

C-C Bond Formations by Cross-Dehydrogenative Coupling of C_{sp³} -H Bonds

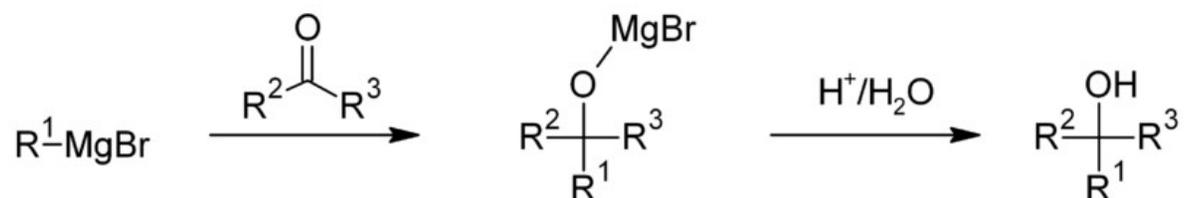
Feng Zhang

Frontiers of Chemistry Seminar

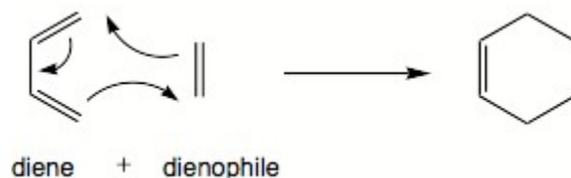
01-04-2014

Introduction

- Carbon-carbon (C-C) bond forming reactions represent one of the most vital tools for the synthesis of complex natural products, bioactive molecules developed as drugs and agrochemicals.
- The important of the synthesis of carbon-carbon bonds is reflected by the fact that Nobel Prizes in Chemistry have previously been given to this area: The Grignard reaction (1912),



- the Diels-Alder reaction (1950),

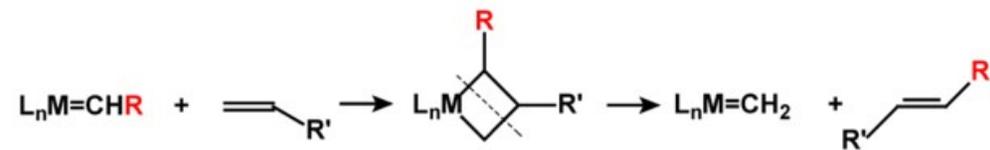


Introduction

- the Wittig reaction (1979),



- and olefin metathesis to Y. Chauvin, R. H. Grubbs, and R. R. Schrock (2005)



Strategies for selective C-C bond formation

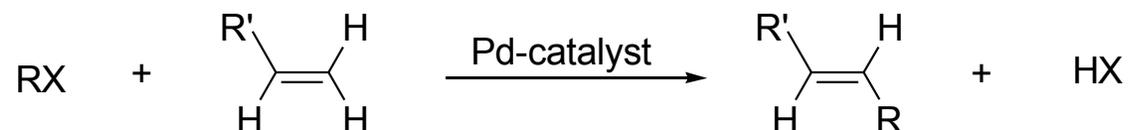
- During the second half of the 20th century, transition metals, and in particular palladium, have been of importance for the development of reactions for the formation of carbon-carbon bonds.
- Traditional coupling reaction for the construction of the C-C bond involves the coupling of an electrophilic species (C-X) with an unactivated substrate (C-H) or a reactive nucleophile, usually an organometallic reagent (C-M)



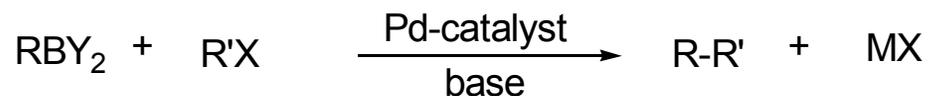
X = Cl, Br, I, OTf, OTs, OMs, etc.;
M = H, MgX, Li, BX₂, SnX₃, Zn etc.

Strategies for selective C-C bond formation

- **Mizoroki-Heck reaction**



- **Suzuki reaction**

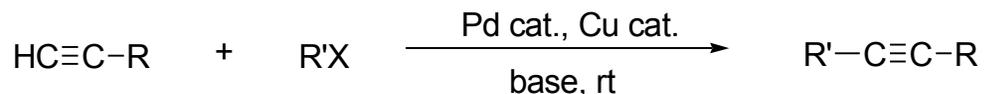


- **Negishi coupling reaction**



R, R' = aryl, vinyl, alkyl
X = halide, triflate, etc.

- **Sonogashira coupling reaction**



Strategies for selective C-C bond formation



Richard. F. Heck

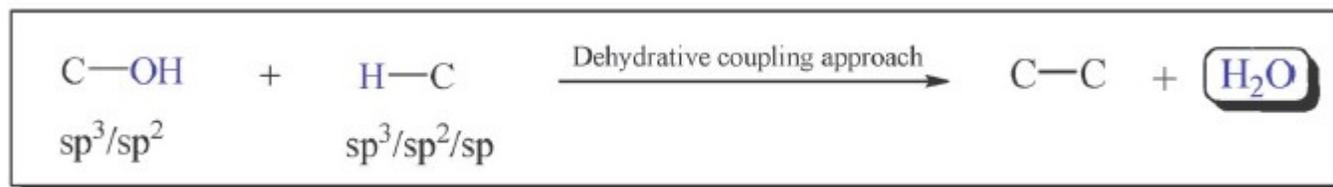
Ei-ichi Negishi

Akira Suzuki

- The year of 2010, the Nobel Prize in Chemistry is awarded to the formation of carbon-carbon single bonds through palladium-catalyzed cross-coupling reactions. Three researchers shared this Prize.
- The great success of coupling reactions is the predictable regioselectivity of the C-C bond formation. The new C-C bond is selectively formed at positions which are determined by the leaving groups on both substrates.

C-C bond formation *via* direct dehydrative coupling strategies

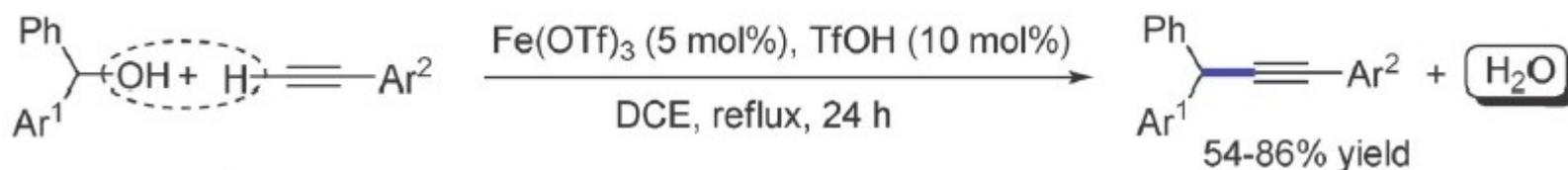
- Recently, a number of alternative strategies for C–C bond formation utilizing abundantly available/unactivated precursors via C–H activation, decarboxylative coupling, use of arylhydrazones as coupling partners etc., have been developed.
- In particular, the direct use of aryl alcohols/tautomerizable heterocycles/phenols (C–OH) as proelectrophiles is receiving huge attention because these building blocks are abundant in nature, have a relatively low toxicity and are an economical alternative for C–X species.



Chem. Soc. Rev., 2013, 42, 1121-1146

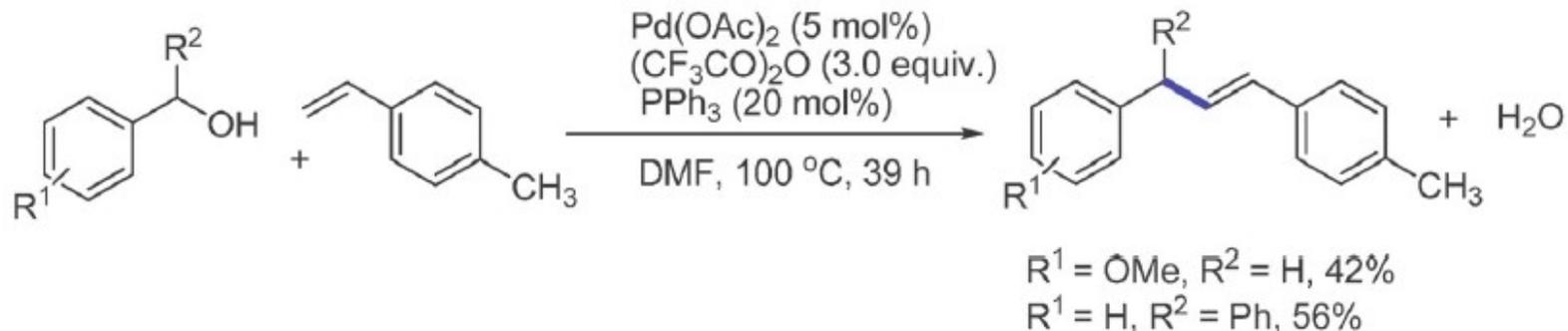
C-C bond formation *via* direct dehydrative coupling strategies

- Direct dehydrative functionalization of the C_{sp3}-OH bond
- C_{sp3}-C_{sp} bond formation



Chem. Commun., 2009, 6487–6489.

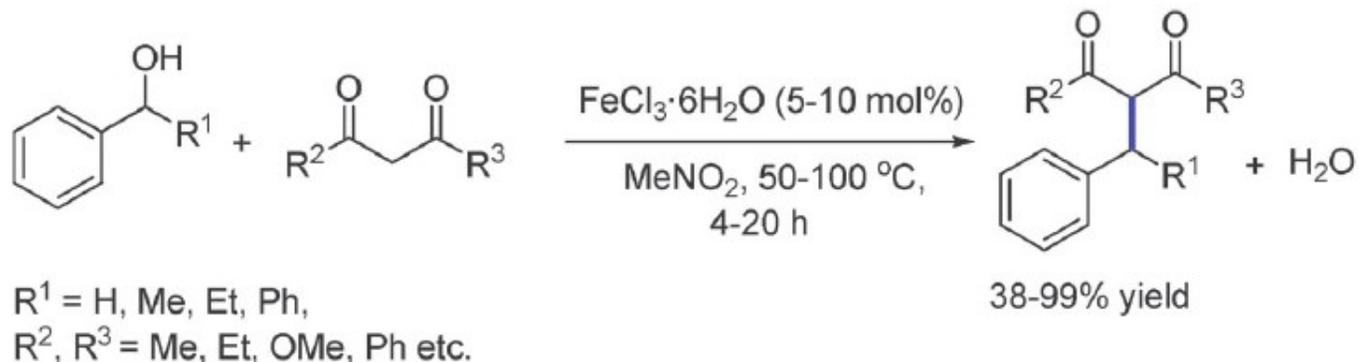
- C_{sp3}-C_{sp2} bond formation



J. Organomet. Chem., 2008, 693, 283–296.

C-C bond formation *via* direct dehydrative coupling strategies

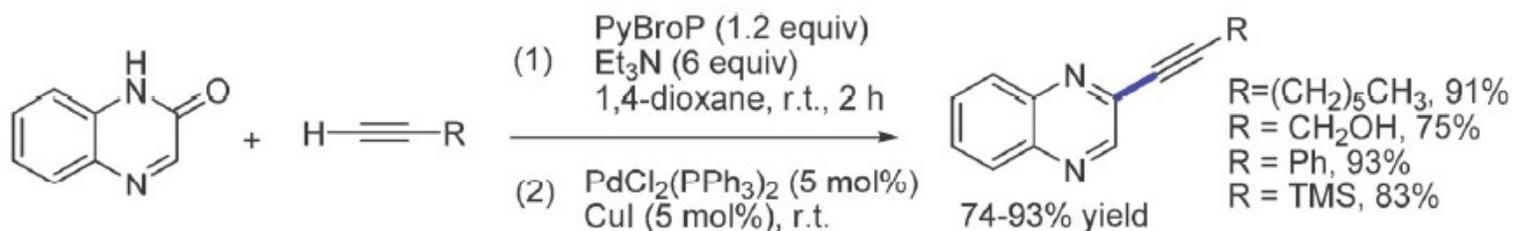
▪ $C_{sp^3}-C_{sp^3}$ bond formation



Synlett, 1996, 557–559.

▪ Direct dehydrative functionalization of the $C_{sp^2}-\text{OH}$ bond

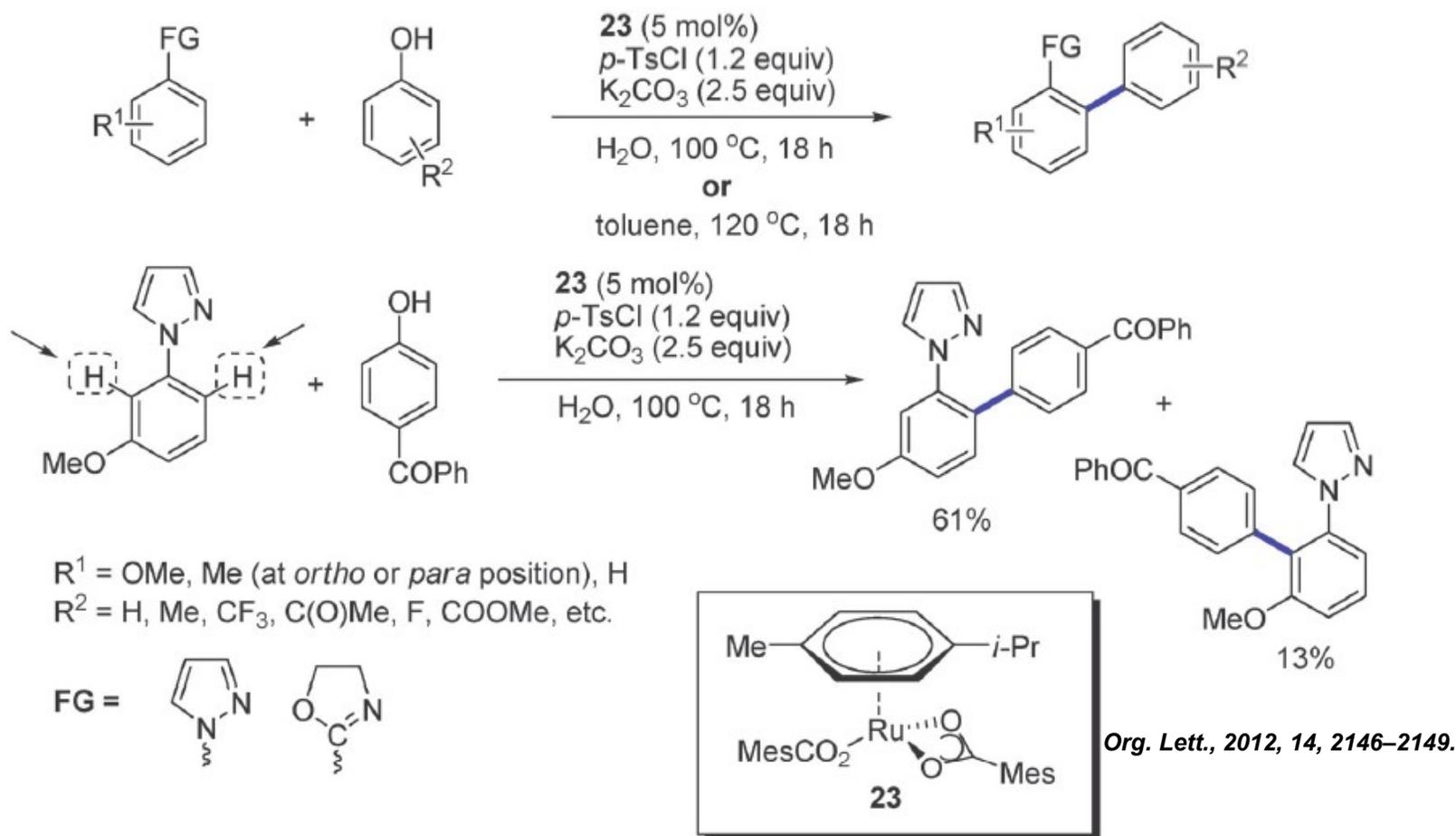
▪ $C_{sp^2}-C_{sp}$ bond formation



Org. Lett., 2010, 12, 2286–2289.

