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Cross-Dehydrogenative Coupling (CDC): Exploring C#C Bond Formations beyond Functional Group Transformations

Chao-Jun Li

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Cross-Dehydrogenative Coupling (CDC): Exploring C−C Bond Formations beyond Functional Group Transformations

CHAO-JUN LI*

Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montreal, Quebec H3A 2K6, Canada

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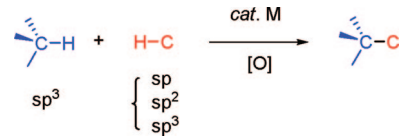

Synthetic chemists aspire both to develop novel chemical reactions and to improve reaction conditions to maximize resource efficiency, energy efficiency, product selectivity, operational simplicity, and environmental health and safety. Carbon−carbon bond formation is a central part of many chemical syntheses, and innovations in these types of reactions will profoundly improve overall synthetic efficiency.

This Account describes our work over the past several years to form carbon−carbon bonds directly from two different C−H bonds under oxidative conditions, cross-dehydrogenative coupling (CDC). We have focused most of our efforts on carbon−carbon bonds formed via the functionalization of sp^3 C−H bonds with other C−H bonds. In the presence of simple and cheap catalysts such as copper and iron salts and oxidants such as hydrogen peroxide, dioxygen, *tert*-butylhydroperoxide, and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), we can directly functionalize various sp^3 C−H bonds by other C−H bonds without requiring preactivation. We demonstrate (1) reaction of α-C−H bonds of nitrogen in amines, (2) reaction of α-C−H bonds of oxygen in ethers, (3) reaction of allylic and benzylic C−H bonds, and (4) reaction of alkane C−H bonds. These CDC reactions can tolerate a variety of functional groups, and some can occur under aqueous conditions. Depending on the specific transformation, we propose the in situ generation of different intermediates.

These methods provide an alternative to the separate steps of prefunctionalization and defunctionalization that have traditionally been part of synthetic design. As a result, these methods will increase synthetic efficiencies at the most fundamental level. On an intellectual level, the development of C−C bond formations based on the reaction of only C−H bonds (possibly in water) challenges us to rethink some of the most fundamental concepts and theories regarding chemical reactivities. A successful reaction requires the conventionally and theoretically less reactive C−H bonds to react selectively in the presence of a variety of functional groups. With further investigation, we expect that C−C bond formations based on cross-dehydrogenative coupling will have a positive economic and ecological impact on the next generation of chemical syntheses.

Introduction

The development of methods for forming C−C bonds plays a central role in synthesis design.[1] Historically, nucleophilic additions, substitutions, and Friedel−Crafts-type reactions are the central methods of connecting two simpler molecules to generate a more complex one via the formation of a C−C bond in acyclic structures. The development of pericyclic reactions[2] and transition metal catalyzed reactions increased the efficiency of C−C bond formations in modern organic chemistry and greatly extended their scope.[3] However, since state-of-the-art C−C bond formation reactions must use prefunctionalized starting materials, transition metal catalyzed C−H bond activation and subsequent C−C bond formations have attracted much interest in recent years.[4] These reactions still require a functionalized partner to generate the desired C−C bond formation product. In the last several years, our laboratory has been exploring the possibility of constructing functional molecules by only using C−H bonds

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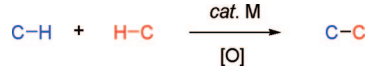
SCHEME 1



under oxidative conditions (via in situ generation of various reactive intermediates), a method that we termed cross-dehydrogenative coupling (CDC; Scheme 1). Such a coupling would eliminate the preparation of functional groups and thus make synthetic schemes shorter and more efficient, highly desirable features for the next generation of C–C bond formations. Notable progress has also recently been made by several other laboratories in arene–arene coupling via the oxidative reaction of sp^2 C–H/sp^2 C–H bonds.[5] The present Account describes the development of cross-dehydrogentative couplings and focuses on the functionalization of sp^3 C–H bonds with other C–H bonds, mostly from our own laboratory.

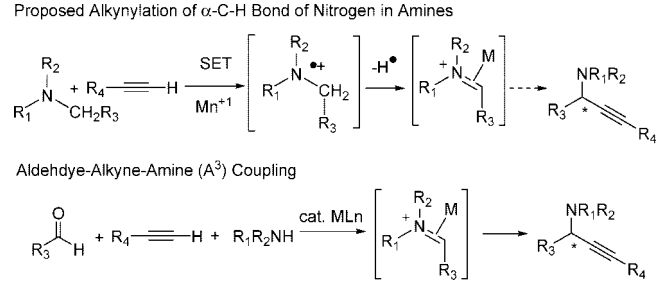
Background

Developing green chemistry[6] for chemical syntheses has been a long-term objective of our laboratory. We have explored various unconventional chemical reactivities that can potentially simplify synthesis, decrease overall waste, and maximize resource utilization. We planned our research in three progressive stages: (1) developing Grignard-type reactions in aqueous media to simplify protection–deprotection steps,[7] (2) developing nucleophilic addition reactions by using C–H bonds as surrogates for organometallic reagents to simplify halogenation–dehalogenation steps and avoid the utilization of a stoichiometric amount of metal for such reactions (possible in water),[8] and (3) developing direct C–H and C–H coupling to explore the possibility of chemical transformations beyond functionalization and defunctionalization in syntheses. The significant progress made in the first two stages led us to explore the third, most challenging objective several years ago.

