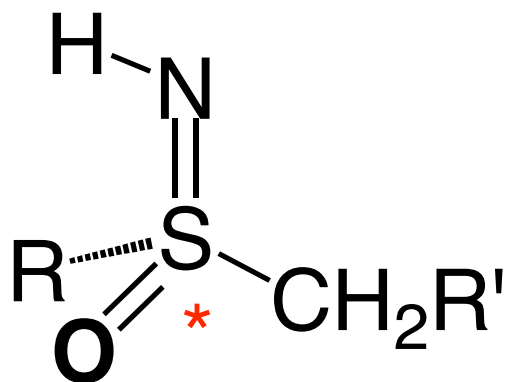


**Ligand effects in
catalyzed organic reactions**

Carsten Bolm

RWTH Aachen University

Sulfoximines

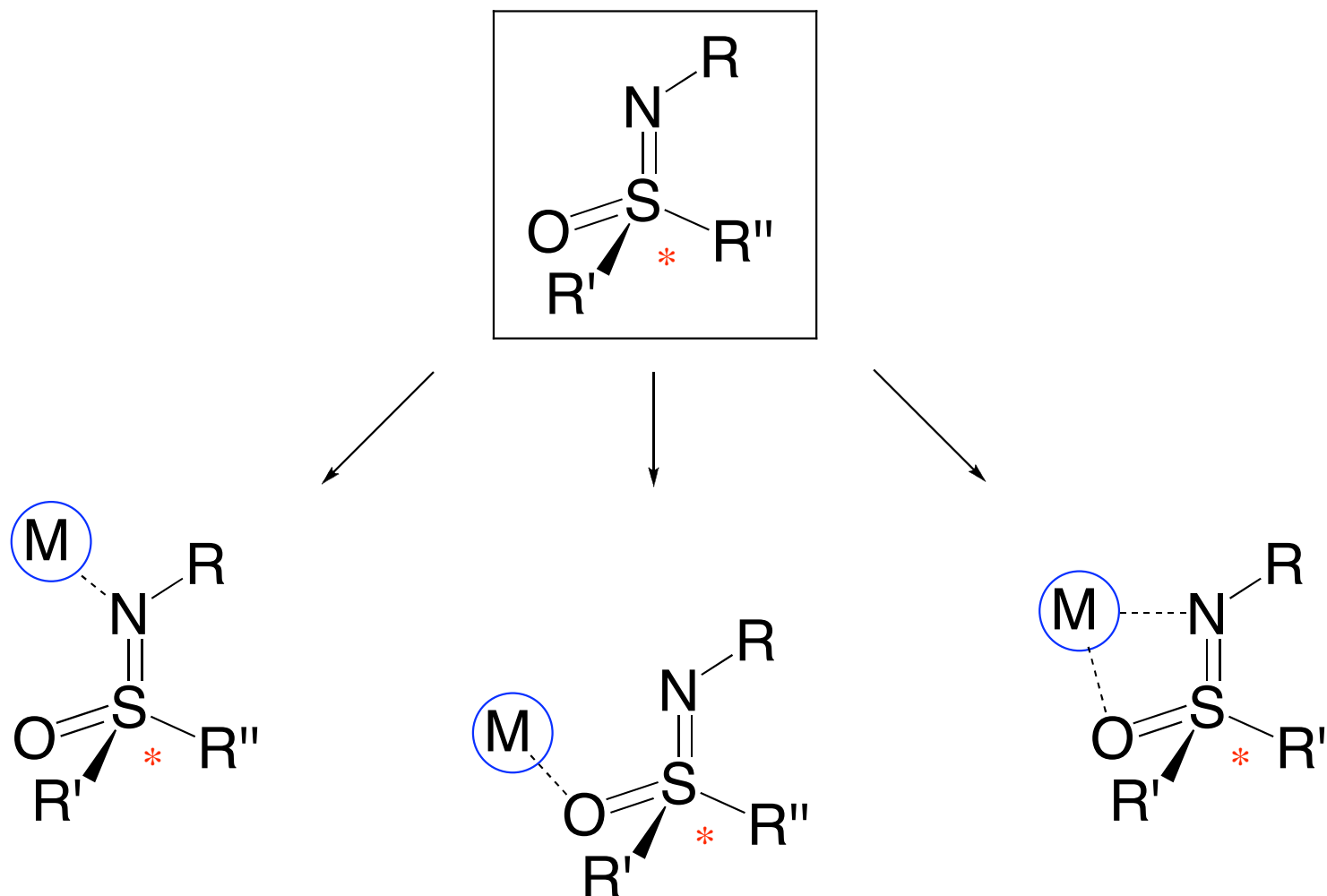


asymmetric sulfur

acidic hydrogens

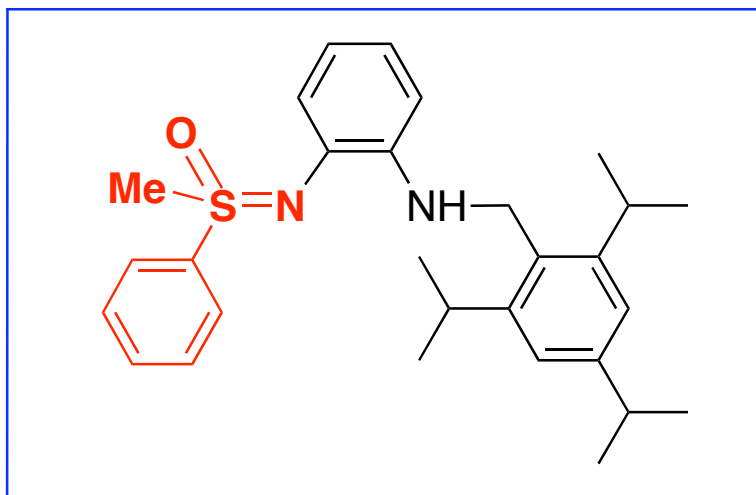
nucleophilic and
basic nitrogen

Sulfoximines as chiral ligands in metal catalysis?



Zehnder, Bolm, *Liebigs Ann.* **1995**, 125. Bolm, Zehnder, *Chem. Eur. J.* **1995**, 1, 312.
Bolm, *Chem. Eur. J.* **2004**, 10, 2942. Bolm, Fleischhauer, Raabe et al., to be published.

C₁-symmetric amino sulfoximines in aldol-type catalyses



ALDRICH
Chemistry

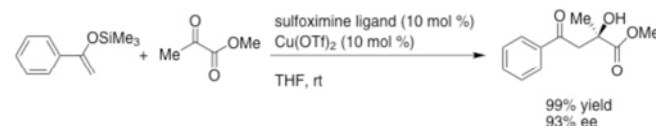
R-enantiomer: **669857**

S-enantiomer: **669970**

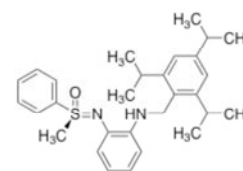


Sulfoximine Ligands for Asymmetric Aldol Reactions

Chiral sulfoximine ligands have been studied for the past 15 years for use in catalytic asymmetric reactions. Bolm's group developed a new class of sulfoximine used with copper salts for asymmetric aldol reactions. Using these bidentate ligands, Bolm and co-workers reported up to 93% ee's and 99% yields for the Mukaiyama-type aldol reaction of 1-phenyl-1-(trimethylsilyloxy) ethane and methyl pyruvate. This new class of ligands is offered exclusively by Sigma-Aldrich.



Reference: Okamura, H.; Bolm, C. *Chem. Lett.* **2004**, *33*, 482.



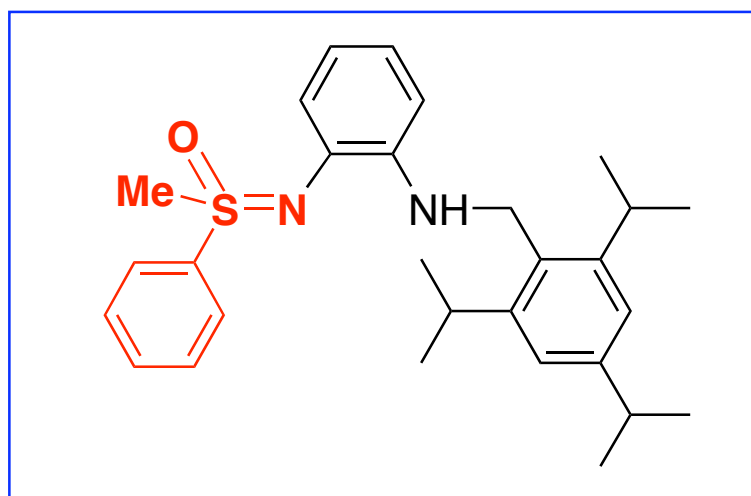
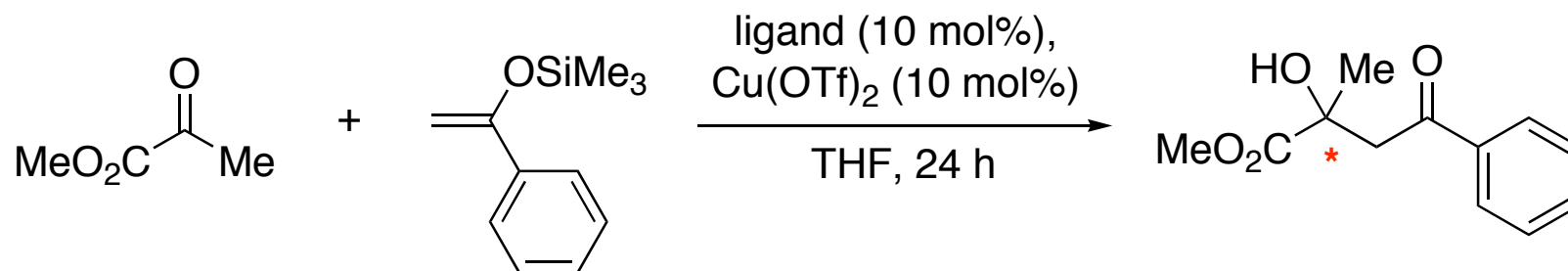
(*R*)-*S*-Methyl-*S*-phenyl-*N*-[2-(2,4,6-triisopropylbenzylamino)-phenyl]sulfoximine
669857

(*S*)-*S*-Methyl-*S*-phenyl-*N*-[2-(2,4,6-triisopropylbenzylamino)-phenyl]sulfoximine
669970

Langner, Bolm, *Angew. Chem. Int. Ed.* **2004**, *43*, 5984.

Langner, Rémy, Bolm, *Chem. Eur. J.* **2005**, *11*, 6254.

C₁-symmetric amino sulfoximines in aldol-type catalyses



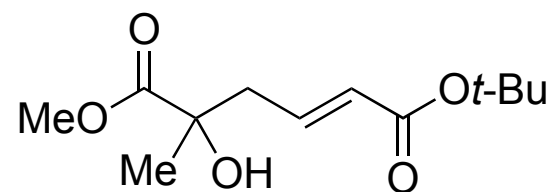
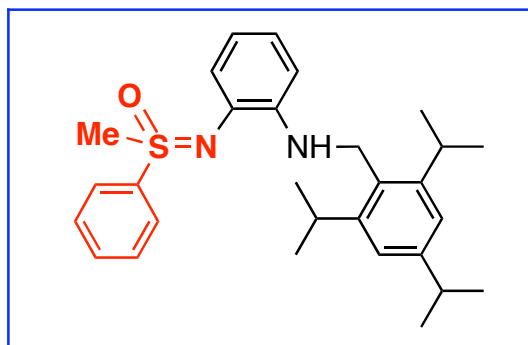
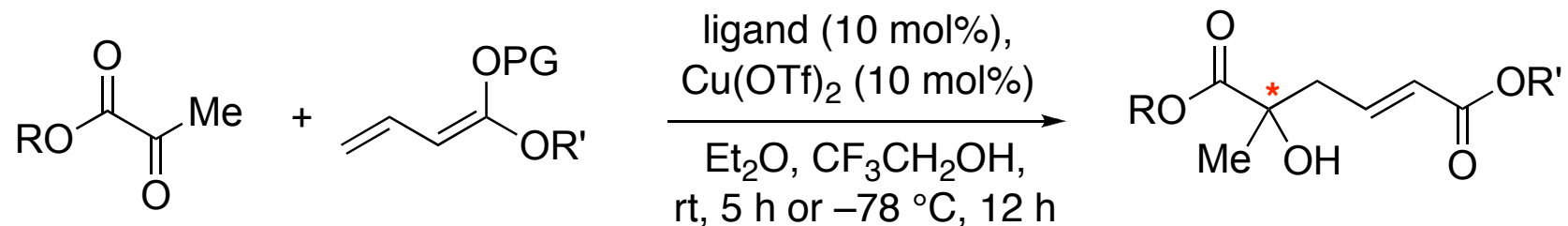
at room temp:
>99% yield, 93% ee

at -55 °C (for 10 d):
83% yield, >98% ee

Langner, Bolm, *Angew. Chem. Int. Ed.* **2004**, *43*, 5984.

