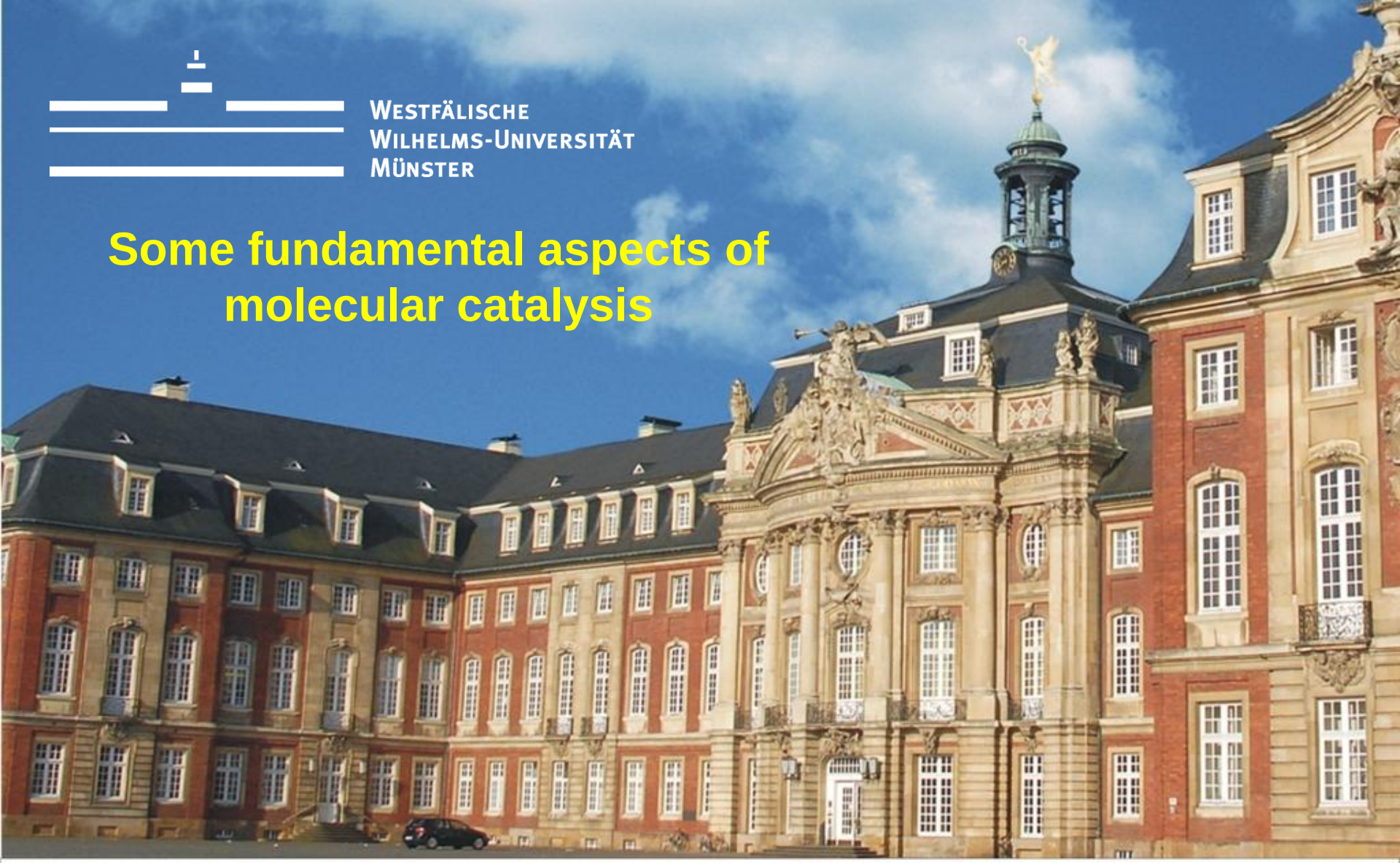


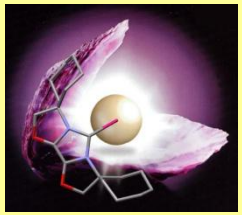
Westfälische Wilhelms-Universität Münster

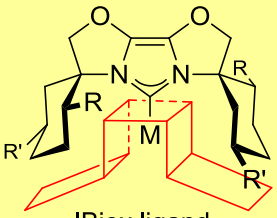
Some fundamental aspects of molecular catalysis

wissen.leben
WWU Münster

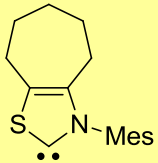
Prof. Dr. Frank Glorius

New N-heterocyclic carbenes (NHCs)



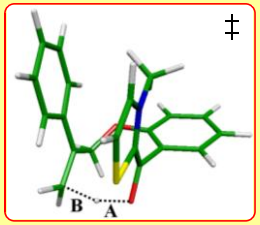


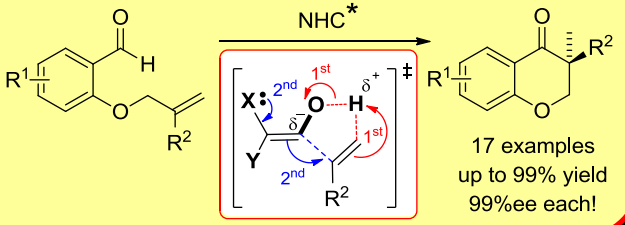
IBiox ligand



Easy-NHC

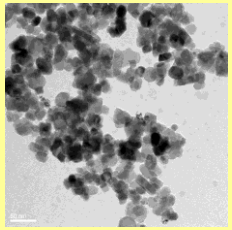
Organocatalysis

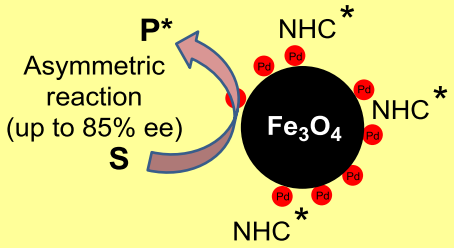




17 examples
up to 99% yield
99%ee each!

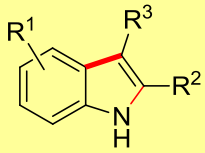
Nanoparticles (NPs)

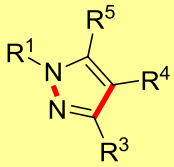


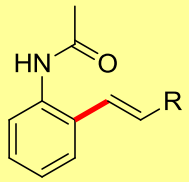


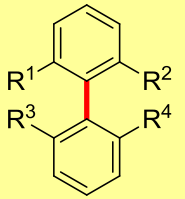
Magnetic
Recovery

C-H Activations & Cross-couplings

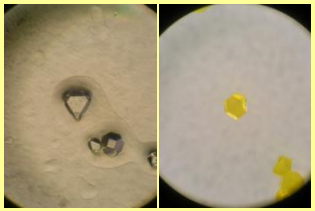


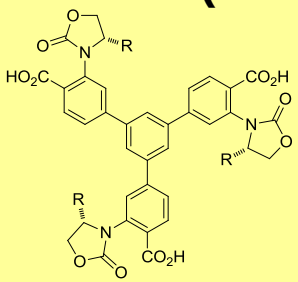




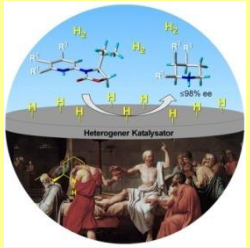


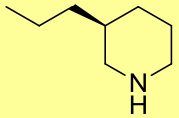
Metal-Organic Frameworks (MOFs)



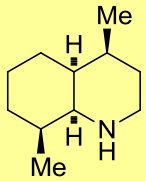


Hydrogenations





95% ee



99% ee

Heterocyclic chemistry

Indoles, pyrroles, pyrazoles,
indolines, oxazolines, piperidines,
imidazolium salts, thiazolium salts,
benzofuranes, dibenzofuranes, benzimidazoles,
γ-butyrolactones, β-lactones

Asymmetric catalysis

α-arylation (up to **99% ee**)
Mannich reaction (up to **99% ee**)
Intramolecular hydroacylation (**99% ee**)
Intermolecular Stetter reaction (up to **99% ee**)
Asymmetric pyridine hydrogenation (up to **98% ee**)

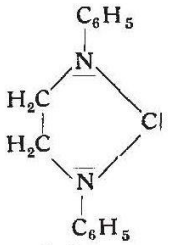
N-Heterocyclic carbenes (NHCs)

Ein neuer Zugang zur Carben-Chemie

Von Priv.-Doz. Dr.-Ing. H.-W. WANZLICK
und Dipl.-Ing. E. SCHIKORA

Organisch-Chemisches Institut
der Technischen Universität Berlin

Dianilino-äthan, das glatt mit Aldehyden reagiert[1]), läßt sich unter geeigneten Bedingungen auch mit Chloral umsetzen. Aus dem erhaltenen 1.3-Diphenyl-2-trichlormethyl-imidazolidin läßt sich, z. B. durch Erhitzen in einem indifferenten Lösungsmittel, Chloroform abspalten. Hierbei entsteht eine farblose, kristalline Verbindung, die sich chemisch wie I verhält. Lösungen nehmen schnell Luftsauerstoff auf und liefern 1.3-Diphenyl-imidazolidon-(2), Wasseranlagerung führt zur Monoformyl-Verbindung des Dianilinoäthans u.s.w. Bisher vorliegende Molekulargewichtsbetimmungen (in Campher) brachten bei 300 liegende Werte (I: theor.: 222), die für ein Gleichgewicht:



I (bzw. mesomere Formen)

$$2\ \mathrm{I} \rightleftharpoons (\mathrm{I})_2$$

sprechen.

Die Untersuchungen werden fortgesetzt, wobei die weitere Erforschung der I-Chemie, die Synthese anderer Verbindungen vom I-Typ und die Suche nach neuen Zugängen zu dieser neuartigen Verbindungsklasse im Vordergrund stehen.

Eingegangen am 4. Juli 1960 [Z 930]

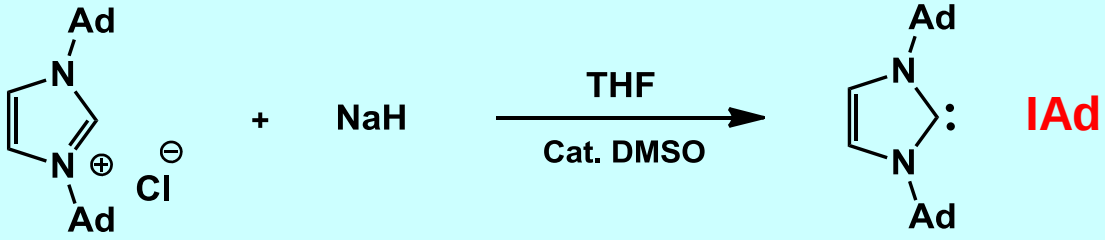
[1]) *H.-W. Wanzlick* u. *W. Löchel*, Chem. Ber. *86*, 1463 [1953].

Wanzlick, Schikora, *Angew. Chem.* **1960**, *72*, 494.

"*Stable Carbenes – Illusion or Reality?*", M. Regitz, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 674.

Stable N-Heterocyclic carbenes (NHCs)

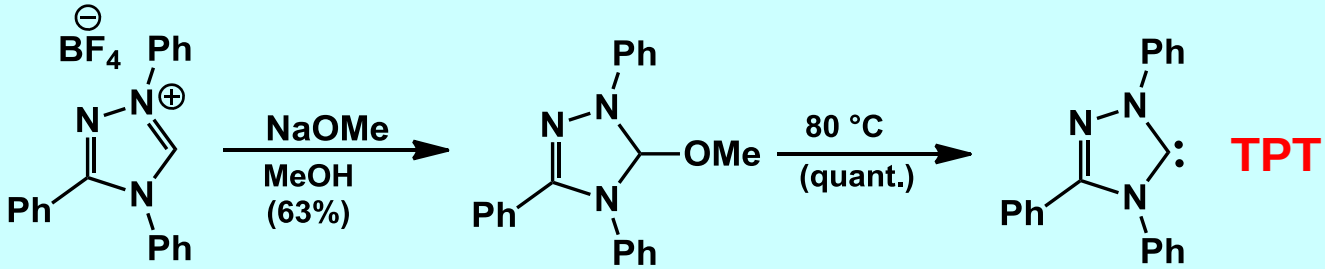
First Stable Crystalline NHC



Anthony J. Arduengo III

A. J. Arduengo, III et al., *J. Am. Chem. Soc*. **1991**, *113*, 361.

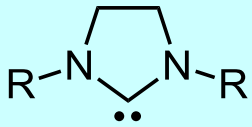
Stable, Commercially Available Carbene



Dieter Enders

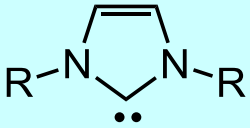
D. Enders, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1021.

Structurally diverse: N-Heterocyclic carbenes (NHCs)



Imidazolin-ylidene

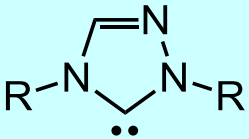
SIMes: R = Mes
SIPr: R = 2,6(iPr)$_2$(C_6H_3)



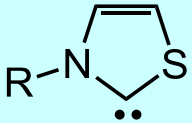
Imidazol-ylidene

IMes: R = Mes
IPr: R = 2,6(iPr)$_2$(C_6H_3)
ItBu: R = tBu
IAd: R = 1-Adamantyl
IMe: R = Me

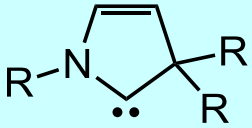
Benzimidazol-ylidene



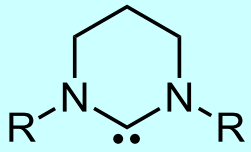
Triazol-ylidene



Thiazol-ylidene



Pyrrolidin-ylidene



Tetrahydro-pyrimidinylidene

"Metal Complexes of N-Heterocyclic Carbenes –

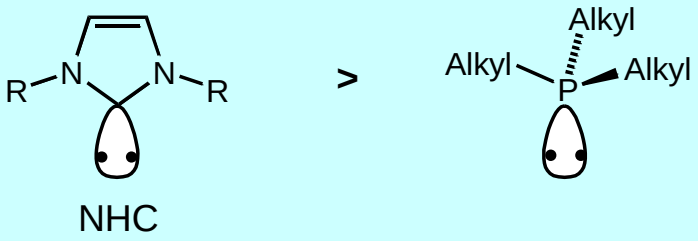
A New Structural Principle for Catalysts in Homogeneous Catalysis"

W. A. Herrmann et al., *ACIE* **1995**, *44*, 2602.

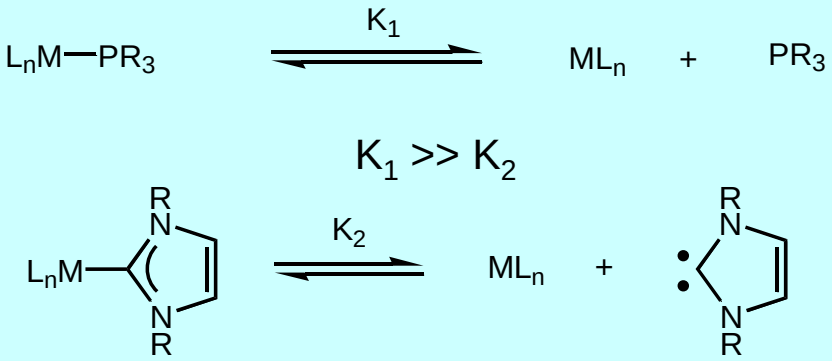
Wolfgang A. Herrmann

N-Heterocyclic carbenes (NHCs)- attractive ligand properties

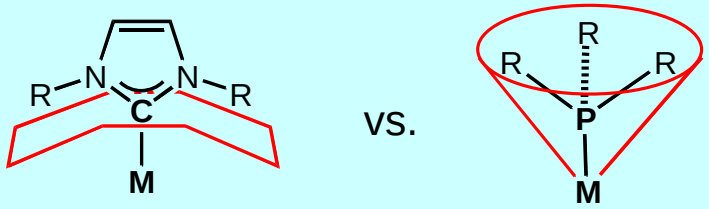
1) Strong σ-donor
(in addition: π-acceptor &
even π-donor properties)



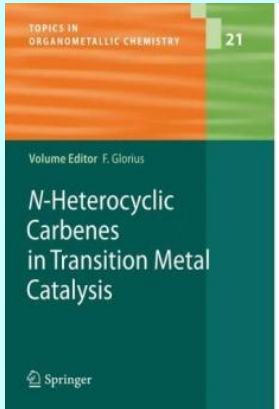
2) „Inert“ metal-carbene-bond, robust against heat, oxygen or moisture



3) Sterically demanding



Review: Herrmann, *Angew. Chem.* **2002**, *114*, 1421.
NHCs in synthesis, Nolan (Ed.), Wiley-VCH **2006**.
NHCs in transition metal catalysis, Glorius (Ed.), Springer **2007**.
Dröge, Glorius, *Nachr. Chemie* **2010**, *58*, 112.
Dröge, Glorius, *Angew. Chem. Int. Ed.* **2010**, *49*, 6940.



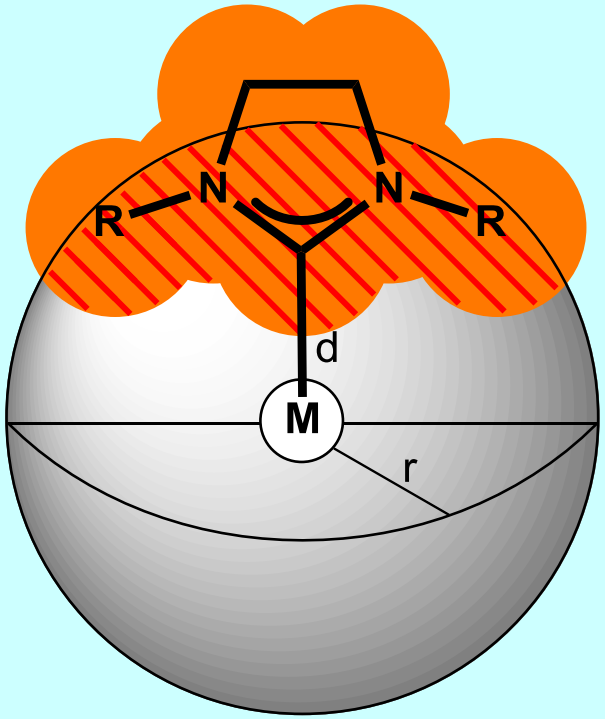
IBiox

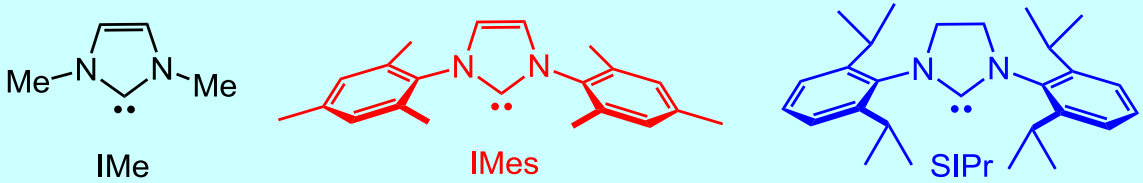
-

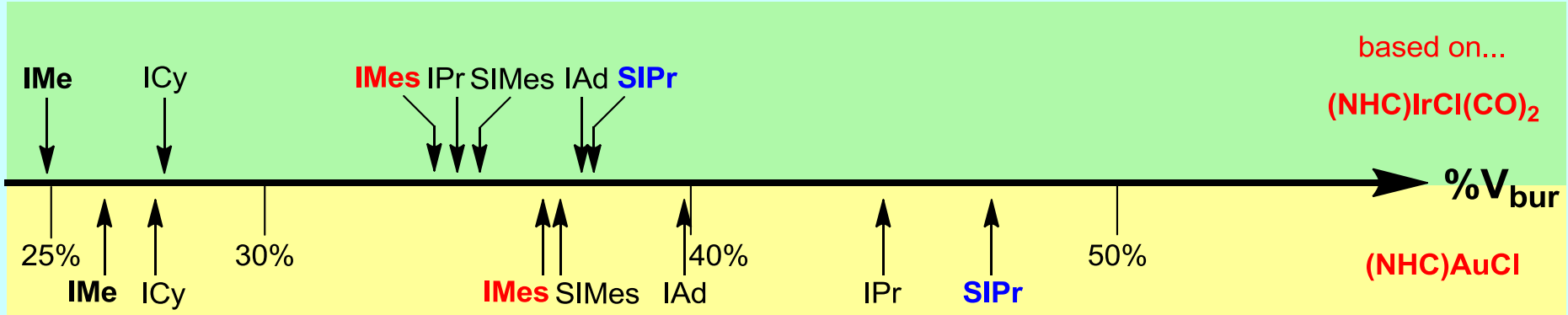
exploring steric bulk

Steric demand? Buried volume %V_{bur} !

Cavallo, Nolan, *Organometallics* **2003**, *22*, 4322.
Cavallo, *Eur. J. Inorg. Chem.* **2009**, 1759.

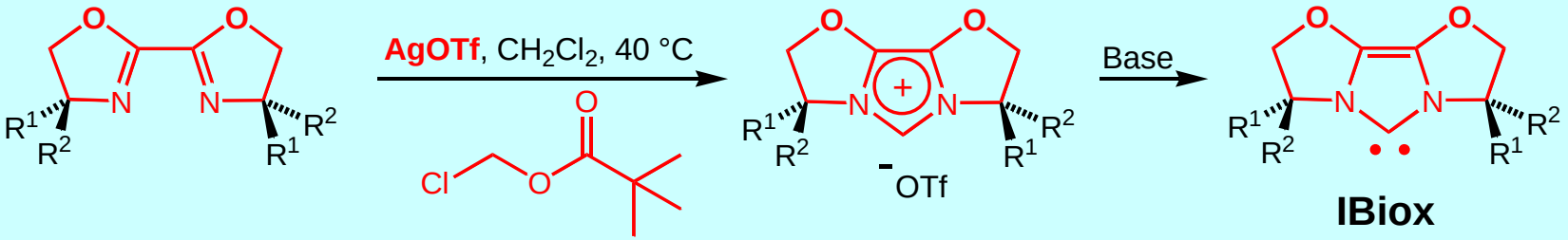






Dröge, Glorius, *Nachr. Chemie* **2010**, *58*, 112.
Dröge, Glorius, *Angew. Chem. Int. Ed.* **2010**, *49*, 6940.

From oxazolines to NHCs: IBiox-family of NHCs



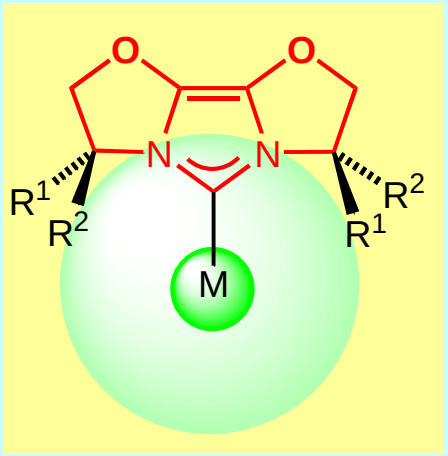
IBiox

=

Bioxazoline derived

NHC (**I**midazolium-type)

Influencing the coordination sphere:



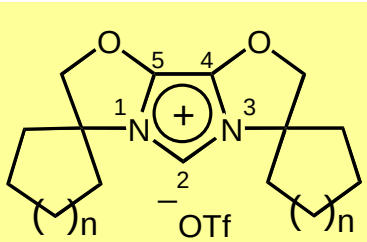
Glorius, Altenhoff, Goddard, Lehmann, *Chem. Commun.* **2002**, 2704.

Altenhoff, Goddard, Lehmann, Glorius, *Angew. Chem.* **2003**, *115*, 3818.

Altenhoff, Goddard, Lehmann, Glorius, *J. Am. Chem. Soc.* **2004**, *126*, 15195.

Würtz, Glorius, *Acc. Chem. Res.* **2008**, *41*, 1523.

