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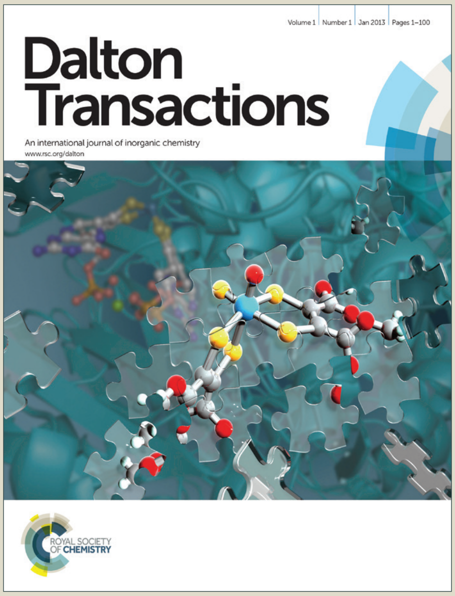

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PERSPECTIVE

Direct Oxidative Esterification of Alcohols

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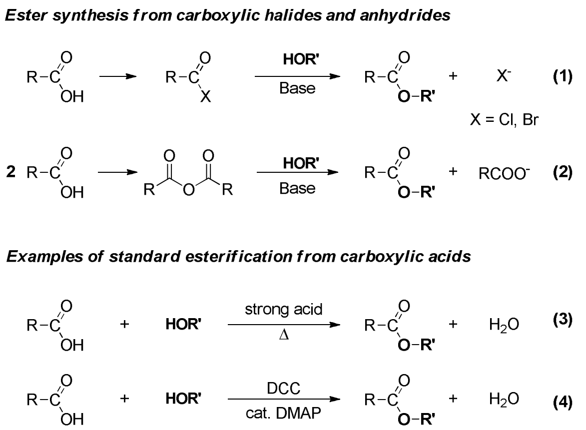
Esterification is a fundamental transformation in chemistry. Traditional esterification only largely occurs between carboxylic acid derivatives and alcohols, which often goes through multistep processes. Developments in the transition-metal-catalysed and metal-free direct esterification of alcohols under oxidative conditions opened a door for efficient, sustainable and environmentally friendly synthesis of esters from readily available materials. This *Perspective* gives an overview which covers the recent development of this emerging field.

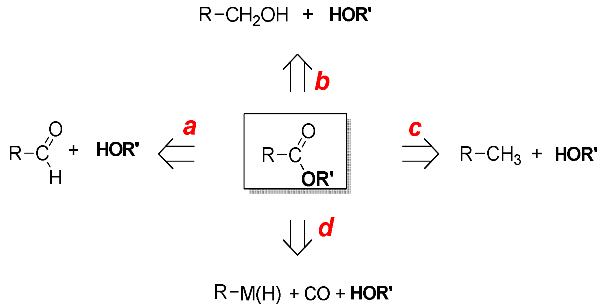
1. Introduction

Alcohols, as one class of the most fundamental compounds, are usually readily available as bulk chemicals. Esterification is a fundamental transformation for converting alcohol to esters in chemical community.[1] The development of synthetic strategies towards esters has occupied chemists for more than 100 years owning to their significance and omnipresence. However, traditional esterification depends on the nucleophilic substitution between carboxylic acid derivatives and alcohols (Scheme 1). Generally, carboxylic halides and anhydrides are synthesized from corresponding carboxylic acids. As a consequence, esterification needs to go though several steps along with the production of undesired side products, which are incongruent with the current demand of environmentally benign processes.[2-4]



Scheme 1. Traditional esterification of alcohols

Therefore, continuous efforts have been made on the direct esterification of alcohols with other readily available chemicals in the presence of oxidants. However, challenges still remain. The key issue is the selectivity between esterification and direct alcohol oxidation (aldehyde formation).[5] Thus, it is essential to find the factors that control the selectivity for alcohols in oxidative esterification. Aldehydes are one of the bulk chemials which have been widely used in such process (Scheme 2, path a). Many successful efforts during the past ten years had been employed on the direct esterification of aldehydes with alcohols in the presence of oxidants and catalysts.[6] Compared with ester synthesis from aldehydes, direct oxidative esterification between two alcohols would be a much more appealing approach since aldehydes are usually prepared by the oxidation of alcohols. This method has been gradually developed and also drawn more and more attention (Scheme 2, path b). What's more, even unactivated alkanes have been employed to perform oxidative esterification with alcohols, which might exhibit great potential in green chemistry (Scheme 2, path c). Meanwhile, organometallic compounds (R-M) or hydrocarbons (R-H) along with CO also serve as esterification partners in oxidative carbonylation of alcohols, which provides an alternative way to the synthesis of esters (Scheme 2, path d).[7] Due to the novel breakthroughs in this area, we herein review the recent progress achieved in the developments of the direct oxidative esterification of alcohols. The cross oxidative esterification of alcohol with other nucleophiles will be discussed. Oxidative lactonization,[8-12] namely, intramolecular oxidative esterification, will not be discussed in this perspective.

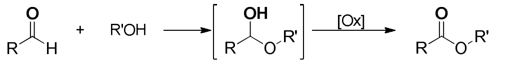


Scheme 2. Oxidative esterification of alcohols.

2. Oxidative esterification of alcohols with aldehydes

2.1 Transition-metal-free oxidation of aldehydes to esters

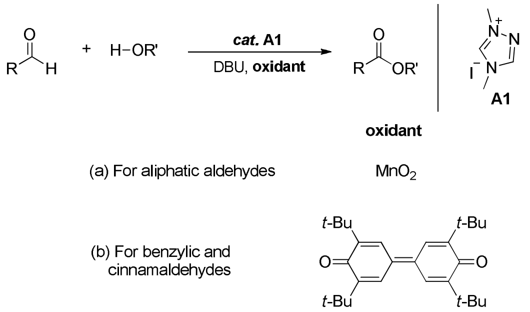
Aldehydes are readily available and abundant raw chemicals in the industries. Therefore, the oxidative esterification of aldehydes with alcohols has recently attracted much attention as an alternative for traditional protocols. Oxidative transformation of aldehydes to esters is often fairly demanding, and hence many efforts have been devoted to find novel methods for this type of process. The direct formation of esters from aldehydes through the oxidation of intermediate hemiacetals formed *in situ* has gained wide popularity (Schem 3). Over the past few decades, many organic and inorganic oxidants have been reported to have accomplished this process in alkaline alcoholic solutions.[13-18] Though this transformation has been largely studied, most of the achievements only cover methyl esters due to the selectivity factors. In order to overcome this problem, new catalytic systems are highly desirable for this approach. Inorganic reagents which include cyanide[19], and 3,4,5-trimethylthiazolium[20] have been reported to catalyse the direct oxidative esterification between aldehydes and alcohols successfully. In 2008, since a review summarized the above issues already, we will not discuss them in detail.[6] Recent progresses will be discussed so as to complement the previous systems.



