Cross-Coupling

DOI: 10.1002/anie.201304268

The Cross-Dehydrogenative Coupling of C_{sp^3}–H Bonds: A Versatile Strategy for C–C Bond Formations

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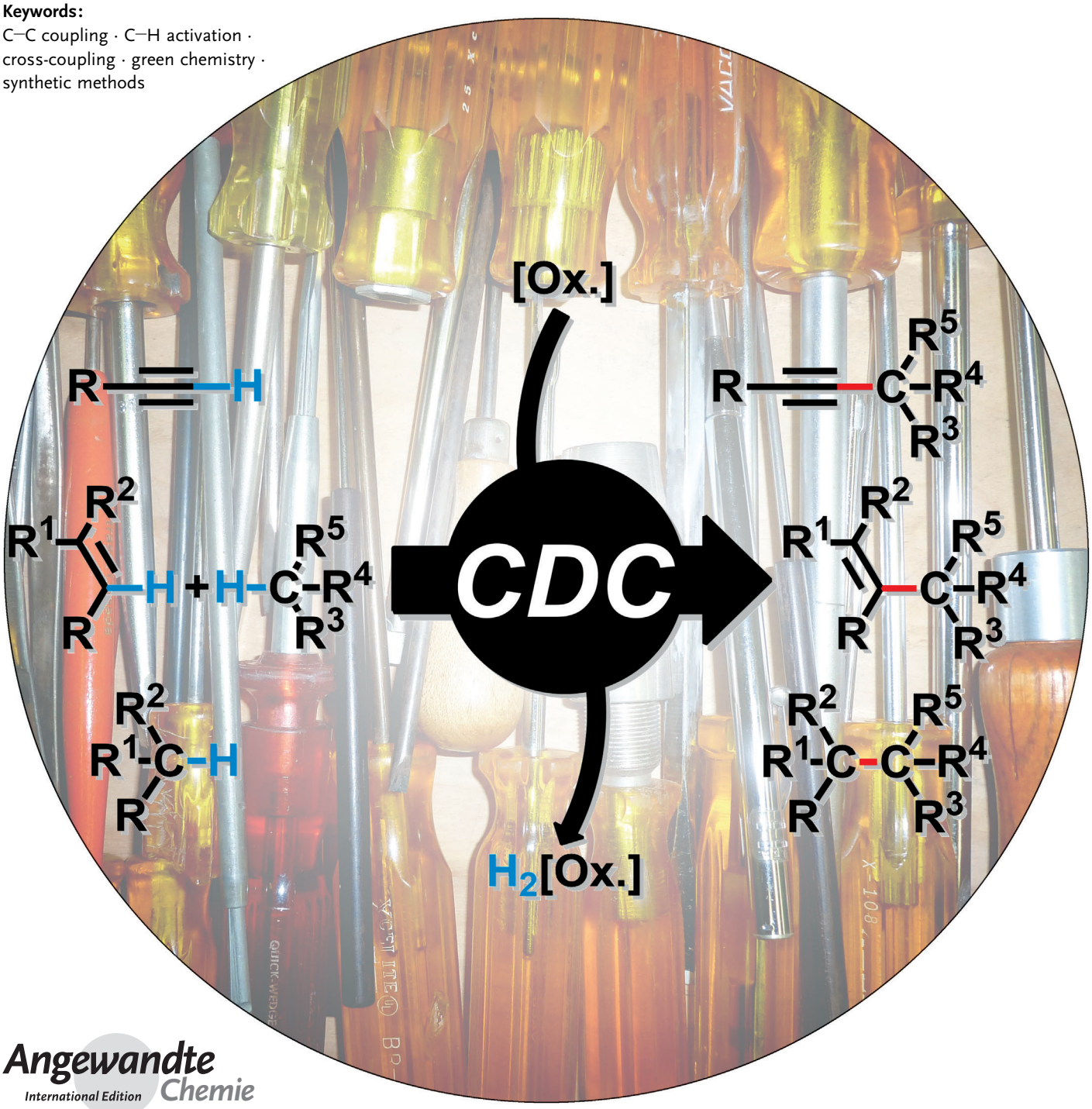
Keywords:
C–C coupling · C–H activation · cross-coupling · green chemistry · synthetic methods



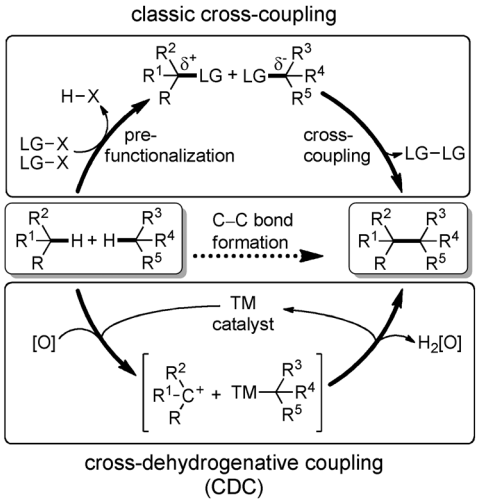
Angewandte International Edition Chemie

Over the last decade, substantial research has led to the introduction of an impressive number of efficient procedures which allow the selective construction of C–C bonds by directly connecting two different C–H bonds under oxidative conditions. Common to these methodologies is the generation of the reactive intermediates in situ by activation of both C–H bonds. This strategy was introduced by the group of Li as cross-dehydrogenative coupling (CDC) and discloses waste-minimized synthetic alternatives to classic coupling procedures which rely on the use of prefunctionalized starting materials. This Review highlights the recent progress in the field of cross-dehydrogenative C_{sp^3}–C formations and provides a comprehensive overview on existing procedures and employed methodologies.

From the Contents

1. Introduction

Transition-metal-catalyzed coupling reactions have emerged as a powerful tool for the selective construction of C–C bonds as well as an integral part of organic synthesis.[1] One reason for 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. Substantial research has introduced highly efficient catalyst systems which even allow the activation of challenging leaving groups such as mesylates (methanesulfonates),[2] ethers[3] or carboxylic acids.[4] However, the use of any kind of leaving group inevitably results in the co-production of unwanted stoichiometric amounts of chemical waste (Scheme 1, top).



Scheme 1. Strategies for selective C–C bond formation. LG = leaving group, TM = transition metal.

In addition, every leaving group has to be installed on the corresponding substrate in preceding synthetic steps. This is unsatisfying from an ecological and economical point of view.[5] To explore more efficient synthetic methodologies, a one-pot, three-component aldehyde-amine-alkyne coupling, the A^3-reaction,[6] as well as various Grignard–Barbier-type reactions in aqueous media were developed by us earlier.[7] Inspired by the groundbreaking successes in catalytic C–H functionalizations,[8] our group became interested in developing catalytic methodologies which enable C–C formations directly from the coupling of two different C–H bonds. For this strategy, one of the C–H bonds is hypothetically activated by the catalyst/mediator to form a carbon nucleophile in situ and subsequently couples with a carbon electrophile which is also generated in situ by oxidation of the second C–H bond (Scheme 1, bottom). Under ideal situations, water would be the only waste product formed by using this methodology with molecular oxygen as the terminal oxidant. The oxidative coupling of two different C–H bonds was termed cross-dehydrogenative coupling (CDC)[9] by our group in 2004 and has become a growing field of interest.

In the last 10 years, an impressive number of efficient procedures and novel methodologies have been introduced and they allow the connection of C_{sp}–H, C_{sp^2}–H, and even C_{sp^3}–H bonds with each other.[9,10] In particular, the development of chemo-, regio-, and stereoselective cross-dehydrogenative C_{sp^3}–C bond formations is highly desirable but it is still considered one of the most challenging tasks in organic synthesis.

The focus of this review article is on the advances in the field of cross-dehydrogenative C_{sp^3}–C bond formations. The existing procedures and methodologies have been summarized and discussed. This article is structured by the hybridization of the C–H coupling partner. Cross-dehydrogenative alkylations of terminal alkynes will be discussed first, followed by coupling reactions with C_{sp^2}–H bonds, and concluded with the oxidative bond formation of two different C_{sp^3}–H bonds. The intention of this article is to give

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a comprehensive overview on the topic, shed light on new perspectives, and inspire the use, the completion, and the improvement of cross-dehydrogenative C_{sp^3}–H functionalizations. The appropriate discussion of the larger field of CDC reactions for the formation of C_{sp}–C_{sp}, C_{sp^2}–C_{sp} and C_{sp^2}–C_{sp^2} bonds is far beyond the scope of this article and their recent progress has already been extensively covered, and we refer herein to these excellent contributions.[9,10]

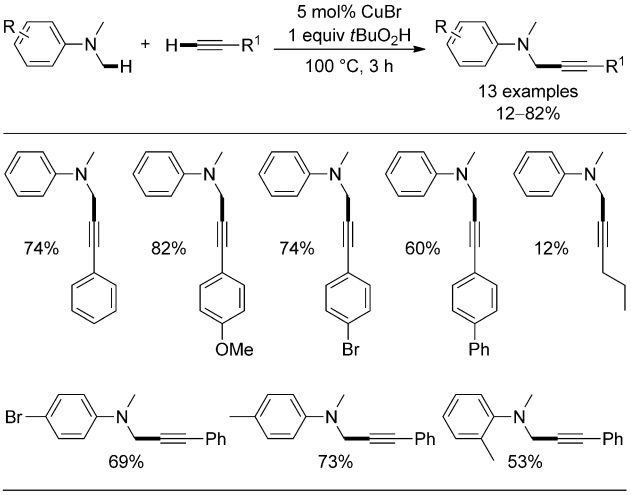
2. Coupling of C_{sp^3}–H with C_{sp}–H Bonds

Inspired by the groundbreaking work of Murahashi et al.,[11] who demonstrated that preformed as well as in situ generated iminium ions can smoothly react with cyanide anions, the group of Li succeeded in 2004 in developing the first catalytic alkynylation reaction of C_{sp^3}–H bonds adjacent to a nitrogen atom as a proof-of-concept for the CDC.[12] The oxidative cross-coupling of *N*,*N*-dimethylaniline with phenylacetylene is mediated in the presence of catalytic amounts of copper salts in combination with the oxidant *tert*-butyl hydroperoxide (TBHP). Among the copper salts investigated, CuBr and CuCl proved to be the most efficient catalysts, thus furnishing the desired product in 77% and 75% yield, respectively.

The reaction conditions were optimal with 5 mol% of CuBr, 1 equivalent of TBHP, and a 2:1 ratio of *N*,*N*-dimethylaniline/phenylacetylene, thus affording the desired α-alkynylation compound in 74% yield upon isolation (Scheme 2). Interestingly, almost 1 equivalent of *N*,*N*-dimethylaniline remained in the reaction mixture after the completion of the reaction. However, reducing the excess of aniline resulted in a drop in the yield.

This catalyst system led to the successful alkynylation of various aromatic *N*,*N*-dimethylanilines with a variety of alkynes in low to good yields (12–82%). The stability and electronic properties of the alkynes have a strong effect on the reaction outcome. 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.

The Li group proposed a mechanistic rationale which involves the generation of an iminium intermediate in the



Scheme 2. Copper-catalyzed alkynylation of *N*,*N*-dimethylaniline.

presence of the copper catalyst. They thus envisaged that the use of a chiral ligand could allow the development of an enantioselective alkynylation. Consequently, the influence of a series of chiral nitrogen-containing as well as phosphine ligands was investigated (Scheme 3). In 2004, the authors succeeded in demonstrating that an enantioselective CDC of alkynes with tetrahydroisoquinolines is indeed feasible.[13] The best results were obtained with the PyBox-based chiral ligand **L1** in combination with CuOTf. The phenylacetylene partner smoothly coupled with *N*-phenyl tetrahydroisoquinoline in the presence of molecular sieves to give the desired product in a moderate 63% *ee* at 50 °C in THF. Various substrates were examined, and aromatic alkynes provided the desired products in both good yields and enantiomeric excesses. Substituents on the aryl ring did not show a significant influence on either the yield or the enantioselectivity of the reaction. However, the use of aliphatic alkynes resulted in moderate to low enantiomeric excesses.

Recently, the group of Su showed that tetrahydroisoquinolines could be alkynylated in the presence of 1 equivalent of the oxidant DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) under solvent-free, high-speed, ball-milling conditions (Scheme 4).[14] The use of copper rather than stainless steel balls affords the desired alkynylated product in 78% after 20 minutes at 30 Hz. The reaction proceeded smoothly with both aliphatic and aromatic alkynes. However, slightly better

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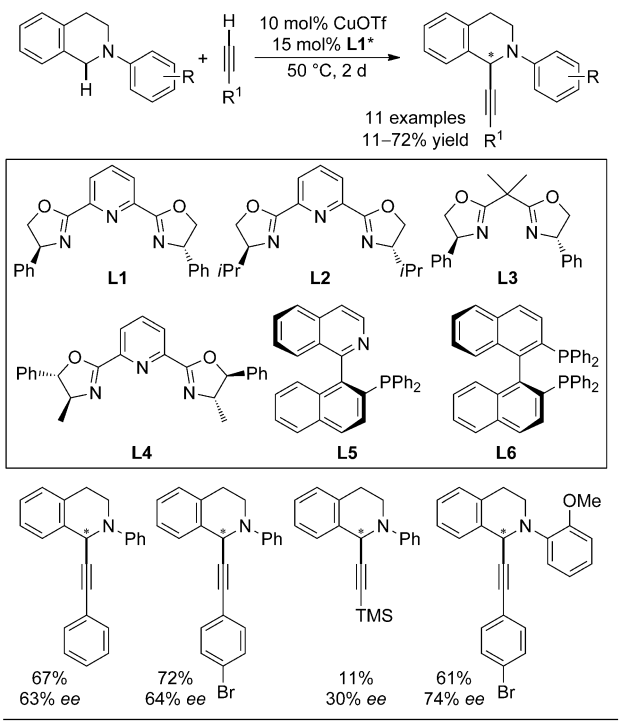
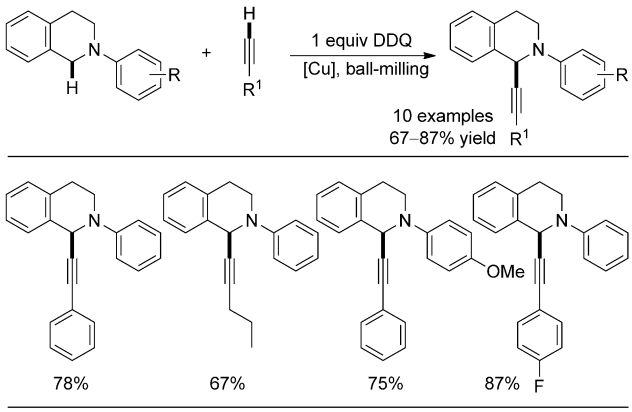
Thomas Knauber earned his doctorate in 2011 in the group of Prof. Dr. L. J. Gooßen at the Technical University of Kaiserslautern (Germany). Currently, he is a DAAD (German Academic Exchange Service) postdoctoral fellow in the group of Prof. Dr. C.-J. Li at McGill University in Montréal (Canada). His research interests focus on the development of new sustainable catalytic methodologies for selective constructions of carbon–carbon and carbon–heteroatom bonds.



Scheme 3. Enantioselective alkynylation of tetrahydroisoquinolines. TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl.



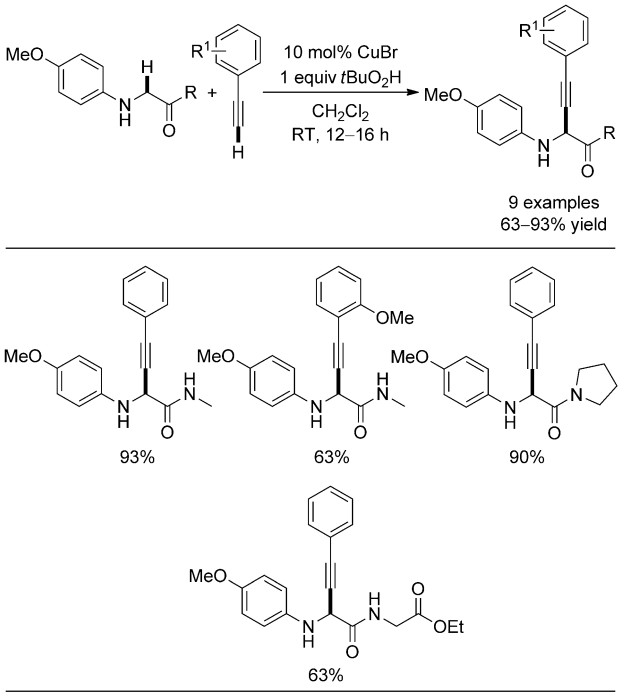
Scheme 4. Functionalization of tetrahydroisoquinolines under ball-milling conditions.

Chao-Jun Li received his PhD in 1992 at McGill University with Profs. T.-H. Chan and D. N. Harpp and was a NSERC postdoctoral fellow at Stanford with Prof. B. M. Trost. He started his academic career at Tulane University in 1994 and moved to McGill University in 2003, where he currently holds the E. B. Eddy Chair of Chemistry and Canada Research Chair (Tier I) in Green Chemistry. His research includes Grignard-type reactions in water, aldehyde-alkyne-amine (A^3) couplings, and the cross-dehydrogenative couplings (CDC).

yields were obtained with aromatic substrates. An enantioselective version of this methodology has been recently introduced by the same group using a PyBox ligand.[15]

The CDC of *N*,*N*-dialkylanilines and tetrahydroisoquinolines with alkynes has been established as a reference system for benchmarking the performance of new catalyst systems.

Similarly, the scope of the cross-dehydrogenative alkynylation reaction was successfully extended to the use of secondary amines as substrates. In 2008, the group of Li introduced the first cross-dehydrogenative alkynylation of glycine derivatives.[16] The reaction is catalyzed by CuBr in combination with TBHP at room temperature. Under optimized reaction conditions, various *para*-methoxyphenyl-(PMP)-protected glycine derivatives were successfully functionalized with aromatic alkynes (Scheme 5). However the

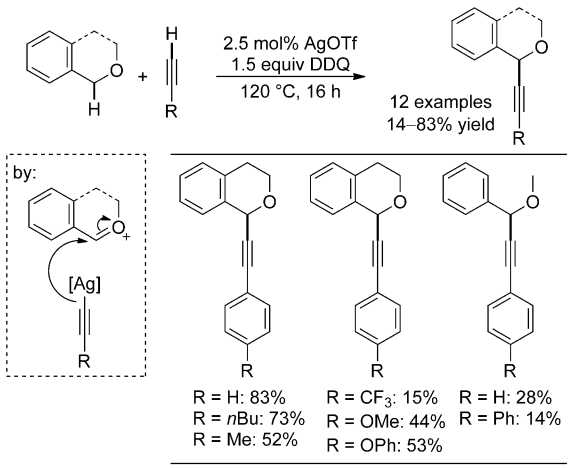


Scheme 5. Copper-catalyzed alkynylation of protected amino acids.

reaction appeared to be sensitive to sterically hindered groups on the aromatic alkyne, and consequently a low yield was obtained with 2-methoxyphenylacetylene. Interestingly, the coupling reaction did not occur with 4-ethoxyphenyl- or *N*-phenyl-protected tetrahydroisoquinolines. Moreover, the reaction is broadly applicable on the conversion of both secondary and tertiary amides, and the corresponding products were obtained in good yields. This methodology is also applicable to the functionalization of simple peptides (Scheme 5, bottom). The reaction conditions were re-optimized for the coupling of dipeptides and the alkynylation occurred regioselectively at the PMP-protected glycine terminus under an inert atmosphere in DCE at 70 °C. The desired product was obtained in 63 % yield and the formation of regioisomers was not detected. The catalyst system also mediates cross-dehydrogenative site-specific C_{sp^3}–H aryla-

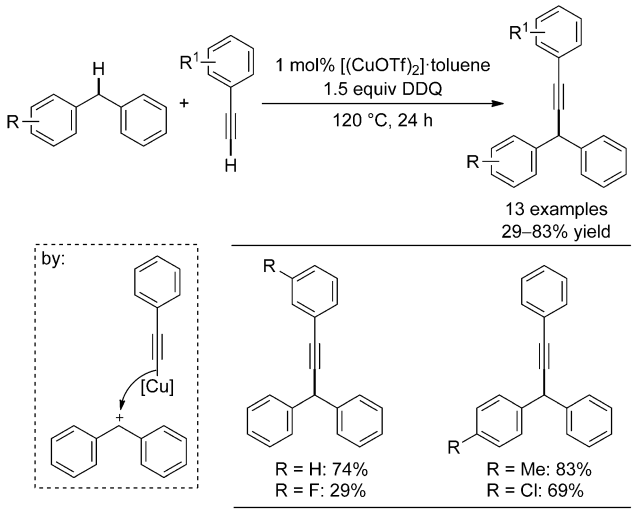
tions, vinylations, and indolylations of glycine derivatives, and these reactions will be discussed in detail in the following sections.[17]

A silver-catalyzed oxidative coupling of terminal alkynes and benzylic ethers was introduced in 2010 by the group of Li.[18] By using 2.5 mol% of silver triflate, 1.5 equivalents of DDQ, and a 4:1 mixture toluene/chlorobenzene at 120°C, they successfully accessed functionalized benzylic ether derivatives (Scheme 6). Acyclic methyl benzyl ethers could be activated but the desired coupling product was obtained in a poor yield.