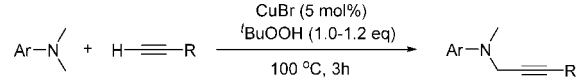
CDC Reaction Involving α-C–H Bonds of Nitrogen in Amines

Alkynylation (sp^3–sp Coupling). As our starting point, we chose the formation of C–C bonds from alkynyl sp C–H bonds and α-sp^3 C–H bonds of nitrogen in amines to generate propargylic amines. We decided on this reaction for three reasons: (1) propargylic amines are of great pharmaceutical interest and are synthetic intermediates for various nitrogen compounds;[9] (2) the sp^3 C–H bond α to nitrogen in amines can be readily activated to generate iminium ions via single-electron-transfer (SET) processes or by transition metals as described by Leonard[10] and Murahashi;[11] and (3) we[12] and

SCHEME 2



SCHEME 3. Copper-Catalyzed Alkynylation of *N*,*N*-Dimethylanilines



Ar= Ph, 4-MeC_6H_4, 2-MeC_6H_4, 4-BrC_6H_4

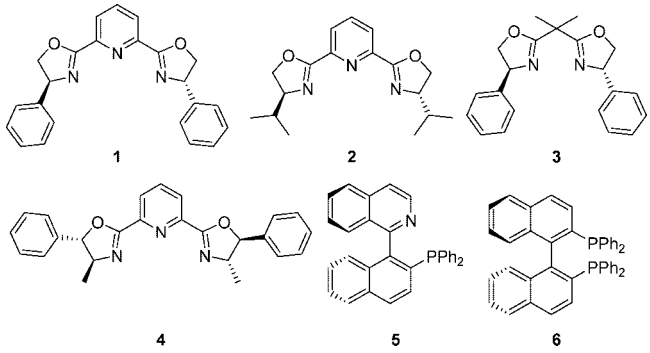
R= Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-BrC_6H_4, 4-PhC_6H_4, 2-Py, $HOCH_2$, $EtCO_2CH_2$, CH_3OCO, Bu, Ph, Ph, Ph

others[13] have described the aldehyde–alkyne–amine coupling (A^3) reactions to afford propargyl amines catalyzed by various transition metals via the formation of the same intermediate (Scheme 2). We reasoned that the catalytic alkynylation of the sp^3 C–H α to nitrogen with a terminal alkyne should thus occur readily under oxidative conditions.

We used *N*,*N*-dimethylaniline and phenylacetylene as the starting materials for our initial test. Several oxidants, including O_2, H_2O_2, and some peroxides, were evaluated as the hydrogen acceptor/remover. Transition metal catalysts are also important in achieving this cross-coupling reaction for two main reasons: they usually efficiently promote cross-coupling reactions, and they are an expected oxidant activator. We found that the desired product was obtained in good yield with the combination of a copper catalyst and *tert*-butyl hydroperoxide (TBHP). Thus, various copper salts were examined as catalysts for the alkynylation of *N*,*N*-dimethylaniline. CuBr, $CuBr_2$, CuCl, and $CuCl_2$ were all proven to be highly effective. No reaction was observed in the absence of a copper catalyst or *tert*-butyl hydroperoxide. The best yield was obtained when the ratio of *N*,*N*-dimethylaniline to alkynes to *tert*-butyl hydroperoxide was 2:1:1. Nearly 1 equiv of *N*,*N*-dimethylaniline remained after the reaction was completed. However, if the amount of *N*,*N*-dimethylaniline was reduced, the yields also decreased. Various alkynes were reacted with dimethylaniline derivatives to give the alkynylation products in 12–82% yields (Scheme 3).[14] The nature of the alkyne has a strong influence on the reaction yield: aromatic alkynes often provided good yields, whereas aliphatic alkynes resulted in lower yields. The reactions tolerated various functional groups such as alcohol and ester.

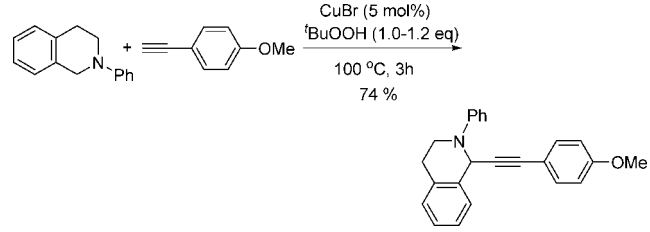
When benzyldimethylamine was reacted with phenylacetylene under the standard conditions, alkynylation of the methyl group was the main product. We discovered that tetrahydroisoquinoline derivatives could be selectively converted into the corresponding α-alkynylation compounds. For example, the reaction of *N*-phenyltetrahydroisoquinoline with *p*-methoxyphenylacetylene under the standard conditions gave the alkynylation product in 74% isolated yield (Scheme 4). Interestingly, the reaction of 1-phenyl-piperidine with phenylacetylene gave the desired direct alkynylation product in 12% yield together with a *tert*-butoxyl alkynylation compound (12%) (Scheme 5).

Most asymmetric C−C bond formations are based on double bonds (prochiral faces) being converted into chiral carbon centers. It would be interesting to see whether it is possible to achieve enantioselective C−C bond formations based on the direct reaction of prochiral CH_2 groups via CDC. Tetrahydroisoquinoline alkaloids with a stereocenter at C-1 carbons exist widely in nature and are compounds of extensive interest due to their biological and pharmacological properties.[15] We decided to examine the asymmetric alkynylation of tetrahydroisoquinolines to generate optically active C-1 substituted derivatives. Various copper salts together with chiral bisoxazolines **1**−**4**, Quinap **5**, and Binap **6** as ligands[16] were examined as catalysts under different conditions.

