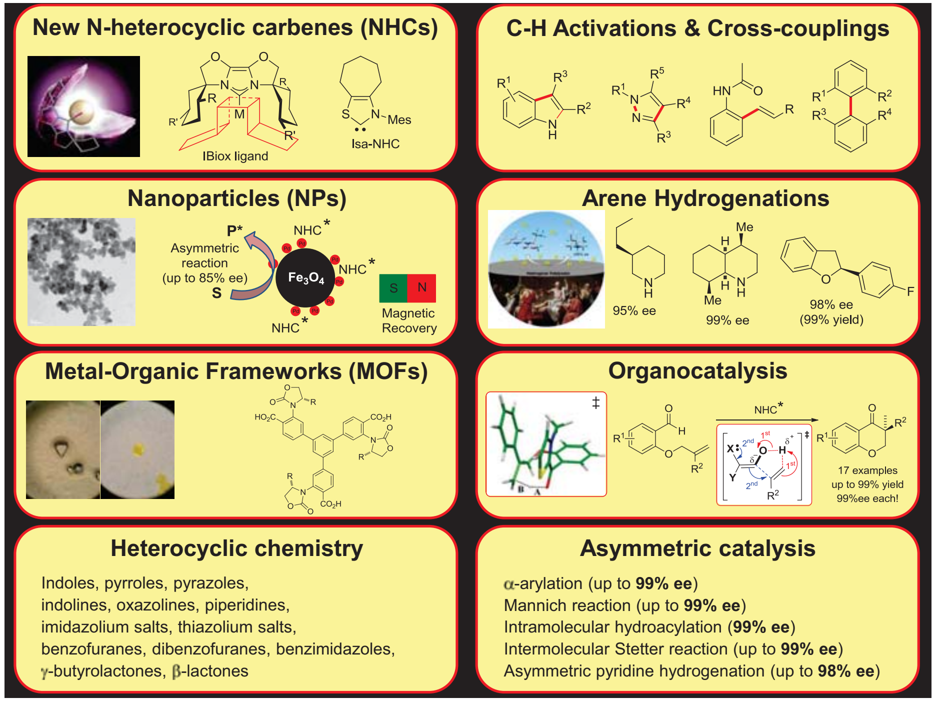


Utilizing a Ubiquitous (Non-)Functional Group –
C-H Bond Activation
for Increased Efficiency in Organic Synthesis

C–H ⟶ [C–M] ⟶ C–Y

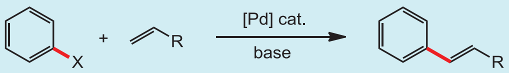
Dehydrogenative (oxidative) Heck coupling

A dehydrogenative Mizoroki-Heck reaction

The traditional pre-activation approach:

Richard F. Heck

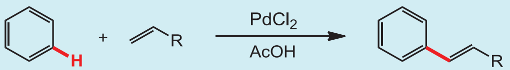
1971



Nobel 2010

The direct cross-coupling: no pre-activation:

Ichiro Moritani and Yuzo Fujiwara 1967

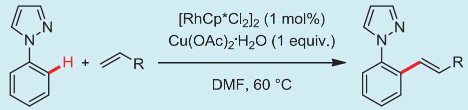


Catalytic version: 1969

"Forgotten" for more than 30 years!

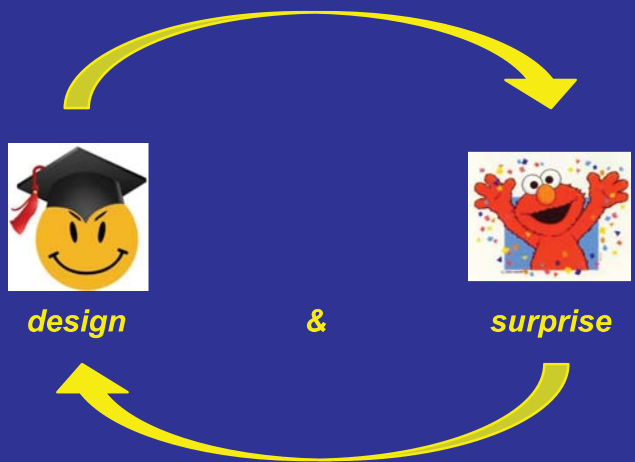
Fujiwara et al. *Science* **2000**, *287*, 1992.

The dehydrogenative Heck reaction: use of directing groups

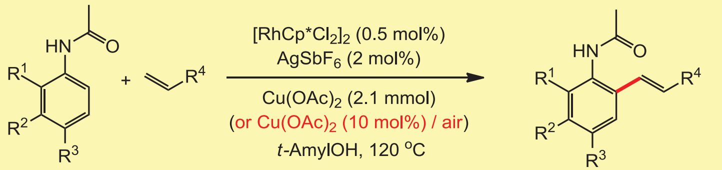


Satoh, Miura et al. *JOC* **2009**, *74*, 7094.

Stories on ...



Dehydrogenative Heck-type reaction: versatile directing group



high regio and *trans* selectivity

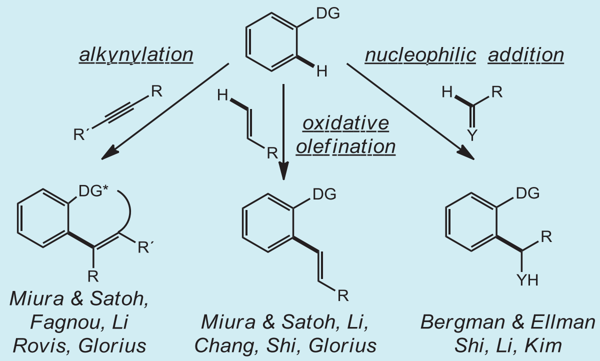
17 examples, R^4 = Ar, CO_2Bu, H

possible problem: overreaction

Patureau, Glorius, *JACS* **2010**, *132*, 9982.

State of the art in Rh(III)Cp*-catalyzed C-H activation 2011

Known Rh(III)-catalyzed C-H activation:

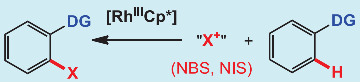


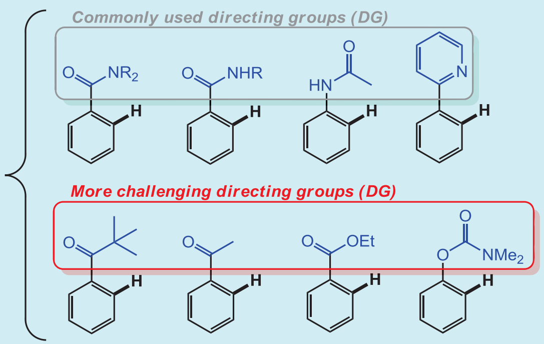
"Towards Mild Metal-Catalyzed C-H Bond Activation"

MILD!

Review: Wencel-Delord, Dröge, Liu, Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740-4761

[Rh(III)Cp*]-catalyzed *ortho*-bromination and iodination of arenes



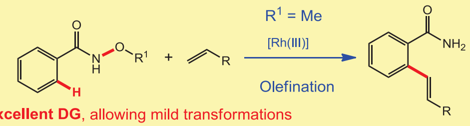


+ *ortho*-bromination and iodination
+ convenient X^+ sources
+ highly general method
+ valuable products
+ compatible with various directing groups

mild reaction: broad scope, high yields!

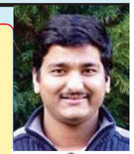
Schröder,‡ Wencel-Delord,‡ Glorius, *JACS* **2012**, *just accepted.* ‡These authors contributed equally.