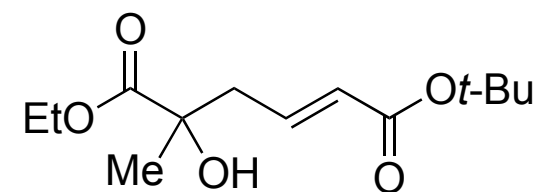
Langner, Rémy, Bolm, *Chem. Eur. J.* **2005**, *11*, 6254.

Sulfoximines in *vinyllogous* Mukaiyama-type aldol reactions



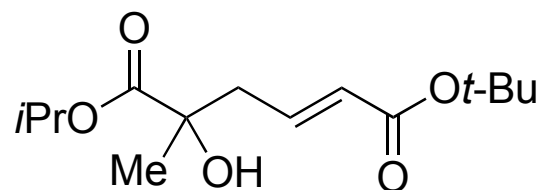
80%, 96% ee

PG = TBDMS



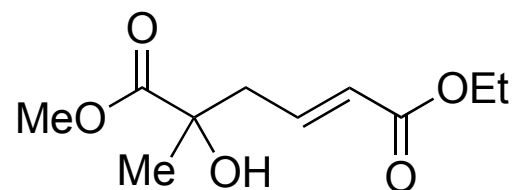
77%, 97% ee

PG = TBDMS



69%, 99% ee

PG = TBDMS

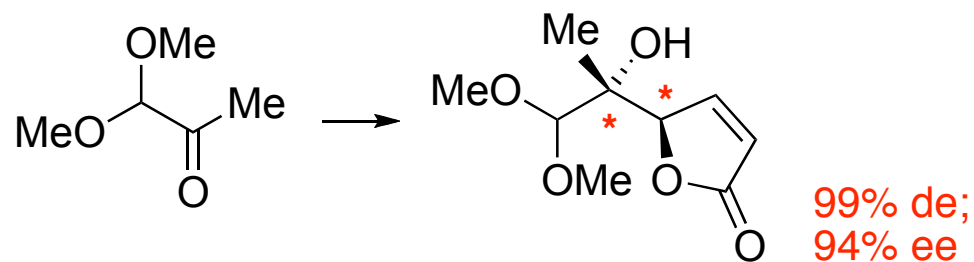
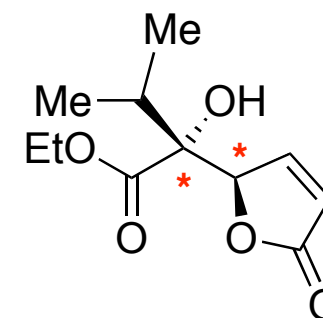
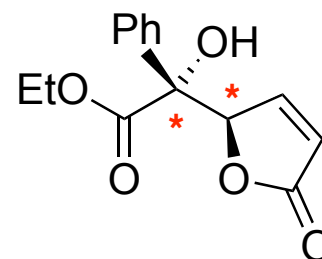
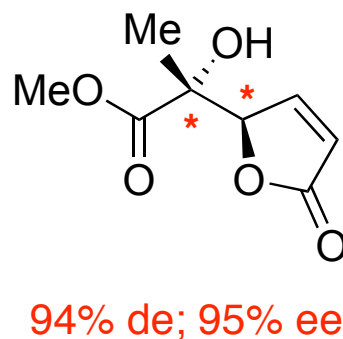
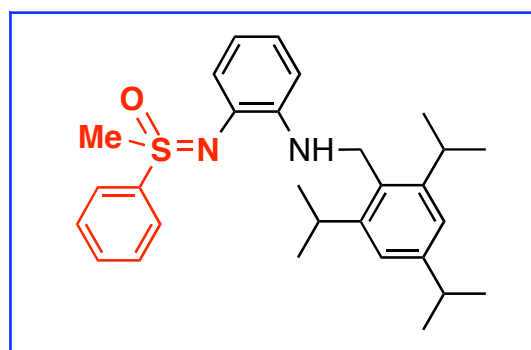
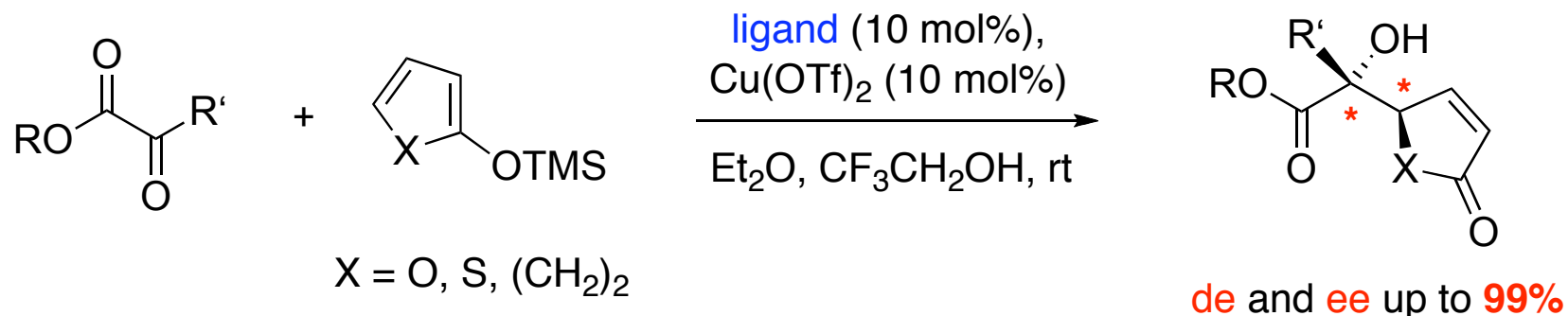


81%, 99% ee

PG = TMS

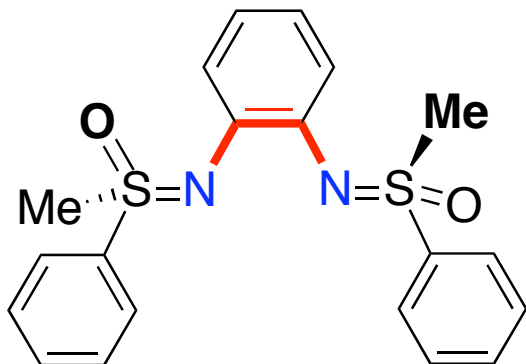
Rémy, Langner
Bolm, *Org. Lett.*
2006, 8, 1209.

Sulfoximines in *vinylogous* Mukaiyama-type aldol reactions

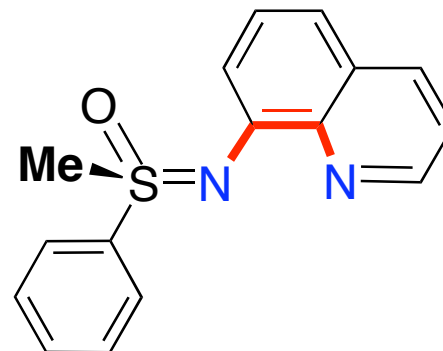


Frings, Atodiresei, Raabe, Runsink, Bolm, *Chem. Eur. J.* **2009**, *15*, 1566.
Full paper: *Chem. Eur. J.*, accepted.

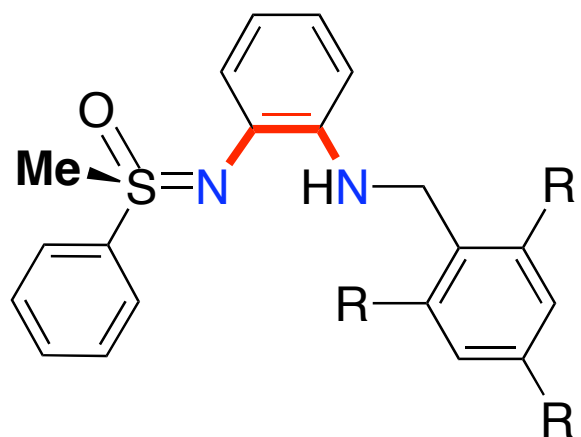
N,N- and P,N-sulfoximines as potential ligands



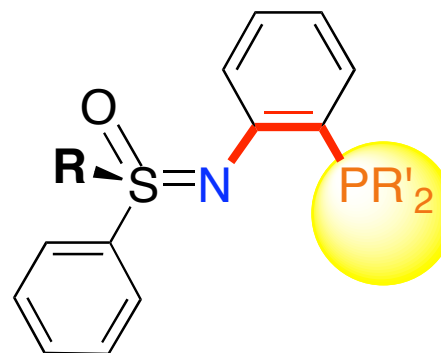
C_2 -symmetric bisulfoximine (N,N-)



C_1 -symmetric monosulfoximine (N,N-)

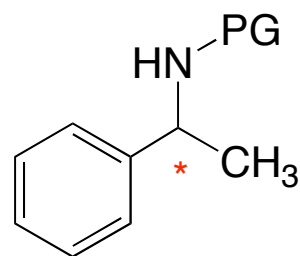
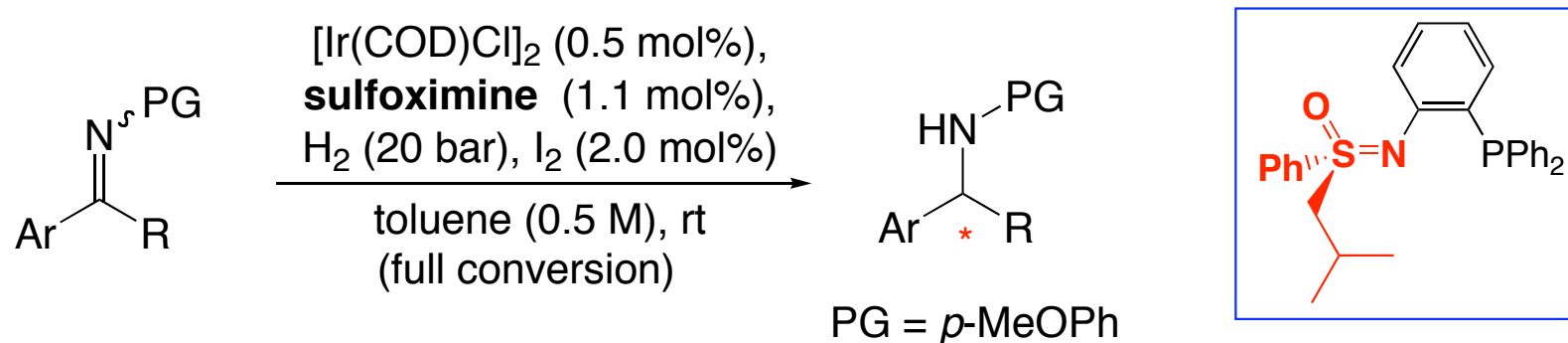


C_1 -symmetric monosulfoximine (N,N-)

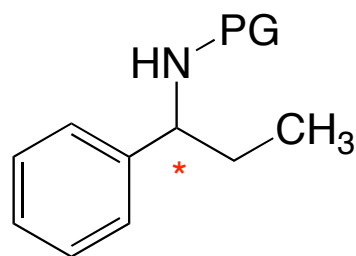


C_1 -symmetric monosulfoximine (P,N-)