C-C bond formation *via* direct dehydrative coupling strategies

▪ C_{sp2}-C_{sp2} bond formation

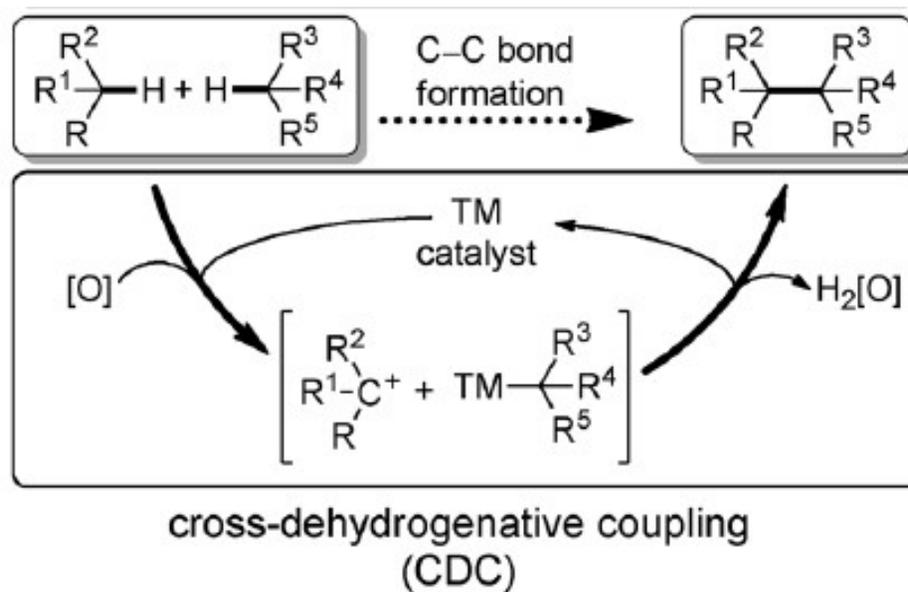


C-C bond formation *via* direct dehydrogenative coupling strategies

- The oxidative coupling of two different C-H bonds was termed cross-dehydrogenative coupling (CDC) by Dr. Li in 2004 and has become a growing field of interest.



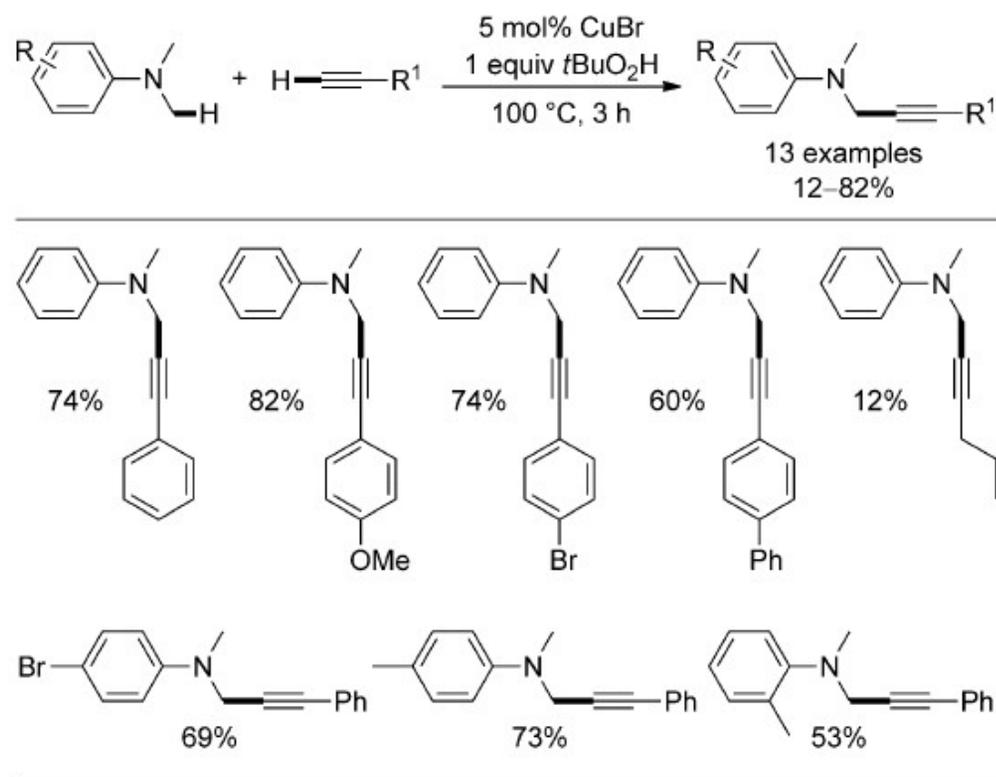
Chao-jun Li



Acc. Chem. Res. 2009, 42, 335 – 344.

Coupling of C_{sp^3} -H with C_{sp} -H Bonds

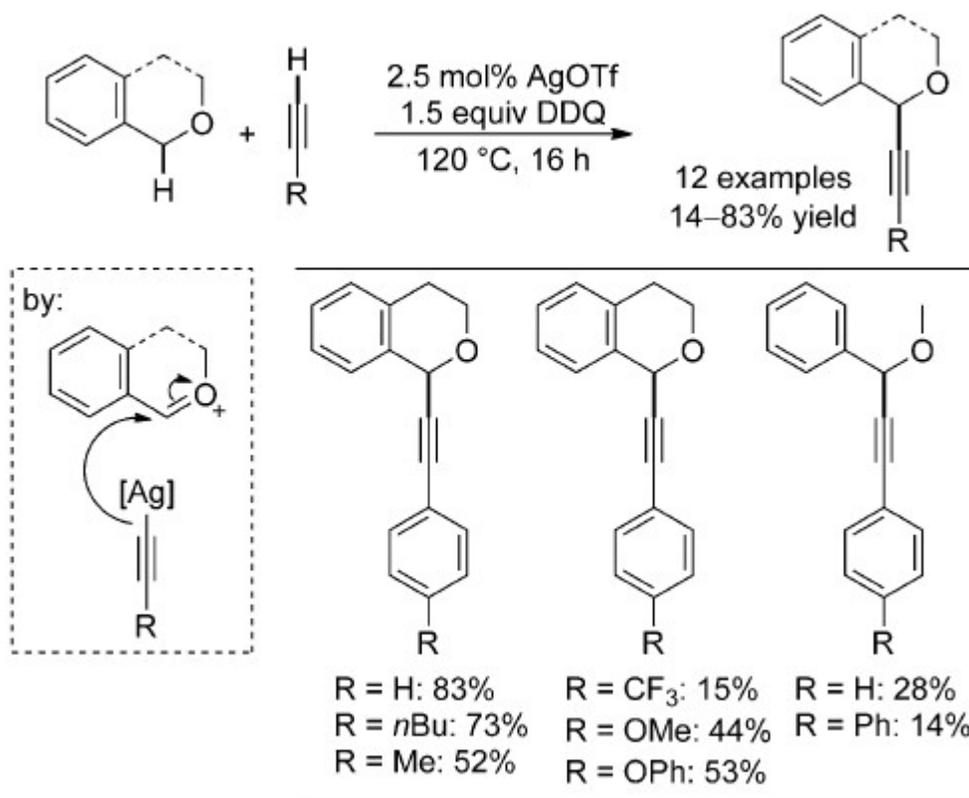
- The group of Li succeeded in 2004 in developing the first catalytic alkyne reaction of C_{sp^3} -H bonds adjacent to a nitrogen atom as a proof-of-concept for the CDC.



Aromatic alkynes provide the desired products in 60% to 82% yield whereas the use of aliphatic derivatives generally resulted in low to moderate yields (12–58%). The substituents on the aniline coupling partner influenced the reactivity, and the presence of either sterically demanding groups in the 2-position or electron-withdrawing groups on the 4-position resulted in a decrease of yield.

J. Am. Chem. Soc. 2004, 126, 11810 – 11811.

Coupling of C_{sp3} -H with C_{sp} -H Bonds

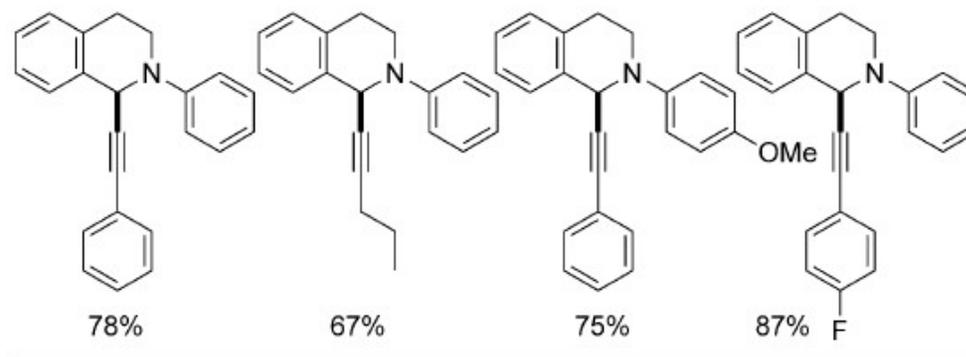
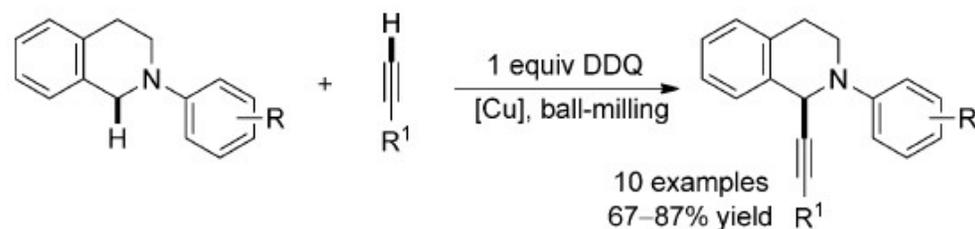


A silver-catalyzed oxidative coupling of terminal alkynes and benzylic ethers was introduced in 2010 by the group of Li

Heterocycles 2010, 82, 555 – 562.

Silver-catalyst alkynylation of benzylic ethers

Coupling of C_{sp3} -H with C_{sp} -H Bonds

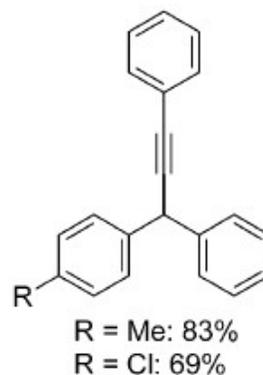
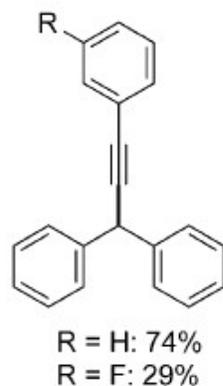
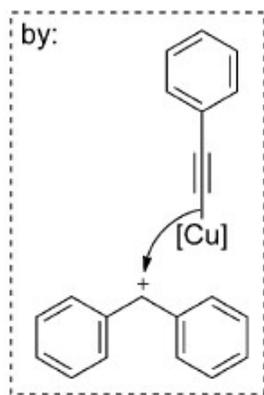
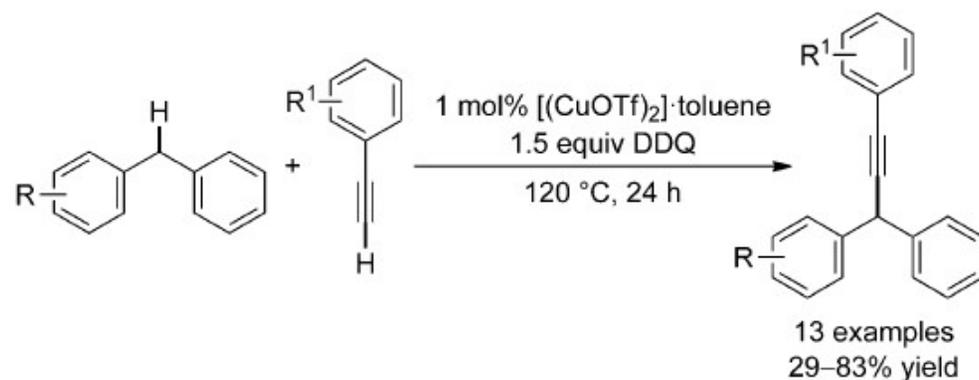


The group of Su showed that tetrahydroisoquinolines could be alkynylated in the presence of 1 equivalent of the oxidant DDQ under solvent-free, high-speed, ball-milling conditions. The reaction proceeded smoothly with both aliphatic and aromatic alkynes.

J. Org. Chem. 2011, 76, 9144 – 9150.

Functionalization of tetrahydroisoquinolines under ball-milling conditions

Coupling of C_{sp3} -H with C_{sp} -H Bonds

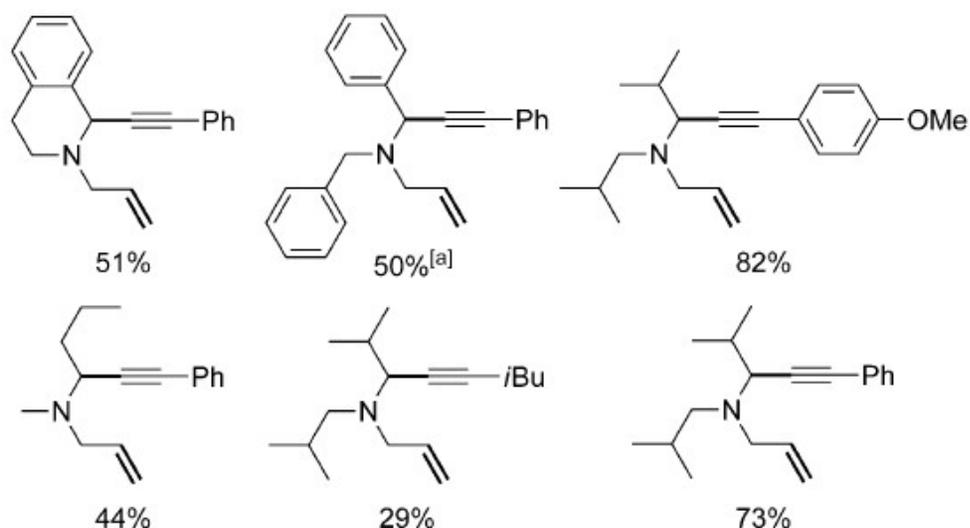
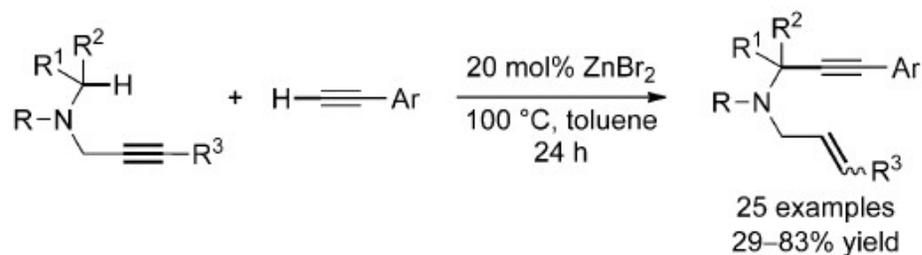


More recently, Li and co-workers reported the first alkylation of benzylic C-H bonds which are not adjacent to a heteroatom. Aromatic alkynes were smoothly converted, and the use of electron-rich derivatives resulted in slightly improved yields.

