Abstract: The development of cross-dehydrogenative coupling in recent years has simplified the synthesis of many materials, as a result of facile C–H activation, which, together with its greater atom economy and environmental friendliness, has made an impact on modern organic chemistry. Indeed, many C–C and C–X (X = N, O, P, S, B, or Si) coupling reactions can now be performed directly between two C–H bonds or a C–H and an X–H bond, simply by adding catalytic amounts of a metal salt to a mixture of the two and an oxidant to accept the two hydrogen atoms released. Chiral organocatalysts or chiral ligands have been joined to promote enantioselective processes, resulting in the development of efficient reaction cascades that provide products in high yields and high levels of asymmetric induction through cooperative catalysis. In recent years, photochemical oxidation and electrochemistry have widened even more the scope of cross-dehydrogenative coupling (CDC). In this review, we summarized the recent literature in this subject, hoping that it will inspire many new synthetic strategies.

Keywords: oxidative coupling; C–H functionalization; amines; ethers; binaphthyls; organocatalysis; photoredox catalysis; electrochemical catalysis; cooperative catalysis; synergistic catalysis

1. Introduction

Cross-dehydrogenative coupling (CDC) or oxidative coupling, as it is also referred to, has emerged as a powerful new technique for synthesis, mainly in the last 16 years [1–9]. It allows the direct coupling of two unactivated C–H bonds, or a C–H bond and an X–H bond (X = N, O, P, S, B, or Si) [6]. An oxidant is required, which acts as the terminal acceptor of the two hydrogen atoms, driving the reaction forward and thus keeping the whole process electroneutral. CDC circumvents the need for pre-functionalization, for example, through the conversion of a C–H bond to an electrophilic C–halogen bond, frequently utilized in synthesis, including in cross-coupling. It is an efficient, atom-economic, step-economic, “green” method of synthesis. The oxidants more commonly used are tert-butyl hydroperoxide (TBHP), tert-butyl perbenzoate (TBPB), hydrogen peroxide, K$_2$S$_2$O$_8$, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), and even dioxygen, as well as some metal-based oxidants, e.g., [Cu(OAc)$_2$]$_2$ and Ag(OAc). Reactive species can also be created by photoredox catalysis, through the interaction of the substrate or a catalyst with light [10–12], or by electrochemical oxidation, in which a mechanism based on electrode electron transfer is involved [13,14]. Recent reviews have highlighted the different mechanisms by which CDC reactions may take place [1,15]. The metals frequently used as catalysts are earth-abundant and easy to handle like Cu, Fe, and Co, which have the advantage of being relatively non-toxic and cheap, as well as some of the noble metals like Pd, Rh, Ru, and Ir.
Despite the great progresses achieved so far, the enantioselective cross-dehydrogenative coupling is still very under-developed [16–19]. Both chiral ligand-metal complexes, as well as organocatalysts, have been used to induce chirality. Enantioselective cross-dehydrogenative coupling of C(sp³)−H bonds has only been known since 2004 when Li and coworkers revealed the first enantioselective cross-coupling of N-phenyl tetrahydroisoquinolines (THIQs) with alkynes [20]. The majority of examples encountered in the literature involve the enantioselective α-C–H functionalization of amines, although recently the enantioselective α-C–H functionalization of ethers has also been achieved. Oxidative C(sp²)–H/C(sp²)–H coupling (aryl-aryl coupling) has been known for a while, being particularly relevant in atropselective biaryl synthesis [21–24]. Nevertheless, the hetero(cross)-coupling of two aryl molecules bearing different substituents, as in cross-dehydrogenative coupling, has had slower progress due to problems of regioselectivity [25].

A survey of the data available in the Web of Knowledge, based simply on the words “cross-dehydrogenative coupling”, revealed that of all the papers published since 2009, only 6% involve enantioselective synthesis, with the distribution shown in Figure 1. One of the reasons for this slow progress is the fact that frequently strong stoichiometric oxidants have to be used, which are incompatible with some nucleophiles and chiral ligands or catalysts. The high temperatures required by some reactions are also not conducive to high ees. However, despite these setbacks, there have been many developments in this field. In this review, we summarized the progresses achieved on enantioselective CDC, particularly those reported in the last five years. Not included in this review are oxidative Heck-type couplings or the use of organic radical initiators or radical precursors in free radical chain reactions.

![Figure 1. Evolution of the number of publications on enantioselective CDC in the period 2009–2020.](image)

The contents are divided as follows: Section 1. Introduction; Section 2. Transition metal-catalyzed enantioselective CDC; Section 3. Cooperative/synergistic catalysis by a metal-organocatalyst combination in enantioselective CDC, including Section 3.1. Aminocatalysis, Section 3.2. Brønsted acid catalysis, Section 3.3. Photocatalysis, Section 3.4. Electrochemical catalysis; Section 4. Bimetallic cooperative/synergistic and relay catalysis in enantioselective CDC; Section 5. Organocatalyzed CDC; Section 6. Conclusions.

2. Transition Metal-Catalyzed Enantioselective CDC

One of the more common strategies utilized to bring about an enantioselective cross-dehydrogenative coupling reaction is the use of a chiral metal complex, usually prepared in situ from a metal salt and a chiral ligand, together with an oxidant. This technique has been
utilized for the enantioselective functionalization of amino acids and peptides [26]. The production of non-natural α-amino carbonyl compounds is of particular interest in the fields of proteomics and drug discovery. Optically active α-amino acids are not only present as structural components of many pharmaceutical agents, but they also have many applications as chiral auxiliaries and catalysts in organic synthesis. CDC strategies have the potential to provide easy access to these substances. Wang and coworkers were the first to show that a catalytic CDC approach could be used to functionalize N-aryl glycine esters with β-ketoesters [27]. DDQ was used as the oxidant. Arylacetylenes, which have the advantage of a broad synthetic utility for further transformations, were also utilized as reaction partners for glycine amides, by C.-J. Li and coworkers, in a non-enantioselective approach [28,29], in which TBHP was the oxidant. It was observed at the same time that simple alkyl acetylenes, as well as the corresponding glycine esters, did not react under the conditions utilized. In 2016, the Liu group showed that oxygen could also be used as the oxidant, reacting N-aryl glycine acetylenes (1) with terminal acetylenes (2) in the presence of a copper catalyst (Figure 2) [30]. Upon addition of a chiral ligand (L1), the desired functionalized products (3) were obtained in very high yields and ees. N-alkyl glycine esters and glycine amides did not react under these conditions too. The utilization of oxygen as an oxidant is advantageous since it provides a more economical and greener approach to CDC transformations than the use of other oxidants. H2O is the only by-product.

\[
\text{Cu(OTf)}_2 (10 \text{ mol\%}) \quad \text{L1} (10 \text{ mol\%}) \\
\text{O}_2 \text{ balloon, 40 °C, 2 h} \quad \text{then} \\
\text{up to 87\% ee} \quad \text{up to 80\% yield} \quad \text{(20 examples)}
\]

\[
\begin{align*}
R^1 \quad &= 4\text{-Me, 4-MeO-, 4-Br, 2,4-diMe} \\
R^2 \quad &= \text{Et, } \text{Pr, } \text{Bu} \\
R^3 \quad &= \text{Ph, 4-Me-C}_6\text{H}_4, 3\text{-Me-C}_6\text{H}_4, \\
&\quad 4\text{-OMe-C}_6\text{H}_4, 4\text{-Br-C}_6\text{H}_4, \\
&\quad 4\text{-Cl-C}_6\text{H}_4, \text{C}_6\text{H}_9, \text{C}_6\text{H}_{13}, \\
&\quad \text{C}_6\text{H}_{17}, \text{cyclopropyl,} \\
&\quad -(\text{CH}_2)_2\text{OTBS,} -(\text{CH}_2)_2\text{OBn}
\end{align*}
\]

**Figure 2.** Enantioselective CDC of N-aryl glycine esters with terminal alkynes.

CDC of ethers with other species has also become popularized. However, enantioselective procedures are very scarce [6]. Lou, Liu, and coworkers showed in 2014 that a chiral imidazolidinone could catalyze the addition of benzylic ethers, e.g., isochroman, to aldehydes, with DDQ as oxidant, and high ees were obtained [31]. The presence of a metal salt was required as an additive, whose function was assumed to be to activate DDQ by increasing its reduction potential. LiClO4 was found to be the best.