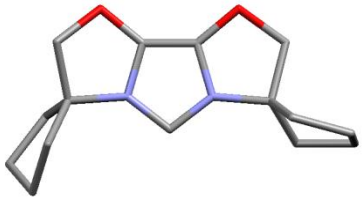
Increasing steric demand: X-Ray structures of the IBiox·HOTf



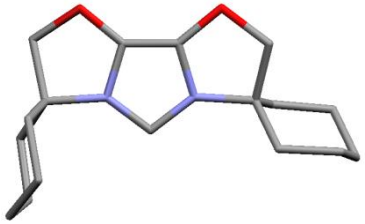
IBiox·HOTf

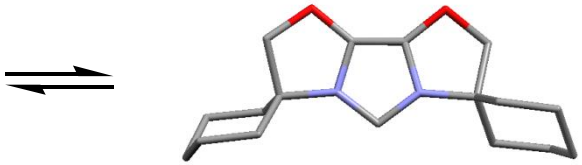
TEP = 2050 cm^{-1}

IBiox5·HOTf
n = 1



IBiox6·HOTf
n = 2

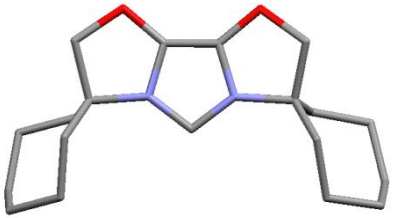




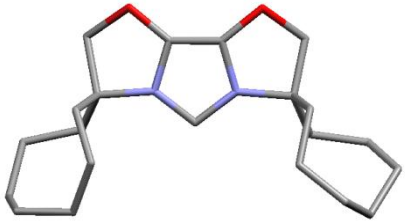
Flexible steric bulk

Concept 1

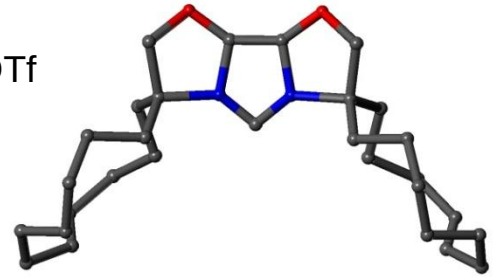
IBiox7·HOTf
n = 3



IBiox8·HOTf
n = 4



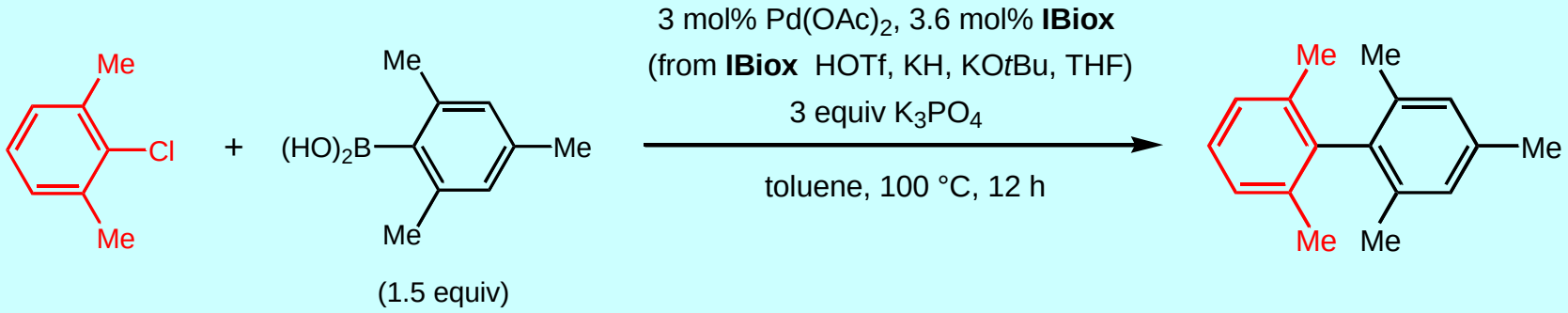
IBiox12·HOTf
n = 8

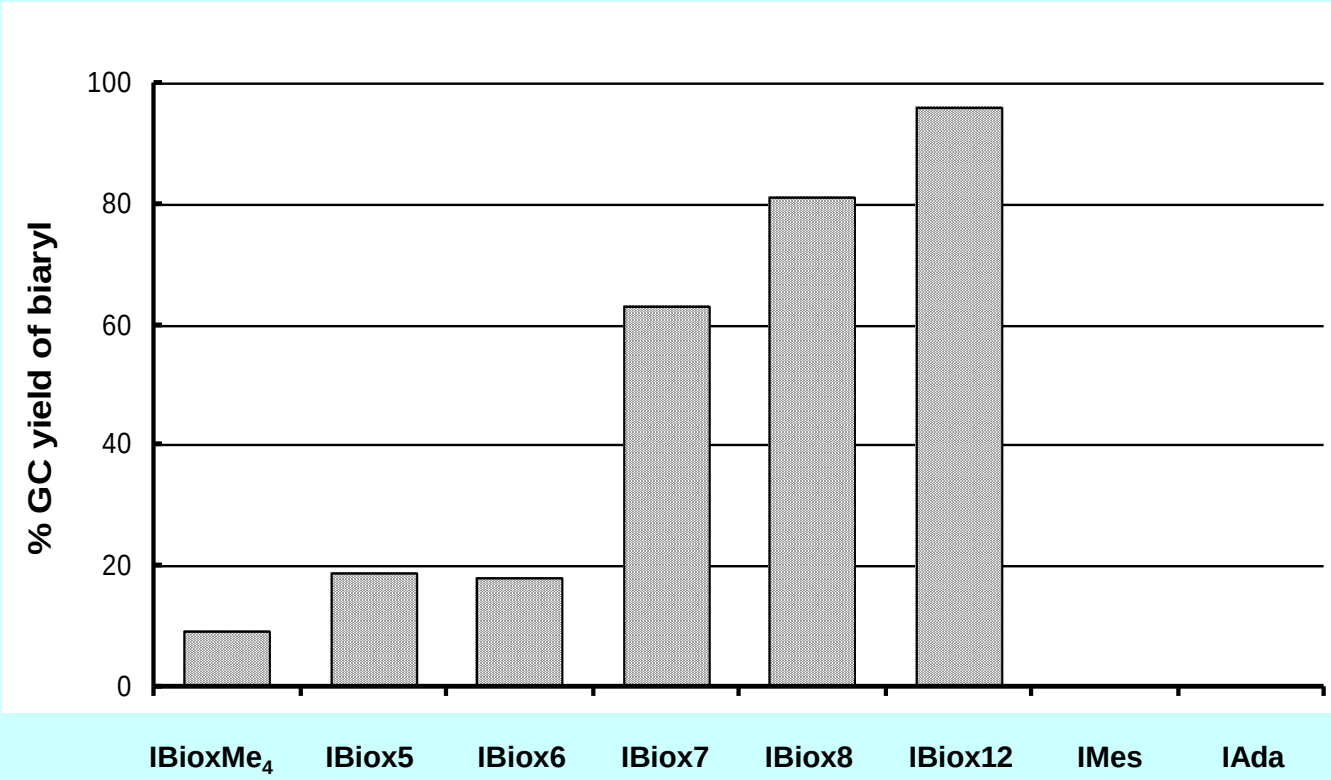


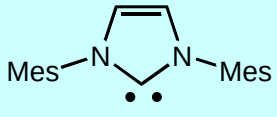
Series of electronically similar
&
sterically different NHCs

Concept 2

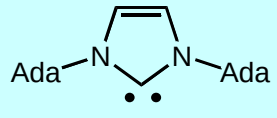
A challenging transformation: formation of tetra-orthosubstituted biaryls







IMes



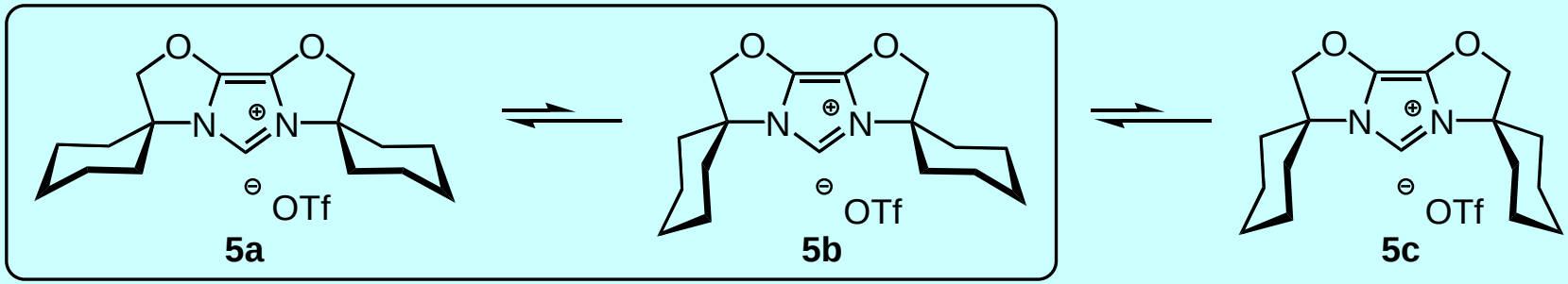
IAda

Altenhoff, Goddard, Lehmann, Glorius, *J. Am. Chem. Soc.* **2004**, *126*, 15195.

Tetra-orthosubstituted biaryls from **aryl bromides**: Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 1162.

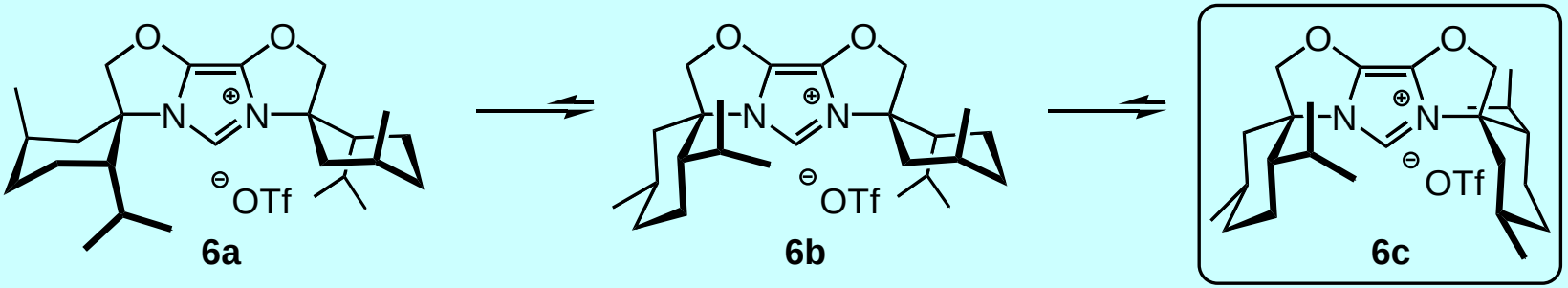
STERIC demand: IBiox6 vs. IBiox[(-)-menthyl]

Dynamic !



5a **5b** **5c**

31% **39%**



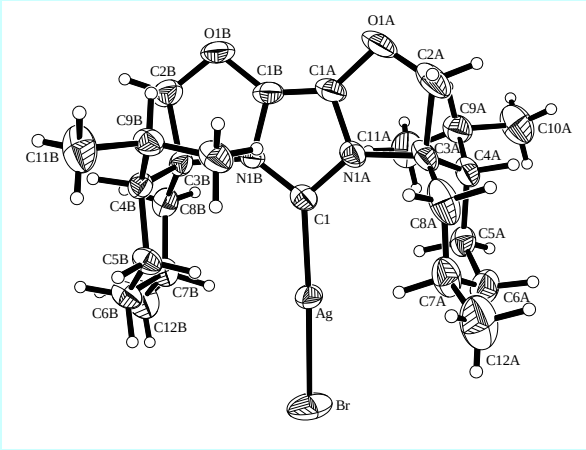
6a **6b** **6c**

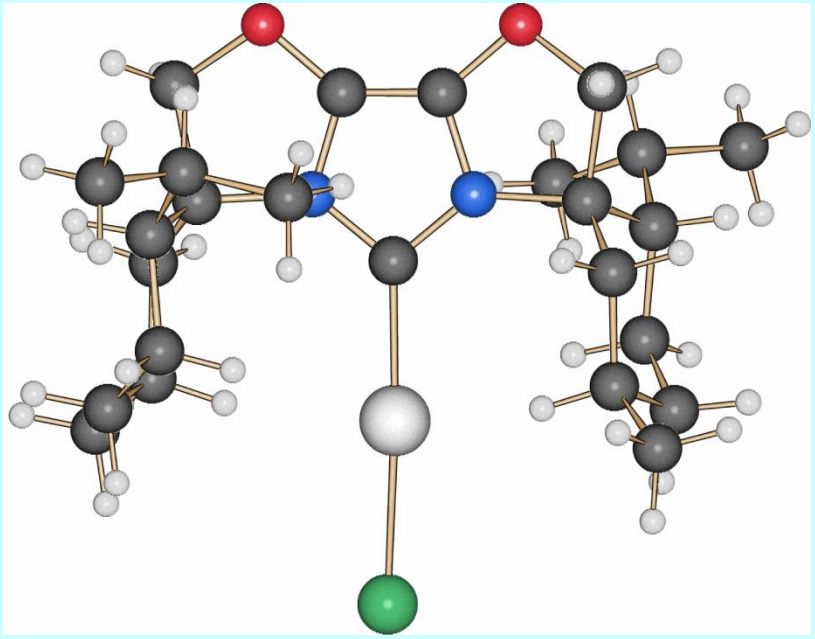
48%

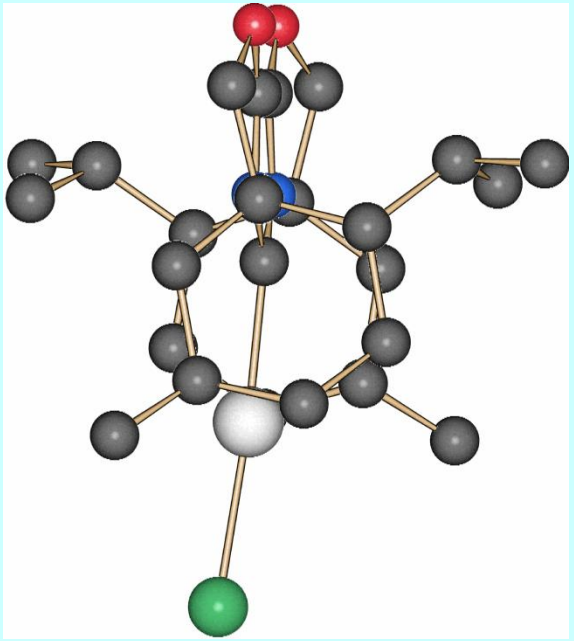
Rigid !

For comparison: Buried volume von IAd: 40% (NHCAuCl complex)

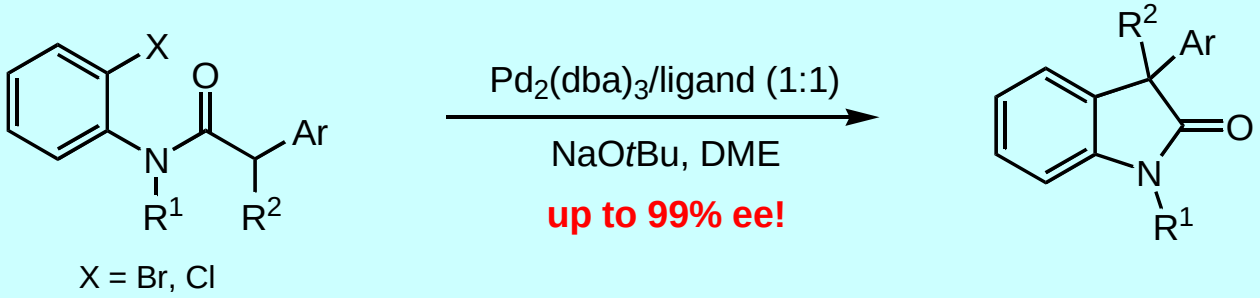
IBiox[(-)-menthyl] silver bromide complex

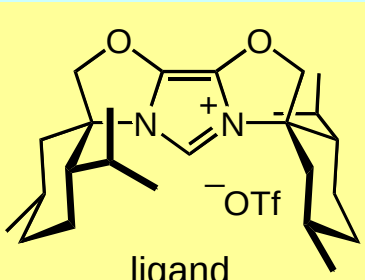


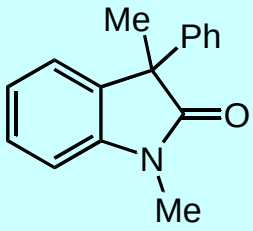




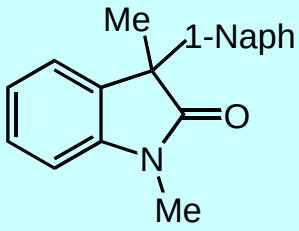
ENANTIOSELECTIVE α-arylation of amides



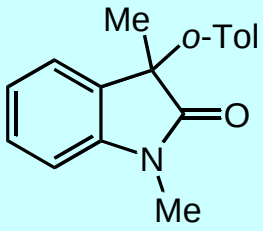




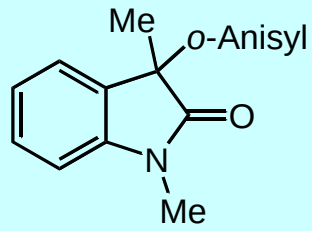
91%, **84% ee**



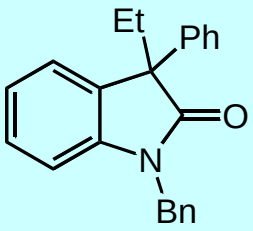
99%, **96% ee**



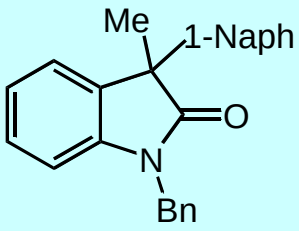
82%, **95% ee**



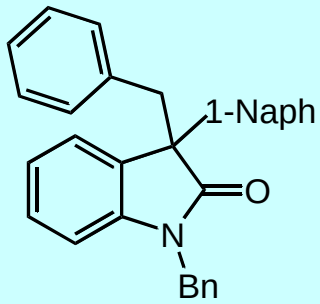
89%, **95% ee**



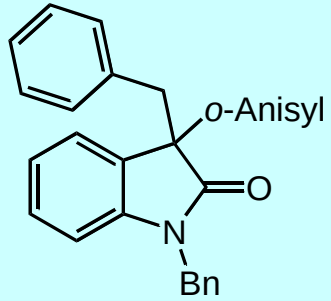
94%, **87% ee**



95%, **97% ee**



83%, **92% ee**



80%, **92% ee** @ 90 °C
37%, **99% ee** @ 80 °C

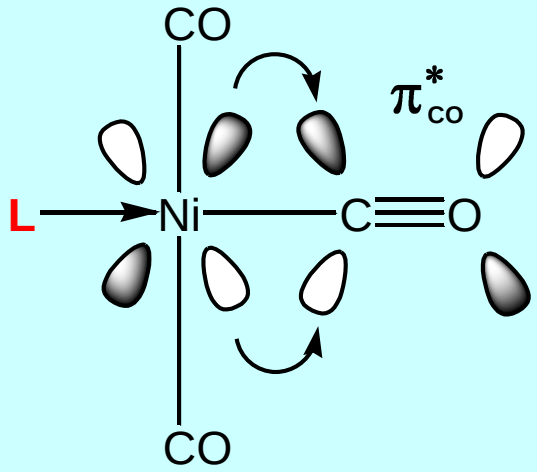
Würtz, Lohre, Fröhlich, Glorius, *JACS* **2009**, *131*, 8344.

See also: Lautens, *Org. Lett.* **2010**, *12*, 3160 (Rh(IBiox[menthyl] catalyzed highly asymmetric hydroarylation)

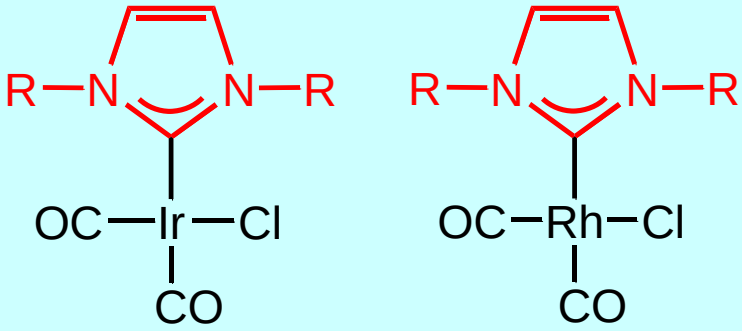
Electronically switchable NHCs

Electronic properties of NHC ligands

Tolmans Electronic Parameter:



For NHCs:



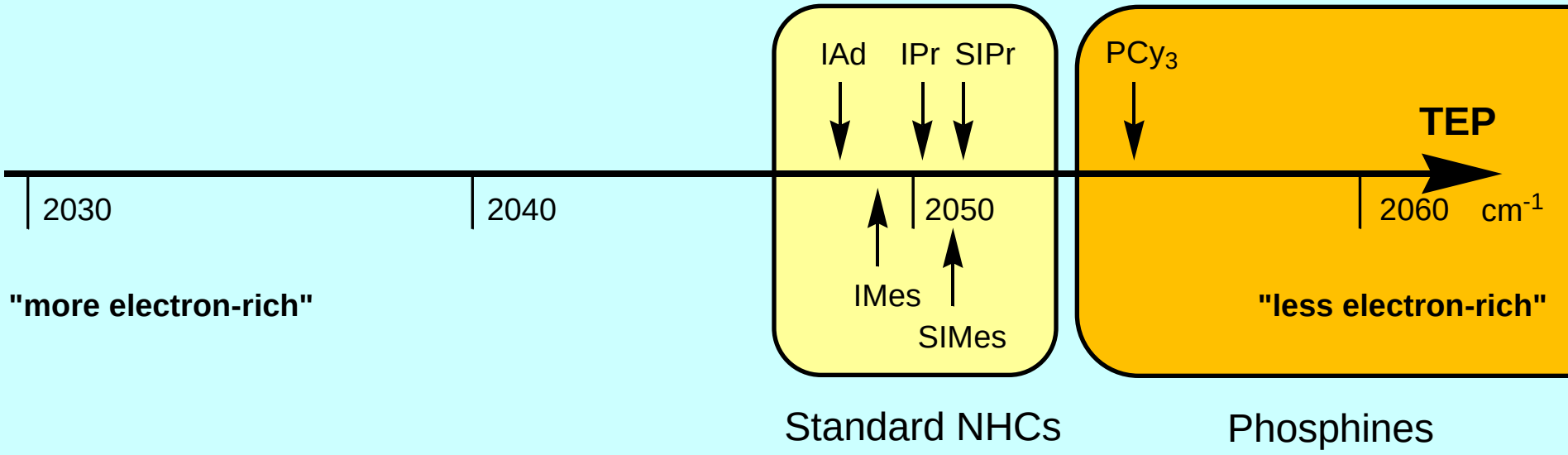
- Electron-rich ligand
- Electron-rich metal
- Backdonation in π^*_{CO}
- IR: ν_{CO}^{av}

See: Crabtree, *Organometallics* **2003**, *22*, 1663.

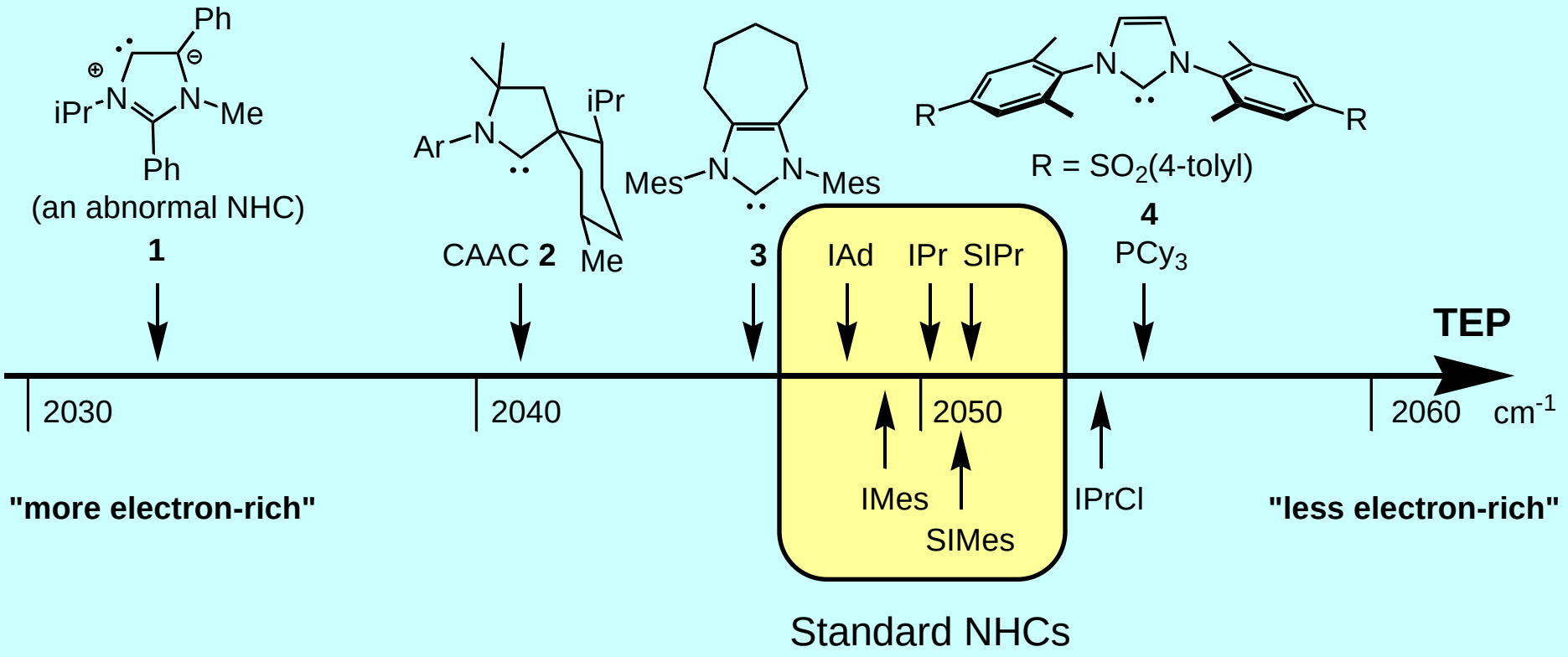
See also: Nolan, *Organometallics* **2008**, *27*, 202.

Tolman, *Chem. Rev.* **1977**, *77*, 313.