Adv. Synth. Catal. 2010, 352, 1446 – 1450.

CuOTf-catalyst CDC reaction of dephenylmethanes and aromatic alkynes

Coupling of C_{sp3} -H with C_{sp} -H Bonds



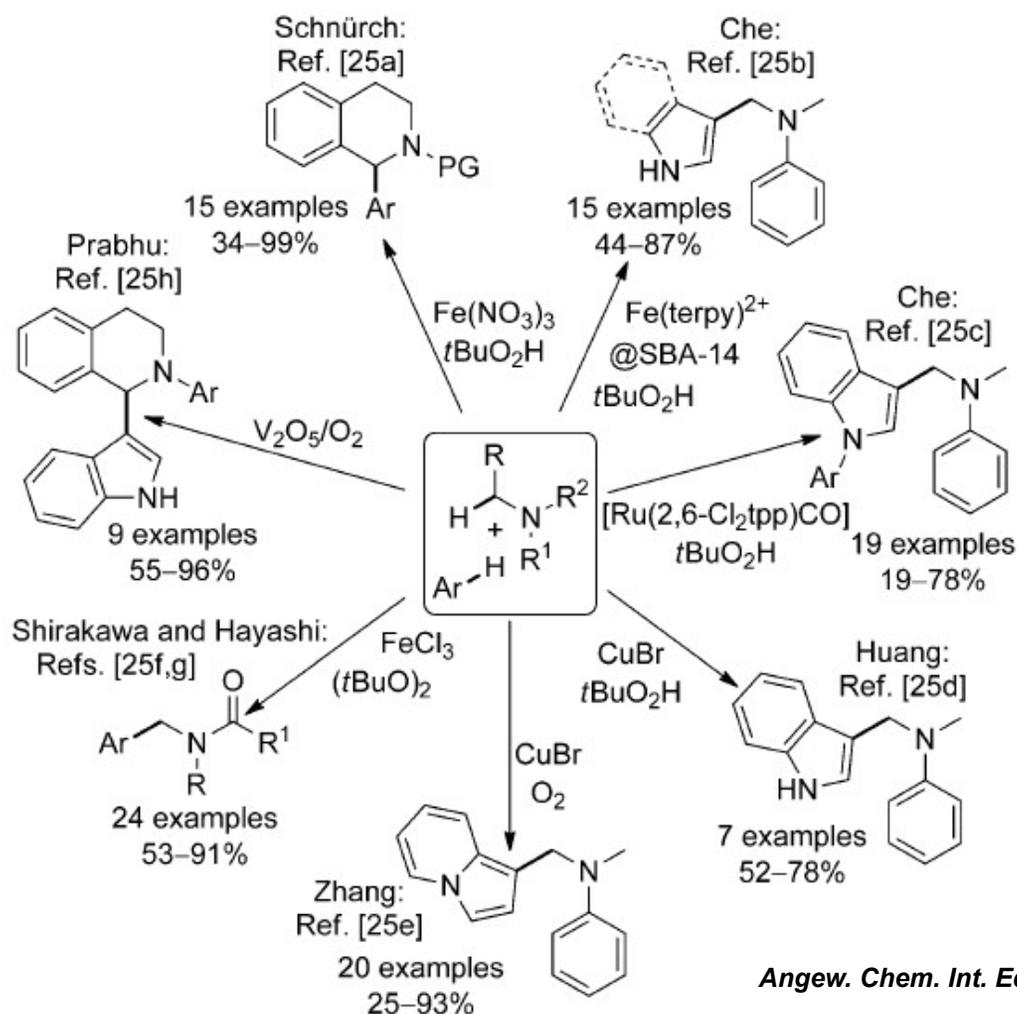
The group of Nakamura presented an original approach for the synthesis of N-tethered 1,6-enynes by a zinc(II)-catalyzed redox CDC reaction. The use of 20 mol% of ZnBr₂ allowed the synthesis of various enynes from the coupling reaction between propargylic amines and terminal alkynes. The reaction does not require the addition of an external oxidant as the propargylic amine reacts as a hydrogen acceptor. The triple bond is reduced into the corresponding alkene.

J. Am. Chem. Soc. 2012, 134, 2504 - 2507.

Zinc-catalyst synthesis of N-tethered 1,6-enynes

Coupling of C_{sp3}-H with C_{sp2}-H Bonds

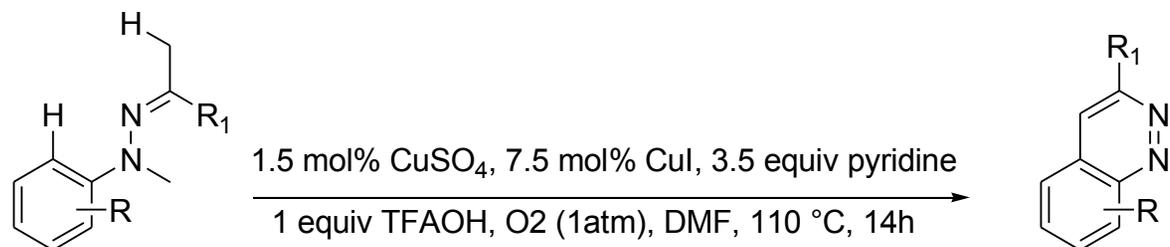
- Catalytic cross-dehydrogenative Friedel-Crafts-type arylations.



The first catalytic coupling of C_{sp3}-H bonds with C_{sp2}-H bonds using a cross-dehydrogenative Friedel-Crafts approach was reported by the group of Li in 2005. In the following years, the scope of cross-dehydrogenative Friedel-Crafts-type arylation was significantly improved by the development of highly efficient catalyst systems

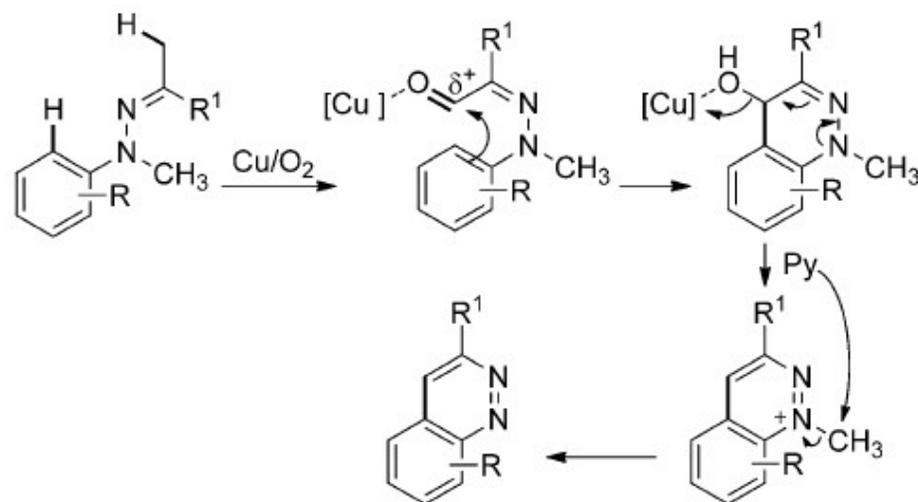
Angew. Chem. Int. Ed. 2014, 53, 74 -100

Coupling of C_{sp3}-H with C_{sp2}-H Bonds



30 examples, 47-95%

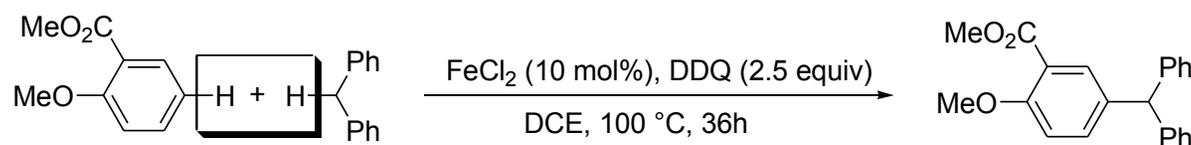
Angew. Chem. 2012, 124, 8443 – 8446; *Angew. Chem. Int. Ed.* 2012, 51, 8318 – 8321.



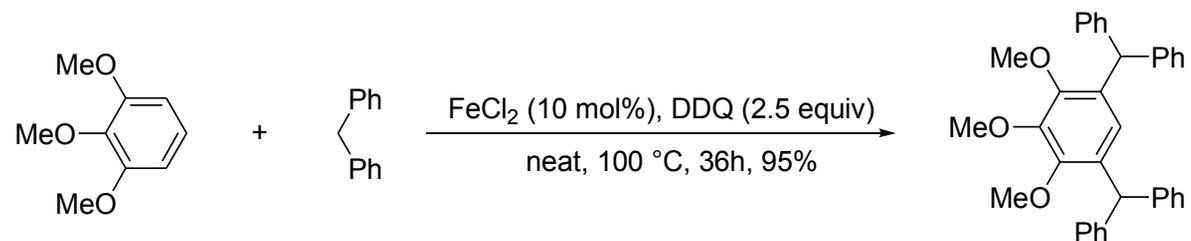
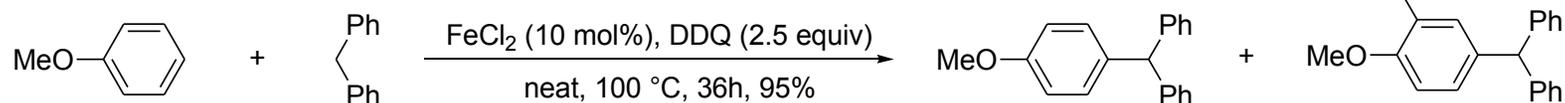
Recently, an intramolecular version of the dehydrogenative Friedel-Crafts-type arylation has been developed. The reaction is believed to start with the copper-catalyzed aerobic oxidation of the hydrazone and the obtained carbonyl intermediate is activated by the copper-catalyst to undergo a Friedel-Crafts cyclization. Demethylation with pyridine furnishes the desired products.

Coupling of C_{sp3}-H with C_{sp2}-H Bonds

▪ Friedl-Crafts-type cross-dehydrogenative benzylation



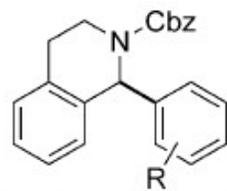
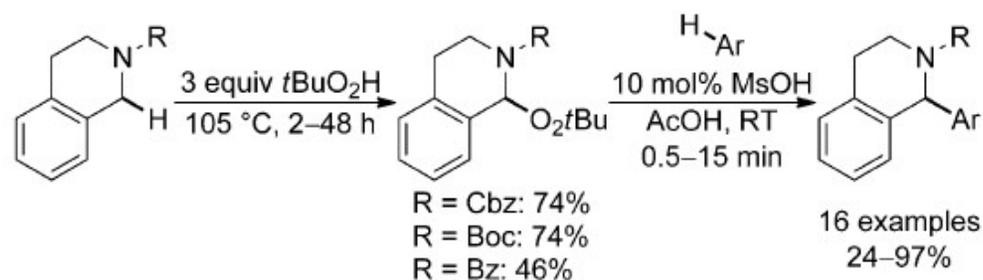
The group of Shi introduced a FeCl₂-catalyzed benzylation reaction of electron-rich arenes with diphenylmethanes



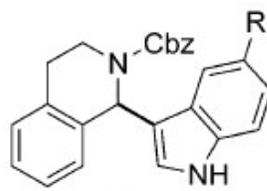
Angew. Chem Int Ed, 2009, 48: 3817–3820

Coupling of C_{sp3} –H with C_{sp2} –H Bonds

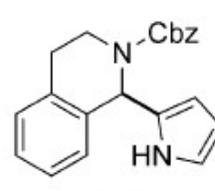
▪ Metal-Free Procedures



R = 2,4,6-(OMe)₃: 83%
R = 4-OMe: 24%
R = 4-OH: 72%



R = OMe: 95%
R = Br: 89%
R = CN: 86%



51%

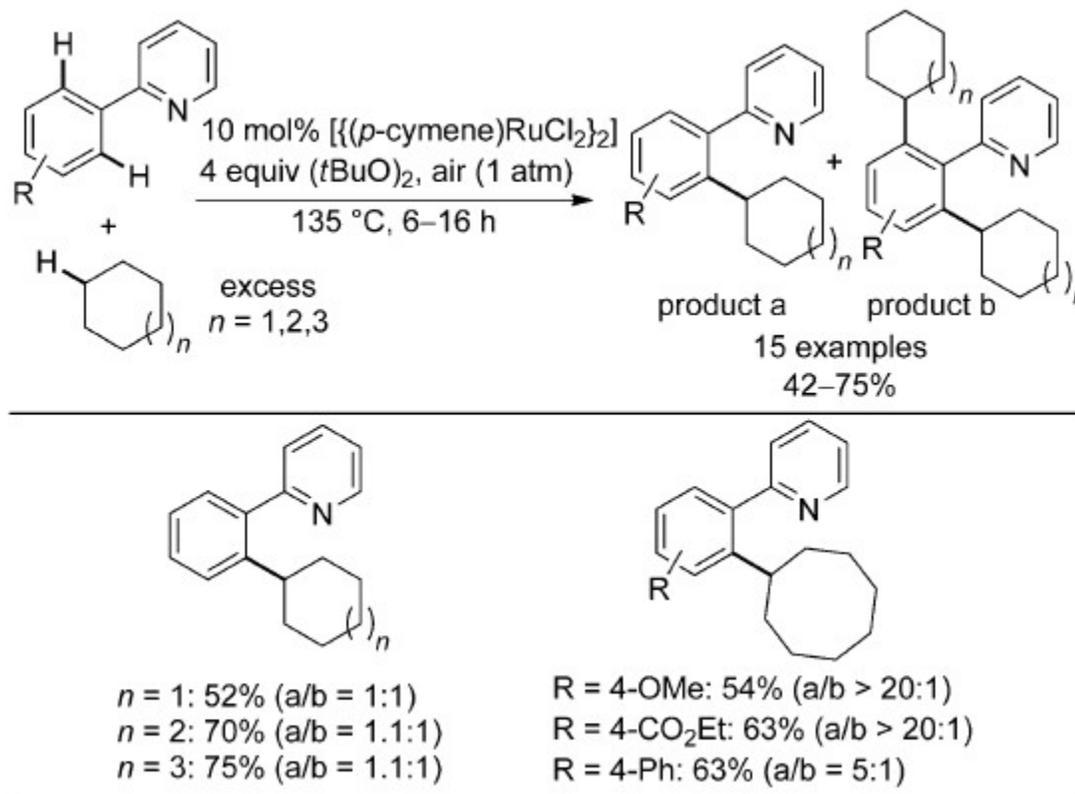
The group of Klussmann introduced a two-step procedure for the arylation of N protected tetrahydroisoquinolines in which the cationic intermediates are generated from the corresponding Peroxides in the absence of a transition-metal catalyst.