[Ox] = NIS, Oxone, I_2, $KHSO_5$, $PhI(OAc)_2/I_2$ *etc.*

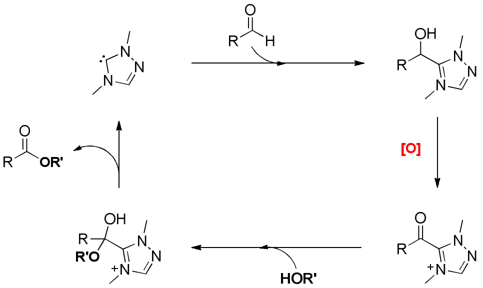
Scheme 3. Novel pathway for direct oxidative esterification without catalyst

N-heterocyclic carbenes (NHCs) are known to be catalysts for interesting redox processes.[21] In 2008, Scheidt *et al.* introduced carbene to catalyse the oxidative transformation of aldehydes to esters without transition metal.[22] By using MnO_2 as the oxidant, numerous aliphatic aldehydes can esterify certain alcohol with good yields. However, the substrates are limited to saturated aldehydes (Scheme 4, a). As to dealing with activated aldehydes, a conjugated two-electron oxidant has been developed. Activated aldehydes like substituted benzaldehydes and cinnamaldehydes are all suitable substrates (Scheme 4, b).[23] Similar results were observed by using azobenzene as the oxidant albeit with lower efficiency.[24]



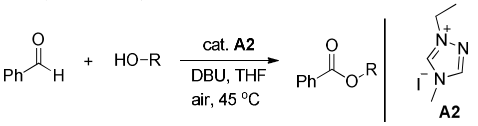
Scheme 4. NHC-catalysed direct esterification of inactivated and activated aldehydes

A widely accepted mechanism was drawn in Scheme 5. Carbene first undergoes nucleophilic addition to aldehyde and generates an activated alcohol. The activated alcohol is then oxidized by an oxidant to form an acyl carbine (Breslow intermediate). At last, nucleophilic substitution takes place by alcohols to give the desired esters. In further study, Scheidt and co-workers found that NHC not merely affects the oxidation of aldehydes. It was found that aromatic aldehyde can achieve preliminary chemoselective acylation of alcohols in the presence of amines. This was due to the reason that the preferable activation of the alcohol by H-bonding to the carbene would increase the nucleophilicity of the hydroxyl group.[23, 25] In other words, carbene not only catalysed the oxidation but also activated the alcohol.



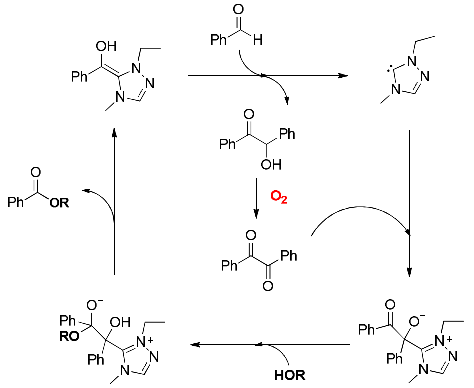
Scheme 5 Proposed mechanism through Breslow intermediate.

Until recently, a NHC-catalysed aerobic oxidative esterification of aldehyde with alcohols was achieved.[26] In this report, the author observed significant differences in yields during esterification by using different alcohols with distinguished pK_a values (Scheme 6). This phenomenon was hard to be explained from the mechanism in Scheme 5 since Breslow intermediate is highly electrophilic. After identifying the active intermediates in the reaction system, Benzoin was unambiguously identified to be an active intermediate which was oxidized by oxygen in the aerobic NHC-catalysed aldehyde esterification (Scheme 7).



R =	pKa (H_2O)	NMR yield (%)
Bn-	15.4	78
Allyl	15.5	75
CCl_3CH_3	12.3	62
CF_3CH_2	12.4	62
$(CF_3)_2CH$	11.2	25

Scheme 6. NHC-catalysed aerobic oxidative esterification of aldehyde with alcohols.

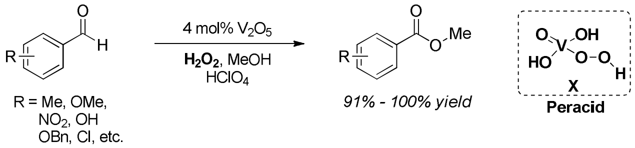


Scheme 7. Proposed mechanism for the aerobic NHC-catalysed oxidative esterification.

2.2 Transition-metal-catalysed oxidation of aldehydes to esters

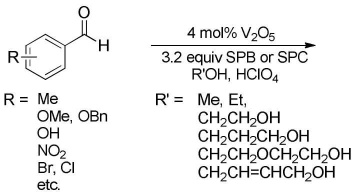
2.2.1 Vanadium and titanium catalysis

In 1999, effective conversion of aldehydes to methyl esters was achieved by using methyltrioxorhenium (VII) as the catalyst, with hydrogen peroxide as the oxidant, and a co-catalyst such as bromide or chloride ions was also required.[27] However, complicated, harsh and sensitive reaction conditions were required, which prevented it from further application. Moreover, it failed to generate the desired product from specific oxidation of aldehydes in systems containing deactivating groups and olefin as functional groups. Subsequently, Patel and co-workers did significant works to improve this procedure. Vanadium pentoxide was used as the catalyst and hydrogen peroxide was employed as oxidant (Scheme 8).[28] These reagents are cheap and nontoxic, and the inorganic salts can be removed easily. In the presence of methanol, aldehydes undergo oxidative transformation into the corresponding methyl esters with high efficiency.



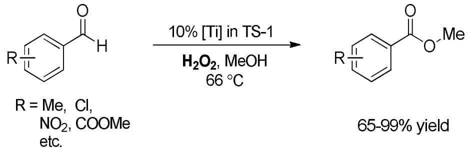
Scheme 8. Vanadium catalysed esterification of aldehydes with H_2O_2 as the oxidant.

As a mechanism assumption, aldehyde was proposed to form hemiacetal under acidic conditions with alcohol. Then the hemiacetal was oxidized by the peracid formed by the addition of H_2O_2 to vanadium (V) oxide to give the desired esters (Scheme 8, X). Later study found that sodium perborate (SPB) or sodium percarbonate (SPC) in combination with perchloric acid could be used to replace the concentrated hydrogen peroxide in an environmentally friendly view.[29] Other alcohols could be substituted for methanol to yield the corresponding esters. Linear alkyl alcohols like ethanol, 1-propanol and 1-butanol were all effective substrates. Whereas, branched alcohols and benzyl alcohols were not suitable in this transformation. Interestingly, the present methodology is able to achieve the monoesterification of diols (Scheme 9).