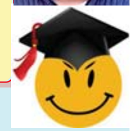
Internal oxidant allows mild and (mono)selective olefination

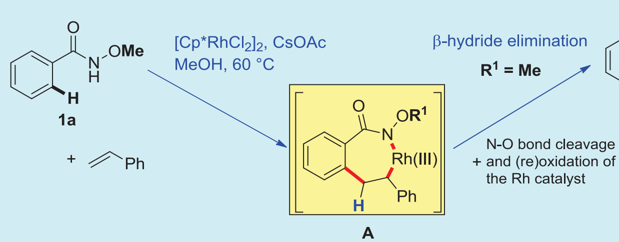


+ **excellent DG**, allowing mild transformations
+ **internal oxidant**, thus no external oxidant required
+ **highly selective**, broad scope, high-yielding
+ **reactivity switchable** by choice of R^1 group

34 examples



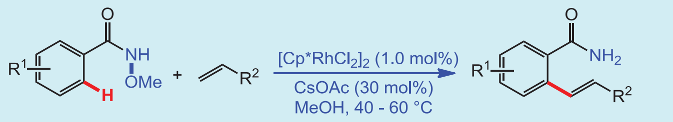




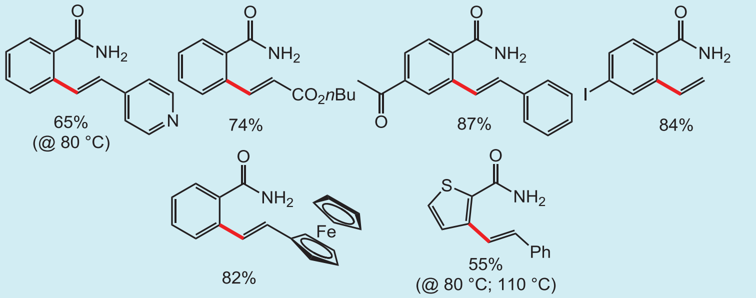
inherently no overreaction!

Glorius et al. *J. Am. Chem. Soc.* **2011**, *133*, 2350. Computational elucidation by Xia et al.: *JOC* **2012**, *77*, 3017.
See also: Fagnou et al. *J. Am. Chem. Soc.* **2011**, 133, 6449.

Internal oxidant allows **mild** and (mono)selective olefination



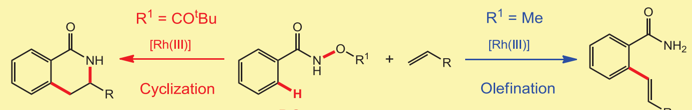
Selected products:



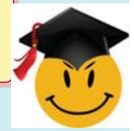
very broad scope!

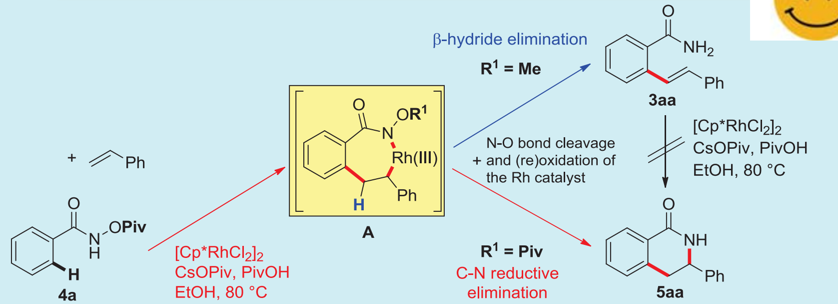
S. Rakshit, C. Grohmann, T. Besset, F. Glorius, *J. Am. Chem. Soc.* **2011**, *133*, 2350.

Internal oxidant allows **mild** and (mono)selective olefination



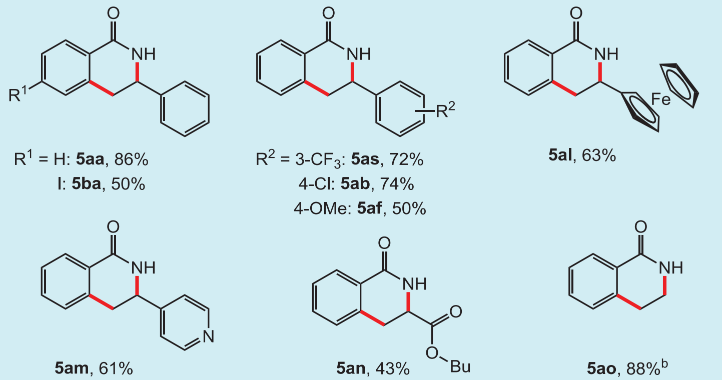
+ **excellent DG**, allowing mild transformations
+ **internal oxidant**, thus no external oxidant required
+ **highly selective**, broad scope, high-yielding
+ **reactivity switchable** by choice of R^1 group



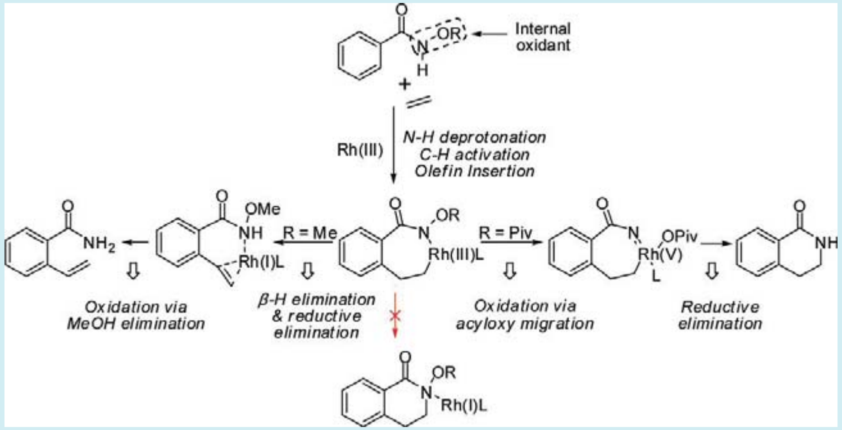


Glorius et al. *J. Am. Chem. Soc.* **2011**, *133*, 2350. Computational elucidation by Xia et al.: *JOC* **2012**, *77*, 3017.
See also: Fagnou et al. *J. Am. Chem. Soc.* **2011**, 133, 6449.

Internal oxidant allows new **tetrahydroisoquinolinone** synthesis

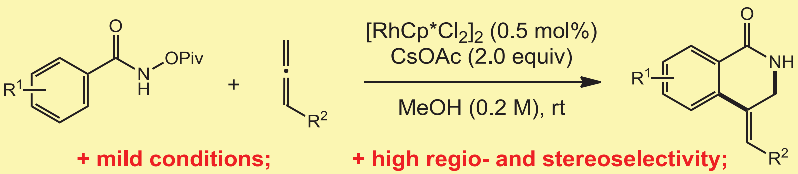


Proposed mode of action of internal N-O oxidant



Computational elucidation by Xia et al.: *JOC* **2012**, *77*, 3017.

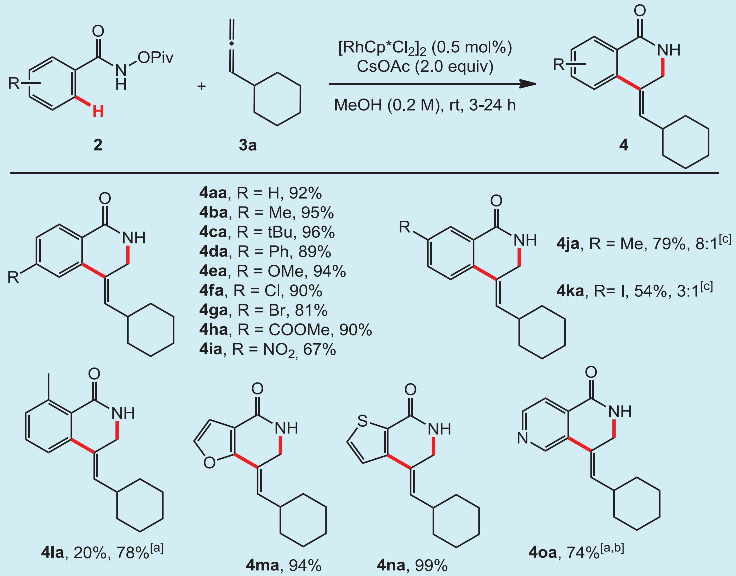
Mild Rh(III)-Catalyzed C-H Activation and Intermolecular Annulation with Allenes



+ mild conditions;
+ low catalyst loading;
+ internal oxidant;
+ high regio- and stereoselectivity;
+ high yield;
+ excellent substrate scope.

Honggen Wang, Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, EV.