Eur. J. Org. Chem. 2013, 666 – 671.

Metal-free cross-dehydrogenative Friedel-Crafts arylation sequence

Coupling of C_{sp3} –H with C_{sp2} –H Bonds

- Cross-Dehydrogenative Coupling Involving Radical Intermediates
- Intermolecular Radical Alkylations

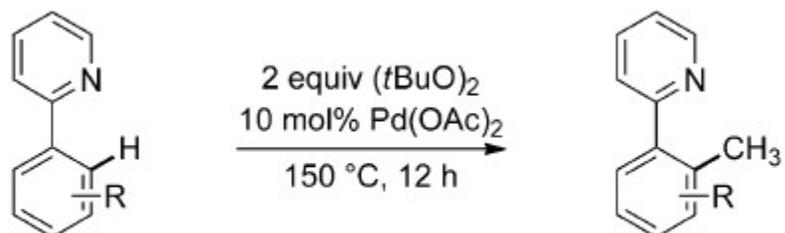


Various 2-aryl pyridines were successfully coupled with cyclohexane, cycloheptane, and cyclooctane. The reaction is sensitive toward the ring size. However, overalkylation was observed in many cases, and the products were obtained as isomeric mixtures.

Angew. Chem. 2008, 120, 6374–6378; *Angew. Chem. Int. Ed.* 2008, 47, 6278–6282.

Coupling of C_{sp3} –H with C_{sp2} –H Bonds

Intermolecular Radical Alkylations

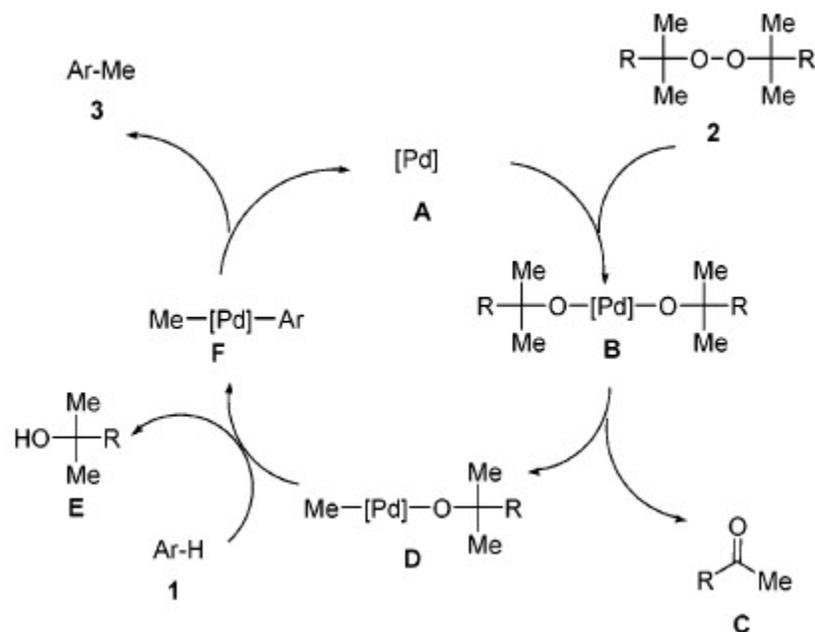


13 examples
33–95%

J. Am. Chem. Soc. 2008, 130, 2900 – 2901.

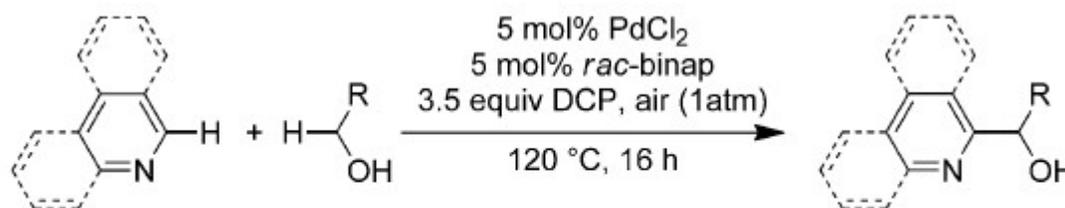
The peroxide compounds as both methylating reagents and hydrogen acceptor.

The methylation of the heterocyclic palladacycle might proceed through radical intermediates which are generated from the thermal decomposition of TBP.



Palladium species **A**, at a lower oxidation state, inserts into the weak O-O bond of peroxide **2** to generate a higher oxidation state intermediate **B**. Heterolytic β -methyl elimination of **B** leads to ketone **C** and the methyl palladium intermediate **D**. Reaction of **D** with arenes generates alcohol **E** and intermediate **F**, which leads to methylation product **3** via reductive elimination, and regenerates the active palladium species **A**.

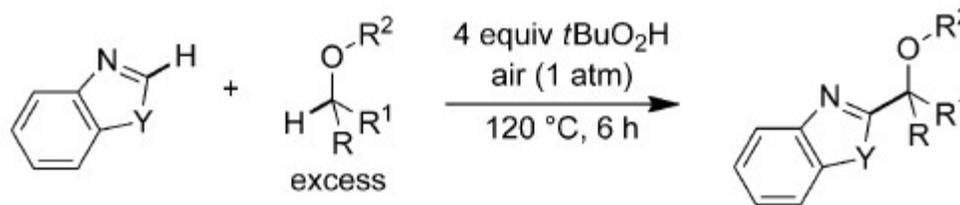
Coupling of C_{sp3} –H with C_{sp2} –H Bonds



Org. Lett. 2011, 13, 4581 – 4583.

13 examples
25–78%

the synthetic scope of the radical cross dehydrogenative alkylations was continuously improved. The group of Li presented the palladium-catalyzed coupling of N-heterocycles with simple alcohols.



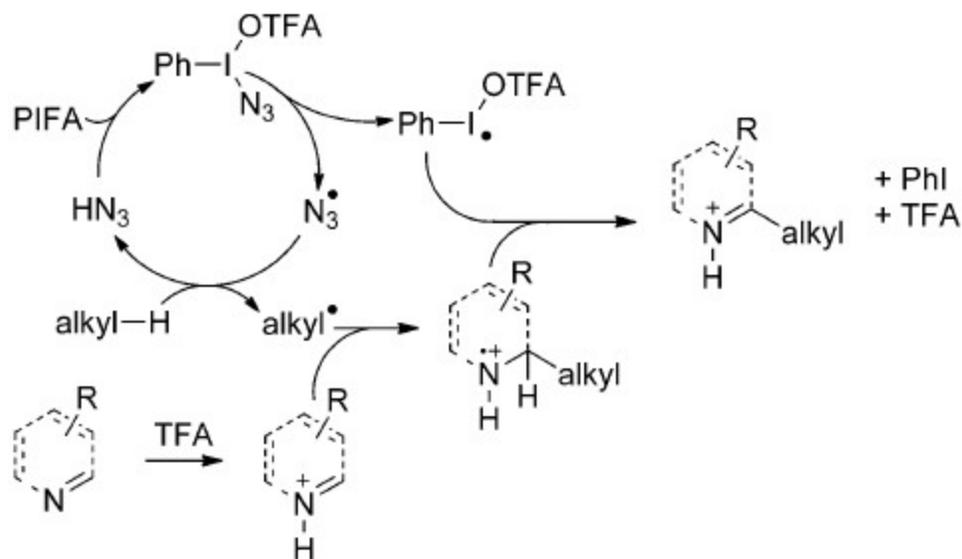
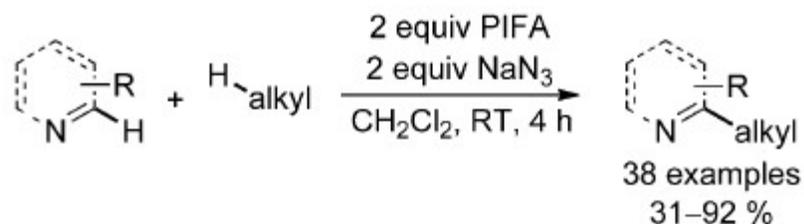
Y = NH, O, S

Org. Lett. 2011, 13, 5016 – 5019.

17 examples
50–90%

The group of Wang disclosed the radical coupling of benzothiazoles, benzoxazoles, and benzimidazoles with alcohols or ethers in the presence of excess TBHP.

Coupling of C_{sp3} –H with C_{sp2} –H Bonds



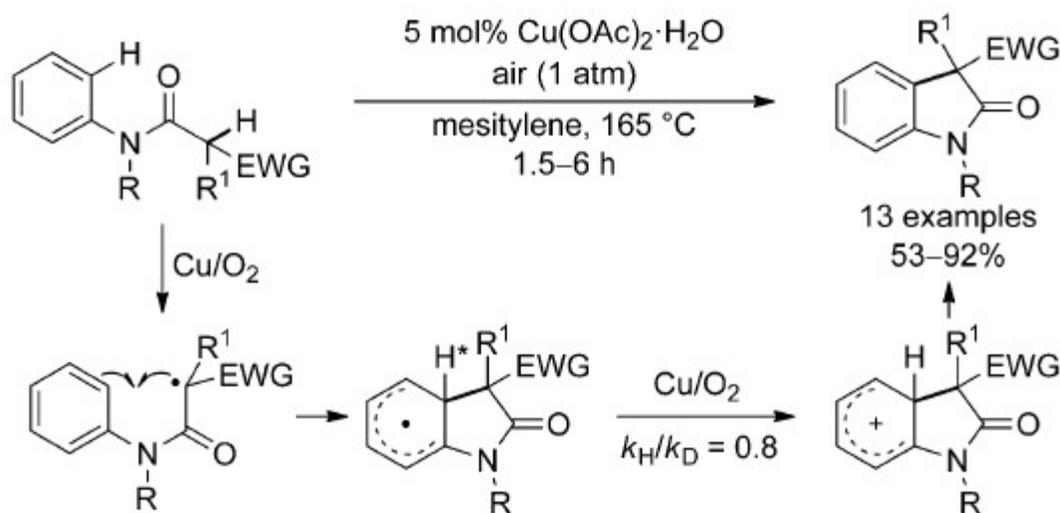
Angew. Chem. 2013, 125, 3349 – 3353; *Angew. Chem. Int. Ed.* 2013, 52, 3267 – 3271.

the group of Antonchick recently introduced a combination of (bis(trifluoroacetoxy) iodo)benzene (PIFA) and sodium azide as a synthetic alternative to peroxide based oxidants.

starts with the generation of a (trifluoroacetoxy) iodobenzene radical and an azide radical. The azide radical abstracts a hydrogen atom from the cyclic alkane and the resulting hydrazoic acid reacts with a second PIFA molecule under release of trifluoroacetic acid, which protonates the heterocycle and activates it for the addition of the alkyl radical. The resulting heterocyclic radical cation is oxidized into the corresponding product by the (trifluoroacetoxy) iodobenzene radical.

Coupling of C_{sp3} –H with C_{sp2} –H Bonds

▪ Intramolecular Radical Cyclizations



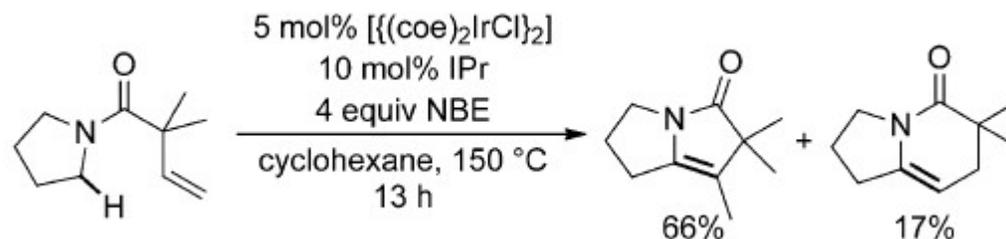
In 2010, the group of Taylor succeeded in developing a Cu(OAc)₂-catalyzed aerobic variant. The procedures are believed to proceed by the generation of benzyl radical intermediates which subsequently add to the aniline moiety. Oxidation of the resulting radical and re-aromatization provides the product.

Angew. Chem. 2009, 121, 1664 – 1667; *Angew. Chem. Int. Ed.* 2009, 48, 1636 – 1639;
Chem. Commun. 2009, 3249 – 3251; *Org. Lett.* 2010, 12, 3446 – 3449.

Copper-Catalyzed bicyclic radical indole synthesis

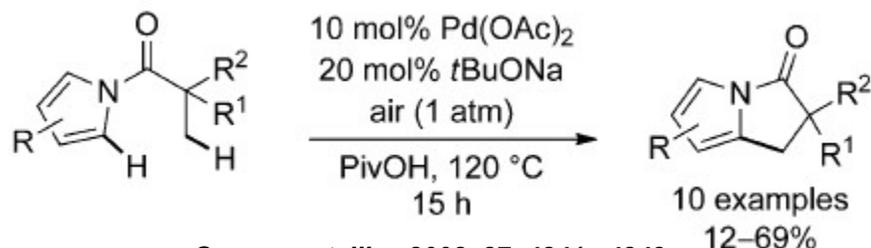
Coupling of C_{sp3} –H with C_{sp2} –H Bonds

▪ Cross-Dehydrogenative Alkylation by Transition-Metal-Catalyzed C-H Activation



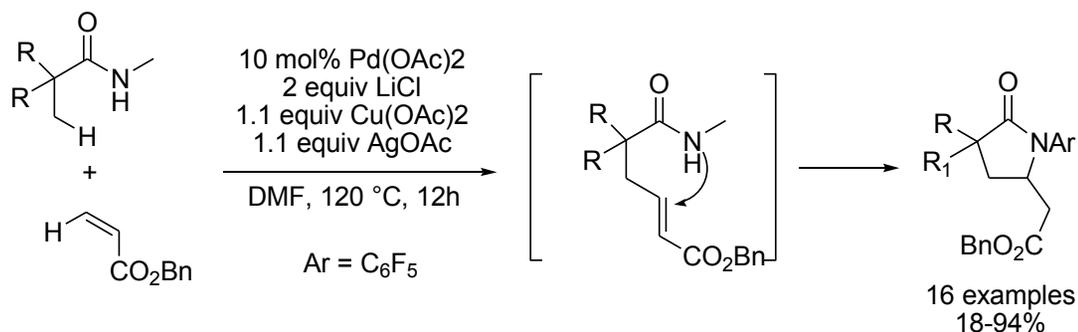
J. Am. Chem. Soc. 2004, 126, 6556 – 6557.