Scheme 9. Vanadium catalysed esterification of aldehydes with SPB or SPC as the oxidant

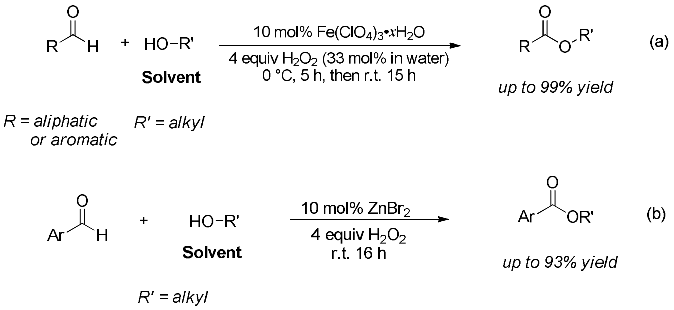
Quite similar to the vanadium-catalysed system, Chavan and co-workers developed heterogeneous catalytic system by using a titanium-containing molecular sieve TS-1 to accomplish the oxidation of aromatic aldehydes.[30] By using 30% H_2O_2 as the oxidant in methanol under reflux, aromatic esters were isolated in the yields of 65-99% (Scheme 10). This report also proposed a mechanism of oxidation of hemiacetal by peracid formed by the addition of H_2O_2 to titanium oxide.



Scheme 10. Titanium catalysed esterification of aldehydes with H_2O_2 as the oxidant

2.2.2 Iron and Zinc catalysis

In 2009, Darcel and co-workers demonstrated the first example of the iron catalysed oxidative esterification of aldehydes.[31] Both aliphatic and aromatic aldehydes were compatible in this reaction. Primary alcohols such as ethanol, 1-butanol, and 1-pentanol reacted with *p*-methoxybenzaldehyde smoothly. More interestingly, the functional alcohols such as allylic alcohols or propargyl alcohols, as well as the classical primary alcohols, also underwent esterification smoothly (Scheme 11, a). In this reaction system, $Fe(ClO_4)_3{\cdot}xH_2O$ was proved to be crucial for the successful esterification. It had been noted that the major role of iron was the Lewis acid to activate the aldehydes. After the aldehyde activation with iron catalyst, the alcohol undergoes nucleophilic addition to the electrophilic carbonyl group, which generates an activated hemiacetal intermediate. Then the hemiacetal was oxidized by H_2O_2, which leads to the formation of the desired esters. As the Lewis acid activation of aldehydes is quite common with zinc salts, zinc compounds were employed as catalysts in the oxidative esterification by Wu and co-workers recently.[32] This work represented a follow-up to the iron catalysis system, in which zinc salts can also act as Lewis acids to activate aldehydes. Unfortunately, only aromatic aldehydes can afford esters in good to excellent yields (Scheme 11, b). The major drawbacks in these systems are that alcohols were used as solvents and H_2O_2 needed to be 4 equivalent excess.

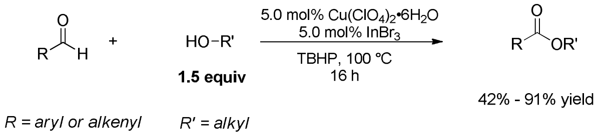


Scheme 11. Iron and zinc catalysed esterification of aldehydes with H_2O_2 as the oxidant

2.2.3 Copper catalysis

In 2006, Li and co-workers first achieved the copper-catalysed oxidative esterification between aldehyde and the *in situ* generated enol by using *tert*-butyl hydroperoxide (TBHP) as the oxidant.[33] In the next year, they found that by adding an Lewis acid into the reaction system, the oxidative esterification with simple alcohols could be achieved under similar conditions.[34] $InBr_3$ was the key factor responsible for the efficiency of the reaction, which might promote the formation of hemiacetals during the reaction. Both aliphatic and aromatic aldehydes were compatible under the reaction conditions. Moreover, a big advance in this system is that only 1.5 equivalent of alcohol was needed for the successful esterification

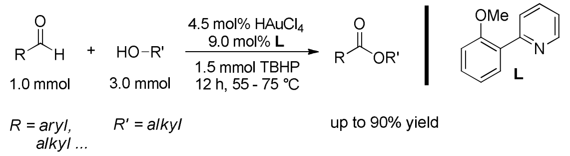
(Scheme 12). As an extension example of this system, Kim and co-workers described oxidative esterification between 2-carbonyl substituted phenols and various alcohols.[35]



Scheme 12. Copper catalysed esterification of aldehydes with TBHP as the oxidant

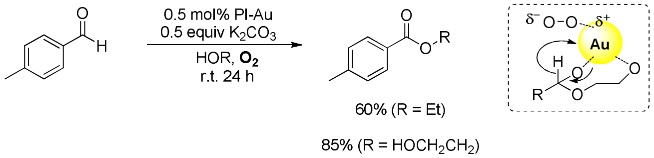
2.2.4 Gold catalysis

Both gold nanoparticles and mononuclear gold complexes can also be active catalysts in oxidative esterification. In a recent study, $HAuCl_4$ was proved to be a suitable catalyst to achieve oxidative esterification with TBHP as the oxidant.[36] Both aromatic and aliphatic aldehydes are suitable substrates which esterify aliphatic alcohols in good yields (Scheme 13). Based on the *in situ* extended X-ray absorption fine structure (EXAFS) study and the ligand effect in the reaction, the author concluded that the reaction proceeds through a homogeneous gold-catalysed approach.



Scheme 13. Homogeneous gold-catalysed esterification of aldehydes with TBHP as the oxidant.

Gold nanoparticles were also proved to be fine catalyst to realize this transformation. It was reported in 2011 that aerobic oxidative esterification of aldehydes with 1,2- and 1,3-diols and their derivatives proceeded smoothly in the presence of polymer-incarcerated gold nanoclusters.[37] In this system, esterification proceeded much faster with 1, 2- and 1, 3-diols and their derivatives than that with methanol, which may be explained by the effect of neighboring group participation between the oxygens of diols. This is because that both the oxygen and the left hydroxyl group could coordinate with the gold nanoparticle, which stabilized the hemiacetal intermediate and benefited the following oxidation step. (Scheme 14).

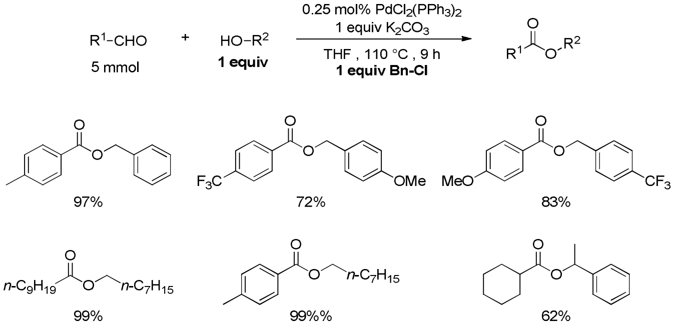


Scheme 14. Heterogeneous gold-catalysed esterification of aldehydes with O_2 as the oxidant.