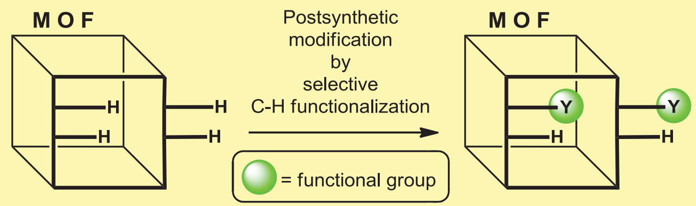
Mild Rh(III)-Catalyzed C-H Activation and Intermolecular Annulation with Allenes



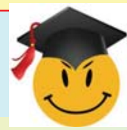
Mild conditions allow …the C-H functionalization of a MOF

Postsynthetic modification of MOFs

MOF = Metal-organic framework
(coordination polymers)
Porous, highly ordered, 3D, tunable
Used for gas storage, separation, catalysis

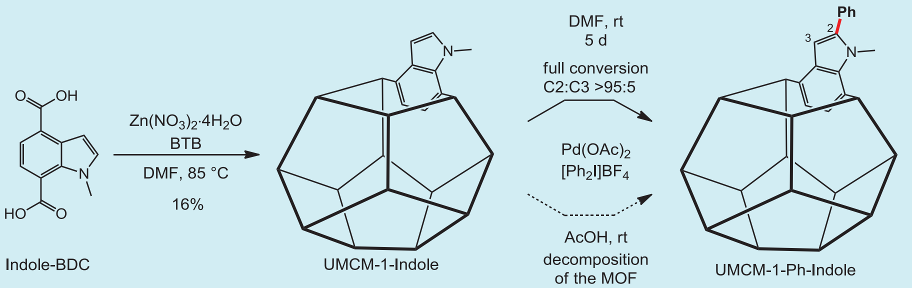


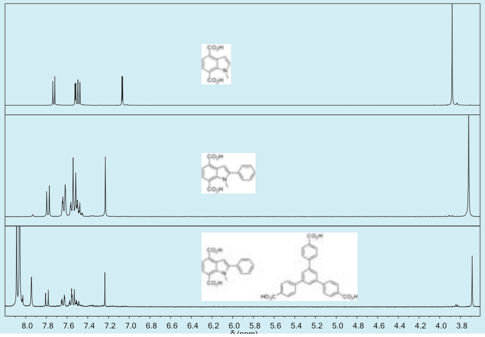
sensitive materials

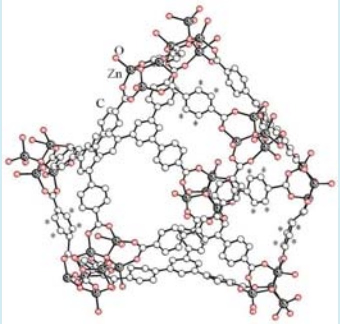


Dröge, Notzon, Fröhlich, Glorius, *Chem. Eur. J.* **2011**, *17*, 11974.
Review on postsynthetic modification of MOFs: Cohen, *Chem. Soc. Rev.* **2010**, *40*, 498.
Review on mild C-H activations: Wencel-Delord, Dröge, Liu, Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740.

Postsynthetic modification of MOFs





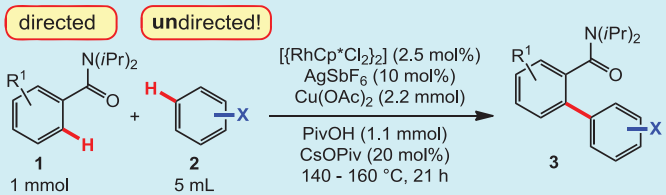


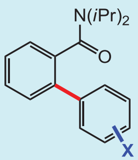
„First“ Rh(III)Cp*-catalyzed undirected C-H activation

UNDIRECTED!

Review: Kuhl, Hopkinson, Wencel-Delord, Glorius, *Angew. Chem. Int. Ed.* **2012**, accepted for publication.

„First“ Rh(III)Cp*-catalyzed undirected C-H activation

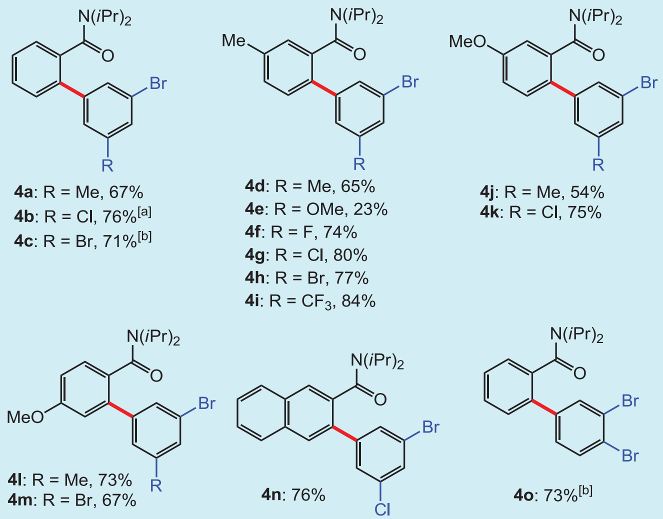




3a (X = F): 0%[a]
3b (X = Cl): 76%,[a] *m/p* = 2.6:1
3c (X = Br): 81%,[b] *m/p* = 2.8:1
3d (X = I): 66%,[a] *m/p* = 3.1:1
3e (X = Me): 16%,[b] *m/p* = 1.5:1

Wencel-Delord, Nimphius, Patureau, Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 2247.

„First“ Rh(III)Cp*-catalyzed undirected C-H activation



4a: R = Me, 67%
4b: R = Cl, 76%[a]
4c: R = Br, 71%[b]

4d: R = Me, 65%
4e: R = OMe, 23%
4f: R = F, 74%
4g: R = Cl, 80%
4h: R = Br, 77%
4i: R = CF_3, 84%

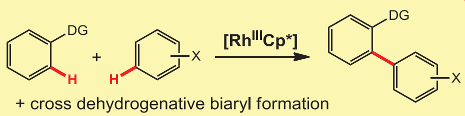
4j: R = Me, 54%
4k: R = Cl, 75%

4l: R = Me, 73%
4m: R = Br, 67%

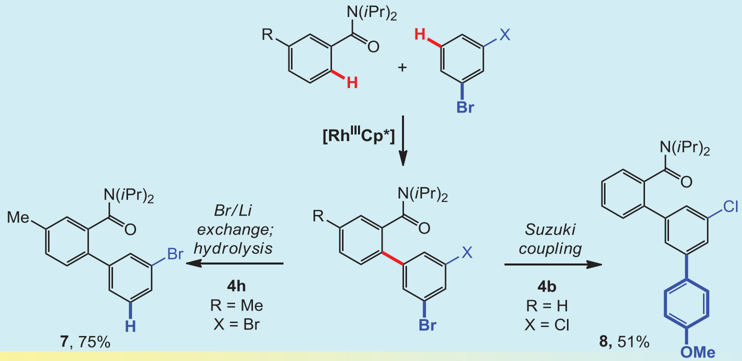
4n: 76%

4o: 73%[b]

„First“ Rh(III)Cp*-catalyzed undirected C-H activation

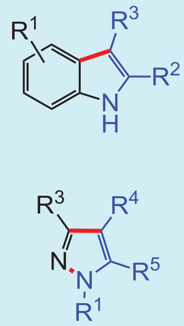


+ cross dehydrogenative biaryl formation
+ versatile (>30 examples) and efficient
+ high selectivities for 1,3-disubstituted halo arenes



Wencel-Delord, Nimphius, Patureau, Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 2247.
See also: Wencel-Delord, Nimphius, Patureau, Glorius, *Chem. Asian J.* **2012**, early view. Patureau, Nimphius, Glorius, *Org. Lett.* **2011**, *13*, 6346.

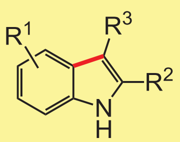
“Heterocycles by C-H activation”



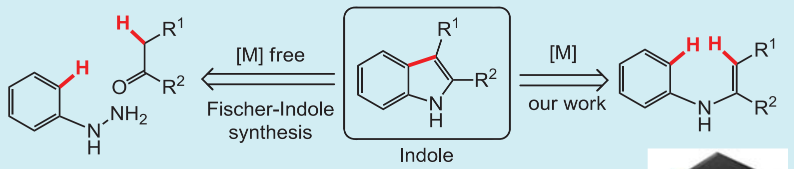
Heterocycles!