The group of Sames in 2004, who demonstrated the feasibility of an iridium-catalyzed intramolecular cyclization of 2,2-dimethylvinyl acid pyrrolidine Amide.



Organometallics 2008, 27, 4841 – 4843

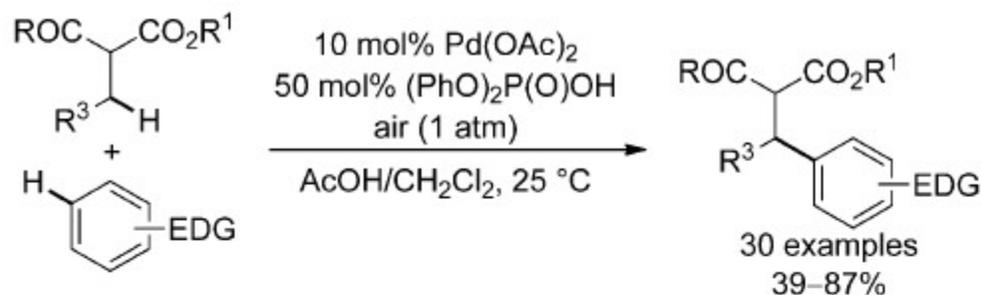
The group of Fagnou introduced an aerobic cyclization of N-pivaloyl pyrroles.



J. Am. Chem. Soc. 2010, 132, 3680 – 3681

Yu and co-workers disclosed a one-pot sequence for the synthesis of functionalized 2-pyrrolidinones, and it starts with an intramolecular C_{sp3} –H olefination of the pivaloyl amides and subsequent conjugate addition.

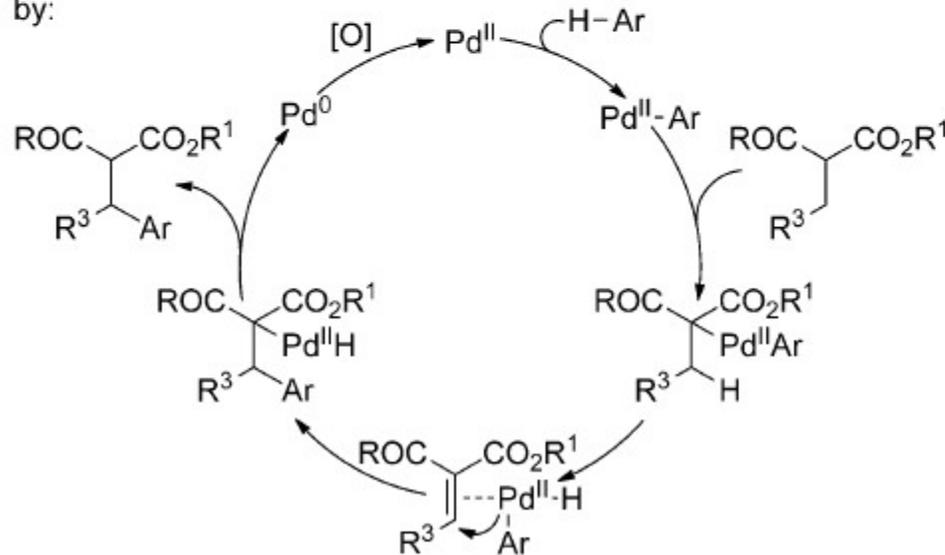
Coupling of C_{sp3} –H with C_{sp2} –H Bonds



The group of Pihko reported an aerobic palladium catalyzed dehydrogenative arylation of 2-alkyl-1,3-dicarbonyl compounds.

Chem. Eur. J. 2012, 18, 12590 – 12594.

by:

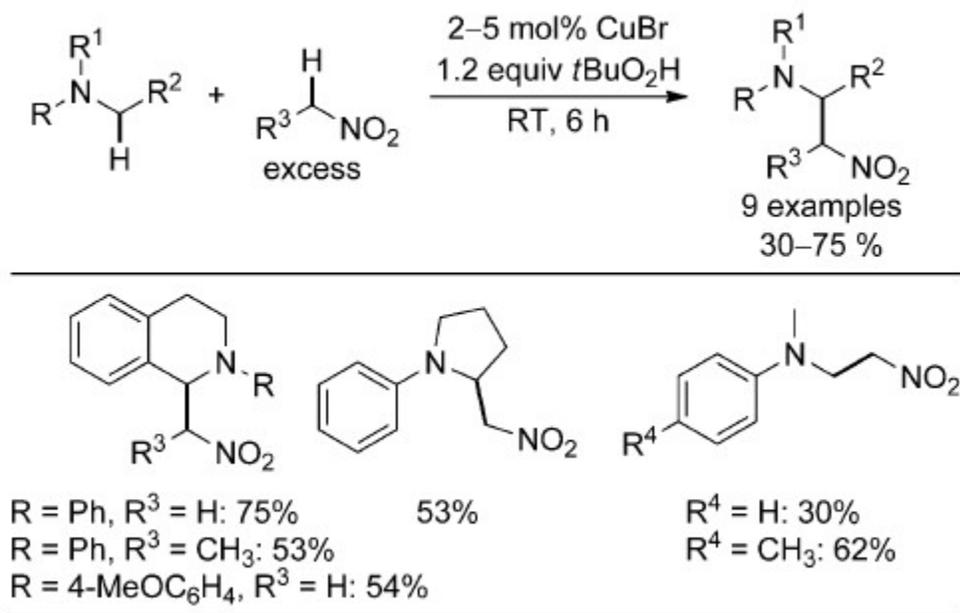


Arylation of 2-alkyl acetoacetates

The reaction is believed to proceed by the palladation of the arene and subsequent coordination of the resulting aryl complex with the nucleophilic α -carbon atom of the ketoester. Subsequent β -hydride elimination generates an acrylic species and the palladium hydride aryl complex transfers the aryl group onto the double bond. Protonolysis by the diphenylphosphoric acid or hydride transfer liberates the product and releases a palladium(0) species which is reoxidized into the initial catalyst.

Coupling of C_{sp3} –H with C_{sp3} –H Bonds

- Various CH acidic compounds with pKa values ranging from pKa = 17 (e.g. nitromethane in DMSO) to pKa = 26 (e.g. acetone in DMSO) have been successfully used in CDC reactions. The procedures are categorized herein by the related named reaction.
- Aza-Henry-Type reactions**



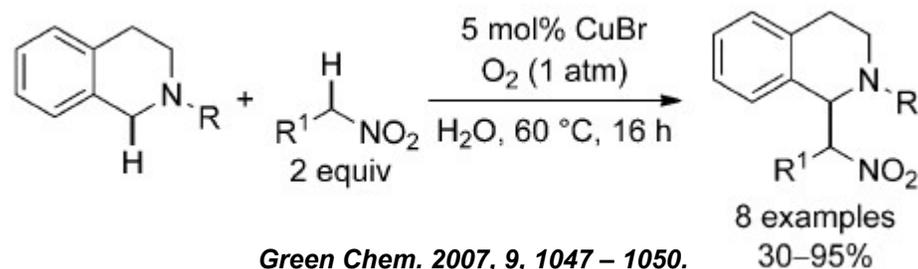
J. Am. Chem. Soc. 2005, 127, 3672 – 3673.

Copper-catalyzed aza-Henry reaction

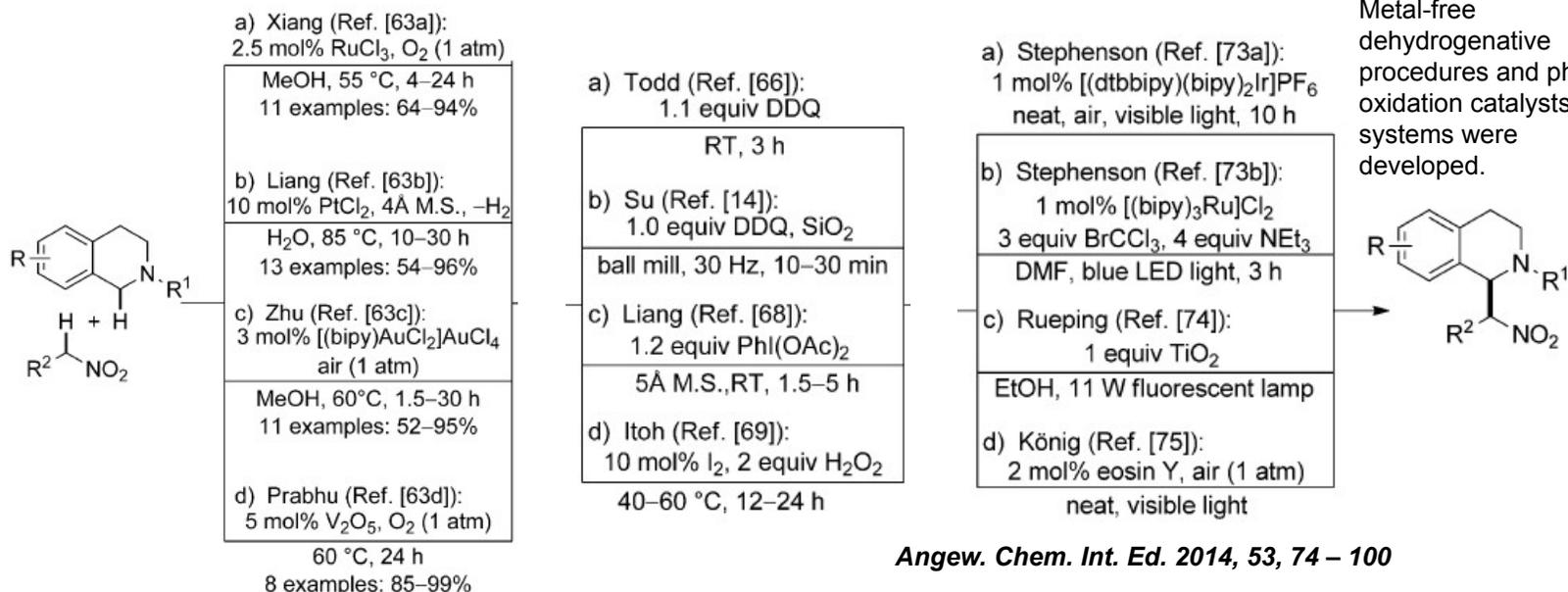
In 2005, the first broadly applicable procedure for the cross-dehydrogenative aza-Henry reaction was introduced by the group of Li. Various N-arylated tetrahydroisoquinolines were successfully coupled with an excess of the nitroalkanes in the presence of catalytic quantities of CuBr and 1.2 equivalents of TBHP at room temperature. Other copper salts such as CuBr₂ (92%), CuI (80%), CuCl₂ (80%), Cu(OAc)₂·H₂O (80%), or CuCl (75%) also catalyze the reaction but higher catalyst loadings (10 mol%) were required.

Coupling of C_{sp3} –H with C_{sp3} –H Bonds

Aza-Henry-Type reactions



Improved aerobic copper-catalyzed aza-Henry reaction in water



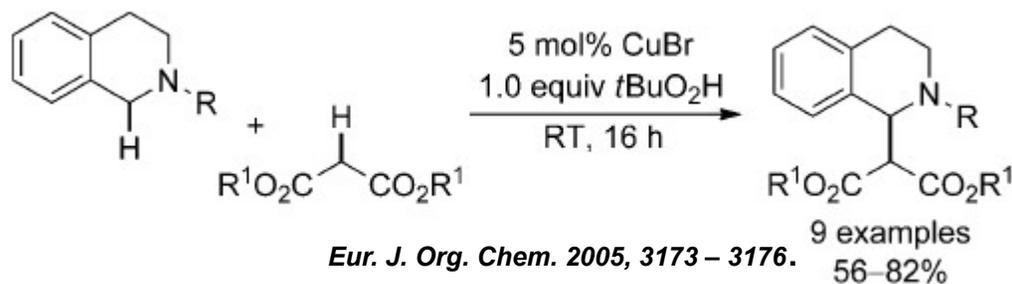
The atom economy and process safety were significantly improved in 2007 by developing an aerobic protocol which proceeds in water. Various homogeneous catalyst systems were developed which efficiently mediate the aerobic cross-dehydrogenative aza-Henry reactions. Metal-free dehydrogenative procedures and photo-oxidation catalysts systems were developed.

Coupling of C_{sp3} –H with C_{sp3} –H Bonds

▪ Mannich-Type Reactions

The coupling of in situ generated iminium cations with in situ enolized carbonyl compounds resulted in the cross dehydrogenative access to Mannich-type products.

▪ Mannich-type reactions with tertiary amines

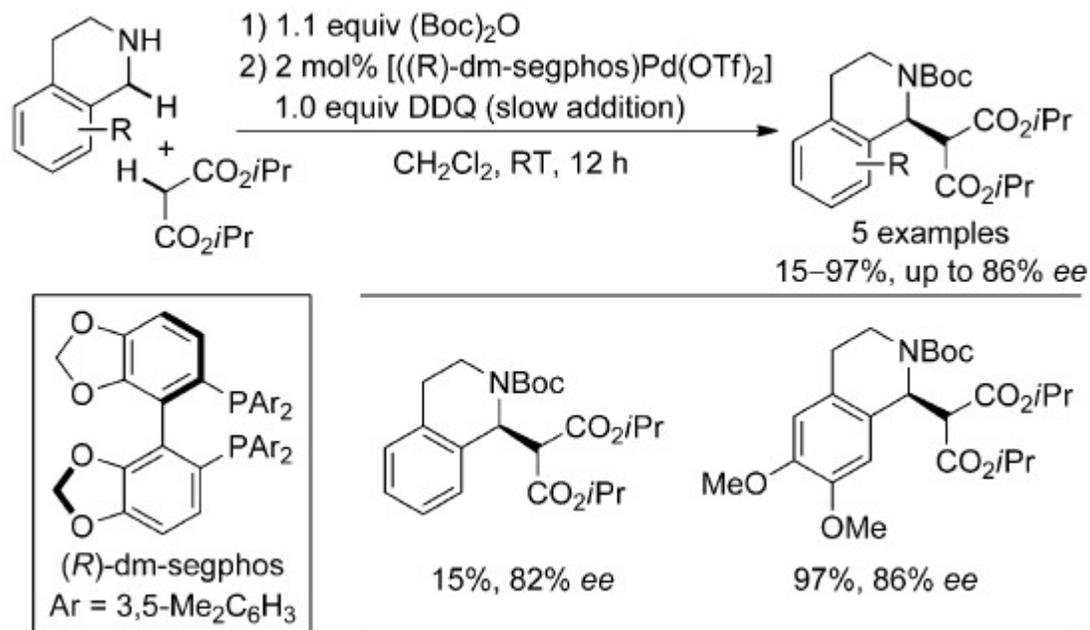


Copper-catalyzed cross-dehydrogenative Mannich reaction

The reaction proceeds smoothly at room temperature with 5 mol% of CuBr and 1 equivalent of TBHP. Good results were obtained even with an equimolar quantity of the substrates under neat conditions. Interestingly, the addition of a solvent resulted in significantly decreased yields.