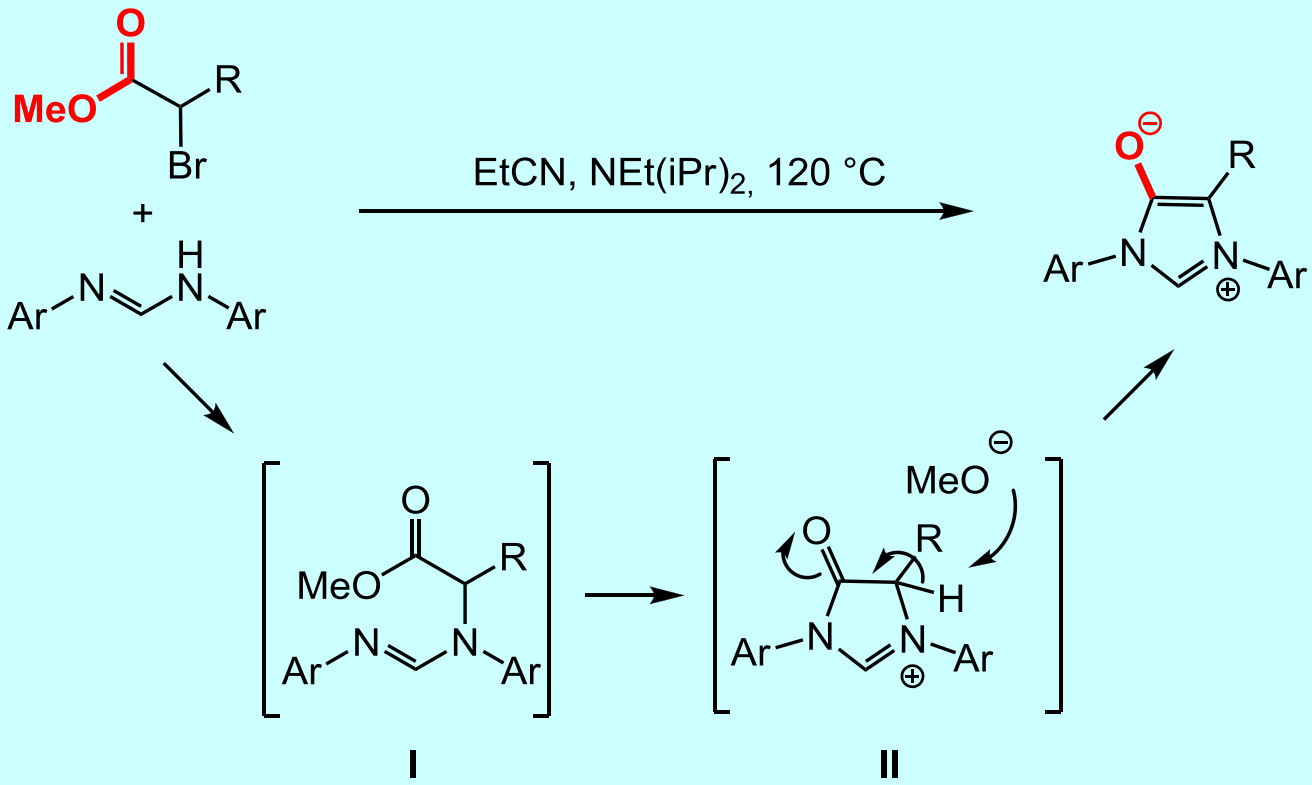
NHCs – quantification of electronic properties



NHCs – quantification of electronic properties



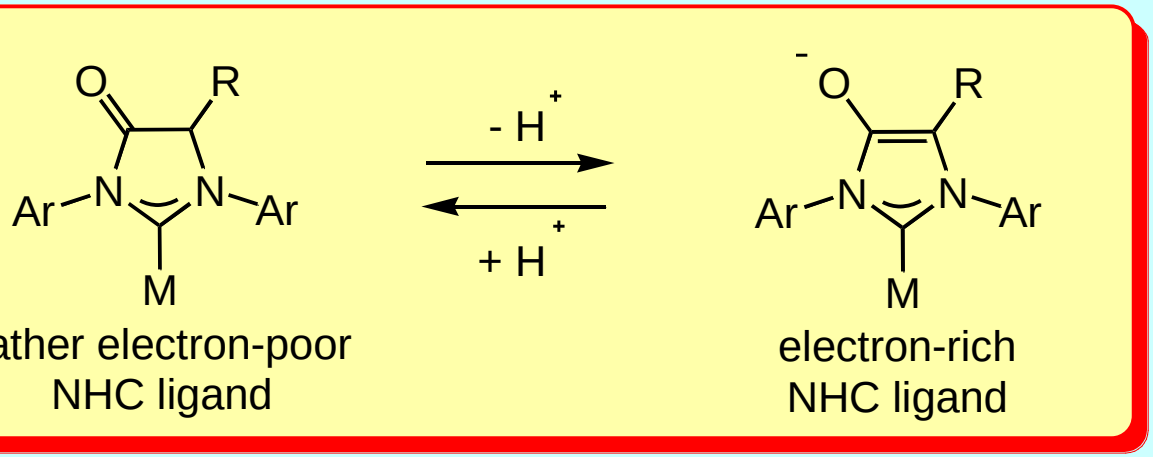
Synthesis of zwitterionic imidazolium salts



Biju, Hirano, Fröhlich, Glorius, *Chem. Asian J.* **2009**, *4*, 1786.

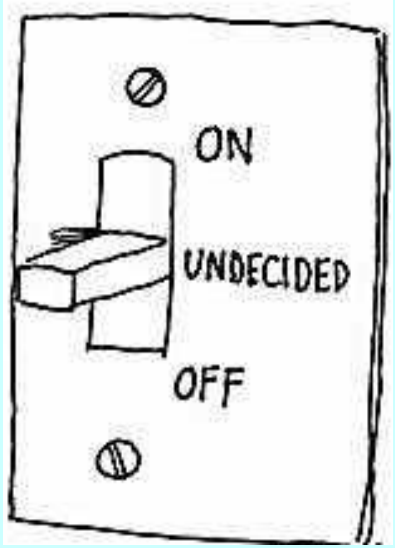
For a related system (but without the switch), see: Cesar, Lavigne, *Chem. Commun*. **2009**, 4711.

A reversibly electronically SWITCHABLE NHC



rather electron-poor NHC ligand

electron-rich NHC ligand



Flip the switch!

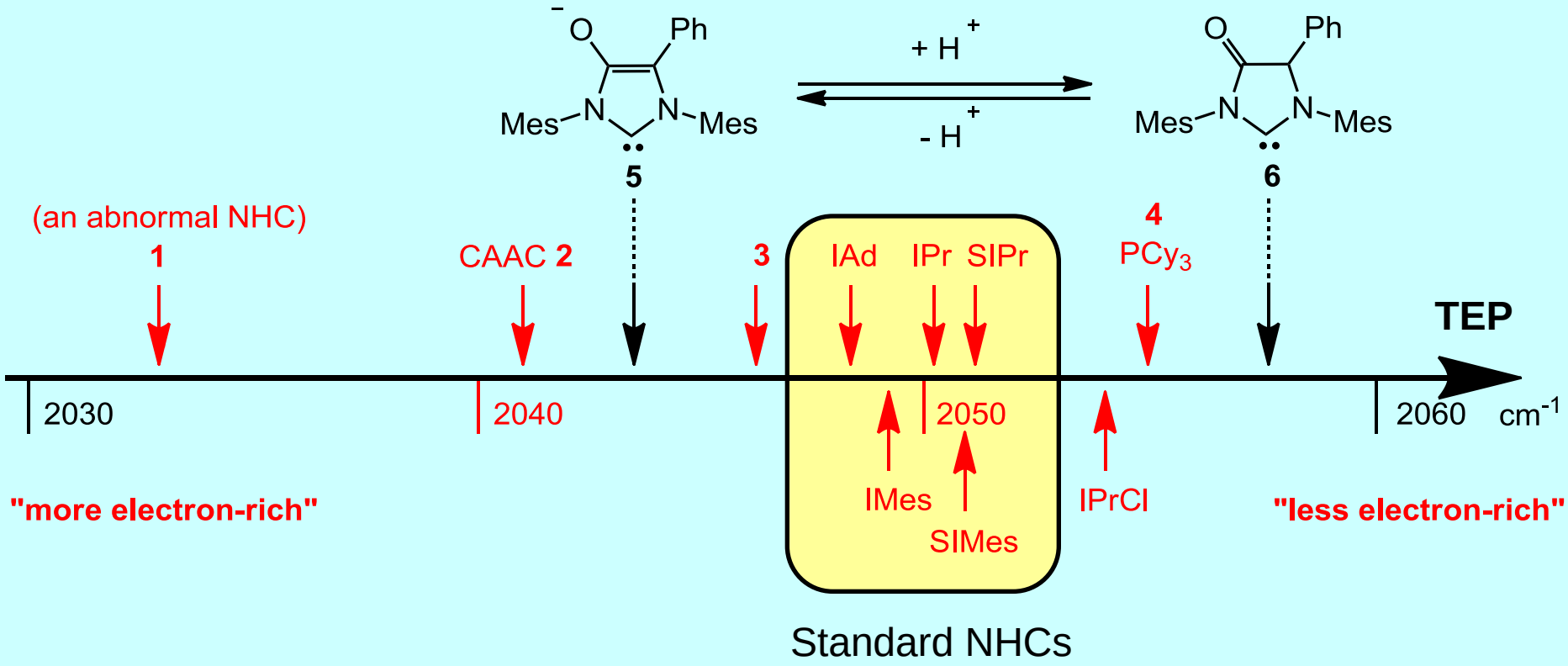
A simple **deprotonation/protonation** can render the NHC to be an electron-poor or an electron-rich NHC ligand: one ligand, two electronic natures.

Biju, Hirano, Fröhlich, Glorius, *Chem. Asian J.* **2009**, *4*, 1786.

For a related system (but without the switch), see: **Cesar, Lavigne**, *Chem. Commun*. **2009**, 4711.

For other switchable NHCs, see the work of **Bielawski** et al. (oxidation/reduction) and **Zhu** et al. (hυ), and, very recently, **Richeter** et al. (protonation/metallation).

A reversibly electronically switchable NHC

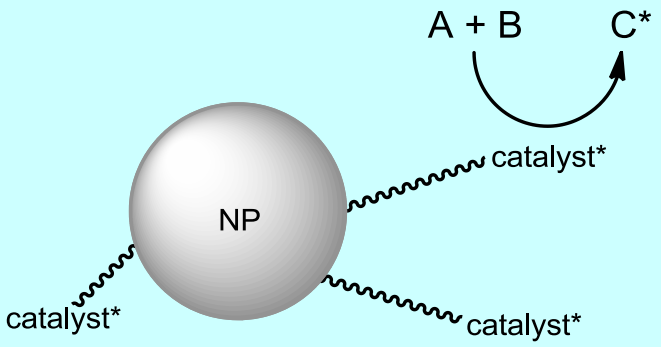


Physico-chemical properties of NHCs: Dröge, Glorius, *Angew. Chem. Int. Ed.* **2010**, *49*, 6940.

Asymmetric nanocatalysis

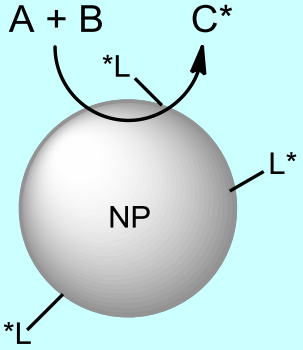
Asymmetric catalysis using NANOPARTICLES (NPs)

a) Reaction taking place on an attached catalyst
(NP as support, NP catalytically inactive)



+/- same modes of action as for the homogeneous system

b) Reaction taking place on the NP
(NP as active catalyst)

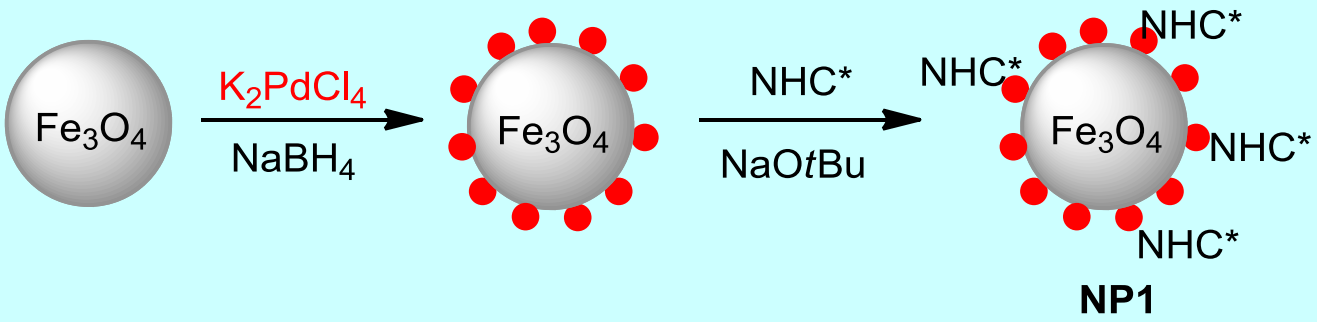


+ new modes of action possible
+ high activity due to large surface area

+ ease of handling and work-up
+ recycling possible
+ if magnetic: magnetic decanting possible, thus very fast separation

Ranganath, Glorius, *Catalysis Science and Technology* **2011**, online.

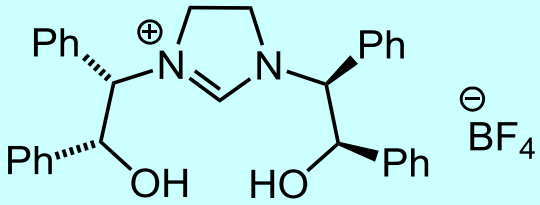
Chiral NHCs on magnetic nanoparticles - a perfect match

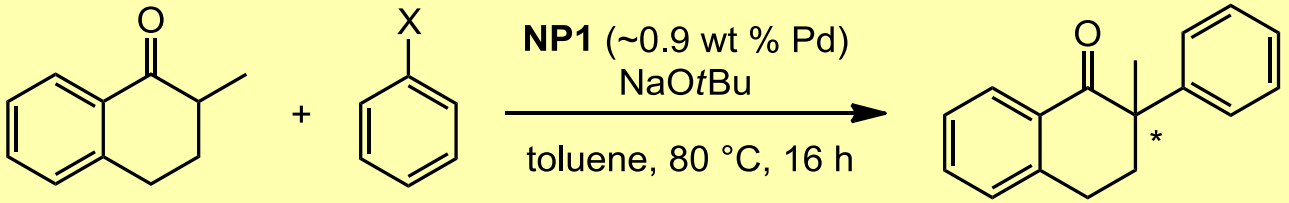


NP1

● = Pd-NP

NHC* =





X = Br, 72% yield, 48% ee
Cl, 56% yield, 60% ee

Magnetic Recovery

Investigation of secondary functional group (OH, olefin…; scope (other reactions).

Ranganath, Kloesges, Schäfer, Glorius *Angew. Chem. Int. Ed.* **2010**, *49*, 7786.

Difficult hydroacylations

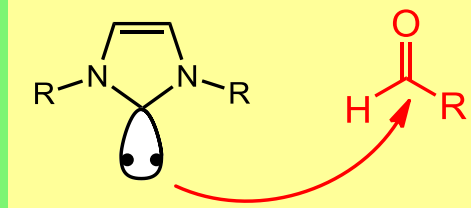
NHC-organocatalysis

N-Heterocyclic carbenes (NHCs) - attractive organocatalyst properties

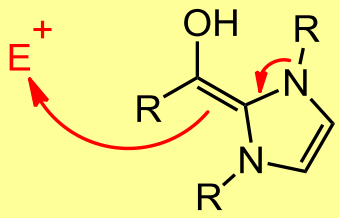
1) Multiple roles in catalytic cycle possible:

Electron-donor properties

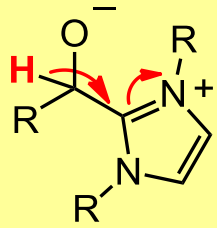
Nucleophilicity



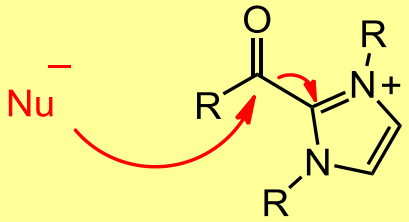
Enamine reactivity



Azolium salt acidifies α-position



Azolium salt is good leaving group



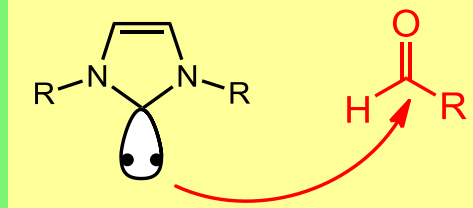
Electron-acceptor properties

N-Heterocyclic carbenes (NHCs) - attractive organocatalyst properties

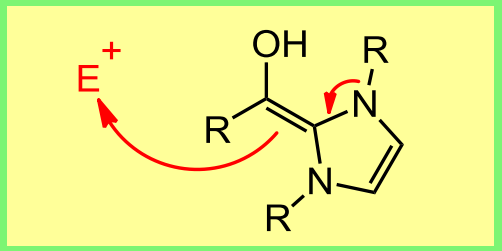
1) Multiple roles in catalytic cycle possible:

Electron-donor properties

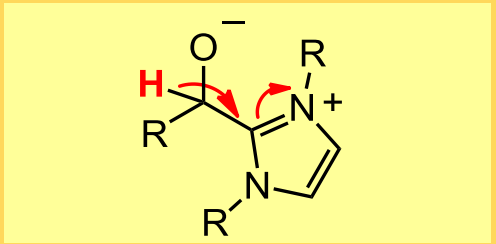
Nucleophilicity



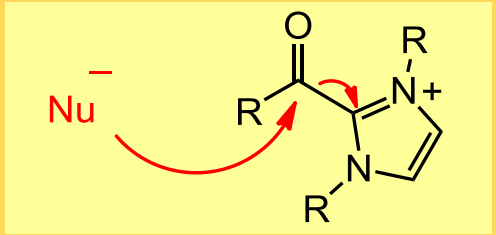
Enamine reactivity



Azolium salt acidifies α-position

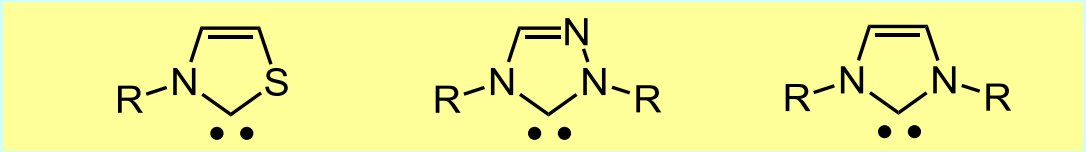


Azolium salt is good leaving group

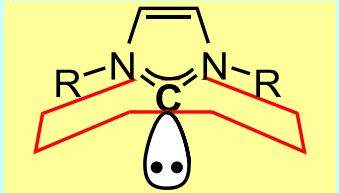


Electron-acceptor properties

2) Different (azolium)types of NHC with dramatically different reactivity

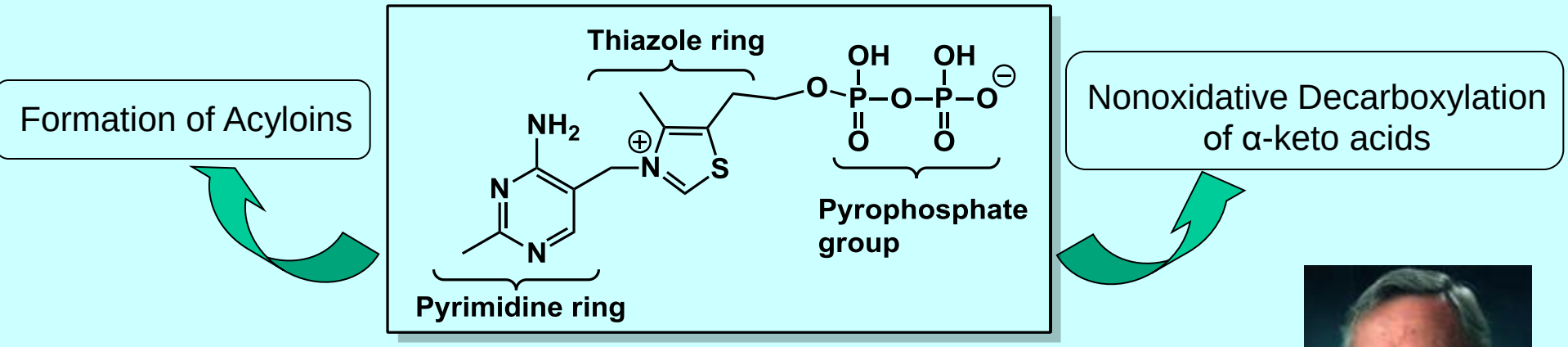


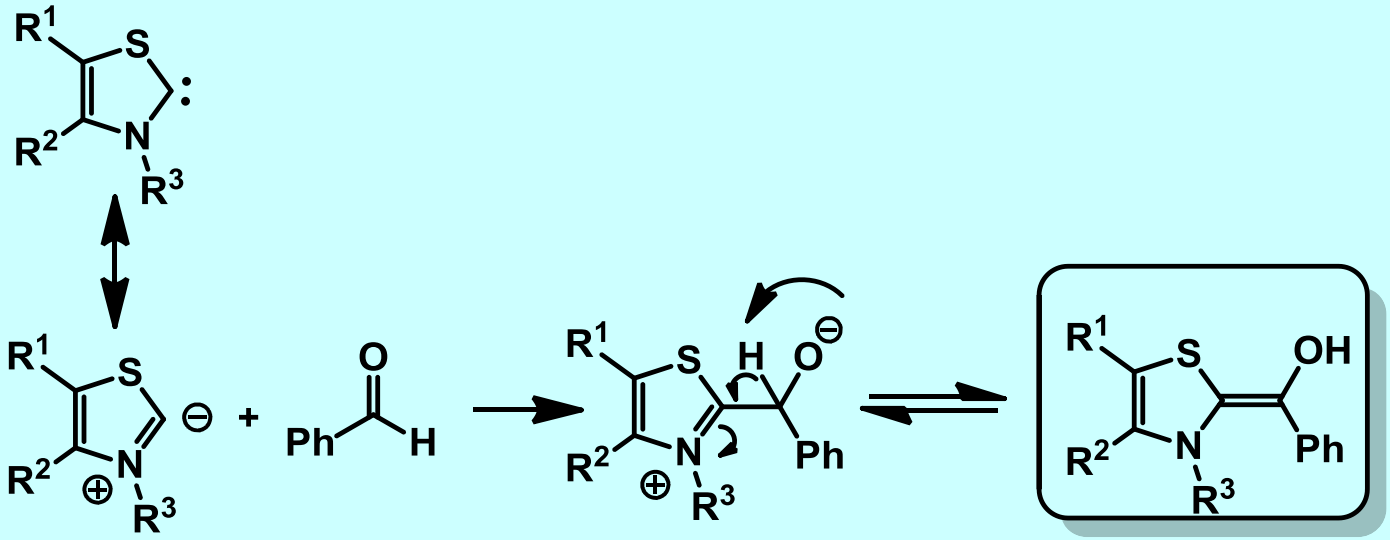
3) Novel geometry („fence like“)



Nature teaches NHC organocatalysis

Coenzyme Thiamine pyrophosphate (TPP)



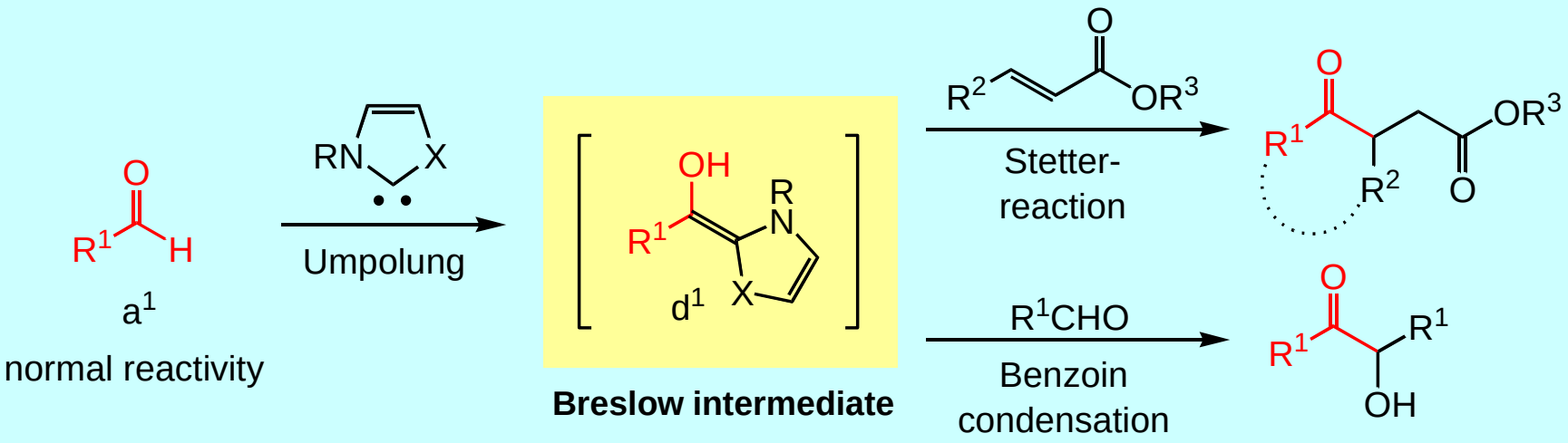


Breslow Intermediate

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

Thiamine = Vitamin B_1

Umpolung organocatalysis



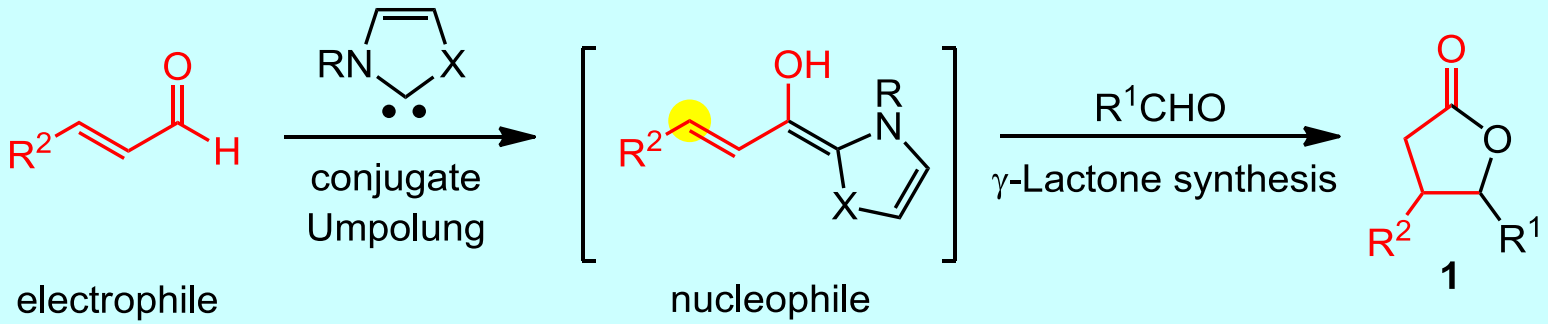
Wöhler, Liebig, *Ann. Pharm.* **1832**, *3*, 249 (First Benzoin condensation using CN^-).