From anilines to indoles:

A cross-dehydrogenative coupling (cdc)



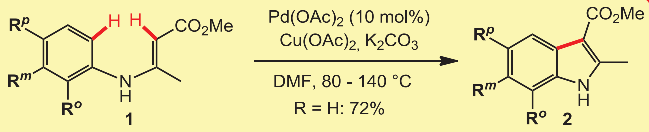
Fischer-Indole as role model for a CDC: our first C-H activation



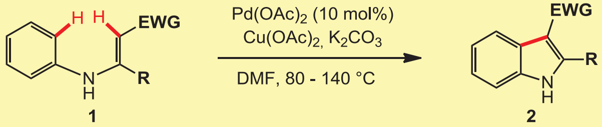
Two cross-dehydrogenative couplings (CDC)

Würtz, Rakshit, Neumann, Dröge, Glorius, *Angew. Chem. Int. Ed.* **2008**, *47*, 7230 (hot paper).
Neumann, Rakshit, Dröge, Glorius, *Chem. Eur. J.* **2011**, *17*, 7298.
For general reviews on the synthesis of indoles, see:
Cacchi, Fabrizi, *Chem. Rev.* **2005**, *105*, 2873; Gribble, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 1045.

Broad substrate scope, but EWG required on enamine



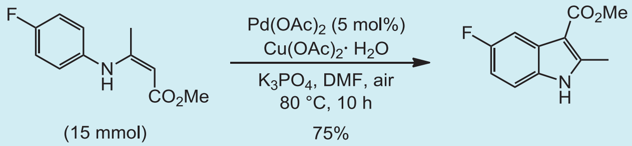
for example, **R** = Me, OMe, F, Cl, Ac, CO_2Et, $CONEt_2$, CN, CF_3, NO_2...



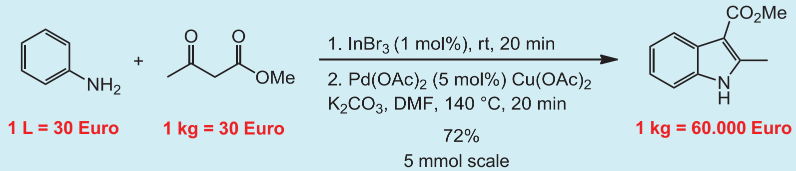
for example, **R** = Me, iPr, OEt, CF_3, Ph, thiophenyl...
limitation: EWG required; **EWG** = CO_2Me, CO_2Et, CO_2tBu, CN

Non-anhydrous & one-pot

Non-anhydrous:

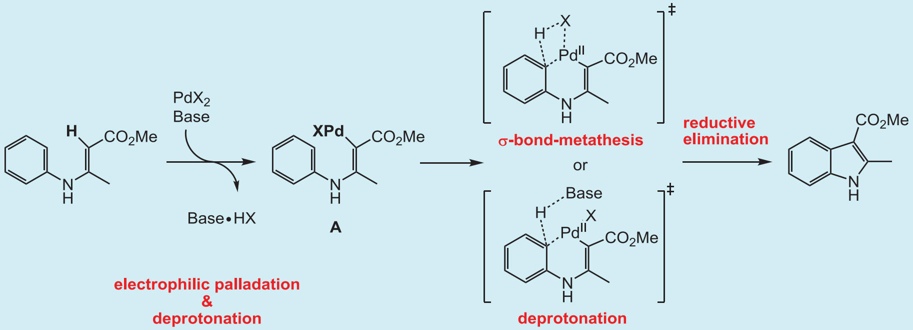


One-pot:

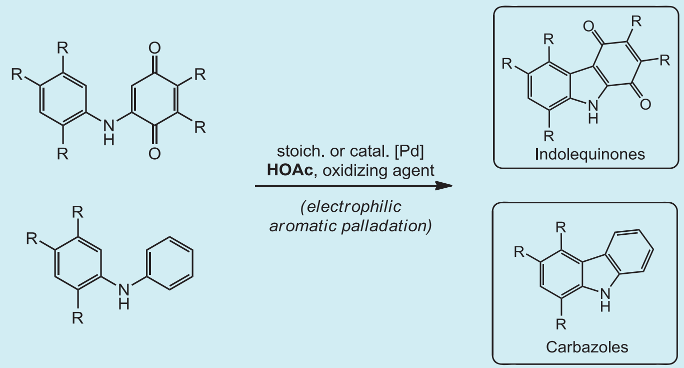


Würtz, Rakshit, Neumann, Dröge, Glorius, *Angew. Chem. Int. Ed.* **2008**, *47*, 7230 (hot paper).
Neumann, Rakshit, Dröge, Glorius, *Chem. Eur. J.* **2011**, *17*, 7298.

Mechanistic proposal



Synthesis of indoles by electrophilic aromatic palladation: Åkermark, Knölker

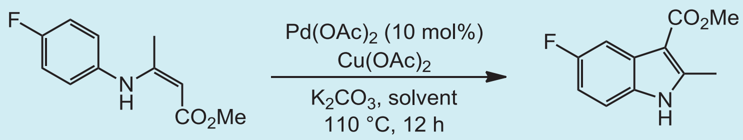


- LIMITED scope
- Often low yields
- Often stoichiometric amounts of [Pd]

For lead references on the displayed oxidative coupling, see:
a) Åkermark, *Chem. Eur. J.* **1999**, *5*, 2413; b) Knölker, *Curr. Org. Chem.* **2005**, *9*, 1601; c) Åkermark, *J. Org. Chem.* **1975**, *40*, 1365; d) Knölker, *Org. Biomol. Chem.* **2006**, *4*, 3215; e) Fujii, Ohno, *Chem. Commun.* **2007**, 4516.

Attempted optimization: solvent screen!

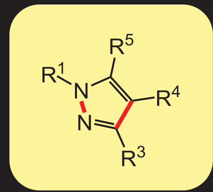
An optimization?



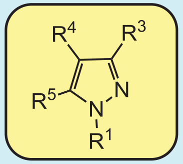
CH_3CN as solvent:
- hardly any indole
- but new product forms

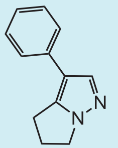
Dr. Julia J. Neumann

…a new approach to pyrazoles

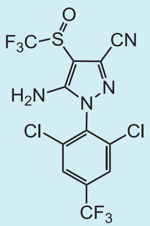


Pyrazoles

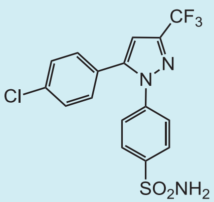




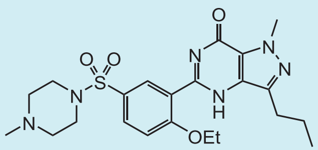
Withasomine
(an alkaloid)



Fipronil
(an insecticide)



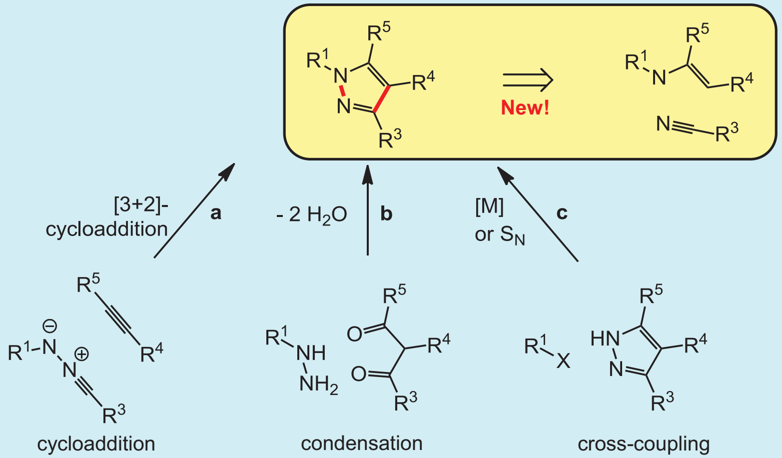
Celecoxib
(a COX 2 inhibitor)



Viagra (Sildenafil)
(treatment of erectile dysfunction)

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

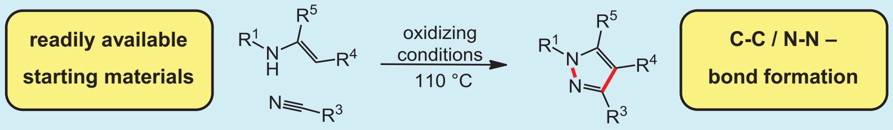
Pyrazoles: most common synthetic routes

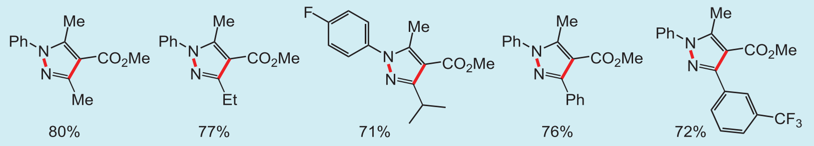


⊖ **Use of hydrazines** ⊖ **Regioselectivity (R^3 vs. R^5)**

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

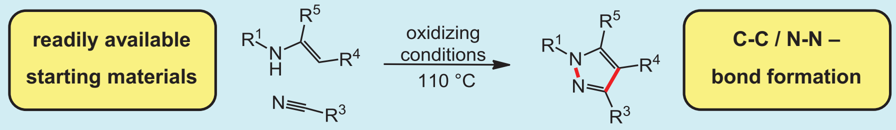
Broad scope

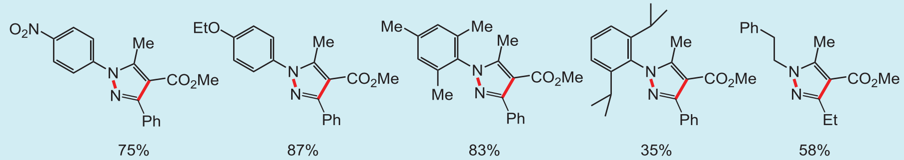




Neumann, Suri, Glorius, *Angew. Chem. Int. Ed.* **2010**, *49*, 7790.