In 2018, Scheidt and coworkers reported the second example of the enantioselective CDC in which transient oxocarbenium electrophiles were involved (Figure 3) [32]. Starting from β-ketoester substrates 4, this enantioselective intramolecular CDC approach catalyzed by copper provided access...
to substituted tetrahydropyran-4-ones (5) in high yields. The products were obtained as single diastereoisomers in high ees, and their absolute configuration was determined by X-ray analysis.

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Figure 3. Enantioselective CDC of β-ketoesters for the synthesis of tetrahydropyrans.

The CDC of a related enol acetate was also attempted, giving rise to 6, but, in this case, the product was racemic, which suggested that the formation of a two-point/chelate bound species as I1, not possible in the case of the enol acetate, might be responsible for the enantiocontrol observed with the β-ketoesters. The catalytic asymmetric alkylation of unactivated benzylic C–H bonds, leading to the formation of C–C bonds, is also challenging [33]. They are difficult to activate, and the generation of transient radicals requires harsh conditions [34]. The highly oxidizing conditions required are not compatible with many chiral ligands, which is a handicap. In 2010, L.-Z. Gong showed that an enantioselective CDC reaction between unreactive 3-arylmethyl indoles and 1,3-dicarbonyl compounds was possible with copper catalysis and DDQ as oxidant [35]. High yields and enantioselectivities were obtained. More recently, in 2020, W. Su and coworkers showed that this reaction could be facilitated by liquid-assisted grinding (Figure 4) [36]. A few drops of a liquid additive were crucial to obtaining high yields and ees in a reaction performed with the aid of ball milling, and silica gel as grinding auxiliary. The nature of the solvent, albeit used only in a very small quantity, was very important. For example, in the presence of MeCN, the yield was 16% (67% ee) in a model experiment with 7a (Ar1 = Ar2 = Ph, R1 = H) and diethyl malonate, whereas, with n-butyl acetate (n-BuOAc), it was 65% (88% ee). The liquid additive helped dispersion during grinding and could even help with the formation of a Cu(II)-ligand complex, favoring a very fast enantioselective reaction.
Figure 4. Copper-catalyzed enantioselective CDC of benzyl indoles and malonates.

It was also shown in this work that in the case of substrates with Ar$_2^\text{ortho}$-hydroxy-substituted arene (Figure 4), by prolonging the reaction time under ball-milling conditions, chiral dihydrocoumarins (10) could be obtained through a one-pot tandem asymmetric CDC-cyclization reaction with $dr > 99:1$ and excellent enantioselectivities.

S.-L. You and coworkers were the first to achieve enantioselective cross-coupling of two unfunctionalized arenes (Ar$^\text{-H}$) via double C–H bond activation, to prepare planar chiral ferrocenes [37]. All that was required was a palladium catalyst [Pd(OAc)$_2$, an amino acid as a chiral source, and air as oxidant. There was no need for the use of an excess of reagents, and the only by-product was water. Dialkylaminoferrocenes (11) were utilized as substrates, with the amino group serving as a directing group for the first palladation. The reactions were regioselective and highly enantioselective. Since ferrocenes possessing planar chirality have many applications, including in the synthesis of industrial, pharmaceutical, and agrochemical substances, methods like this can become particularly useful [38].

A range of commercially available chiral amino acid derivatives was tested, with Boc-$\text{L}$-Ile-OH providing the best yields, but the ees did not vary much. The addition of water (4.0 equiv.) and benzoquinone (BQ) also made the process more efficient. In this way, ferrocenes 11 were reacted with a series of heteroarenes (12), e.g., (benzo)furans, (benzo)thiophenes, pyrroles, and indoles, yielding planar chiral ferrocenes (13) in high yields and ees up to 99% (Figure 5).
In 2019, S.-L. You, Q. Gu, and co-workers showed that ferrocenes could be cross-coupled in a similar manner with azoles, i.e., oxazoles and thiazoles, to produce optically active planar ferrocenes [39]. The reactions could be performed under the same conditions as those used previously with the other heteroarenes (Figure 5), and the products were obtained regioselectively in high yields and with very high ees (Figure 6). The highest yields were obtained with 4-arylated azoles, and they were also higher with 2-arylated azoles than with the 2-arylated thiazoles, but there was not much change in the ees, which were in the range 94–99% overall.

A reaction mechanism was proposed (Figure 7), based on kinetic and computational studies. It was assumed that the reaction started with the formation of a chiral Pd(II) intermediate by C–H bond cleavage, giving rise to intermediate A. Electrophilic palladation of an azole, e.g., 15, generated B, which then underwent reductive elimination to yield the final product, 14a, in this case. The palladium catalyst was regenerated by air oxidation to continue the catalytic cycle.
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Figure 7. The mechanism proposed for the enantioselective CDC between ferrocenes and azoles.

Oxidative C(sp²)–H/C(sp²)–H coupling has been of interest for biaryl synthesis for a while [21–25]. It has been very much used as one of the synthetic approaches for the homocoupling of naphthols, phenols, and hydroxycarbazoles. The axially chiral products are found in many natural products and chiral catalysts or ligands, e.g., 16–20, which are widely used in asymmetric synthesis, e.g., 16–20, which are widely used in asymmetric synthesis, e.g., 1,1'-bi-2-naphthol (BINOL) (16), 1,1'-bi-2-naphthylamine (BINAM) (17), or BINAP (2,2'-bis(diary1phosphino)-1,1'-binaphthyl) (18) and their derivatives (Figure 8). Figure 9 highlights some of the very successful catalysts utilized recently in biaryl homo-coupling [40–44].
The hetero(cross)-coupling of two aryl molecules bearing different substituents, as in cross-dehydrogenative coupling, has had slower progress due to problems of regioselectivity, even though it can give access to important molecules with $C_1$-symmetry, for example, the catalysts 2-amino-2'-'hydroxy-1,1'-binaphthyl (NOBIN) (19) and 2-amino-2'-diphenylphosphino-1,1'-binaphthyl (MAP) (20) and their derivatives (Figure 8) [22–25]. The electron-rich arenes can lose an electron to form a radical cation in the presence of a strong oxidant and function as electrophiles. If the nucleophile is another arene (or alkene), the ability to selectively oxidize one of them and prevent overoxidation and homocoupling is difficult. It was postulated by Kočovský and coworkers that for successful aryl CH–CH cross-coupling under oxidative conditions, the redox potentials of the coupling partners should be sufficiently different ($\Delta E_p \geqslant 0.25$ V) [25]. Under these circumstances, one reaction partner is oxidized preferentially, and the oxidation product is captured by the species with the higher oxidation potential [19]. The first catalytic reaction, which employed 10 mol % of CuCl$_2$ (the oxidant), 20 mol % of (−)-sparteine (the chiral source), and 1.1 equiv of AgCl (to regenerate Cu(II)), was described by Smrčina, Kočovský, and coworkers in 1993, affording NOBIN in 43% yield and 46% ee [45]. Temma and Habaue described in 2005 the first highly efficient synthesis of unsymmetrically substituted binaphthols (≤ 99.7%, 65% ee) in preference to homocoupled products, with air as oxidant (Figure 10) [46]. During the period covered by this review, a few interesting examples were reported.