Ukai, *J. Pharm. Soc. Chem.* **1943**, *63*, 296 (First NHC-catalyzed Benzoin condensation).

Breslow, *JACS* **1958**, *80*, 3719.

Stetter, *ACIE* **1973**, *12*, 81.

Organocatalysis: umpolung vs. „conjugated“ umpolung



a homoenolate equivalent

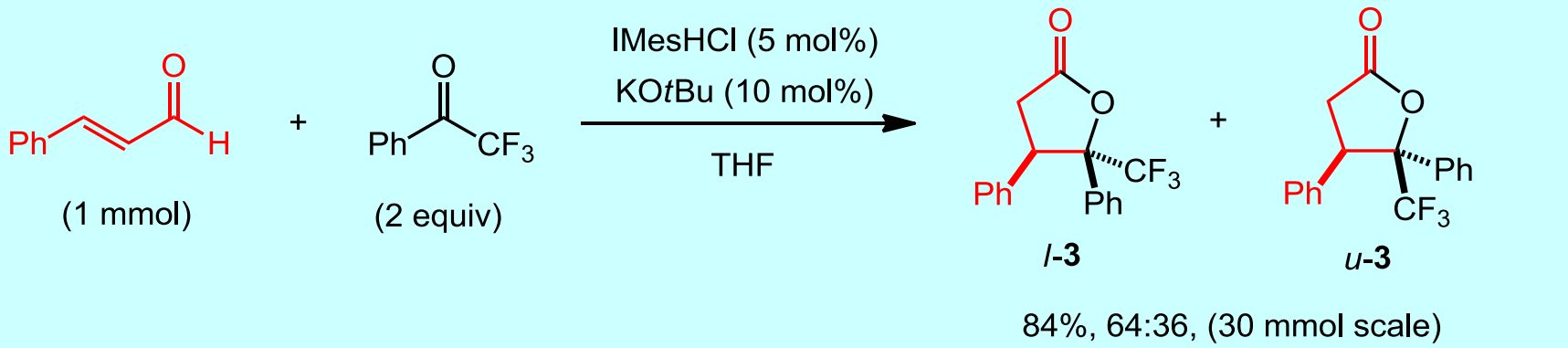
Initial publications:

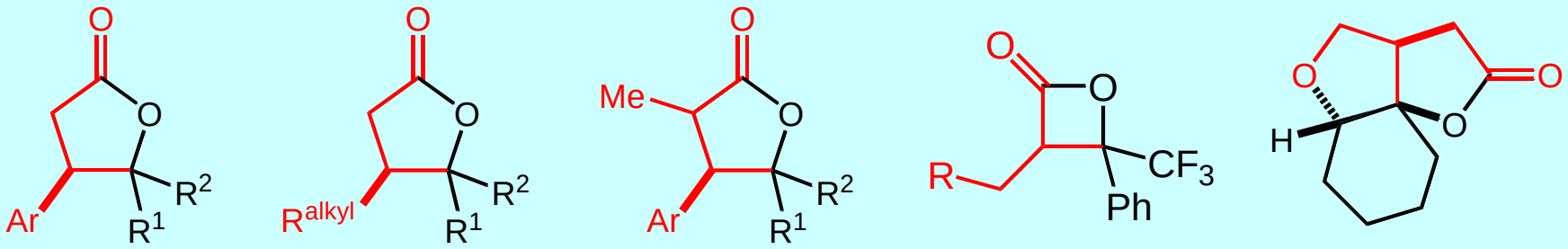
Burstein, **Glorius**, *Angew. Chem. Int. Ed.* **2004**, *45*, 6205.

Bode et al., *J. Am. Chem. Soc.* **2004**, *126*, 14370 (1:2 ratio of sm leads to higher yields).

For an excellent review, see: Enders et al., *Chem. Rev*. **2008**, *107*, 5606.

Variations





Our work:

Burstein, Glorius, *Angew. Chem. Int. Ed.* **2004**, *43*, 6205.

Burstein, Tschan, Xie, Glorius, *Synthesis* **2006**, 2418 (feature article).

Schrader,* Handayani, Burstein, Glorius, *Chem. Commun*. **2007**, 716.

Glorius, Hirano, *Ernst Schering Foundation Symposium Proceedings* ***2008****, Vol. 2, 159-181.*

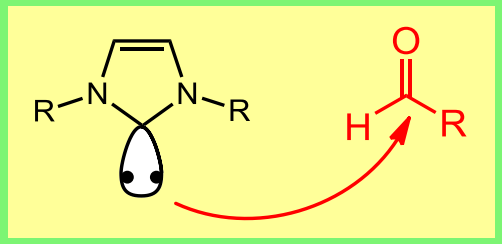
Hirano, Piel, Glorius, *Adv. Synth. Catal.* **2008**, *350*, 984.

Lebeuf, Hirano, Glorius, *Org. Lett.* **2008**, *10*, 4243.

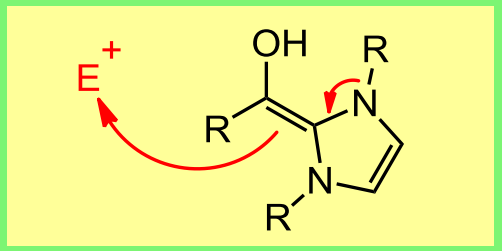
Common modes of action in NHC organocatalysis

Electron-donor properties

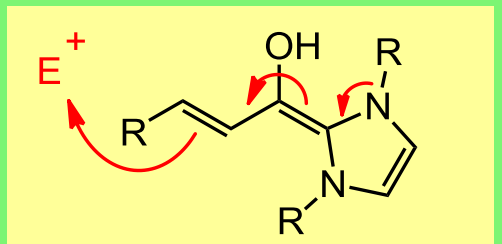
Nucleophilicity



Enamine reactivity

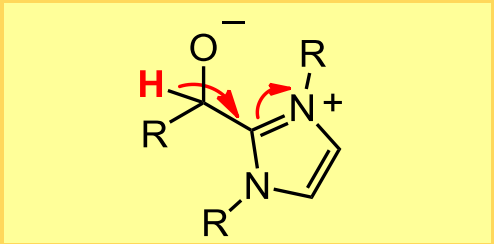


Conjugate enamine reactivity

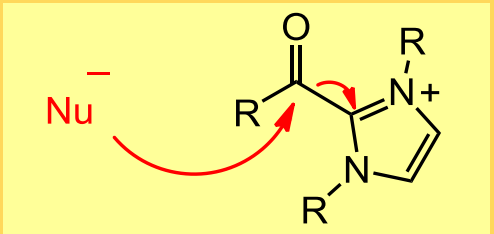


New!

Azolium salt acidifies α-position



Azolium salt is good leaving group

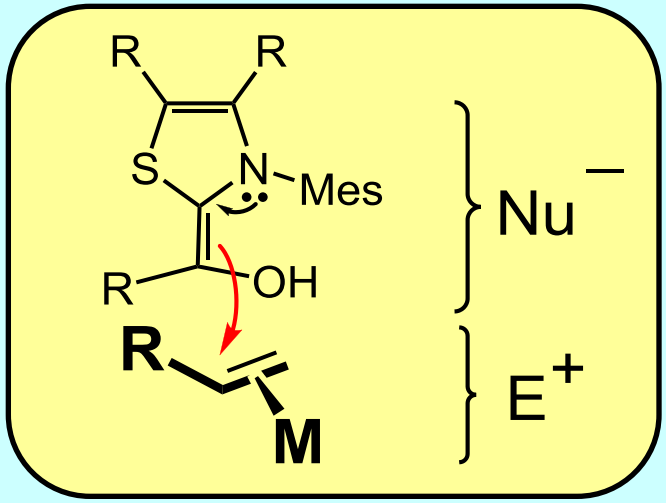


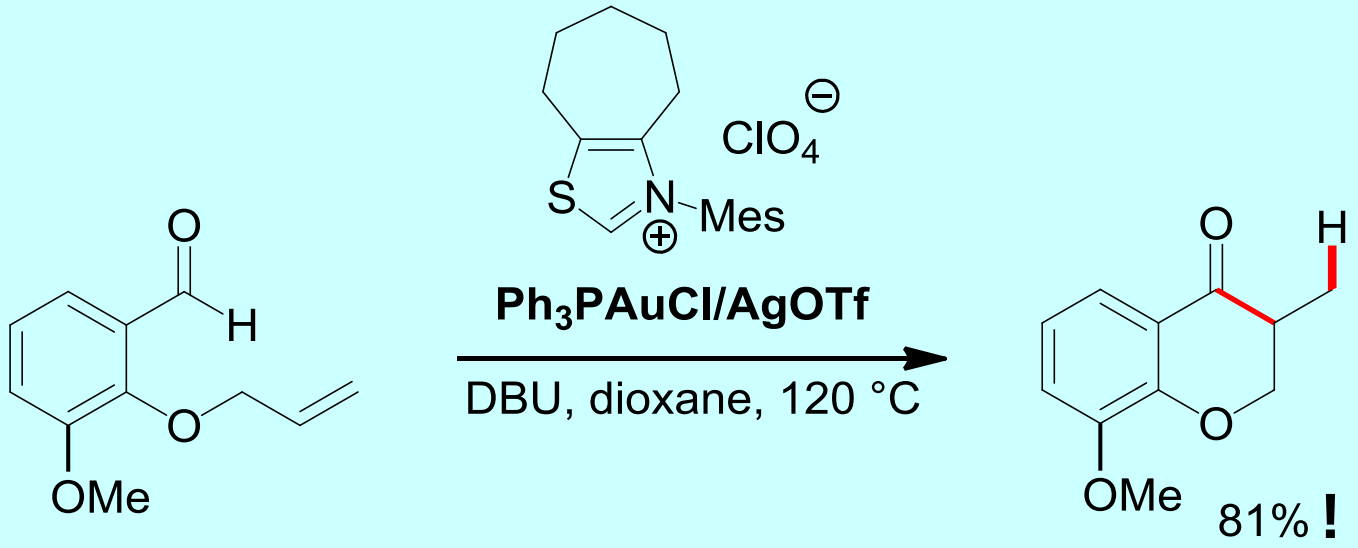
Electron-acceptor properties

Hydroacylation of unactivated alkenes

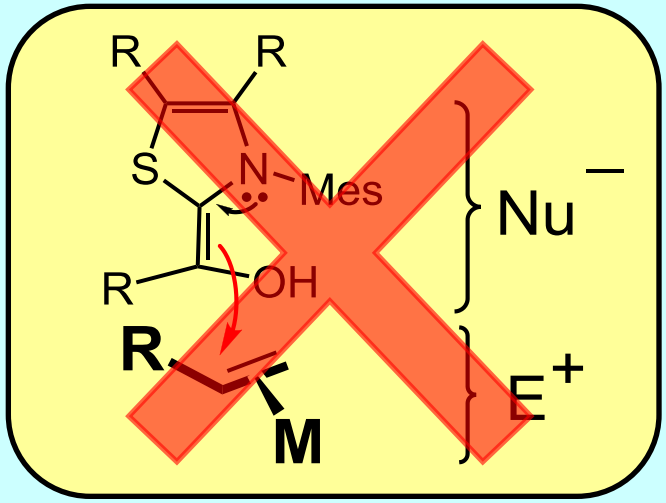
Concept:

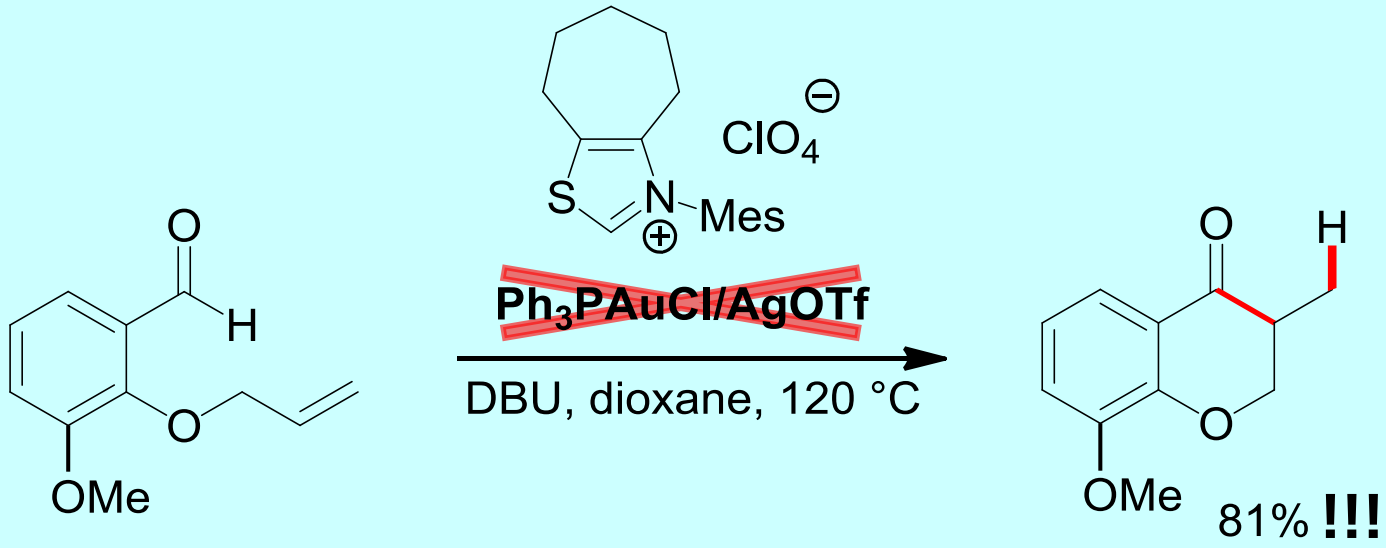
(dual catalysis)



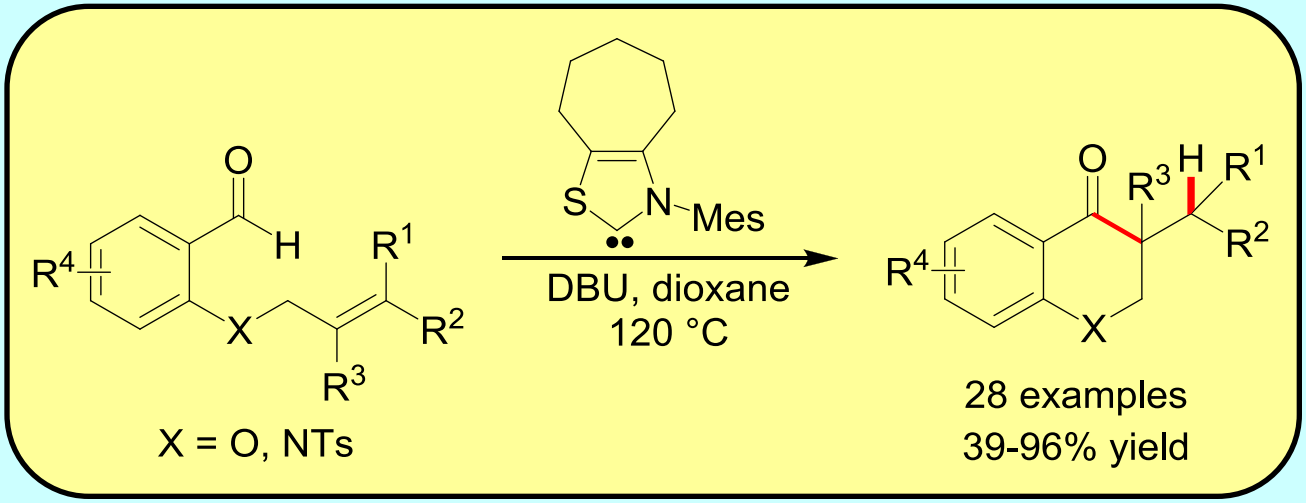


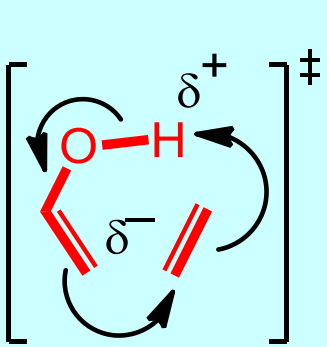
Hydroacylation of unactivated alkenes



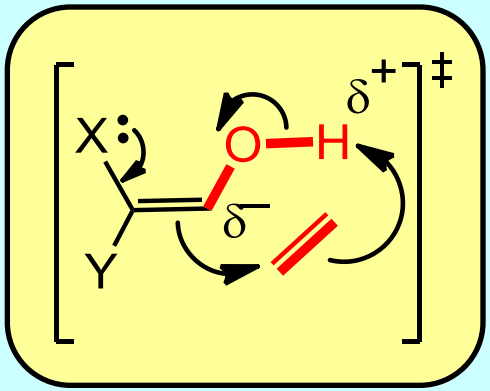


A new, concerted mode of action

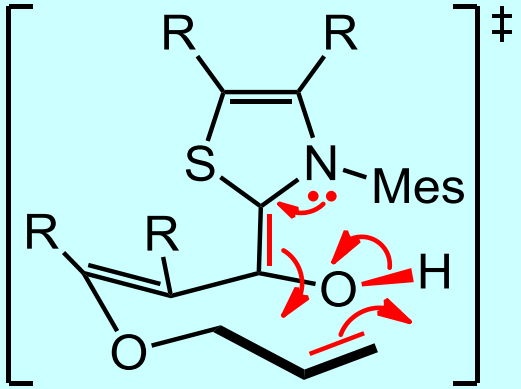




vs.



≡



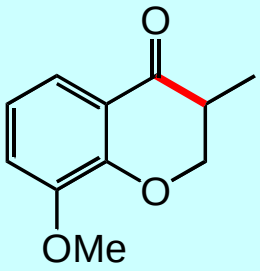
Conia-Ene

our work

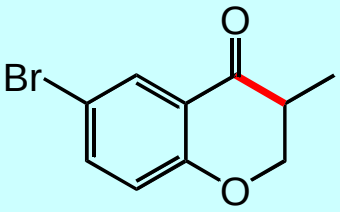
Hirano, Biju, Piel, Glorius, *J. Am. Chem. Soc.* **2009**, *131*, 14190.

See also: She, *Tetrahedron* **2008**, *64*, 8797.

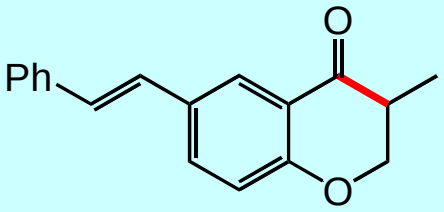
Hydroacylation of unactivated alkenes: scope



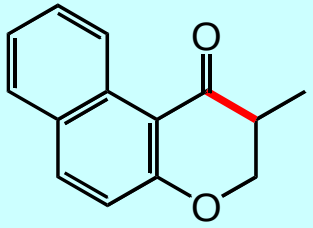
2a, 85%



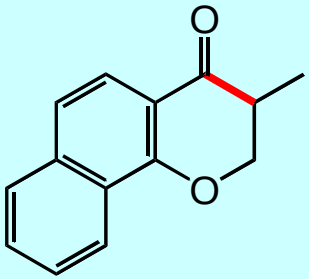
2g, 56%



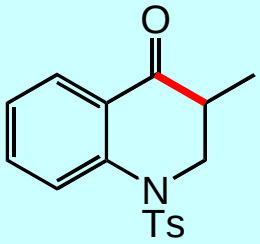
2k, 62%



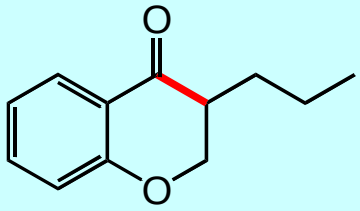
2q, 95%



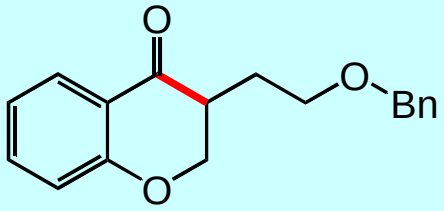
2r, 81%



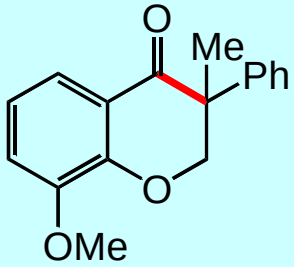
2u, 71%



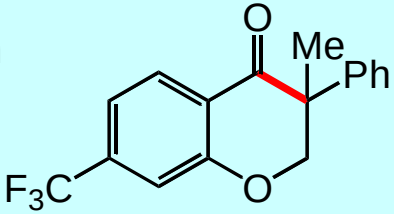
9c, <5%



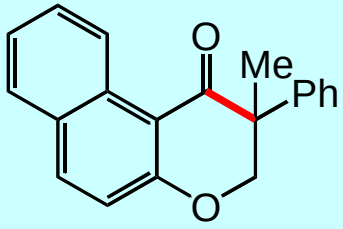
9d, 93%



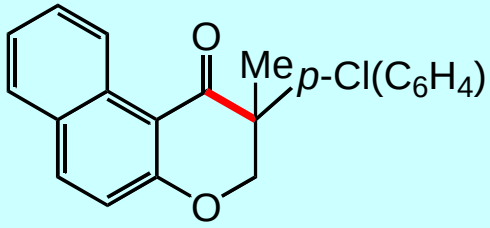
11a, 87%



11b, 76%



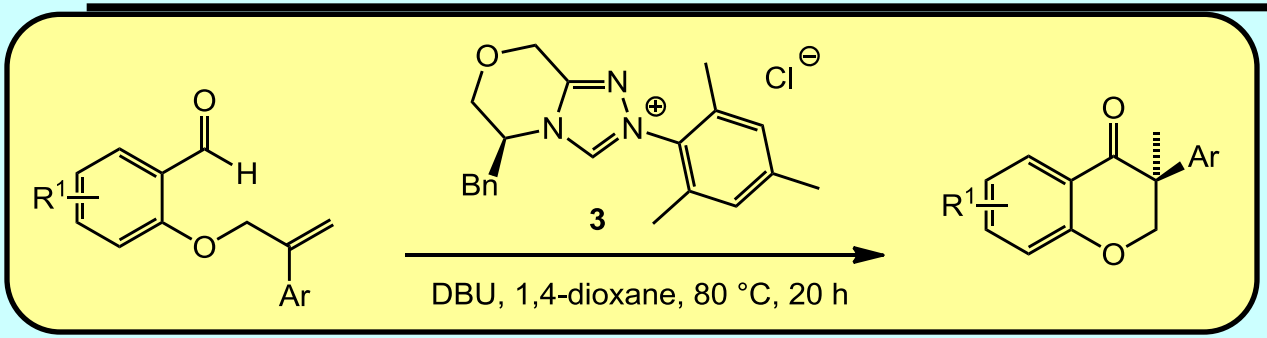
11c, 94%



11d, 94%

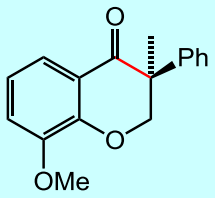
Hirano, Biju, Piel, Glorius, *J. Am. Chem. Soc.* **2009**, 131, 14190.

Highly asymmetric hydroacylation of unactivated alkenes

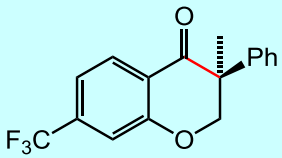


18 examples

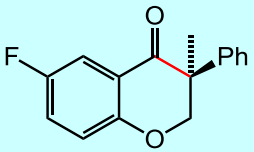
99% ee each !