Broad scope

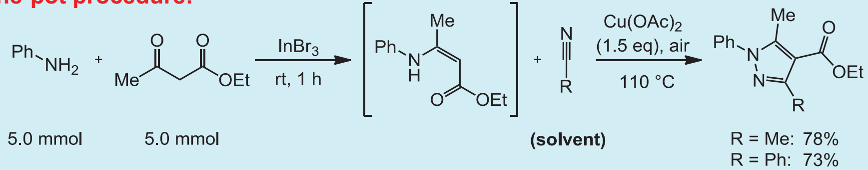




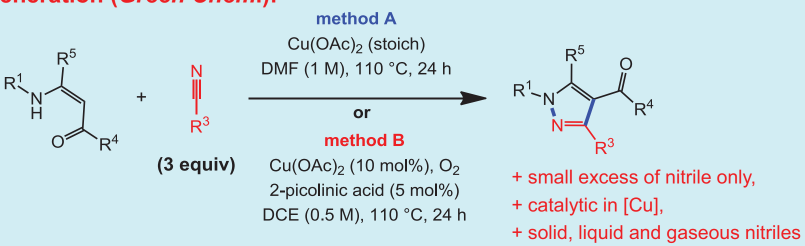
Neumann, Suri, Glorius, *Angew. Chem. Int. Ed.* **2010**, *49*, 7790.

Convenient and cheap: one-pot procedure + second generation

One-pot procedure:



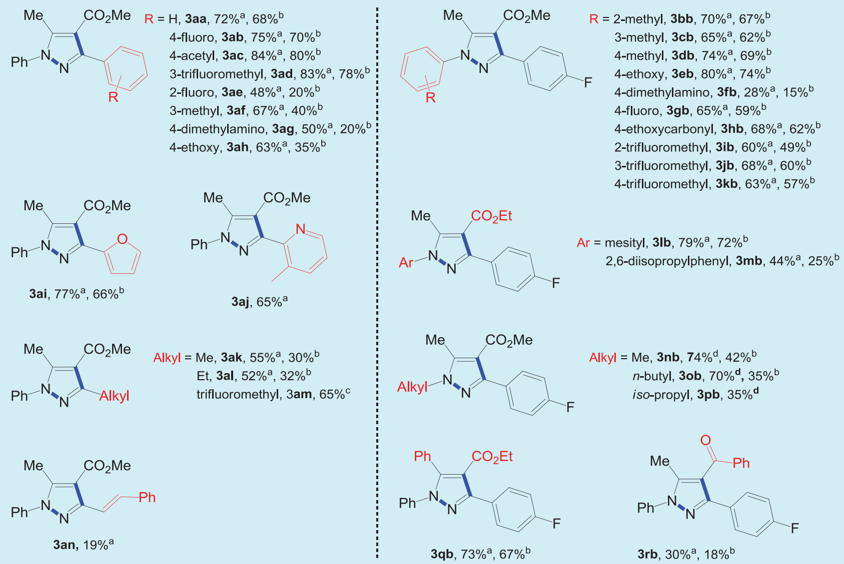
Second generation (*Green Chem.*):



+ small excess of nitrile only,
+ catalytic in [Cu],
+ solid, liquid and gaseous nitriles

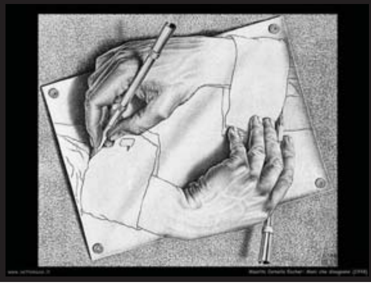
Neumann, Suri, Glorius, *Angew. Chem. Int. Ed.* **2010**, *49*, 7790.
Neumann, Suri, Glorius, PCT/EP2011/054484.
Suri, Jousseaume, Neumann, Glorius, *Green Chem.* **2012**, DOI: 10.1039/C2GC35476D

Second generation conditions: scope

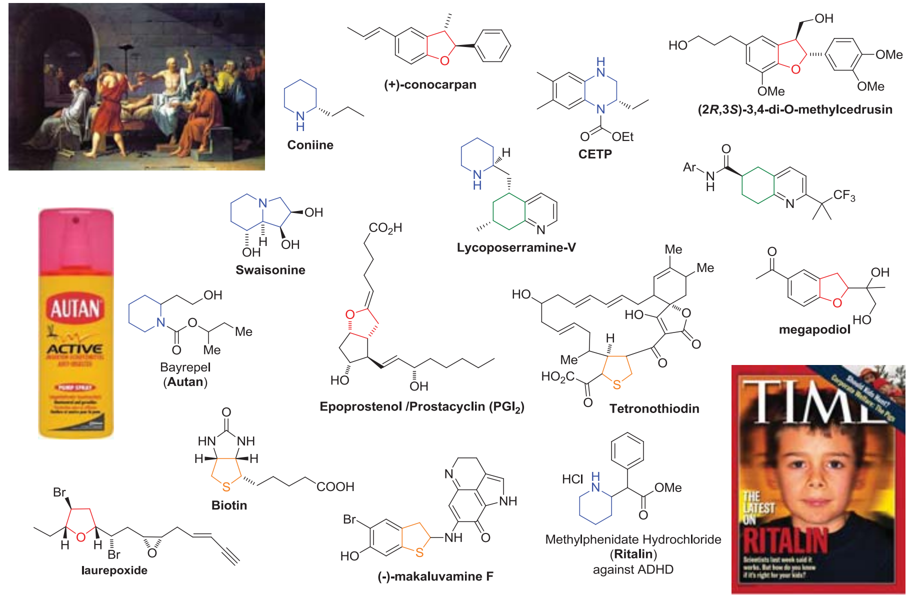


Suri, Jousseaume, Neumann, Glorius, *Green Chem.* **2012**, DOI: 10.1039/C2GC35476D

Ru-NHC-catalyzed asymmetric arene hydrogenation

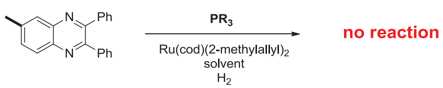


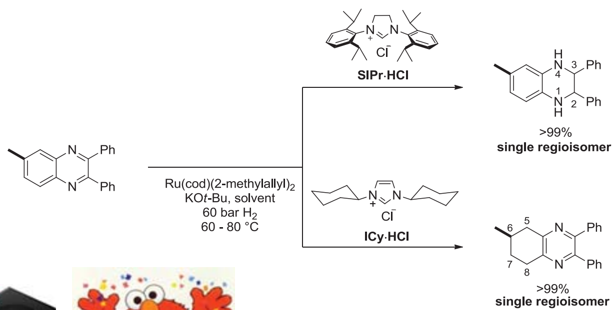
Heterocycles, heterocycles, heterocycles



Hydrogenation of Quinoxalines

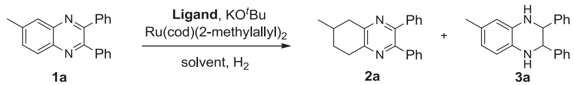
Switching from **Phosphines** to ***N*-Heterocyclic Carbenes (NHC)**:



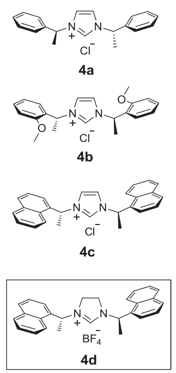


Ligand-controlled switching of regioselectivity!!!