Scheme 6. Silver-catalyzed alkynylation of benzylic ethers.

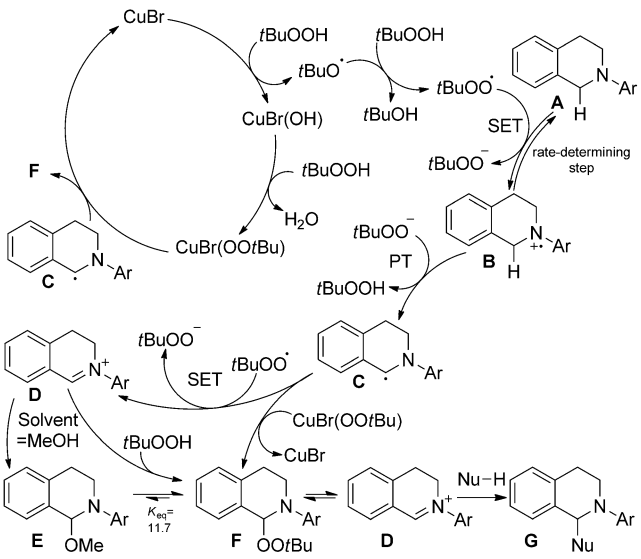
More recently, Li and co-workers reported the first alkynylation of benzylic C–H bonds which are not adjacent to a heteroatom. Various alkynes were successfully coupled with diphenylmethane derivatives using 1 mol% of a CuOTf toluene complex in the presence of 1.5 equivalents of DDQ (Scheme 7).[19] Aromatic alkynes were smoothly converted,



Scheme 7. CuOTf-catalyzed CDC reaction of diphenylmethanes and aromatic alkynes.

and the use of electron-rich derivatives resulted in slightly improved yields. The authors rationalized this observation by the nucleophilicity of the substrates. However, aliphatic alkynes (e.g. *n*-hexyne) could not be converted using this procedure. The authors proposed a mechanism which proceeds by the generation of radical intermediates. A benzylic cation is formed in the presence of DDQ through two successive single-electron transfer (SET) steps, and the resulting hydroquinone subsequently abstracts the acidic proton from the alkyne to form the copper acetylide which adds to the benzylic cation to afford the desired product.

The mechanism of the copper-catalyzed cross-dehydrogenative functionalization of tertiary amines was investigated by the groups of Klussmann[20] and Doyle.[21] Detailed studies including isotope-labeling experiments and kinetic studies were performed, and their results are summarized in Scheme 8. Both groups proposed that the catalytic cycle

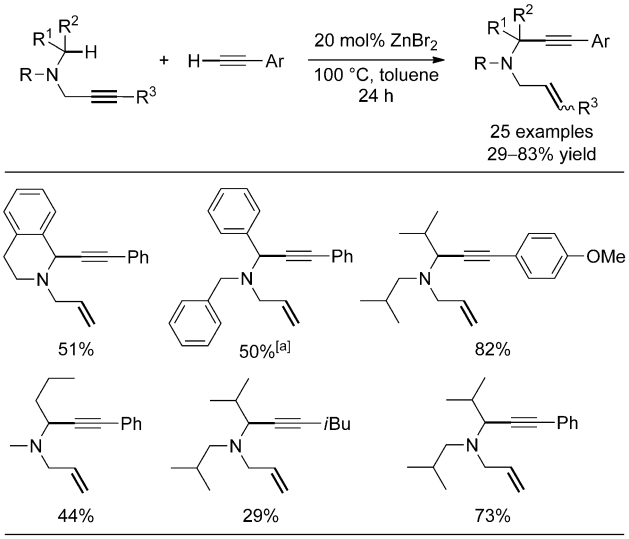


Scheme 8. Proposed mechanism for the oxidation of tetrahydroisoquinoline by TBHP in presence of CuBr.

starts with the reaction of CuBr with TBHP to form a copper(II) species and a *tert*-butyloxy radical which then reacts with a second molecule of TBHP to generate a *tert*-butylperoxy radical and a copper-*tert*-butylperoxy complex. The linear free energy relationship (LFER) analysis demonstrated that the *tert*-butylperoxy radical is the thermodynamically favored oxidant and that the single-electron transfer with **A** is the rate-determining step of the reaction. A difference between the kinetic isotope effect (KIE) and the product isotope effect (PIE) were observed for the oxidation of *N*,*N*-dimethylaniline. The group of Doyle rationalized this observation by suggesting a competition between a reverse SET and the irreversible proton-transfer (PT). The subsequent proton transfer occurs at the most acidic C–H bond of the cation radical **B**. The regioselectivity in unsymmetrical *N*,*N*-dialkylanilines can be rationalized using the report of Albini, Falvey, Mariano, and co-workers on acidity of carbon atoms adjacent to nitrogen atoms[22] (note that steric effect

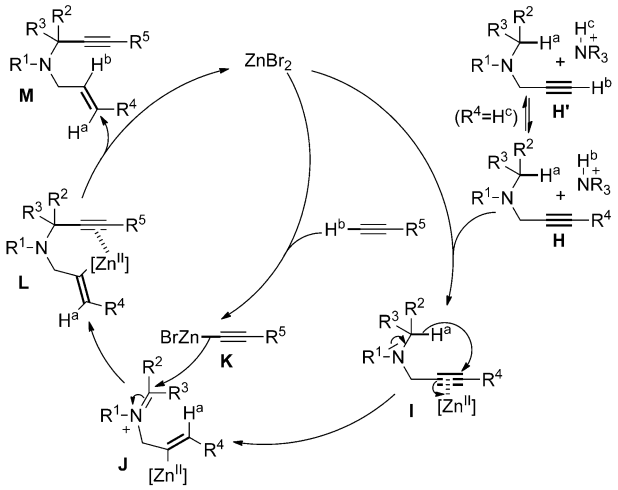
might also be involved). The α-amino radical **C** is transformed into the corresponding iminium species **D** by a second SET with the *tert*-butylperoxy radical. Nucleophilic solvents such as methanol can react with the cationic intermediate to form the species **E**. The formation of **E** is thermodynamically less favored and is formed under kinetic control. All three species (**D**, **E**, **F**) are in an equilibrium which lies toward **F** with an equilibrium constant $K_{eq} = 11.7$. Test experiments demonstrated that **E** and **F** are both precursors for the desired product. Finally, the carbon nucleophile reacts with the iminium intermediate to form the product **G**.

Very recently, 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.[23] The use of 20 mol% of $ZnBr_2$ allowed the synthesis of various enynes from the coupling reaction between propargylic amines and terminal alkynes (Scheme 9.) 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



Scheme 9. Zinc-catalyzed synthesis of *N*-tethered 1,6-enynes. [a] Used 50 mol% $ZnBr_2$.

the corresponding alkene during the alkynylation reaction and, consequently, 1,6-enynes are obtained. Under the optimized reaction conditions, both tertiary and secondary C_{sp^3}–H bonds adjacent to the nitrogen atom have been successfully activated for the alkynylation reaction. The reaction preferentially takes place on secondary rather than on primary C–H bonds (Scheme 9, bottom left), and aromatic alkynes generally give a better yield than aliphatic alkynes. The proposed mechanism is illustrated in Scheme 10. The authors investigated the reaction mechanism by isotope-labeling experiments, and demonstrated that the reaction is indeed an intramolecular process. In the case of terminal alkynes, a proton exchange has been observed. The zinc complex can coordinate to the propargylic amine **H** and facilitates a 1,5-hydride shift from **I** to afford the iminium intermediate **J**. In the meantime, the zinc bromide reacts with



Scheme 10. Proposed mechanism for the $ZnBr_2$-catalyzed CDC reaction of propargylic amines with alkynes.

the alkyne to form the zinc acetylide **K**. The addition of the acetylide onto the iminium cation and subsequent protonation of the vinyl zinc complex furnishes the desired product **M** and closes the catalytic cycle.

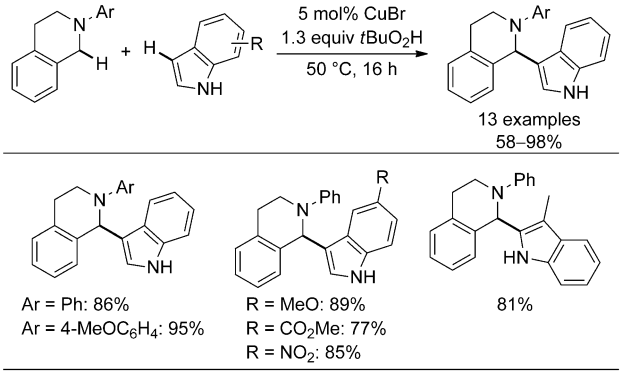
3. Coupling of C_{sp^3}–H with $_{sp^2}$–H Bonds

CDC reactions of C_{sp^3}–H with C_{sp^2}–H bonds have been successfully achieved by using three major strategies. The first consists of a Friedel–Crafts-type approach in which electron-rich arenes are coupled with in situ generated cationic species. The second strategy involves the generation of free radicals which subsequently react with an olefin or an arene. Finally, the third strategy relies on a transition-metal-catalyzed activation of the C_{sp^3}–H bond followed by a cross-coupling step.

3.1. Friedel–Crafts-Type Reactions of Carbon Electrophiles and Electron-Rich Arenes

3.1.1. Transition-Metal-Catalyzed Procedures

The first catalytic coupling of C_{sp^3}–H bonds with C_{sp^2}–H bonds using a cross-dehydrogenative Friedel–Crafts approach was reported by the group of Li in 2005.[24] A series of *N*-aryl tetrahydroisoquinolines was successfully arylated with unprotected indoles in the presence of catalytic quantities of CuBr and a slight excess of the oxidant TBHP (Scheme 11). The reaction proved to be insensitive toward traces of water and air. The desired *N*-phenyl-1-(3-indolyl)tetrahydroisoquinoline was still obtained in a reasonable yield of 50% in a 1:2 mixture of water and toluene. Interestingly, *N*-phenyl-1-(*tert*-butyl peroxy)tetrahydroisoquinoline was obtained in 70% yield when the reaction was performed in the presence of a large excess of water. The formation of this intermediate is not very surprising in light of the mechanistic investigations of the groups of Klussmann[20] and Doyle[21] (Scheme 8). However, the best result was obtained under neat conditions and



Scheme 11. Copper-catalyzed cross-dehydrogenative Friedel–Crafts arylation.

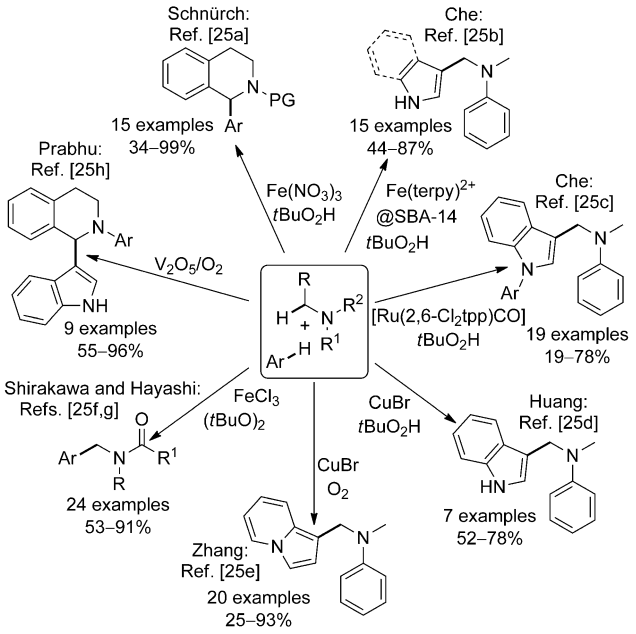
the desired product was isolated in 80% yield. The optimized reaction conditions were broadly applicable with regard to the indole substrates. Electron-donating as well as electron-withdrawing groups were well tolerated and the corresponding products were isolated in good yields. The alkylation occurred selectively at C3 and the C2 isomer was only obtained when C3 was blocked.

Interestingly, unprotected indoles performed better (64–98%) than *N*-methyl indole which yielded the corresponding product in a moderate 58% yield. The Li group proposed a mechanism which proceeds by the copper-catalyzed generation of tetrahydroisoquinoline cations which subsequently react with the indoles in an electrophilic aromatic substitution. The oxidative activation of the tetrahydroisoquinoline with TBHP is believed to proceed as previously discussed in Scheme 8. In the following years, the scope of cross-dehydrogenative Friedel–Crafts-type arylation was significantly improved by the development of highly efficient catalyst systems, which are depicted in Scheme 12.[25]

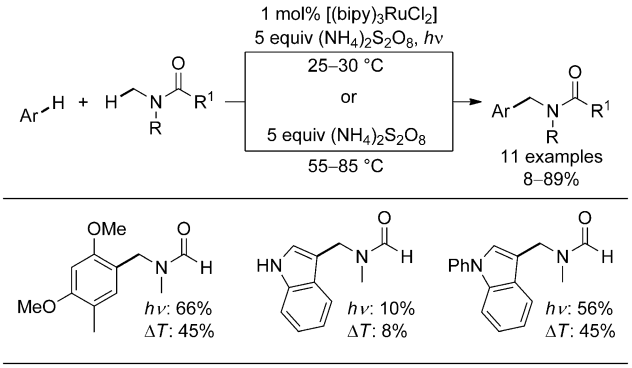
Various proelectrophiles including *N*,*N*-dialkylanilines and *N*-alkyl amides were successfully coupled with a broad variety of electron-rich arenes such as indoles, indolizines, furanes, and anisoles.

A photocatalytic protocol was recently developed by the group of Stephenson[26] on the basis of their previous studies on light-mediated reactions, and will be discussed in detail in the context of the connection of two C_{sp^3}–H bonds.[73,76] A catalytic quantity of the photocatalyst $[(bipy)_3Ru]Cl_2\cdot 6H_2O$ in combination with excess ammonium persulfate allowed the arylation of *N*-alkylamides, such as DMF, DMA, and NMP, with a set of anisoles and indoles (Scheme 13).[26] The reaction proceeds smoothly at room temperature under irradiation with blue light. The mechanism of the photocatalytic procedures will be discussed later (Scheme 41).[76] Interestingly, the arylation also occurs under thermal conditions in the absence of the ruthenium photocatalyst at temperatures above 55 °C. In direct comparison, the photocatalytic protocol proved to be more efficient than the thermal variant, and better yields were detected. However, overalkylation and the formation of regioisomers were observed with both protocols.

Recently, an intramolecular version of the dehydrogenative Friedel–Crafts-type arylation has been developed by the



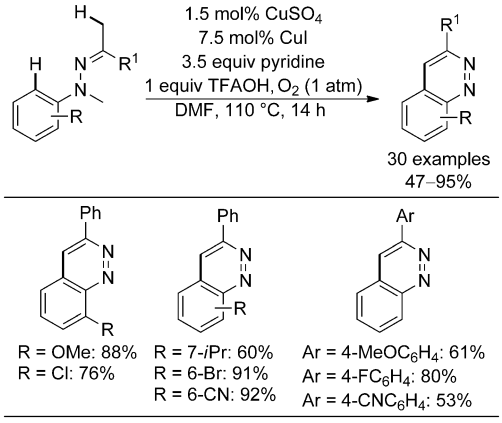
Scheme 12. Catalytic cross-dehydrogenative Friedel–Crafts-type arylations. PG = protecting group, terpy = terpyridine, tpp = tetraphenylporphyrin.



Scheme 13. Photocatalytic cross-dehydrogenative amidation. bipy = 2,2′-bipyridine.

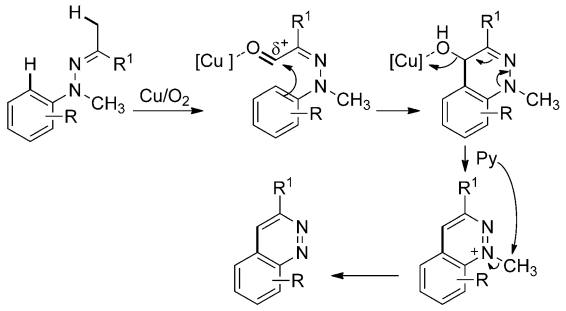
group of Ge, and it allows the copper-catalyzed aerobic synthesis of functionalized cinnolines (Scheme 14).[27] The cyclization is performed in DMF at 110 °C under an atmosphere of molecular oxygen. The authors found that the addition of a pyridine/trifluoroacetic acid buffer (3.5:1) was crucial for obtaining high conversions. Interestingly, among the tested copper catalysts, a combination of 1.5 mol% $CuSO_4$ and 7.5 mol% CuI showed the highest catalytic activity.

The optimized reaction conditions were broadly applicable with regard to the phenylhydrazones and electron-rich, electron-deficient, or bulky substrates were smoothly converted into the corresponding cinnolines. 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



Scheme 14. Cross-dehydrogenative cinnoline synthesis. DMF = *N*,*N*-dimethylformamide, TFAOH = trifluoroacetic acid.

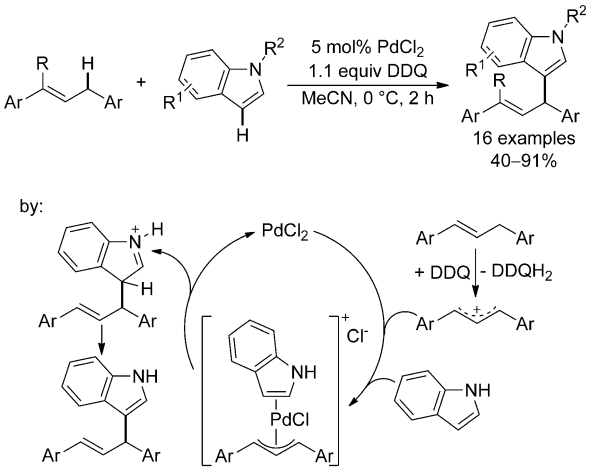
cyclization (Scheme 15). Demethylation with pyridine furnishes the desired products.



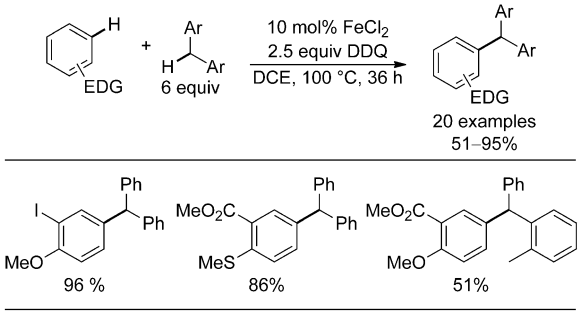
Scheme 15. Proposed mechanism of the cinnoline synthesis.

The previous procedures have focused on the oxidative activation of nitrogen-containing proelectrophiles. In complementary contributions, allylic compounds as well as diphenylmethanes have been disclosed as substrate classes for cross-dehydrogenative arylations.[28] A $PdCl_2$-catalyzed allylation reaction of indole derivatives was introduced by the group of Bao in 2009 (Scheme 16).[28a] DDQ proved to be the oxidant of choice. Under optimized reaction conditions, various indole derivatives were successfully coupled with 1,3-diarylpropenes. The authors propose that the reaction proceeds by a DDQ-mediated oxidation of the allylic substrates into palladium-stabilized allyl cations which subsequently react with the indoles in a Friedel–Crafts-type reaction.

The group of Shi introduced a $FeCl_2$-catalyzed benzylation reaction of electron-rich arenes with diphenylmethanes (Scheme 17).[28b] Among the tested oxidants, the best results were also obtained with DDQ and the authors propose that the reaction is initiated by a single-electron transfer (SET) oxidation of the diphenylmethane by DDQ, thus generating a diphenyl radical, which is supported by the detection of trace amounts of the corresponding homocoupling products. A second SET oxidation transfers the radical intermediate



Scheme 16. Cross-dehydrogenative allylation.



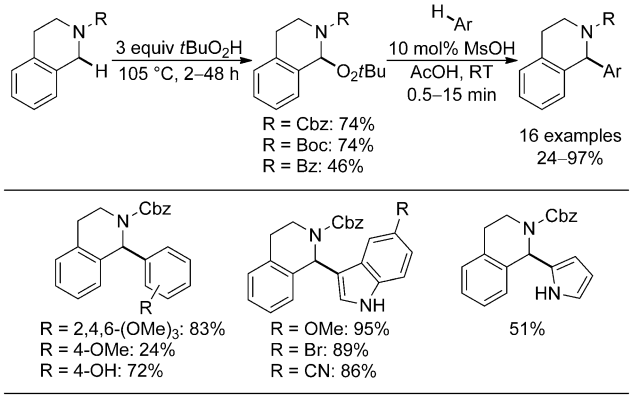
Scheme 17. Friedel–Crafts-type cross-dehydrogenative benzylation. DCE = 1,2-dichloroethane, EDG = electron-donating group.

into a carbocation which subsequently reacts with the electron-rich arene.