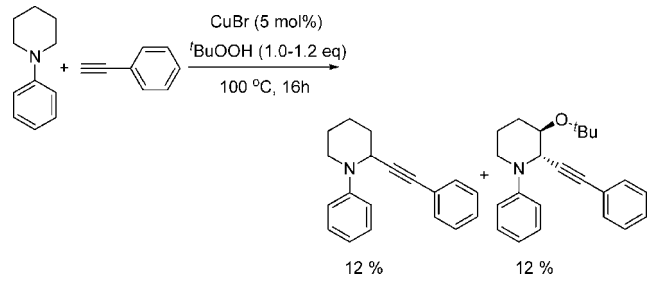


The use of pybox **1** provided the highest enantioselectivity in the reaction. Although both Cu(I) and Cu(II) were found to be effective catalysts, slightly higher enantioselectivities were observed with Cu(I) catalysts. Cu(OTf) provided better enantioselectivities than CuBr. Various solvents can be used, and the highest enantioselectivity was obtained by using THF as solvent. The catalytic asymmetric alkynylation also proceeded in water and without a solvent, but both the yields and the enantioselectivities were decreased. A variety of substrates were alkynylated asymmetrically by using the combination of Cu(I)OTf/**1** as the chiral catalyst (Scheme 6).[17] Aromatic substituted alkynes provided both good yields and enantiomeric

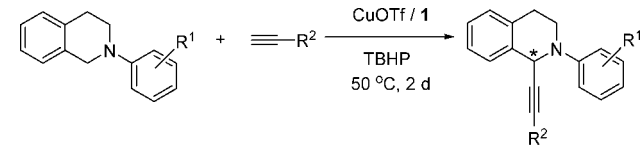
SCHEME 4. Alkynylation of Tetrahydroisoquinoline Derivatives



SCHEME 5. Alkynylation of Piperidine Derivatives



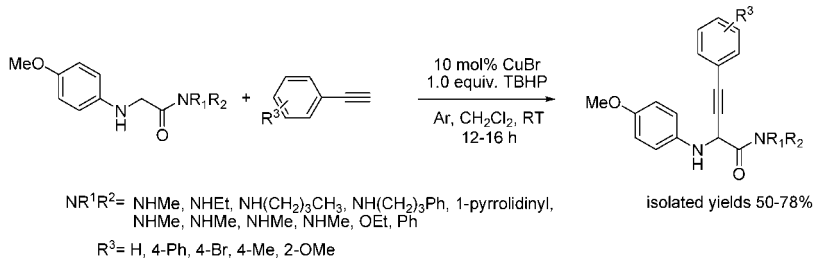
SCHEME 6. Asymmetric Alkynylation of Tetrahydroisoquinolines with Terminal Alkynes



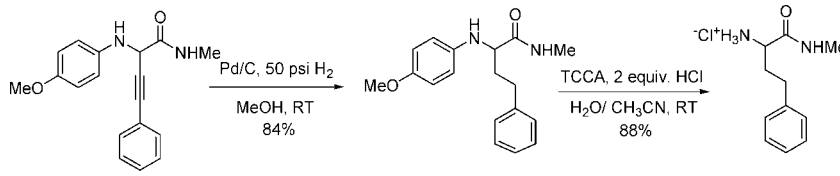
excesses; aliphatic substituted alkynes gave lower enantioselectivity. While no effect was observed with a 4-methoxy group (R^1) on the phenyl ring, the presence of an *ortho*-methoxy substitutent improved the enantiomeric excess up to 74%. The enhanced enantioselectivity is likely due to either the coordination of the oxygen in the *ortho*-methoxy substituent to copper or the steric effect of the *ortho*-substituent on the aryl ring.

With recent advances in proteomics, there has been a great deal of interest in the properties and functions of both natural and non-natural (synthetic) amino acids.[18] General methods of synthesizing non-natural α-amino acids or rapidly modifying natural amino acids are highly desirable. The direct α-functionalization of natural peptides takes advantage of existing structures and can potentially provide rapid access to diverse new peptides. We found that various PMP glycine amides could be directly alkynylated with phenylacetylene readily at room temperature via the CDC reaction (Scheme 7).[19] No reaction was observed with the corresponding glycine ester. This methodology provides a versatile method of synthesizing homophenylalanine derivatives, an important synthon in many important angiotensin-converting enzyme

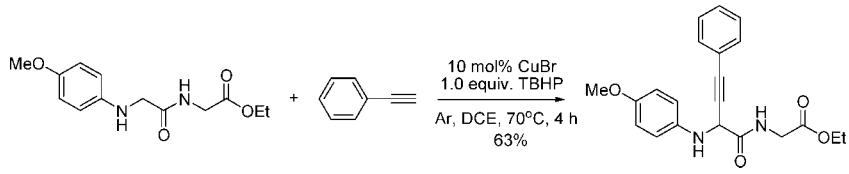
SCHEME 7. Direct Alkynylation of Glycine Amides via CDC Reaction



SCHEME 8. Synthesis of Homophenylalanine Derivative via CDC



SCHEME 9. Site-Specific Alkynylation of a Dipeptide

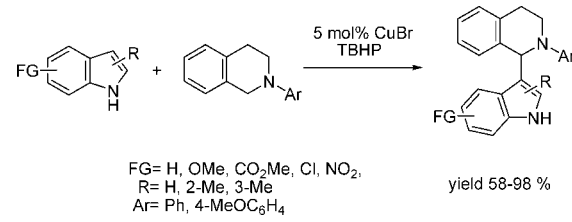


inhibitors, via the hydrogenation of the alkyne and removal of PMP (Scheme 8).[20]