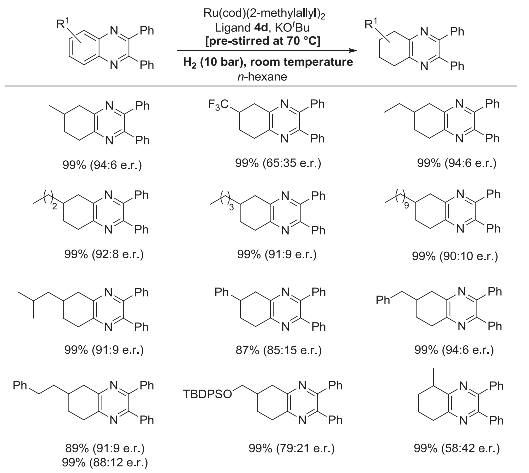
Hydrogenation of Quinolines



Entry	Ligand	Solvent	T [°C]	H_2 [bar]	Yield [%] 2a 3a	e.r.
1	PCy_3	toluene	80	60	0 0	n.d.
2	**SIPr**	**toluene**	**80**	**60**	**<1 99**	**n.d.**
3	**4a**	toluene	80	65	99 <1	38:62
4	**4b**	toluene	80	65	99 <1	64:36
5	**4c**	toluene	80	65	99 <1	83:17
6	**4c**	toluene	40	65	99 <1	84:16
7	**4c**	hexane	40	65	99 <1	85:15
8	**4c**	hexane	30	65	0 0	n.d.
9	**4c**	hexane	40	20	99 <1	88:12
10	**4c**	hexane	40	10	<13 0	n.d.
11[a]	**4c**	hexane	25	10	99 <1	90:10
12[a]	**4d**	**hexane**	**25**	**10**	**99 <1**	**94:6**



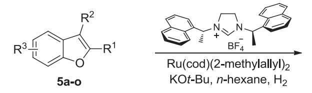
Hydrogenation of Quinolines

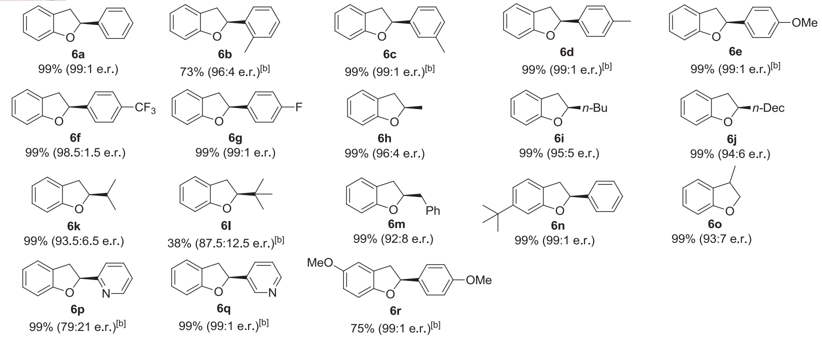


Reaction conditions: [Ru] 0.015 mmol, NHC·HBF$_4$ (0.03 mmol), KO^{t}Bu (0.035 mmol), hexane (1 mL), 70 °C, 16 h. Substrate (0.15 mmol) 10 bar H$_2$, 25 °C, 16 h.

S. Urban, N. Ortega, Glorius, *Angew. Chem.* **2011**, *123*, 3887; *Angew. Chem. Int. Ed.* **2011**, *50*, 3803; also highlighted in *Synfacts* **2011**, *6*, 633.

Hydrogenation of Benzofurans



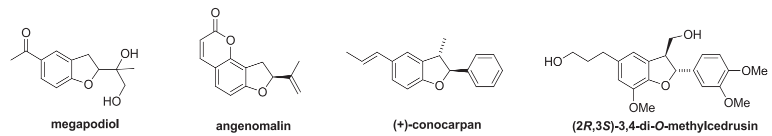


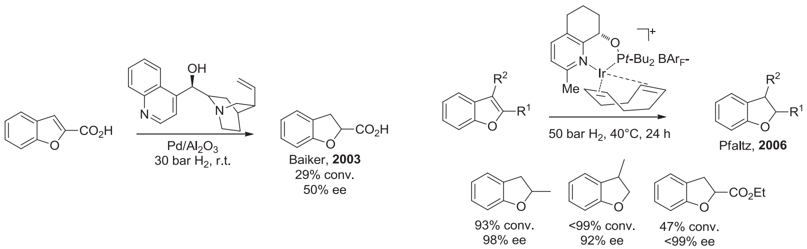
[a] [Ru(cod)(2-methylallyl)$_2$] (0.015 mmol), **4d** (0.03 mmol), KO*t*-Bu (0.045 mmol), *n*-hexane (2 mL) were stirred at 70 °C for 12 h, after which it was added to substrate **5a-q** (0.3 mmol). Hydrogenation was performed at 10 bar H$_2$, 25 °C, 16 h. Isolated yields are given. Enantiomeric ratio was determined by HPLC on a chiral stationary phase. [b] Reaction was performed at 60 bar H$_2$, 40 °C, 16 h.

a) Ortega, Urban, Beiring, Glorius, *Angew. Chem. Int. Ed.* **2012**, *51, 1710.* b) Urban, Ortega, Beiring, Glorius, Method for Catalytic Hydrogenation of Heteroaromatic Compounds, *Patent Application*
c) R. Kuwano et al., *Angew. Chem. Int. Ed.* **2012**, *51*, 4136 (***Catalytic Asymmetric Hydrogenation of Naphthalenes***)!

Hydrogenation of Benzofurans

Benzofurans: Other type of challenging substrates for asymmetric hydrogenation

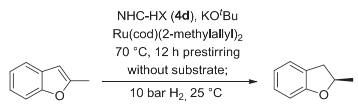


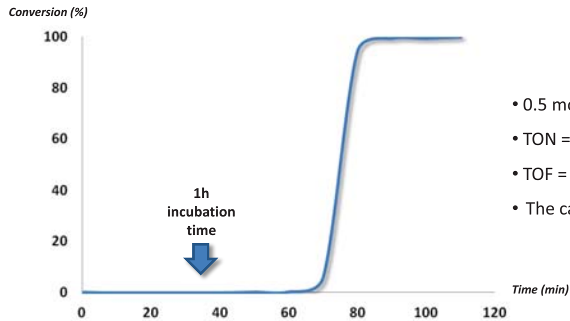


For a review on the synthesis of 2,3-dihydrobenzofurans, see: F. Bertolini, M. Pineschi, *Org. Prep. Proced. Int.* **2009**, *41*, 385.
Baralt, Smith, Hurwitz, Horvatz, R. H. Fish, *J. Am. Chem. Soc.* **1992**, *114*, 5187.
Maris, Huck, Mallat, A. Baiker, *J. Catal.* **2003**, *219*, 52.
Kaiser, Smidt, A. Pfaltz, *Angew. Chem. Int. Ed.* **2006**, *45*, 5194.

Kinetics

Kinetic experiments:

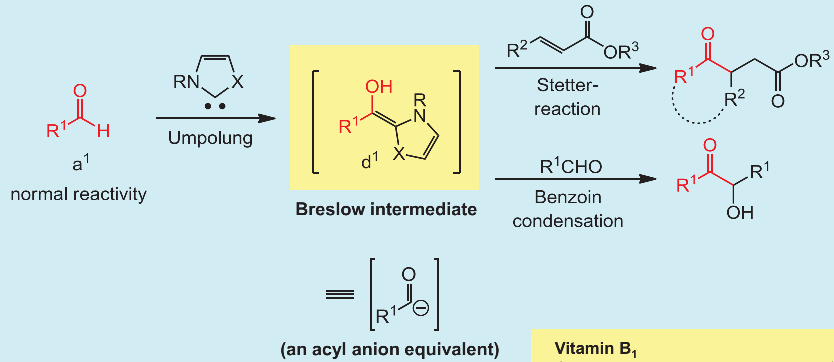




- 0.5 mol% of catalyst loading
- TON = 200
- TOF = 1092 h^{-1}
- The catalysis occurs within 10 minutes!!!