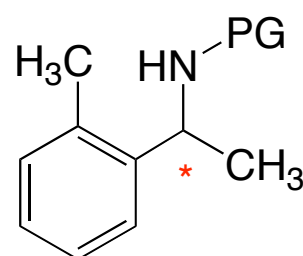
Iridium-catalyzed asymmetric imine hydrogenation



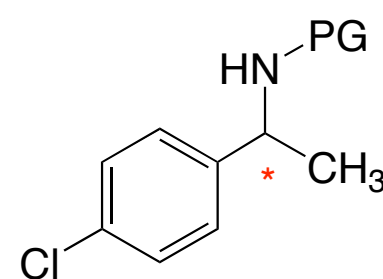
96% ee



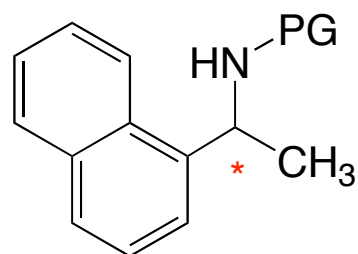
92% ee



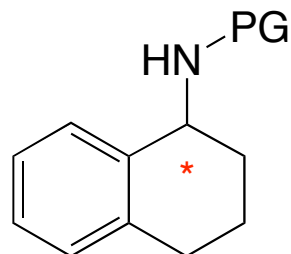
94% ee



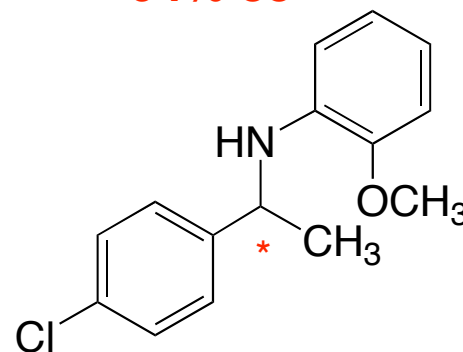
95% ee



98% ee



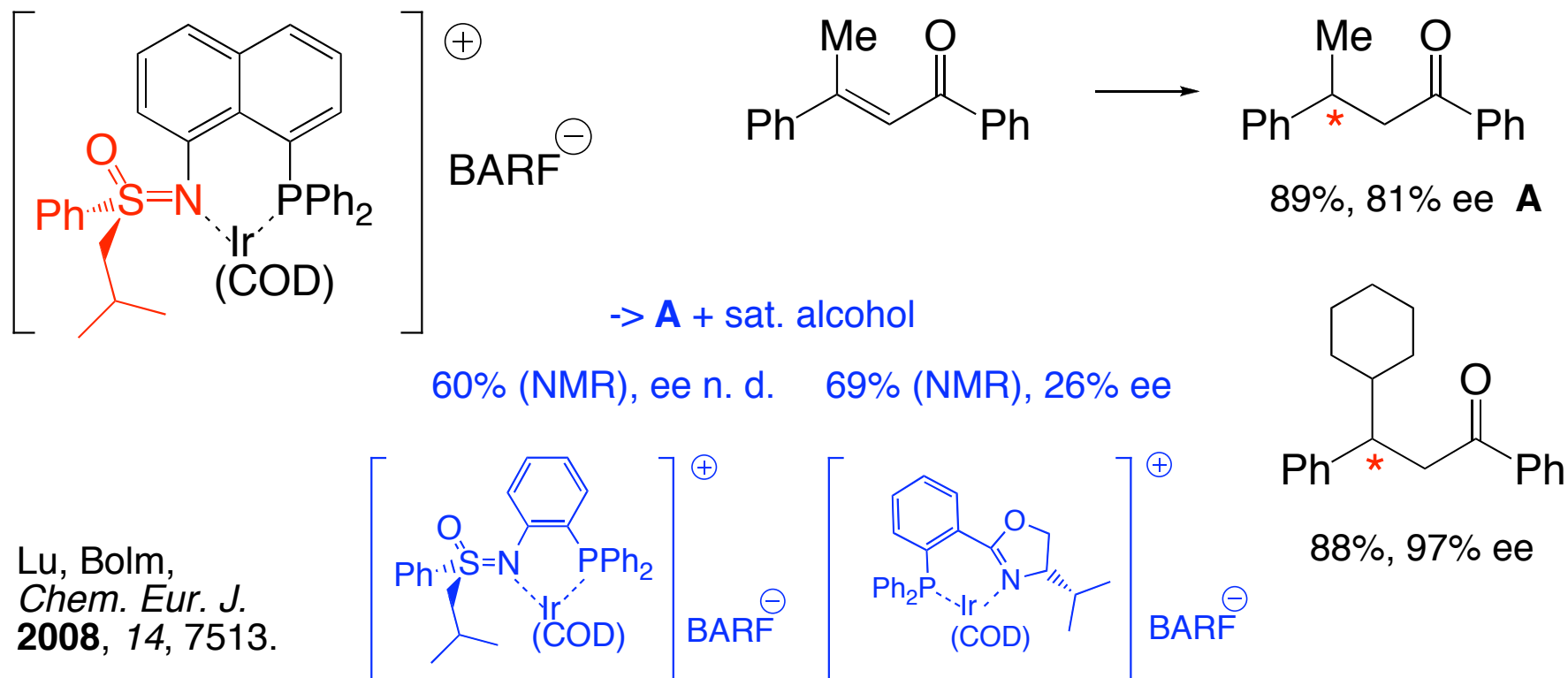
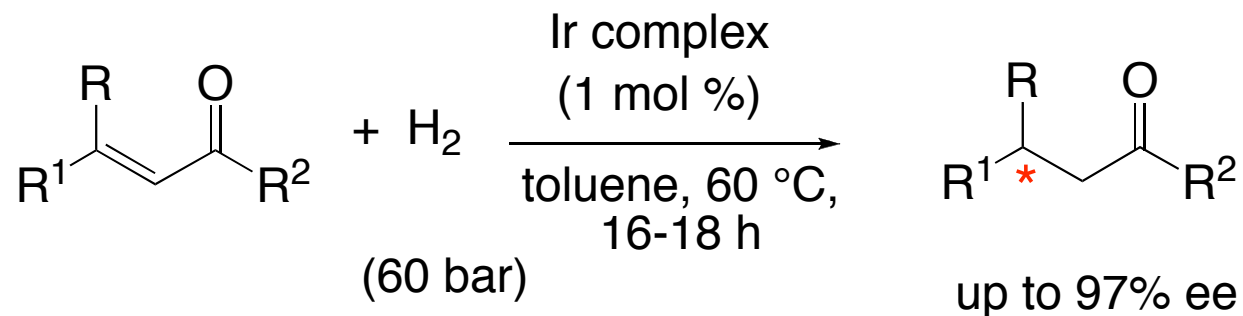
91% ee



79% ee

Moessner, Bolm,
Angew. Chem. Int. Ed.
2005, 44, 7564.

Iridium-catalyzed asymmetric enone hydrogenation



Recent reviews on "our" sulfoximine chemistry

Sulfoximines as ligands in asymmetric metal catalysis (Personal Account)

C. Bolm, in *Asymmetric Synthesis with Chemical and Biological Methods* (Eds.: D. Enders, K.-E. Jaeger), Wiley/VCH, Weinheim, **2007**, 149 - 176.

Sulfoximines: Synthesis and catalytic application (Highlight Review)

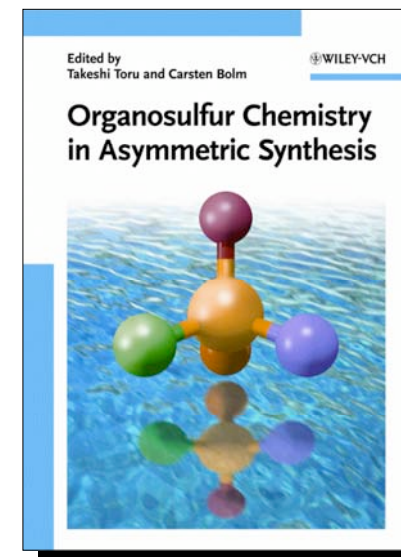
H. Okamura, C. Bolm, *Chem. Lett.* **2004**, *33*, 482 - 487.

Synthesis and use of chiral sulfoximines

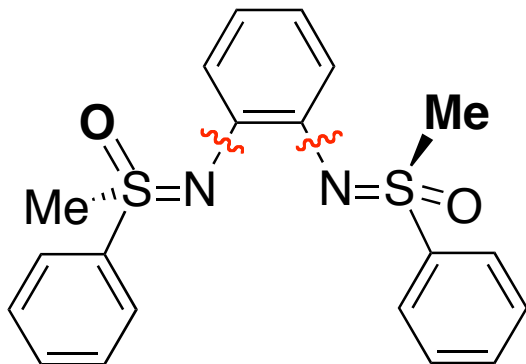
C. Worch, A. C. Mayer, C. Bolm, in

Organosulfur Chemistry in Asymmetric Synthesis

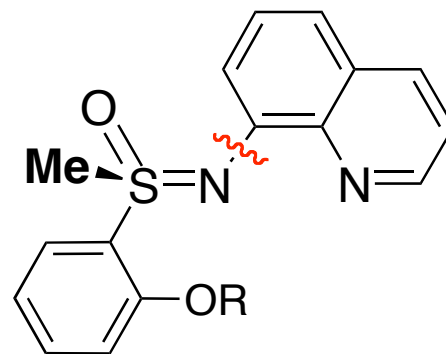
(Eds.: T. Toru, C. Bolm), Wiley/VCH, Weinheim, **2008**, 209 - 229.



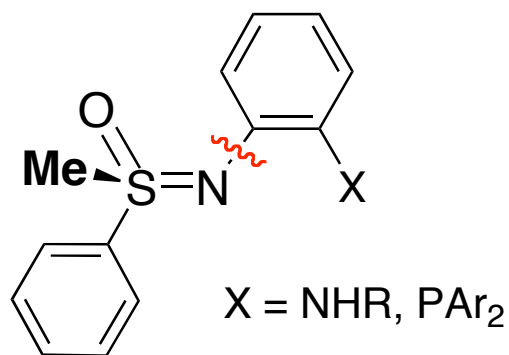
Preparation of *N*-arylated sulfoximines



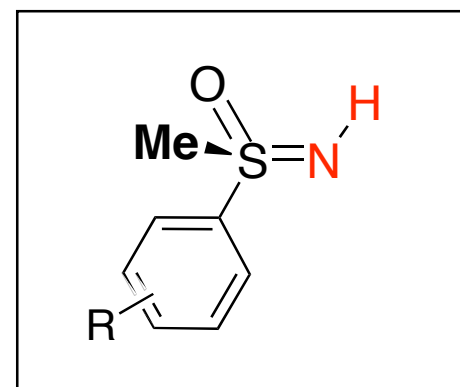
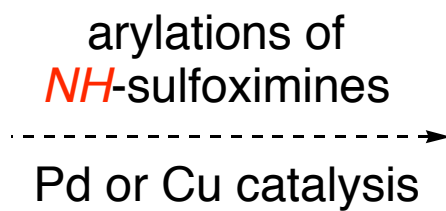
C₂-symmetric bisulfoximine



C₁-symmetric monosulfoximine

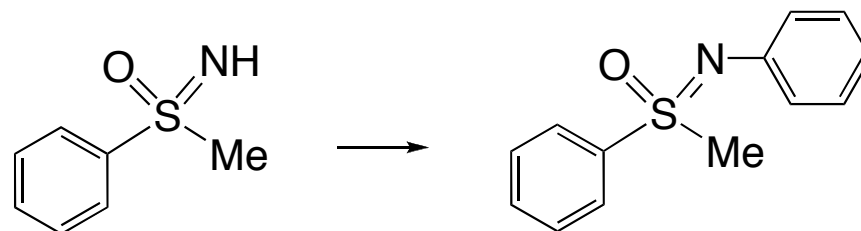


C₁-symmetric monosulfoximine



Bolm, *J. Org. Chem.* **2000**, *65*, 169.