3.1.2. Metal-Free Procedures

Very recently, the first cross-dehydrogenative Friedel–Crafts-type arylations of C_{sp^3}–H bonds were disclosed which proceed in the absence of a transition-metal catalyst. Based on their mechanistic studies,[20] the group of Klussmann introduced a two-step procedure for the arylation of *N*-protected tetrahydroisoquinolines (Scheme 18) in which the cationic intermediates are generated from the corresponding peroxides.[29] In the first step of the reaction sequence, a series of *tert*-butyl peroxides was prepared simply by stirring the *N*-protected tetrahydroisoquinolines with TBHP at 105 °C. The temperature proved to be crucial and low conversions were obtained at different temperatures. The best results were obtained with Cbz- and Boc-protected derivatives which yielded the corresponding peroxides in 74 %. In the second step, a catalytic quantity of methanesulfonic acid converts the preformed peroxides into the corresponding iminium cations which subsequently react with the arenes. Satisfying yields were obtained with anisoles as well as with electron-rich heterocycles such as indoles or pyrroles.

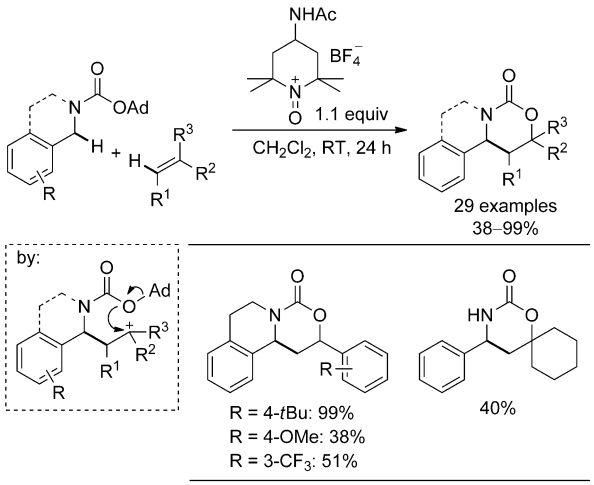
Prabhu and co-workers demonstrated that a catalytic quantity of iodine in combination with oxygen mediates the



Scheme 18. Metal-free cross-dehydrogenative Friedel–Crafts arylation sequence. Cbz = benzyloxycarbonyl, Ms = methanesulfonyl.

arylation of tetrahydroisoquinolines with indoles even at room temperature.[30]

An interesting cross-dehydrogenative heterocycle synthesis was recently introduced by the group of Garcia Mancheño in 2012.[31] Various polycyclic tetrahydro-1,3-oxazin-2-one derivatives were obtained in good yields from the 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoro borate mediated coupling of tertiary amines with aliphatic or aromatic olefins (Scheme 19) Interestingly, 4-



Scheme 19. Metal-free cross-dehydrogenative oxazinone synthesis.

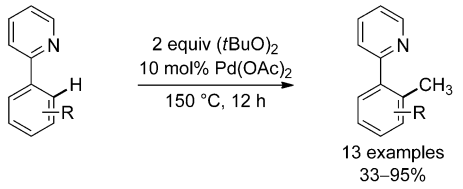
acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoro borate outperformed other organic oxidants, including DDQ and TBHP which gave the product in only trace amounts. The reaction proceeds by the oxidation of the protected amines into the corresponding cations, which readily cyclize with the olefin and cleavage of the alkyl substituent of the carbamate. Good results have been obtained with adamantyl carbamates while the use of Boc-protected derivatives resulted in the release of isoprene and product mixtures were obtained. Electron-deficient styrenes proved to be less reactive while highly electron-rich olefins were sensitive toward polymerization.

3.2. Cross-Dehydrogenative Couplings Involving Radical Intermediates

In groundbreaking contributions, the group of Minisci demonstrated that alkylated pyridine derivatives are accessible from the reaction of free alkyl radicals with protonated heterocycles.[32] However, the relatively harsh reaction conditions limit the applicability of these pioneering procedures to robust substrates. Considerable efforts led to the development of selective and efficient procedures which allow the CDC of C_{sp^3}–H with C_{sp^2}–H bonds through free-radical intermediates under mild reactions conditions.

3.2.1. Intermolecular Radical Alkylations

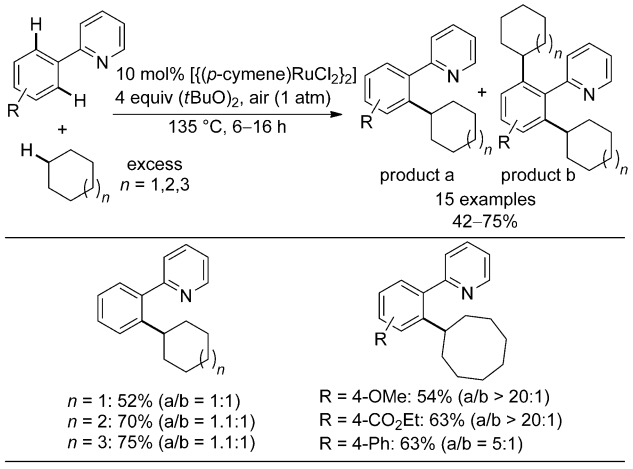
In 2008, the group of Li demonstrated that 2-phenylpyridines are smoothly methylated with di-*tert*-butyl peroxide (TBP) in the presence of catalytic quantities of $Pd(OAc)_2$ at elevated temperatures (Scheme 20).[33] The peroxide served



Scheme 20. Palladium-catalyzed oxidative *ortho*-methylation.

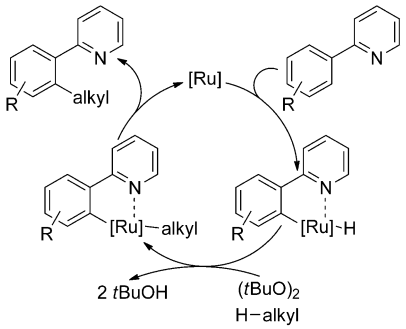
both as the oxidant and the methylating reagent. The authors suggested that the methylation of the heterocyclic palladacycle[34] might proceed through radical intermediates which are generated from the thermal decomposition of TBP. This procedure led to the basis for the development of the first intermolecular radical CDC of arenes with simple non-activated alkanes (Scheme 21).[35]

Various 2-aryl pyridines were successfully coupled with cyclohexane, cycloheptane, and cyclooctane (Scheme 21). Among the tested transition-metal salts, the best results



Scheme 21. Cross-dehydrogenative *ortho*-alkylation. *p*-cymene = 4-isopropyltoluene.

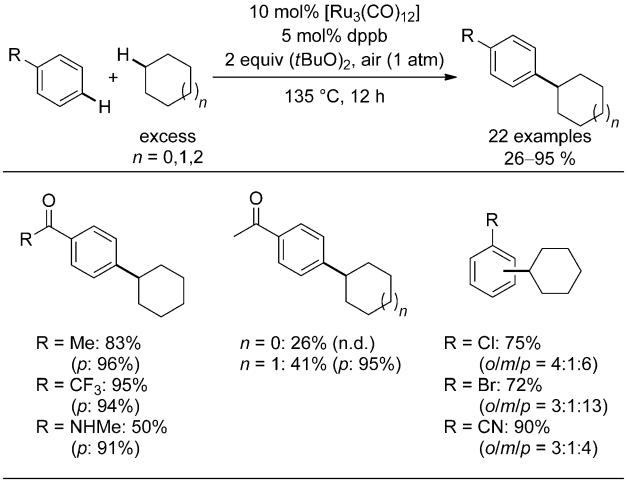
were obtained with 10 mol% $[\{(p\text{-cymene})RuCl_2\}_2]$. Interestingly, $Pd(OAc)_2$ was ineffective and only trace amounts of the desired products have been detected. TBP proved to be the most efficient oxidant, and high yields were obtained by using it in excess (4 equiv). Under optimized reaction conditions, electron-rich and electron-deficient 2-phenylpyridines were alkylated in satisfactory yields. The reaction is sensitive toward the ring size of the hydrocarbon and cyclooctane showed the highest reactivity while the use of cyclohexane resulted in moderate yields. However, overalkylation was observed in many cases, and the products were obtained as isomeric mixtures. The authors proposed a tentative mechanism which starts with the chelation-assisted aromatic C–H activation of the phenyl pyridine by the ruthenium catalyst (Scheme 22).[36] The resulting complex reacts with the cyclo-



Scheme 22. Proposed mechanism of the *ortho*-alkylation.

alkane and the peroxide with formation of an aryl/alkyl/Ru complex which reductively eliminates the product.

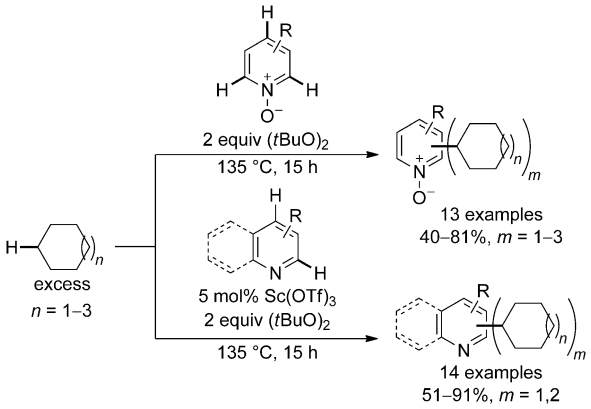
The same group further developed this methodology for the *para*-selective CDC reaction of arenes and cycloalkanes.[37] By using $[Ru_3(CO)_{12}]$ in combination with 1,4-bis(diphenylphosphino)butane (dppb) in the presence of TBP a wide range of arenes were functionalized with simple cycloalkanes (Scheme 23).



Scheme 23. Ruthenium-catalyzed *para*-selective alkylation of arenes. dppe = 1,2-bis(diphenylphosphino)ethane.

Electron-deficient as well as electron-rich arenes were both suited for this reaction. The corresponding coupling products were isolated in good yields and with high *para* selectivities, even with chelating *ortho*-directing substituents. Beside cyclohexane, other cycloalkanes were also effective in this reaction. However, the ring size had a dramatic influence on the reaction yield, with the lowest yield obtained using cyclopentane. A kinetic isotope effect ($k_H/k_D = 1.00$) was not observed with chlorobenzene/$[D_5]$chlorobenzene as substrates, thus leading the authors to conclude that the reaction proceeds most likely through a radical mechanism. Therefore the regioselectivity could be rationalized by the stabilization of the radical intermediate by both electron-donating and electron-withdrawing groups through FMO interactions.[38]

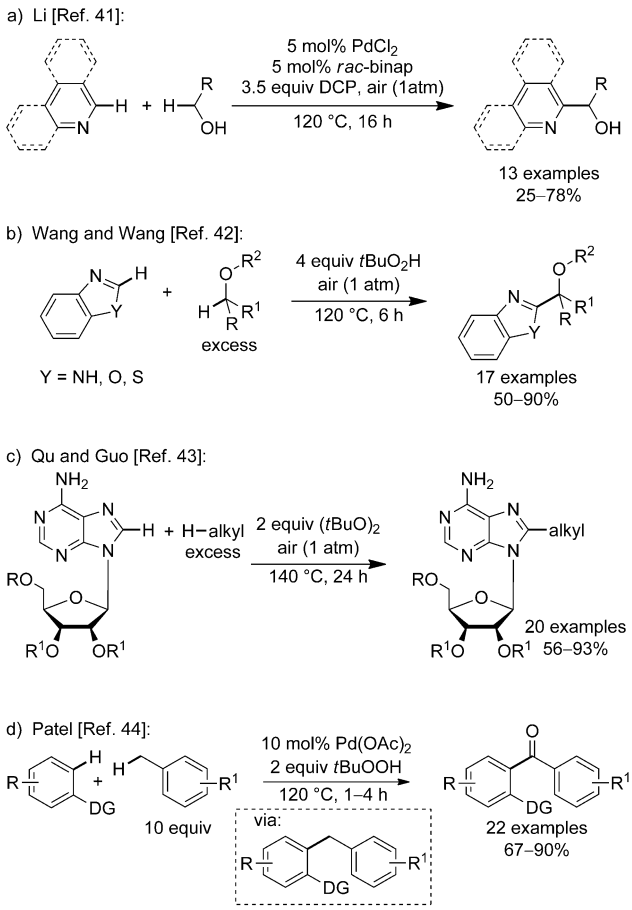
In subsequent efforts, the group of Li succeeded in introducing significantly improved variants of the Minisci reaction.[32] Pyridine-*N*-oxide proved to be reactive enough to undergo radical alkylation with cyclic hydrocarbons, even in the absence on an activator (Scheme 24).[39] Catalytic quanti-



Scheme 24. Improved Minisci-type alkylations of heterocycles.

ties of scandium triflate efficiently activated various pyridines and quinolines for the alkylation reaction under neutral reaction conditions (Scheme 24).[40] The Lewis-acidic catalyst decreases the electron density of the aromatic system by coordinating to the nitrogen atom of the heterocycle and thus facilitates the nucleophilic attack of the alkyl radical. However, overalkylation was observed in both procedures.

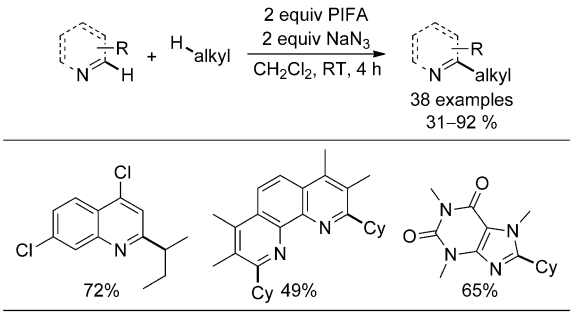
In subsequent contributions, the synthetic scope of the radical cross-dehydrogenative alkylations was continuously improved (Scheme 25). The group of Li presented the palladium-catalyzed coupling of N-heterocycles with simple alcohols. The reaction is initiated by an excess of dicumyl peroxide (Scheme 25).[41] The group of Wang and Wang disclosed the radical coupling of benzothiazoles, benzoxazoles, and benzimidazoles with alcohols or ethers in the presence of excess TBHP (Scheme 25).[42] The groups of Qu and Guo developed a TBP-mediated alkylation of various purines and purine glycosides with cycloalkanes by using a modified version of Li's procedure[17] (Scheme 25).[43] Patel and co-workers extended the scope of the palladium-catalyzed, chelation-assisted *ortho* alkylations to the synthesis of benzophenone derivatives. Various 2-phenylpyridines were



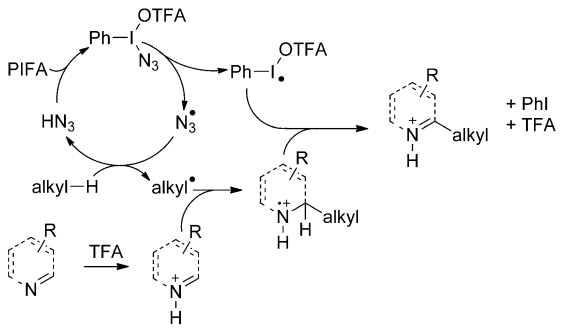
Scheme 25. Radical cross-dehydrogenative alkylations. binap = 2,2′-bis-(diphenylphosphanyl)-1,1′-binaphthyl, DCP = dicumylperoxide, DG = directing group.

coupled with toluenes in the first step with subsequent oxidation of the resulting diphenyl methanes into the corresponding ketones (Scheme 25).[44]

In completion of the previous protocols, 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 (Scheme 26).[45] Under optimized reaction conditions, various nitrogen-containing heterocycles were alkylated with cyclic hydrocarbons even at room temperature. The authors propose a mechanism which starts with the generation of



Scheme 26. PIFA/NaN_3-mediated metal-free alkylation.



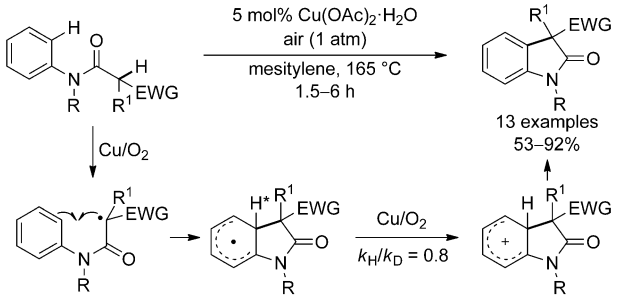
Scheme 27. Proposed mechanism of the PIFA-mediated alkylation.

a (trifluoroacetoxy)iodobenzene radical and an azide radical (Scheme 27). 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.

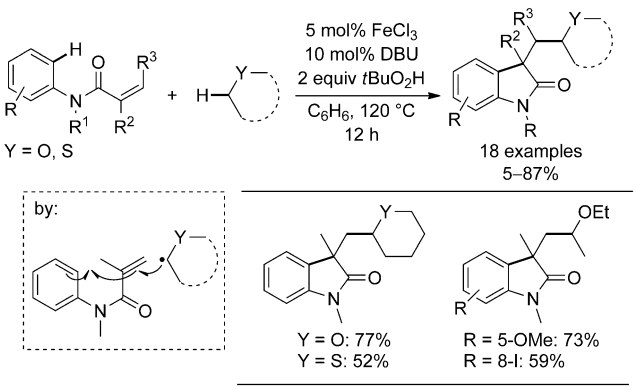
Interestingly, the group of Todd demonstrated that the $CuCl_2$/DDQ-catalyzed arylations of isochromanes with anisoles proceed by the formation of aryl radicals rather than the expected Friedel–Crafts reaction.[46]

3.2.2. *Intramolecular Radical Cyclizations*

Several efficient procedures have been developed for the cross-dehydrogenative synthesis of oxindole derivatives by intramolecular cyclizations of acetanilide radicals. The methodology was independently explored by the groups of Kündig[47] and Taylor[48] in 2009. Both groups demonstrated that phenylacetic acid anilides are converted into the corresponding heterocycles in the presence of stoichiometric amounts of copper salts. In 2010, the group of Taylor succeeded in developing a $Cu(OAc)_2$-catalyzed aerobic variant.[49] The key to achieving a catalytic turnover was to omit any basic additives and to perform the reaction in a nonpolar, high-boiling-point solvent such as mesitylene (Scheme 28). 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.



Scheme 28. Copper-catalyzed aerobic radical oxindole synthesis.

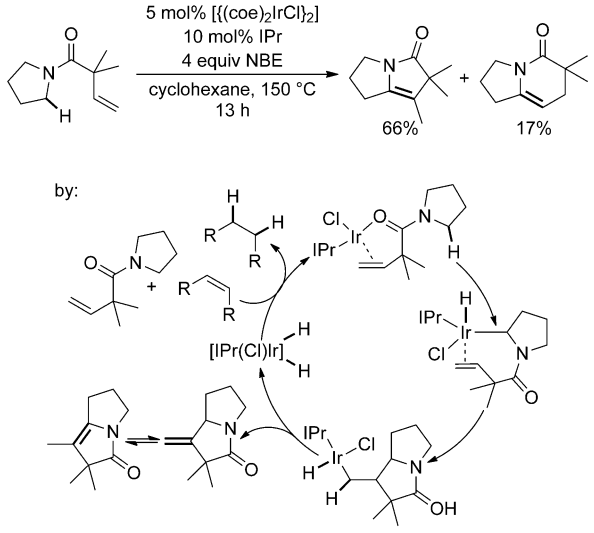


Scheme 29. Radical cyclization sequence. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene.

Recently, the group of Li extended this strategy to the synthesis of various 3-alkylated oxindole derivatives (Scheme 29).[50] The reaction starts with the iron(III)-catalyzed degradation of TBHP with subsequent formation of an alkyl radical adjacent to the heteroatom which adds to the double bond of the acrylanilide substrate. The resulting radical undergoes an intramolecular 5-*exo*-trig cyclization and subsequent oxidation step to afford the corresponding products.