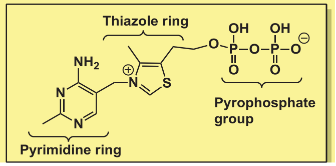
NHC-catalyzed hydroacylations

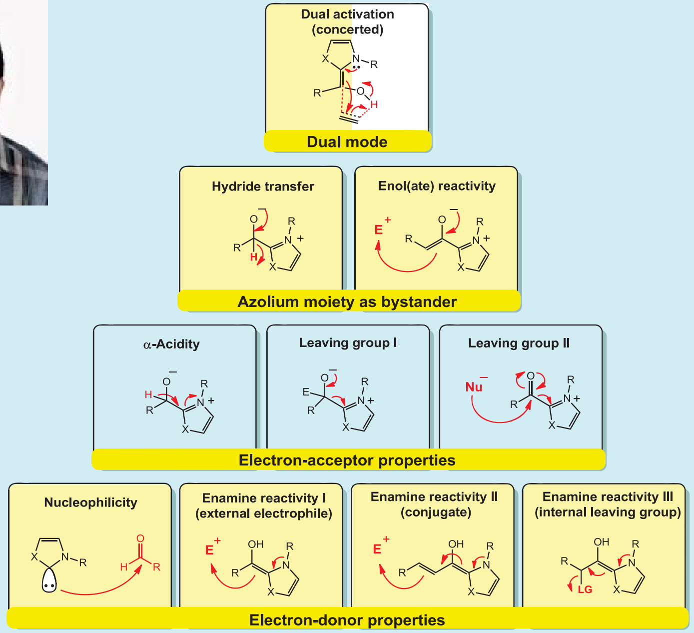
Umpolung organocatalysis



Wöhler, Liebig, *Ann. Pharm.* **1832**, *3*, 249
Ukai, *J. Pharm. Soc. Chem.* **1943**, *63*, 296
Breslow, *JACS* **1958**, *80*, 3719.
Stetter, *ACIE* **1973**, *12*, 81.

Vitamin B_1
Coenzyme Thiamine pyrophosphate (TPP)

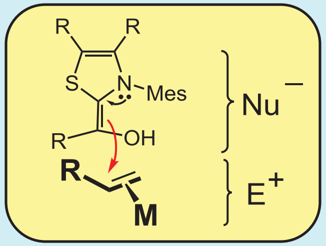


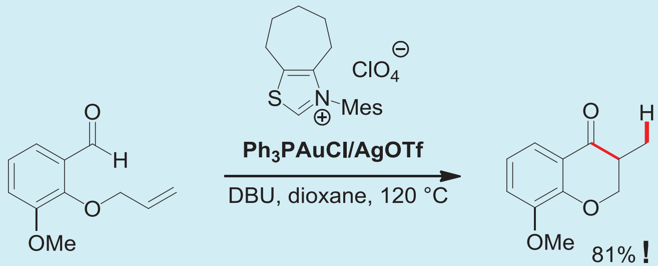


Biju, Kuhl, Glorius, *Acc. Chem. Res.* **2011**, *44*, 1182. Bugaut*, Glorius*, *Chem. Soc. Rev.* **2012**, online.

Hydroacylation of unactivated alkenes: synthesis of chromanones

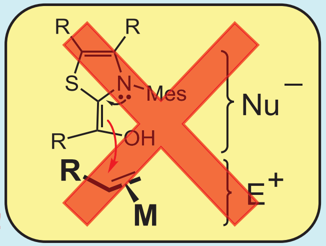
Concept:
(dual catalysis)

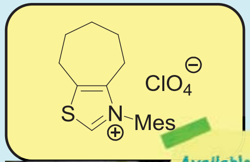




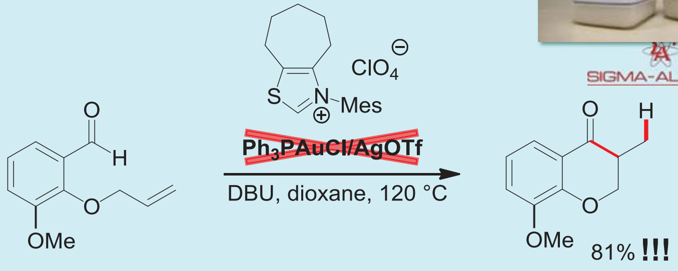
Hydroacylation of unactivated alkenes

Right for the wrong reason!

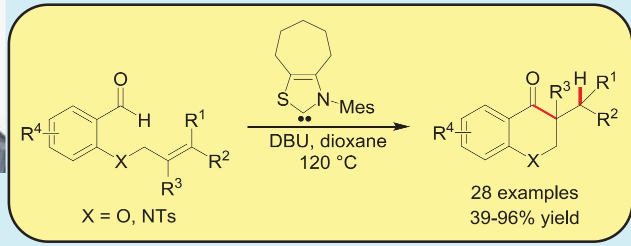


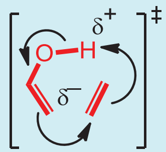


SIGMA-ALDRICH



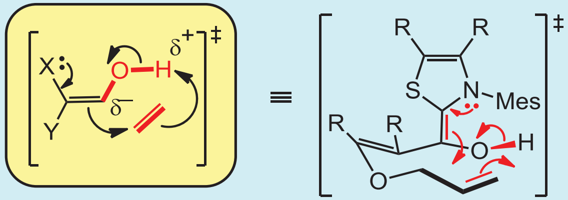
A new, concerted mode of action





Conia-Ene

vs.

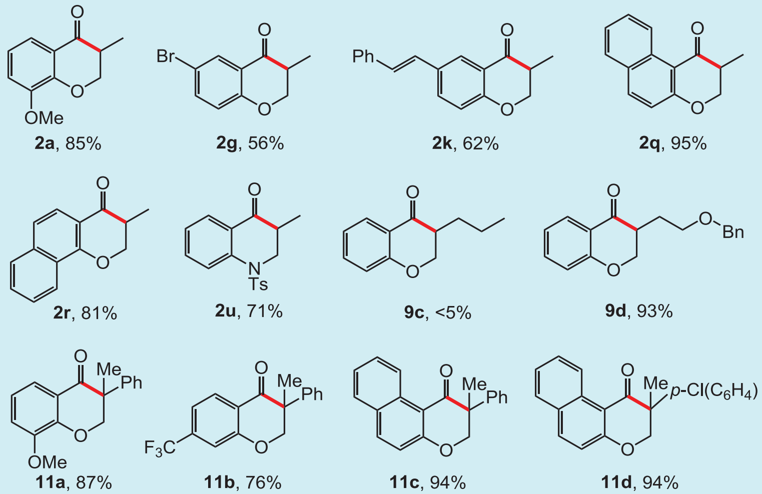


our work

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

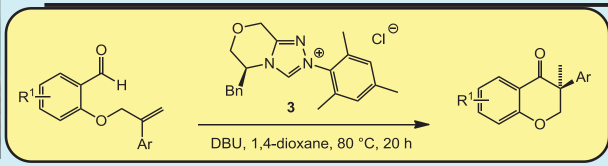
See also: She, *Tetrahedron* **2008**, *64*, 8797.

Hydroacylation of unactivated alkenes: scope



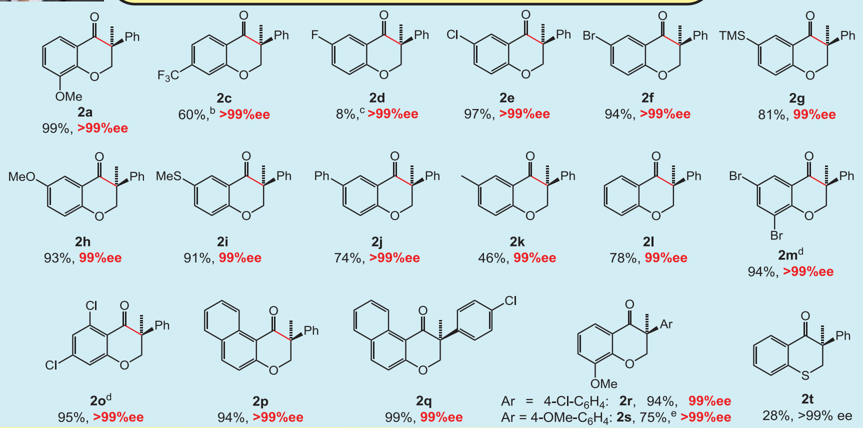
Hirano, Biju, Piel, Glorius, *J. Am. Chem. Soc.* **2009**, 131, 14190.

Highly asymmetric hydroacylation of unactivated alkenes



18 examples

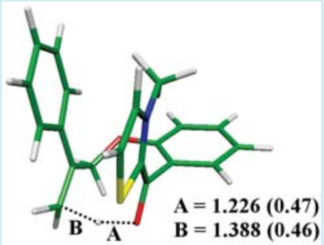
99% ee each !



