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One-Pot Oxidative Esterification and Amidation of Aldehydes

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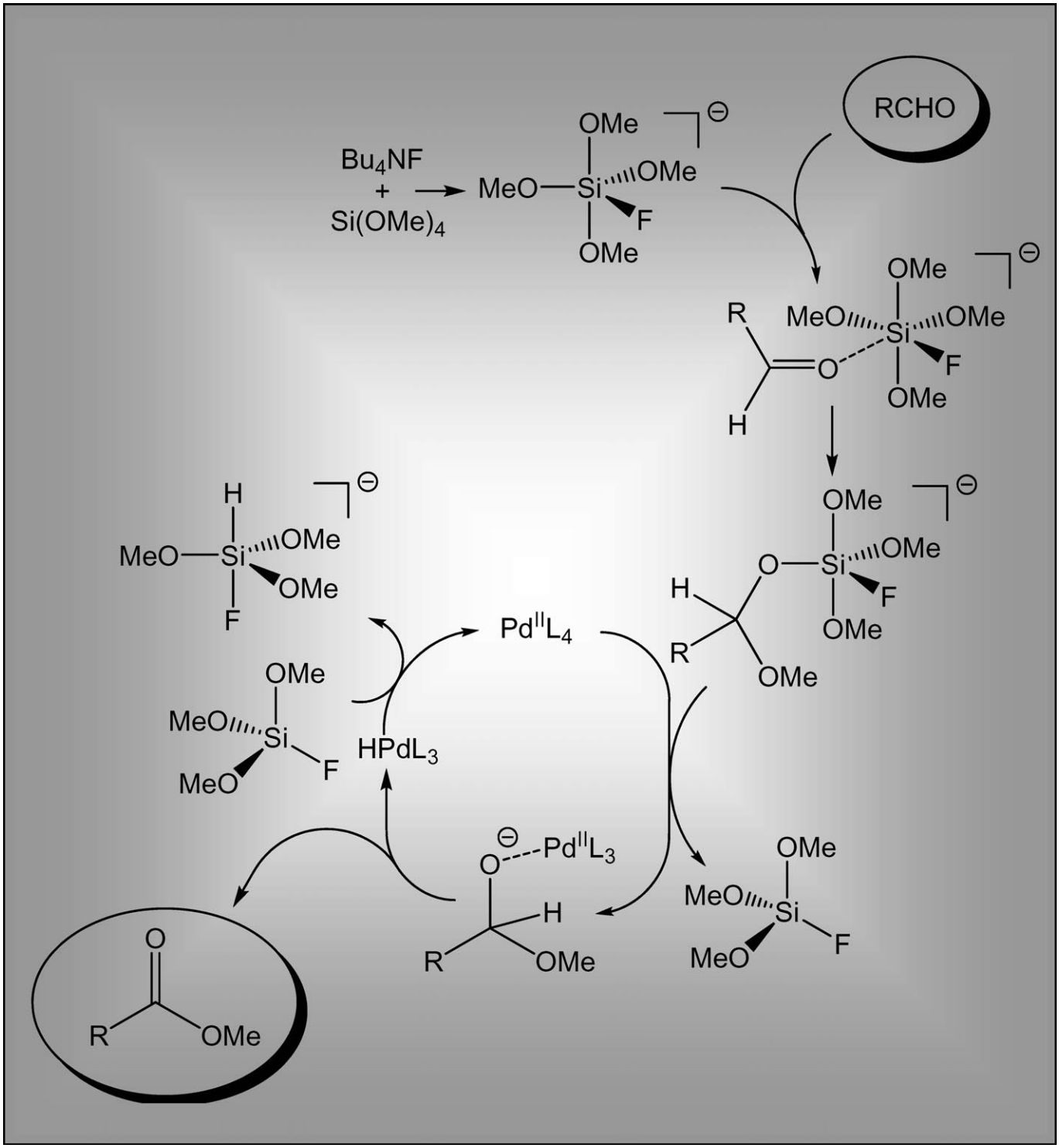


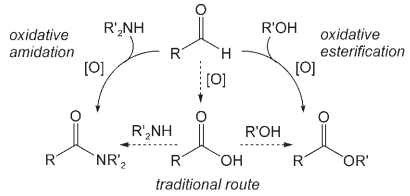
Abstract: During recent years, the direct transformation of aldehydes into esters or amides has developed into a vigorous research area and powerful one-pot oxidative esterification and amidation procedures have been reported. Several concepts that are often complementary in substrate scope, functional group tolerance, and reaction outcome have emerged, thus providing a wide range of alternatives to classical ester and amide synthesis via carboxylic acid intermediates.