In 2016, Pappo and coworkers described the enantioselective oxidative homocoupling and cross-coupling of 2-naphthols under catalysis by chiral iron phosphate complexes [47]. A range of enantio-enriched $C_1$- and $C_2$-symmetric BINOLs, with 3 and 3' positions available for further reactions, was synthesized. The homocoupled products could be obtained in up to 94% yield and 88% ee in a DCE/HFIP solution (DCE = dichloroethane; HFIP = 1,1,1,3,3,3-hexafluoropropan-2-ol). The cross products could be obtained under the same conditions but as mixtures (Figure 11).
The absolute configuration of some products was determined to be R by multi-step synthesis, and that of the others assumed to be the same by analogy. The synthesis of 33a (R = 3-Br) was performed on a gram-scale synthesis, and similar results were obtained. The same observations were made on a gram-scale of homocoupled BINOL. Despite the fact that the chemoselectivity was only moderate, this was the first report on the synthesis, by direct oxidative coupling, of C1-symmetric 1,1′-bi-2-naphthols with 3- and 3′-positions available for further modifications. It was also the first report of the oxidative synthesis of unsubstituted BINOL and 6,6′-disubstituted BINOLs. The authors proposed a mechanism for the reactions too (Figure 12), suggesting that they proceeded via an oxidative radical-anion coupling. High valent complex (coordinated to the peroxide) after peroxide bond cleavage. 2-Naphthol (38), formed from t-BuOO−, yielded B. The product (38) was obtained after ligand exchange with one of the phosphate ligands, presumably due to its ability to transfer electron density to the metal. Radical C, formed from B by single-electron transfer, underwent radical-anion coupling with the second naphthol (35), yielding D. The product (38) was obtained after ligand exchange. An undesired secondary racemization process, competing with enantioselective carbon–carbon bond formation, was found to occur, previously observed by others too [48]. In fact, it was thought that it was due to this type of racemization that previous attempts to produce pure BINOL directly from naphthol by oxidative coupling were unsuccessful [49]. Racemization was particularly fast in the presence of...
redox metals, and the present method was only successful because conditions, which were kinetically favored over racemization, could be found.

Narute and Pappo developed a procedure to couple 2-naphthols with β-ketoesters in 2017 [50]. A racemic version was tried with [FeCl₃·6H₂O] and t-BuOO-t-Bu in 1,2-dichloroethane. Product 40a resulting from the coupling of 2-naphthol 35a (R₁ = H) with α-substituted-β-ketoester 39a, bearing a chiral auxiliary (R₂ = (−)-menthyl), was obtained as a mixture of diastereoisomers (7aR,10aS) and (7aS,10aR) in ca. 46:54 ratio (Figure 13). Several BINOL derivatives were subsequently tested in the search for a suitable chiral anion for asymmetric induction. When the reaction was performed under the same conditions as those shown in Figure 11, at rt, only homocoupled product was obtained, i.e., enantio-enriched (R)-BINOL. However, at high temperatures, high regioselectivity and diastereoselectivity could be reached. A variation in the 3,3' substituents revealed that the least sterically hindered one, i.e., R = H, as in L5, afforded the highest asymmetric induction.

The Pappo group later revealed a procedure for the synthesis of NOBIN derivatives from an oxidative cross-coupling reaction between 2-naphthol and 2-aminonaphthalene, catalyzed by iron [51]. It allowed access to (Rₐ)- and (Sₐ)-NOBINs, which could not be made by any other means. Rather than a chiral catalyst, a chiral auxiliary was used, allowing point-to-axial chirality transfer. Although a survey of enantioselective synthesis using chiral auxiliaries was not the main aim of this review, this was a rare example of a point-to-axial chirality transfer in oxidative coupling reactions, and for its usefulness too, it was included here [23]. The previous synthesis of racemic NOBIN was achieved by direct oxidative coupling of naphthol and 2-aminonaphthalene using stoichiometric amounts of copper(II) amine or iron(III) complexes [51]. For this procedure, 10 mol% FeCl₃ was effective, and tBuOOtBu as oxidant. It was also found that the aminonaphthalene coupling partner was not completely consumed, but if CF₃COOH (1.25 equiv) was added, there was a complete reaction. A range of optically pure diastereoisomeric-substituted NOBIN pairs—(Rₐ)-23 and (Sₐ)-24—was obtained with good to excellent combined yields (Figure 14). The chiral auxiliary could be removed by hydrogenolysis on Pd–C to give the optically (99% ee) pure amine.
were not observed, and in the case of 51, chiral spirocyclic pyrrolidine oxazoline-based ligand (L6) was employed, with Cu catalysis (Figure 15) [52]. One of the interests in this work was the fact that C1-symmetric BINOL-derived catalysts [53] were shown, in some cases, to display better enantioinduction than the corresponding C2-symmetric ligands and catalysts bearing di-

By hydrogenolysis on Pd–C to give the optically (99% ee) pure amine.

Figure 13. Iron-catalyzed asymmetric CDC of 2-naphthols with \( \beta \)-ketoesters.

Figure 14. Iron-catalyzed stereoselective synthesis of optically pure 2-amino-2'-hydroxy-1,1'-binaphthyls.

The enantioselective synthesis of 3,3'-disubstituted C1-symmetric BINOLs via oxidative coupling was studied by Y.-Q. Tu and coworkers, who reported their results in 2019 [52]. In this case, Cu catalysis was employed, with chiral spirocyclic pyrrolidine oxazoline-based ligand (L6) and air as oxidant (Figure 15) [52]. One of the interests in this work was the fact that C1-symmetric BINOL-derived ligands and catalysts bearing different functional groups at the 3,3'-positions (e.g., PPh\(_3\) and Bn) have been shown, in some cases, to display better enantioinduction than the corresponding C2-symmetric catalysts [53]. The catalyst system used in this work was found to be highly chemoselective, as well as to have wide substrate tolerance.

Generally, the aromatic esters gave better ee values than the aliphatic ones, probably due to lack of aromatic \( \pi-\pi \) stacking in the latter. Much higher yields were also obtained. Substrates bearing electron-withdrawing or electron-neutral groups also gave better results than those with electron-donating groups. In addition, the homocoupled products of compounds 45, 46, and 50 were not observed, and in the case of 51, less than 10% of the homocoupled product was obtained.
A radical-anion coupling process was proposed in the face of the experimental results. Figure 16 shows the proposed model for asymmetric induction, with a radical-anion coupling process. The Cu(I)-L6 complex formed in the presence of air coordinated to 50, forming complex A, which then coupled to a radical B generated from 51 by an outer sphere electron transfer with another Cu(II) complex. Intermediate C was formed, which tautomerized to the product with the loss of Cu. The S product was obtained because B approached the Si face of complex A preferentially since the attack at the Re face was disfavored by steric hindrance.