1.2.6 Palladium catalysis

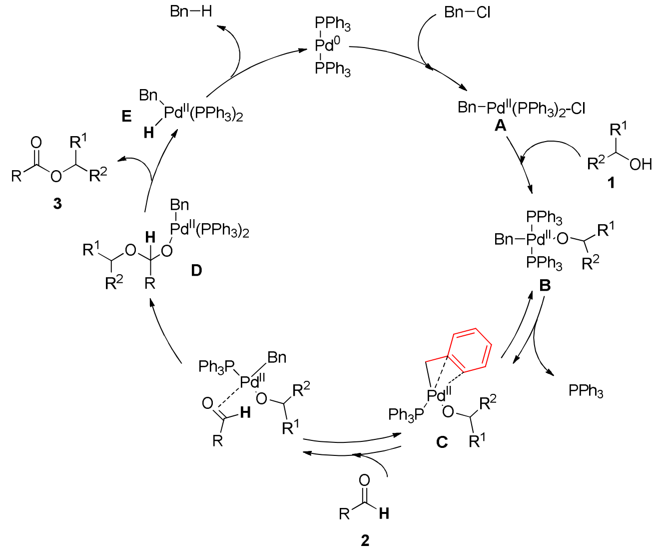
The oxidation of primary alcohols to aldehydes in the presence of palladium catalysts has been widely studied, in which various oxidants, such as aryl halides and O_2 have been applied in these transformations.[38-41] In such transformations, aldehyde is produced and remains unreacted, resulting in selective aldehyde formation. These facts suggest that in most cases, the selective Pd-catalysed oxidation of an alcohol into an aldehyde occurs in advance of esterification of an aldehyde with an alcohol.

By using benzyl chloride as an oxidant in a palladium catalysed system, Lei and co-workers reported a versatile and selective synthesis of different esters by using stoichiometric amounts of aldehyde and alcohol (Scheme 15).[42] It was demonstrated that the oxidant, benzyl chloride, was responsible for the high selectivity of the esterification. Aromatic, alkenyl and aliphatic aldehydes all could react with alcohols smoothly. At the same time, aliphtic alcohols, phenyl, allylic and even secondary alcohols were esterified in high efficiency. More importantly, electronic properties had little influence on the yields. Further study showed that this approach could be scaled up in a solvent-free system with low catalyst loading.



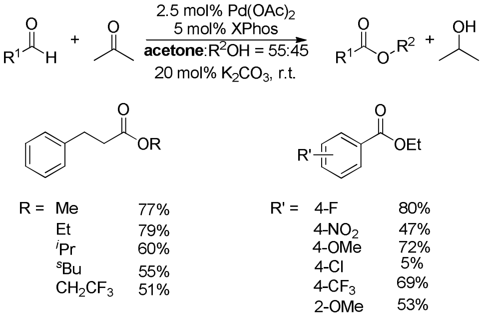
Scheme 15. Palladium catalysed esterification of aldehydes with Bn-Cl as the oxidant.

The Pd-catalysed oxidative esterification between aldehyde and alcohol was presented as the catalytic cycle shown in Scheme 16. At first, the oxidative addition of benzyl chloride to Pd(0) generates intermediate **Bn**-Pd(II)-**Cl** (**A**). The following alcoholysis step selectively occurs at the Pd-**Cl** bond of **A** with alcohol to generate an alkoxy palladium intermediate **B** in the presence of a base. Following η^3 coordination by benzyl group facilitates the dissociation of PPh_3 to generate **C** which favors the coordination of aldehyde to the palladium center. Subsequently, the aldehyde coordinates and inserts into intermediate **C** to generate hemiacetal palladium intermediate **D**. Then, *beta*-hydride elimination occurs to release esters and Pd-H intermediate **E**. Through this catalytic cycle, alcohols are selectively esterified by aldehydes. It had been noted that benzyl chloride not only served the oxidant but also acted as a covalent carbon ligand.[42]



Scheme 16. Proposed mechanism for the oxidative esterification of aldehydes with Bn-Cl as the oxidant.

Recently, a hydrogen transfer protocol has been developed to achieve the direct oxidative esterification between aldehydes and alcohols.[43] Aliphatic and aromatic aldehydes are successfully converted into their corresponding esters by using $Pd(OAc)_2$ as the catalyst and XPhos as the ligand. Concomitant reduction of acetone to isopropanol provides an inexpensive and sustainable approach that mitigates the need for other oxidants. In this system, alcohols needed to be used as the solvent and the reaction efficiency was not very high together with limited substrate scope (Scheme 17). Similar to this process, Iridium-catalyzed oxidative esterification of aldehydes with alcohols was described though hydrogen transfer processes as early as 2007.[44] However, the unsaturated bonds in the substrate acted as the hydrogen accepter which was of disadvantage.

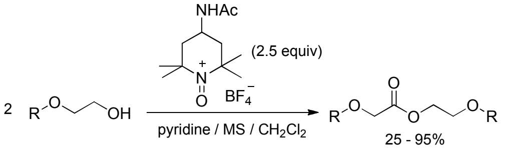


Scheme 17. Palladium catalysed esterification of aldehydes with acetone as the oxidant.

3. Oxidative esterification between two alcohols

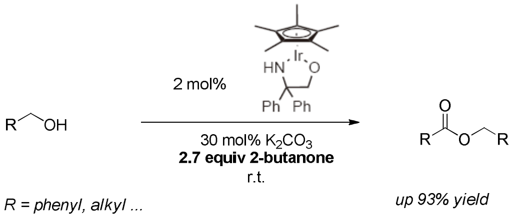
3.1 Direct oxidation of primary alcohols to esters

In 2004, Bobbitt and co-corkers achieved the oxidative dimeric esterification of primary alcohols in the presence of 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate in combination with pyridine.[14] Selective esterification could be observed in the alcohols containing α-oxygen (Scheme 18). Very recently, this reaction system has been introduced to the oxidative esterification of a wide range of aldehydes to hexafluoroisopropyl (HFIP) esters with the same oxidant.[45]



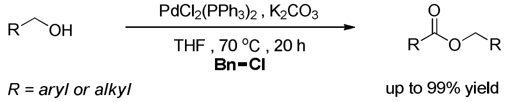
Scheme 18. Direct oxidation of primary alcohols to esters with 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium as the oxidant.