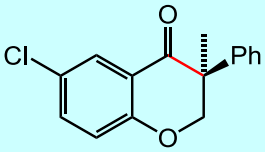
2a
99%, **>99%ee**



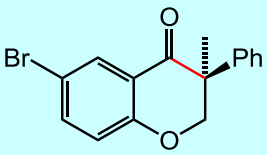
2c
60%,[b] **>99%ee**



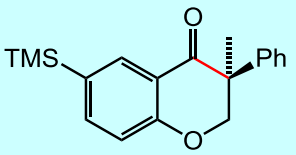
2d
8%,[c] **>99%ee**



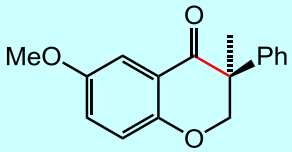
2e
97%, **>99%ee**



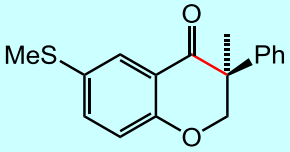
2f
94%, **>99%ee**



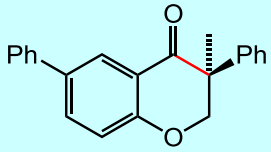
2g
81%, **99%ee**



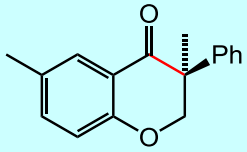
2h
93%, **99%ee**



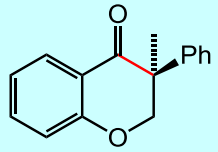
2i
91%, **99%ee**



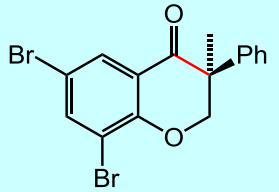
2j
74%, **>99%ee**



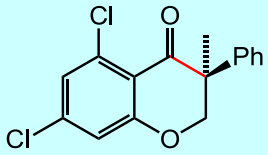
2k
46%, **99%ee**



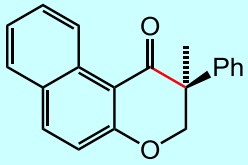
2l
78%, **99%ee**



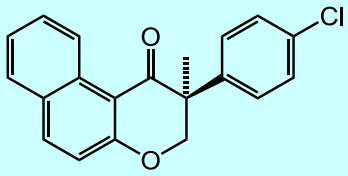
2m[d]
94%, **>99%ee**



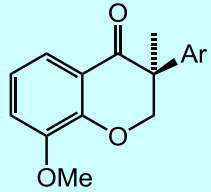
2o[d]
95%, **>99%ee**



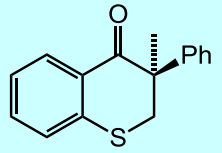
2p
94%, **>99%ee**



2q
99%, **99%ee**



Ar = 4-Cl-C_6H_4: **2r**, 94%, **99%ee**
Ar = 4-OMe-C_6H_4: **2s**, 75%,[e] **>99%ee**

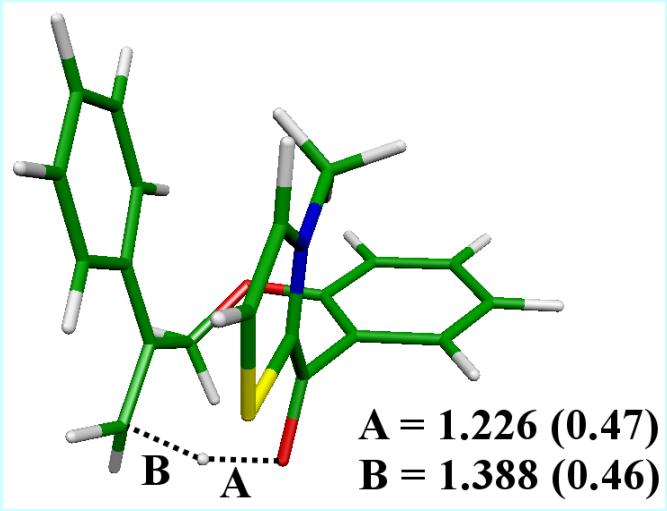


2t
28%, >99% ee

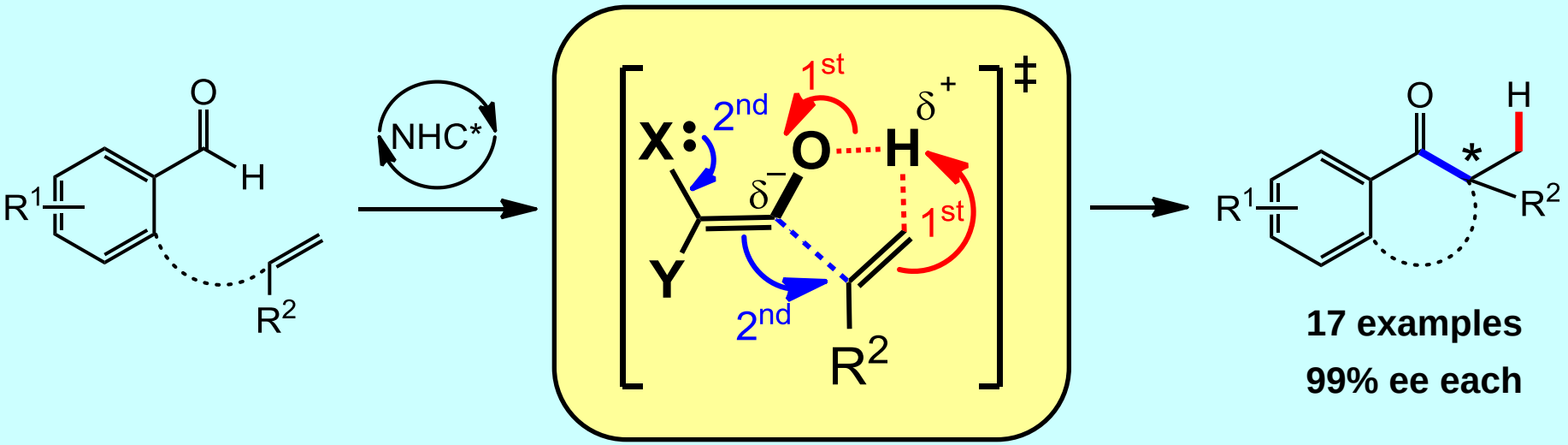
Piel, Steinmetz, Hirano, Fröhlich, Grimme,* Glorius,* *in revision*.

Mechanistic insight

Proton transfer TS with achiral NHC



B2PLYP-D/TZVPP/BP86-D/TZVP level



17 examples

99% ee each

Piel, Steinmetz, Hirano, Fröhlich, Grimme,* Glorius,* *in revision*.

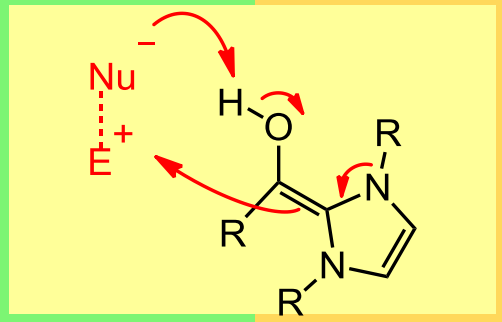
New mode of NHC organocatalysis!?

Electron-donor properties

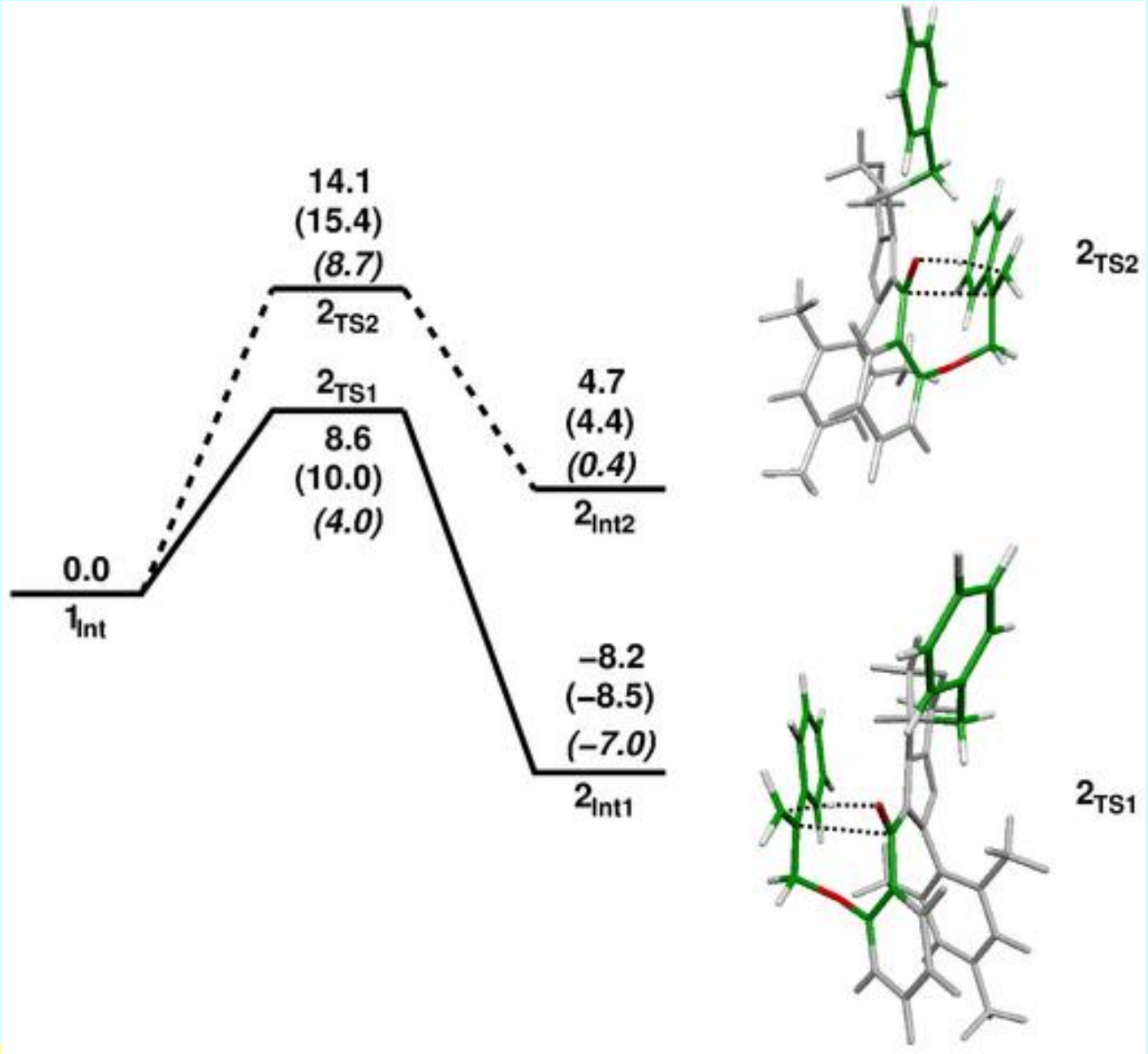
Electron-acceptor properties

New!

Concerted (protonation, enamine addition)

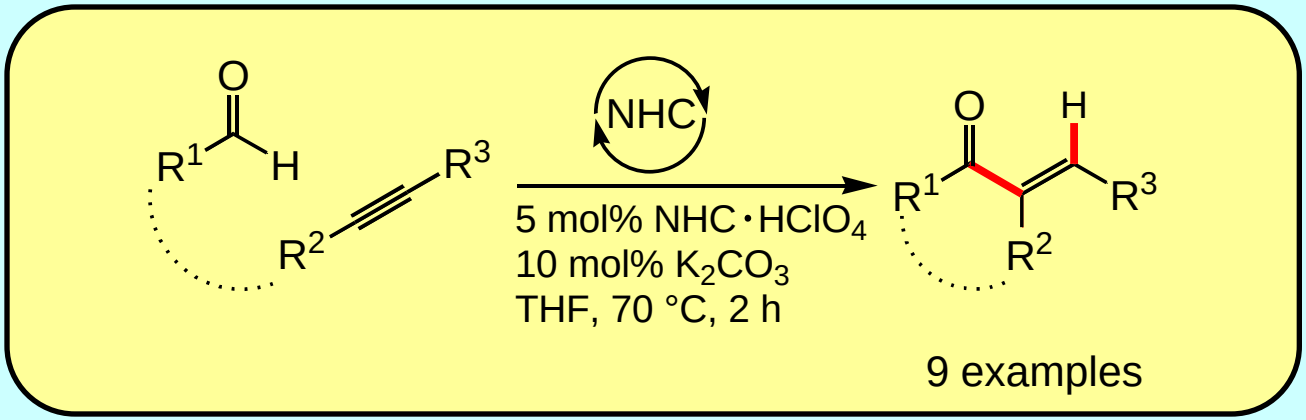


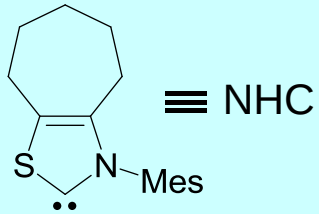
Mode of enantioinduction



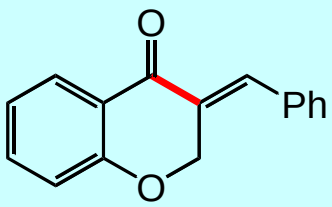
Piel, Steinmetz, Hirano, Fröhlich, Grimme,* Glorius,* *in revision*.

NHC-catalyzed cascade involving the hydroacylation of unactivated alkynes

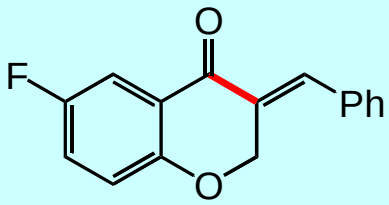




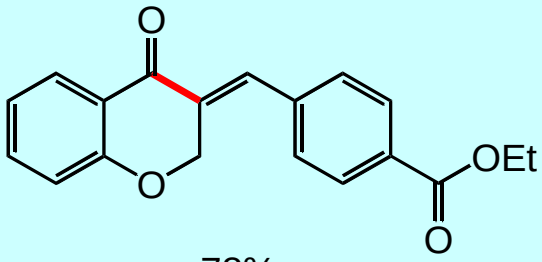
Representative examples:



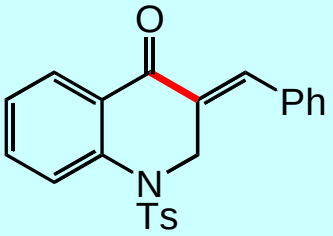
86%



84%



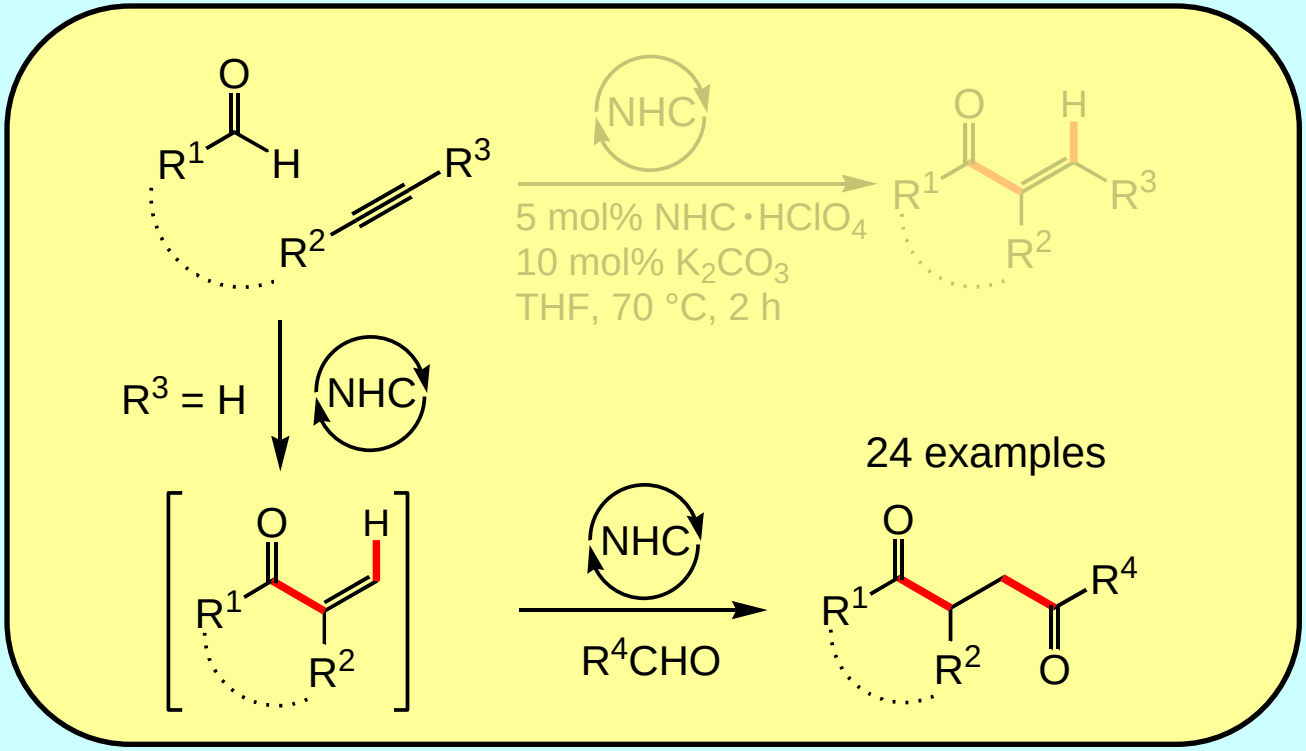
78%



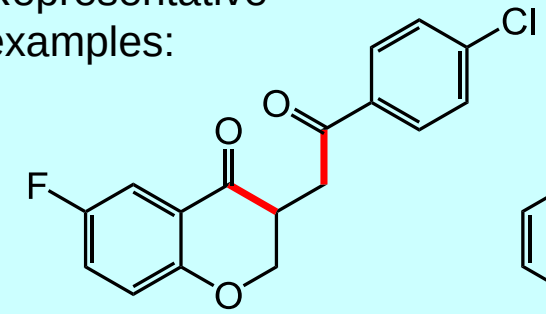
63%

Biju, Wurz, Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 5970.

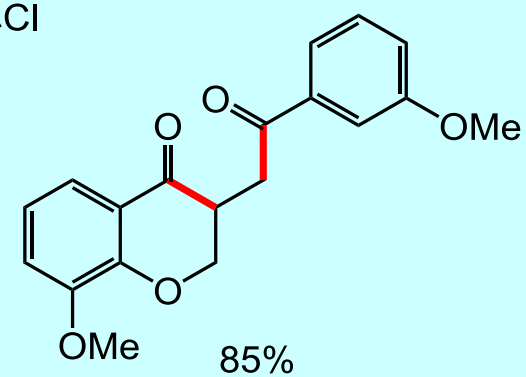
NHC-catalyzed cascade involving the hydroacylation of unactivated alkynes



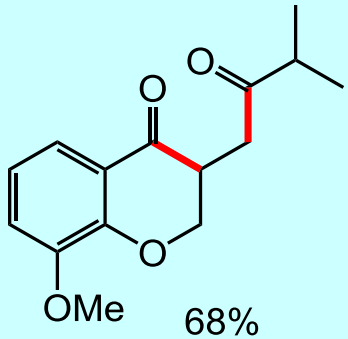
Representative examples:



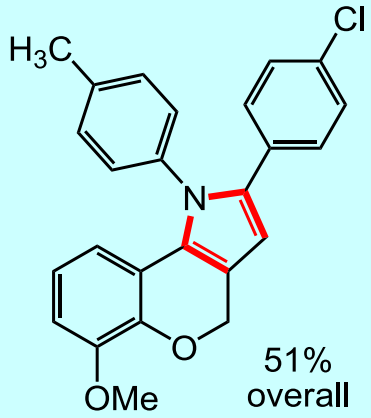
88%



85%

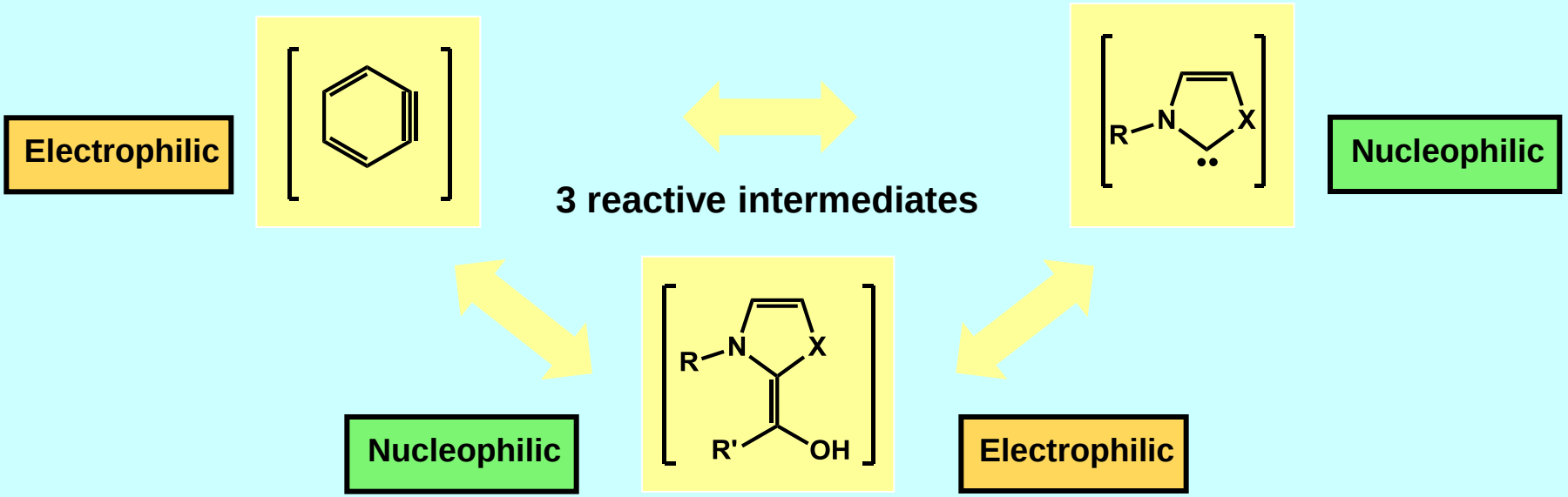


68%

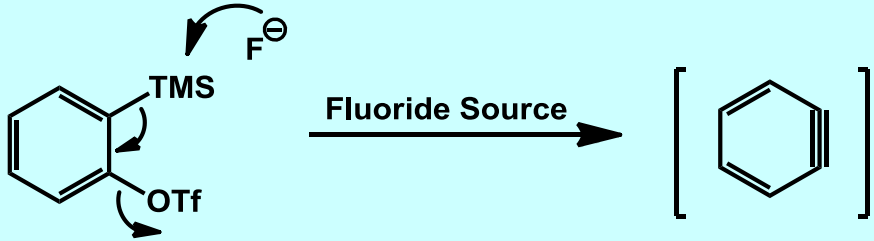


51% overall

Intermolecular hydroacylation of Arynes



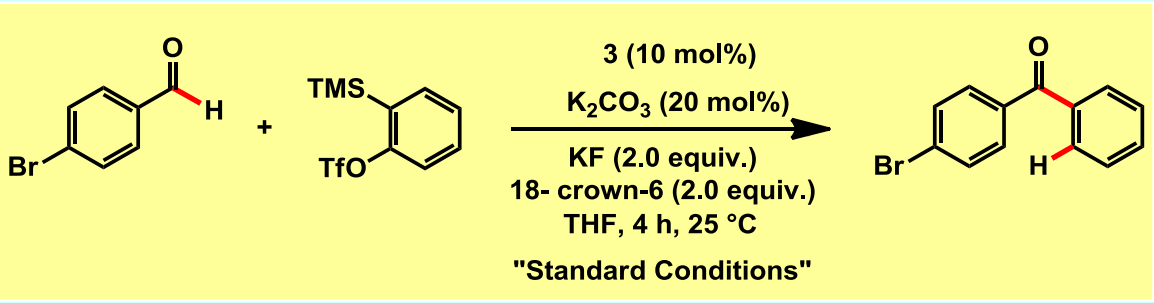
Mild Conditions for the Generation of Arynes

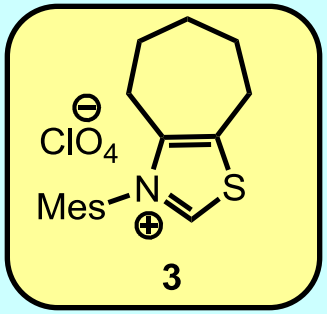


Common Fluoride Sources are CsF/CH_3CN, KF/ 18-crown-6/THF, TBAF/ THF

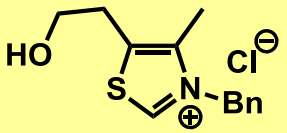
Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.

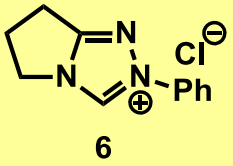
Optimization Study for the Hydroacylation of Arynes

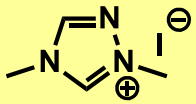




Entry	Variation of the standard conditions	Yield (%)
1	None	60
2	**5** instead of **3**	5
3	**6** instead of **3**	4
4	**7** instead of **3**	0
5	**8** instead of **3**	12
6	DBU instead of K_2CO_3	0
7	KO*t*-Bu instead of K_2CO_3	78
8	TBAF as the fluoride source	13
9	CsF and CH_3CN instead of KF and THF	30
10	15 mol% **3** and 15 mol% K_2CO_3	90
11	15 mol% 3 and 15 mol% KO*t*-Bu	98 (92)

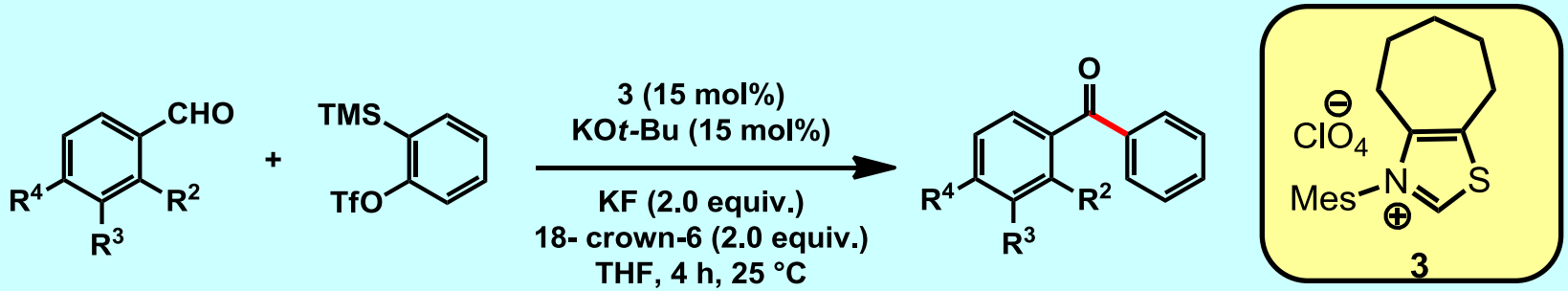


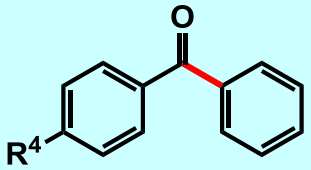




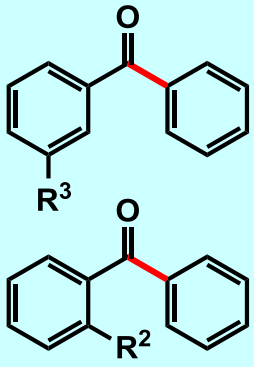
Biju, Glorius, *Angew. Chem., Int. Ed.* **2010**, *49*, 9761.