![Diagram of the proposed model for asymmetric induction](image)

**Figure 15.** Enantioselective synthesis of 3,3'-substituted C1-symmetric BINOLs by Cu-catalyzed CDC.

![Diagram of the steroselectivity of the Cu-catalyzed synthesis of 3,3'-substituted C1-symmetric BINOLs](image)

**Figure 16.** The stereoselectivity of the Cu-catalyzed synthesis of 3,3'-substituted C1-symmetric BINOLs.

The spirocyclization of 1-alkyl-2-naphthols could also be achieved by an aerobic oxidative dearomatizing strategy. In this work, reported by Katsuki and coworkers in 2020, high chemo- and the enantioselective reaction was attained with iron catalysis and oxygen as the terminal oxidant [54]. The reaction between compounds 53 and phenols 54 yielded the spirocyclic ketones 56 as the sole products. The regioisomers 57 were not observed. A variety of functional groups were well-tolerated, with the exception of the formyl group, which decomposed under the conditions used (Figure 17).
The regioisomers of type 57 could be achieved under the same conditions used to prepare compounds position, moderate chemo- and enantioselectivities were observed. This is a very useful application of this type of coupling in synthesis. Besides having very good functional group tolerance, it provides access to biologically active molecules, e.g., dopamine transporter inhibitors, difficult to access by other means.

Cross-dehydrogenative coupling was also used as a means to obtain acetals, which were converted, “in one-pot”, with high enantioselectivity, through nickel(II)-catalyzed asymmetric alkylation, into α,β-chiral carboxylic acid derivatives [56]. In this research, reported by L. Liu and coworkers in 2019, a broad range of saturated ethers, including medium and large-sized cyclic ones, could be used (Figure 19). Although mechanistically, the enantioinduction step is the alkylation reaction and not the cross-dehydrogenative coupling, this method was included here because it is a very useful application of this type of coupling in synthesis. Besides having very good functional group tolerance, it provides access to biologically active molecules, e.g., dopamine transporter inhibitors, difficult to access by other means.
Figure 20 illustrates the pathway for the formation of 65a. Species 70 entered a catalytic cycle from which 65a was produced (not shown). Only 10 mol % of the Ni-diphosphine catalyst was required in this method.

One limitation of the method was the fact that α-aryl- or α-alkenyl acetic acid derivatives had to be used since no product could be obtained with the α-alkyl derivatives, e.g., 66a (R^4 = Et, X = S). The oxa- and thiazolidinethione moieties could also be easily removed if wished, by reduction with diisobutylaluminum hydride (DIBAL-H), followed by treatment with Ru(PPh_3)_3Cl, to afford α-chiral ethers with very high degrees of enantiopurity.

Figure 19 illustrates the pathway for the formation of 65a. Species 70 entered a catalytic cycle from which 65a was produced (not shown). Only 10 mol % of the Ni-diphosphine catalyst was required in this method.
3. Cooperative/Synergistic Catalysis by a Metal-Organocatalyst Combination in Enantioselective CDC

The possibility of using more than one catalyst in a reaction pot opens-up a whole new range of possibilities. Of course, they have to be compatible. This practice has allowed a whole range of new transformations to take place in a very efficient manner in recent years. The catalysts may act on the same substrate, giving rise to double activation, or activate different substances to react with one another, which is commonly referred to as cooperative or synergistic catalysis. It may also happen that one catalyst activates the first substrate for a reaction, and the product undergoes a second reaction activated by the second catalyst, a special case commonly referred to as relay catalysis. These cases are all different from bifunctional catalysis, in which one catalyst activates two substrates at the same time, bringing them in close proximity to react, a technique often used in enantioselective catalysis. This section covers examples in which a metal and an organocatalyst are used in the same pot to catalyze one or more reactions. Organocatalyzed reactions in which an inorganic salt additive plays an important role in the mechanism are also included in this section.

3.1. Aminocatalysis

By 2018, only two examples of enantioselective CDC of ethers had been reported, as referred to above. The 2014 report by Liu and coworkers on the reaction of cyclic benzylic ethers with aldehydes [31] and the 2018 report by Scheidt and co-workers on the Cu(OTf)$_2$-catalyzed enantioselective intramolecular CDC of allylic ethers with appended $\beta$-ketoesters, which gave access to tetrahydropyrones with high yields and enantioselectivities [32]. The delay in the development of the ether chemistry in contrast to the successes achieved with analogous amines has been attributed both to the higher oxidation potentials of the first, as well as to a lack of sites to which chiral catalysts can coordinate. Then, L. Liu and coworkers developed a procedure to couple 2H-chromenes and aldehydes, thinking of the potential of the products, enantiopure $\alpha$-substituted 2H-chromenes, structural components of many biologically active natural products and pharmaceuticals with many types of activities [57]. This new procedure, catalyzed by a chiral imidazolidinone in the presence of LiOTf, used o-chloranil as the oxidant. The aldehydes produced were reduced in situ to the more stable corresponding alcohols prior to isolation. The presence of H$_2$O simultaneously with the lithium salt was found to cause a significant improvement in ee (from 66 to 94%) in the model reaction between 2H-chromene and pentanal. Good functional tolerance, together with high enantiocontrol, make this a useful method to achieve the desired compounds (Figure 21). A variety of functional groups could be used successfully, with 2H-chromenes bearing electron-withdrawing groups at the C6 position, showing a slightly decreased efficiency, presumably due to the increased oxidation potential of the substrate. 2-Methylchromene failed to react (<5% yield), presumably due to steric hindrance.

![Proposed pathway for the CDC of 2H-chromenes and aldehydes.](image_url)

**Figure 21.** Catalytic asymmetric CDC of 2H-chromenes and aldehydes.
Although LiOTf was not a true catalyst in this reaction, its presence brought large benefits to the results. It was postulated that it acted as a Lewis acid, helping to break down the ion pair A generated by oxidation of the chromene with o-chloranil and creating a new ion pair B, which was a better electrophile (Figure 22). Reaction with the enamine generated in the reaction between the aldehyde and catalyst 75•TFA (TFA = trifluoroacetic acid) with B then took place preferentially on the less sterically hindered face of the double bond of the enamine (the Si face) to produce 76a with the stereochemistry observed. The role of additives in asymmetric synthesis has been reviewed recently [58,59].

**Figure 22.** Proposed pathway for the CDC of 2H-chromenes and aldehydes.

Subsequently, L. Liu and coworkers investigated the catalytic enantioselective cross-dehydrogenative coupling of 3,6-dihydro-2H-pyran with aldehydes [60]. Imidazolidinone 75 was also found to be the best chiral catalyst, particularly when used in combination with triflic acid and zinc triflate, with DDQ as oxidant. The products, isolated as alcohols, were obtained with ees as high as 99%, although the diastereoselectivity remained low as it is usually observed in cross-dehydrogenative coupling reactions. The new reaction tolerated a wide range of substrates, with the exception of a dihydropyran bearing an o-methyl substituted aryl group at the 4-position (Figure 23). Oxidation was possible, but the desired product was not obtained, presumably due to the high steric hindrance.

X-ray diffraction analysis, performed on the benzoic ester analogs, provided the information on the absolute and relative configurations of the products. The R configuration of 77a (R1 = Ph, R2 = propyl) at the C2 position was thought to arise from the fact that in the enamine intermediate 78, arising from the reaction between the chiral imidazolidinone catalyst and aldehyde 74a, the benzyl moiety shields the Re face. Hence, the oxocarbenium intermediate 79 was attacked preferentially from the Si face (Figure 23). The configuration at C3 depended on the direction of attack at C2.
was compatible with a wide range of substituents on the allene (81) as co-catalyst circumvented these problems. The Pd-CPA (CPA = chiral phosphoric acid) complex proceeding via selective insertion of CO, olefin, and CO, was reported previously by the same group [62]. The major challenge in the new method was to find a suitable source of chirality since the ligands more commonly used with palladium (e.g., phosphine ligands) are quite sensitive under the required oxidative conditions, and polydentate ligands can prevent the required allene coordination to the metal and hence suppress the reaction. The use of a chiral phosphoric acid (VAPPOL-PA, 80) (Figure 23) as co-catalyst circumvented these problems. The Pd-CPA (CPA = chiral phosphoric acid) complex was prepared in situ by mixing together at the start of the synthesis Pd(OAc)\(_2\) and the acid. p-Benzoinone was used to oxidize the palladium(0) produced in the reaction to Pd(II), so as to render the whole process catalytic.