Coupling of C_{sp3} –H with C_{sp3} –H Bonds

- Mannich-type reactions with tertiary amines



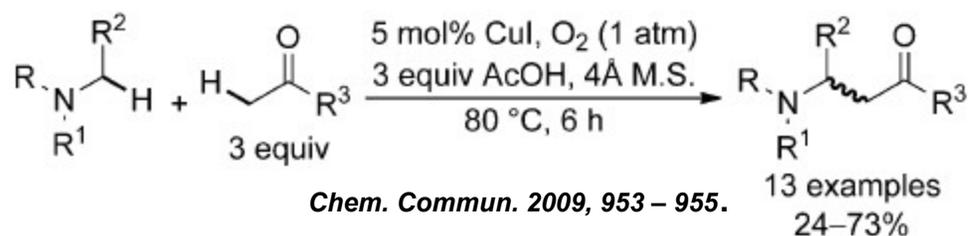
The use of the [(R)-dm-segphos)Pd(OTf)₂] complex in combination with DDQ as the oxidant allowed the coupling of isopropyl malonate with a set of in situ Boc-protected tetrahydroisoquinolines to deliver the product in high enantiomeric excess.

Enantioselective cross-dehydrogenative Mannich reaction.

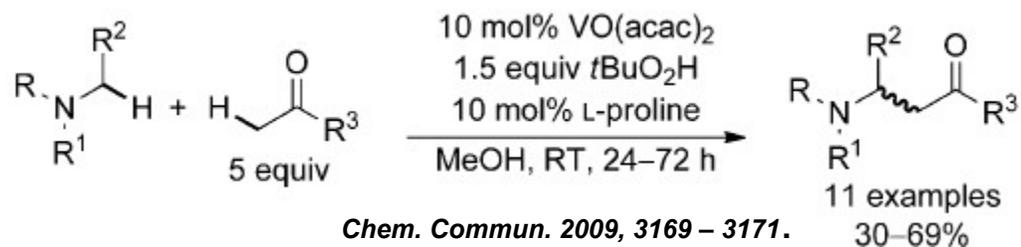
J. Org. Chem. 2008, 73, 5859 – 5871.

Coupling of C_{sp3} –H with C_{sp3} –H Bonds

- Mannich-type reactions with tertiary amines
- Less C-H-acidic aldehydes or ketones (pK_a = 25 in DMSO) have to be activated by a cocatalyst to serve as substrates in cross-dehydrogenative Mannich reactions.
- Bronsted or Lewis acids in the reaction mixtures to facilitate the enolization of the carbonyl compounds.



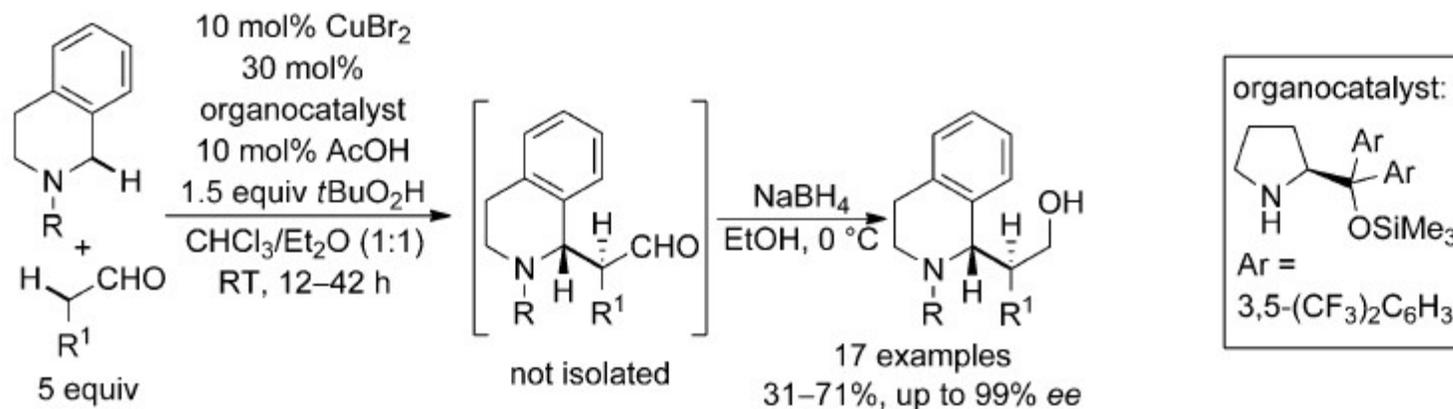
- The second method is based on the addition of a secondary amine which converts the carbonyl compounds into the more reactive enamines in situ.



Coupling of C_{sp3} –H with C_{sp3} –H Bonds

▪ Mannich-type reactions with tertiary amines

an enantioselective procedure is feasible by adding a chiral organocatalyst.



Enantioselective cross-dehydrogenative Mannich reaction.

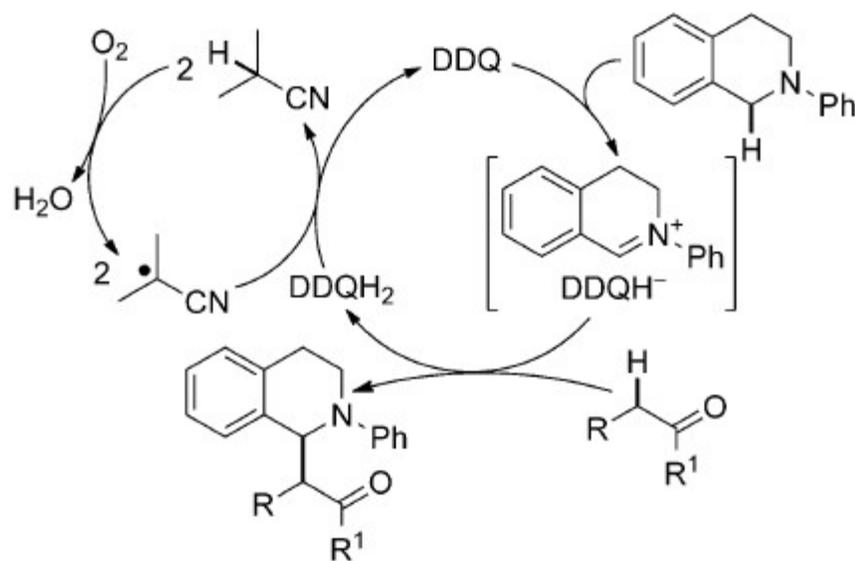
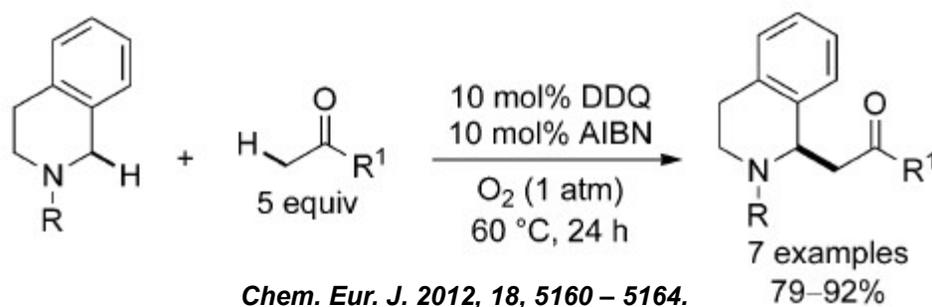
Angew. Chem. 2012, 124, 3709 – 3712; *Angew. Chem. Int. Ed.* 2012, 51, 3649 –3652.

High enantioselectivities and acceptable diastereoselectivities were obtained with a chiral catalyst in combination with CuBr₂, acetic acid, and TBHP. A solvent mixture of chloroform and diethyl ether proved to be crucial in achieving good selectivities.

The addition products were sensitive to racemization, and a final reduction step with NaBH₄ simplified the isolation procedure and prevented unwanted side reactions.

Coupling of C_{sp3} –H with C_{sp3} –H Bonds

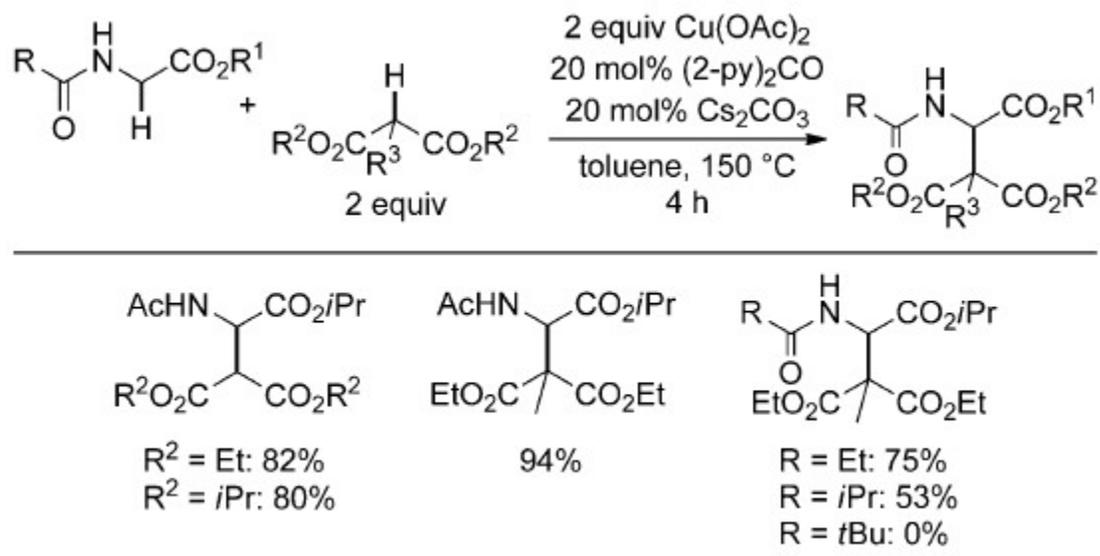
- Mannich-type reactions with tertiary amines



At around the same time, alternative oxidants and photocatalytic procedures were disclosed for cross-dehydrogenative Mannich reactions of ketones and aldehydes. The first metal-free DDQ-catalyzed dehydrogenative Mannich reaction was introduced by the group of Prabhu. The mechanism which starts with the oxidation of the tetrahydroisoquinoline by DDQ. Hydrogen abstraction from the resulting 2,3-dicyano-4,5-dichlorohydroquinone by butyronitrile radicals regenerates the DDQ catalyst and liberates 2-butyronitrile which readily reacts with oxygen to regenerate the radical intermediates.

Coupling of C_{sp3} –H with C_{sp3} –H Bonds

- Mannich-type reactions with Glycine Derivatives
- The group of Li demonstrated in 2008 that various N-acetyl glycine esters are selectively coupled at the α-position with a series of malonates.



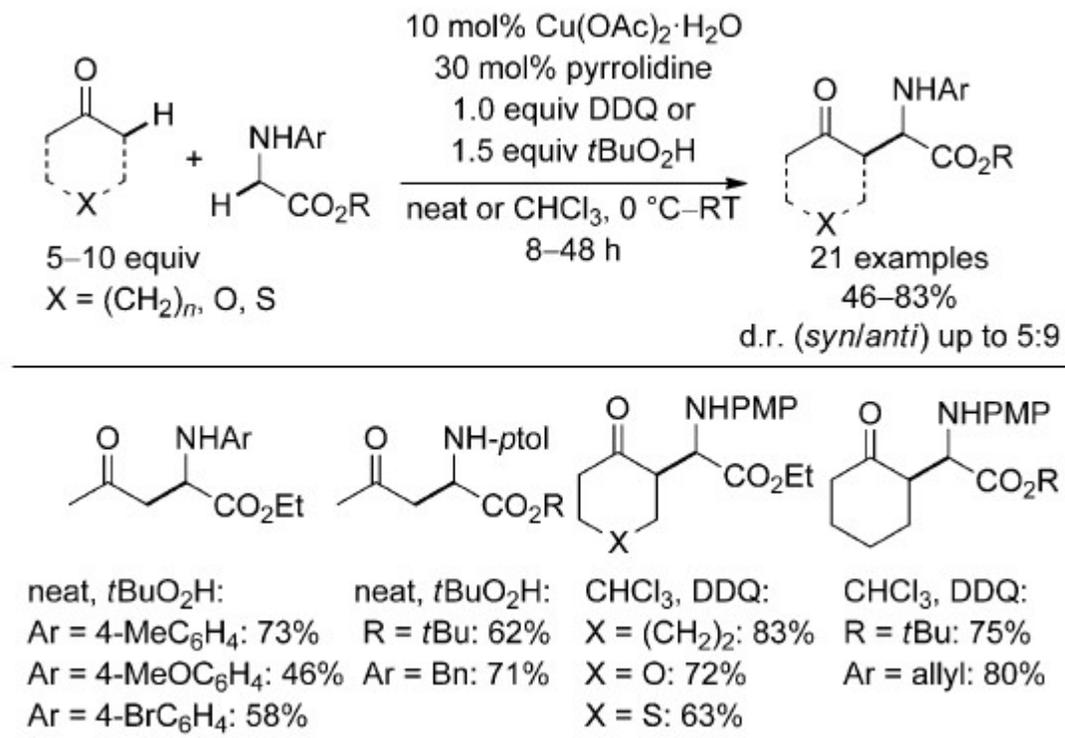
Cu(OAc)₂ which serves both as catalyst and oxidant. The yield was significantly improved by the addition of Cs₂CO₃ and di-(2-pyridyl) ketone.

In contrast, the steric properties of the glycine derivatives showed a significant impact on the reaction outcome. Bulky and electron-donating ester groups, as well as small acetyl groups on the nitrogen atom proved to be beneficial.

Angew. Chem. 2008, 120, 7183 – 7186; *Angew. Chem. Int. Ed.* 2008, 47, 7075 – 7078.

Coupling of C_{sp3} –H with C_{sp3} –H Bonds

- Mannich-type reactions with Glycine Derivatives
- A Cu(OAc)₂·H₂O/pyrrolidine-catalyzed version of this reaction was developed by the group of Huang in 2010.

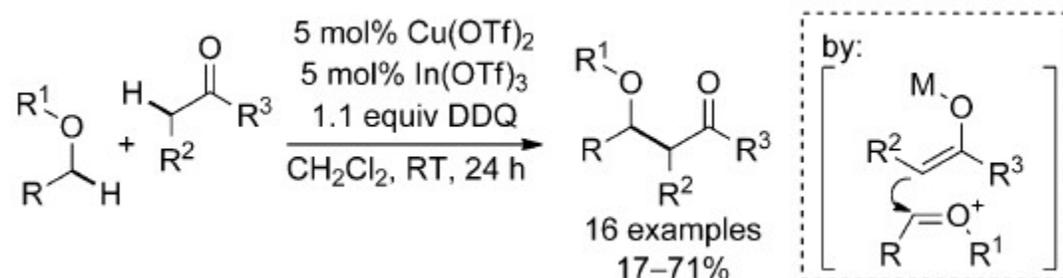


The α-functionalization of glycine derivatives with acetone could be performed under neat conditions with TBHP. The conversion of cyclic ketones required the use of DDQ as an oxidant and CHCl₃ as solvent.

Angew. Chem. 2010, 122, 10379 – 10383; *Angew. Chem. Int. Ed.* 2010, 49, 10181 – 10185.