Transition-metal catalysed selective oxidation of primary alcohols to corresponding dimeric esters has also been studied. Iridium is widely known for its ability in hydrogen transfer. In 2005, Katoh and co-workers introduced Iridium as the catalyst for the selective oxidation of alcohols (Scheme 19). In this system, 2-butanone was used as the oxidant which accepted the hydrogen atoms.[46]



Scheme 19. Iridium catalysed direct oxidation of primary alcohols to esters with 2-butanone as the oxidant.

As for palladium catalysed selective oxidation of primary alcohols to esters, the selectivity of the formation of aldehyde and ester is always problematic. In most cases, primary benzyl alcohols tend to form aldehydes while primary aliphatic alcohols tend to form esters. As a follow-up work of the palladium catalysed esterification of aldehydes with alcohol, Lei and co-workers discovered that selective alcohol oxidation was achieved for primary alcohols in the absence of aldehyde (Scheme 20).[5]

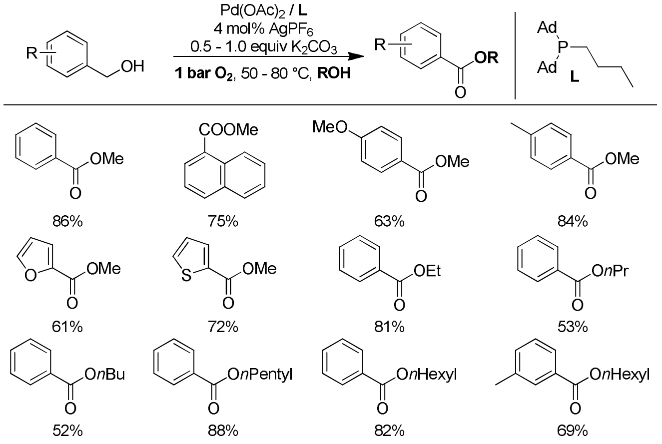


Scheme 20. Palladium catalysed direct oxidation of primary alcohols to esters with Bn-Cl as the oxidant.

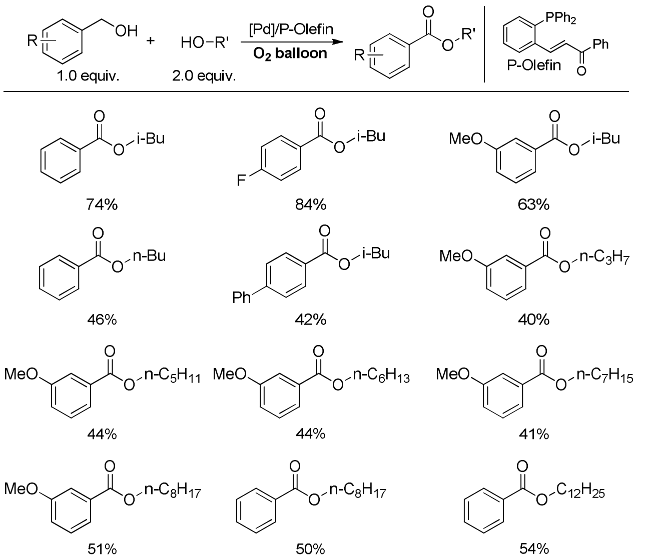
3.2 Oxidative esterification between two different alcohols

Generally, the oxidative esterification between two different alcohols was considered to be challenging since both of the alcohols can be oxidized. As a consequence, these reactions usually end up with a poor selectivity. Obviously, the most challenging task in this field is how to control the selectivity of two esters. As methanol is not easy to be oxidized, reports about the methyl ester synthesis with benzyl alcohols have been accomplished by several catalytic systems. Ru[47, 48], Rh[49] and Ir [50] were subsequently used in this trasformations through a hydrogen transfer approach.

A breakthrough was made in 2011, when the first Palladium catalysed direct aerobic oxidative esterification of benzylic alcohols with methanol and various long-chain aliphatic alcohols was first developed by Beller and Lei separately at the same time.[51, 52] Long chain aliphatic alcohols were first applied to get the direct esterification product. Beller and co-workers successfully achieved this transformation for long-chain aliphatic alcohols by using a bulky phosphine ligand. The major drawback is that the alcohols need to be used as the solvent (Scheme 21).[51]



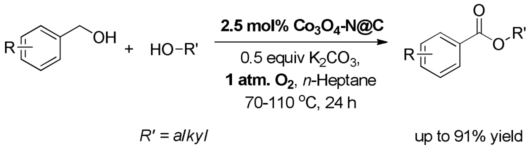
Scheme 21. Palladium catalysed aerobic oxidative direct esterification of different alcohols in alcoholic solutions.



Scheme 22. Palladium catalysed aerobic oxidative direct esterification of different alcohols in hexane solutions.

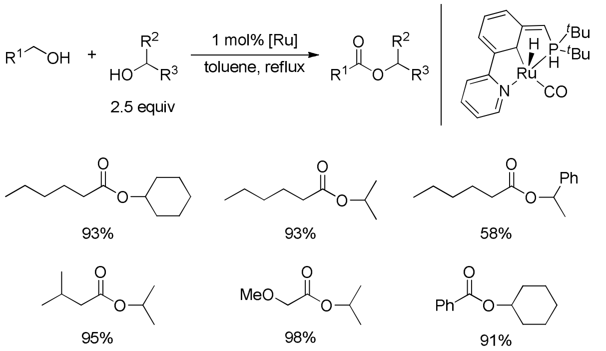
In Lei's work, the challenging esterification reactions of long-chain aliphatic alcohols were accomplished by using a P-olefin ligand to control the selectivity, which lowered the amount of long-chain aliphatic alcohols to two equivalent compared to benzylic alcohols.[52] Though there is still a long way to go for the industrial application, the nature of this route and the use of O_2 as the oxidant represent a step toward an environmentally benign and sustainable process (Scheme 22).

Later on, Beller and co-corkers developed a novel cobalt-based heterogeneous catalysts for the direct aerobic oxidative esterification of alcohols (Scheme 23). By using a heterogeneous Co_3O_4–N@C catalyst under aerobic condition, the cross and self-esterification of alcohols to esters proceed in good to excellent yields. Despite that alcohol still needed to be large excess, this process was simple, cost-effective, and environmentally benign compared with the formal reports.



Scheme 23. Heterogeneous cobalt-catalysed aerobic esterification of aldehydes with O_2 as the oxidant.

Interestingly, the oxidative esterification of primary and secondary alcohols was first reported by Milstein through a pincer ruthenium catalysis system (Scheme 24).[53] In most cases, the yield of the cross-esterification was excellent, although in some cases a small amount of the homocoupling product of the primary alcohol is observed. In addition, ketone, another byproduct, can be obtained in low yield by dehydrogenation of the secondary alcohol occasionally. Interestingly, the dehydrogenation of the secondary alcohols to the corresponding ketones is slower than the dehydrogenative coupling of the alcohols to esters, resulting in excellent yields of the desired cross-esterification products. In addition, the self-esterification product was observed only as a minor product.

