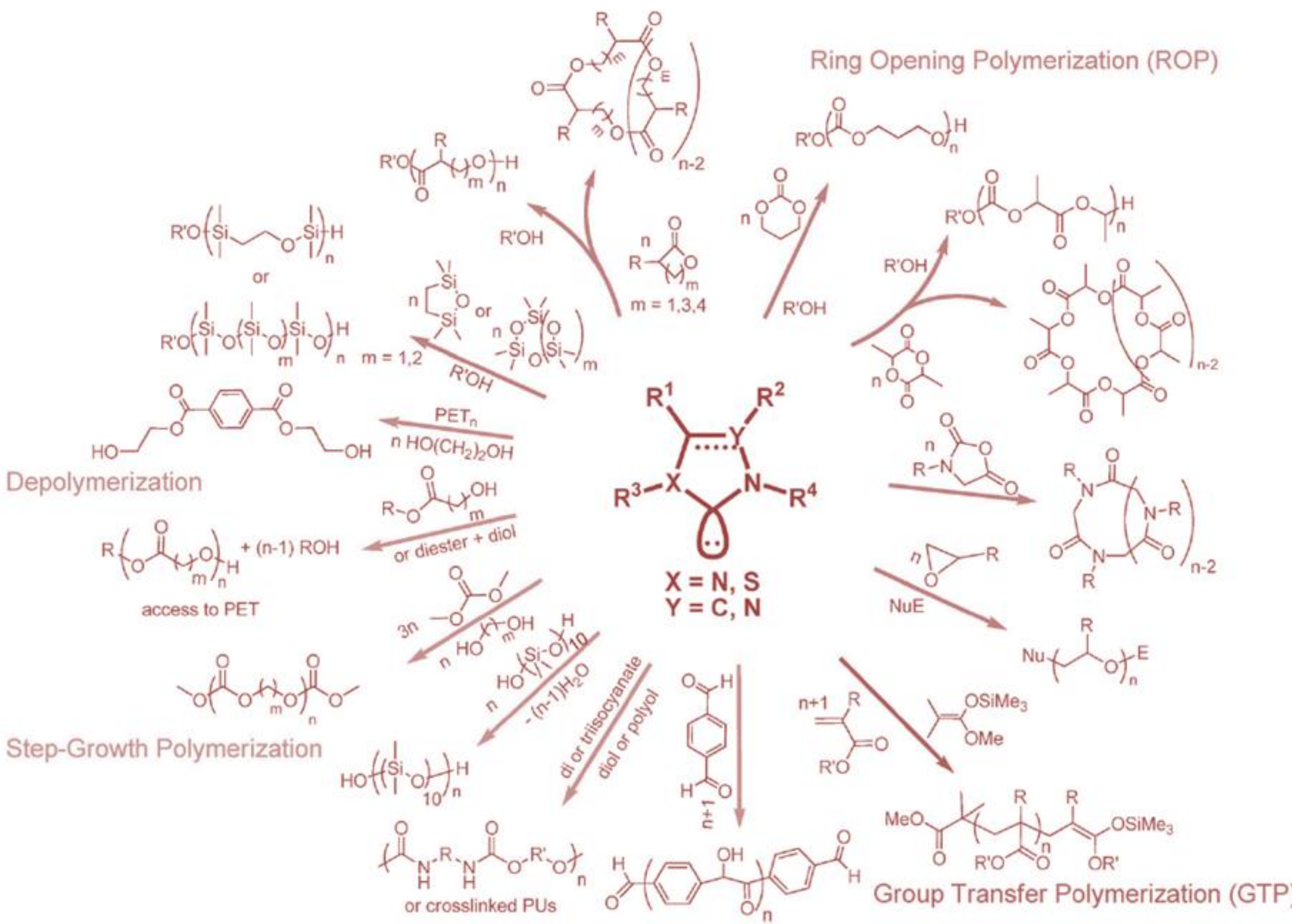
Angew Chem Int Ed 2010, 49, 7718

NHCs in Polymer Science