As a model for direct and site-selective peptide functionalizations, we tested this methodology on a simple dipeptide (Scheme 9). The coupling reaction proceeded at 70 °C in dichloroethane, affording the alkynylation selectively in 63% isolated yield at the glycine amide site without touching the glycine ester. Its functionalization of glycine derivatives distinguished it from other methods where such site selectivity is not possible.[21]

Arylation (sp^3-sp^2 Coupling). The proposed iminium intermediate in the alkynylation reaction implies that other C−H based nucleophiles besides terminal alkyne can also couple with an α-sp^3 C−H bond of nitrogen in amines via CDC. Electron-rich arenes are one such nucleophile. The reaction of *N*-phenyl-tetrahydroisoquinoline with indole under the CuBr/TBHP system produced the desired CDC reaction product in good to excellent yields (Scheme 10).[22] The reaction was not sensitive to moisture or air. Even when the reaction was carried out in water under an atmosphere of air, the desired product was obtained in reasonable yield. The yield was improved when the temperature was increased to 50 °C. The reactions selectively occurred at the C3 position of the indoles, if both the C2 and C3 positions of the indoles were unoccupied. When the C3 position of the indoles was substituted, the C2-substituted products were obtained. Indoles with electron-withdrawing groups or electron-donating groups also worked well under the present CDC conditions.

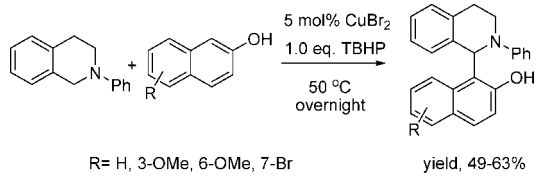
SCHEME 10. CDC Reactions of Various Indoles with Tetrahydroisoquinolines



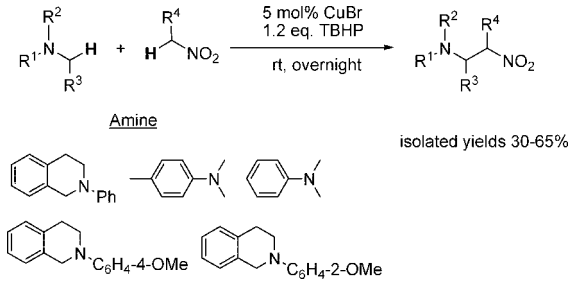
2-Naphthol is another electron-rich aromatic compound. We predicted that a new type of Betti base would be formed via the CDC reaction of tetrahydroisoquinoline with 2-naphthol. Indeed, the reaction of tetrahydroisoquinoline with various 2-naphthols under our CuBr/TBHP system generated the corresponding CDC product in good yields, together with a small amount of 2,2′-binaphthol (BINOL) formed as a byproduct (Scheme 11).[23] Various copper salts such as CuI, CuCl, $Cu(OTf)_2$, CuBr, $CuBr_2$, and $CuSO_4$ were all effective, with $CuBr_2$ providing the highest yield.

Alkylation (sp^3-sp^3). The success of the CDC reactions between sp^3 C−H and sp C−H, as well as between sp^3 C−H and sp^2 C−H, led us to next react sp^3 C−H with sp^3 C−H. Our first target was the reaction of an α-sp^3 C−H bond of nitrogen in amines with nitroalkanes, which provided aza-Henry-

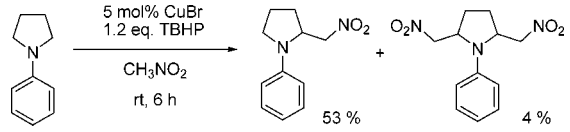
SCHEME 11. CDC Reaction of Tetrahydroisoquinoline with 2-Naphthol Derivatives



SCHEME 12. CDC Reaction of Tertiary Amines with Nitroalkanes



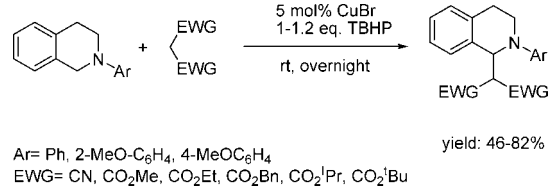
SCHEME 13. Reaction of 1-Phenyl-pyrrolidine with Nitromethane



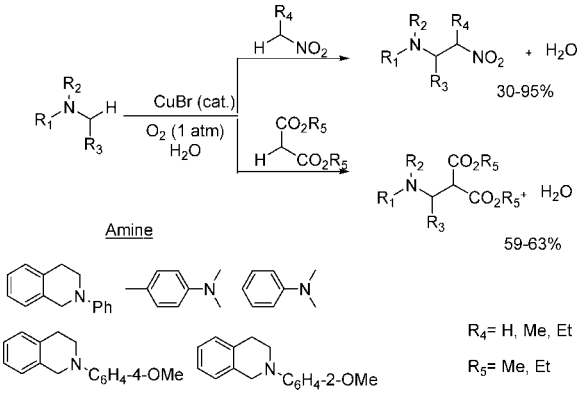
type reaction products. The reaction of 1,2,3,4-tetrahydroisoquinoline with nitromethane, in which nitromethane was used as solvent, was examined with various copper catalysts such as CuCl, CuBr, CuI, Cu(OTf), $CuCl_2$, $CuBr_2$, $Cu(OTf)_2$, and $Cu(OAc)_2 \cdot H_2O$ under an ambient temperature. The desired product was obtained in all cases, and once again CuBr was found to be the most effective catalyst. The desired product was obtained with over 90% NMR yield even when the amount of CuBr was reduced to 2 mol %. Under the optimized conditions, various β-nitroamine derivatives were generated by this new methodology (Scheme 12). The use of nitroethane instead of nitromethane gave the desired compounds with good isolated yields (the ratios of two diastereoisomers are 1.5−2:1). In the case of *N*,*N*-dimethylaniline, a low yield was obtained due to the formation of a demethylated compound and other unidentified byproduct. Other cyclic amines such as 1-phenyl-pyrrolidine also generated the desired product in good yield (Scheme 13). In this case, a small amount (4%) of the bis-CDC product was also formed along with the mono-CDC product.