3.3. Cross-Dehydrogenative Alkylation by Transition-Metal-Catalyzed C–H Activation

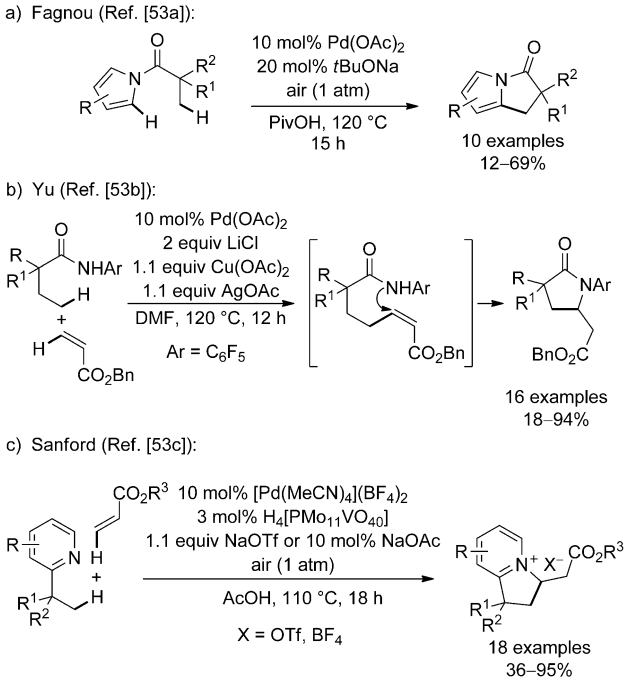
Transition-metal-catalyzed C–H activations represent the third strategy for the CDC of C_{sp^3}–H with C_{sp^2}–H bonds. This strategy was pioneered by the group of Sames in 2004, who demonstrated the feasibility of an iridium-catalyzed intramolecular cyclization of 2,2-dimethyl-vinylacid pyrrolidine amide (Scheme 30).[51] The cyclization reaction starts with the



Scheme 30. Iridium-catalyzed cross-dehydrogenative cyclization. coe = cyclooctane. NBE = norbornene.

oxidative addition of an in situ generated [{(IPr)IrCl}$_2$] carbene complex (IPr = *N*,*N*-(2,6-diisopropylphenyl)imidazole-2-ylidene) into the C–H bond adjacent to the nitrogen atom. The bulky N-heterocyclic carbene (NHC) ligand minimizes the rate of unproductive β-hydride elimination and favors both the 5-*exo*-trig (Scheme 30) as well as the 6-*endo*-trig cyclization. The resulting iridium complex liberates the product after β-hydride elimination, and the initial iridium catalyst is regenerated by hydride transfer onto norbornene. The scope of this procedure was later extended to intermolecular 1,2-additions with olefins and alkynes.[52]

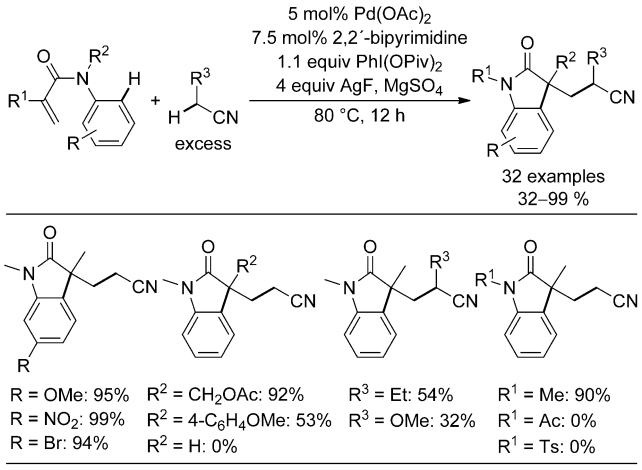
In subsequent contributions, several palladium-catalyzed cross-dehydrogenative cyclizations were developed to efficiently synthesize nitrogen-containing heterocycles (Scheme 31).[53] The group of Fagnou introduced an aerobic



Scheme 31. Cross-dehydrogenative cyclizations.

cyclization of *N*-pivaloyl pyrroles.[53a] Yu and co-workers disclosed a one-pot sequence for the synthesis of functionalized 2-pyrrolidinones, and it starts with an intramolecular C_{sp^3}–H olefination of the pivaloyl amides and subsequent conjugate addition.[53b] An intramolecular aerobic palladium-catalyzed synthesis of various 2,3-dihydroindolizinium salts was provided by the group of Sanford.[53c]

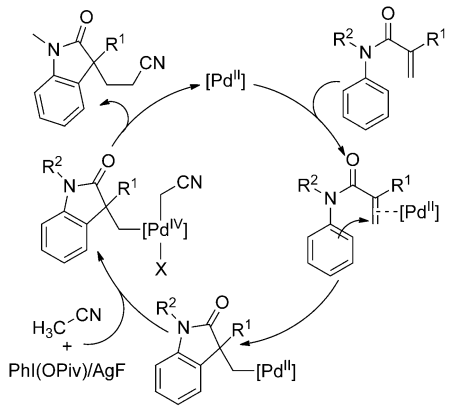
The group of Liu reported in 2011 a palladium-catalyzed cross-dehydrogenative synthesis of 3,3-dialkyloxindoles (Scheme 32).[54] Various *N*-protected methacrylic acid anilides were smoothly coupled with aliphatic nitriles, and the corresponding heterocycles were obtained in good yields. The reaction is mediated by a catalyst system which is generated in situ from $Pd(OAc)_2$ and 2,2′-bipyrimidine at 80 °C and the corresponding nitrile serves both as reagent and solvent. A combination of $PhI(OPiv)_2$ and AgF serves as the oxidant. Interestingly, silver fluoride proved to be crucial to



Scheme 32. Palladium-catalyzed synthesis of 3,3-dialkyloxindoles. Piv = pivaloyl, Ts = 4-toluenesulfonyl.

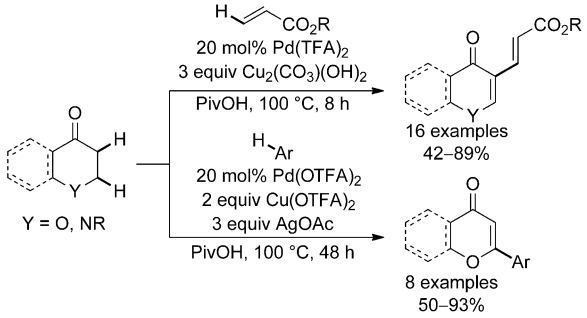
the reaction outcome, and no conversion of the substrate was observed either in its absence or when it was replaced with silver carbonate. The protocol is broadly applicable with regard to the anilides and the methacrylic acid moieties. Many functional groups including nitro, ester, trifluoromethyl, and bromide groups are well tolerated. However, no product was detected either in the absence of a functional group at the α-position of the acrylate moiety or with electron-withdrawing acyl or tosyl (4-tolylsulfonyl) protective groups on the anilide. Among the tested nitriles, the best results were obtained with acetonitrile whereas the use of butyronitrile and ispropylnitrile resulted in moderate and trace yields, respectively.

The group of Liu proposed a mechanism (Scheme 33) which starts with the coordination of the double bond to the palladium catalyst. A nucleophilic attack of the arene onto the activated olefin generates a palladium(II) alkyl complex which is transferred into a palladium(IV) intermediate by reacting with the nitrile in the presence of the oxidant. Reductive elimination liberates the product and closes the catalytic cycle. The scope of the protocol was extended to methacrylic acid anilides with electron-withdrawing protective groups by the addition of a catalytic quantity of pyridine.[55]



Scheme 33. Proposed mechanism of the oxindole synthesis.

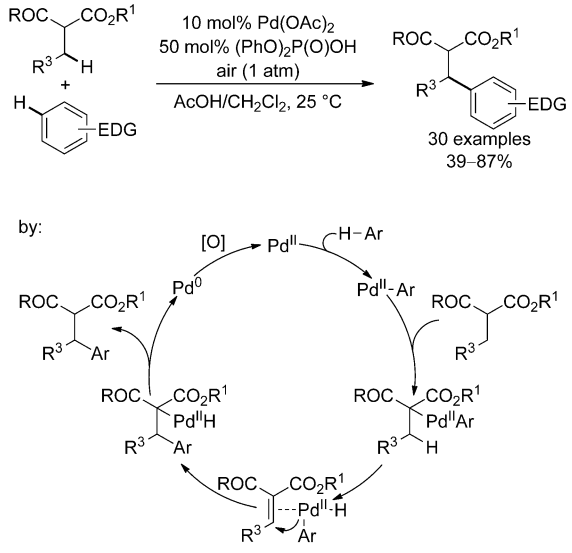
At about the same time, two procedures for a formal CDC of C_{sp^3}–H with C_{sp^2}–H bonds were independently introduced. Both methods proceed by the generation of an unsaturated intermediate which is subsequently coupled with an arene or an olefin.[56] The group of Hong developed two complementary $Pd(OTFA)_2$-catalyzed protocols for the arylation and olefination of a series of chromanones and dihydroquinolinones (Scheme 34).[56a] Both substrate classes were selectively



Scheme 34. Formal cross-dehydrogenative functionalization of chromanones and dihydroquinolinones.

vinylated at the 3-position in the presence of basic $CuCO_3$. However, the arylation reaction proved to be more challenging, and good results were reported with chromanones. The reaction required a combination of AgOAc and $Cu(OTFA)_2$ as the oxidant and the arylation occurred selectively at the 2-position.

The group of Pihko reported an aerobic palladium-catalyzed dehydrogenative arylation of 2-alkyl-1,3-dicarbonyl compounds (Scheme 35).[56b] The reaction is believed to proceed by the palladation of the arene and subsequent



Scheme 35. Arylation of 2-alkyl acetoacetates. EDG = electron-donating group.

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.

4. Coupling of C_{sp^3}–H with C_{sp^3}–H Bonds

The rather challenging regio- and stereoselective CDC of two C_{sp^3}–H bonds has been achieved by the development of bifunctional catalyst systems which allow the simultaneous activation of the proelectrophilic as well as the pronucleophilic C_{sp^3}–H bonds in situ. Following this strategy, various C-H acidic compounds with pK_a values ranging from $pK_a = 17$ (e.g. nitromethane in DMSO) to $pK_a = 26$ (e.g. acetone in DMSO)[57] have been successfully used in CDC reactions. The procedures are categorized herein by the related named reaction.

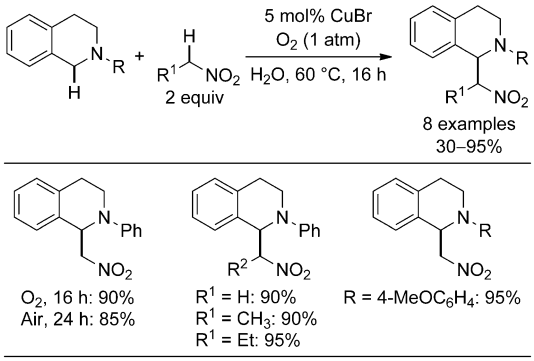
4.1. Aza-Henry-Type

The cross-dehydrogenative aza-Henry reaction[58] dates back to the pioneering studies of Leonard and Leubner in 1949.[59] The authors studied the reaction of phenylnitromethane with tetrahydroisoquinolinium iodide, which was generated from the oxidation of tetrahydroisoquinoline with iodine. Unfortunately, the desired product decomposed upon characterization as the corresponding picrate salt and the scope of the procedure was not investigated.

In 2005, the first broadly applicable procedure for the cross-dehydrogenative aza-Henry reaction was introduced by the group of Li.[60] 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 (Scheme 36).

Other copper salts such as $CuBr_2$ (92%), CuI (80%), $CuCl_2$ (80%), $Cu(OAc)_2 \cdot H_2O$ (80%), or CuCl (75%) also catalyze the reaction but higher catalyst loadings (10 mol%) were required. Nitromethane proved to be slightly more reactive than nitroethane which gave the corresponding products in moderate yields as diastereomeric mixtures.

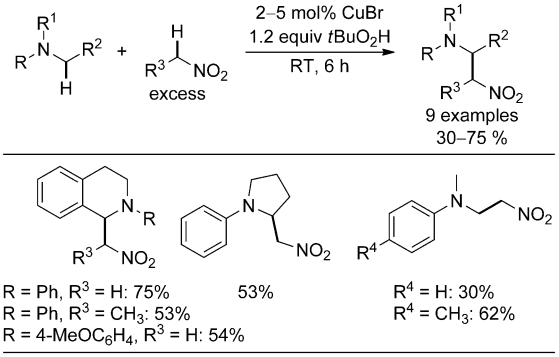
The atom economy[5] and process safety were significantly improved in 2007 by developing an aerobic protocol which proceeds in water (Scheme 37).[61] The use of water as solvent[62] allowed reduction of the amount of nitroalkane to 2 equivalents. The coupling reaction proceeded smoothly in the presence of 5 mol% CuBr at 100 °C under an atmosphere of molecular oxygen, which could be replaced by air when the reaction time was increased to 24 h.



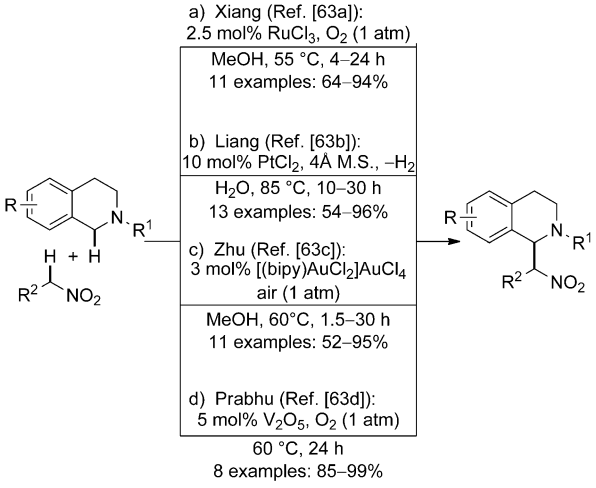
Scheme 37. Improved aerobic copper-catalyzed aza-Henry reaction in water.

These seminal contributions provided the basis for the development of various homogeneous catalyst systems which efficiently mediate the aerobic cross-dehydrogenative aza-Henry reactions depicted in Scheme 38.[63]

In parallel efforts, recoverable heterogeneous nanoparticles have been successfully introduced as catalysts for this reaction class. The groups of Li, Song, and Moores pioneered in this research area with the introduction of magnetic iron oxide nanoparticles which efficiently catalyze the aerobic coupling of *N*-arylated tetrahydroisoquinolines with nitro-



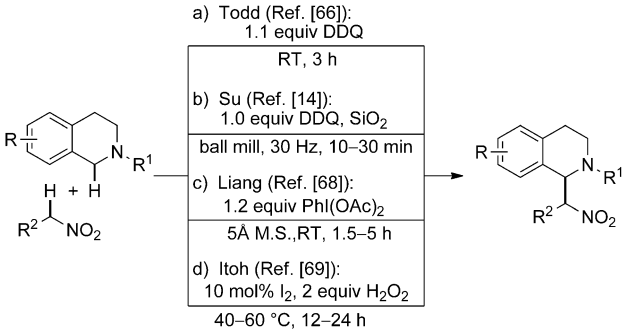
Scheme 36. Copper-catalyzed aza-Henry reaction.



Scheme 38. Catalyst systems for cross-dehydrogenative aza-Henry reactions. M.S. = molecular sieves.

alkanes under neat conditions.[64] The nanoparticles are easily separated from the reaction mixture with a magnet and can be reused without a significant loss of reactivity. Wu et al. reported that the aerobic aza-Henry reaction is efficiently catalyzed in water by $RuO_2 \cdot n H_2O$ nanoparticles which have been dispersed on the surface of a water-soluble sulfonated graphene.[65] The nanocomposite catalyst can be recovered by filtration, however a loss of reactivity was detected after the fourth recyclization.

The introduction of alternative oxidants allowed the development of several metal-free dehydrogenative procedures (Scheme 39). In a seminal report by Todd et al. in 2009, DDQ was introduced as an efficient oxidant to mediate the aza-Henry reaction at room temperature under neat conditions.[66] The intermediate *N*-phenyl tetrahydroisoquinolinium 2,3-dicyano-3,4-dichloro-1,4-dihydroxybenzene salt crystallized out of the reaction mixture and was characterized by X-ray diffraction.[67]



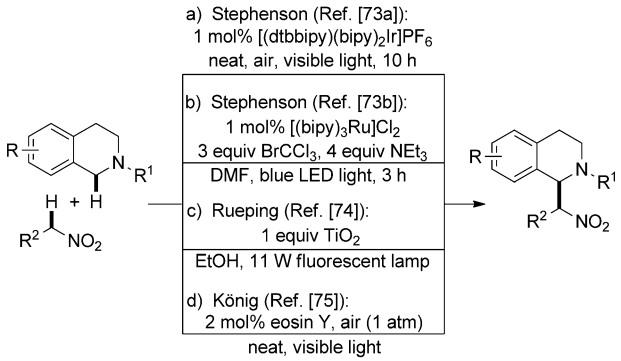
Scheme 39. Metal-free aza-Henry reactions.

The reaction is also feasible under high-speed ball-milling conditions, thus furnishing the products in good yields within 10–30 minutes depending on the reactivity of the substrates.[14] However, the influence of stainless steel balls and the reaction vessel was not investigated.

The organic oxidant (diacetoxy)iodobenzene (DIB) was introduced for this reaction type by Liang and co-workers.[68] The group of Itoh demonstrated that catalytic amounts of iodine in combination with hydrogen peroxide effectively catalyze the nitroalkylation of various tetrahydroisoquinoline derivatives by generating the catalytic active hypoiodous acid (HIO) in situ.[69]

Encouraged by innovative contributions to the field of electrochemical oxidations of tertiary amines,[70] the groups of Li, Chan, and Lessard demonstrated that the CDC of *N*-phenyl tetrahydroisoquinoline with nitromethane is also feasible under electrochemical conditions.[71] The potentiostatic electrolysis (0.7 V) was performed with a large-area platinum electrode in an electrochemical H-cell using the ionic liquid [BMIm][BF_4] (1-butyl-3-methylimidazolium tetrafluoroborate) as the solvent and triethylamine to trap the protons which are generated during oxidation. The corresponding iminium ions accumulate in the reaction mixture and serve as a cationic pool.[72] The subsequent addition of nitromethane furnished the product in 80% yield and 93% faradaic yield. Interestingly, the CuBr-catalyzed protocol proceeds well in the ionic liquid under an oxygen atmosphere. The catalyst-containing ionic liquid can be reused, without loss of reactivity, after extraction of the product with diethyl ether. However the scope of both protocols was not investigated.

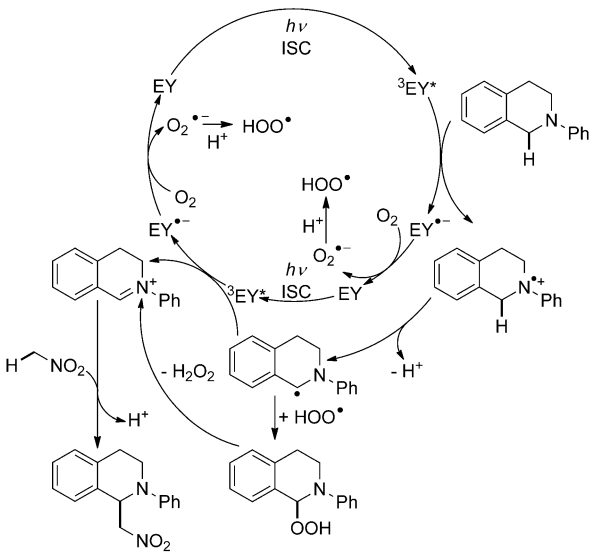
In related work, photo-oxidation catalysts have been successfully employed in cross-dehydrogenative aza-Henry reactions and enables the use of visible light as a primary oxidant (Scheme 40).[73–76] The group of Stephenson demon-



Scheme 40. Photoredox catalyst systems for light-mediated aza-Henry reactions.

strated that both [(bipy)$_3$Ru]Cl$_2$ and [(ppy)$_2$(dtbpipy)Ir]PF$_6$ catalyze the coupling of tetrahydroisoquinoline derivatives with nitroalkanes under irradiation with visible light.[73] The iridium complex is slightly more effective in aza-Henry-type reactions, whereas the ruthenium complex can be used in various other CDC reactions such as alkynylations, Friedel–Crafts-type arylations, or Mannich-type alkylations.[73b,88a] The alkylation did not occur in the dark, and the presence of oxygen was found to be beneficial but not strictly required.

Cheap and broadly available TiO_2 nanoparticles were introduced as photo-oxidation catalysts by the group of Rueping in 2012.[74] Good yields were obtained with stoichiometric amounts of the catalyst, which could be recovered by centrifugation and reused several times without a detectable loss of activity. The use of the organic dye eosin Y allowed the group of König to develop the first metal-free photoredox procedure.[75] The reaction proceeds smoothly under irradiation with visible light at room temperature. The photocatalytic protocol is best performed under neat conditions in the presence of air. The reaction mechanism was investigated in detail by the group of Wu (Scheme 41),[76] and the authors propose that the reaction starts with a photoinduced electron transfer from the tetrahydroisoquinoline derivative to the excited triplet state of the eosin dye. The eosin radical anion reacts with a molecule of oxygen with regeneration of the photocatalyst and formation of a superoxide radical anion. The tetrahydroisoquinoline radical cation first combines with the superoxide radical anion with formation of a peroxide intermediate which eliminates one equivalent of hydrogen peroxide. The resulting iminium cation reacts with the nitroalkane and generates the desired product. In an alter-



Scheme 41. Proposed mechanism of the Eosin-Y-catalyzed aza-Henry reaction.