Hydroacylation of Arynes: Scope of Aldehydes



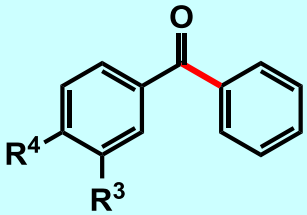


R^1 = Br: 92%
H: 72%
CH_3: 74%
t-Bu: 69%
Cl: 93%
Ph: 74%
CN: 70%
CO_2Me: 77%
CF_3: 88%

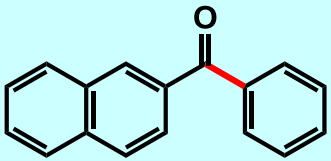


R^3 = OMe: 78%
Br: 85%
F: 90%

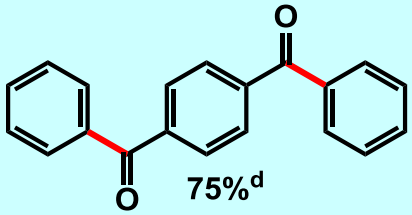
R^2 = F: 60%
Cl: 49%[b]



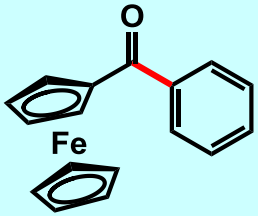
$R^1 = R^2$ = OMe: 62%[c]
Cl: 89%



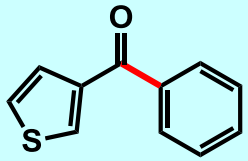
76%



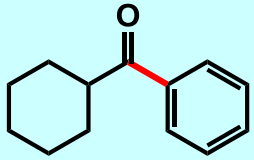
75%[d]



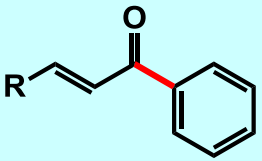
42%



70%



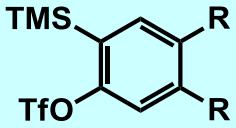
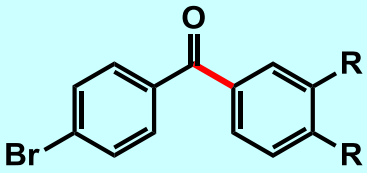
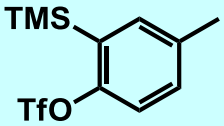
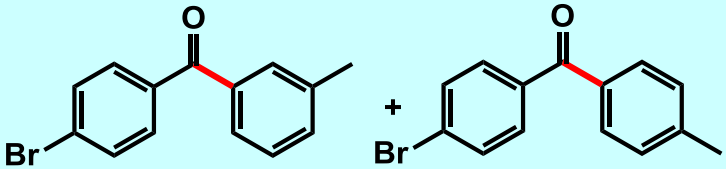
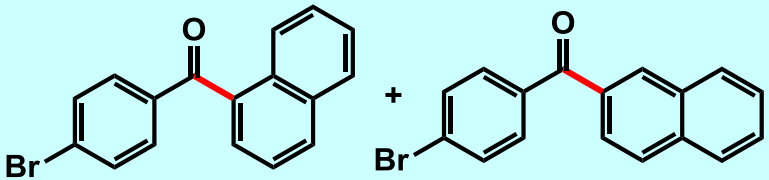
48%



R = phenyl: 58%[e]
2-furyl: 43%

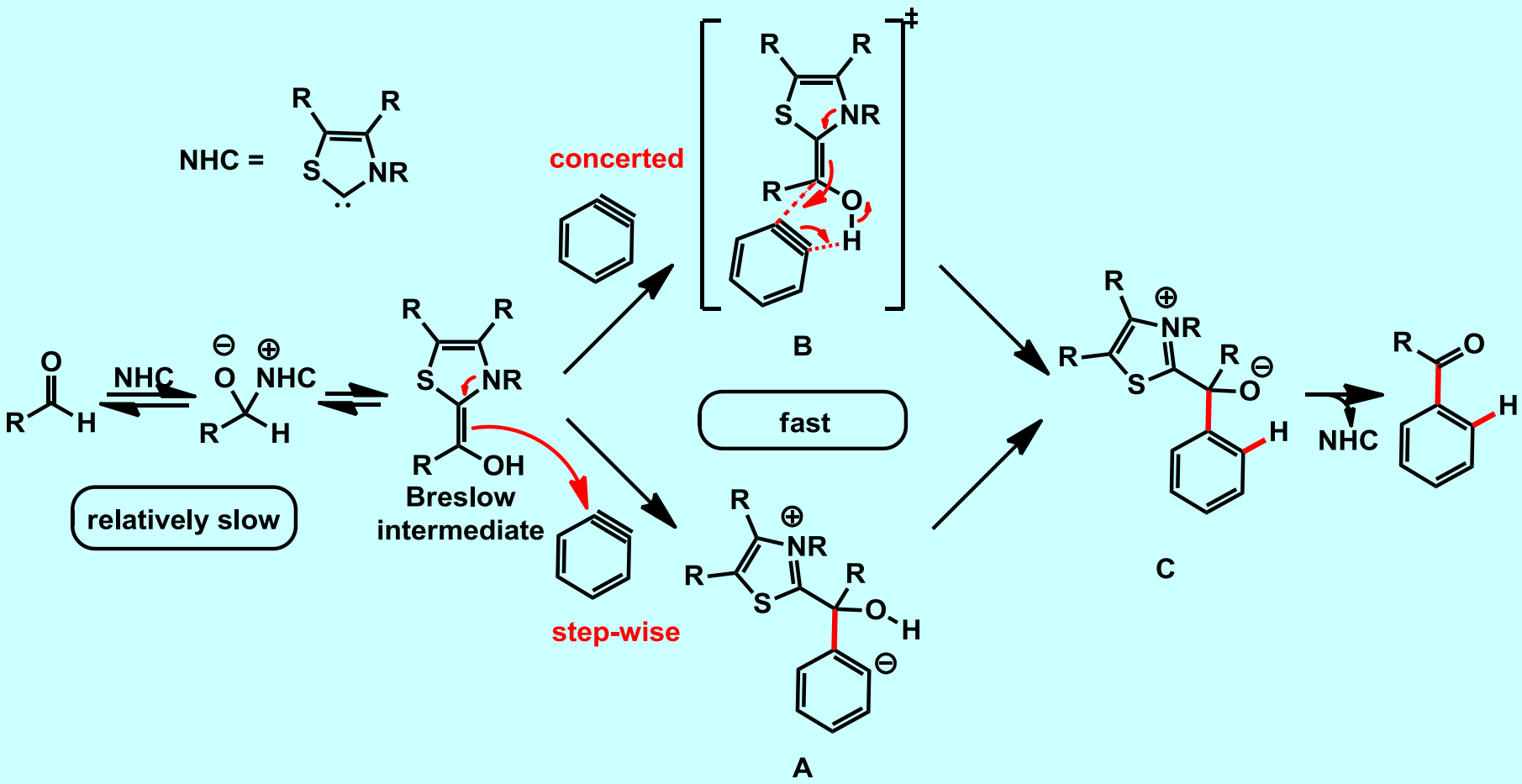
Biju, Glorius, *Angew. Chem., Int. Ed.* **2010**, *49*, 9761.

Hydroacylation of Arynes: Variation of Aryne Moiety

Entry	Aryne precursor	Product(s), Yield (%)
1		 R = Me: 70%
2		R = O(CH_2)O: 77%
3		 34% 33%
4		 21% 54%

Biju, Glorius, *Angew. Chem., Int. Ed.* **2010**, *49*, 9761.

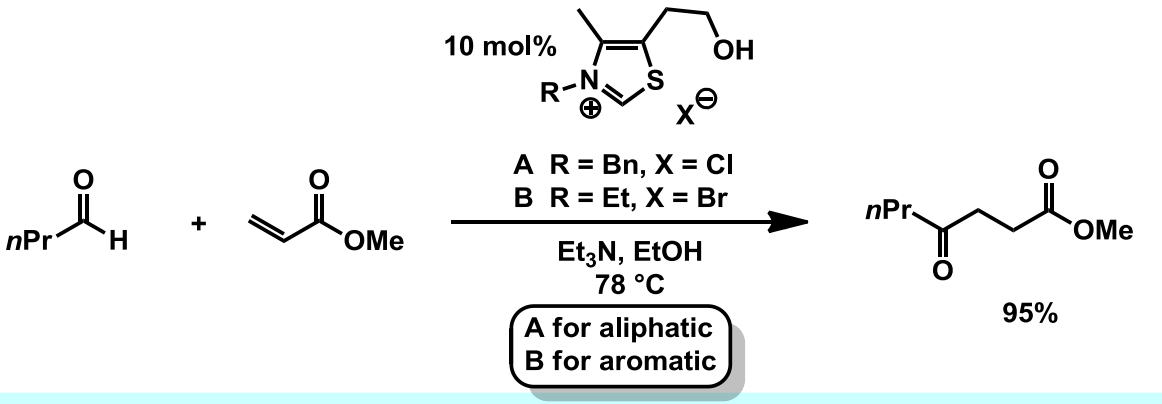
Proposed Mechanism of the Hydroacylation of Arynes



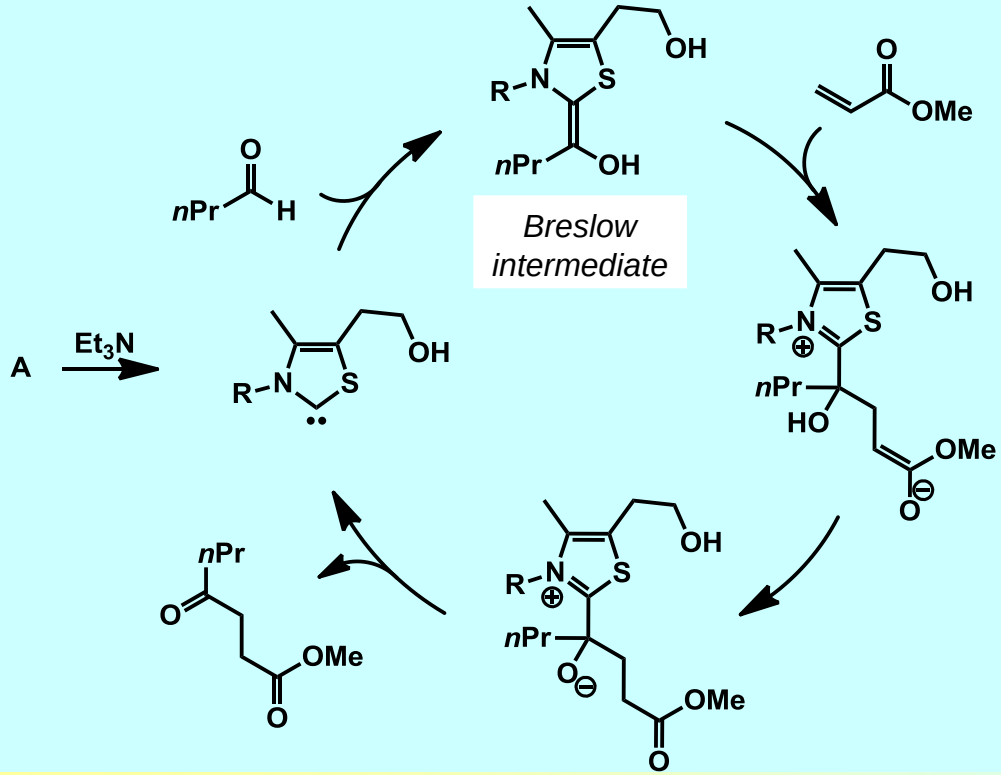
Biju, Glorius, *Angew. Chem., Int. Ed.* **2010**, *49*, 9761.

Asym. intermol. Stetter

Stetter reaction

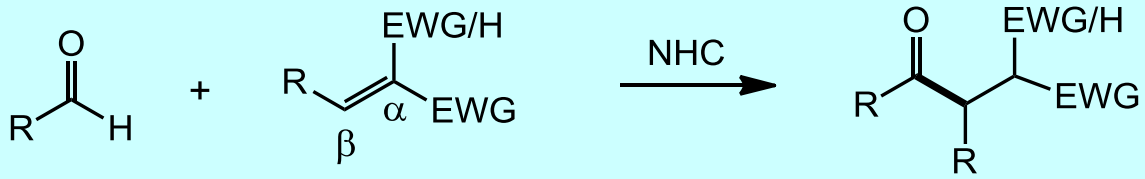


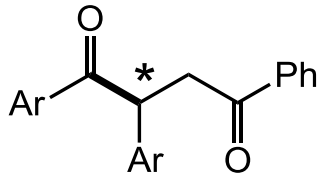
Umpolung addition of aldehydes to *activated, electrophilic*, C=C double bonds



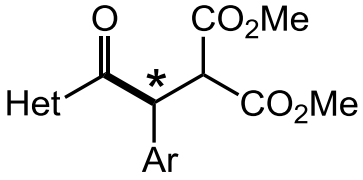
H. Stetter, *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 639.

A longstanding challenge: asymmetric intermolecular Stetter reaction



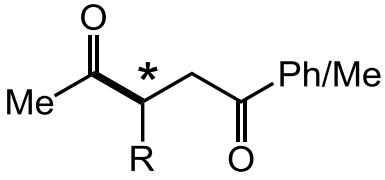


(up to 78% ee)[11a]



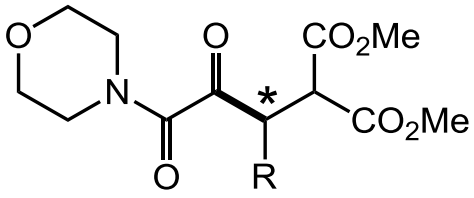
(up to 78% ee)[11b]

D. Enders et al.

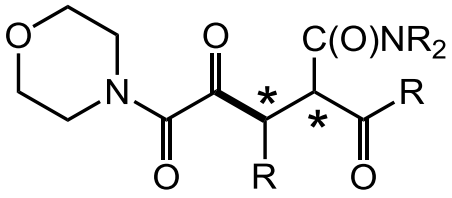


(up to >99% ee)[13]

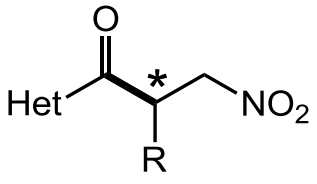
M. Müller et al.



(up to 91% ee)[12a]



(up to 98% ee, 19:1 dr)[12b]



(up to 96% ee)[12c]

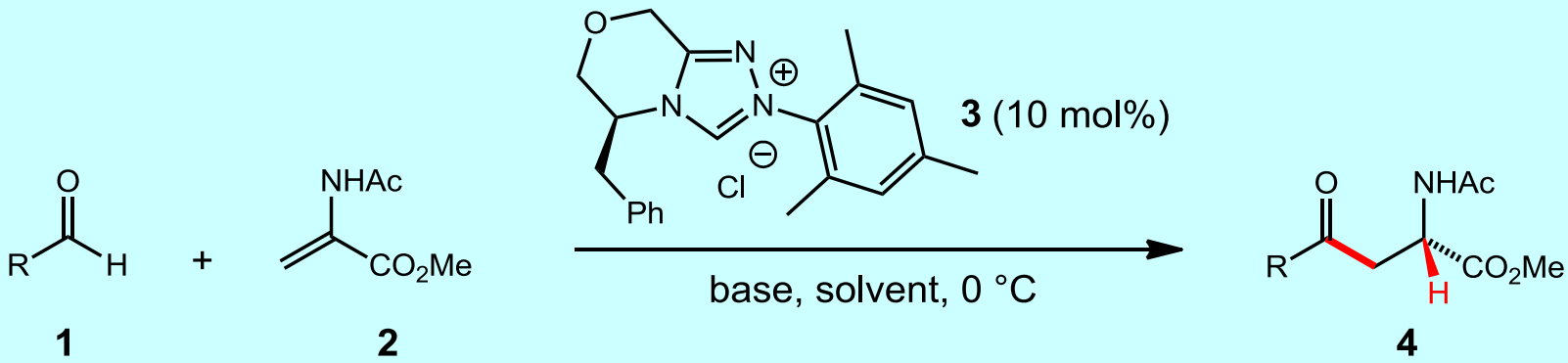
T. Rovis et al.

D. Enders: 11a) *Chem. Commun.* **2008**, 3989; 11b) *Synthesis* **2008**, 3864.

T. Rovis: 12a) *JACS* **2008**, *130*, 14066; 12b) *Org. Lett.* **2009**, *11*, 2856; 12c) *JACS* **2009**, *131*, 10872.

M. Müller: 13) *Angew. Chem. Int. Ed.* **2010**, *49*, 6600.

A longstanding challenge: asymmetric intermolecular Stetter reaction



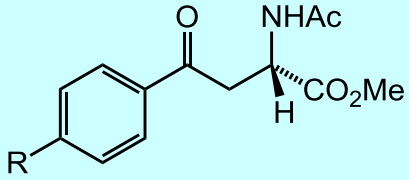
1 **2** **4**

15 examples

93-99% ee

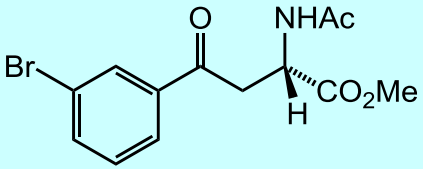
Jousseaume, Wurz, Glorius, *Angew. Chem. Int. Ed.* **2011**, in press

Asymmetric intermolecular Stetter reaction



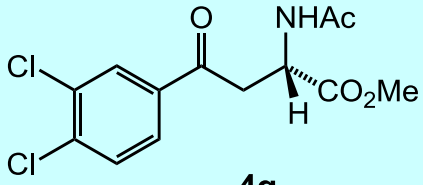
4a-e,k,l,n

R = Cl: 93%, **95% ee**
R = CO_2Me: 83%, **96% ee**
R = CF_3: 73%, **93% ee**
R = CN: 87%, **95% ee**
R = Br: 98%, **96% ee**
R = Ph: 42%, **98% ee**
R = Me: 48%, **97% ee**
R = H: 80%, **97% ee**



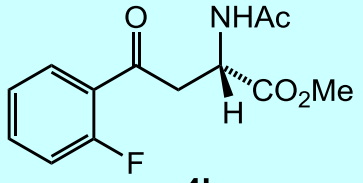
4f

81%, **97% ee**



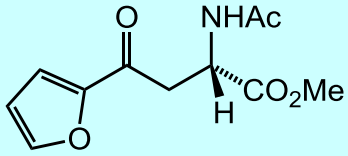
4g

71%, **94% ee**



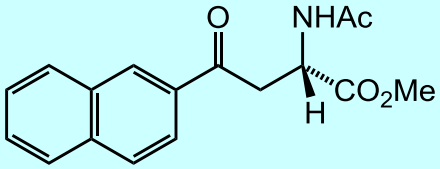
4h

38%, **99% ee**



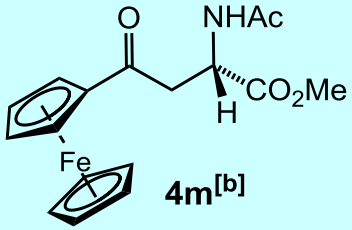
4i

86%, **98% ee**



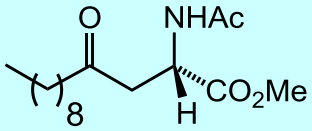
4j

89%, **97% ee**



4m[b]

56%, **99% ee**

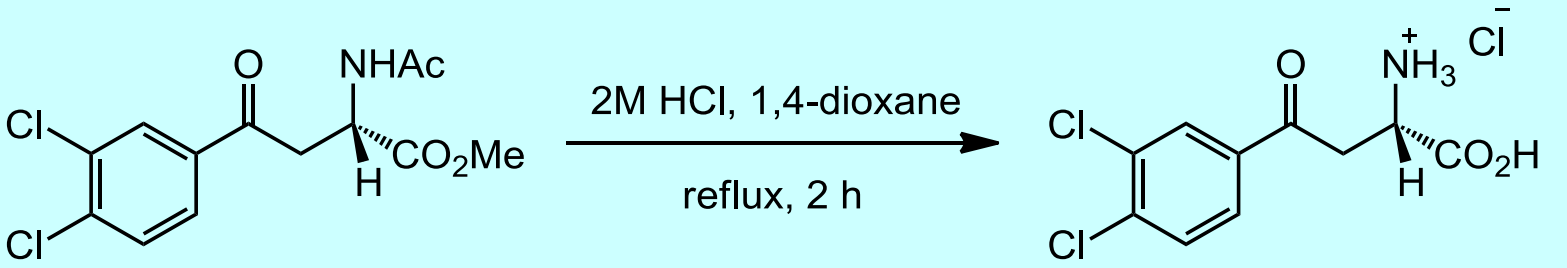


4o[b]

52%, **97% ee**

Jousseaume, Wurz, Glorius, *Angew. Chem. Int. Ed.* **2011**, in press

Follow up transformation



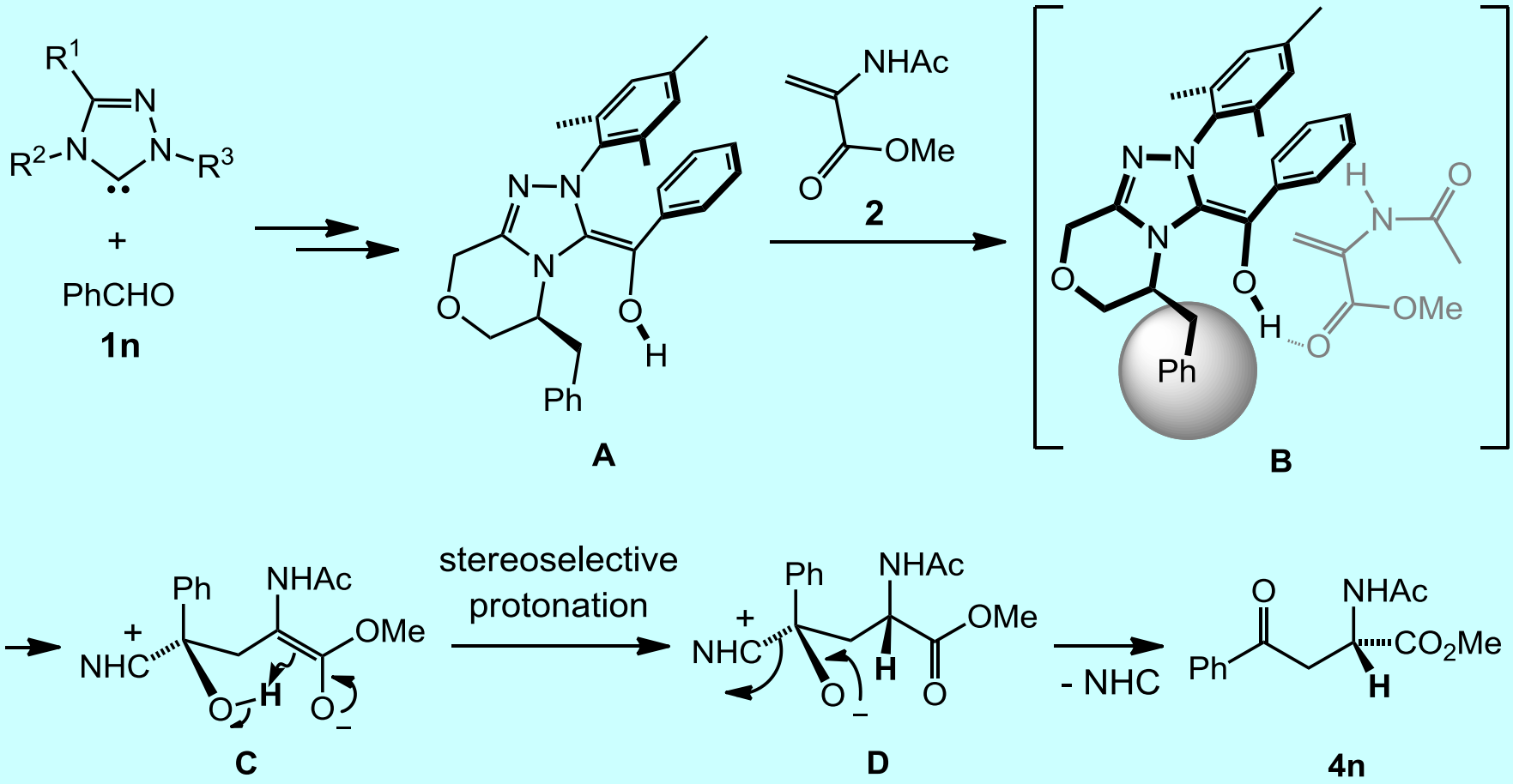
4g

FCE28833 (**6g**): 97% yield

a selective kynurenine 3-hydroxylase inhibitor

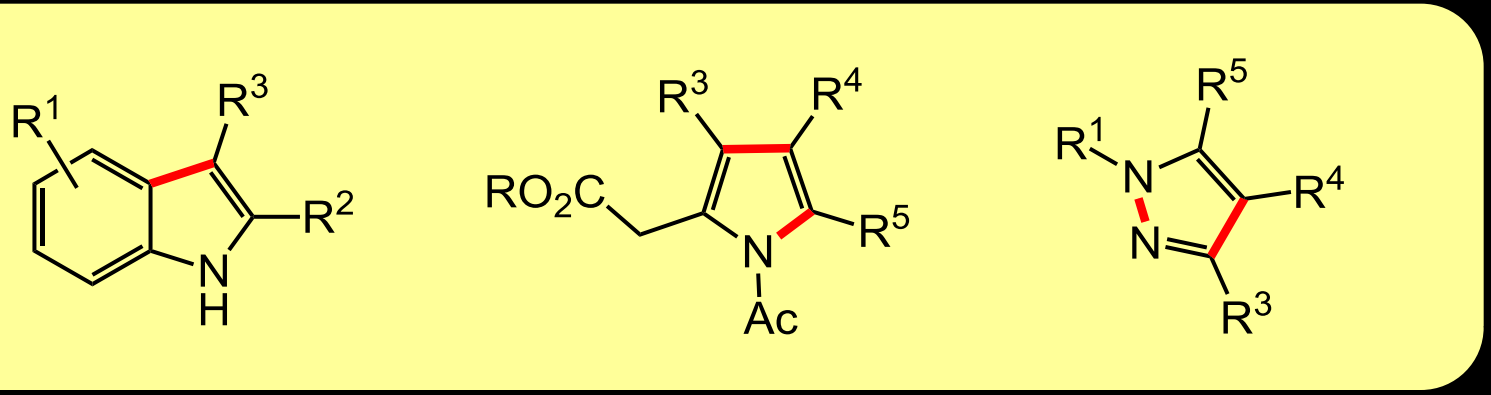
Jousseaume, Wurz, Glorius, *Angew. Chem. Int. Ed.* **2011**, in press