Dialkyl malonates are another type of important synthon with relatively reactive sp^3 C−H bonds, and can thus be examined similarly. The reaction of tetrahydroisoquinolines with various dialkyl malonates in the presence of 5 mol % CuBr and TBHP at room temperature gave the CDC products, β-diester amine derivatives, in high yields (Scheme 14). The

SCHEME 14. CDC Reaction of Tertiary Amines with Malonates



SCHEME 15. CDC Reaction of Tertiary Amines with Oxygen in Water

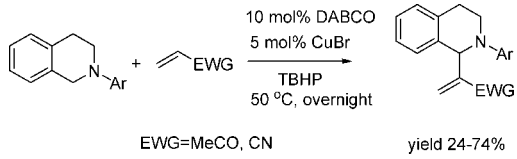


desired product was obtained in 72% isolated yield even with only 0.5 mol % CuBr. The use of malononitrile as the pronucleophile generated β-dicyano tetrahydroisoquinolines under the standard reaction conditions. The use of Meldrum's acid as the pronucleophile made the CDC reaction of the free (NH) 1,2,3,4-tetrahydroisoquinoline possible. Recently, Sodeoka and co-workers reported the CDC reaction of malonate with *N*-Boc-protected tetrahydroisoquinoline asymmetrically by using a chiral palladium catalyst together with DDQ as the dehydrogenating reagent. The reaction generated the desired product in 86% ee.[24]

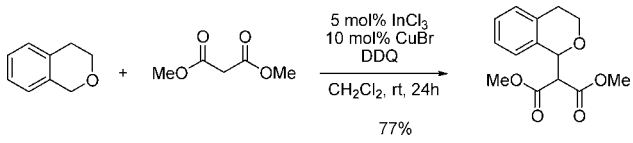
Peroxide is potentially hazardous in large-scale reactions. Replacing peroxides with molecular oxygen (and using water as a solvent) offers a safer and more atom-economical process. Interestingly, when water is used as the reaction solvent, molecular dioxygen can efficiently serve as the hydrogen acceptor. Both the nitroalkane reaction and the malonate reaction gave the corresponding CDC products via the reaction of two sp^3 C−H bonds catalyzed by copper bromide under an oxygen atmosphere in water (Scheme 15).[25] It is important to note that the CDC reaction also proceeded efficiently in air and water without the need for oxygen gas, albeit with a reduced reaction rate. After 24 h, 85% of the desired product was obtained with a 99% conversion of the starting material.

Besides arenes, the CDC reaction between α-sp^3 C−H bonds of nitrogen in tetrahydroisoquinolines and sp^2 C−H bonds was also investigated with electron-deficient alkenes,

SCHEME 16. Aza-Baylis–Hillman-type CDC Reaction



SCHEME 17. CDC Reaction of Isochroman with Dimethyl Malonate



generating the Morita–Baylis–Hillman (MBH) reaction product. DABCO was found to be an effective catalyst in this reaction. Moderate yields were obtained with 5 mol % CuBr and 10 mol % DABCO at 50 °C (Scheme 16). Triphenylphosphine was found to be nearly ineffective due to the generation of triphenylphosphine oxide during the reaction.

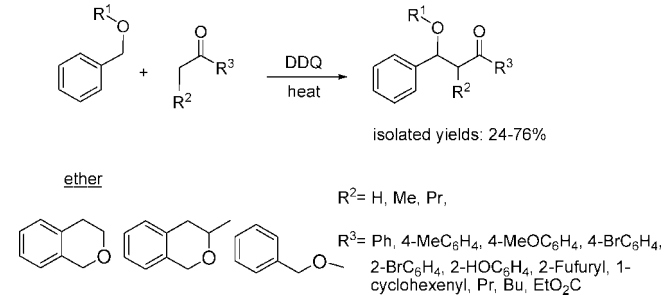
CDC Reaction of α-C–H Bonds of Oxygen in Ethers (sp^3–sp^3)

The functionalization of the α-C–H bond of oxygen in ethers is a more challenging task than functionalizing the α-C–H bond of nitrogen in amines due to the former's higher oxidation potential. A stronger hydrogen acceptor (oxidant) than TBHP or oxygen would be required. It is widely stated in the literature that 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) can react with benzyl ether to generate oxonium ions. With a combination of indium and copper as catalysts in the presence of DDQ, CDC reaction of an sp^3 C–H bond adjacent to an oxygen atom with an sp^3 C–H bond in pronucleophiles proceeds efficiently (Scheme 17).[26] The role of $InCl_3$ is most likely activating DDQ to further increase its oxidative potential, while the role of the Cu catalyst may be to activate the malonates (or to activate both). The CDC reaction provides a simple and efficient catalytic method of constructing β-diester ethers.