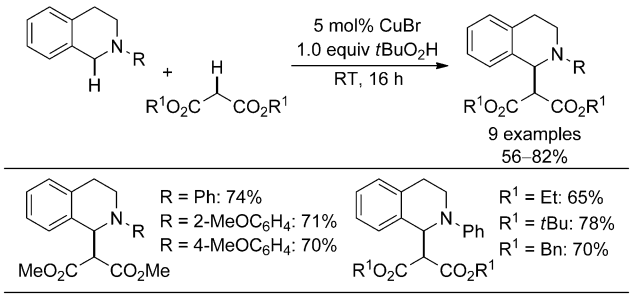
native pathway, the iminium cation can also be generated directly from the radical cation by quenching a second molecule of excited eosin. The accumulation of tetrahydroisoquinoline peroxide is responsible for a significant product generation after stopping initial light irradiation.

4.2. 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[77] products. Tertiary amines and glycine derivatives have been successfully introduced as substrates. The latter gives access to non-natural amino acids and the progress in this field will be discussed in a separate subchapter because of its great importance.[78]

4.2.1. Mannich-Type Reactions with Tertiary Amines

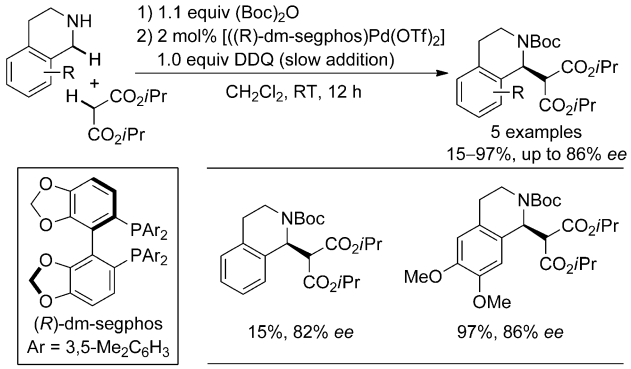
In 2005, the group of Li carried out pioneering work which led to the first cross-dehydrogenative Mannich-type reaction in which tetrahydroisoquinolines were successfully coupled with readily enolizable malonates ($pK_a \approx 15$ in DMSO, Scheme 42).[79] The reaction proceeds smoothly at room



Scheme 42. Copper-catalyzed cross-dehydrogenative Mannich reaction.

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. Under optimized reaction conditions, a set of *N*-aryl tetrahydroisoquinolines was coupled with various malonates in good yields. The use of malonitrile resulted in a product mixture consisting of 29% of the desired product analogue with 7% of a cyanation product which was generated from the competing oxidative coupling with cyanide anions[80] originating from the decomposition of the malonitrile. The authors proposed a mechanism in which the nucleophilicity of the malonate is increased by formation of a copper enolate complex which subsequently reacts with a copper-stabilized iminium cation. The Mannich-type reaction of tetrahydroisoquinolines with malonates has become a reference tool to benchmark the performance of new cross-dehydrogenative catalysts.[61,63,68,69,73b,75,76]

An enantioselective palladium-catalyzed protocol was introduced by the group of Sodeoka (Scheme 43).[81] In previous studies, the authors demonstrated that malonates could be enantioselectively coupled with imines in the presence of chiral palladium phosphine complexes.[82] The

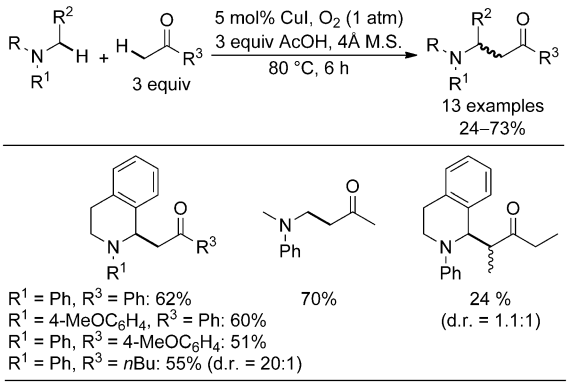


Scheme 43. Enantioselective cross-dehydrogenative Mannich reaction. Boc = *tert*-butoxycarbonyl.

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 (*S* enantiomer). The key to achieving high enantioselectivities and good yields was the slow addition of the oxidant.

Less C-H-acidic aldehydes or ketones ($pK_a \approx 25$ in DMSO)[57] have to be activated by a cocatalyst to serve as substrates in cross-dehydrogenative Mannich reactions. Two strategies proved to be successful for increasing the nucleophilicity at the α-carbon atom. The first strategy relies on the presence of Brønsted 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.

In an innovative contribution, the group of Wanner demonstrated in a series of trapping experiments that in situ deprotected enol ethers couple with preformed tetrahydroisoquinolinium salts. However the desired products were only obtained in low yields.[83] The first CuI-catalyzed aerobic cross-dehydrogenative Mannich-type reaction of tertiary amines with ketones was disclosed by the group of Tan and Guo in 2009 (Scheme 44).[84] The key to achieving good

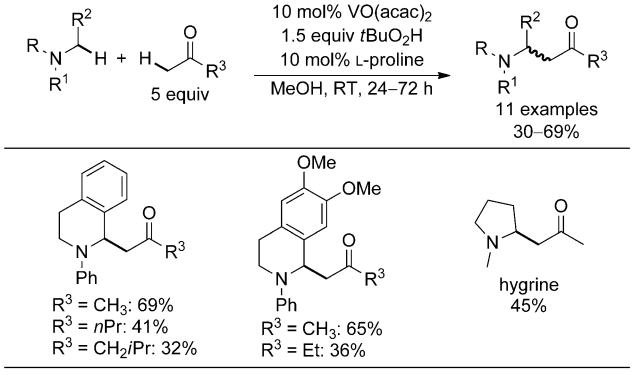


Scheme 44. Copper-catalyzed aerobic dehydrogenative Mannich reaction in acidic media.

conversions was the addition of acetic acid and molecular sieves. Consequently, the use of asymmetric ketones resulted in the formation of regioisomers. The presence of acetic acid in combination with molecular sieves was also crucial in the gold-catalyzed protocol as reported by the group of Zhu.[63c]

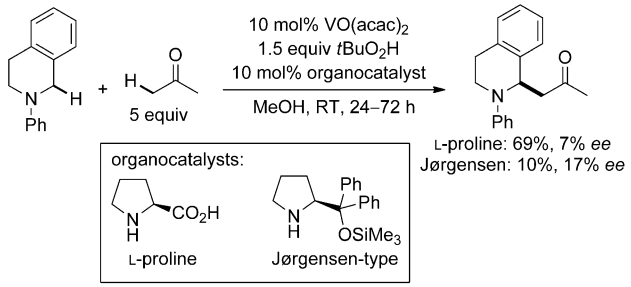
Interestingly, the magnetically removable iron oxide nanoparticles which had been introduced by Li, Moores, and Song proved to be sufficiently Lewis-acidic to catalyze the aerobic coupling of *N*-phenyl tetrahydroisoquinoline with acetone under neat conditions.[64]

In pioneering work, the group of Klussmann demonstrated that a set of simple ketones could be efficiently activated to undergo [VO(acac)$_2$]-catalyzed cross-dehydrogenative Mannich reactions by the addition of 10 mol% of L-proline (Scheme 45).[85] The reaction is highly regioselective, and asymmetric ketones were functionalized exclusively at



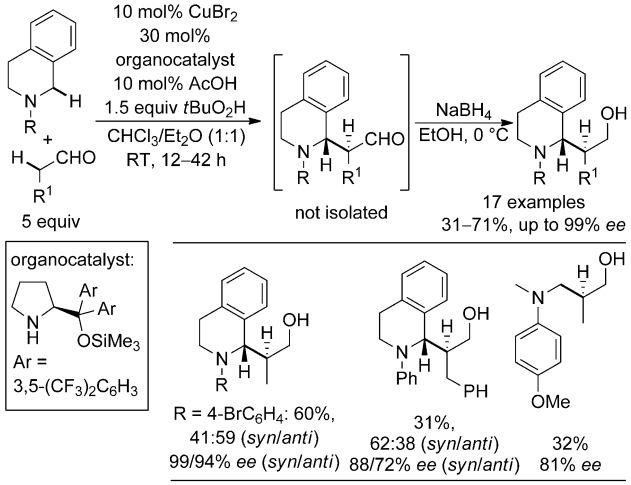
Scheme 45. Organocatalytic vanadium-catalyzed dehydrogenative Mannich reaction. acac = acetylacetonoate.

the less bulky α-position. As a proof of concept, the authors also demonstrated that the development of an enantioselective procedure is feasible by adding a chiral organocatalyst (Scheme 46). An encouraging enantiomeric excess of 17% *ee* was obtained for the reference reaction in the presence of 10 mol% of a Jørgensen-type catalysts.[86]



Scheme 46. Enantioselective organocatalytic dehydrogenative Mannich reaction.

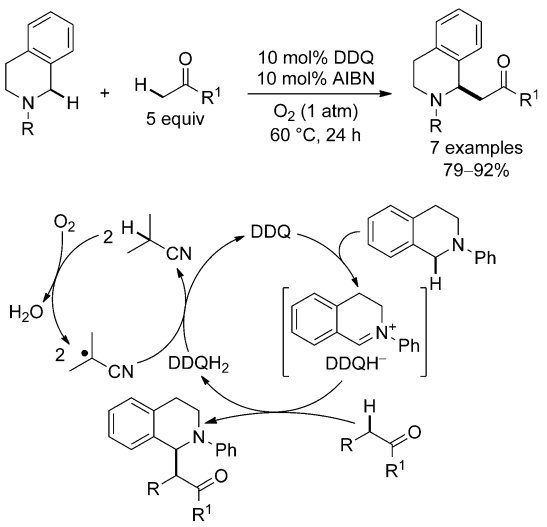
On the basis of this concept, the group of Chi succeeded in developing an efficient enantioselective cross-dehydrogenative Mannich reaction of *N*-aryl tetrahydroisoquinolines with aliphatic aldehydes (Scheme 47).[87] The addition products were sensitive to racemization, and a final reduction step



Scheme 47. Enantioselective dehydrogenative Mannich reaction.

with $NaBH_4$ simplified the isolation procedure and prevented unwanted side reactions. High enantioselectivities and acceptable diastereoselectivities were obtained with a chiral Jørgensen-type catalyst[86] in combination with $CuBr_2$, acetic acid, and TBHP. A solvent mixture of chloroform and diethyl ether proved to be crucial in achieving good selectivities.

At around the same time, alternative oxidants and photocatalytic procedures were disclosed for cross-dehydrogenative Mannich reactions of ketones and aldehydes.[73b–76,88] The first metal-free DDQ-catalyzed dehydrogenative Mannich reaction was introduced by the group of Prabhu (Scheme 48).[89] The reaction is smoothly catalyzed by

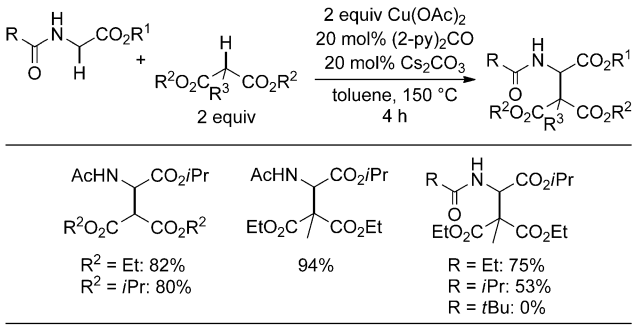


Scheme 48. DDQ-catalyzed dehydrogenative Mannich reaction. AIBN = 2,2′-azobis(2-methylpropionitrile).

10 mol% DDQ and 10 mol% AIBN under an oxygen atmosphere. The authors proposed a 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. The protocol is also applicable to the conversion of 4-hydroxycoumarines.

4.2.2. Mannich-Type Reactions with Glycine Derivatives

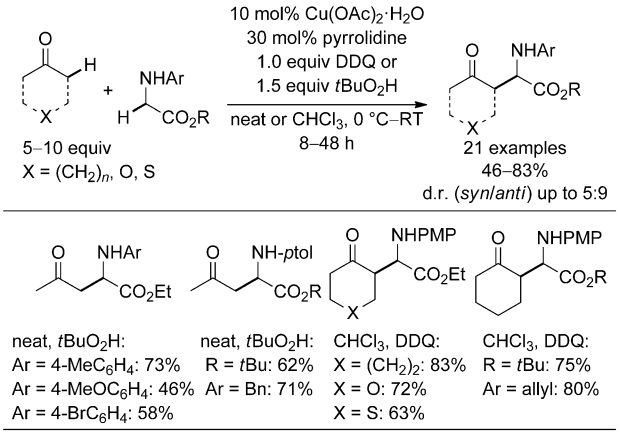
Cross-dehydrogenative Mannich reactions introduced a waste-minimized, regio- and stereoselective access to non-natural α-amino acids.[78] In a groundbreaking report, the group of Li demonstrated in 2008 that various *N*-acetyl glycine esters are selectively coupled at the α-position with a series of malonates (Scheme 49).[16] The reaction is mediated by a stoichiometric quantity of $Cu(OAc)_2$ which serves both as catalyst and oxidant. The yield was significantly improved by the addition of 20 mol% of Cs_2CO_3 and 20 mol% of di-(2-pyridyl) ketone. Interestingly, low yields were detected with a catalytic amount of the copper salt under an oxygen atmosphere. The reaction is broadly applicable



Scheme 49. Dehydrogenative functionalization of glycines.

with regard to the malonate, and even sterically demanding compounds were converted in good yields. 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.

A $Cu(OAc)_2{\cdot}H_2O$/pyrrolidine-catalyzed version of this reaction was developed by the group of Huang in 2010 (Scheme 50).[90] The α-functionalization of glycine derivatives



Scheme 50. Copper-catalyzed functionalization of glycine esters.

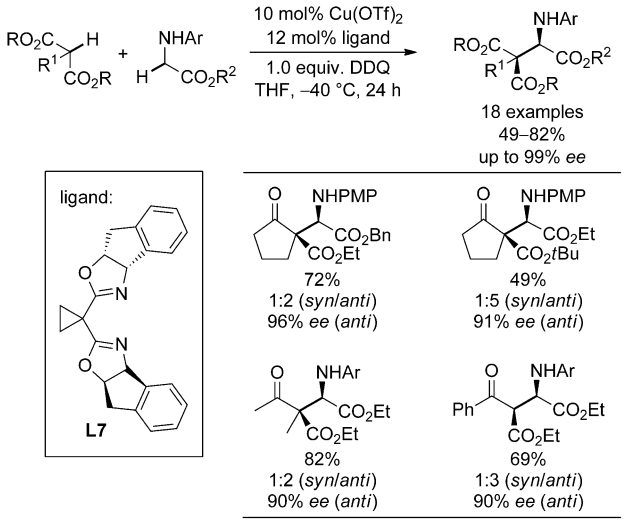
with acetone could be performed under neat conditions with TBHP. The conversion of cyclic ketones required the use of DDQ as an oxidant and $CHCl_3$ as solvent. A slight enantiomeric excess of 15% *ee* was obtained when the pyrrolidine cocatalyst was replaced by L-proline methyl ester.

The group of Hu extended the scope of this reaction to various cyclic ketones by employing a $FeCl_3$/pyrrolidine catalyst system.[91] The corresponding amino acids were obtained in good yields as diastereomeric mixtures.

Recently, the group of Wang succeeded with the development of the first highly enantioselective copper-catalyzed cross-dehydrogenative Mannich-type functionalization of glycine derivatives (Scheme 51).[92] The key to achieving high enantioselectivities lay in the addition of a chiral-box-type ligand. The optimal catalyst system is generated in situ from 10 mol% of $Cu(OTf)_2$, 12 mol% of the chiral ligand, and 1 equivalent of DDQ in THF at −40 °C, and mediates the coupling of various *N*-aryl glycine esters with 1,3-diketoesters. The corresponding products were isolated in good yields with enantioselectivities of greater than 80% *ee* as diastereomeric mixtures. However, the development of efficient catalyst systems that allow control of the diastereoselectivity and the enantioselectivity still remains challenging.

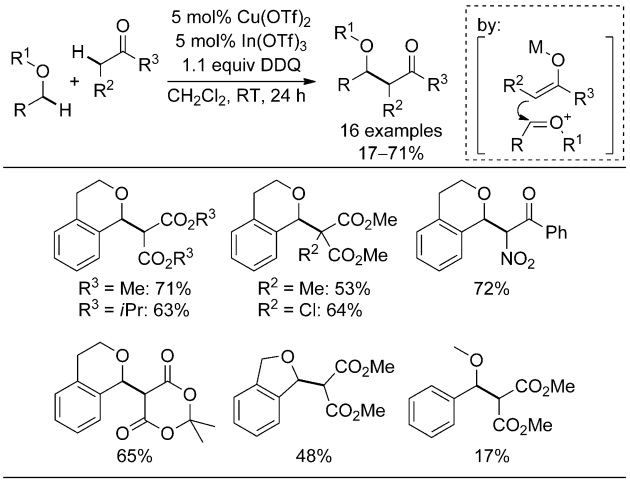
4.3. Aldol-Type Reactions

Aldol-reaction-type[93] products are accessible by the oxidative activation of alkyl ethers and the subsequent coupling with enolizable carbonyl compounds. In 2006, the



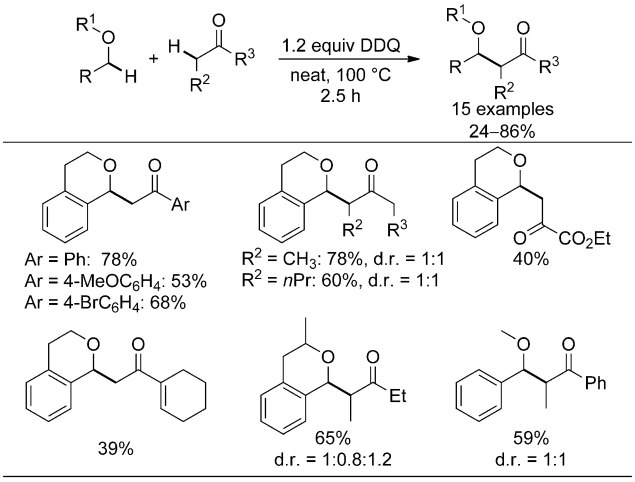
Scheme 51. Enantioselective functionalization of glycines. PMP = 4-$MeOC_6H_4$.

use of DDQ enabled the group of Li to develop of the first cross-dehydrogenative aldol reaction of isochromanes, phthalanes, and even benzyl methyl ether with carbonyl compounds.[94] Malonates and Meldrum's acid were successfully converted in the presence of a bimetallic $Cu(OTf)_2/In(OTf)_3$ catalyst system in dichloromethane at room temperature (Scheme 52). The authors proposed a mechanism in which



Scheme 52. Copper/Indium-catalyzed cross-dehydrogenative aldol reaction.

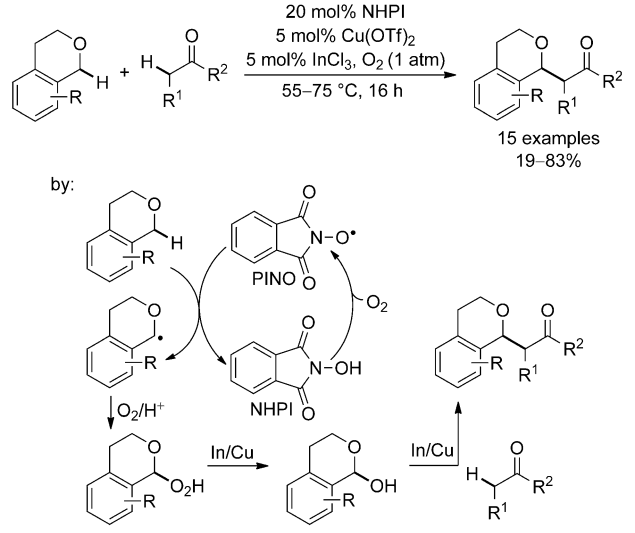
DDQ converts the ether into the corresponding oxonium cation which is then intercepted by a copper or indium enolate complex. However acyclic ethers were not fully converted and low yields were obtained.[94a] The development of an improved procedure using DDQ allowed the group of Li to present the first metal- and solvent-free coupling of various aliphatic ketones, acetophenones, and pyrovates with isochromanes (Scheme 53).[94b] The authors suggested that the



Scheme 53. Improved metal-free dehydrogenative aldol reaction.

in situ generated 2,3-dicyano-4,5-dichlorohydroquinone anions facilitate the enolization of the carbonyl compounds.