Coupling of C_{sp3} –H with C_{sp3} –H Bonds

- Aldol-Type Reactions
- Aldol-reaction-type products are accessible by the oxidative activation of alkyl ethers and the subsequent coupling with enolizable carbonyl compounds.



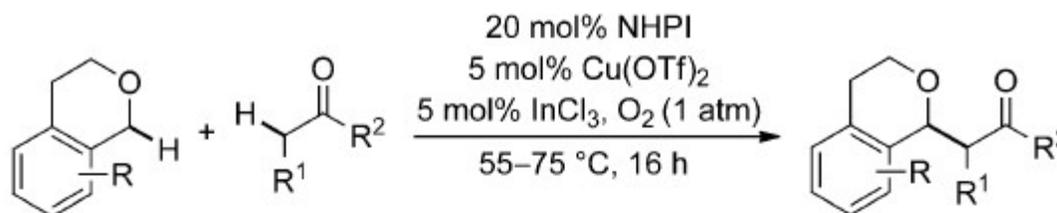
Angew. Chem. 2006, 118, 1983-1986; *Angew. Chem. Int. Ed.* 2006, 45, 1949-1952; *J. Am. Chem. Soc.* 2006, 128, 4242-4243.

DDQ converts the ether into the corresponding oxonium cation which is then intercepted by a copper or indium enolate complex.

The development of an improved procedure using DDQ allowed the group of Li to present the first metal- and solvent-free coupling of various aliphatic ketones, acetophenones, and pyrovalates with isochromanones

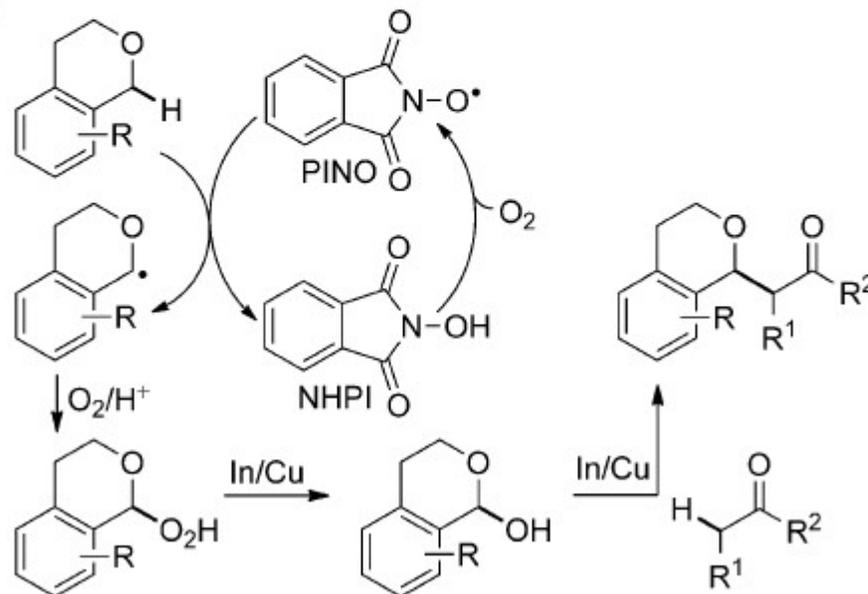
Coupling of C_{sp3} –H with C_{sp3} –H Bonds

Aldol-Type Reactions



Adv. Synth. Catal. 2001, 343, 393-427; *Angew. Chem.* 2008, 120, 4868-4874; *Angew. Chem. Int. Ed.* 2008, 47, 4790-4796.

by:



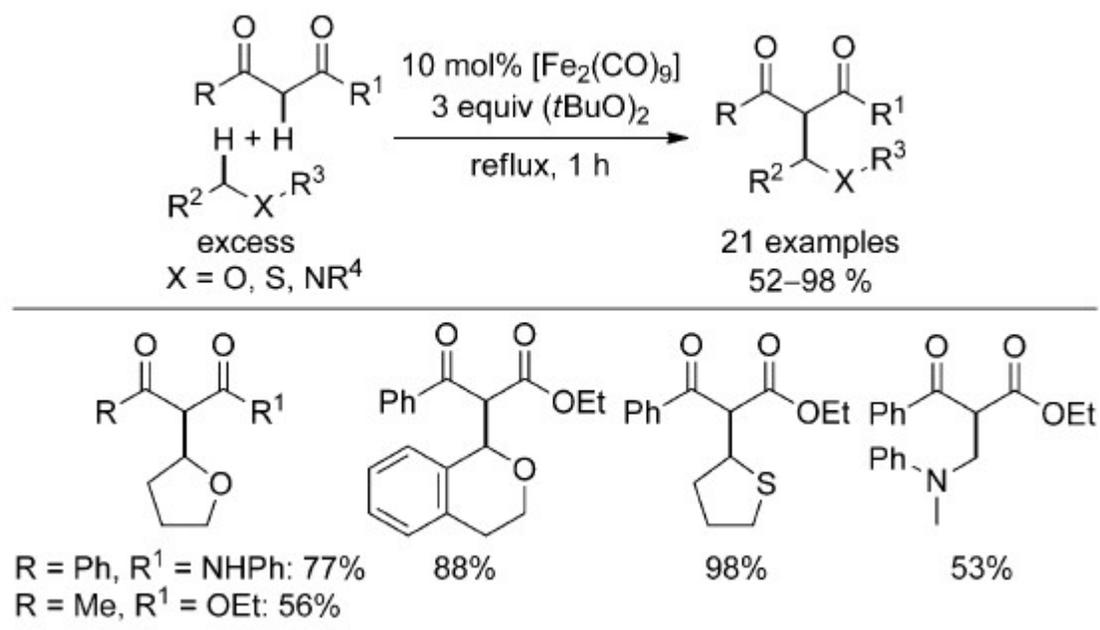
Aerobic copper / indium-catalyzed alkylation of benzyl

The use of a catalytic amount of NHPI (N-hydroxyphthalimide) allowed the development of an aerobic version of the indium/copper-catalyzed dehydrogenative coupling of cyclic benzylethers with carbonyl compounds.

The reaction is believed to proceed by the aerobic generation of a PINO radical which abstracts a hydrogen atom from the cyclic ether, and the resulting benzyl ether radical subsequently reacts with a molecule of oxygen. The resulting peroxide intermediate is transferred to the corresponding hemiketal in the presence of the indium/copper catalyst and subsequently coupled with the carbonyl compound.

Coupling of C_{sp3} –H with C_{sp3} –H Bonds

Aldol-Type Reactions



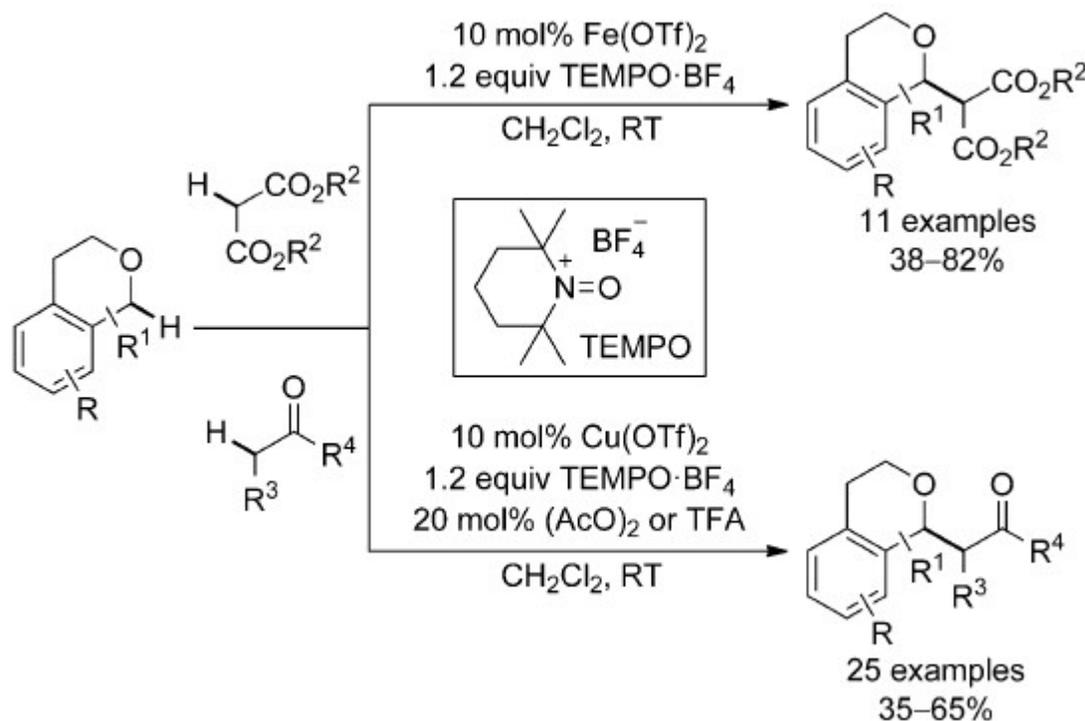
The group of Li demonstrated that 1,3-diketones are efficiently coupled with cyclic and alicyclic saturated heterocycles in the presence of catalytic amount of [Fe₂(CO)₉] in combination with 3 equivalents of TBP. The heterocycles served both as reagent and solvent.

Iron-catalyzed α -functionalization of heterocycles. X=O,S,NR.

Angew. Chem. 2008, 120, 7607 – 7610; *Angew. Chem. Int. Ed.* 2008, 47, 7497 – 7500.

Coupling of C_{sp3} –H with C_{sp3} –H Bonds

Aldol-Type Reactions



The group of Mancheno disclosed TEMPO as an alternative oxidant for this reaction class.

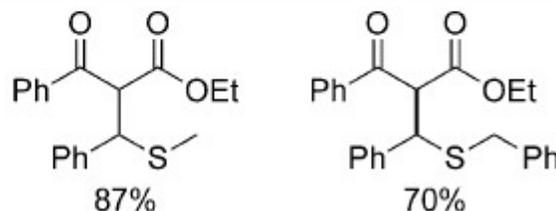
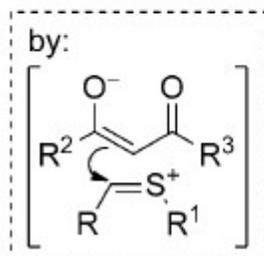
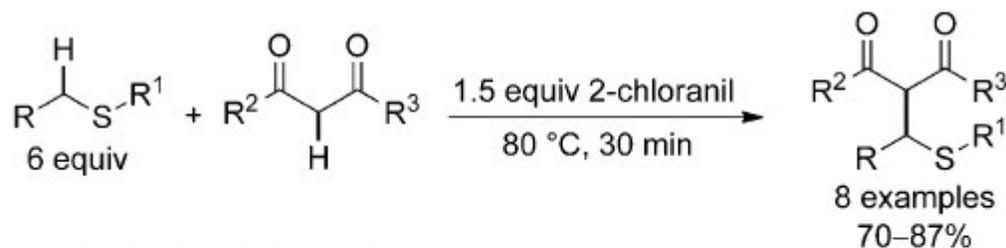
Aliphatic aldehydes and ketones, the substrates required the activation by a catalytic amount of either acetic anhydride or aqueous trifluoroacetic acid.

Chem. Eur. J. 2011, 17, 11622 – 11627; *Eur. J. Org. Chem.* 2010, 4460 – 4467.

2,2,6,6-Tetramethylpiperidine-1-oxoammonium tetrafluoroborate mediated aldol reaction.

Coupling of C_{sp3} –H with C_{sp3} –H Bonds

Aldol-Type Reactions



Org. Lett. 2008, 10, 803 – 805.

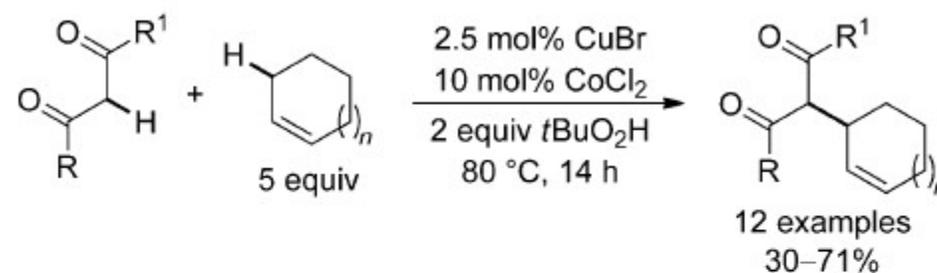
Cross-dehydrogenative alkylation of thioethers.

The scope of the metal-free, cross-dehydrogenative, aldol type reaction was extended to thioethers by the group of Li in 2008.

The coupling reaction is believed to proceed by the formation of thionium intermediates that subsequently react with the carbonyl compound.

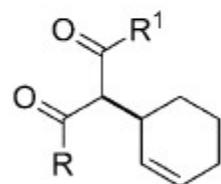
Coupling of C_{sp3} –H with C_{sp3} –H Bonds

Tsuji-Trost-Type Reactions



The reaction was disclosed by Li in 2006

A series of 1,3-dicarbonyl compounds was successfully coupled with cyclic olefins in the allylic position. The cycloalkene served both as reagent and solvent.

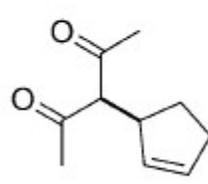


R, R¹ = Et: 61%

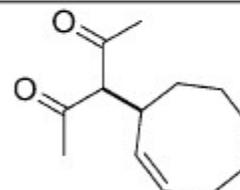
R = Ph, R¹ = Me: 64%, d.r. = 1:1

R = Me, R¹ = OMe: 41%, d.r. = 1:1

R = CH₂Cl, R¹ = OEt: 55%, d.r. = 1:1



53%



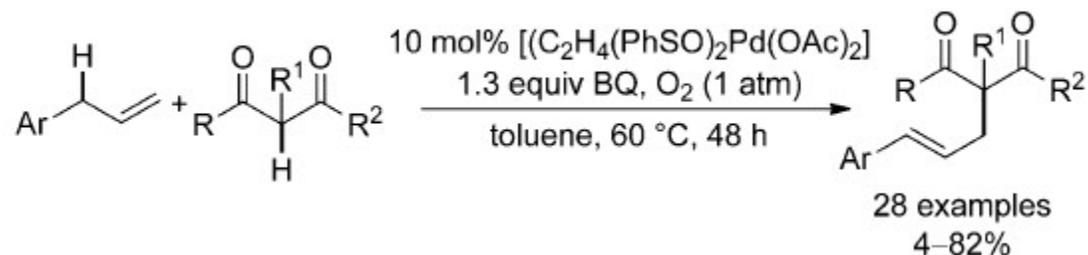
35%

Copper/cobalt-catalyzed cross-dehydrogenative allylation.