Unfortunately, the In/Cu/DDQ reaction system is limited to CDC reactions between benzyl ethers and relatively reactive malonate. It would be more desirable if simple ketones could be used with ethers. We found that a CDC reaction between benzyl ethers and simple ketones mediated by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) without using any metal catalyst is highly efficient (Scheme 18).[27]

A tentative mechanism for the coupling is proposed in Scheme 19. A single-electron transfer from the benzyl ether to DDQ generates a radical cation and a DDQ radical anion. The radical oxygen of the DDQ radical anion then abstracts a

SCHEME 18. CDC Reaction between Benzyl Ethers and Simple Ketones



H-atom from the radical cation and generates a benzoxy cation, and the anionic oxygen of DDQ radical anion then abstracts an α-hydrogen from the ketone to generate an enolate. Finally, the attack of the enolate on the benzoxy cation generates the CDC product and quinone derivative.

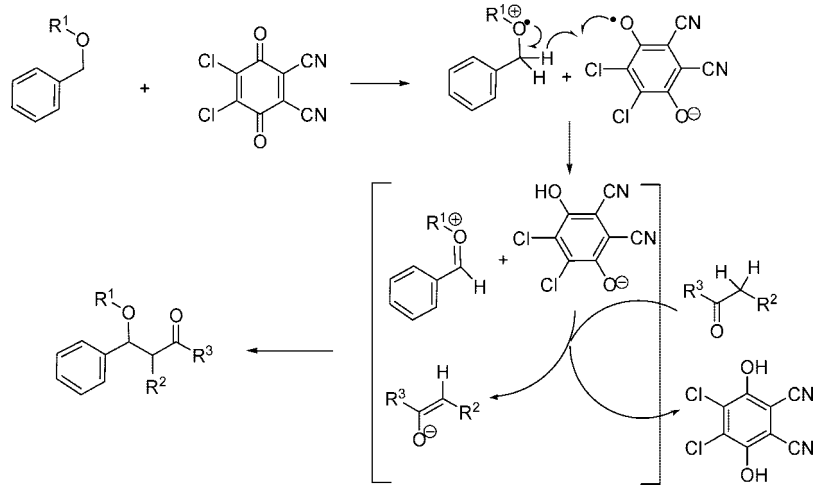
CDC Reaction of Allylic and Benzylic C–H Bonds

Allylic Alkylation (sp^3–sp^3). Palladium-catalyzed allylic alkylation (the Tsuji–Trost reaction; Scheme 20, route A) is an important reaction for constructing C–C bonds.[28] The methodology allows for easy tuning of chemo-, regio-, and stereoselectivities in complex organic transformations. As a general protocol, a carboxylate (or another leaving group) is required at the allylic position, which is activated by a palladium catalyst during the reaction with a pronucleophile. In theory, the direct utilization of an allylic C–H bond rather than an allylic functional group would avoid the need to synthesize the allylic functional group and thus lead to increased synthetic efficiency. In their pioneering work of directly using allylic C–H bonds to form π-allyl palladium complexes, Trost and co-workers reported the formation of an allylic alkylation from an allylic sp^3 C–H in two steps in the late 1970s.[29] However, because the *in situ* reoxidation of the reduced Pd(0) into Pd(II) is difficult, this reaction was stoichiometric with respect to Pd(II), serving as both the catalyst and the oxidant.

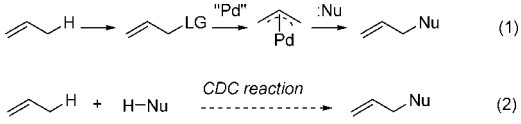
We found that by using a combination of CuBr (2.5 mol%) and $CoCl_2$ (10 mol%) as a catalyst, various 1,3-dicarbonyl compounds reacted smoothly with cyclohexene by directly using allylic sp^3 C–H and methylenic sp^3 C–H bonds (e.g, Scheme 21).[30]

Diallylic systems are also reactive in such CDC conditions. When cycloheptatriene was reacted with 2,4-pentadione, the corresponding tropylacetylacetone was obtained in 41% isolated yield. Interestingly, if cyclopentadiene was used, the major product obtained was dihydrofuran derivative due to the further transformation of the alkylation product *in situ* (Scheme 22).

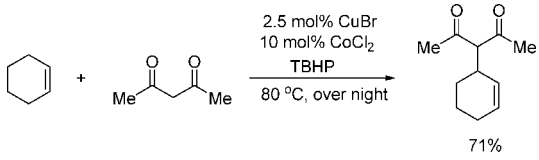
SCHEME 19. Proposed Mechanism for the CDC Reaction of Benzyl Ethers with Ketones Mediated by DDQ



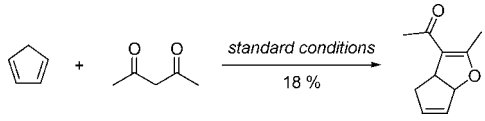
SCHEME 20. Tsuji–Trost Reaction and Allylic CDC Reaction



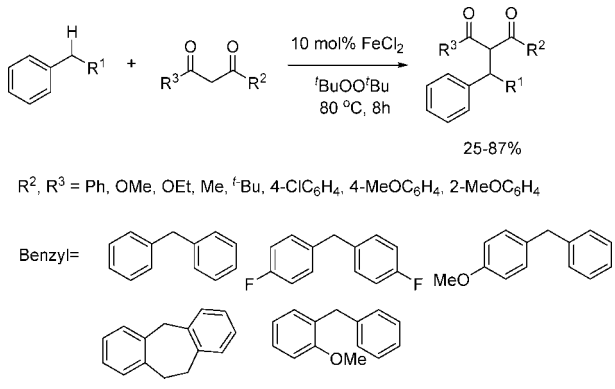
SCHEME 21. Allylic Alkylation via CDC Reaction