Mechanism / Mode of enantioinduction

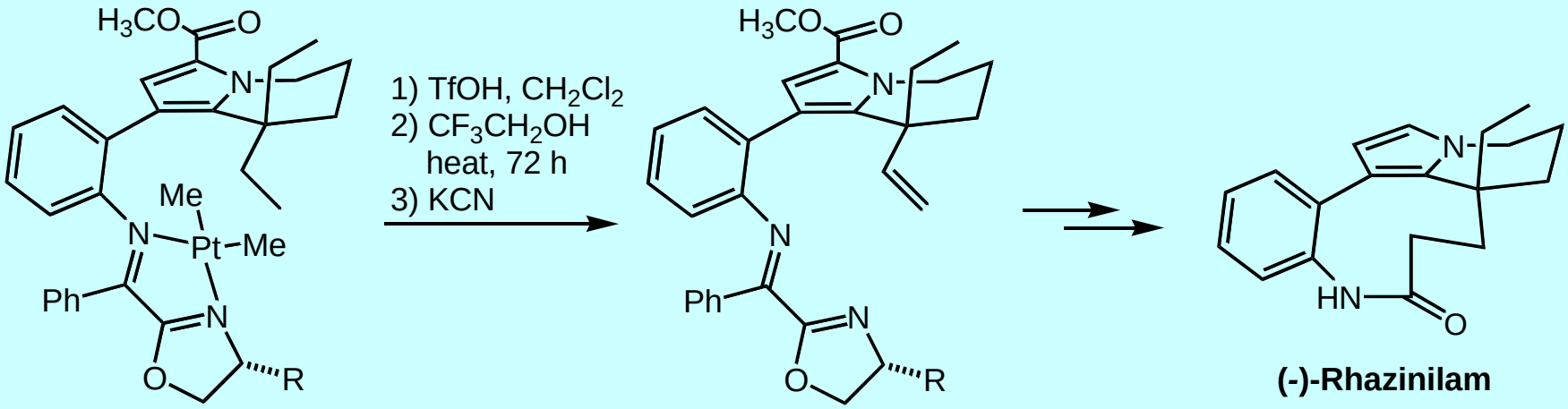


Jousseaume, Wurz, Glorius, *Angew. Chem. Int. Ed.* **2011**, in press

C-H activation reactions



A dream come true: application of C-H activation in total synthesis



A

@ 60 °C:

R = Ph: 15%, 72% de
R = *i*Pr: 10%, 70% de
R = *c*Hex: 20%, 76% de
R = *t*Bu, <10% conversion, >90% de

(*R*)-**B**

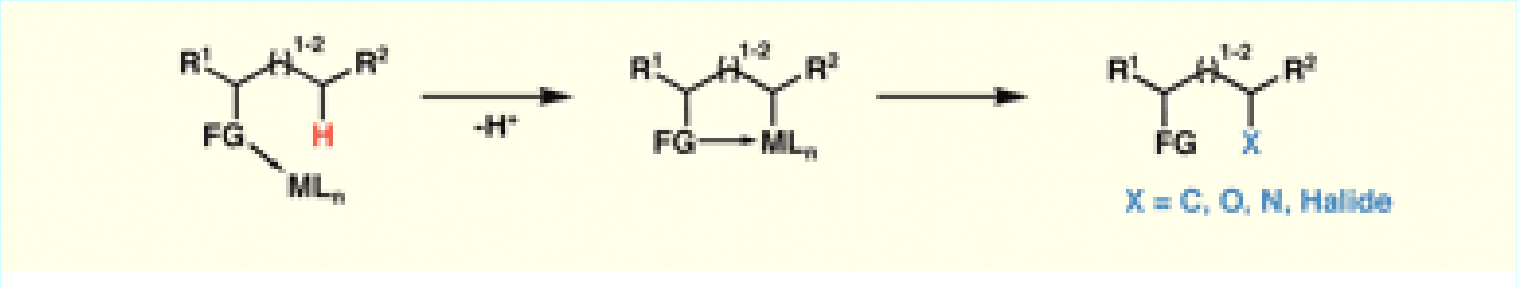
@ 70 °C:

R = Ph: 40%, 50% de
R = *i*Pr: 40%, 50% de
R = *c*Hex: 42%, 63% de

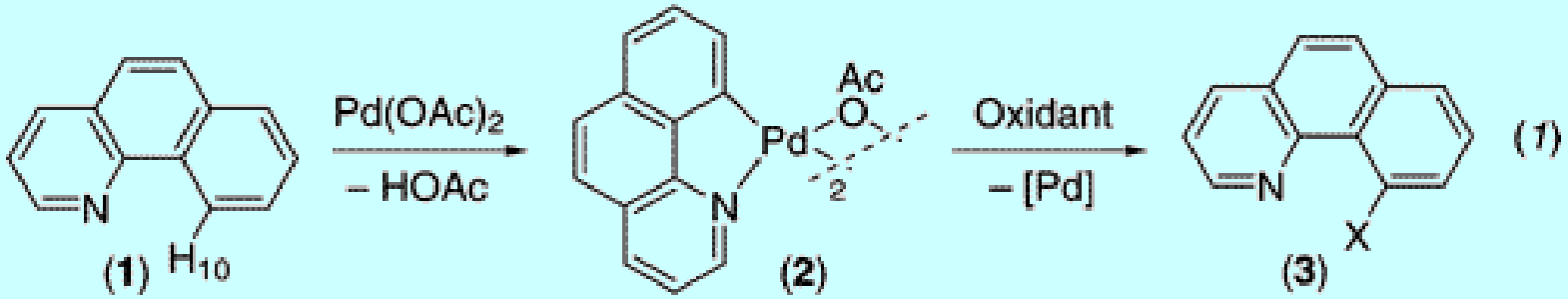
(-)-Rhazinilam
(an antitumor agent)

Sames et al., *JACS* **2002**, *124*, 6900:
„Total Synthesis of (-)-Rhazinilam: Asymmetric C-H Bond Activation via the Use of a Chiral Auxiliary“

Precomplexation allows C-H activation

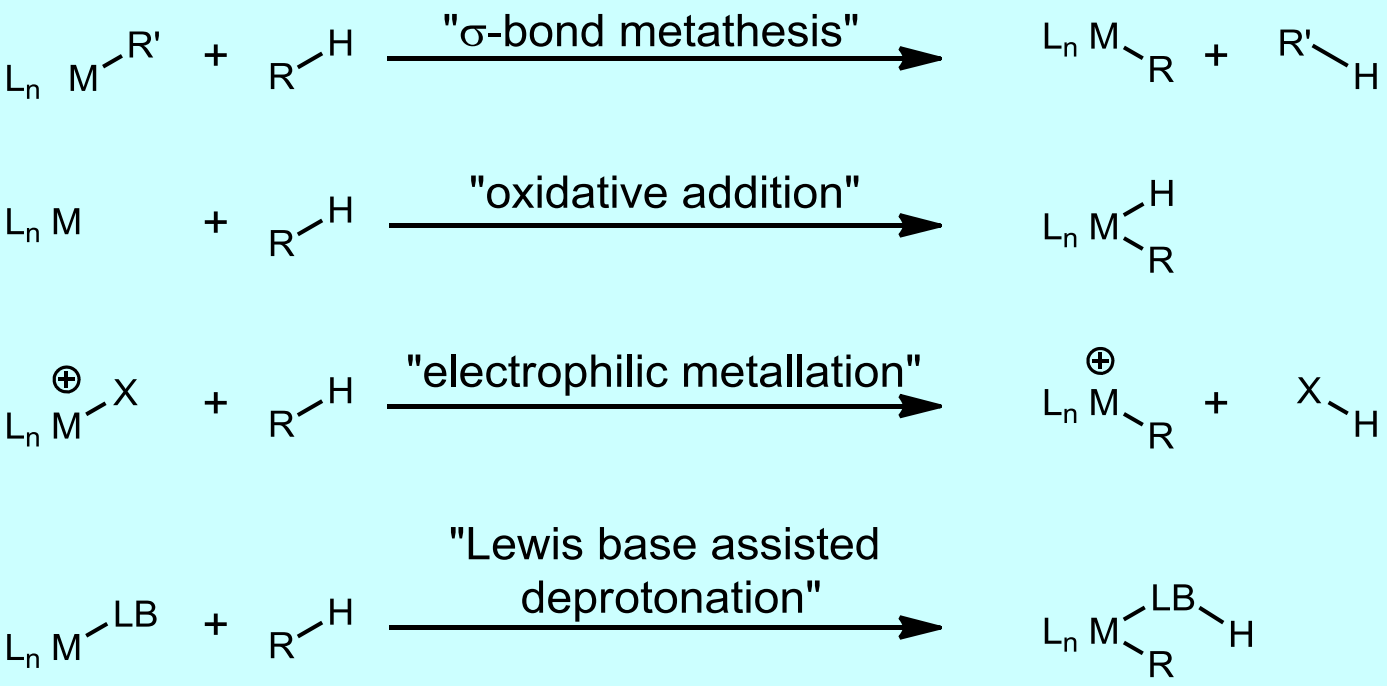


Sames et al., *SCIENCE* **2006**, *312*, 67:
„C-H Bond Functionalization in Complex Organic Synthesis“



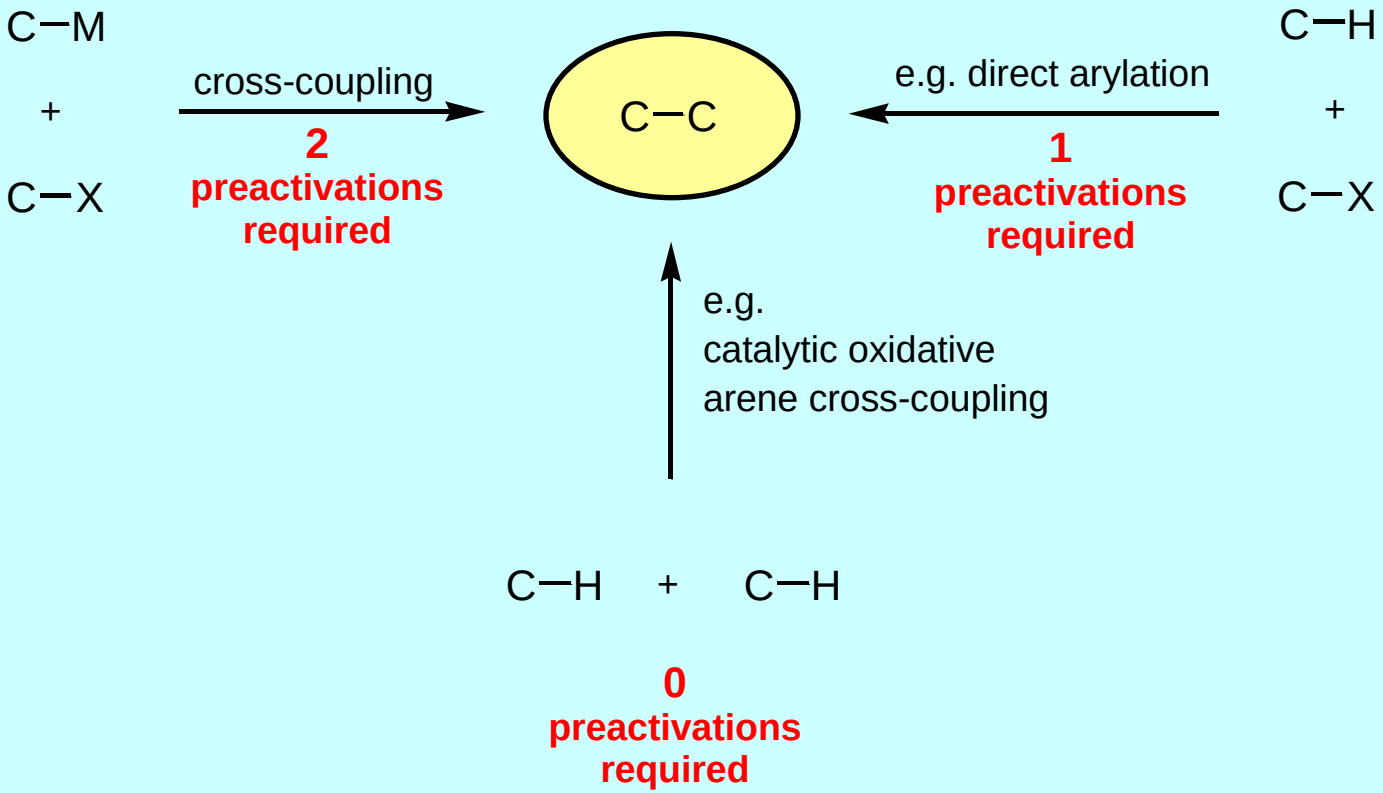
Sanford et al., *JACS* **2004**, *126*, 2300:
„A Highly Selective Catalytic Method for the Oxidative Functionalization of C-H Bonds“

Activation modes



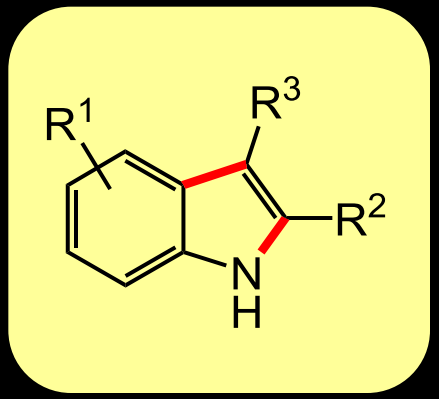
Glorius et al., *Chem. Soc. Rev.* **2011**, submitted:
„Towards mild C-H bond activation“

Cross-dehydrogenative coupling

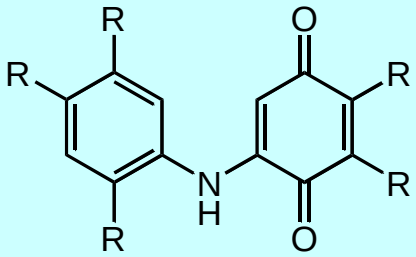


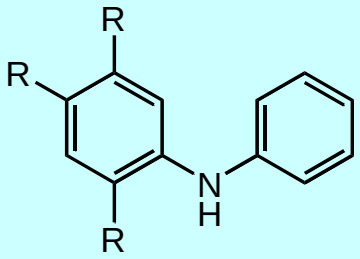
From anilines to indoles:

A **c**ross-**d**ehydrogenative **c**oupling (**cdc**)



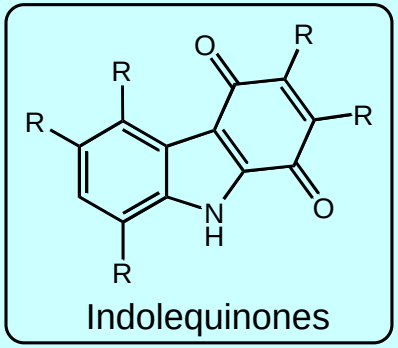
Synthesis of indoles by electrophilic aromatic palladation



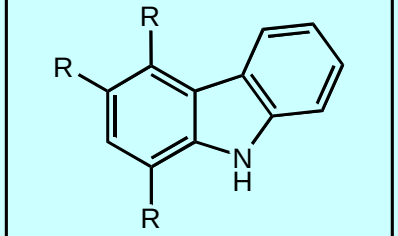


stoich. or catal. [Pd]
HOAc, oxidizing agent

(electrophilic aromatic palladation)



Indolequinones



Carbazoles

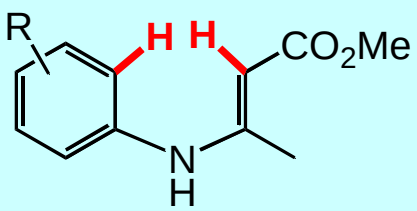
- LIMITED scope

-Often low yields

- Often stoichiometric amounts of [Pd]

For reviews on the synthesis of indoles, see:
a) Cacchi, Fabrizi, *Chem. Rev.* **2005**, *105*, 2873; b) Gribble, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 1045.
For lead references on the displayed oxidative coupling, see:
c) Åkermark, *Chem. Eur. J.* **1999**, *5*, 2413; d) Knölker, *Curr. Org. Chem.* **2005**, *9*, 1601; e) Åkermark, *J. Org. Chem.* **1975**, *40*, 1365; f) Knölker, *Org. Biomol. Chem.* **2006**, *4*, 3215; g) Fujii, Ohno, *Chem. Commun.* **2007**, 4516.

Substrate scope

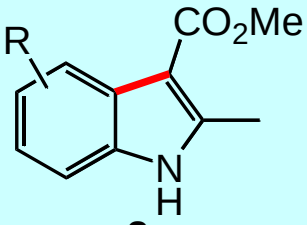


1

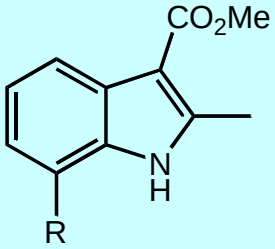
$Pd(OAc)_2$ (10 mol%)
$Cu(OAc)_2$, K_2CO_3

DMF, 80 - 140 °C

R = H: 72%



2

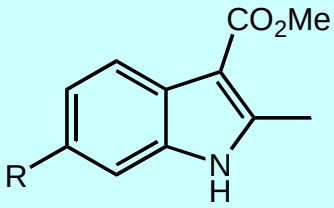


R = Me: 82%

R = OMe: 64%

R = F: 78%

R = Cl: 53%



(main regioisomer)

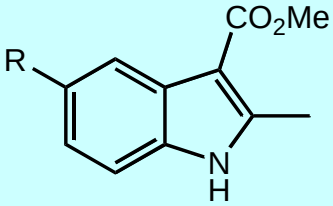
R = Me: 68% (12:1)

R = OMe: 68% (>99:1)

R = F: 74% (1.1:1)

R = Cl: 76% (7:1)

R = Ac: 54% (>99:1)



R = Me: 72%

R = OMe: 64%

R = F: 74%

R = Cl: 64%

R = Ac: 52%

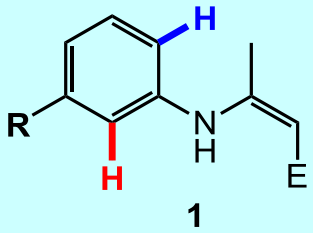
R = COOEt: 64%

R = $CONEt_2$: 70%

R = CN: 65%

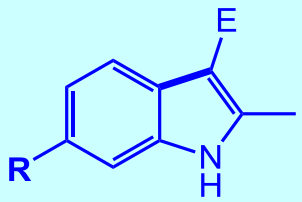
Würtz, Rakshit, Neumann, Dröge, Glorius, *Angew. Chem. Int. Ed.* **2008**, *47*, 7230.

Substrate scope



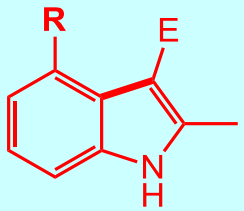
1

$Pd(OAc)_2$ (10 mol%)
$Cu(OAc)_2$, K_2CO_3
DMF, 80 - 140 °C
E = CO_2Me

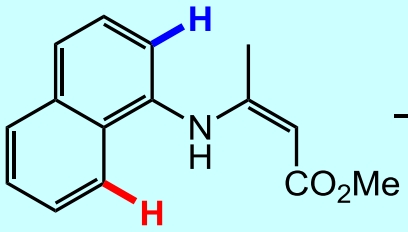


(main regioisomer)

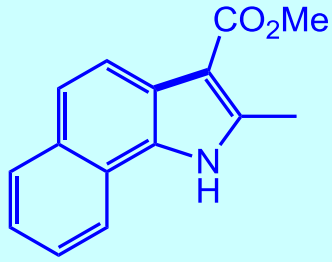
+



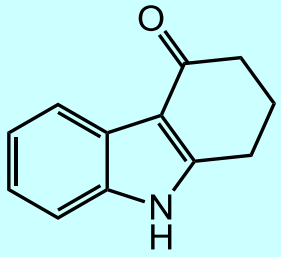
R = OMe: 68% (>99:1)
R = Ac: 54% (>99:1)
R = Me: 68% (92:8)
R = Cl: 76% (88:12)
R = F: 74% (53:47)



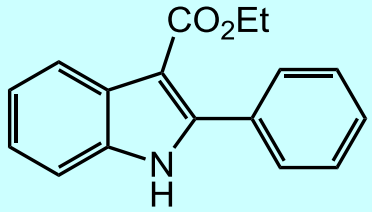
$Pd(OAc)_2$ (10 mol%)
$Cu(OAc)_2$, K_2CO_3
DMF, 80 °C



85% (>99:1)



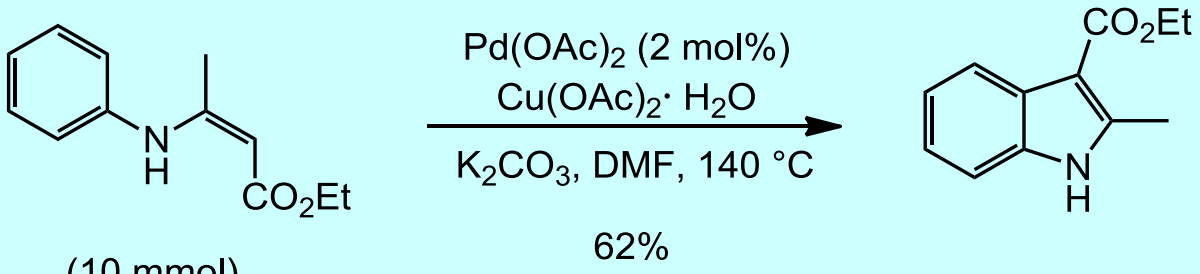
85%



68%

Non-anhydrous & one-pot

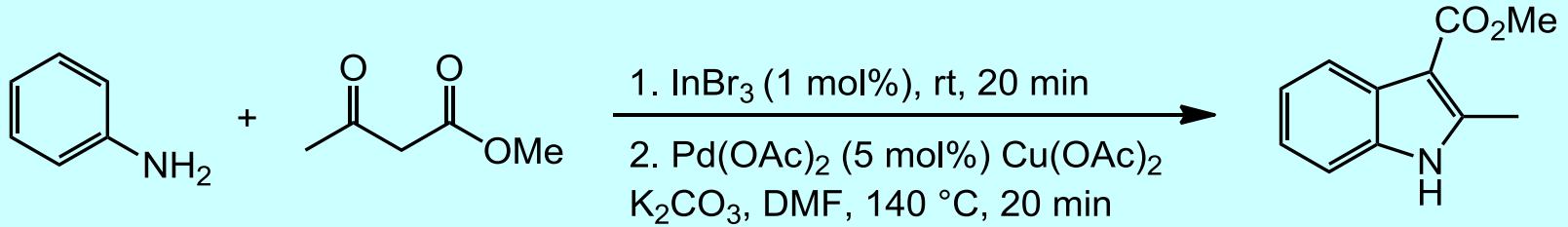
Non-anhydrous:



(10 mmol)

62%

One-pot:



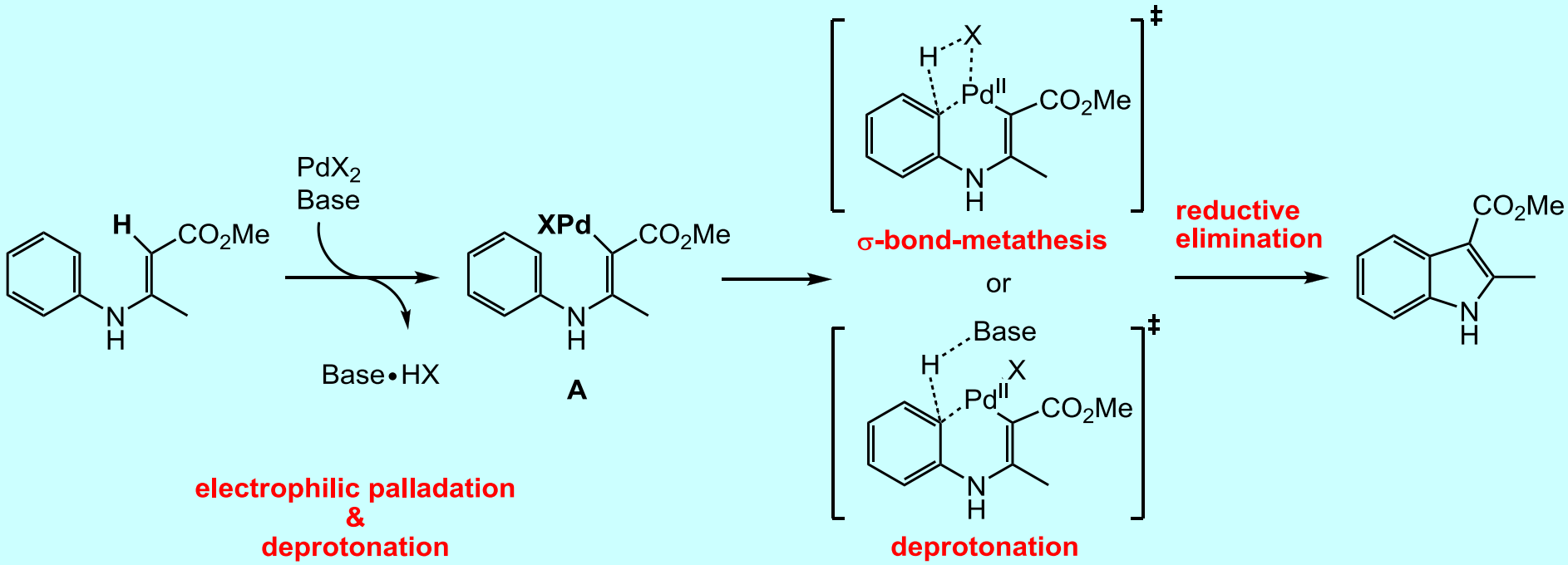
1 L = 30 Euro

1 kg = 30 Euro

72%

1 kg = 60.000 Euro

Mechanistic proposal



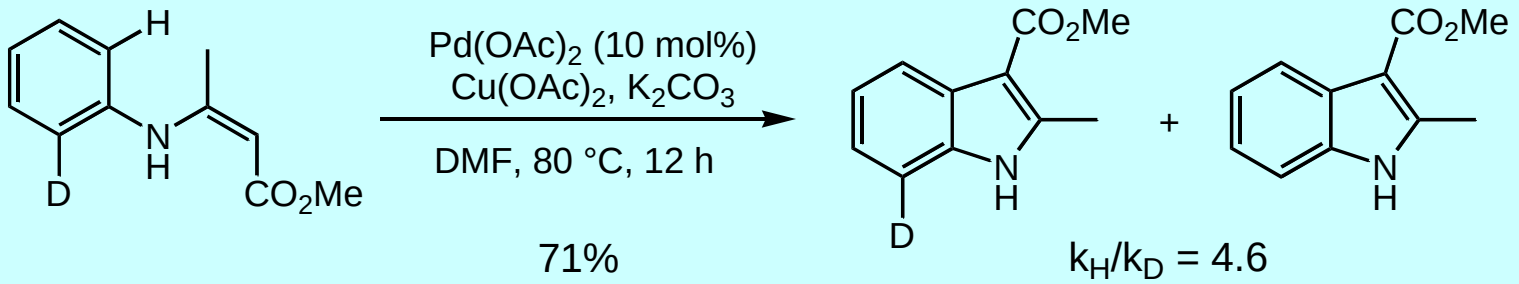
Mechanistic investigation

- Basic reaction conditions do not favor the formation of an electrophilic Pd species

- Only small additive effect with donor additives like DMSO or PPh_3.