Development of metal-catalyzed *N*-arylations of sulfoximines



- 1998:** Pd(OAc)₂, BINAP, Cs₂CO₃ (mono-couplings) *Tetrahedron Lett.* **1998**, 39, 5731.
J. Org. Chem. **2000**, 65, 169.
- 2001:** [Pd₂dba₃], BINAP, NaOt-Bu (bis-couplings) *J. Am. Chem. Soc.* **2001**, 123, 3830.
- 2004:** CuI, Cs₂CO₃ (stoichiometric in copper) *Org. Lett.* **2004**, 6, 3293.
- 2005:** CuI, diamine, Cs₂CO₃ (catalytic in copper) *J. Org. Chem.* **2005**, 70, 6904.
(*Org. Lett.* **2005**, 7, 2667.)
- 2007:** Cu₂O, Cs₂CO₃ (catalytic in copper; *ligand-free*) *Adv. Synth. Catal.* **2007**, 349, 2673.

And how about an iron catalysis?

Can we simplify by changing metals?

(Pd -> Cu -> ???)

Can Fe catalysts be used?

"Iron is one of the most abundant metals on earth, and consequently one of the most inexpensive and environmentally friendly ones. Moreover, many iron salts and complexes are commercially available, or described in the literature."

IRON-CATALYZED REACTIONS IN ORGANIC SYNTHESIS

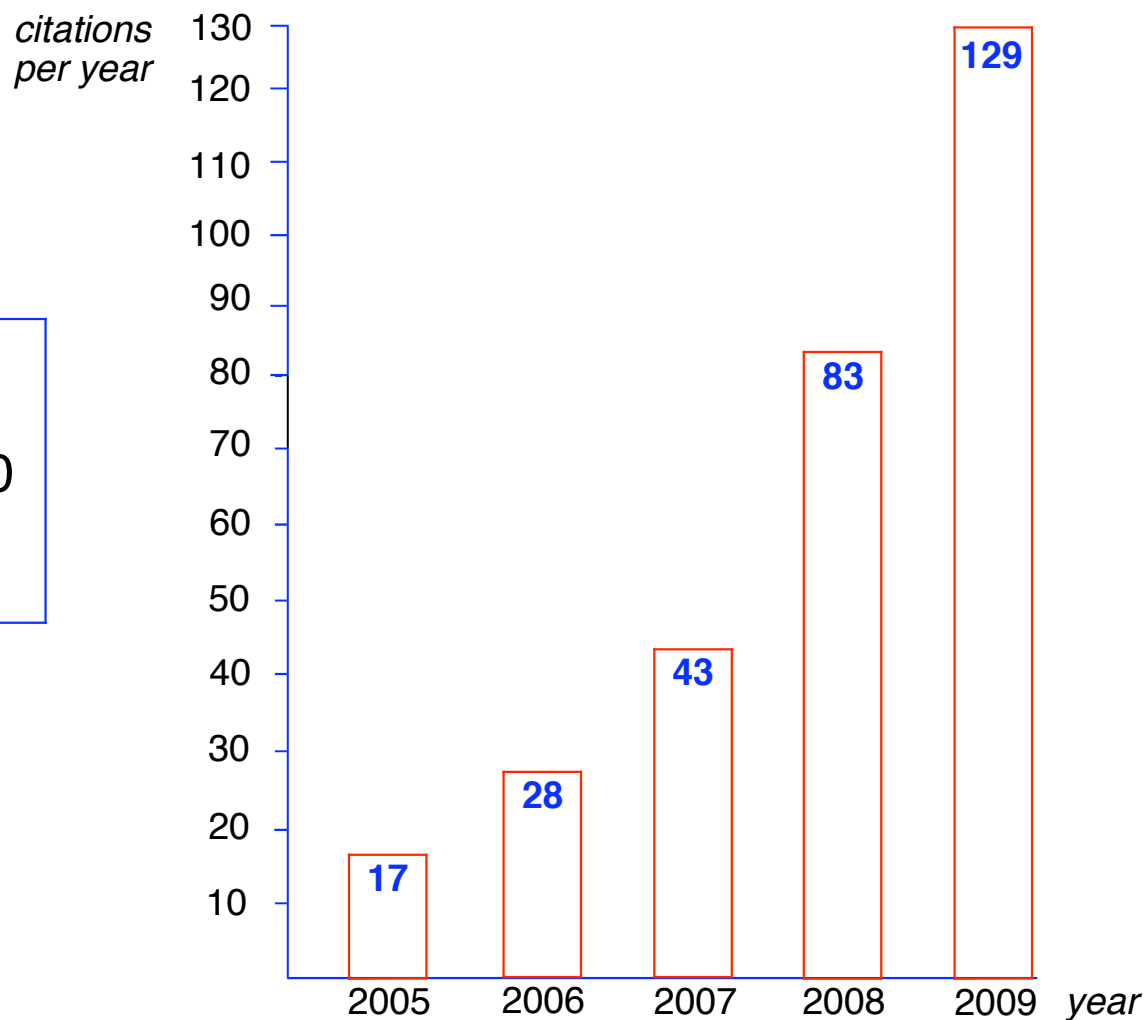
C. Bolm, J. Legros, J. Le Pailh, L. Zani

Chem. Rev. **2004**, *104*, 6217-6254.

The scientific impact of that review over time (from ISI)

IRON-CATALYZED REACTIONS IN ORGANIC SYNTHESIS

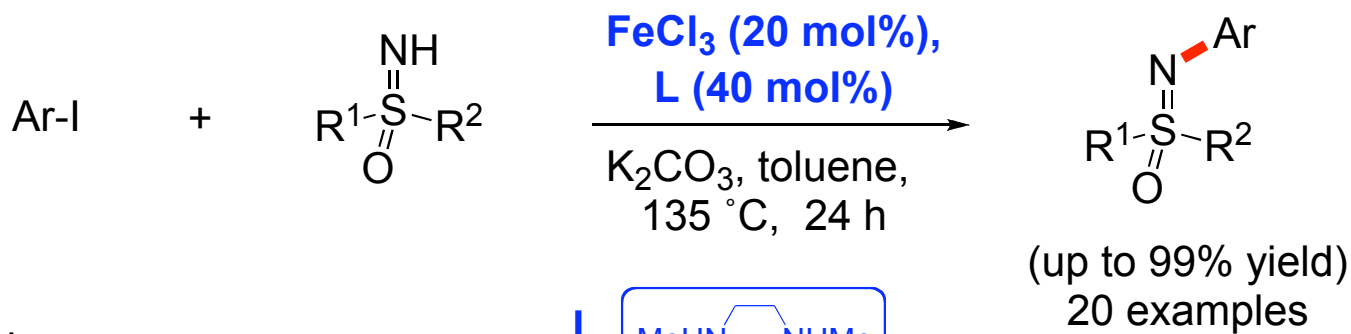
C. Bolm, J. Legros, J. Le Pailh, L. Zani, *Chem. Rev.* **2004**, *104*, 6217-6254.



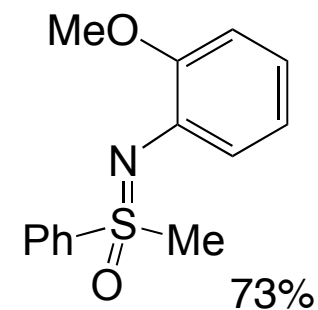
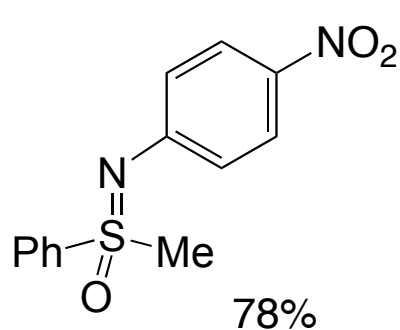
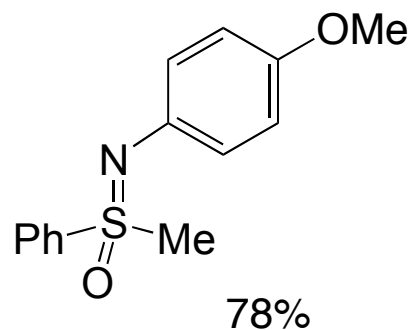
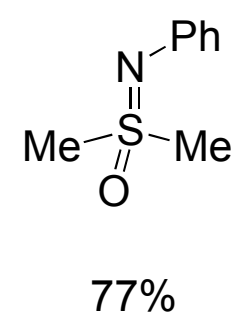
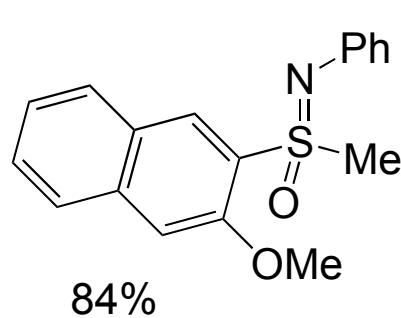
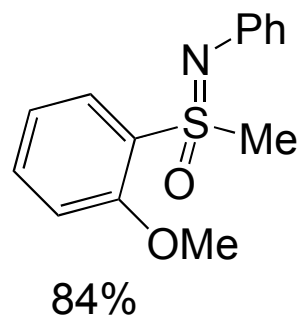
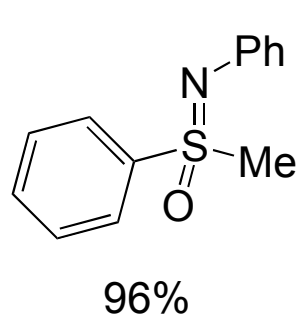
published in December 2004

- 318 citations on Feb. 11, 2010
- 53.00 citations per year

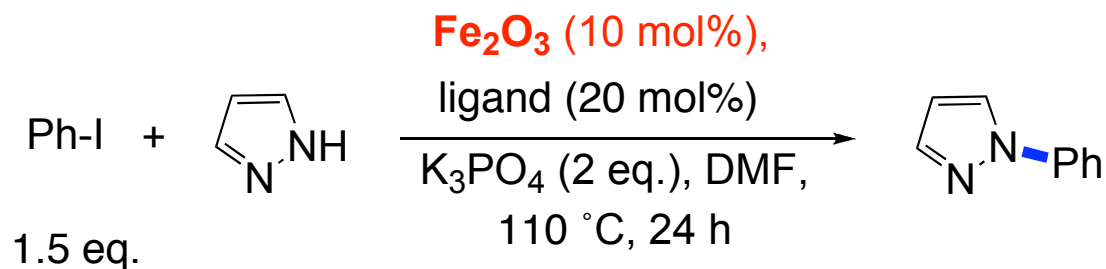
Iron-catalyzed *N*-arylation of sulfoximines



Correa, Bolm,
Adv. Synth. Catal. **2008**, 350, 391.