The use of a catalytic amount of NHPI (*N*-hydroxyphthalimide)[95] allowed the development of an aerobic version of the indium/copper-catalyzed dehydrogenative coupling of cyclic benzylethers with carbonyl compounds (Scheme 54).[95] The reaction proceeds smoothly under an

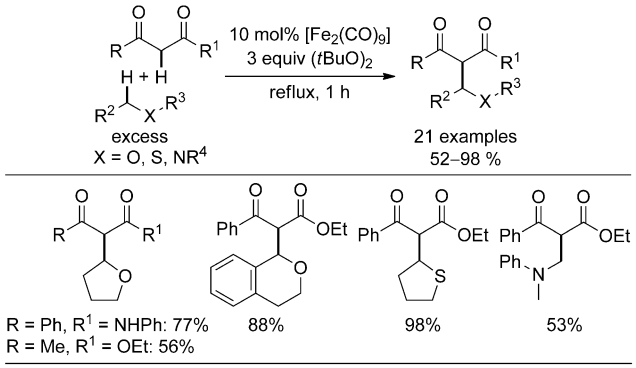


Scheme 54. Aerobic copper/indium-catalyzed alkylation of benzyl ethers.

atmosphere of molecular oxygen with of 20 mol% NHPI, 5 mol% $Cu(OTf)_2$, and 5 mol% of $InCl_3$. The reaction temperature proved to be crucial in achieving good conversions. Malonates were efficiently converted at 55 °C while ketones required a slightly higher temperature of 75 °C. 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

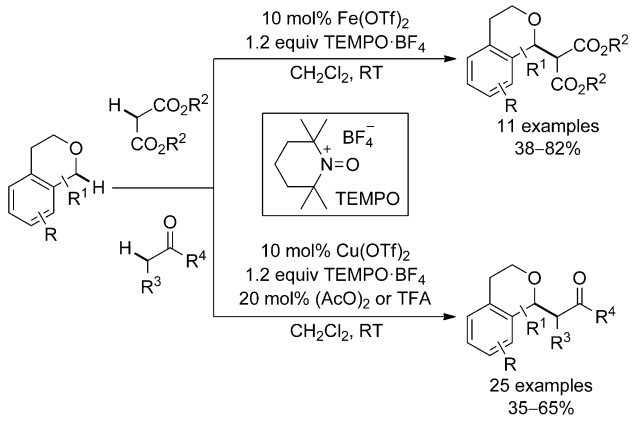
peroxide intermediate is transferred to the corresponding hemiketal in the presence of the indium/copper catalyst and subsequently coupled with the carbonyl compound. In a control experiment, the authors demonstrated that the preformed hemiketal was readily converted into the desired product under the optimized reaction conditions.

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 $[Fe_2(CO)_9]$ in combination with 3 equivalents of TBP (Scheme 55).[97] The heterocycles served both as reagent and solvent. Under optimized reactions conditions, various ethers and tetrahydrothiophene were smoothly converted. However, *N*,*N*-dimethylaniline was coupled in moderate yield.

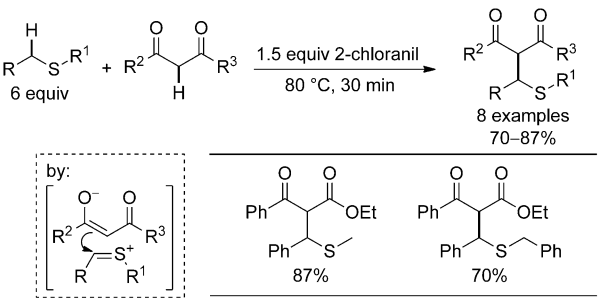


Scheme 55. Iron-catalyzed α-functionalization of heterocycles. X = O,S,NR.

The group of Mancheño disclosed 2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoro borate as an alternative oxidant for this reaction class (Scheme 56).[98] Isochromanes were efficiently coupled with malonates in the presence of catalytic quantities of $Fe(OTf)_2$ whereas aliphatic aldehydes and ketones were efficiently converted in the presence a $Cu(OTf)_2$ catalyst. The substrates required the activation by a catalytic amount of either acetic anhydride or aqueous trifluoroacetic acid. The copper catalyst is also efficient for the cross-dehydrogenative Mannich-type reaction.



Scheme 56. 2,2,6,6-Tetramethylpiperidine-1-oxoammonium tetrafluoroborate mediated aldol reaction.



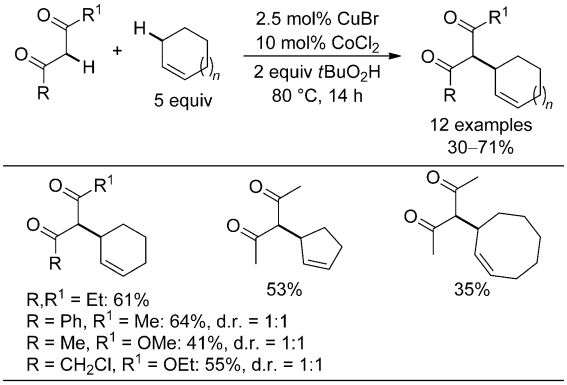
Scheme 57. Cross-dehydrogenative alkylation of thioethers.

The scope of the metal-free, cross-dehydrogenative, aldol-type reaction was extended to thioethers by the group of Li (Scheme 57).[99] The coupling of benzylic thioethers with 1,3-dicarbonyl compounds was smoothly mediated by *ortho*-chloranil (tetrachloro-1,2-benzoquinone) at 80 °C and the corresponding Pummerer-type products[100] were isolated in good yields. The alkylation occurs selectively at the more reactive benzylic C_{sp^3}–H bond, and the monoalkylation product was formed exclusively when dibenzyl thioether was used as substrate. The coupling reaction is believed to proceed by the formation of thionium intermediates that subsequently react with the carbonyl compound. Interestingly, Knoevenagel-condensation[101] products were obtained at 100 °C from overoxidation of the thioether followed by elimination of the sulfoxide.

4.4. Tsuji–Trost-Type

The cross-dehydrogenative alkylation of allylic C–H bonds provides a complementary way to access to Tsuji–Trost coupling products.[102] The reaction was disclosed by Li and Li in 2006 (Scheme 58).[103] 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. The best results were obtained with a bimetallic catalyst system consisting of 2.5 mol% CuBr and 10 mol% $CoCl_2$ in combination with TBHP.

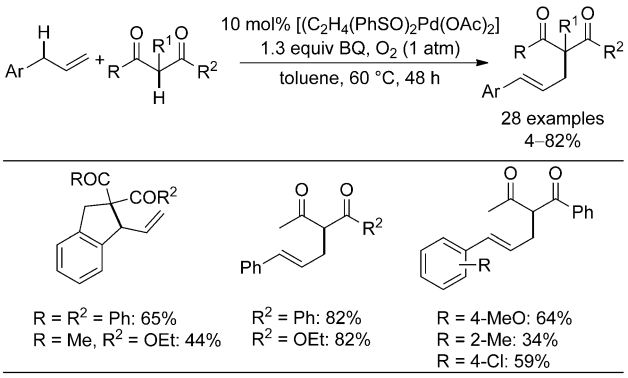
Among the tested substrates, 1,3-diketones possessed the highest reactivity, and the corresponding products were



Scheme 58. Copper/cobalt-catalyzed cross-dehydrogenative allylation.

obtained in good yields. Aliphatic β-ketoesters were less reactive, and low yields were obtained with cyclic ketoesters. The ring size of the cycloalkenes showed a significant influence on the reaction outcome. Good yields were obtained with five- and six-membered rings while the use of cycloheptene and cyclooctene resulted in low conversions. The authors propose a mechanism which starts with a TBHP-mediated hydrogen abstraction, thus generating either a π-allyl copper or a cobalt complex which reacts with the activated 1,3-dicarbonyl. A metal-free, DDQ-mediated version of this reaction was introduced by the group of Bao[104] in 2008 and further modified by Venkateswarlu and co-workers in 2010.[105]

In 2008, two palladium-catalyzed cross-dehydrogenative allylation procedures were reported.[106] Sulfur-containing ligands[106b,107] proved to be crucial in both protocols. The group of Shi reported on the development of a $[(PhSOC_2H_4SOPh)Pd(OAc)_2]$/benzoquinone-catalyzed intra- and intermolecular allylic alkylation of various allylbenzenes with 1,3-dicarbonyls (Scheme 59).[106a]

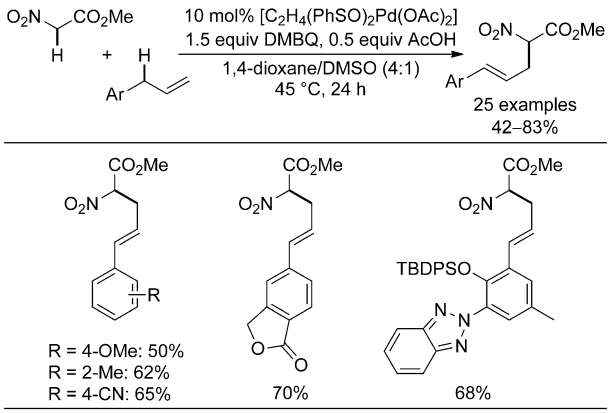


Scheme 59. Palladium-catalyzed allylic alkylation. BQ = 1,4-benzoquinone.

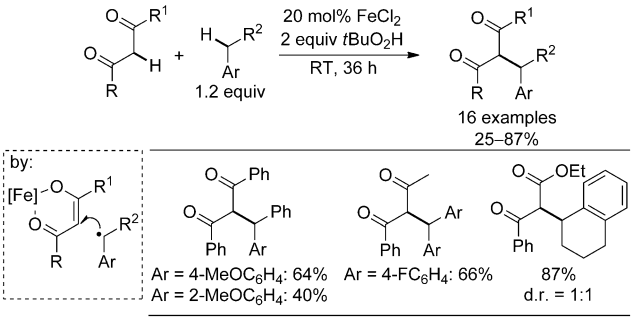
The group of White disclosed methyl nitroacetate as a versatile substrate for the cross-dehydrogenative Tsuji–Trost-type allylation (Scheme 60).[106b] Various electron-rich, electron-deficient, and heterocyclic allyl arenes were coupled in moderate yields in the presence of $[(PhSOC_2H_4SOPh)Pd(OAc)_2]$, 2,6-dimethoxybenzoquinone (DMBQ), and acetic acid in a 4:1 solvent mixture of 1,4-dioxane and DMSO.

4.5. Alkylation-Type Reactions

In 2007, the first cross-dehydrogenative benzylation and alkylation reactions of C_{sp^3}–H bonds were reported. The groups of Li and Li demonstrated that 1,3-diketones are smoothly benzylated in the presence of a $FeCl_2$ catalyst (Scheme 61).[108] Other transition-metal salts such as CuBr or $CoCl_2$ were far less efficient, and the benzylated products were obtained in yields of less than 30%. TBP gave the best results among the tested oxidants. A decrease of the reaction



Scheme 60. Allylic alkylation with methyl nitroacetate. DMSO = dimethylsulfoxide, DMBQ = 2,6-dimethoxybenzoquinone, TBDPS = *tert*-butyldiphenylsilyl.



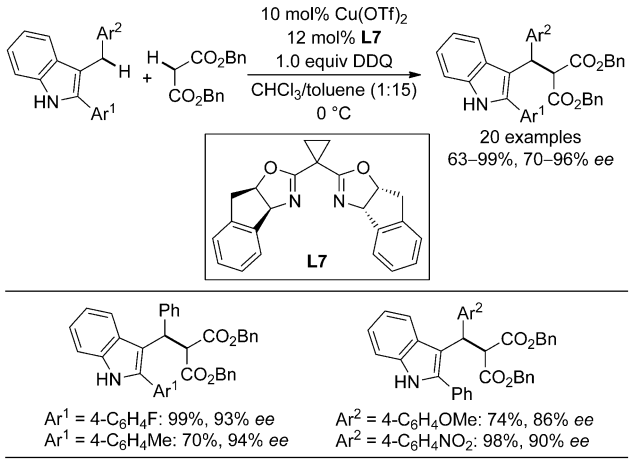
Scheme 61. Iron-catalyzed dehydrogenative benzylation.

temperature from 80 °C to room temperature resulted in a significant improvement of the yields from 66% to 80%.

The reaction is applicable to both cyclic and acyclic benzylic compounds, and the electronic properties of substituents showed a minor influence on the reaction outcome. In contrast, decreased yields were obtained with substrates which contained bulky groups, either in the *ortho*-position of the diphenylmethane or on the 1,3-dicarbonyl compound. The authors proposed that the reaction proceeds by the formation of benzyl radicals which add to in situ generated iron enolate complexes.

A DDQ-mediated, metal-free version of this procedure was reported by the group of Venkateswarlu.[105] Bao and co-workers extended the scope of the benzylation procedure to the DDQ-mediated coupling of 1,3-dicarbonyl compounds with diarylpropargylic C_{sp^3}–H bonds.[109] The group of Cozzi developed a DDQ-mediated diastereoselective α-benzylation of aliphatic aldehydes which were activated in situ by enamine condensation with a MacMillan-type[110] organocatalyst.[111]

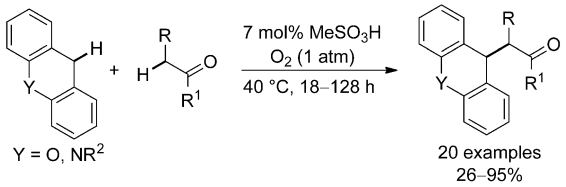
In 2010, the group of Gong succeeded in developing the first enantioselective copper-catalyzed cross-dehydrogenative benzylation reaction of malonic esters with indole derivatives (Scheme 62).[112] The reaction is mediated by a catalyst system that is generated in situ from $Cu(OTf)_2$ and the chiral pybox ligand **L7** in combination with an equimolar amount of DDQ. The pybox derivative **L7** outperformed the other tested



Scheme 62. Enantioselective benzylation of malonates.

ligands, and the best results were obtained with dibenzyl malonate in a 1:15 mixture of chloroform and toluene at 0 °C. Under optimized reaction conditions, various 2-aryl-3-benzyl indoles were coupled with dibenzyl malonates in excellent yields and high enantioselectivities. Both electron-donating as well as electron-withdrawing groups on the benzyl moiety were well tolerated. However, indoles without an aryl group at C2 were not investigated. The use of different 1,3-dicarbonyl compounds such as dimethyl malonate resulted in moderate yields (63 %) and enantioselectivities (70 % *ee*). The authors postulated a mechanism in which DDQ transfers the benzyl indole into the corresponding vinylogous iminium cation which subsequently reacts with a chiral copper enolate complex.

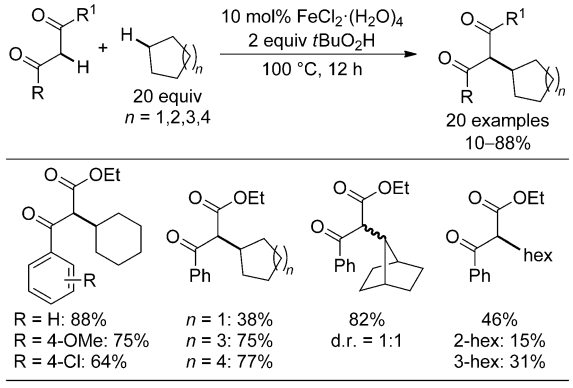
The same year, the group of Klussmann reported the development of an interesting autoxidative benzylation reaction of carbonyl compounds with xanthanes and acridanes catalyzed by methane sulfonic acid (Scheme 63).[113]



Scheme 63. Autoxidative acid-catalyzed benzylation. Y = O, N<u>R</u>.

The heterocycles smoothly underwent autoxidation with molecular oxygen, thus generating in situ the corresponding hydroperoxides which were subsequently converted into benzyl cations by the strong Brønsted acid. The subsequent addition of the activated carbonyl compounds furnished the desired coupling products.

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 (Scheme 64).[114] The reaction is



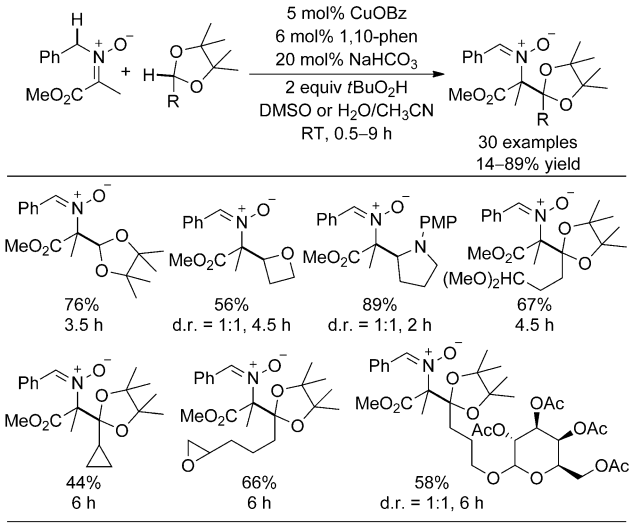
Scheme 64. Iron-catalyzed cross-dehydrogenative alkylation.

mediated by a substoichiometric quantity of $FeCl_2 \cdot 4H_2O$. Among the tested oxidants, the best results were obtained with TBP at 100 °C. Under the optimized reaction conditions electron-rich and electron-deficient β-ketoesters were alkylated with cyclohexane, cyclooctane, norbornane, adamantane, and even *n*-hexane. Unsurprisingly, the use of non-symmetric hydrocarbons resulted in a mixture of regioisomers.

4.6. Miscellaneous C_{sp^3}–H Coupling Reactions

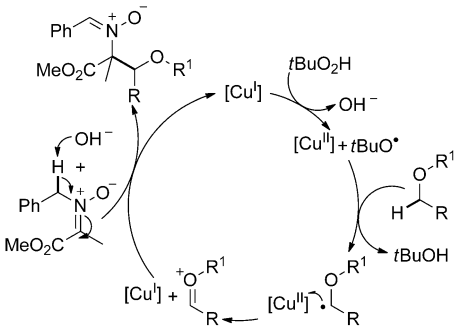
Recently, two innovative CDC procedures have been disclosed and they involve additional isomerization or elimination steps after the activation of both C_{sp^3}–H bonds.

In 2011, the group of Oisaki and Kanai reported on the development of a copper-catalyzed oxidative migratory synthesis of non-natural α-amino acid derivatives from benzyl nitrones and functionalized acetals (Scheme 65).[115] The reaction proceeds by an additional C=N isomerization step after activation of the benzylic position of the nitrone



Scheme 65. Oxidative migratory coupling reaction. phen = 1,10-phenanthroline.

coupling partner. The transformation is catalyzed by a copper(I) benzoate/1,10-phenanthroline system in combination with a substoichiometric amount of $NaHCO_3$ and 2 equivalents of TBHP. Polar solvents proved to be beneficial, and good results were both obtained in DMSO as well as in H_2O/CH_3CN (1:1). Under the optimized reaction conditions, an impressive number of diversely functionalized dimethyl acetals, cyclic ethers, and a series of secondary amines were successfully coupled in satisfactory yields and excellent selectivities. The authors proposed a mechanism commencing with the copper-mediated generation of a *tert*-butoxy radical which subsequently abstracts a proton from an acetal molecule (Scheme 66). The resulting radical intermediate is readily oxidized by the copper catalyst into the corresponding cationic species which subsequently reacts with the benzylidene isomer of the nitrone coupling partner which was generated by deprotonation of the benzylic C–H bond.

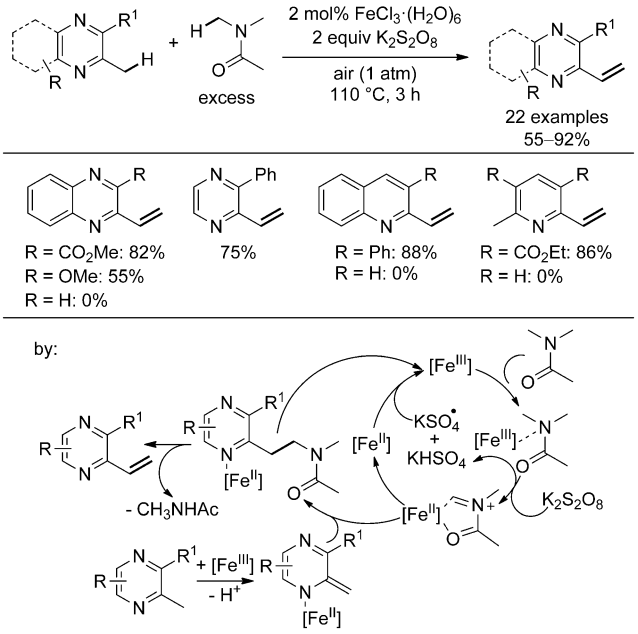


Scheme 66. Mechanism of the oxidative migratory coupling.

The group of Xu recently reported an original protocol that allows $FeCl_3 \cdot 6H_2O/K_2S_2O_8$-catalyzed vinylation of various 2-methyl (benzo)-1,4-pyrazines with dimethyl acetamides (Scheme 67).[116] The procedure involves a cross-dehydrogenative C_{sp^3}–C_{sp^3} coupling which is followed by a final elimination step to generate the vinylic product. The best results were obtained with dimethyl acetamide as methylene source. Slightly decreased yields were obtained with *N*,*N*-dimethylbenzamide whereas no conversion of the substrate was detected in DMF or NMP. Under optimized reaction conditions, various 2-methylated 1,4-prazines, 1,4-quinoxalines, and pyridines were successfully converted into the corresponding vinylated heterocycles. However, a substituent in the 3-position was required for the reaction to occur. The authors propose a mechanism in which the dimethyl acetamide is transferred onto an iron(II)-stabilized iminium cation which reacts with the enamine tautomer of the 2-methyl 1,4-pyrazine. A final elimination step of *N*-methyl acetamide furnishes the desired product.