SCHEME 22. Tandem Allylic Alkylation–Cyclization via CDC

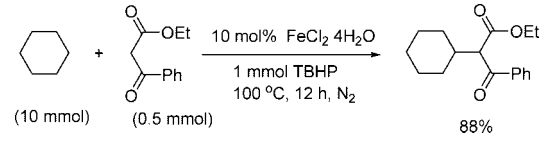


SCHEME 23. Benzylic Alkylation via CDC

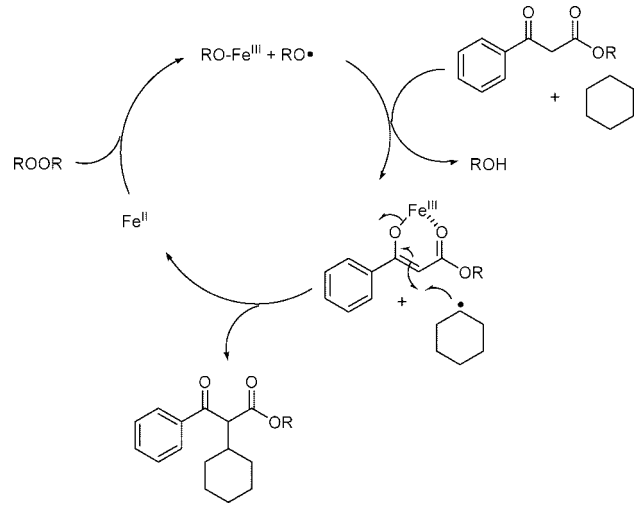


Benzylic Alkylation (sp^3–sp^3). In order to effect the CDC reaction with benzylic C–H bonds, we chose diphenylmethane and benzoylacetone as the standard substrates with which to investigate suitable reaction conditions. Initially, we used the

SCHEME 24. Alkane Alkylation via CDC



SCHEME 25. Tentative Mechanism for the Fe-Catalyzed Alkylation with Simple Alkanes

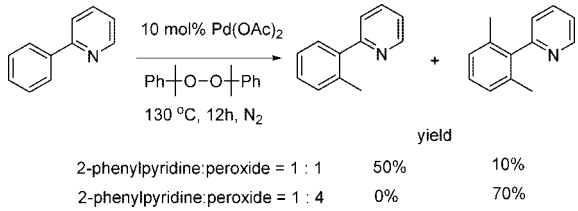


Cu/Co system, which gave the desired CDC reaction product in low yield. Further investigations showed that $FeCl_2$ was a more effective catalyst, giving the corresponding CDC products cleanly in good yields (Scheme 23).[31] The use of *tert*-butyl peroxide instead of TBHP as an oxidant further increased the product yield. Other iron salts were less effective or inactive compared with $FeCl_2$.

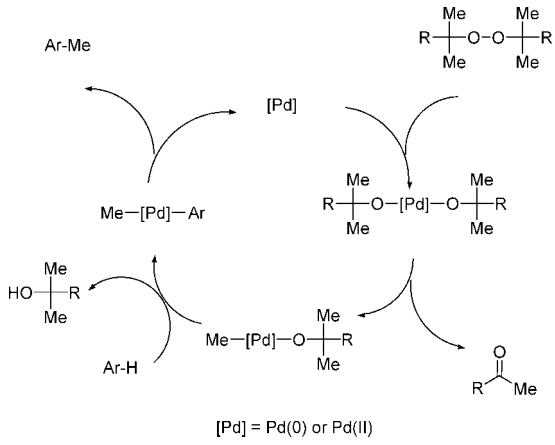
CDC Reaction of Alkane C–H Bonds

Alkane Alkylation (sp^3–sp^3). Among all C–H bonds, CDC reaction with simple alkanes (without any functional groups)

SCHEME 26. Methylation of 2-Phenylpyridine with Dicumyl Peroxide

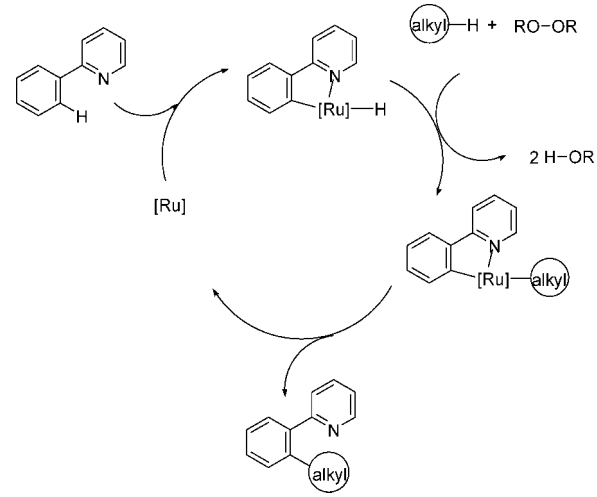


SCHEME 27. Proposed Mechanism for the Palladium-Catalyzed Methylation of Arenes with Peroxides