Iron-catalyzed *N*-phenylation of pyrazole



ligand	yield
none	0
L-proline	35
<i>trans</i> -1,2-diaminocyclohexane	31
TMEDA	traces
DMEDA	52
<i>rac</i> -BINAP	0

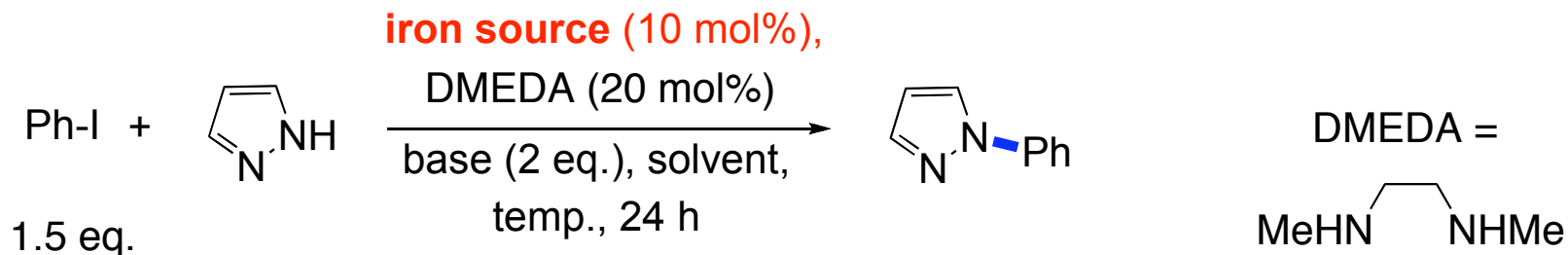
- use of Fe₂O₃ inspired by Taillefer's work (who used Fe/Cu cooperative catalysts)

- use of diamines and proline inspired by Buchwald's and Ma's work on copper catalysis

best ligand = DMEDA



Iron-catalyzed *N*-phenylation of pyrazole

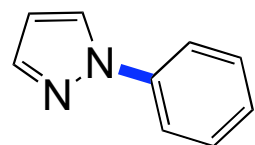
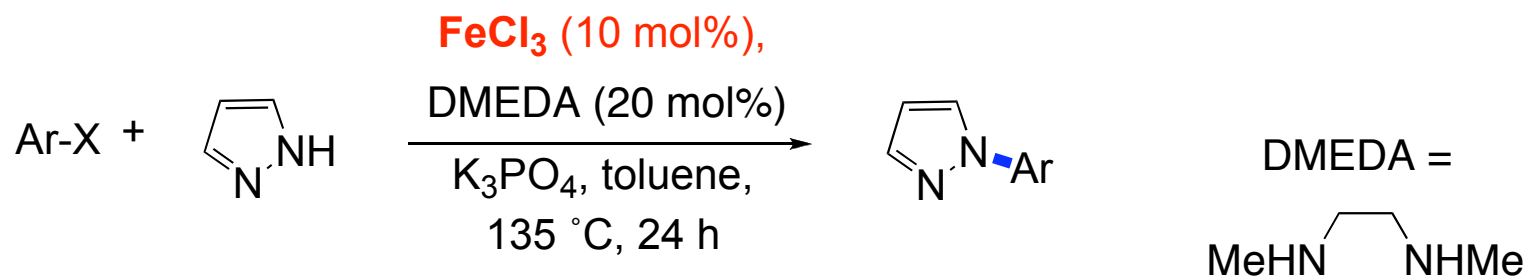


- best solvent = toluene (at 135 °C)
lower yields in DMF at 110 °C or 135 °C
- best base = K₃PO₄
lower yields with NaOt-Bu, Cs₂CO₃, K₂CO₃

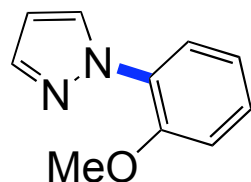
-> Fe source optimization

Fe source	yield
none	0
Fe	50
FeCl ₂ ·4H ₂ O	61
Fe(acac) ₂	48
Fe ₂ O ₃	70
Fe(acac) ₃	62
FeCl₃ (>98%)	85

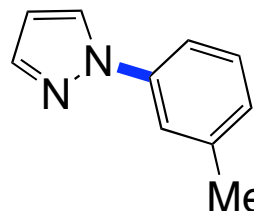
Iron-catalyzed *N*-arylations of heterocycles



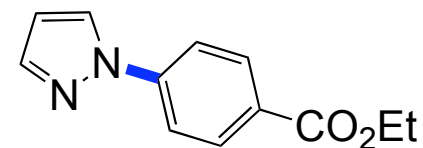
from Ar-I: 80%
from Ar-Br: 34%



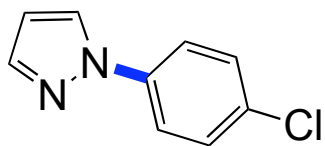
41% (Ar-I)



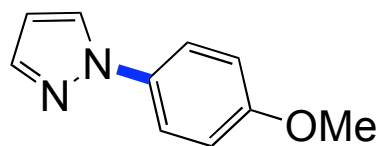
82% (Ar-I)



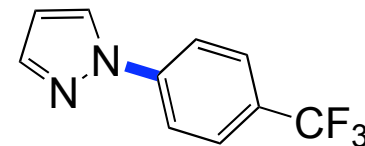
74% (Ar-I)



56% (Ar-I)

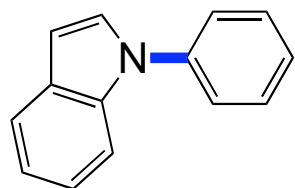
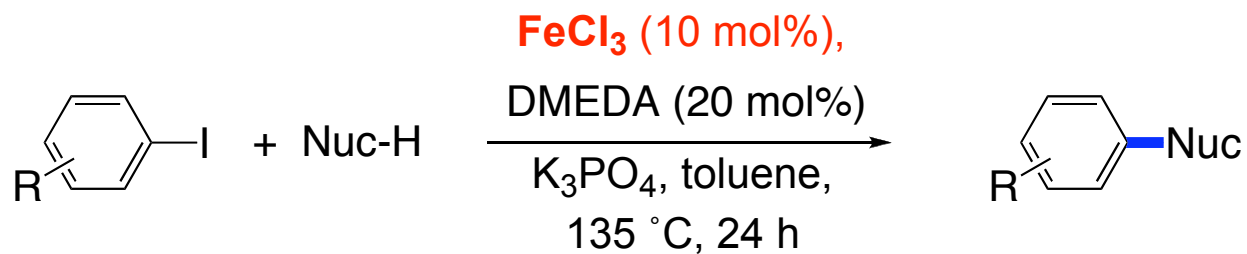


64% (Ar-Br)

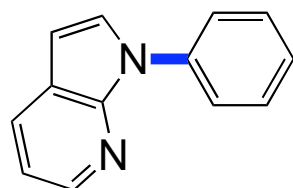


37% (Ar-Br)

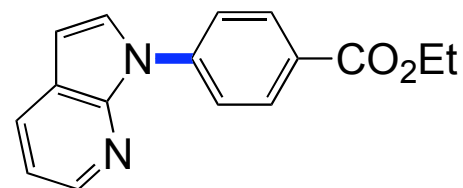
Iron-catalyzed *N*-arylations of heterocycles



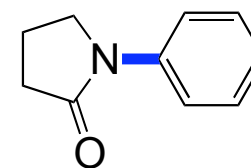
60%



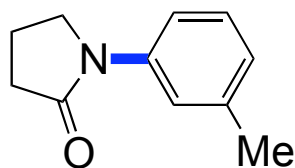
84%



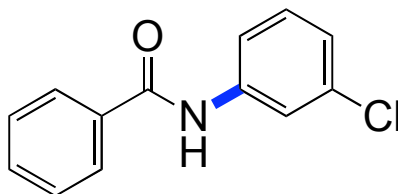
74%



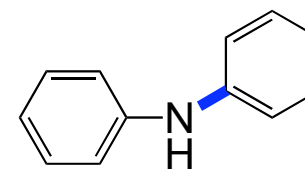
53%



48%



97%

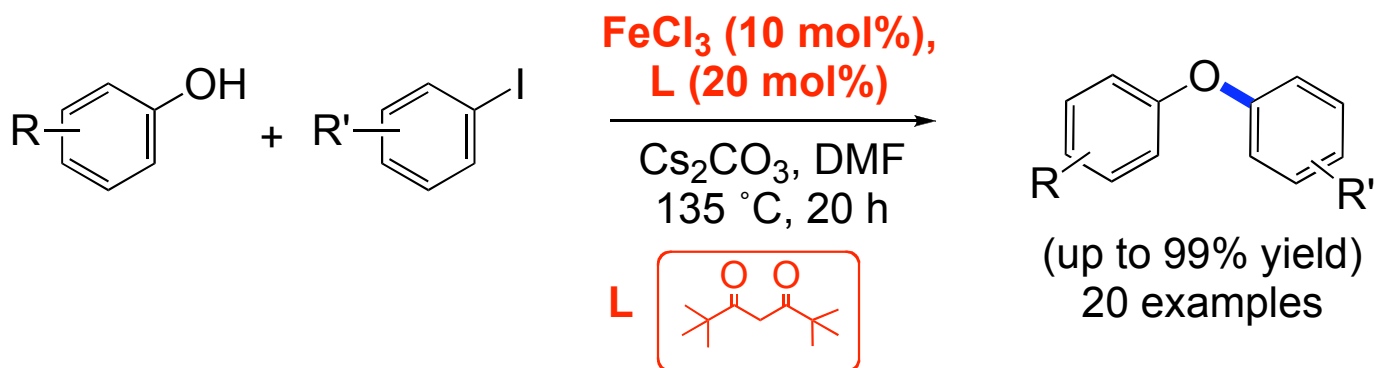


trace

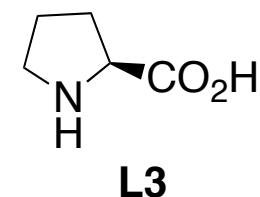
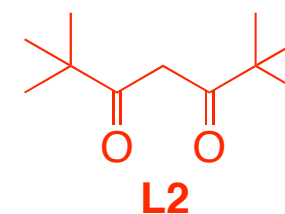
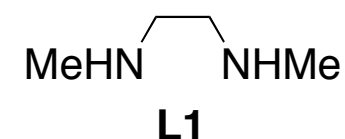
Correa, Bolm, *Angew. Chem. Int. Ed.* **2007**, *46*, 8865.

for Fe-catalyzed
C-C cross-couplings, see:
Kharasch, Kochi, Cahiez,
Fürstner, Knochel, Nakamura,
Nakamura ...

Iron-catalyzed *O*-arylations of phenols

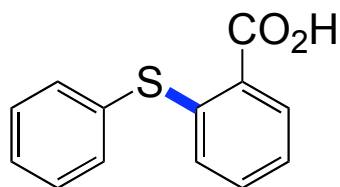
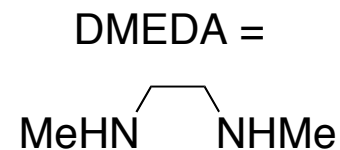
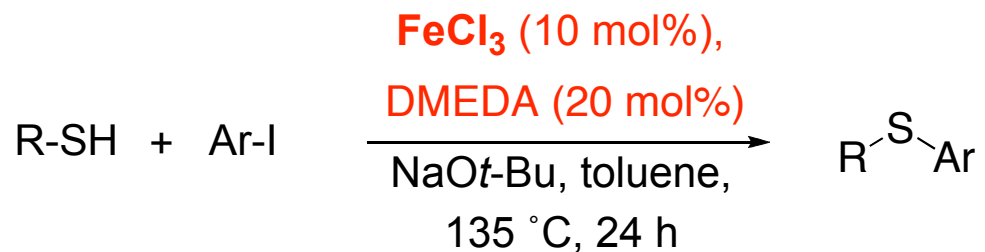


iron source	ligand	base	solvent	yield
FeCl ₃	L1	K ₃ PO ₄	toluene	0
FeCl ₃	L1	Cs ₂ CO ₃	DMF	18
FeCl ₃	L2	Cs ₂ CO ₃	toluene	17
FeCl ₃	L2	Cs ₂ CO ₃	DMF	85
FeCl ₃	L2	NaO- <i>t</i> -Bu	DMF	0
FeCl ₃	L3	Cs ₂ CO ₃	DMF	trace
Fe(acac) ₃	--	Cs ₂ CO ₃	DMF	35

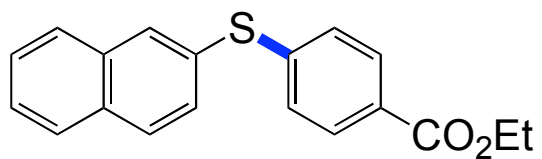


Bistri, Correa, Bolm, *Angew. Chem. Int. Ed.* **2008**, 47, 586.