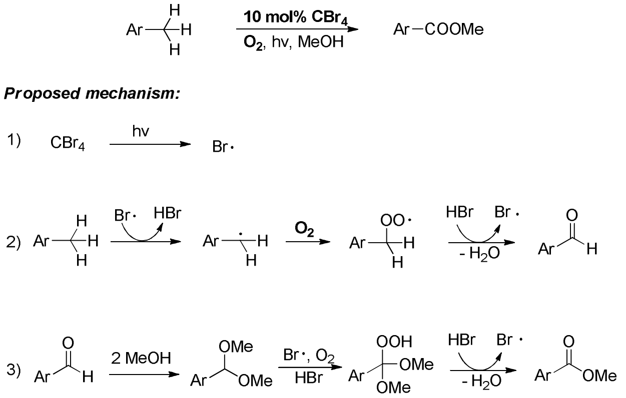


Scheme 24. Pincer-ruthenium-catalysed cross-dehydrogenative esterification of primary alcohols with secondary alcohols.

As oxidative esterification between two alcohols is a highly atom economic process, more and more attention will be paid to this emerging area. Selectivity and efficiency are the key factors of selective cross oxidative esterification of different alcohols, which remain to be problems in this field.

4. Oxidative esterification of alcohols with alkanes

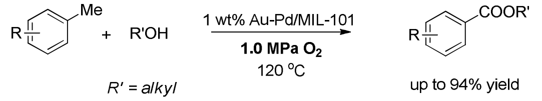
Alkanes are highly attractive esterification reagents since they are cheap and available compared with other common esterification reagents, including acids, acyl chlorides and alcohols. Alkanes, however, are seldom utilized in oxidative esterification due to the low reactivity of sp^3 C-H bonds. To date, only few reports have described the selective oxidative esterification of alcohols with methyl aromatics to give aromatic esters.



Scheme 25. CBr_4-catalysed aerobic oxidative esterification of methyl aromatics.

In 2010, the first direct oxidative esterification of methyl aromatics was reported by Itoh and co-workers by employing aerobic photo-oxidation process with CBr_4 as a photo catalyst to yield methyl carboxylates (Scheme 25).[54] The reaction should be conducted in alcoholic solutions. The methyl aromatics with an electron-donating group were good substrates that afforded the corresponding methyl carboxylates in high yields, while methyl aromatics with electron-withdrawing substituents exhibited low efficiency. The key intermediate of the reaction is dimethyl acetal, which is obtained from aerobic photo-oxidation of toluene. During the reaction, the dimethyl acetal is oxidized by oxygen to give the product. The method is facile, efficient and productive in green chemistry due to the use of O_2 as oxidant, instead of heavy metal, but the toxicity of CBr_4 limits its further application. Afterwards, improvements were made for the reaction. CBr$_4$ was replaced by non-toxic organophotocatalyst anthraquinone-2,3-dicarboxylic acid, and alkyl alcohols other than methanol could perform the oxidative esterification with methyl aromatics.[55]

Although the reaction performs well by using homogeneous photo catalyst, the low turnover numbers limit the further application. In order to overcome the disadvantage, Au-Pd bimetallic heterogeneous catalyst was employed by Li and co-workers (Scheme 26, b)).[56] A variety of alkyl alcohols can react with methyl aromatics to afford aromatic esters with low catalyst loading and O$_2$ as the oxidant. Alcohols other than methanol also afford good to excellent yields. Additionally, the catalyst is recyclable, which exhibits great potential for industrially process.

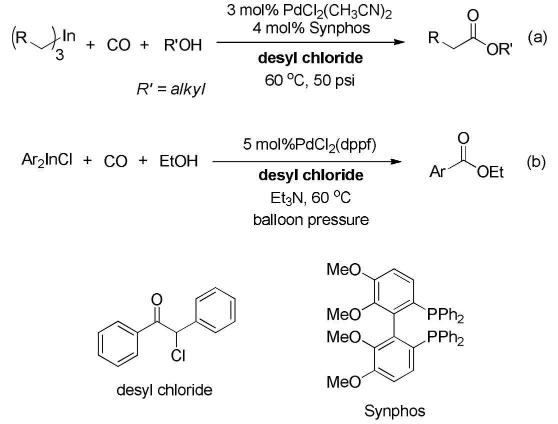


Scheme 26. Oxidative esterification of methyl aromatics promoted by heterogeneous catalyst.

5. Esterification of alcohols through oxidative carbonylation

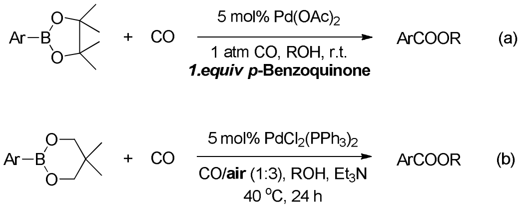
5.1 Oxidative carbonylation esterification of organometallic reagents

Oxidative carbonylation that directly utilises various cheap and accessible nucleophiles, including organometallic reagents and simple hydrocarbons, provides alternative ways for the synthesis of multiple esters from alcohols. In 2008, Lei and co-workers demonstrated the oxidative carbonylation esterification of alkyl organoindium compounds.[57] By using palladium catalyst with desyl chloride as oxidant, primary and secondary alkyl indium reagents underwent oxidative carbonylation esterification smoothly to obtain corresponding esters (Scheme 27, a). Similar to the alkyl indium reagents, aryl indium reagents could also be transformed into corresponding esters under similar conditions (Scheme 28, b).



Scheme 27. Oxidative carbonylation esterification of alkyl indium reagents with aliphatic alcohols.

In 2010, Yamamoto and co-workers achieved the first Palladium catalysed oxidative carbonylation esterification of arylboronates.[58] The reaction was conducted in alcoholic solutions with *p*-benzoquinone as the sole oxidant at room temperature (Scheme 28, a). Various substituted aromatic arylboronates afforded methyl esters in good to excellent yields. Long chain alcohols also afforded corresponding esters in moderate yields. In the same year, Lei and co-workers developed a new system by employing air as the sole oxidant. With CO/air balloon and palladium catalyst, the esters could be obtained in good yields starting from the corresponding arylboronates (Scheme 28, b).[59] This was the first example of aerobic carbonylation esterification of organoboron compounds. The mechanism study indicated that the [(η-O$_2$)Pd(PPh$_3$)$_2$] complex which generated from [Pd^0] and O$_2$ was the key intermediate in the reaction.