- Competition experiments give the following order of reactivity: *p*-Cl > *p*-H > *p*-MeO.

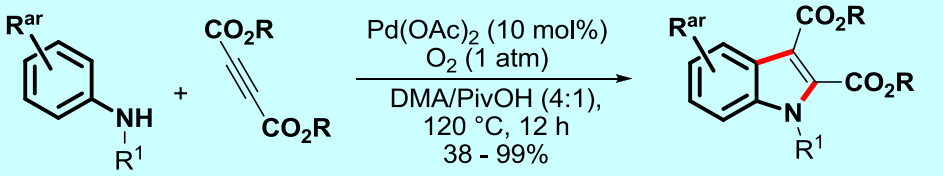
- Intramolecular kinetic isotope effect:



Würtz, Rakshit, Neumann, Dröge, Glorius, *Angew. Chem. Int. Ed.* **2008**, *47*, 7230; hot paper.

Follow up: related work

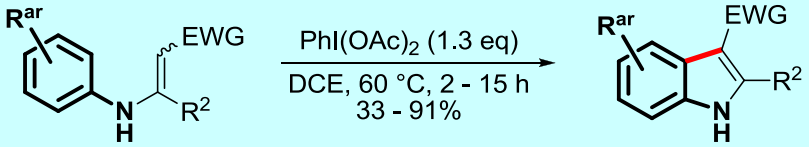
Palladium-catalyzed oxidative coupling of anilines with alkynes:



R^1 = H, alkyl
R = Me, Et, ^{i}Pr
R^{ar} = Me, ^{i}Pr, ^{c}Hex, OMe
OCF_3, CO_2Et, F, Cl, OH

Jiao *et al.*,
Angew. Chem. Int. Ed. **2009**, *48*, 4572.

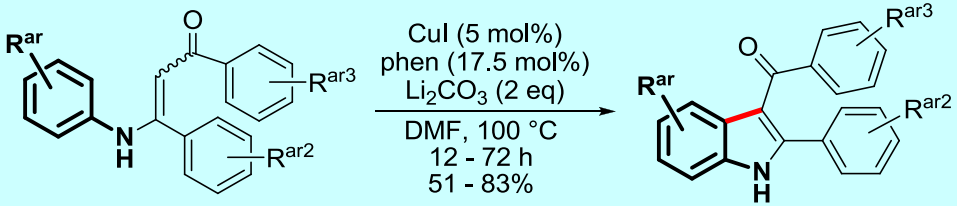
Oxidative cyclization of enaminones mediated by hypervalent iodine reagents:



EWG = CN, NO_2, CO_2Me, C(O)Ph
R^2 = aryl, Et, ^{i}Pr, ^{t}Bu, Bn, CO_2Et
R^{ar} = Me, Br, OMe, F

Zhao *et al.*,
Org. Lett. **2009**, *11*, 2417.

Copper-catalyzed oxidative cyclization of bis-aryl-substituted enaminones :

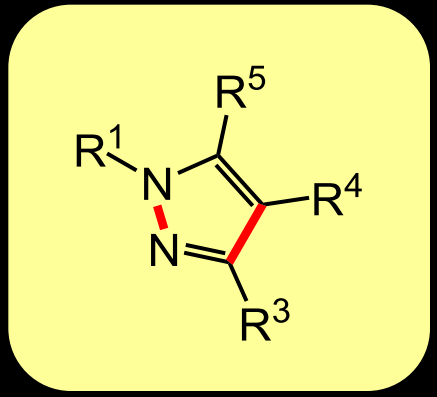


R^{ar} = Me, OMe, F, Cl, Br, I, CO_2Et, acetal, Ph
R^{ar2} = Me, OMe, CN, CO_2Me, C(O)Me
R^{ar3} = Me, OMe, CF_3, Cl, Br, CN

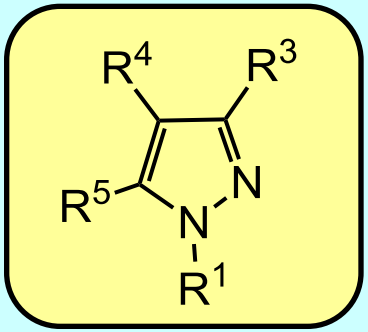
Cacchi *et al.*,
Angew. Chem. Int. Ed. **2009**, *48*, 8078.

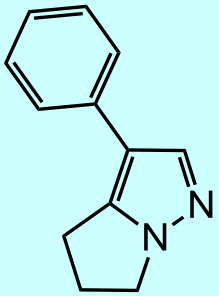
See also: Liang, *Chem. Commun.* **2010**, *46*, 2823 (Fe catalyzed).

… and finally: a new synthesis of pyrazoles

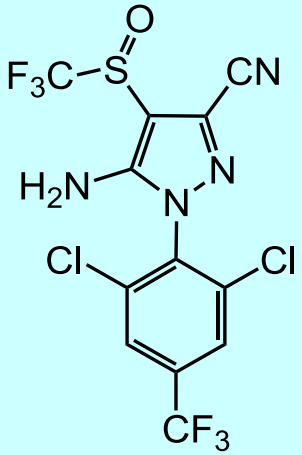


Pyrazoles

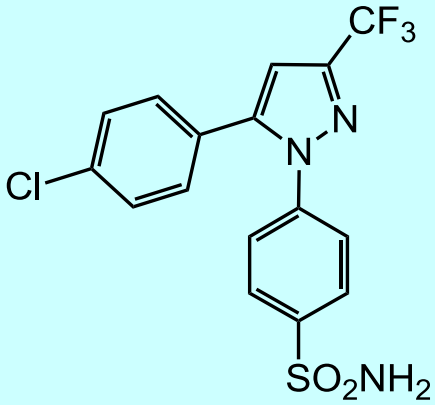




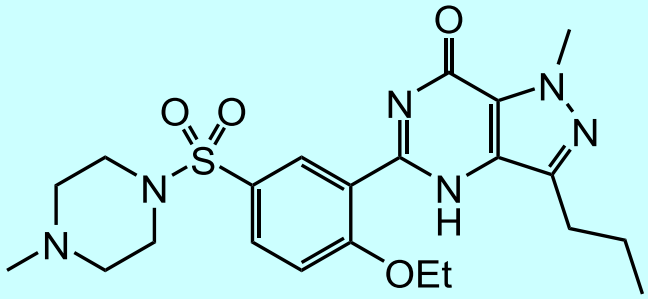
Withasomine
(an alkaloid)



Fipronil
(an insecticide)



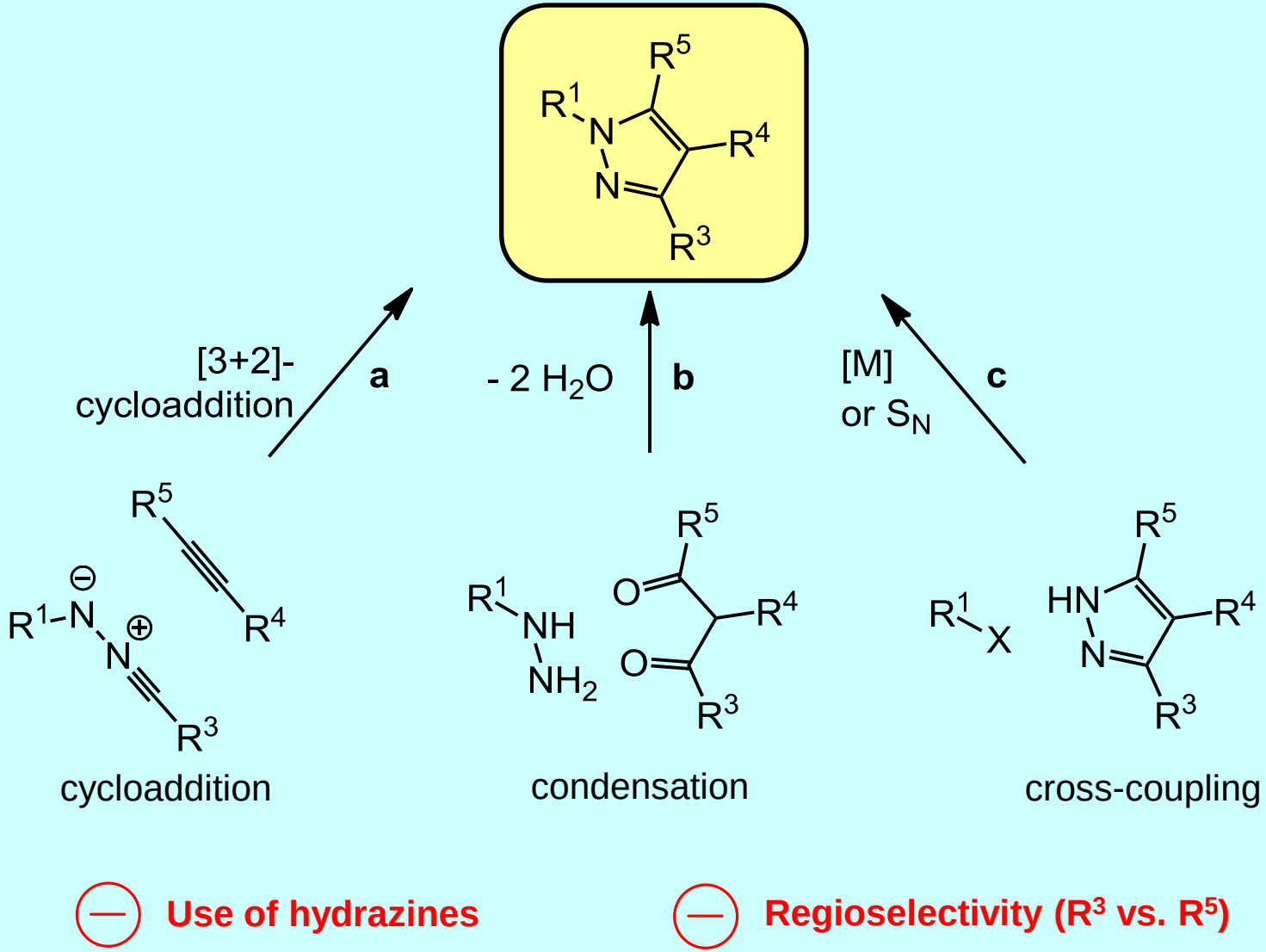
Celecoxib
(a COX 2 inhibitor)



Viagra (Sildenafil)
(treatment of erectile dysfunction)

Comprehensive review: Yet in Comprehensive Heterocyclic Chemistry III, Vol. 4, Elsevier, **2008**, 1.

Pyrazoles: most common synthetic routes

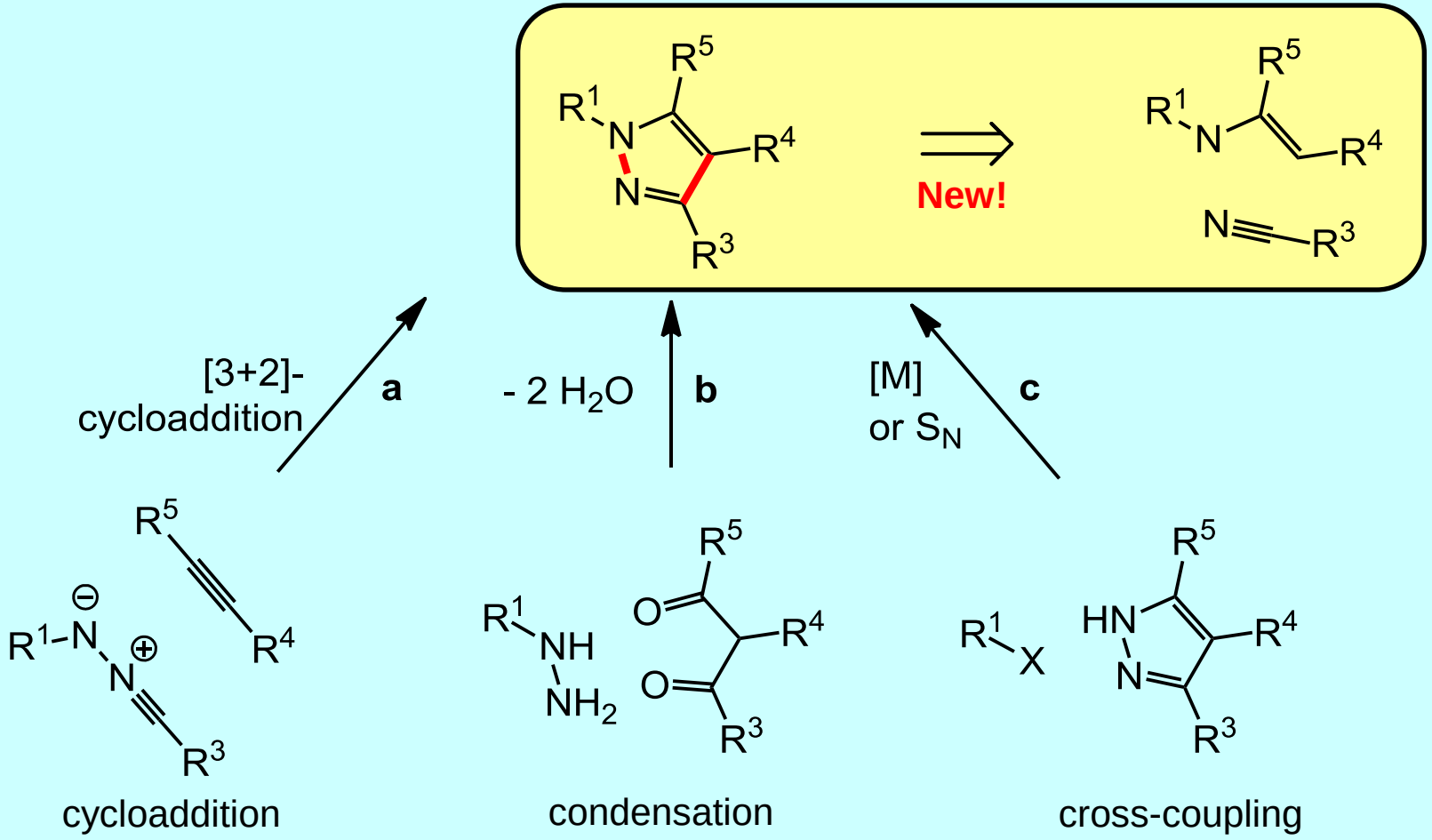


⊖ **Use of hydrazines**

⊖ **Regioselectivity (R^3 vs. R^5)**

Comprehensive review: Yet in Comprehensive Heterocyclic Chemistry III, Vol. 4, Elsevier, **2008**, 1.

Pyrazoles: most common synthetic routes



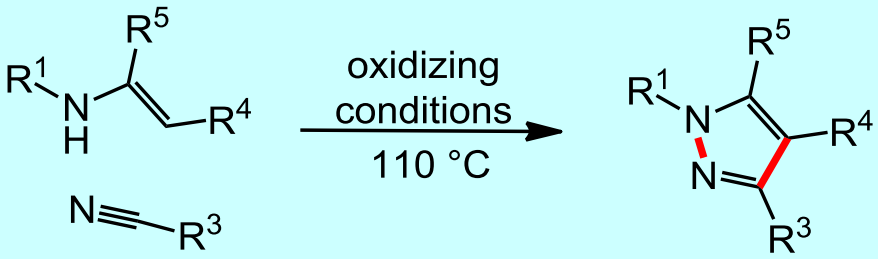
⊖ **Use of hydrazines**

⊖ **Regioselectivity (R^3 vs. R^5)**

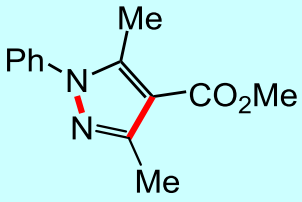
Comprehensive review: Yet in Comprehensive Heterocyclic Chemistry III, Vol. 4, Elsevier, **2008**, 1.

Broad scope

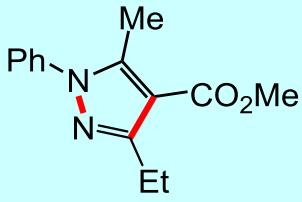
readily available starting materials



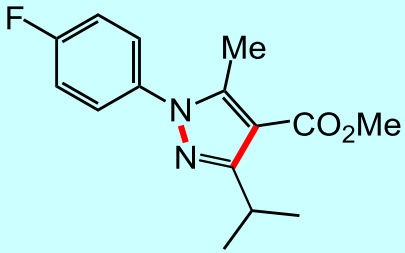
C-C / N-N – bond formation



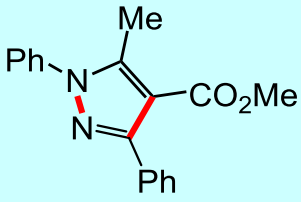
80%



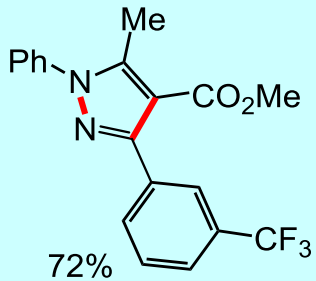
77%



71%



76%

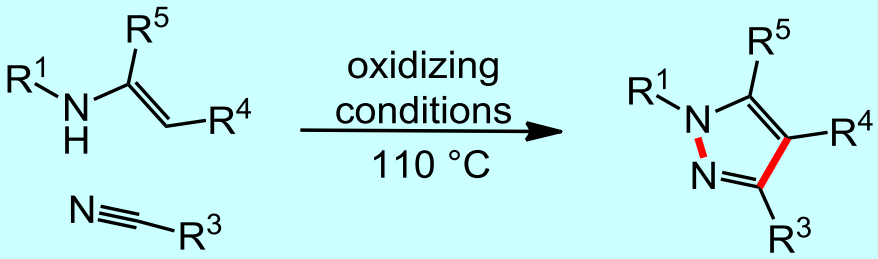


72%

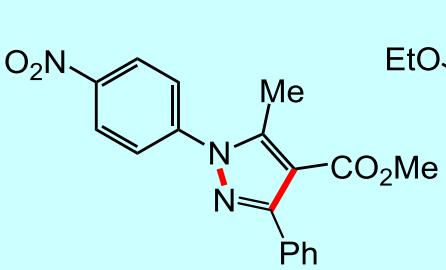
Neumann, Suri, Glorius, *Angew. Chem. Int. Ed.* **2010**, *49*, 7790.

Broad scope

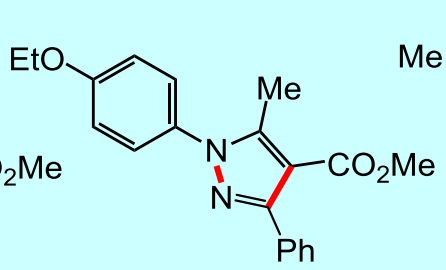
readily available starting materials



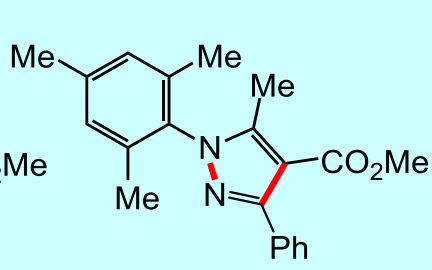
C-C / N-N – bond formation



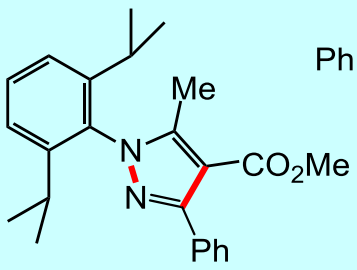
75%



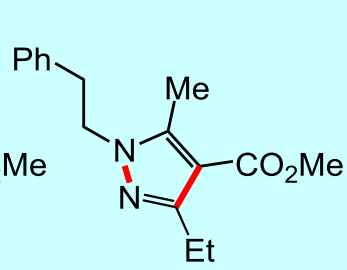
87%



83%



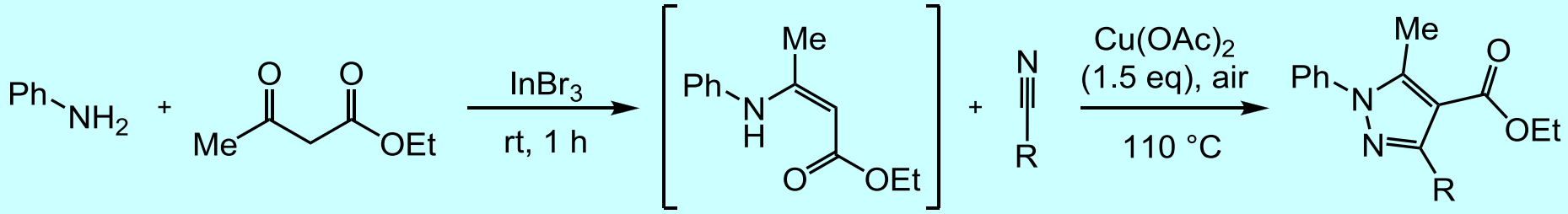
35%



58%

Neumann, Suri, Glorius, *Angew. Chem. Int. Ed.* **2010**, *49*, 7790.

Convenient and cheap: one-pot procedure



5.0 mmol 5.0 mmol

R = Me: 78%
R = Ph: 73%

Neumann, Suri, Glorius, *Angew. Chem. Int. Ed.* **2010**, *49*, 7790.

Glorius group


Dr. Biju T. Akkattu


Bernhard Beiring


Dr. Tatiana Besset


Dr. Xavier Bugaut


Thomas Dröge


Christoph Grohmann


Dr. Holger Frank


Laura Hoffmeister


Dr. T. Jousseaume


Dr. Ranganath Kalluri


Nadine Kuhl


Fan Liu


Claudia Lohre


Svenja Röwer


Corinna Nimphius


Andreas Notzon


Dr. Nuria Ortega


Mohan Padmanaban


Dr. Frederic Patureau


Marius Pawelczyk


Karin Gottschalk


Isabel Piel


Christian Richter


Mamta Suri


Slawek Urban


Jens Willwacher


Nathalie Wurz


Cornelia Weitkamp

Group

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Xavier Bugaut,
Thomas Dröge,
Christoph Grohmann,
Laura Hoffmeister,
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