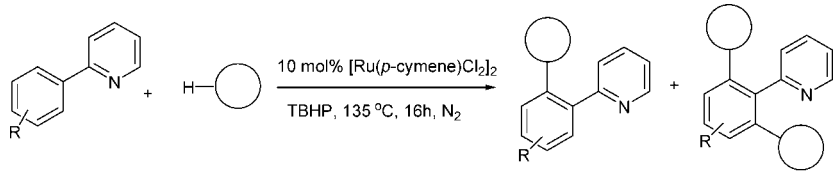
will be most challenging. The Fenton chemistry[32] and the Gif processes[33] established the conversion of aliphatic C−H bonds into C−O bonds under mild conditions by using peroxides catalyzed by various iron catalysts. We rationalized that the process might be adapted to form C−C bonds with the interception of intermediates in such reactions. With 10 mol % $FeCl_2 \cdot 4H_2O$ as the catalyst and *t*-butyl peroxide as the oxidant at 100 °C for 12 h under an atmosphere of nitrogen, various activated methylene substrates were reacted with cyclohexane, cyclopentane, cycloheptane, cyclooctane, norbornane, and adamantane to give the corresponding alkane alkylation products in good yields in most cases (Scheme 24).[34] Other iron salts such as $FeCl_2$, $FeBr_2$, $FeCl_3$, and $FeCl_3 \cdot 6H_2O$ also gave good yields for this reaction. No desired product was detected from ^1H NMR when $Fe(NO)_3 \cdot 9H_2O$, $FeSO_4 \cdot xH_2O$, $Fe(C_2O_4) \cdot 2H_2O$, $Fe(acac)_3$, or other metal salts such as $CuCl \cdot 5H_2O$, $Cu(OAc)_2$, $CuSO_4 \cdot 5H_2O$, or $CuCl_2$ were used as the catalyst. The mechanism was proposed involving an Fe(II)-catalyzed decomposition of the peroxide to give an Fe-enolate and an $RO^{\bullet}$ radical, which then reacted with cyclohexane to give a cyclohexyl radical. The cyclohexyl radical reacted with the enolate to form the alkylated β-keto ester and regenerated Fe(II) for further reactions (Scheme 25).

SCHEME 29. Proposed Mechanism for the Ruthenium-Catalyzed Cycloalkylation of Arenes via CDC



Alkane Arylation (sp^3-sp^2). The success of turning the Fenton and Gif C−O bond formation process of alkanes into a C−C bond formation reaction by intercepting the intermediate is greatly encouraging in our pursuit of CDC between alkanes with other C−H bonds, such as aryl C−H bonds. Recently, direct functionalizations of aryl C−H to form C−C bonds have been investigated intensively by using a variety of transition metal catalysts such as palladium, ruthenium, and gold. To begin our study, we discovered that the reaction of 2-phenylpyridine with dicumyl peroxide with 10 mol % $Pd(OAc)_2$ as the catalyst at 130 °C under an atmosphere of nitrogen generated mono-methylation and bis-methylation products depending on the ratio of the reactants (Scheme 26).[35] Other peroxides and palladium catalysts could also be used, although they generated lower yields of the methylation products. With benzo[*h*]quinoline (only one reactive site

SCHEME 28. CDC Reaction between Phenylpyridines and Cycloalkanes



being available for the reaction) as the substrate, 76% of the monomethylation product was obtained. Acetanilides were also effective in this transformation, generating the methylation product in moderate yields. The mechanism of the reaction was proposed to involve a palladium-catalyzed fragmentation of the peroxide to generate a methylpalladium species, which underwent a nitrogen-assisted aryl C−H activation followed by reductive elimination to give the final methylation product (Scheme 27)

The success of methylation led us to investigate the alkylation by adding alkanes to the reaction mixture. However, the reaction of 2-phenylpyridine with cyclooctane in the presence of *tert*-butyl peroxide under the palladium-catalyzed reaction conditions only gave a trace (<1%) amount of the desired product. Subsequently, we found that 42−75% yield of the corresponding CDC products were obtained between various 2-arylpyridines and various cycloalkanes by using 10 mol % $[Ru(p\text{-cymene})Cl_2]_2$ as the catalyst, and TBHP as the hydrogen acceptor at 135 °C for 16 h under an atmosphere of air (Scheme 28).[36]

The proposed mechanism of the reaction involved a ruthenium-catalyzed aryl C−H activation followed by an H-alkyl exchange.[37] Reductive elimination of this intermediate generated the arene−cycloalkane coupling product and regenerated the active ruthenium catalyst (Scheme 29). Deuterium isotope experiments showed a large negative kinetic isotope effect, which suggested that the ruthenium-catalyzed aryl C−H activation is a fast equilibrium and the H-alkyl exchange is the rate-limiting step.

Conclusion and Outlook

As an effort to develop green chemistry in the field of chemical synthesis, a new concept of cross-coupling reaction, cross-dehydrogenative coupling, was established. Various C−C bonds were formed directly from C−H and C−H bonds under oxidative conditions. Such reactions present the most direct and efficient synthetic methods of C−C bond formation and provide a foundation for the next generation of chemical syntheses with an eye on green chemistry.

I am indebted to my colleagues, whose names are cited in the references, who made this research possible. We also thank the Canada Research Chair (Tier I) foundation, the CFI, NSERC, FQRNT, and the (US) NSF-EPA Joint Program for a Sustainable Environment for partial support of our research.

BIOGRAPHICAL INFORMATION

Chao-Jun Li received his B.S. at Zhengzhou University (1983), M.S. at the Chinese Academy of Sciences in Beijing (1988) and Ph.D. at McGill University (1992, with T. H. Chan and D. N. Harpp). After an NSERC Postdoctoral research term with B. M. Trost at Stanford University, he became Assistant Professor (1994), Associate Professor (1998), and Full Professor (2000−2003) at Tulane University. In 2003, he became a Canada Research Chair (Tier I) in Organic/Green Chemistry and a Professor of Chemistry at McGill University in Canada. Currently, he serves as the Co-Chair (with Bernard West) of the Canadian Green Chemistry and Engineering Network. His current research efforts are focused on developing innovative and fundamentally new organic reactions that will defy conventional reactivities and have high synthetic efficiency.

FOOTNOTES

*E-mail address: cj.li@mcgill.ca.

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