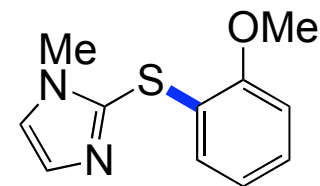
Iron-catalyzed S-arylations



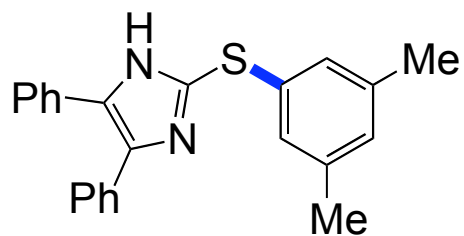
90%



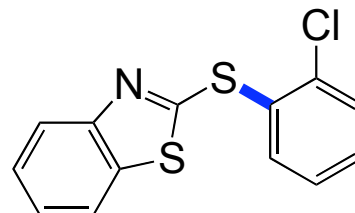
81%



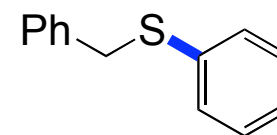
71%



32%



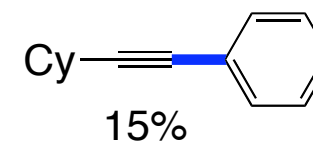
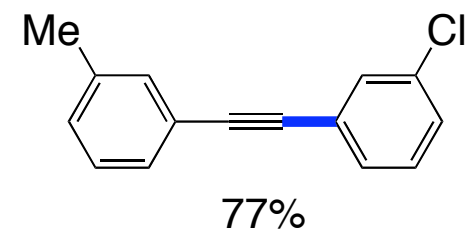
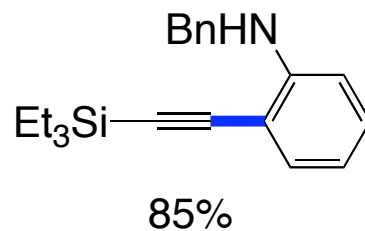
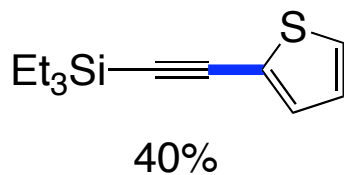
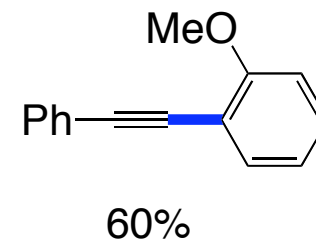
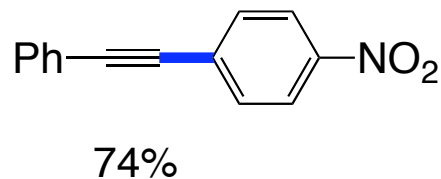
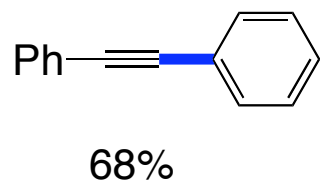
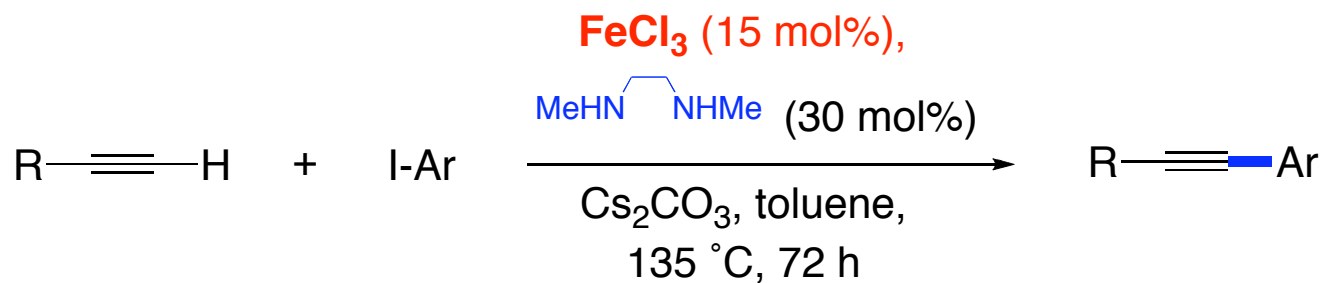
80%



0%

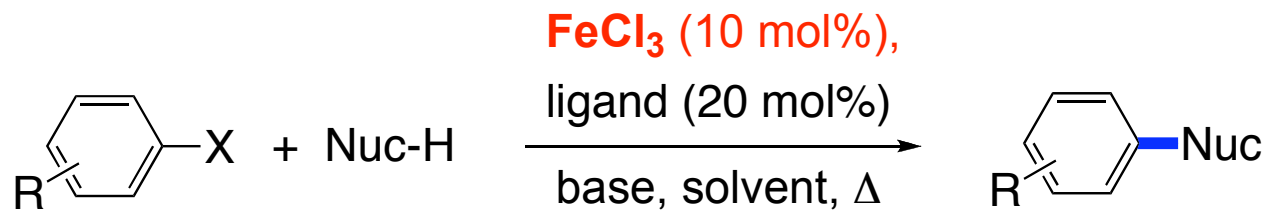
Correa, Carril, Bolm, *Angew. Chem. Int. Ed.* **2008**, 47, 2880.

Iron-catalyzed C-arylation (Sonogashira coupling)



Carril, Correa, Bolm, *Angew. Chem. Int. Ed.* **2008**, 47, 4862.

Important observations

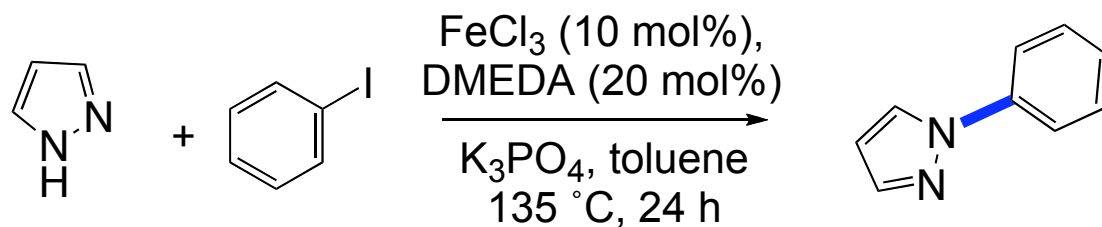


- best iron source: FeCl₃ (>98% purity)
- strong ligand impact
- strong effect by base, solvent and temperature; pressure?
- required use of closed reaction vials for high conversion
- slow reaction (no microwave acceleration)
- high water tolerance, but FeCl₃·6H₂O less suitable

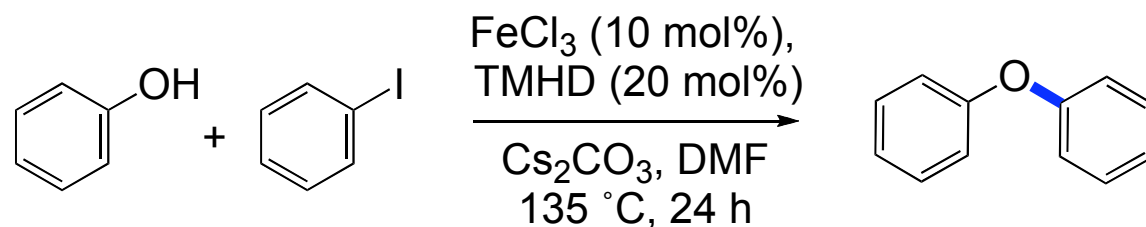
*in collaboration with P.-O. Norrby and P.-F. Larsson
(Göteborg University)*

- small amounts of water appear to have a positive effect
- problematic kinetic studies (due to heterogeneous reaction)

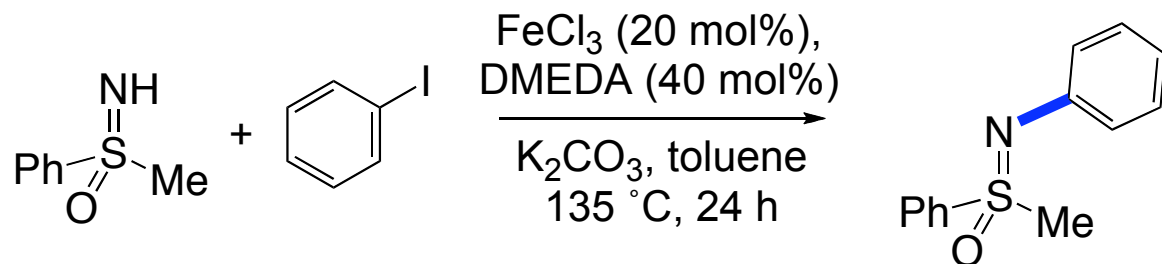
Iron purity



Fe source	Yield (%)
>98% (Merck)	80
>99.99% (Aldrich)	34
>97% (Fluka)	70



Fe source	Yield (%)
>98% (Merck)	85
>99.99% (Aldrich)	43
>97% (Fluka)	78



Fe source	Yield (%)
>98% (Merck)	99
>99.99% (Aldrich)	41
>97% (Fluka)	85

See also comments on "Fe purity" in the SI of Cahiez, *Angew. Chem. Int. Ed.* **2007**, *46*, 4364.

Iron or copper catalysis?

e-mail by Steve Buchwald on July 24, 2008

"Dear Carsten:

We have been intrigued by the results that you have recently published. One reason is that many years ago, we thought we had discovered the same thing. However, upon reinvestigation we found it was due to copper contamination.

We have performed a number of experiments, the results are enclosed

We have found good evidence that the copper is responsible for these reactions.

I am sorry to be the bearer of this news. I would suggest that you, if you wish, test our results.

Of course we can speak about this further.

with best regards (and wish under better circumstances),

Steve"

Selected initial answers: Iron or copper catalysis?

- **Fe salts and purity:**

- Use >99.99% FeCl₃ gave lower yield, but in some cases still 43%.
- The yields with FeCl₃ of 97% purity were lower than those obtained with FeCl₃ of 98%.
- Many iron sources worked. Did all contain copper?

- **Ligands:**

In contrast to catalyses of CN couplings with copper *only* DMEDA worked as ligand with iron.

- **Temperature:**

With FeCl₃ a temperature of 135 °C was required (in contrast to the copper catalysis)

- **Substrates:**

Several compounds known to couple under Cu catalysis did not convert with iron.

- **Catalyst loading:**

Why are 5-10 mol% of copper salts common if ppm quantities are enough?

- **Others** (Taillefer, Teo, ...) obtained essentially the same results with FeCl₃ as us
(How about other reactions such as cross-couplings and conjugate additions?)

Complex synthesis and isolation



according to McGregor, *J. Chem. Soc.* **1958**, 136.

(characterization in Proserpio, *Inorg. Chem.* **1997**, 36, 1437.)

⇒ DMEDA induced reduction of Fe(III) to Fe(II)

also known:

FeCl₃ in aromatic solvents under reflux lead to Fe(II)

Kovacic, *J. Am. Chem. Soc.* **1954**, 76, 5491.

Catalysis in Sonogashira reactions!

Carril, Bolm, to be published.

Iron or copper catalysis?

e-mail by Per-Ola Norrby on September 9, 2008

"Dear Carsten,

..... I've refrained from sending premature emails, but he does have quite a bit of data now, indicating that some of the results could be due to trace amounts of copper, not to iron itself. If we can convince you I hope we can find some way to publish this together, but let's talk about that when you're here.

.....

Looking forward to having you here!

/Per-Ola"

Trace metals - everywhere!

determined by **Atom Absorption Spectroscopy (AAS)**

(Prof. Dr. R. Dronskowski, L. Stork, RWTH Aachen University, Inorganic Chemistry)

Reagent	<i>in ppm</i>				Comments
	Ni	Mn	Cu	Pd	
FeCl ₃ (98%)	190	1'715	344*	13	
FeCl ₃ (99.99%)	--	46	--	--	but up to 43% yield!
FeCl ₃ (97%)	148	877	180	--	less Cu, lower yield?
FeBr ₃	54	130	54	49	
Fe	129	116	8	5	up to 50% yield
Fe ₂ O ₃	13	2	--	30	up to 70% yield
K ₃ PO ₄	8	2	--	29	
Cs ₂ CO ₃	6	--	--	13	
DMEDA (99%)	1	--	--	1	
PhI	2	--	--	--	

* Corresponding to 0.034%

Concerning the use of FeCl₃ in catalysis

Korrespondenz

Iron or Copper?