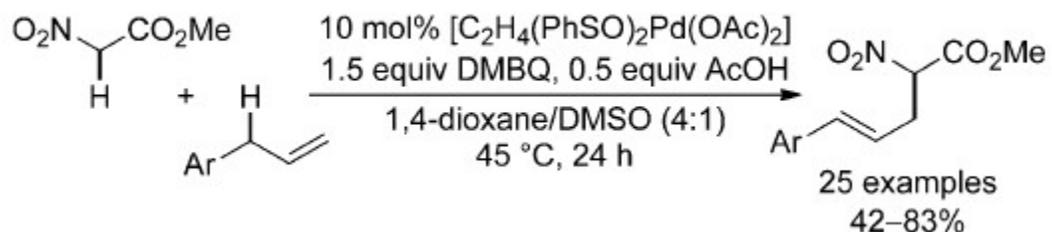
J. Am. Chem. Soc. 2006, 128, 56 – 57.

Coupling of C_{sp3} –H with C_{sp3} –H Bonds

▪ Tsuji-Trost-Type Reactions



J. Am. Chem. Soc. 2008, 130, 12901 – 12903;

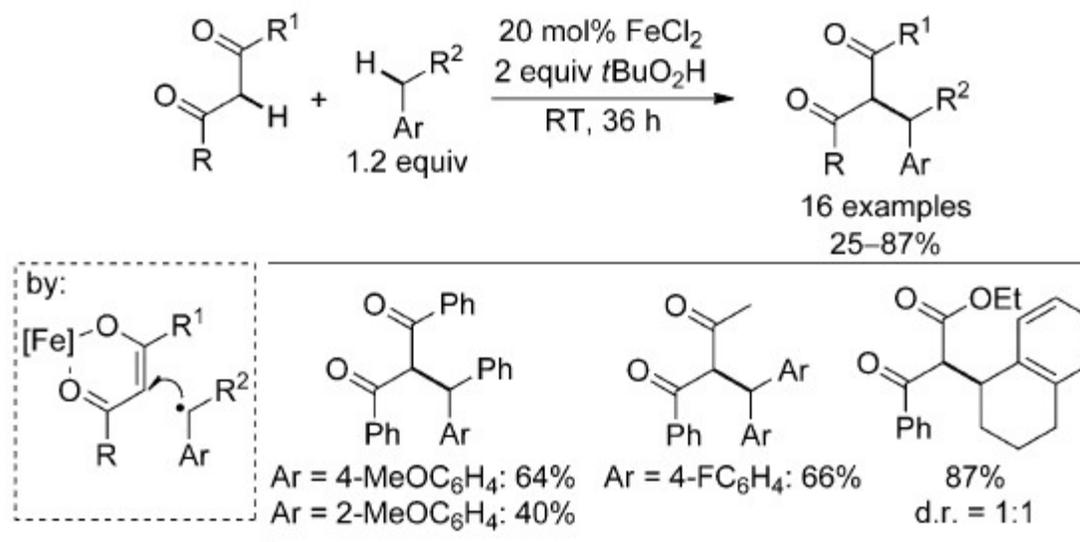


J. Am. Chem. Soc. 2008, 130, 14090 – 14091.

In 2008, two palladium-catalyzed cross-dehydrogenative allylation procedures were reported. Sulfur-containing ligands proved to be crucial in both protocols.

Coupling of C_{sp3} –H with C_{sp3} –H Bonds

Alkylation-Type Reactions



In 2007, the first cross-dehydrogenative benzylation and alkylation reactions of C_{sp3} –H bonds were reported: 1,3-diketones are smoothly benzylation in the presence of a FeCl₂ catalyst.

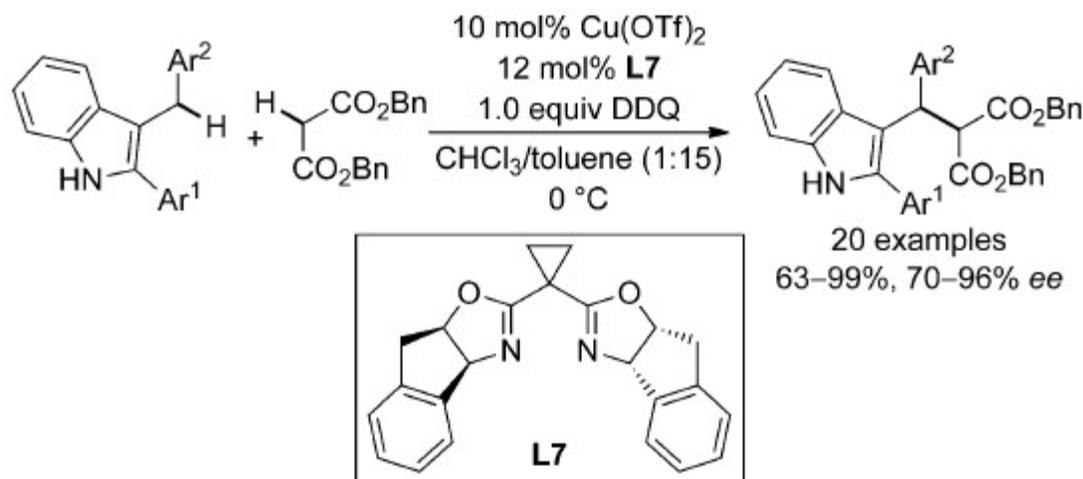
The authors proposed that the reaction proceeds by the formation of benzyl radicals which add to in situ generated iron enolate complexes.

Iron-catalyzed dehydrogenative benzylation.

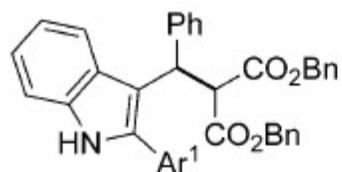
Angew. Chem. 2007, 119, 6625 – 6627; *Angew. Chem. Int. Ed.* 2007, 46, 6505 – 6507.

Coupling of C_{sp3} –H with C_{sp3} –H Bonds

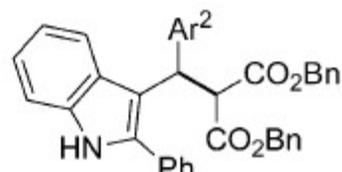
Alkylation-Type Reactions



In 2010, the group of Gong succeeded in developing the first enantioselective copper-catalyzed cross dehydrogenative benzylation reaction of malonic esters with indole derivatives.



Ar¹ = 4-C₆H₄F: 99%, 93% ee
Ar¹ = 4-C₆H₄Me: 70%, 94% ee



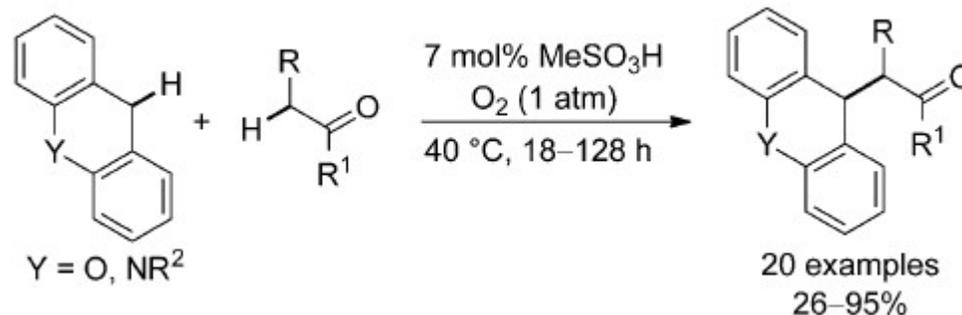
Ar² = 4-C₆H₄OMe: 74%, 86% ee
Ar² = 4-C₆H₄NO₂: 98%, 90% ee

Enantioselective benzylation of malonates.

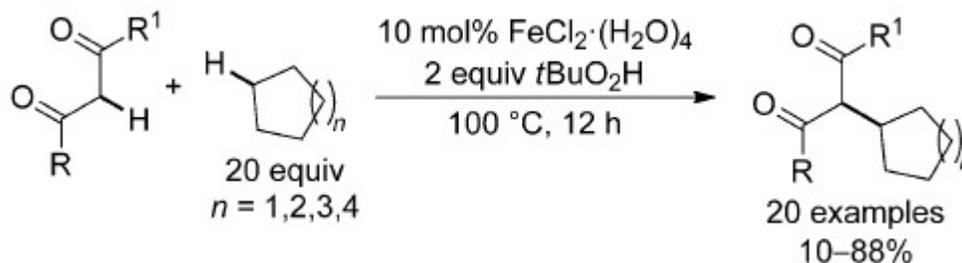
Angew. Chem. 2010, 122, 5690 – 5694; *Angew. Chem. Int. Ed.* 2010, 49, 5558 – 5562.

Coupling of C_{sp3} –H with C_{sp3} –H Bonds

Alkylation-Type Reactions



Angew. Chem. 2010, 122, 5124 – 5128; *Angew. Chem. Int. Ed.* 2010, 49, 5004 – 5007.



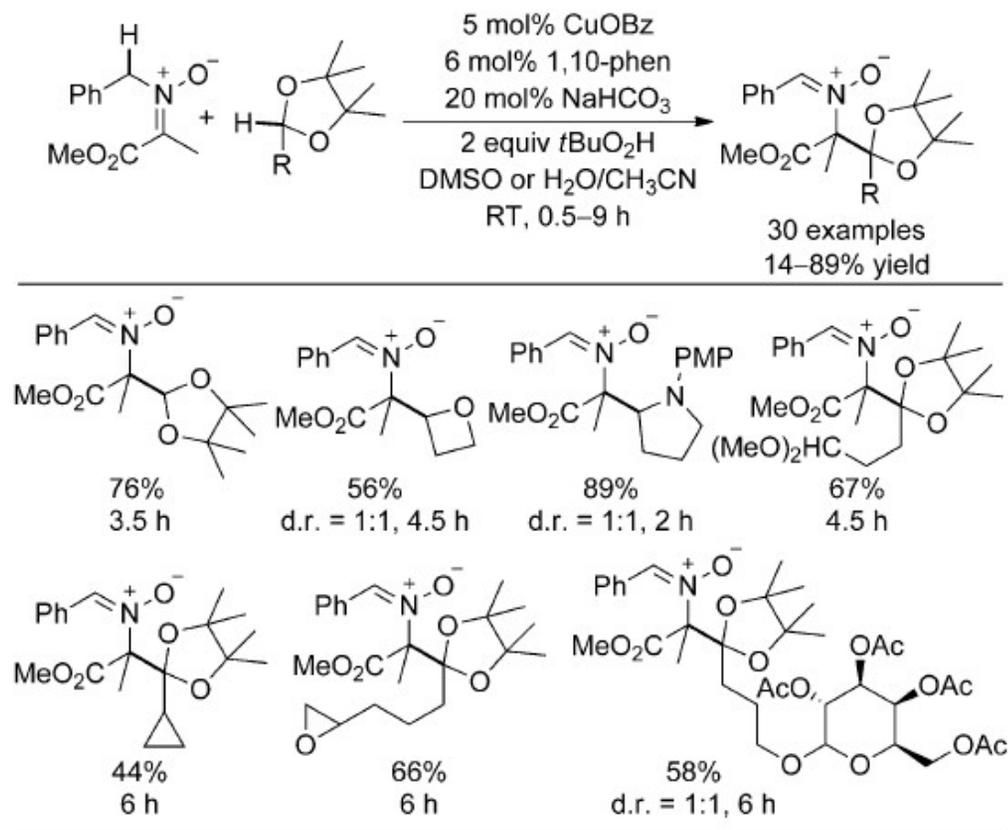
Eur. J. Org. Chem. 2007, 4654 – 4657.

The same year, the group of Klussmann reported the development of an interesting autoxidative benzylation reaction of carbonyl compounds with xanthenes and acridanes catalyzed by methane sulfonic acid.

The group of Li succeeded in developing a cross-dehydrogenative alkylation reaction of various 1,3-dicarbonyl compounds in which simple nonfunctionalized hydrocarbons served as alkylation reagents

Coupling of C_{sp3} –H with C_{sp3} –H Bonds

Miscellaneous C_{sp3} –H Coupling Reactions



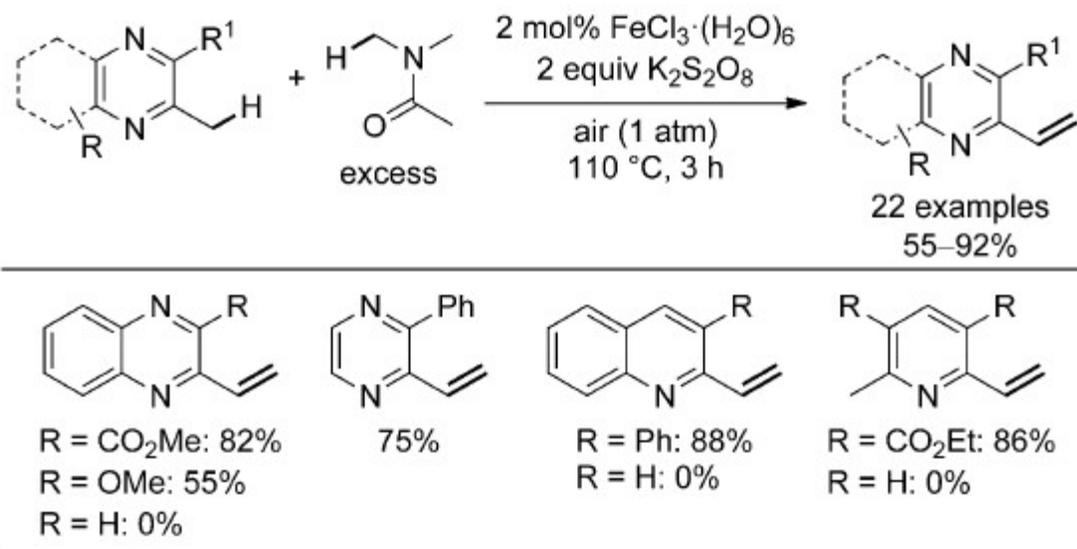
The reaction proceeds by an additional C=N isomerization step after activation of the benzylic position of the nitronium coupling partner.

Org. Lett. 2011, 13, 4288 – 4291; *Chem. Rev.* 2011, 111, 236 – 241; *Chem. Asian J.* 2012, 7, 2600 – 2606.

Oxidative migratory coupling reaction.

Coupling of C_{sp3} –H with C_{sp3} –H Bonds

Miscellaneous C_{sp3} –H Coupling Reactions



The procedure involves a cross-dehydrogenative C_{sp3}–C_{sp3} coupling which is followed by a final elimination step to generate the vinylic product.

Cross-dehydrogenative vinylation of pyrazine derivatives.

Chem. Commun. 2012, 48, 11993 – 11995.

Summary and Outlook

- **C-H activation/C-C coupling reactions catalyzed by transition metals or metal-free, which are one of the most popular approaches in modern organic synthesis, have emerged as a powerful tool for making C-C bonds.**
- **Under ideal situations, water would be the only waste product formed by using this methodology with molecular oxygen as the terminal oxidant. Air has yet to be further established as a broadly available and safe terminal oxidant.**
- **The development of efficient catalyst systems that allow control of the diastereoselectivity and the enantioselectivity still remains challenging.**
- **It is of high interest to develop efficient catalyst systems for the selective activation C_{sp³}-H bonds which are not in close proximity to a heteroatom.**

Acknowledgement

- ❖ *Dr. Peter Wipf.*
- ❖ *Dr. Donna Huryn,*
- ❖ *Wipf group members past & present.*