![Figure 23. Enantioselective CDC of 3,6-dihydro-2H-pyrans with aldehydes.](image1)

### 3.2. Brønsted Acid Catalysis

C. Zhu, J.-E. Bäckvall, and coworkers reported a procedure to obtain highly functionalized cyclopentenones using Pd/HBrønsted acid catalysis [61]. It involved enantioselective carbonylative carbocyclization of enallenes (80) and cross-dehydrogenative coupling with terminal alkynes (2). A related racemic synthesis, a Pd-catalyzed cascade reaction with four C–C bond-forming steps, proceeding via selective insertion of CO, olefin, and CO, was reported previously by the same group [62]. The major challenge in the new method was to find a suitable source of chirality since the ligands more commonly used with palladium (e.g., phosphine ligands) are quite sensitive under the required oxidative conditions, and polydentate ligands can prevent the required allene coordination to the metal and hence suppress the reaction. The use of a chiral phosphoric acid (VAPPOL-PA, 80) (Figure 23) as co-catalyst circumvented these problems. The Pd-CPA (CPA = chiral phosphoric acid) complex was prepared in situ by mixing together at the start of the synthesis Pd(OAc)\(_2\) and the acid. p-Benzoinone was used to oxidize the palladium(0) produced in the reaction to Pd(II), so as to render the whole process catalytic.

![Figure 24. Palladium-catalyzed carbonylative carbocyclization of enallenes.](image2)

This methodology, a new way to introduce chirality at the α-position of carbonyl compounds, was compatible with a wide range of substituents on the allene (81) and on the aryl acetylene (2). Lower yields were obtained when electron-withdrawing substituents were present on the ring in...
acetylenes 2, and when $R^3 = \text{TMS}$ ($\text{TMS} = \text{trimethylsilyl}$), it was less than 5%, otherwise high yields and ees were observed.

In this example of cooperative catalysis, the organocatalyst was not used to activate one of the substrates but to modify the catalyst. In the mechanism proposed (Figure 25), Pd(II)-coordinated enallene $\text{A}$ suffered allene attack and CO insertion, giving rise to species $\text{B}$. Enantioselective migratory insertion of the olefin into the C–P bond gave rise to cyclic species $\text{C}$. This step proceeded in an enantioselective fashion, creating a new chiral center at the position $\alpha$ to the carbonyl group. Carbonylative alkynylation yielded the product releasing Pd(0), which was oxidized and re-entered the catalytic cycle.

![Mechanism diagram](image)

**Figure 25.** The mechanism proposed for the carbonylative carbocyclization of enallenes via CDC with alkynes.

An example of remote inert C–H functionalization, achieved through 1,n-hydrogen atom transfer (HAT), was reported by X.-Y. Liu and coworkers in 2020 [63]. Such a strategy is possible when $n \geq 5$. In this example, a dual Cu$^\text{I}$/chiral phosphoric acid catalytic system was used for enantioselective intramolecular C(sp$^3$)–H amination of allylic and benzylic positions in acyclic alkene and benzylic substrates. Highly functionalized $\alpha$-alkenyl and $\alpha$-aryl pyrrolidines $\text{87}$ and $\text{90}$, respectively, were obtained, with high yields and ees (Figure 26). The nature of the HAT mediator was crucial because it should be able to abstract in a selective manner a hydrogen atom $\alpha$ to an R group in preference to a hydrogen atom $\alpha$ to the amine group. 4-Methoxy-NHPI ($\text{NHPI} = \text{N-hydroxyphthalimide}$) was found to be suitable, stable, and chemoselective when used in catalytic amounts in the presence of a stoichiometric oxidant ($\text{86}$ or $\text{89}$), and copper(I) acetate worked well as the catalyst. Alkenyl ureas were the substrates. This meant that the alkyl amines were protected with urea groups, which deactivated C–H bonds $\alpha$ to the amine function toward HAT. ZnO was also used as an additive, forming zinc phosphate in situ with the CPA. This process provided an example of dual substrate activation.
were more reluctant to proceed, and full conversion was not attained, resulting in lower yields.  

2020 A 3 and a nonlinear e ffected that the rate-determining step involved the hydrogen atom abstraction (HAT) process, some insight into the reaction mechanism. For example, the oxidation of the phenol by DDQ, as shown in Figure 29 [65].

Figure 26. Enantioselective copper-catalyzed intramolecular amination of allylic and benzylic C–H bonds.

All the reactions were highly chemoselective, with allylic C–H amination products being obtained as the only products in all cases. The urea protecting groups could be removed easily with hydrazine hydrate in dimethylformamide (DME), providing products without losses in ee. Although the functional group compatibility was very good, reactions involving substrates in which R2 = H were more reluctant to proceed, and full conversion was not attained, resulting in lower yields. Benzylic substrates were also more difficult to react than the allylic ones, requiring a different copper catalyst, i.e., CuTc (Tc = thiophene-2-carboxylate), and a higher reaction temperature (20 °C rather than 0 °C). The yields were also lower, and some starting material was recovered after a period of 7 days.

Figure 27 shows the mechanism proposed, with allylic or benzylic radical intermediates, e.g., A, based on a set of control experiments. Molecular kinetic isotope effect (KIE) data obtained suggested that the rate-determining step involved the hydrogen atom abstraction (HAT) process, and a nonlinear effect was observed on the ee value of 87a (PG = CONH4-BrC6H4, R1 = Me, and R3 = 3-MeOC6H4), indicating that more than one CPA molecule was involved in the enantioinduction step, for example, as postulated with A.

Figure 27. The mechanism proposed for the intramolecular amination of allylic C–H bonds.
Triarylmethanes are important structural units of many pharmaceutically important compounds and materials [64]. Their asymmetric synthesis is not easy since there is not much difference in the steric hindrance provided by the rings. In 2020, L. Liu and coworkers revealed an enantioselective approach to the construction of quaternary carbon centers, including triarylmethane units, based on CDC [65]. It involved the reaction between 2,2-diarylacetonitriles (91) and (hetero)arenes (92) with DDQ as oxidant and aluminum oxide (activated, basic) as an additive (Figure 28). In the absence of Al₂O₃, both the yield and the ee were much lower than in its presence when the reaction was tried with a simple phosphoric acid as the chiral source, with a change from 9 to 77% in yield and from 30 to 58% in ee being observed. The nature of the substituents on the aryl rings did not have much influence on the ee value.