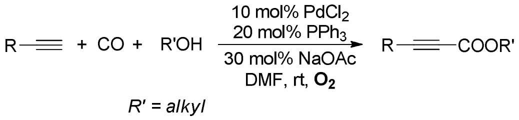


Scheme 28. Oxidative carbonylation esterification of organoboron compounds with aliphatic alcohols.

5.2 Oxidative carbonylation esterification of hydrocarbons

5.2.1 Oxidative carbonylation esterification of alkynes and alkenes

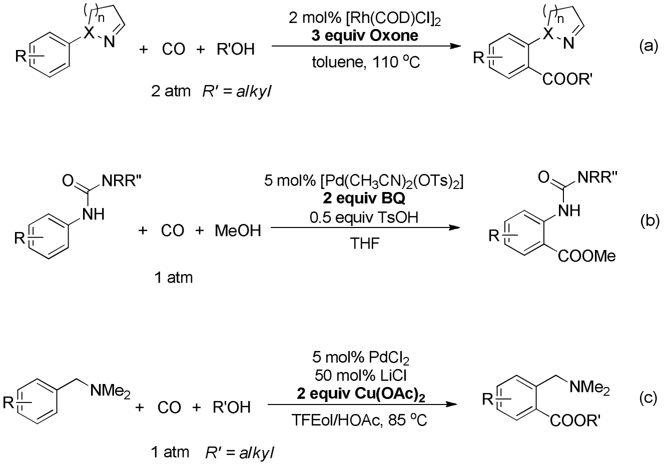
Direct utilization of hydrocarbons in alcohol oxidative esterification represents appealing approaches for ester synthesis. In 1980, alkynes were reported to achieve carbonylation esterification by Tsuji and co-workers.[60] With PdCl$_2$ as the catalyst, alkynoates could be obtained in the presence of Cu^{II} salts as the oxidant. Other oxidants and catalyst precursors were also efficient in this transformation.[61-63] In 2004, Yamamoto and co-workers developed a new Pd-catalysed carbonylation esterification reaction of terminal alkynes at room temperature by using palladium/phosphine catalysts and molecular oxygen as the oxidant (Scheme 29).[64] Both aromatic and aliphatic alkynes were suitable substrates in this transformation. Alcohols needed to be used in large excess in order to guarantee the reaction efficiency. In this system, linear long chain aliphatic alcohols such as *n*-butanol also gave the desired product in high yields. The mechanism of the reaction was investigated. The product alkynoates was generated through reductive elimination of methoxycarbonyl group and alkynyl group which coordinated to the palladium.



Scheme 29. Oxidative carbonylation esterification of alkynes with alcohols.

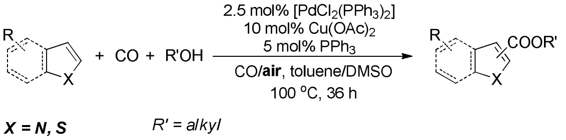
5.2.2 Oxidative carbonylation esterification of arenes

Since the direct aromatic C-H bond activation is usually problematic, initial efforts in utilizing arenes as the coupling partner with CO and alcohols focus on the arenes with directing groups. In 2008, Zhang and co-workers reported an *ortho* carbonylation esterification of 2-arylpyridines catalysed by rhodium using oxone as the oxidant (Scheme 30, a).[65] The reaction exhibited good functional group tolerance. With the use of urea group as the directing group and a mixture of THF/MeOH as the solvent, the arene coupled with CO and alcohol efficiently with Pd(OTs)$_2$(MeCN)$_2$ as the catalyst and BQ as the oxidant (Scheme 30, b). In 2010, a N,N-dimethylamino directed oxidative carbonylation esterification of aromatic C-H bond in the presence of catalytic amount of PdCl$_2$ and stoichiometric amount of $Cu(OAc)_2$ as the oxidant was reported by Shi and co-workers (Scheme 30, c).[66] The reaction product could be transformed into *ortho*-alkyl benzoate by using a one-pot procedure. With the assistance of LiCl, the *N,N*-dimethylbenzylamines could perform oxidative esterification with CO and alcohols in the presence of $PdCl_2$ as the catalyst and $Cu(OAc)_2$ as the oxidant.



Scheme 30. Oxidative carbonylation esterification of aromatic C-H bond with directing group.

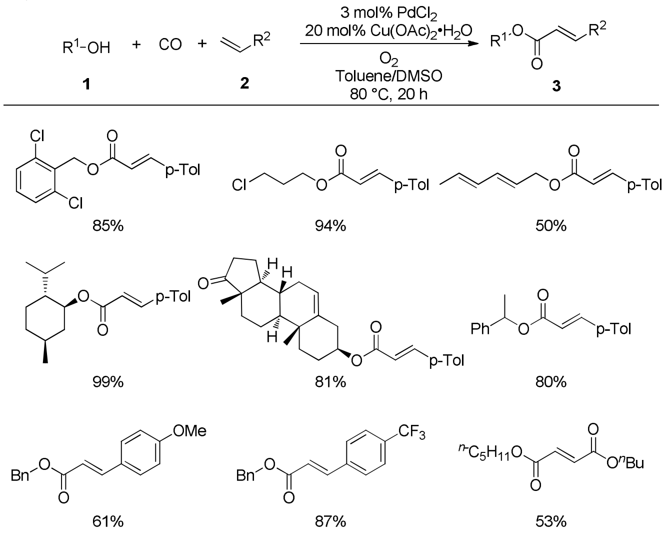
In 2011, Lei and co-workers reported an aerobic oxidative C-H carbonylation of heteroarenes without directing group.[67] Simple indoles and thiophenes could be converted into corresponding heterocyclic esters using balloon pressure of CO and O_2 mixture in the presence of palladium catalyst (Scheme 32). The electrophilic palladation of C-3 position of indoles and C-2 position of thiophenes may be the key process of the reaction.