DOI: 10.1002/ange.200902237

On the Role of Metal Contaminants in Catalyses with FeCl₃**

Stephen L. Buchwald and Carsten Bolm**

arylation · copper · homogeneous catalysis ·
iron trichloride · metal impurities

Angew. Chem. Int. Ed. **2009**, *48*, 5586.

Angewandte
Chemie

Copper Catalysis

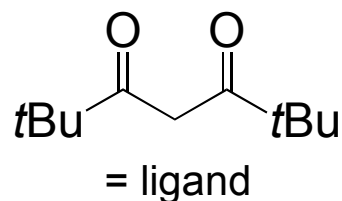
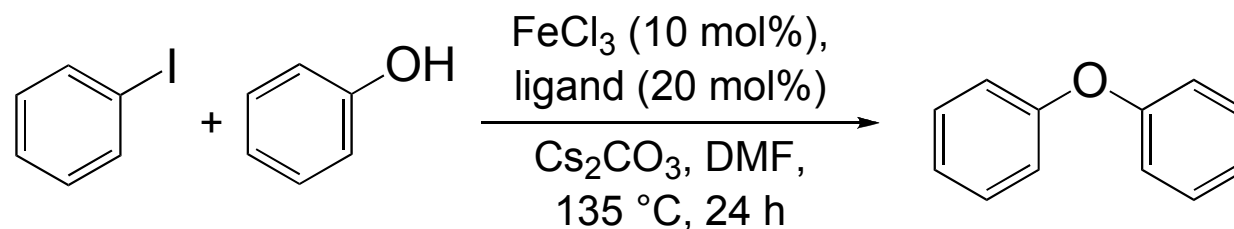
DOI: 10.1002/ange.200902236

Copper-Catalyzed Cross-Couplings with Part-per-Million Catalyst Loadings**

Per-Fredrik Larsson, Arkaitz Correa, Monica Carril, Per-Ola Norrby, and Carsten Bolm**

Angew. Chem. Int. Ed. **2009**, *48*, 5691.

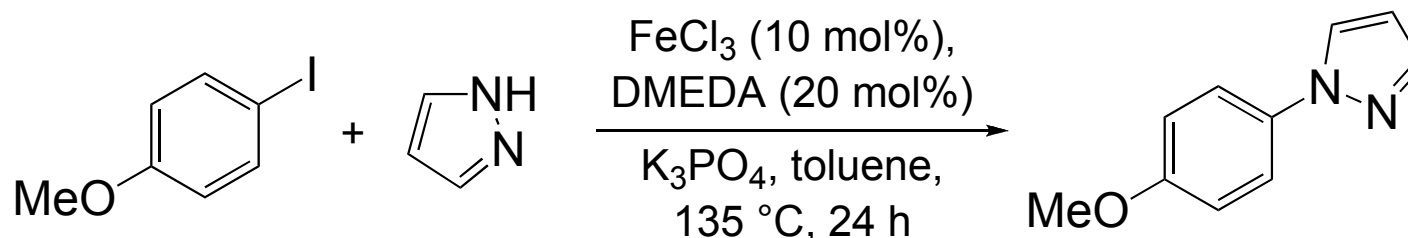
Concerning the use of FeCl₃ in C-O-couplings



FeCl ₃	GC Yield (%)
>98% (Merck)	85
>98% (Aldrich)	81
>99.99 (Aldrich)	32
>99.99% + 10 ppm Cu ₂ O	92
>99.99% + 100 ppm Cu ₂ O	98
>99.99% + 1000 ppm Cu ₂ O	99

Buchwald, Bolm, *Angew. Chem. Int. Ed.* **2009**, *48*, 5586.

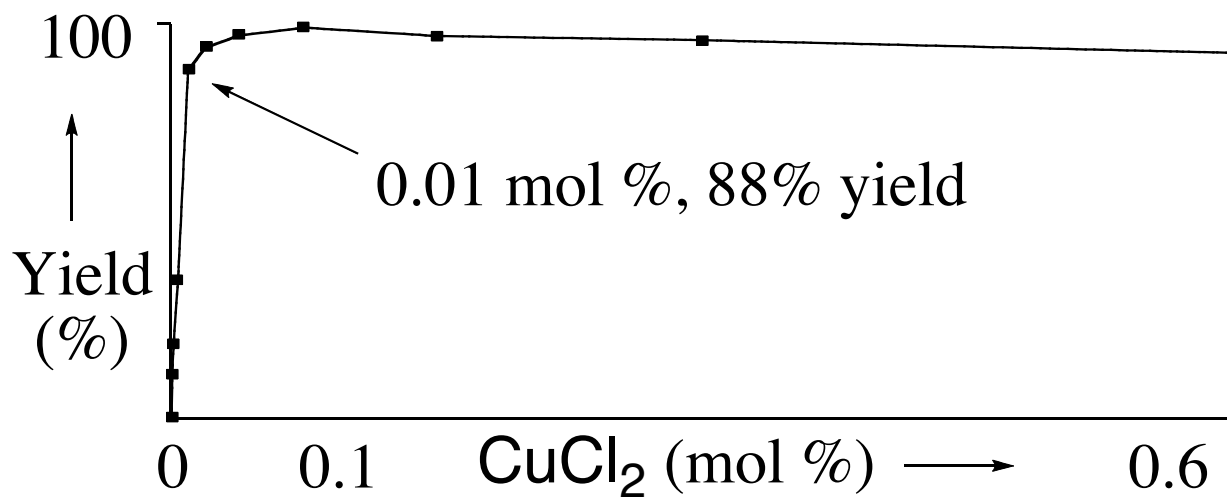
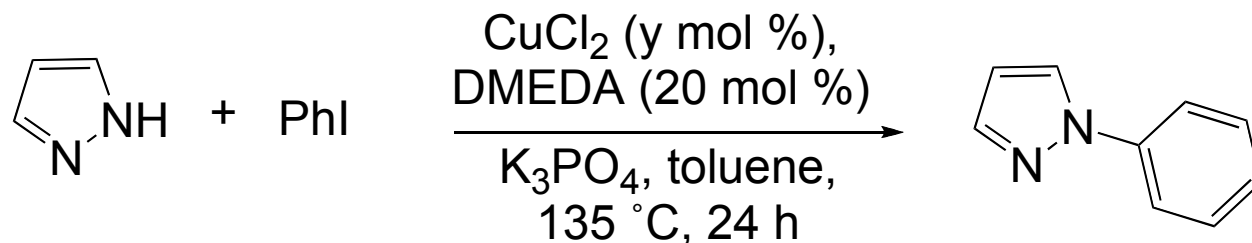
Concerning the use of FeCl₃ in C-N-couplings



FeCl ₃	GC Yield (%)
>98% (Merck)	87
>98% (Aldrich)	26
>99.99 (Aldrich)	9
>99.99% + 5 ppm Cu ₂ O	78
>99.99% + 10 ppm Cu ₂ O	79
no Fe + ligand + 5 ppm Cu ₂ O	77
no Fe + no ligand + 5 ppm Cu ₂ O	23

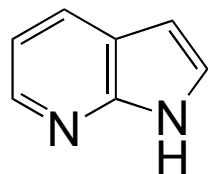
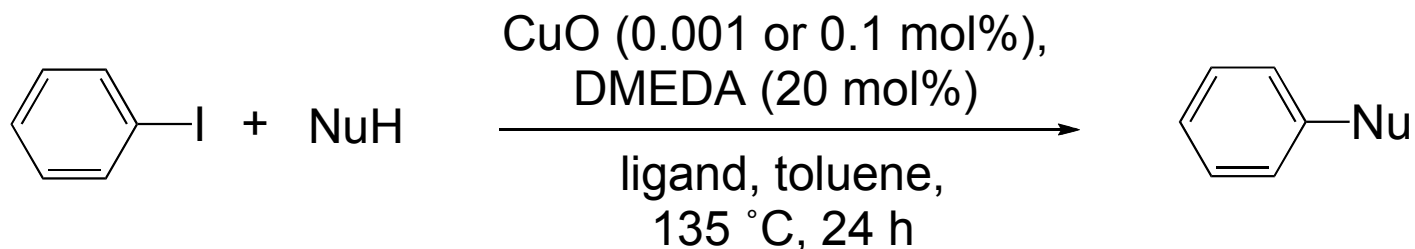
Buchwald, Bolm, *Angew. Chem. Int. Ed.* **2009**, 48, 5586.

Catalysis with ppm quantities of a copper catalyst

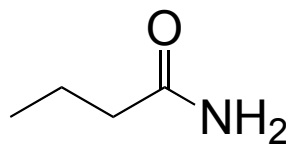


Larsson, Correa, Carril, Norrby, Bolm, *Angew. Chem. Int. Ed.* **2009**, 48, 5691.

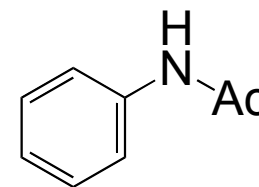
Catalysis with ppm quantities of a copper catalyst



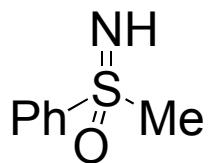
86% (0.001 mol%)



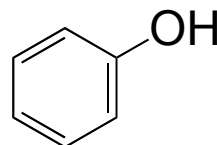
33% (0.001 mol%)
56% (0.1 mol%)



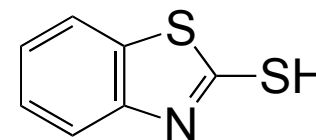
0% (0.001 mol%)
38% (0.1 mol%)



51% (0.001 mol%)
89% (0.1 mol%)



87% (0.001 mol%)



24% (0.001 mol%)
76% (0.1 mol%)

Larsson, Correa, Carril, Norrby, Bolm, *Angew. Chem. Int. Ed.* **2009**, 48, 5691.

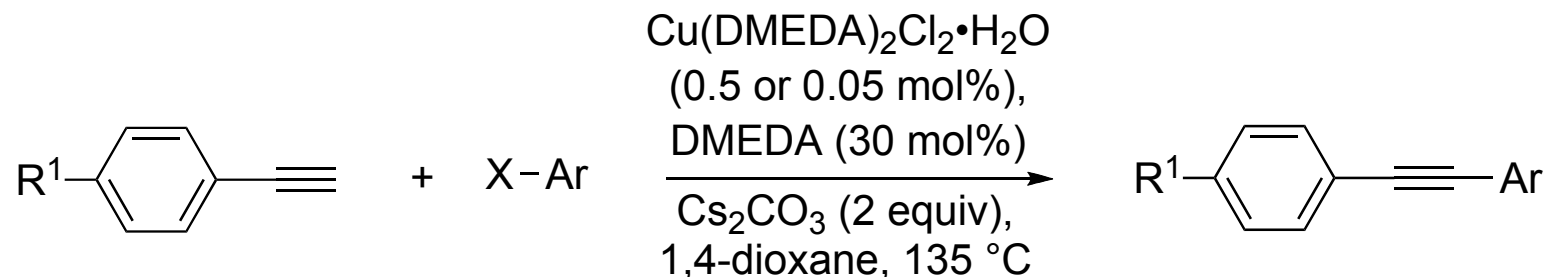
Interesting observations with ppm amounts of copper

Reminds on the work by Beletskaya, de Vries and Reetz on the use of "homeopathic doses" of palladium catalysts.

- The reaction is so sensitive towards metal traces that it is necessary to either use new equipment (glassware, stir-bar etc.) each time or to wash used vials with KOH/*iso*-propanol followed by rinsing with distilled water and drying over night at 150 °C in order to entirely suppress the formation of coupling products by metal traces from previous reactions.
- The ligand-to-metal ratio has to be high (with 20 mol % of DMEDA, 0.4 M in toluene, independent of the metal concentration).