5. Summary and Outlook

Over the past few decades, impressive progress has been made in CDC reactions of C_{sp^3}–H bonds, and the developed procedures have reached a remarkable level of versatility,



Scheme 67. Cross-dehydrogenative vinylation of pyrazine derivatives.

selectivity, and efficiency. The oxidative coupling of C_{sp^3}–H with different C–H bonds supplements well-established coupling reactions of prefunctionalized starting materials and provides waste-minimized access to functionalized molecules more rapidly. However, several challenges still remain. It is of high interest to develop efficient catalyst systems for the selective activation C_{sp^3}–H bonds which are not in close proximity to a heteroatom. Air has yet to be further established as a broadly available and safe terminal oxidant. A deeper mechanistic understanding of cross-dehydrogenative C–H coupling reactions would facilitate the rational development of more enantioselective C_{sp^3}–H functionalizations. We are excited to witness future developments, especially in the interest of of green chemistry, in the coming years.

We would like to thank the DAAD (German Academic Exchange Service) (fellowship to T.K.), McGill University, NSERC, FQRNT, CFI, E. B. Eddy Endowment Fund, and Canada Research Chair (to C.J.L.) for supporting our research.

Received: May 17, 2013
Revised: July 23, 2013
Published online: November 8, 2013

[1] Textbooks: a) J. E. Bäckvall, J. F. Normant, L. E. Overman, P. Knochel, K. Sonogashira, A. de Meijere, A. Suzuki, T. N. Mitchel, J. Tsuji, E. Negishi, *Metal-Catalyzed Cross-Coupling Reactions*, *Vol. 1–2* (Eds.: A. de Meijere, F. Diederich), Wiley-Interscience, Weinheim, **1998**; b) *Handbook of Organopalladium Chemistry for Organic Synthesis*, *Vol. 1 and 2* (Eds.: E. Negishi, A. de Meijere, J. E. Bäckvall, S. Cacchi, T. Hayashi, Y. Itoh, M. Kosugi, S. I. Murahashi, K. Oshima, Y. Yamamoto), Wiley-Interscience, New York, **2002**; reviews: c) D. S. Surry,

S. L. Buchwald, *Chem. Sci.* **2010**, *1*, 13 – 31; d) J. Magano, J. R. Dunetz, *Chem. Rev.* **2011**, *111*, 2177 – 2250; e) I. Vasilevich, R. V. Kombarov, D. V. Genis, M. A. Kirpichenok, *J. Med. Chem.* **2012**, *55*, 7003 – 7009; f) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem.* **2012**, *124*, 5150 – 5174; *Angew. Chem. Int. Ed.* **2012**, *51*, 5062 – 5085.

[2] a) C. M. So, F. Y. Kwong, *Chem. Soc. Rev.* **2011**, *40*, 4963 – 4972; b) B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg, V. Percec, *Chem. Rev.* **2011**, *111*, 1346 – 1416.

[3] a) M. Tobisu, N. Chatani in *Inventing Reactions* (Ed.: L. J. Gooßen), Springer, Heidelberg, **2012**, pp. 35 – 53; b) D.-G. Yu, B.-J. Li, Z.-J. Shi, *Acc. Chem. Res.* **2010**, *43*, 1486 – 1495; selected references: c) J. Cornella, E. Gómez-Bengoa, R. Martin, *J. Am. Chem. Soc.* **2013**, *135*, 1997 – 2009; d) J. He, C. Zhao, J. A. Lercher, *J. Am. Chem. Soc.* **2012**, *134*, 20768 – 20775; e) L.-G. Xie, Z.-X. Wang, *Chem. Eur. J.* **2011**, *17*, 4972 – 4975; f) L. J. Gooßen, K. Gooßen, C. Stanciu, *Angew. Chem.* **2009**, *121*, 3621 – 3624; *Angew. Chem. Int. Ed.* **2009**, *48*, 3569 – 3571; g) M. Tobisu, T. Shimasaki, N. Chatani, *Angew. Chem.* **2008**, *120*, 4944 – 4947; *Angew. Chem. Int. Ed.* **2008**, *47*, 4866 – 4869; h) B.-T. Guan, S.-K. Xiang, B.-Q. Wang, Z.-P. Sun, Y. Wang, K.-Q. Zhao, Z.-J. Shi, *J. Am. Chem. Soc.* **2008**, *130*, 3268 – 3269; i) J. W. Dankwardt, *Angew. Chem.* **2004**, *116*, 2482 – 2486; *Angew. Chem. Int. Ed.* **2004**, *43*, 2428 – 2432; j) M. E. van der Boom, S.-Y. Liou, Y. Ben-David, L. J. W. Shimon, D. Milstein, *J. Am. Chem. Soc.* **1998**, *120*, 6531 – 6541; k) E. Wenkert, E. L. Michelotti, C. S. Swindell, *J. Am. Chem. Soc.* **1979**, *101*, 2246 – 2247.

[4] a) W. I. Dzik, P. P. Lange, L. J. Gooßen, *Chem. Sci.* **2012**, *3*, 2671 – 2678; b) N. Rodríguez, L. J. Gooßen, *Chem. Soc. Rev.* **2011**, *40*, 5030 – 5048; c) J. D. Weaver, A. Recio, A. J. Grenning, J. A. Tunge, *Chem. Rev.* **2011**, *111*, 1846 – 1913; d) L. J. Gooßen, F. Collet, K. Gooßen, *Isr. J. Chem.* **2010**, *50*, 617 – 629; e) B. Song, T. Knauber, L. J. Gooßen, *Angew. Chem.* **2013**, *125*, 3026 – 3030; *Angew. Chem. Int. Ed.* **2013**, *52*, 2954 – 2958.

[5] a) B. Trost, *Science* **1991**, *254*, 1471 – 1477; b) R. A. Sheldon, *J. Chem. Technol. Biotechnol.* **1997**, *68*, 381 – 388; c) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695 – 705; d) C.-J. Li, B. M. Trost, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 13197 – 13202; e) A. D. Curzons, D. N. Mortimer, D. J. C. Constable, V. L. Cunningham, *Green Chem.* **2001**, *3*, 1 – 6; f) D. J. C. Constable, A. D. Curzons, V. L. Cunningham, *Green Chem.* **2002**, *4*, 521 – 527.

[6] Reviews: a) V. A. Peshkov, O. P. Pereshivko, E. V. Van der Eycken, *Chem. Soc. Rev.* **2012**, *41*, 3790 – 3807; b) W.-J. Yoo, L. Zhao, C.-J. Li, *Aldrichimica Acta* **2011**, *44*, 43 – 51; c) C. Wei, Z. Li, C.-J. Li, *Synlett* **2004**, 1472 – 1483;d) L. Zani, C. Bolm, *Chem. Commun.* **2006**, 4263 – 4275.

[7] Reviews: a) C.-J. Li, *Acc. Chem. Res.* **2010**, *43*, 581 – 590; b) C.-J. Li, *Acc. Chem. Res.* **2002**, *35*, 533 – 538; selected articles: c) C. C. K. Keh, C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2003**, *125*, 4062 – 4063; d) C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2002**, *124*, 5638 – 5639; e) C.-J. Li, C. Wei, *Chem. Commun.* **2002**, 268 – 269; f) X.-H. Yi, Y. Meng, C.-J. Li, *Chem. Commun.* **1998**, 449 – 450; g) T. H. Chan, C. J. Li, Z. Y. Wei, *J. Chem. Soc. Chem. Commun.* **1990**, 505 – 507; h) J. Nokami, J. Otera, T. Sudo, R. Okawara, *Organometallics* **1983**, *2*, 191 – 193.

[8] Textbooks on C–H functionalizations: a) *Modern Arylation Methods* (Eds.: L. Ackermann), Wiley-VCH, Weinheim, **2009**; reviews on C-H functionalizations: b) C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* **2001**, *34*, 633 – 639; c) Y. Fujiwara, C. Jia, *Pure Appl. Chem.* **2001**, *73*, 319 – 324; d) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173 – 1193; e) M. Catellani, E. Motti, N. Della Ca', *Acc. Chem. Res.* **2008**, *41*, 1512 – 1522; f) J. C. Lewis, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2008**, *41*, 1013 – 1025; g) B.-J. Li, S.-D. Yang, Z.-J. Shi, *Synlett* **2008**, 949 – 957; h) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196 – 5217; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094 – 5115; i) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074 – 1086; j) L. Joucla, L. Djakovitch, *Adv. Synth. Catal.* **2009**, *351*, 673 – 714; k) G. P. McGlacken, L. M. Bateman, *Chem. Soc. Rev.* **2009**, *38*, 2447 – 2464; l) F. Bellina, R. Rossi, *Chem. Rev.* **2010**, *110*, 1082 – 1146; m) F. Bellina, R. Rossi, *Chem. Rev.* **2010**, *110*, 3850 – 3850; n) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624 – 655; o) J. Roger, A. Gottumukkala, H. Doucet, *ChemCatChem* **2010**, *2*, 20 – 40; p) M. Wasa, K. M. Engle, J.-Q. Yu, *Isr. J. Chem.* **2010**, *50*, 605 – 616; q) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147 – 1169; r) J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740 – 4761; s) C. Verrier, P. Lassalas, L. Théveau, G. Quéguiner, F. Trécourt, F. Marsais, C. Hoarau, *Beilstein J. Org. Chem.* **2011**, *7*, 1584 – 1601; t) S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res.* **2012**, *45*, 936 – 946; u) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem.* **2012**, *124*, 9092 – 9142; *Angew. Chem. Int. Ed.* **2012**, *51*, 8960 – 9009; v) D. A. Colby, A. S. Tsai, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2012**, *45*, 814 – 825; w) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788 – 802; x) G. Song, F. Wang, X. Li, *Chem. Soc. Rev.* **2012**, *41*, 3651 – 3678; y) L. G. Mercier, M. Leclerc, *Acc. Chem. Res.* **2013**, 10.1021/ar3003305; z) J. J. Mousseau, A. B. Charette, *Acc. Chem. Res.* **2013**, *46*, 412 – 424; aa) A. Sharma, D. Vacchani, E. Van der Eycken, *Chem. Eur. J.* **2013**, *19*, 1158 – 1168.

[9] C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335 – 344.

[10] Reviews on cross-dehydrogenative C–H bond functionalizations: a) P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem.* **2000**, *112*, 2740 – 2767; *Angew. Chem. Int. Ed.* **2000**, *39*, 2632 – 2657; b) Z. Li, D. S. Bohle, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 8928 – 8933; c) C.-J. Li, Z. Li, *Pure Appl. Chem.* **2006**, *78*, 935 – 945; d) A. A. O. Sarhan, C. Bolm, *Chem. Soc. Rev.* **2009**, *38*, 2730 – 2744; e) C. J. Scheuermann, *Chem. Asian J.* **2010**, *5*, 436 – 451; f) J. A. Ashenhurst, *Chem. Soc. Rev.* **2010**, *39*, 540 – 548; g) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Rev.* **2011**, *111*, 1293 – 1314; h) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215 – 1292; i) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068 – 5083; j) M. Klussmann, D. Sureshkumar, *Synthesis* **2011**, 353 – 369; k) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780 – 1824; l) L. Yang, H. Huang, *Catal. Sci. Technol.* **2012**, *2*, 1099 – 1112; m) K. Hirano, M. Miura, *Chem. Commun.* **2012**, *48*, 10704 – 10714; n) F. W. Patureau, J. Wencel-Delord, F. Glorius, *Aldrichimica Acta* **2012**, *45*, 31 – 41; o) X. Shang, Z.-Q. Liu, *Chem. Soc. Rev.* **2013**, *42*, 3253 – 3260; p) S. I. Kozhushkov, L. Ackermann, *Chem. Sci.* **2013**, *4*, 886 – 896.

[11] a) S.-I. Murahashi, D. Zhang, *Chem. Soc. Rev.* **2008**, *37*, 1490 – 1501; b) S.-I. Murahashi, N. Komiya, H. Terai, T. Nakae, *J. Am. Chem. Soc.* **2003**, *125*, 15312 – 15313.

[12] Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2004**, *126*, 11810 – 11811.

[13] a) Z. Li, C.-J. Li, *Org. Lett.* **2004**, *6*, 4997 – 4999; b) Z. Li, P. D. MacLeod, C.-J. Li, *Tetrahedron: Asymmetry* **2006**, *17*, 590 – 597.

[14] W. Su, J. Yu, Z. Li, Z. Jiang, *J. Org. Chem.* **2011**, *76*, 9144 – 9150.

[15] J. Yu, Z. Li, K. Jia, Z. Jiang, M. Liu, W. Su, *Tetrahedron Lett.* **2013**, *54*, 2006 – 2009.

[16] L. Zhao, C.-J. Li, *Angew. Chem.* **2008**, *120*, 7183 – 7186; *Angew. Chem. Int. Ed.* **2008**, *47*, 7075 – 7078.

[17] L. Zhao, O. Baslé, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 4106 – 4111.

[18] C. A. Correia, C.-J. Li, *Heterocycles* **2010**, *82*, 555 – 562.

[19] C. A. Correia, C.-J. Li, *Adv. Synth. Catal.* **2010**, *352*, 1446 – 1450.

[20] a) E. Boess, D. Sureshkumar, A. Sud, C. Wirtz, C. Farès, M. Klussmann, *J. Am. Chem. Soc.* **2011**, *133*, 8106 – 8109; b) E. Boess, C. Schmitz, M. Klussmann, *J. Am. Chem. Soc.* **2012**, *134*, 5317 – 5325.

[21] M. O. Ratnikov, M. P. Doyle, *J. Am. Chem. Soc.* **2013**, *135*, 1549 – 1557.
[22] X. Zhang, S.-R. Yeh, S. Hong, M. Freccero, A. Albini, D. E. Falvey, P. S. Mariano, *J. Am. Chem. Soc.* **1994**, *116*, 4211 – 4220.
[23] T. Sugiishi, H. Nakamura, *J. Am. Chem. Soc.* **2012**, *134*, 2504 – 2507.
[24] Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 6968 – 6969.
[25] a) M. Ghobrial, K. Harhammer, M. D. Mihovilovic, M. Schnürch, *Chem. Commun.* **2009**, 8836 – 8838; b) P. Liu, C.-Y. Zhou, S. Xiang, C.-M. Che, *Chem. Commun.* **2010**, *46*, 2739 – 2741; c) M.-Z. Wang, C.-Y. Zhou, M.-K. Wong, C.-M. Che, *Chem. Eur. J.* **2010**, *16*, 5723 – 5735; d) F. Yang, J. Li, J. Xie, Z.-Z. Huang, *Org. Lett.* **2010**, *12*, 5214 – 5217; e) L. Huang, T. Niu, J. Wu, Y. Zhang, *J. Org. Chem.* **2011**, *76*, 1759 – 1766; f) E. Shirakawa, N. Uchiyama, T. Hayashi, *J. Org. Chem.* **2011**, *76*, 25 – 34; g) E. Shirakawa, T. Yoneda, K. Moriya, K. Ota, N. Uchiyama, R. Nishikawa, T. Hayashi, *Chem. Lett.* **2011**, *40*, 1041 – 1043; h) K. Alagiri, G. S. R. Kumara, K. R. Prabhu, *Chem. Commun.* **2011**, *47*, 11787 – 11789.
[26] C. Dai, F. Meschini, J. M. R. Narayanam, C. R. J. Stephenson, *J. Org. Chem.* **2012**, *77*, 4425 – 4431.
[27] G. Zhang, J. Miao, Y. Zhao, H. Ge, *Angew. Chem.* **2012**, *124*, 8443 – 8446; *Angew. Chem. Int. Ed.* **2012**, *51*, 8318 – 8321.
[28] a) H. Mo, W. Bao, *Adv. Synth. Catal.* **2009**, *351*, 2845 – 2849; b) Y.-Z. Li, B.-J. Li, X.-Y. Lu, S. Lin, Z.-J. Shi, *Angew. Chem.* **2009**, *121*, 3875 – 3878; *Angew. Chem. Int. Ed.* **2009**, *48*, 3817 – 3820.
[29] B. Schweitzer-Chaput, M. Klussmann, *Eur. J. Org. Chem.* **2013**, 666 – 671.
[30] J. Dhineshkumar, M. Lamani, K. Alagiri, K. R. Prabhu, *Org. Lett.* **2013**, *15*, 1092 – 1095.
[31] H. Richter, R. Fröhlich, C.-G. Daniliuc, O. García Mancheño, *Angew. Chem.* **2012**, *124*, 8784 – 8788; *Angew. Chem. Int. Ed.* **2012**, *51*, 8656 – 8660.
[32] Alkyl radicals: a) F. Minisci, R. Galli, M. Cecere, V. Malatesta, T. Caronna, *Tetrahedron Lett.* **1968**, *9*, 5609 – 5612; b) F. Minisci, R. Galli, V. Malatesta, T. Caronna, *Tetrahedron* **1970**, *26*, 4083 – 4091; c) F. Minisci, G. P. Gardini, R. Galli, F. Bertini, *Tetrahedron Lett.* **1970**, *11*, 15 – 16; d) F. Minisci, P. Zammori, R. Bernardi, M. Cecere, R. Galli, *Tetrahedron* **1970**, *26*, 4153 – 4166; e) W. Buratti, G. P. Gardini, F. Minisci, F. Bertini, R. Galli, M. Perchinunno, *Tetrahedron* **1971**, *27*, 3655 – 3668; f) F. Minisci, R. Bernardi, F. Bertini, R. Galli, M. Perchinummo, *Tetrahedron* **1971**, *27*, 3575 – 3579; Acyl radicals: g) T. Caronna, A. Quilico, F. Minisci, *Tetrahedron Lett.* **1970**, *11*, 3633 – 3636; h) G. P. Gardini, F. Minisci, *J. Chem. Soc. C* **1970**, 929 – 929; i) G. P. Gardini, F. Minisci, G. Palla, A. Arnone, R. Galli, *Tetrahedron Lett.* **1971**, *12*, 59 – 62; j) T. Caronna, G. Fronza, F. Minisci, O. Porta, *J. Chem. Soc. Perkin Trans. 2* **1972**, 2035 – 2038; k) F. Minisci, A. Citterio, E. Vismara, C. Giordano, *Tetrahedron* **1985**, *41*, 4157 – 4170; l) F. Fontana, F. Minisci, M. C. Nogueira Barbosa, E. Vismara, *J. Org. Chem.* **1991**, *56*, 2866 – 2869; m) M.-L. Bennasar, T. Roca, R. Griera, J. Bosch, *Org. Lett.* **2001**, *3*, 1697 – 1700; Review: n) F. Minisci, *Synthesis* **1973**, 1 – 24.
[33] Y. Zhang, J. Feng, C.-J. Li, *J. Am. Chem. Soc.* **2008**, *130*, 2900 – 2901.
[34] A. R. Dick, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 2300 – 2301.
[35] G. Deng, L. Zhao, C.-J. Li, *Angew. Chem.* **2008**, *120*, 6374 – 6378; *Angew. Chem. Int. Ed.* **2008**, *47*, 6278 – 6282.
[36] a) S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Nature* **1993**, *366*, 529 – 531; b) N. Chatani, Y. Ie, F. Kakiuchi, S. Murai, *J. Org. Chem.* **1997**, *62*, 2604 – 2610; c) I. Özdemir, S. Demir, B. Çetinkaya, C. Gourlaouen, F. Maseras, C. Bruneau, P. H. Dixneuf, *J. Am. Chem. Soc.* **2008**, *130*, 1156 – 1157.
[37] X. Guo, C.-J. Li, *Org. Lett.* **2011**, *13*, 4977 – 7979.
[38] I. Fleming, *Frontier Orbitals and Organic Chemical Reactions* (Eds.: I. Fleming), Wiley-VCH, London, **1976**.
[39] G. Deng, K. Ueda, S. Yanagisawa, K. Itami, C.-J. Li, *Chem. Eur. J.* **2009**, *15*, 333 – 337.
[40] G. Deng, C.-J. Li, *Org. Lett.* **2009**, *11*, 1171 – 1174.
[41] C. A. Correia, L. Yang, C.-J. Li, *Org. Lett.* **2011**, *13*, 4581 – 4583.
[42] T. He, L. Yu, L. Zhang, L. Wang, M. Wang, *Org. Lett.* **2011**, *13*, 5016 – 5019.
[43] R. Xia, H.-Y. Niu, G.-R. Qu, H.-M. Guo, *Org. Lett.* **2012**, *14*, 5546 – 5549.
[44] S. Guin, S. K. Rout, A. Banerjee, S. Nandi, B. K. Patel, *Org. Lett.* **2012**, *14*, 5294 – 5297.
[45] A. P. Antonchick, L. Burgmann, *Angew. Chem.* **2013**, *125*, 3349 – 3353; *Angew. Chem. Int. Ed.* **2013**, *52*, 3267 – 3271.
[46] S. J. Park, J. R. Price, M. H. Todd, *J. Org. Chem.* **2012**, *77*, 949 – 955.
[47] Y.-X. Jia, E. P. Kündig, *Angew. Chem.* **2009**, *121*, 1664 – 1667; *Angew. Chem. Int. Ed.* **2009**, *48*, 1636 – 1639.
[48] A. Perry, R. J. K. Taylor, *Chem. Commun.* **2009**, 3249 – 3251.
[49] J. E. M. N. Klein, A. Perry, D. S. Pugh, R. J. K. Taylor, *Org. Lett.* **2010**, *12*, 3446 – 3449.
[50] W.-T. Wei, M.-B. Zhou, J.-H. Fan, W. Liu, R.-J. Song, Y. Liu, M. Hu, P. Xie, J.-H. Li, *Angew. Chem.* **2013**, *125*, 3726 – 3729; *Angew. Chem. Int. Ed.* **2013**, *52*, 3638 – 3641.
[51] B. DeBoef, S. J. Pastine, D. Sames, *J. Am. Chem. Soc.* **2004**, *126*, 6556 – 6557.
[52] a) S. Kiyooka, Y. Takeshita, *Tetrahedron Lett.* **2005**, *46*, 4279 – 4282; b) K. Tsuchikama, M. Kasagawa, Y.-K. Hashimoto, K. Endo, T. Shibata, *J. Organomet. Chem.* **2008**, *693*, 3939 – 3942; c) K. Tsuchikama, M. Kasagawa, K. Endo, T. Shibata, *Org. Lett.* **2009**, *11*, 1821 – 1823; d) S. Pan, K. Endo, T. Shibata, *Org. Lett.* **2011**, *13*, 4692 – 4695; e) S. Pan, Y. Matsuo, K. Endo, T. Shibata, *Tetrahedron* **2012**, *68*, 9009 – 9015.
[53] a) B. Liégault, K. Fagnou, *Organometallics* **2008**, *27*, 4841 – 4843; b) M. Wasa, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 3680 – 3681; c) K. J. Stowers, K. C. Fortner, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 6541 – 6544.
[54] T. Wu, X. Mu, G. Liu, *Angew. Chem.* **2011**, *123*, 12786 – 12789; *Angew. Chem. Int. Ed.* **2011**, *50*, 12578 – 12581.
[55] H. Zhang, P. Chen, G. Liu, *Synlett* **2012**, 2749 – 2752.
[56] a) Y. Moon, D. Kwon, S. Hong, *Angew. Chem.* **2012**, *124*, 11495 – 11498; *Angew. Chem. Int. Ed.* **2012**, *51*, 11333 – 11336; b) K.-T. Yip, R. Y. Nimje, M. V. Leskinen, P. M. Pihko, *Chem. Eur. J.* **2012**, *18*, 12590 – 12594.
[57] F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456 – 463.
[58] a) L. Henry, *Bull. Soc. Chim. Fr.* **1895**, *13*, 999; b) H. B. Hass, E. F. Riley, *Chem. Rev.* **1943**, *32*, 373 – 430; c) A. Yoshikoshi, M. Miyashita, *Acc. Chem. Res.* **1985**, *18*, 284 – 290; d) A. G. M. Barrett, G. G. Graboski, *Chem. Rev.* **1986**, *86*, 751 – 762.
[59] N. J. Leonard, G. W. Leubner, *J. Am. Chem. Soc.* **1949**, *71*, 3408 – 3411.
[60] Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 3672 – 3673.
[61] O. Baslé, C.-J. Li, *Green Chem.* **2007**, *9*, 1047 – 1050.
[62] a) C. J. Li, *Chem. Rev.* **1993**, *93*, 2023 – 2035; b) C.-J. Li, T.-H. Chan, *Tetrahedron* **1999**, *55*, 11149 – 11176; c) S. Kobayashi, K. Manabe, *Acc. Chem. Res.* **2002**, *35*, 209 – 217; d) K. Manabe, S. Kobayashi, *Chem. Eur. J.* **2002**, *8*, 4094 – 4101; e) R. A. Sheldon, *Green Chem.* **2005**, *7*, 267 – 278; f) L. Chen, C.-J. Li, *Adv. Synth. Catal.* **2006**, *348*, 1459 – 1484; g) C.-J. Li, L. Chen, *Chem. Soc. Rev.* **2006**, *35*, 68 – 82; h) C. I. Herrerías, X. Yao, Z. Li, C.-J. Li, *Chem. Rev.* **2007**, *107*, 2546 – 2562; i) M.-O. Simon, C.-J. Li, *Chem. Soc. Rev.* **2012**, *41*, 1415 – 1427.
[63] a) A. Yu, Z. Gu, D. Chen, W. He, P. Tan, J. Xiang, *Catal. Commun.* **2009**, *11*, 162 – 166; b) X.-Z. Shu, Y.-F. Yang, X.-F. Xia, K.-G. Ji, X.-Y. Liu, Y.-M. Liang, *Org. Biomol. Chem.* **2010**, *8*, 4077 – 4079; c) J. Xie, H. Li, J. Zhou, Y. Cheng, C. Zhu,