In this CDC reaction, the catalyst, a chiral C₂-symmetric imidodiphosphoric acid (93), appeared to have a bifunctional role, activating at the same time both reaction partners and providing stereocontrol by means of hydrogen bonding, as shown in TS1. Control experiments were also performed, which provided some insight into the reaction mechanism. For example, the oxidation of racemic 2,2-diarylacetonitrile 91a by DDQ yielded the δ-CN-δ-phenyl-substituted 3-phenylquinone methide 96 seen reacting in TSI in 90% yield along with DDQH₂ (2,3-dichloro-5,6-dicyanohydroquinone). The role of the aluminum oxide appeared to be the generation of these two species from an adduct 95 generated during the oxidation of the phenol by DDQ, as shown in Figure 29 [65].
3.3. Photoredox Catalysis

Photocatalysis is emerging as an alternative in enantioselective CDC when combined with a chiral organocatalyst or a chiral ligand-metal complex. In this synergistic approach, the required reactive species, radicals, are produced when visible light interacts with a photocatalyst. The most common photocatalysts are transition metal complexes based on ruthenium(II) and iridium(III), which have features adequate for photocatalysts: photostability, long excited-state lifetimes, strong absorption in the visible region, and high redox potentials [10–12]. The reactions also take place under mild and environmentally friendly reaction conditions. When one of the catalysts is irradiated with visible light, the metal undergoes a metal-to-ligand charge transfer, followed by intersystem crossing, and a triplet excited-state species, with a relatively long lifetime, is generated. The excited species can transfer a single electron to an organic substrate, which will then engage in further reactions. The excited-state species can not only act as a strong oxidant but also as a strong reductant, which allows for great flexibility [66]. The development of new photocatalysts is an active area of research. Organic dyes are cheaper, but their photostability is lower. A few examples of cooperative/synergistic catalysis were found in the literature applied to enantioselective CDC reactions, but not many. In 2015, MacMillan developed an iridium catalyst, [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (ppy = 2-phenylpyridine, dtbbpy = 4,4-di-tert-butyl-2,2-dipyridyl) capable of decomposing the persulfate oxidant at room temperature with radiation from a compact fluorescent lamp (CFL) [67]. The Ir(III) catalyst in its triplex state could transfer an electron to the persulfate and generate a sulfate radical anion for hydrogen atom abstraction (HAA). This process allowed the direct α-arylation of ethers.

The synergetic combination of photoredox with enamine catalysis was explored by Pericás and coworkers for the asymmetric coupling of aldehydes with xanthenes in 2017 [68]. Photoredox catalysis, achieved with Ru(bpy)$_3$PF$_6$$_2$ (bpy = bipyridine) (97) and BrCCl$_3$ as oxidant, was used to oxidize xanthene to the corresponding cation. The cation was subsequently trapped by an enamine intermediate generated in situ from an aldehyde and a secondary amine organocatalyst, Jørgensen’s pyrrolidine 98. Oxidants like O$_2$ and CCl$_4$ gave no conversion under the same conditions. The presence of a base was also required. Presumably, the base scavenged HBr, which was another reaction product. In the absence of base, the desired product formed in about 12% only, together with aldehyde self-condensation products. Mild phosphate bases gave a reasonable conversion, with Na$_3$PO$_4$ proving to be the best. A range of aldehydes (74), as well as xanthenes (99), could be coupled successfully, and the products 100 had high ees (Figure 30). Various substituents, such as methoxy, phenolic hydroxyl, diethylamino, bromo, fluoro, were tolerated. An exception was an aldehyde bearing a benzyloxy substituent directly attached to the α-carbon, i.e., to the β-carbon of the intermediate, which gave a racemic product. Diaryl methanes did not react, probably as a result of the lower stability of the corresponding radical intermediates.

A probable mechanism for the reaction showing the photoredox cycle and the organocatalytic cycle is presented in Figure 31. Experiments were performed in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), which resulted in a very low conversion, suggesting the involvement of radicals. An experimentally determined KIE of 4.0 also indicated that the C–H bond cleavage took place during the rate-determining step, which was confirmed by density-functional theory (DFT) studies.

A combination of photoredox and amine catalysis was also chosen by Rueping and coworkers to develop a method to couple THIQs and ketones in an enantioselective manner in 2018 [69]. In 2004, THIQs provided the first examples of enantioselective CDC reactions in coupling to alkynes [20], but they still continue to be the subject of much interest because of the important biological properties associated with some of them, whose framework is also widespread in nature [70–72]. Several oxidants have been used to couple THIQs via CDC reactions with a wide range of nucleophiles, including alkenyl, indolyl, Ar, CN, CH$_2$NO$_2$, CF$_2$COR, PO(OR)$_2$, and so on [1–4].
Figure 30. Asymmetric CDC of aldehydes with xanthenes by cooperative visible-light photoredox catalysis and organocatalysis.

A probable mechanism for the reaction showing the photoredox cycle and the organocatalytic cycle is presented in Figure 31. Experiments were performed in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), which resulted in a very low conversion, suggesting the involvement of radicals. An experimentally determined KIE of 4.0 also indicated that the C–H bond cleavage took place during the rate-determining step, which was confirmed by density-functional theory (DFT) studies.

Figure 31. The mechanism proposed for the enantioselective CDC of aldehydes with xanthenes.

Dual catalysis involving a photoredox catalyst and an organocatalyst has also been utilized in recent years to promote a number of reactions, including for the α-functionalization of tetrahydroisoquinolines; however, in previous reactions of tertiary amines with acyclic ketones, there was either none or low enantioselectivity [69,73,74]. In this work, cyclohexanone, cyclopentanone, and 4-morpholinone were reacted with N-aryl tetrahydroquinolines, bearing a range of substituents on the aromatic rings (Figure 32). It was found that the iridium photocatalyst [Ir(ppy)_2(bpy)]PF_6 was an efficient catalyst when used in combination with d-α-phenylglycine (105) and activated by 11 W fluorescent bulb light, and oxygen was used as an oxidant (Figure 32). The “one-pot” sequential process developed provided the functionalized THIQs 106 in good yields, very high ees, and moderate to good drs. It has the advantage over recent related works that the synthesis of both diastereoisomers of a pair is described.
S. Luo, L.-Z. Wu, and coworkers showed that the enantioselective oxidative coupling of THIQs was possible not only to cyclic ketones (103) but also to acyclic ones (107), using a visible-light-promoted reaction and synergistic multiple catalyses [75]. In this process, a chiral diamine catalyst (108) created an enamine intermediate by reaction with the ketone, whereas an iminium cation intermediate was generated in situ from the reaction between THIQs and coupled Ru/Co catalysis (Figure 33). Under the chosen conditions, a nitro-compound (110), used in substoichiometric amounts, acted as the hydrogen acceptor, eliminating the need for other oxidants, which helped to prevent oxidative consumption of the amine under harsh oxidation conditions. High yields of compounds 111/112 could be obtained with excellent ees, even in the case of some acyclic ketones, e.g., diethyl ketone, which so far had been elusive, although, for the later, ees were somewhat lower. Besides ketones, tetrahydrothiapyrone and tetrahydropyranone also afforded good results (75–91% yield, 75–97% ee, 2:1–8:1 dr), but their isolation required extra care since they underwent easy racemization when isolated by silica gel column chromatography.

Figure 32. Cooperative asymmetric organocatalysis and photoredox catalysis for the α-functionalization of tetrahydroisoquinolines.

Figure 33. Asymmetric CDC of tertiary amines and ketones promoted by synergistic multiple catalyses.
A mechanism was postulated for this reaction (Figure 34) with visible light creating an excited Ru species, \([\text{Ru}(bpy)_3]^{2+}\), which was oxidized to \([\text{Ru}(bpy)_3]^{3+}\) by \([\text{Co}^{III}]\). It oxidized the tertiary amine, which subsequently lost a hydrogen atom (by HAT). The iminium cation thus created reacted with the enamine formed between the keto and organocatalyst 108. The formation of transition state \(\text{TS2}\) was favored over \(\text{TS3}\) since the approach of the two species in the orientation shown avoided unfavorable steric interactions, and the final configuration of the products was primarily \(2\text{S},3\text{S}\). The electron and proton were captured by \([\text{Co}^{II}]\) generating \([\text{Co}^{I}]\) and \([\text{Co}^{III}–\text{H}]\), which hydrogenated m-NO\(_2\)C\(_6\)H\(_4\)COOH to complete the cycle. Organocatalyst 108 reentered the catalytic cycle. The reduction of the nitro-compound by the Ru/Co-mediated e/H shuttle allowed a process free of additional strong oxidants.

Figure 34. The mechanism proposed for the asymmetric CDC of tertiary amines and ketones catalyzed by a synergistic combination of Co and Ru-based catalysts and 108.