Larsson, Correa, Carril, Norrby, Bolm, *Angew. Chem. Int. Ed.* **2009**, 48, 5691.

Copper-catalyzed Castro-Stephens reaction



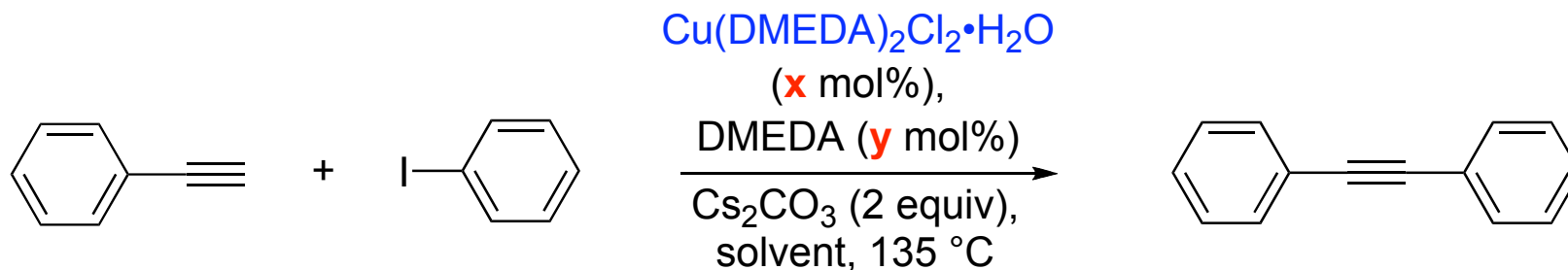
use of isolated **Cu(DMEDA)₂Cl₂·H₂O**

prepared by starting from 99.995% pure CuCl₂,
99%+ pure DMEDA and HPLC-grade solvents

Remaining metal impurities (as determined by ICP-MS):

8 ppm of Mn, 1 ppm of Ni and less than 4 ppb of Pd

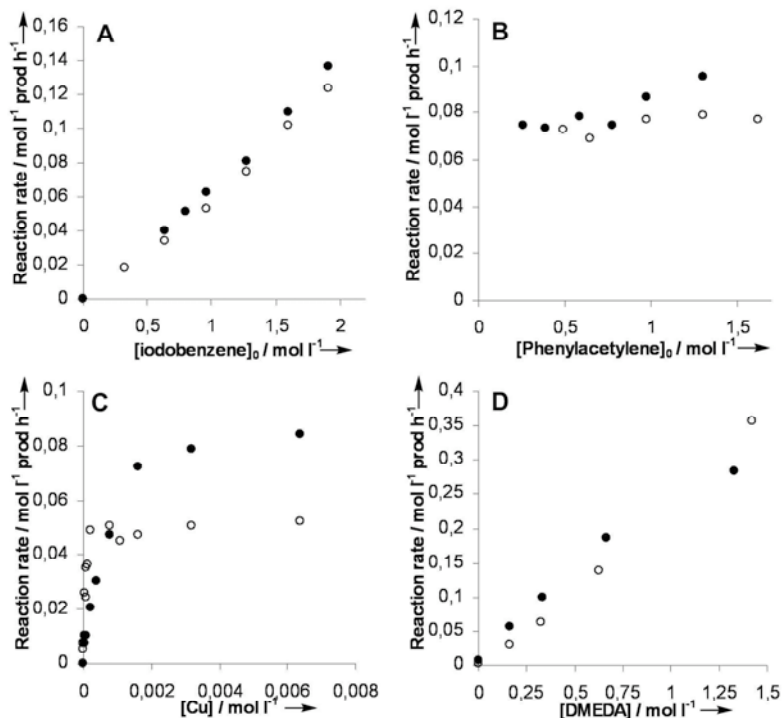
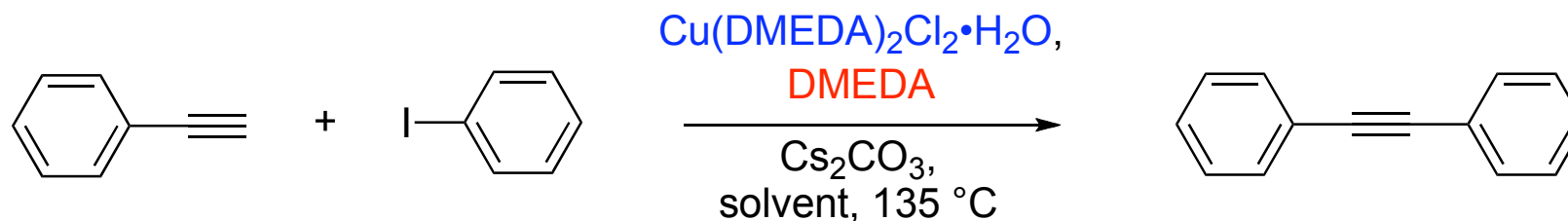
Copper-catalyzed Castro-Stephens reaction



Entry	x	y	Solvent	Amount [%] (GC)	
				3 h	22 h
1	-	-	1,4-dioxane	0	0
2	-	30	1,4-dioxane	0	0
3	1	-	1,4-dioxane	4	20
4	0.5	-	1,4-dioxane	3	14
5	0.5	30	1,4-dioxane	48	>99
6	0.5	1·10 ⁴	DMEDA	>99	>99

E. Zuidema, C. Bolm, *Chem. Eur. J.*, accepted for publication.

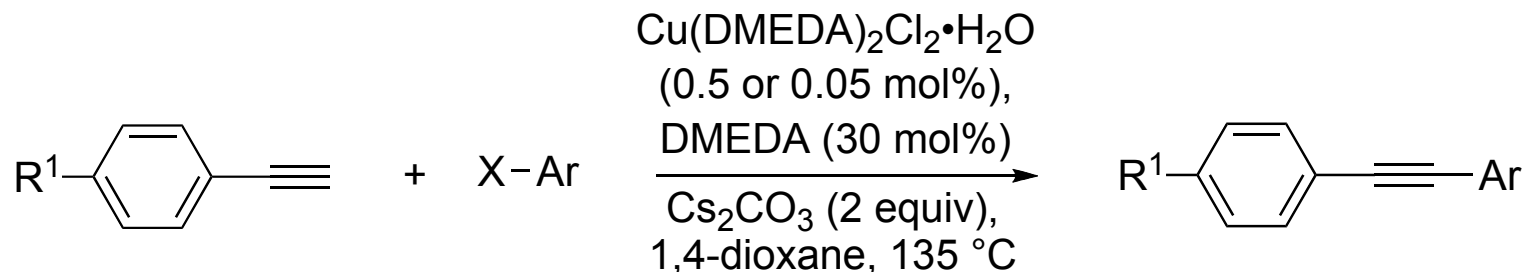
Copper-catalyzed Castro-Stephens reaction



kinetic studies (in toluene and dioxane)

- reaction rate is first-order in iodobenzene concentration
 - rate is independent of alkyne concentration
 - complex rate behavior with respect to copper concentration (in both solvents)
 - in toluene and dioxane, first-order in ligand, but in dioxane, deviation at high concentration
- in both solvents: ligand acceleration*

Copper-catalyzed Castro-Stephens reaction (with ppm of metal)



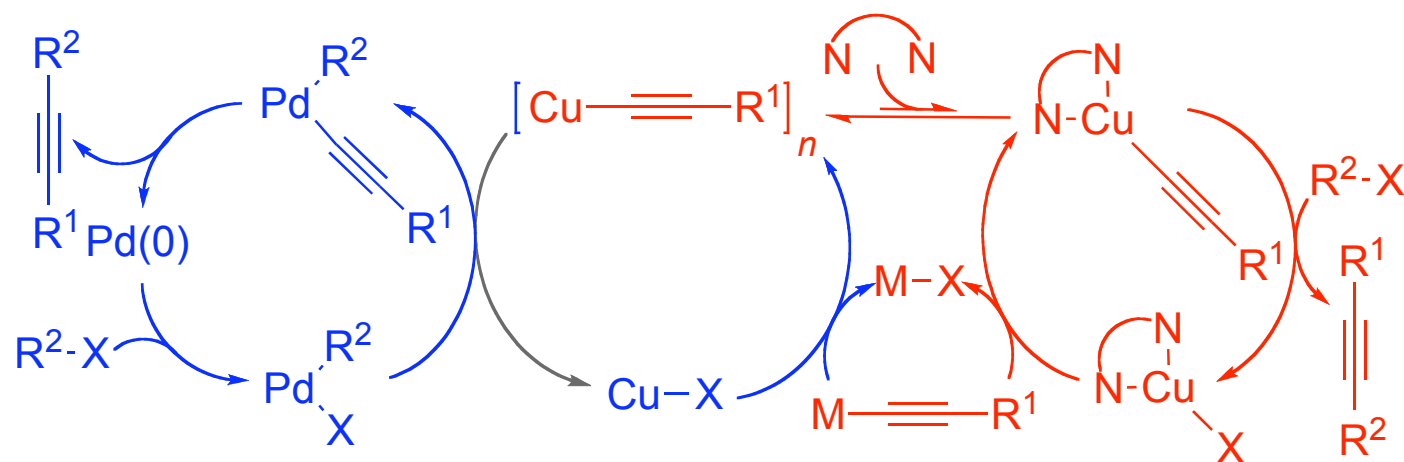
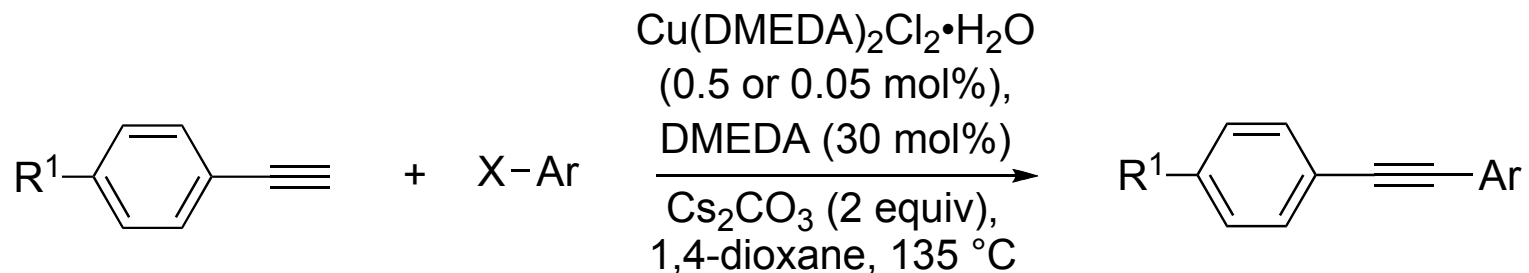
Conclusions (taken from the paper):

- Castro-Stephens reactions can readily be performed using **sub-mol% copper loadings**.
- The process is a striking example of **ligand-accelerated catalysis**, in which the addition of DMEDA ligand converts the resting state of the catalyst into an unprecedentedly active monomeric Cu(I) acetylide species.

Review of **LAC**: Berrisford, Bolm, Sharpless, *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059.

E. Zuidema, C. Bolm, *Chem. Eur. J.*, accepted for publication.

Copper-catalyzed Castro-Stephens reaction (with ppm of metal)



E. Zuidema, C. Bolm, *Chem. Eur. J.*, accepted for publication.

Summary and Acknowledgment

- **sulfoximine chemistry** (reported today)

M. Langner, M. Frings, I. Atodiresei, C. Moessner, P. Rémy, S.-M. Lu

- **arylation reactions**

A. Correa, O. Bistri, M. Carril, J. Bonnamour, I. Thomé, A. Beyer,
T. Semeraro, E. Zuidema

-
- Deutsche Forschungsgemeinschaft
(SFB 380, Graduiertenkolleg 440, Cluster TMBF)
 - Fonds der Chemischen Industrie
 - Alexander von Humboldt-Foundation
 - Spanish Ministerio de Educación y Ciencia (M.E.C.)
 - Basque Government