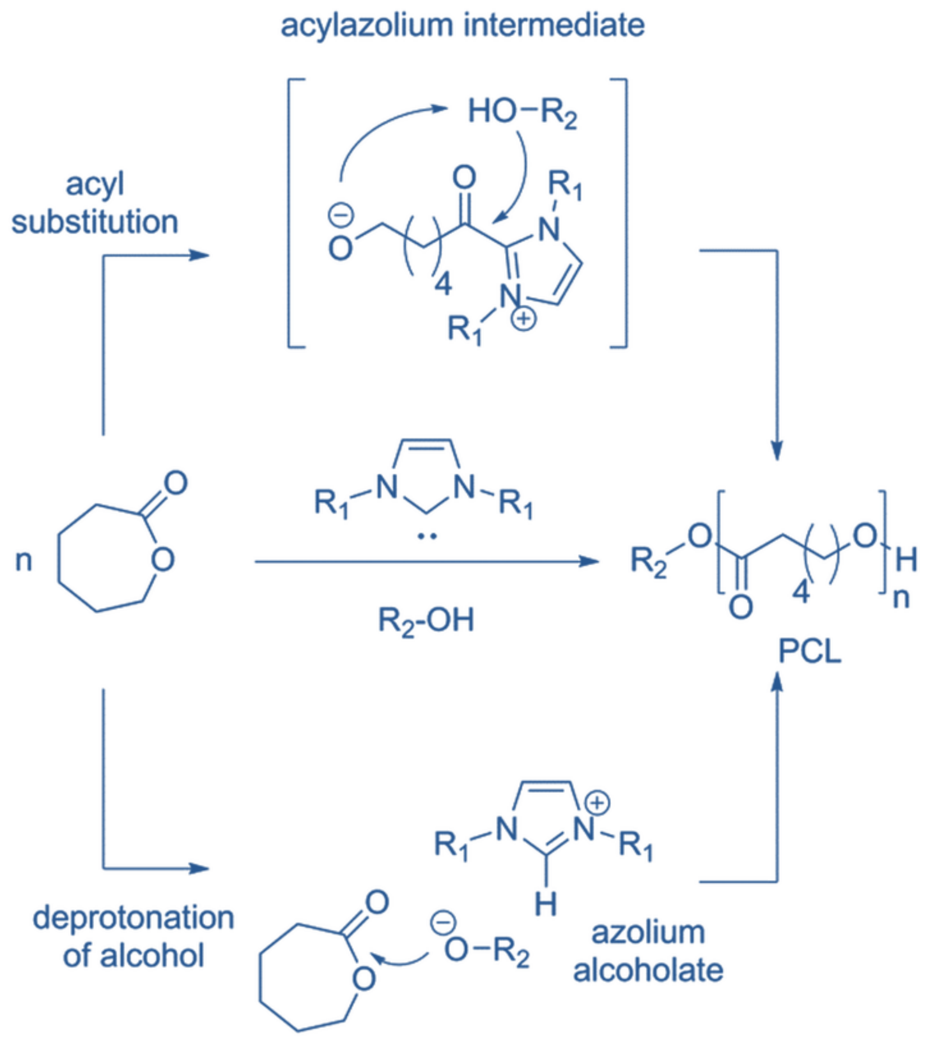
Different modes of substrate activation by NHCs in molecular chemistry and in polymer synthesis