The organic dye Rose Bengal, due to its good photocatalytic properties, has been widely utilized in synthesis in recent years [76]. Its redox potential lies within the range of the redox potentials of several organic molecules, and it can be excited with visible light. Khan and coworkers showed in 2017 that Rose Bengal could be used as an effective photocatalyst to activate THIQ for reactions with terminal alkynes when utilized together with a copper catalyst complexed to a chiral ligand under an oxygen atmosphere [77]. Products with high ees were obtained (Figure 35). The reaction conditions were compatible with the presence of a wide range of functional groups; however, electron-donating groups were favored. In the presence of a 3-chloro substituent on the THIQ aryl group, the ee of the resulting product dropped dramatically from >85% observed in the other cases down to 30%. The authors attributed this difference to a steric effect caused by the meta-substituent.

The mechanism proposed for this CDC reaction is shown in Figure 36. Rose Bengal, upon irradiation with light, generated a radical cation \(A\), which, when converted to a cation \(B\) by hydrogen atom abstraction (HAA), reacted with cuprate 115 originating from the reaction between the alkyne and the chiral copper catalyst, yielding the desired product 114a.

Photoredox activation may also be performed entirely with organic catalysts. One example of this type of reaction was published by Jiang and coworkers in 2016 [78]. An enantioselective aerobic oxidative C(sp\(_3\))−H olefination of tetrahydro-β-carbolines (116) was achieved with a triple-catalyst combination, a dicyanopyrazine-derived chromophore (DPZ, 118) as the metal-free photoredox catalyst, a chiral Lewis base catalyst (119), and an inorganic salt co-catalyst. \(\alpha\)-Substituted tetrahydro-β-carbolines (122) could be synthesized in high yields with excellent regio- and enantioselectivities (up to 95% ee).
(Figure 37). Barely any reaction took place when the reagents were mixed without DPZ (only 15% in 72 h) or with DPZ but without irradiation, showing the importance of both components in the oxidation process. The crucial role of the salt was also established by comparing results obtained in its presence with those acquired in its absence. Both the chemo- and the enantioselectivity increased in the presence of salts with weak coordinating anions, with NaBArF (120) proving to be the best. It was postulated that the role of the salt, known to have a good affinity for carboxylate and carbonyl oxygens, was to activate the carbonyl group of acrolein, assisting the addition of β-ICD (119), stabilizing the intermediate iminium ions, and bringing in close vicinity the nucleophilic intermediate and the iminiums in a multi-sited-coordinated transition state. Other intermediates might also be stabilized by the salt. A range of THIQs could also be obtained using a similar procedure with ees up to 95%.

![Cooperative organo-photocatalysis in the CDC of THIQs and alkynes.](image)

**Figure 35.** Cooperative organo-photocatalysis in the CDC of THIQs and alkynes.

![The mechanism proposed for the cooperative organo-photocatalysis in the CDC of THIQs and alkynes.](image)

**Figure 36.** The mechanism proposed for the cooperative organo-photocatalysis in the CDC of THIQs and alkynes.
proving to be the best. It was postulated that the role of the salt, known to have a good affinity for carboxylate and carbonyl oxygens, was to activate the carbonyl group of acrolein, assisting the enamine catalysis, and aldehydes was also possible under electro-oxidation conditions [80]. The use of enamine catalysis also made enantioinduction possible, and the products were obtained in up to 68% ee (Figure 39).

The replacement of chemical oxidants with anodic oxidation is a fairly new approach in enantioselective CDC [13,14]. In 2010, Jørgensen and coworkers showed that electrochemistry could be used to perform the α-arylation of aldehydes with phenols, and by adding a chiral amine to the reaction mixture, the resulting products were also obtained with high enantioselectivities (Figure 38) [79]. The reaction proceeded via the formation of dihydrobenzofurans, which could either be isolated or reduced in situ to the corresponding diols. The products were single regioisomers, meta-alkylated anilines, which could not be accessed by Friedel–Crafts chemistry of anilines.

3.4. Electrochemical Catalysis

The combination of electrochemical oxidation and chiral primary amine catalysis also allowed the coupling of tetrahydroisoquinolines and ketones. In this method, developed by S. Luo and coworkers in 2017, LiClO₄ salts and trifluoroethanol were used as additives. Initially, high conversions but low yields were obtained [81]. However, upon the addition of a proton source, the yields were greatly improved, presumably because it created a more stable hemiaminal intermediate than the iminium ion initially generated at the electrode surface. C–C bond formation with the enamine intermediate

**Figure 37.** Enantioselective aerobic oxidative C(sp³)-H olefination of tetrahydro-β-carbolines via cooperative photoredox and asymmetric organocatalysis.

**Figure 38.** Electro-organocatalysis in the enantioselective α-arylation of aldehydes.

H.Y. Jang and coworkers showed, soon after, that the enantioselective CDC between xanthenes and aldehydes was also possible under electro-oxidation conditions [80]. The use of enamine catalysis also made enantioinduction possible, and the products were obtained in up to 68% ee (Figure 39).
produced by the reaction of the ketone and the chiral diamine led then to the desired products in high yields and very high ees (Figure 40). The reaction could be performed on a 1 mmol scale without a significant difference in the results with 102a (R1 = H, R2 = 4-OMe) and cyclohexanone. Another role of the added proton source was to help the hydrogen evolution process at the cathode and to increase the conductivity of the reaction mixture. The addition of water was also beneficial. This method has the advantage that the use of stoichiometric oxidants is not required.

Figure 39. Electro-organocatalysis in the enantioselective CDC of xanthenes and aldehydes; TBAP = tetrabutylammonium perchlorate.

Figure 40. Asymmetric electro-organocatalysis in the α-alkylation of ketones.

4. Bimetallic Cooperative/Synergistic and Relay Catalysis in Enantioselective CDC

THIQs have been the subject of several studies involving the CDC, as mentioned above. The use of alkynes as reaction partners in sp³-sp coupling is appealing because the triple bond is very versatile for further synthetic manipulations. However, terminal alkynes are weak nucleophiles. CDC transformations reported up to date have involved aryl amines, with very few exceptions, because the presence of the aryl group facilitates the reaction; the aryl bond weakens the neighboring C–H bond, and it stabilizes the iminium intermediate formed in this way [20]. Reactions can then proceed at room temperature. However, aryl groups are difficult to remove, imposing synthetic limitations. In addition, high enantioselectivities are usually attained only when strong nucleophiles are used, namely, enamines or 1,3-dicarbonyl compounds, since their reaction partner, the stabilized
In addition, high enantioselectivities are usually attained only when strong nucleophiles are used, but the highest ees obtained were only 74%, and the scope of the reactions was limited [20,82,83]. The functionalization of the carbamates, although it appears more appealing since they can be easily converted to amines, has only met with limited success, and of the enantioselective examples, there is only one, by Sodeoka and coworkers [84]. In a reaction between THIQs and β-dicarbonyl compounds, catalyzed by [(R)-dm-segphos]Pd(H₂O)₂[OTf]₂, and with DDQ as oxidant, good ees (up to 86%) were obtained. The oxidant was added over a period of 10 h to avoid the decomposition of unstable acyliminium ions, and the Boc derivatization took place in situ, in a tandem fashion.