Angew. Chem. **2012**, *124*, 1278 – 1281; *Angew. Chem. Int. Ed.* **2012**, *51*, 1252 – 1255; d) K. Alagiri, K. R. Prabhu, *Org. Biomol. Chem.* **2012**, *10*, 835 – 842.

[64] T. Zeng, G. Song, A. Moores, C.-J. Li, *Synlett* **2010**, 2002 – 2008.

[65] Q.-Y. Meng, Q. Liu, J.-J. Zhong, H.-H. Zhang, Z.-J. Li, B. Chen, C.-H. Tung, L.-Z. Wu, *Org. Lett.* **2012**, *14*, 5992 – 5995.

[66] A. S.-K. Tsang, M. H. Todd, *Tetrahedron Lett.* **2009**, *50*, 1199 – 1202.

[67] A. S.-K. Tsang, P. Jensen, J. M. Hook, A. S. K. Hashmi, M. H. Todd, *Pure Appl. Chem.* **2011**, *83*, 655 – 665.

[68] X.-Z. Shu, X.-F. Xia, Y.-F. Yang, K.-G. Ji, X.-Y. Liu, Y.-M. Liang, *J. Org. Chem.* **2009**, *74*, 7464 – 7469.

[69] T. Nobuta, N. Tada, A. Fujiya, A. Kariya, T. Miura, A. Itoh, *Org. Lett.* **2013**, *15*, 574 – 577.

[70] a) S. S. Libendi, Y. Demizu, O. Onomura, *Org. Biomol. Chem.* **2009**, *7*, 351 – 356; b) N. Shankaraiah, R. A. Pilli, L. S. Santos, *Tetrahedron Lett.* **2008**, *49*, 5098 – 5100; c) T. Tajima, A. Nakajima, *J. Am. Chem. Soc.* **2008**, *130*, 10496 – 10497; d) N. Girard, J.-P. Hurvois, *Tetrahedron Lett.* **2007**, *48*, 4097 – 4099; e) E. Le Gall, J.-P. Hurvois, T. Renaud, C. Moinet, A. Tallec, P. Uriac, S. Sinbandhit, L. Toupet, *Liebigs Ann. Chem.* **1997**, 2089 – 2101; f) S. Michel, E. Le Gall, J.-P. Hurvois, C. Moinet, A. Tallec, P. Uriac, L. Toupet, *Liebigs Ann. Chem.* **1997**, 259 – 267; g) F. Effenberger, H. Kottmann, *Tetrahedron* **1985**, *41*, 4171 – 4182; h) G. Bidan, M. Geniès, R. Renaud, *Electrochim. Acta* **1981**, *26*, 275 – 282; i) G. Bidan, M. Genies, *Tetrahedron* **1981**, *37*, 2297 – 2301.

[71] O. Baslé, N. Borduas, P. Dubois, J. M. Chapuzet, T.-H. Chan, J. Lessard, C.-J. Li, *Chem. Eur. J.* **2010**, *16*, 8162 – 8166.

[72] a) J. Yoshida, S. Suga, S. Suzuki, N. Kinomura, A. Yamamoto, K. Fujiwara, *J. Am. Chem. Soc.* **1999**, *121*, 9546 – 9549; b) S. Suga, S. Suzuki, A. Yamamoto, J. Yoshida, *J. Am. Chem. Soc.* **2000**, *122*, 10244 – 10245; c) J. Yoshida, S. Suga, *Chem. Eur. J.* **2002**, *8*, 2650 – 2658.

[73] a) A. G. Condie, J. C. González-Gómez, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2010**, *132*, 1464 – 1465; b) D. B. Freeman, L. Furst, A. G. Condie, C. R. J. Stephenson, *Org. Lett.* **2012**, *14*, 94 – 97.

[74] M. Rueping, J. Zoller, D. C. Fabry, K. Poscharny, R. M. Koenigs, T. E. Weirich, J. Mayer, *Chem. Eur. J.* **2012**, *18*, 3478 – 3481.

[75] D. P. Hari, B. König, *Org. Lett.* **2011**, *13*, 3852 – 3855.

[76] Q. Liu, Y.-N. Li, H.-H. Zhang, B. Chen, C.-H. Tung, L.-Z. Wu, *Chem. Eur. J.* **2012**, *18*, 620 – 627.

[77] a) C. M. van Marle, B. Tollens, *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 1351 – 1357; b) M. Tramontini, *Synthesis* **1973**, 703 – 775; c) M. Tramontini, L. Angiolini, *Tetrahedron* **1990**, *46*, 1791 – 1837; d) L. E. Overman, *Acc. Chem. Res.* **1992**, *25*, 352 – 359; e) M. Arend, B. Westermann, N. Risch, *Angew. Chem.* **1998**, *110*, 1096 – 1122; *Angew. Chem. Int. Ed.* **1998**, *37*, 1044 – 1070; f) A. Córdova, *Acc. Chem. Res.* **2004**, *37*, 102 – 112.

[78] Reviews: a) D. R. W. Hodgson, J. M. Sanderson, *Chem. Soc. Rev.* **2004**, *33*, 422 – 430; b) S. T. Diver, A. J. Giessert, *Chem. Rev.* **2004**, *104*, 1317 – 1382; c) R. E. Connor, D. A. Tirrell, *Polym. Rev.* **2007**, *47*, 9 – 28; d) U. Arnold, *Biotechnol. Lett.* **2009**, *31*, 1141 – 1141.

[79] Z. Li, C.-J. Li, *Eur. J. Org. Chem.* **2005**, 3173 – 3176.

[80] a) See Ref. [11b]; b) S.-I. Murahashi, N. Komiya, H. Terai, *Angew. Chem.* **2005**, *117*, 7091 – 7093; *Angew. Chem. Int. Ed.* **2005**, *44*, 6931 – 6933; c) S. Murahashi, T. Naota, T. Kuwabara, T. Saito, H. Kumobayashi, S. Akutagawa, *J. Am. Chem. Soc.* **1990**, *112*, 7820 – 7822.

[81] C. Dubs, Y. Hamashima, N. Sasamoto, T. M. Seidel, S. Suzuki, D. Hashizume, M. Sodeoka, *J. Org. Chem.* **2008**, *73*, 5859 – 5871.

[82] a) Y. Hamashima, N. Sasamoto, D. Hotta, H. Somei, N. Umebayashi, M. Sodeoka, *Angew. Chem.* **2005**, *117*, 1549 – 1553; *Angew. Chem. Int. Ed.* **2005**, *44*, 1525 – 1529; b) N. Sasamoto, C. Dubs, Y. Hamashima, M. Sodeoka, *J. Am. Chem. Soc.* **2006**, *128*, 14010 – 14011.

[83] K. T. Wanner, I. Praschak, U. Nagel, *Arch. Pharm.* **1990**, *323*, 335 – 350.

[84] Y. Shen, M. Li, S. Wang, T. Zhan, Z. Tan, C.-C. Guo, *Chem. Commun.* **2009**, 953 – 955.

[85] A. Sud, D. Sureshkumar, M. Klussmann, *Chem. Commun.* **2009**, 3169 – 3171.

[86] a) J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296 – 18304; b) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804 – 807; *Angew. Chem. Int. Ed.* **2005**, *44*, 794 – 797; c) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284 – 4287; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212 – 4215; d) S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973 – 12980; e) D. Enders, M. R. M. Hüttl, J. Runsink, G. Raabe, B. Wendt, *Angew. Chem.* **2007**, *119*, 471 – 473; *Angew. Chem. Int. Ed.* **2007**, *46*, 467 – 469; f) E. Maerten, S. Cabrera, K. A. Jørgensen, *J. Org. Chem.* **2007**, *72*, 8893 – 8903; g) H. Xie, L. Zu, H. Li, J. Wang, W. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 10886 – 10894.

[87] J. Zhang, B. Tiwari, C. Xing, X. Chen, Y. R. Chi, *Angew. Chem.* **2012**, *124*, 3709 – 3712; *Angew. Chem. Int. Ed.* **2012**, *51*, 3649 – 3652.

[88] a) M. Rueping, C. Vila, R. M. Koenigs, K. Poscharny, D. C. Fabry, *Chem. Commun.* **2011**, *47*, 2360 – 2362; b) Q. Xue, J. Xie, H. Jin, C. Yixiang, C. Zhu, *Org. Biomol. Chem.* **2013**, *11*, 1606 – 1609.

[89] K. Alagiri, P. Devadig, K. R. Prabhu, *Chem. Eur. J.* **2012**, *18*, 5160 – 5164.

[90] J. Xie, Z.-Z. Huang, *Angew. Chem.* **2010**, *122*, 10379 – 10383; *Angew. Chem. Int. Ed.* **2010**, *49*, 10181 – 10185.

[91] P. Liu, Z. Wang, J. Lin, X. Hu, *Eur. J. Org. Chem.* **2012**, 1583 – 1589.

[92] G. Zhang, Y. Zhang, R. Wang, *Angew. Chem.* **2011**, *123*, 10613 – 10616; *Angew. Chem. Int. Ed.* **2011**, *50*, 10429 – 10432.

[93] a) R. Kane, *J. Prakt. Chem.* **1838**, *15*, 129 – 155; b) C. H. Heathcock, *Science* **1981**, *214*, 395 – 400; c) H. Gröger, E. M. Vogl, M. Shibasaki, *Chem. Eur. J.* **1998**, *4*, 1137 – 1141; d) R. Mahrwald, *Chem. Rev.* **1999**, *99*, 1095 – 1120; e) S. Saito, H. Yamamoto, *Chem. Eur. J.* **1999**, *5*, 1959 – 1962; f) G. Casiraghi, F. Zanardi, G. Appendino, G. Rassu, *Chem. Rev.* **2000**, *100*, 1929 – 1972; g) T. D. Machajewski, C.-H. Wong, *Angew. Chem.* **2000**, *112*, 1406 – 1430; *Angew. Chem. Int. Ed.* **2000**, *39*, 1352 – 1375; h) C. Palomo, M. Oiarbide, J. M. García, *Chem. Eur. J.* **2002**, *8*, 36 – 44; i) C. Palomo, M. Oiarbide, J. M. García, *Chem. Soc. Rev.* **2004**, *33*, 65 – 75; j) S. Saito, H. Yamamoto, *Acc. Chem. Res.* **2004**, *37*, 570 – 579.

[94] a) Y. Zhang, C.-J. Li, *Angew. Chem.* **2006**, *118*, 1983 – 1986; *Angew. Chem. Int. Ed.* **2006**, *45*, 1949 – 1952; b) Y. Zhang, C.-J. Li, *J. Am. Chem. Soc.* **2006**, *128*, 4242 – 4243.

[95] a) Y. Ishii, S. Sakaguchi, T. Iwahama, *Adv. Synth. Catal.* **2001**, *343*, 393 – 427; b) C. Galli, P. Gentili, O. Lanzalunga, *Angew. Chem.* **2008**, *120*, 4868 – 4874; *Angew. Chem. Int. Ed.* **2008**, *47*, 4790 – 4796.

[96] W.-J. Yoo, C. Correia, Y. Zhang, C.-J. Li, *Synlett* **2009**, 138 – 142.

[97] Z. Li, R. Yu, H. Li, *Angew. Chem.* **2008**, *120*, 7607 – 7610; *Angew. Chem. Int. Ed.* **2008**, *47*, 7497 – 7500.

[98] a) H. Richter, R. Rohlmann, O. García Mancheño, *Chem. Eur. J.* **2011**, *17*, 11622 – 11627; b) H. Richter, O. García Mancheño, *Eur. J. Org. Chem.* **2010**, 4460 – 4467.

[99] Z. Li, H. Li, X. Guo, L. Cao, R. Yu, H. Li, S. Pan, *Org. Lett.* **2008**, *10*, 803 – 805.

[100] a) R. Pummerer, *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 2282 – 2291; b) R. Pummerer, *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1401 – 1412; c) S. K. Bur, A. Padwa, *Chem. Rev.* **2004**, *104*, 2401 – 2432.

[101] a) E. Knoevenagel, *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 2345 – 2346; b) E. Knoevenagel, *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 172 – 174; c) F. S. Prout, *J. Org. Chem.* **1953**, *18*, 928 – 933.
[102] a) J. Tsuji, H. Takahashi, M. Morikawa, *Tetrahedron Lett.* **1965**, *6*, 4387 – 4388; b) K. E. Atkins, W. E. Walker, R. M. Manyik, *Tetrahedron Lett.* **1970**, *11*, 3821 – 3824; c) G. Hata, K. Takahashi, A. Miyake, *J. Chem. Soc. Chem. Commun.* **1970**, 1392 – 1393; d) B. M. Trost, T. J. Fullerton, *J. Am. Chem. Soc.* **1973**, *95*, 292 – 294; e) P. W. N. M. van Leeuwen, P. C. J. Kamer, J. N. H. Reek, P. Dierkes, *Chem. Rev.* **2000**, *100*, 2741 – 2770.
[103] Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2006**, *128*, 56 – 57.
[104] D. Cheng, W. Bao, *Adv. Synth. Catal.* **2008**, *350*, 1263 – 1266.
[105] D. Ramesh, U. Ramulu, S. Rajaram, P. Prabhakar, Y. Venkateswarlu, *Tetrahedron Lett.* **2010**, *51*, 4898 – 4903.
[106] a) S. Lin, C.-X. Song, G.-X. Cai, W.-H. Wang, Z.-J. Shi, *J. Am. Chem. Soc.* **2008**, *130*, 12901 – 12903; b) A. J. Young, M. C. White, *J. Am. Chem. Soc.* **2008**, *130*, 14090 – 14091.
[107] a) M. S. Chen, M. C. White, *J. Am. Chem. Soc.* **2004**, *126*, 1346 – 1347; b) K. J. Fraunhoffer, M. C. White, *J. Am. Chem. Soc.* **2007**, *129*, 7274 – 7276; c) S. A. Reed, M. C. White, *J. Am. Chem. Soc.* **2008**, *130*, 3316 – 3318.
[108] Z. Li, L. Cao, C.-J. Li, *Angew. Chem.* **2007**, *119*, 6625 – 6627; *Angew. Chem. Int. Ed.* **2007**, *46*, 6505 – 6507.
[109] D. Cheng, W. Bao, *J. Org. Chem.* **2008**, *73*, 6881 – 6883.
[110] a) A. E. Allen, D. W. C. MacMillan, *Chem. Sci.* **2012**, *3*, 633 – 658; b) A. Mastracchio, A. A. Warkentin, A. M. Walji, D. W. C. MacMillan, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20648 – 20651; c) D. W. C. MacMillan, *Nature* **2008**, *455*, 304 – 308; d) S. Lee, D. W. C. MacMillan, *Tetrahedron* **2006**, *62*, 11413 – 11424; e) J. F. Austin, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5482 – 5487; f) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 2458 – 2460.
[111] F. Benfatti, M. G. Capdevila, L. Zoli, E. Benedetto, P. G. Cozzi, *Chem. Commun.* **2009**, 5919 – 5921.
[112] C. Guo, J. Song, S.-W. Luo, L.-Z. Gong, *Angew. Chem.* **2010**, *122*, 5690 – 5694; *Angew. Chem. Int. Ed.* **2010**, *49*, 5558 – 5562.
[113] Á. Pintér, A. Sud, D. Sureshkumar, M. Klussmann, *Angew. Chem.* **2010**, *122*, 5124 – 5128; *Angew. Chem. Int. Ed.* **2010**, *49*, 5004 – 5007.
[114] Y. Zhang, C.-J. Li, *Eur. J. Org. Chem.* **2007**, 4654 – 4657.
[115] a) S. Hashizume, K. Oisaki, M. Kanai, *Org. Lett.* **2011**, *13*, 4288 – 4291; b) S. Hashizume, K. Oisaki, M. Kanai, *Chem. Rev.* **2011**, *111*, 236 – 241; c) S. Hashizume, K. Oisaki, M. Kanai, *Chem. Asian J.* **2012**, *7*, 2600 – 2606.
[116] S.-J. Lou, D.-Q. Xu, D.-F. Shen, Y.-F. Wang, Y.-K. Liu, Z.-Y. Xu, *Chem. Commun.* **2012**, *48*, 11993 – 11995.