NHCs in Polymer Science

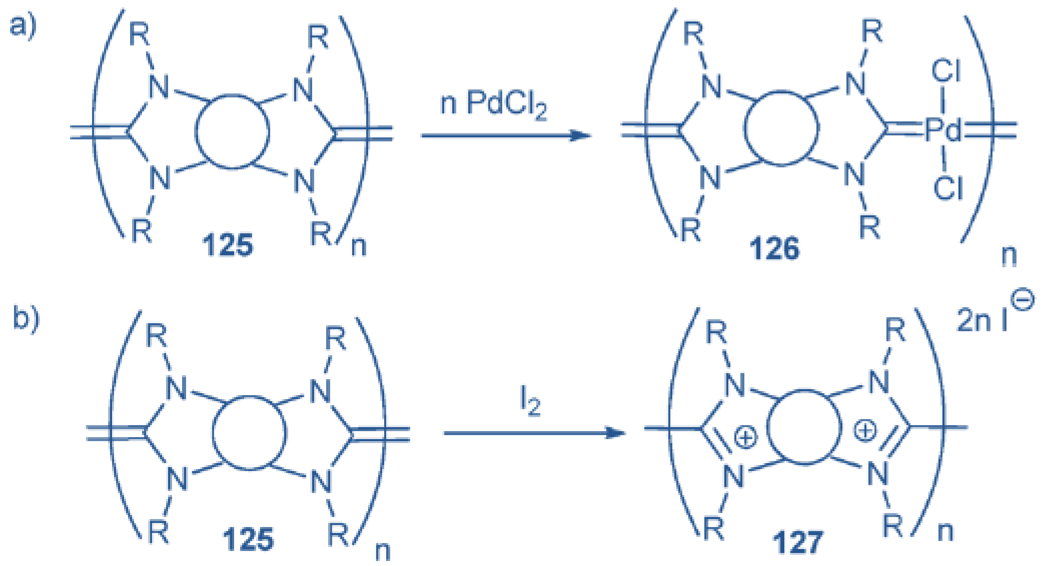


Overview of polymers obtained by NHC-mediated polymerization reactions

NHCs in Polymer Science

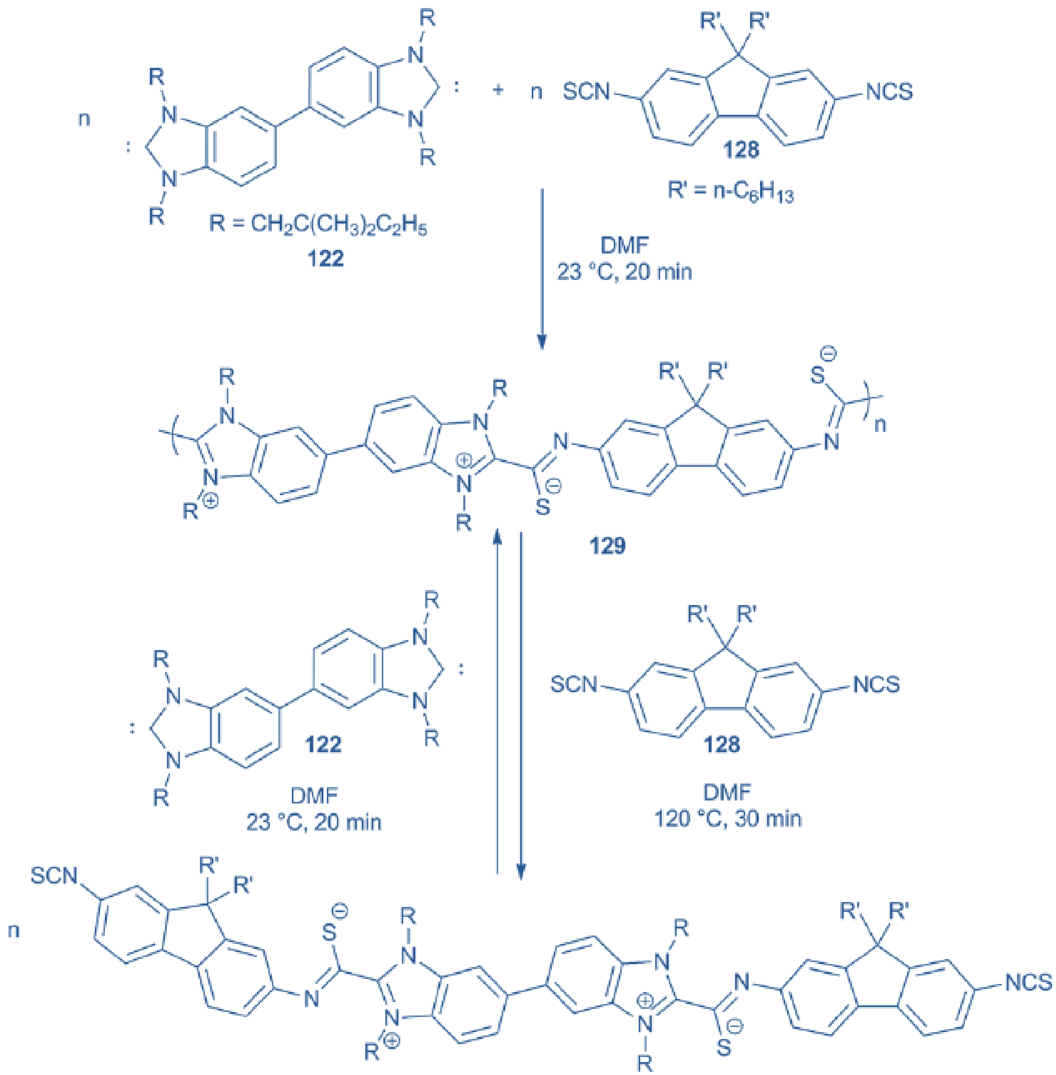


NHCs in Polymer Science



Synthesis of main-chain polymeric organometallic Pd complex and soluble polyelectrolytes

NHCs in Polymer Science



Structurally dynamic polymers