In 2015, Liu and coworkers succeeded in utilizing terminal alkynes as the nucleophilic reaction partners to couple Cbz-protected THIQs (121) [81]. Although CuCl, in combination with a number of oxidants, did not yield any product, when a protic additive (EtOH) was joined to the reaction mixture, full conversion was observed. The thermodynamically unfavorable reaction of the unreactive carbamate, e.g., 129a (Figure 41) and the resulting acyliminium ion of low stability (130), produced in concentrations too low to react with the copper acetylide, was replaced by a thermodynamically favorable more stable N-acyl hemiaminal (131), which reacted readily to yield the desired product 133a. With 2,2,6,6-tetramethylpiperidine N-oxide salt (T+BF₄⁻, 134) as oxidant, L₁₀ proved to be the best chiral ligand for copper. It was also found that the presence of a Lewis acid was favorable for enantioselectivity, with Yb(OTf)₃ proving to be the best. Good to excellent ees could be obtained with a variety of aryl acetylenes (Figure 42), irrespective of whether electron-withdrawing or electron-donating substituents were present in the ring. Carbamates-bearing electron-withdrawing substituents afforded lower yields, presumably due to their reduced reactivity. The presence of water was also beneficial, although its role could not be ascertained. The method developed was used to synthesize a number of biologically active alkaloids, for example, homoprotoberberine and emetine.

![Figure 41. Enantioselective CDC of Cbz-protected THIQs. Proposed mechanistic role of EtOH as additive.](image-url)
Aiming to be able to use dioxygen as the sole oxidant, X. Liu, X. Feng, and coworkers developed a CDC procedure for THIQs (102) and alkynes (2) based on a cooperative catalysis approach (Figure 43) [85]. FeCl₃ had been shown previously to be able to catalyze the aerobic oxidation of tertiary anilines with several nucleophiles, but with phenylacetylene, there was no reaction, probably due to its low nucleophilicity [86]. In this method, iron triflate was used to catalyze the aerobic oxidation of the isoquinoline, whereas the chiral zinc(II) complex was utilized to bring about the C–C coupling step. This one-pot reaction, in which the reagents were all added at the start together, was very efficient and provided a wide range of products 114 in good to high yields and very high ees, showing also good functional group compatibility. The enantioinduction was significantly higher with aryl alkynes than those bearing alkyl substituents. Attempts at using the same procedure to derivatize N-phenyl pyrrolidine and N-benzyl aniline were unsuccessful. The para-methoxyphenyl (PMP) group, utilized in many cases as a protecting (activating) group for the isoquinoline nitrogen, could be easily removed with CAN (ceric ammonium nitrate) in aqueous acetonitrile, to provide the free tetrahydroisoquinolines.

The mechanism proposed for this reaction is outlined in Figure 44. In this example of Zn(II)/Fe(II)/N,N'-dioxide bimetallic cooperative catalysis, the chiral Zn(II) metal complex reacted with a terminal alkyne to form a zinc acetylide intermediate A. The formation of this species was confirmed by high resolution mass spectrometry (HRMS). The oxidation of the iron catalyst in the presence of oxygen produced the amine radical cation of THIQ⁺• and the superoxide radical anion O₂⁻•, which was detected by electron paramagnetic resonance (EPR) spectroscopy. Hydrogen abstraction led to the formation of species B, which was in equilibrium with the iminium ion C, which could react with the zinc acetylde to afford product 114b.
5. Organocatalyzed CDC

Organocatalysis on its own can be used to perform enantioselective oxidative coupling via radical intermediates. This type of chemistry was introduced by MacMillan and coworkers in 2007, and it is usually referred to as SOMO (singly occupied molecular orbital) catalysis [87]. It involves one-electron oxidation of an enamine, generated in situ, by a stoichiometric oxidant, e.g., ceric ammonium nitrate (CAN) or [Fe(phen)3]PF6, or by catalytic amounts of metal complexes with inorganic oxidants, e.g., Cu2+/Na2S2O8. A cationic radical enamine is created in this way, which can react with nonpolar hydrocarbon substrates or radical species [7]. The enantioselective α-arylation of aldehydes catalyzed by MacMillan’s imidazolidinone catalyst was reported in 2007, with the products being obtained in up to 95% ee. Similarly, the α-arylation of aldehydes could be developed, and very high ees were obtained [88,89].

Other approaches to organocatalyzed CDC have been reported since. One of these was reported by Enders and coworkers in 2017 [90]. It involved a desymmetrization reaction of cyclopentenediones with pyrazoles via organocatalytic Michael addition/oxidation, catalyzed by chiral bifunctional thiourea (136) (Figure 45). The desired pyrazole-cyclopentenediones, bearing a chiral quaternary carbon center, were obtained with high yield and good enantioselectivities.

![Figure 44](image-url). The mechanism proposed for the enantioselective CDC of THIQs with alkynes by Zn–Fe activation.

![Figure 45](image-url). Desymmetrization of cyclopentenediones via organocatalytic CDC with pyrazoles.

The pyrazolones and pyrazoles are important compounds, which have applications in pharmaceutical and agrochemical chemistry, as well as dyes and chelating agents [91,92]. In this procedure, there was no need for the addition of oxidants. Experiments performed to elucidate the mechanism included one in which the reaction was performed in the presence of the radical scavenger TEMPO and another in which there was the total exclusion of oxygen (under an argon atmosphere and degassed solution). The yields of products were unaltered in both cases, which suggested that...
neither a radical mechanism was involved, nor was oxygen. The mechanism proposed is shown in Figure 46. It was postulated that the chiral thiourea activated one carbonyl group, making it more electrophilic, while the quinuclidine nitrogen deprotonated the pyrazolone, making it more nucleophilic. The orientation of the reagents coordinated to the catalyst was such that it drove the Michael addition selectively to the Re face of the β-position of the cyclopentenedione, generating A. After rearomatization, further deprotonation by the catalyst of B could lead to hydride elimination, for which the driving force was the formation of the extended conjugated system after tautomerization.

![Figure 46. The mechanism proposed for the desymmetrization of cyclopentenediones.](image)

This new procedure could be scaled-up to furnish nearly 1 g of product 137b [R₁ = Ph, R₂ = Me, R₃ = CH₂-(4-Me)C₆H₄] without losses in yield or enantioselectivity.

In 2019, Jørgensen and coworkers described a novel method to couple α-branched aldehydes (138) with indoles (139), which resulted in the formation of products (141) containing an acyclic quaternary carbon center too [93]. Enantioselective CDC was used. No metals were required, but simply an amino acid-derived catalyst (140) and an organic oxidant (DDQ) (Figure 47). The procedure was compatible with a wide range of substituents (electron-donating and electron-deficient) in the reactants, and the products (141) were obtained with moderate to excellent yield and enantioselectivity.

![Figure 47. Enantioselective organocatalyzed CDC of indoles with aldehydes.](image)
An alternative procedure in which the only terminal oxidant used was O$_2$ was also described, and to achieve this, a sequential procedure was necessary and a second organocatalyst.

6. Conclusions

Although the progress of enantioselective cross-dehydrogenative coupling has been slow, several achievements have now been made in this field. Many of the reactions can be catalyzed by first-row transition metals, i.e., copper, iron, and cobalt, which are abundant and have low toxicity. Simple ethers can now be used as coupling partners in enantioselective reactions, a feat which less than five years ago was still not possible. Chirality can be introduced not only at newly formed sp$^3$ centers with high ees, but axial chirality can also be created for biaryl synthesis and even to obtain planar chiral ferrocenes. Cooperative/synergistic new approaches utilizing organocatalysts, photoredox catalysts, and also electrochemical catalysis have widened the scope of CDC recently. In light of these developments, it is to be expected that CDC will lead to many new advances in synthesis.

Author Contributions: All authors contributed equally to this work. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by Fundaçã o para a Ciência e a Tecnologia (FCT), Portugal, in the form of project UIDB/00100/2020 of Centro de Química Estrutural.

Conflicts of Interest: The authors declare no conflict of interest.

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