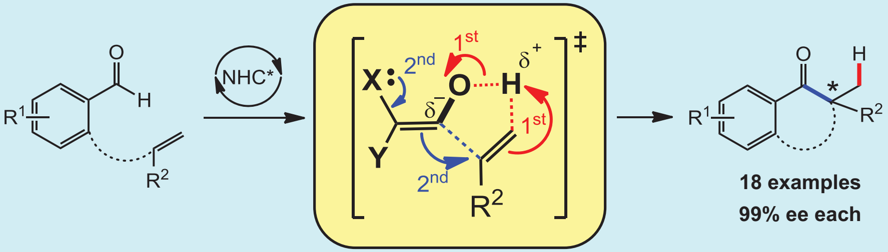
Piel, Steinmetz, Hirano, Fröhlich, Grimme,* Glorius,* *Angew. Chem. Int. Ed.* **2011**, *50*, 4983 (**VIP**).

Mechanistic insight

Proton transfer TS with achiral NHC



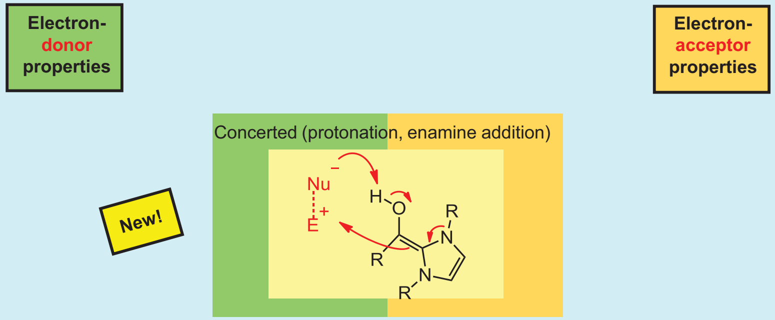
B2PLYP-D/TZVPP/BP86-D/TZVP level



18 examples
99% ee each

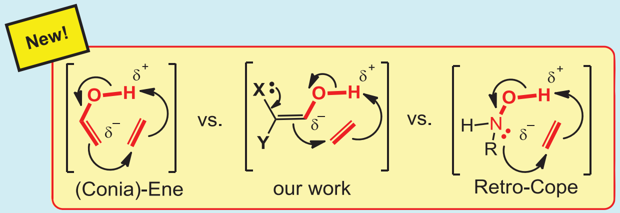
Piel, Steinmetz, Hirano, Fröhlich, Grimme,* Glorius,* *Angew. Chem. Int. Ed.* **2011**, *50*, 4983.

New mode of NHC organocatalysis!?

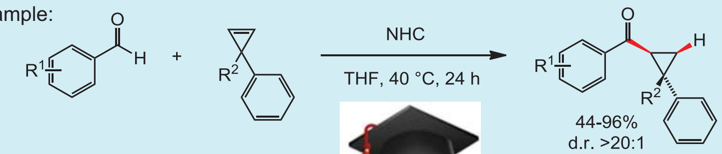


Asym. intermol. hydroacylation to electron-neutral olefins

Hydroacylation of unactivated olefins – concerted mode of action

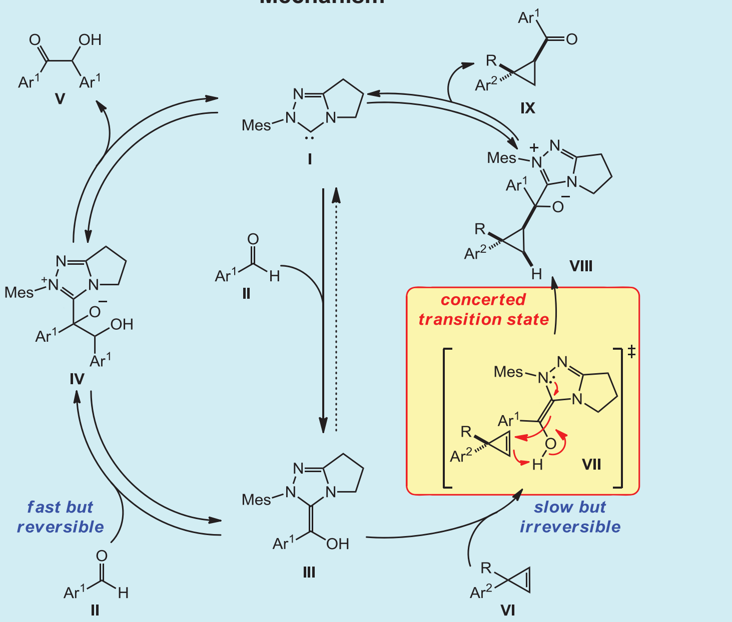


For example:

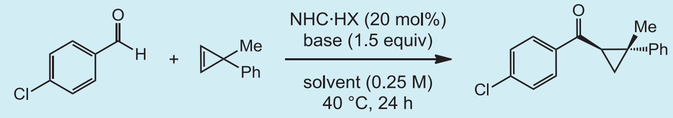


Hirano, Biju, Piel, Glorius, *J. Am. Chem. Soc.* **2009**, *131*, 14190.
Piel, Steinmetz, Hirano, Fröhlich, Grimme,* Glorius,* *ACIE* **2011**, *50*, 4983 (VIP).
Bugaut, Liu, Glorius, *J. Am. Chem. Soc.* **2011**, *133*, 8130.
See also: Biju, Kuhl, Glorius, *Acc. Chem. Res.* **2011**, *44*, 1182.

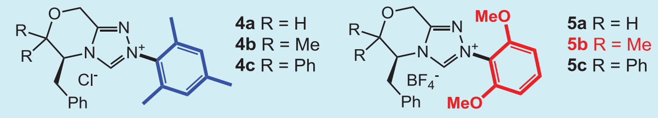
Mechanism



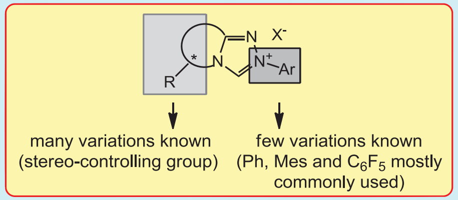
Catalyst design required



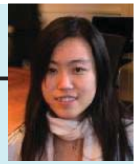
1a (1 equiv) **2a** (1.5 equiv) **3a** (*R*,*R*)



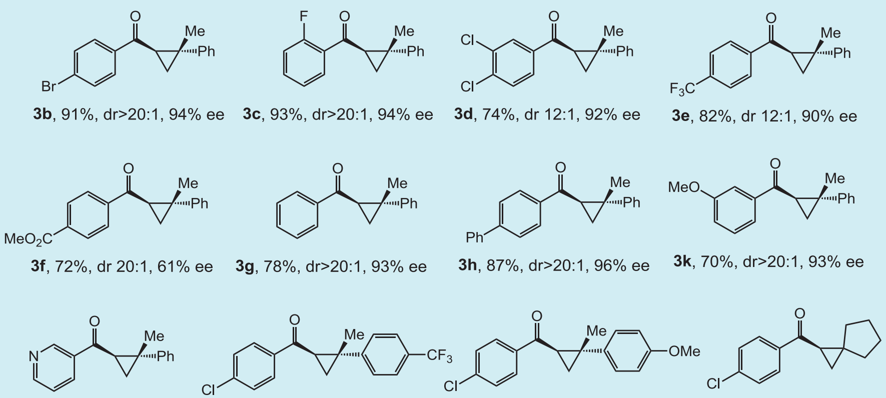
4a-c **5a-c**



Scope



Select examples (from total of 19 examples; 16 examples with ees in the 90ies):



3b, 91%, dr>20:1, 94% ee
3c, 93%, dr>20:1, 94% ee
3d, 74%, dr 12:1, 92% ee
3e, 82%, dr 12:1, 90% ee
3f, 72%, dr 20:1, 61% ee
3g, 78%, dr>20:1, 93% ee
3h, 87%, dr>20:1, 96% ee
3k, 70%, dr>20:1, 93% ee
3n, 82%, dr>20:1, 90% ee
3o, 83%, dr 12:1, 91% ee
3p, 83%, dr>20:1, 94% ee
3r, 95%, 92% ee

Liu, Bugaut, Schedler, Fröhlich, Glorius, *Angew. Chem. Int. Ed.* **2011**, *50*, 12626