Scheme 31 Oxidative carbonylation esterification of heteroarenes

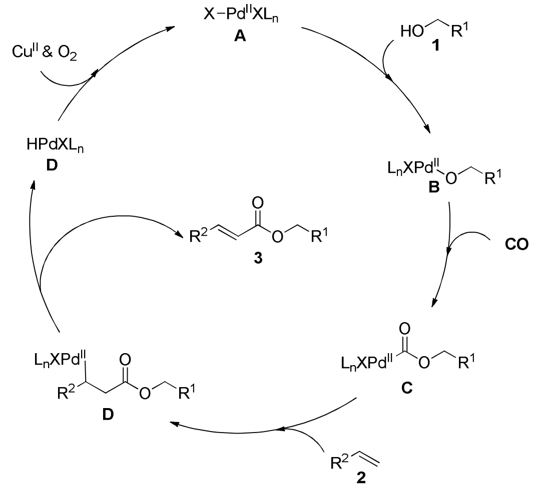
5.2.3 Oxidative alkoxycarbonylation esterification of alkenes

Compared with aryl C(sp^2)-H bonds, the direct oxidative alkoxycarbonylation of alkenyl C(sp^2)-H bonds has received less attention. As early as 1969, Yukawa and Tsutsumi reported the reaction of styrene–palladium complex with CO and alcohols to afford cinnamates.[68] Later on, the palladium catalysed synthesis of cinnamate from alkene, CO and alcohol was developed by Cometti and Chiusoli in 1979.[69] With atmospheric pressure of CO, the reaction was carried out at room temperature and methyl cinnamates were prepared smoothly. More recently, Bianchini and co-workers reported the oxidative alkoxycarbonylation of alkenes to afford methyl cinnamate with diphosphine ligands and palladium catalysts.[70] Similar to the previous reports, the insertion of alkene to alkoxycarbonyl palladium was considered as the key step for the reaction, in which the designed diphosphine ligands with flexible carbon backbones played an important role in promoting the β-H elimination. However, in those reported oxidative carbonylative esterifications, alcohols were all utilized as the solvents to enhance the reaction efficiency. The main issue might be related to the easy oxidation of alcohols in those transformations. Therefore, substrate applicability of different kinds of alcohols is greatly restricted. Very recently, a palladium catalysed aerobic oxidative carbonylative esterification of alcohols to directly construct α, β-unsaturated esters under base- and ligand-free conditions was realized by Lei and co-workers.[71] Only stoichiometric amount of alcohol was needed and the reaction exhibited a wide range of functional-group tolerance. Benzylic, allylic and aliphatic alcohols were all suitable in this transforamtion.Moreover, secondary alcohols can furnish corresponding α, β-unsaturated esters in highly selectivity (Scheme 32).



Scheme 32. Aerobic oxidative carbonylation esterification of alkenes.

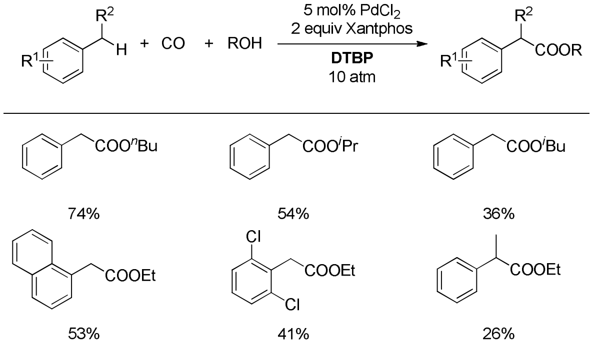
Based on the previous study, a detailed mechanism involving the insertion of alkene to alkoxycarbonyl palladium was brought farward by the authers (Scheme 33). Initially, alcoholysis of the Pd^{II} species (**A**) generates an alkoxy palladium intermediate **B**. Afterwards, CO insertion leads to the formation of a acyl palladium intermediate **C.** Further olefin insertion will generate intermediate **D**. β-Hydride elimination of **D** furnishes the final product and releases a Pd-hydride speices **E** which is oxidized by O_2 and copper catalyst in acidic condition to regenerate the Pd(II) species **A** to complete the catalytic cycle. Experiments have shown that alcohol oxidation is troublesome under the standard condition. Importantly, CO or olefin coordination with pallaium could suppress the oxidation step, which might explain why only one equivalent of alcohol was needed in the reaction system.



Scheme 33. Proposed mechanism for the aerobic oxidative carbonylation esterification of alkenes.

5.2.4 Oxidative carbonylation esterification of alkanes

Alkanes, as bulk chemicals, are attractive substrates of oxidative carbonylation esterification. Similar to the oxidative esterification of alcohols with alkanes, the oxidative carbonylation esterification of C-H bond of alkanes remains challenging due to the high bond energy and poor selectivity to gain mono functionalized products. Therefore, reports focusing on this area are rare. The only carbonylation esterification of alkanes was developed by Huang and co-workers (Scheme 34).[72] They accomplished the oxidative coupling of toluene derivatives with CO and alcohols to afford phenylacetic acid esters in the presence of palladium as the catalyst and *di-tert*-butyl peroxide (DTBP) as the oxidant. One of the problems, the C-H bond activation, was solved by employing DTBP, which underwent homolytic cleavage to give alkoxyl radical and then abstracted the benzylic hydrogen atom to afford benzyl radical. The benzyl radical then reacted with palladium and oxidant to give benzyl palladium species, which underwent carbonylation esterification to afford the product. Various substituted benzyl alkanes could afford esterification product but needed to be used in large excess amount.



Scheme 34. Oxidative carbonylation esterification of methyl aromatics.

5 Conclusions and Outlook

During the last few years, significant advances had been made in the area of direct oxidative esterification of alcohols. Direct alcohol oxidative esterification with other readily available reagents has drawn more and more attention, which is considered as the more eco-friendly processes than the traditional esterification methods. Selective oxidative esterification between an aldehyde and an alcohol has atracted much attention. This approach is quite efficient in a lot of systems. Nevertheless, selective oxidative esterification between two alcohols remains problematic. Quite limited methods have been reported on this issue. Compared with alcohol oxidative esterification with aldehyde, this approach suffers from narrow substrate scope as well as low reaction efficiency. Except for these two methods, alcohol oxidative esterification with alkanes has also been developed, which will be a quite appealing approach in the coming future. Additionally, developments in oxidative carbonylation esterification will lead the esterification proceess to be much more aboundant.

Selectivity in the cross oxidative esterifiction is the most challenging issue. In most of the cases, alcohols need either to be exccess or used as the solvent. Therefore, discovering evironmentally friendly catalysis systems for the selective and stoichiometric alcohol oxidative esterification will remain to be a promissing research area. More importantly, there are little mechanism studies focusing on this topic, which makes it hard to undertand the key factors that control the selectivity. Thus, studies considering the understandings of oxidative esterification transformations are strongly required.

Acknowledgements

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Notes and references

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† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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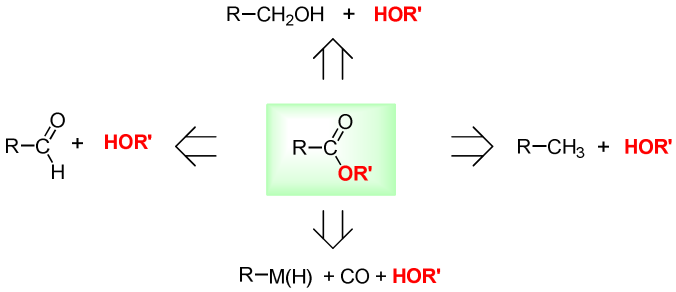

Recent progresses in the direct esterification of alcohols from readily available materials under oxidative conditions were discussed in this perspective.