Keywords: aldehydes · amides · esters · one-pot procedures

Introduction

Ester and amide bonds are inarguably among the most abundant functional groups in natural products, polymers, and pharmaceuticals. The development of synthetic strategies towards esters and amides has occupied chemists for more than 100 years due to the significance and omnipresence of these compounds. Esters and amides are routinely prepared from free carboxylic acids that need to be activated through conversion to acyl chlorides and mixed anhydrides or with carbodiimides, 1-hydroxybenzotriazoles and other expensive coupling agents.[1]

One-pot oxidative esterifications and amidations of aldehydes incorporate two separate reaction steps, that is, oxidation and either C–N or C–O bond formation, into a single operation (Scheme 1). This approach has received increasing



Scheme 1. Comparison of traditional two-step conversion of aldehydes to esters and amides with direct oxidative esterification and amidation.

attention during recent years and it has become a conceptually and economically attractive alternative to traditional ester and amide synthesis. The direct formation of ester and amide bonds from aldehydes utilizes readily available starting materials and avoids isolation of free carboxylic acid intermediates, which can be particularly valuable in natural product synthesis when incompatible functionalities or protecting groups are present in the substrate.

In this paper, the variety of one-pot oxidative esterifications and amidations of aldehydes is reviewed and classified based on the underlying concepts and mechanisms. In each case, special attention has been given to mechanistic details, reaction conditions, and substrate scope. Only methods that utilize isolated aldehydes as starting materials and involve an oxidation step are discussed. One-pot transformations of primary alcohols to esters or amides that proceed via an aldehyde intermediate or an activated formyl equivalent are outside the scope of this review.

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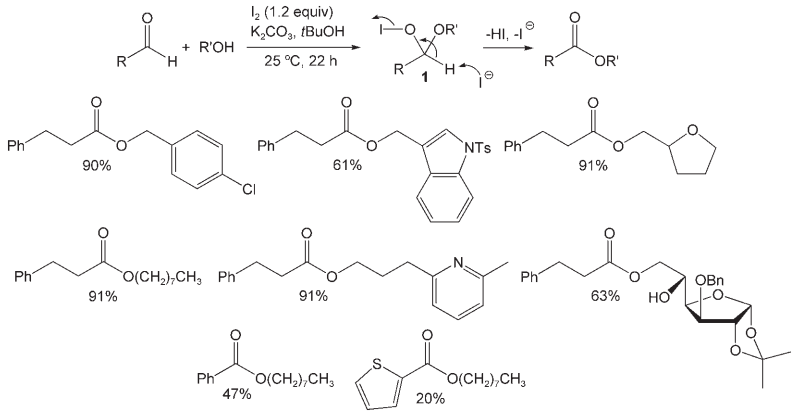
Oxidative Esterification Of Aldehydes

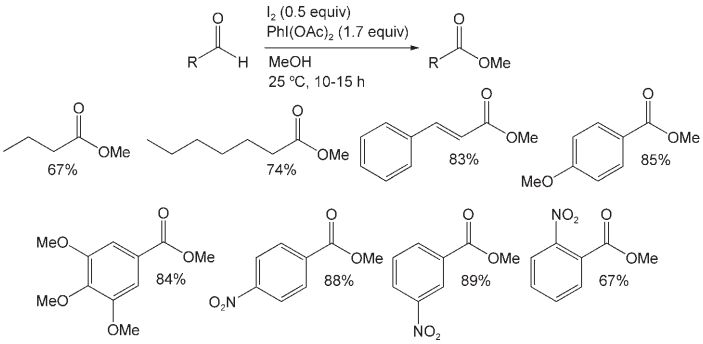
Oxidation of intermediate hemiacetals and acetals: The use of bromine or iodine as mild oxidants in alkaline alcoholic solutions has been inspired by the well-known transformation of aldoses to the corresponding lactones, which was developed in the nineteenth century.[2] Mori and Togo reported that oxidation of a mixture of unbranched aliphatic aldehydes and primary alcohols in the presence of stoichiometric amounts of iodine affords the corresponding esters in up to 91% yield (Scheme 2).[3] The reaction proceeds at room temperature and involves oxidation of an intermediate hemiacetal hypoiodite **1**. This method is quite suitable to multifunctional substrates including carbohydrates bearing a variety of protecting groups, but it is sensitive to steric hindrance; only low to moderate yields are obtained when aromatic aldehydes or secondary alcohols are used.

Some of the limitations described above have been overcome by the use of pyridinium hydrobromide perbromide ($Py{\cdot}HBr_3$) in water[4] or by a combination of iodine and diacetoxyiodobenzene ($PhI(OAc)_2$) in methanol.[5] The latter method is remarkable because it is applicable to aliphatic, α,β-conjugated, and aromatic aldehydes. A range of methyl esters, including benzoates carrying electron-withdrawing and electron-donating groups, have been prepared in good to high yields (Scheme 3).

Oxidation of aldehydes with oxone ($KHSO_5$) or peroxymonosulfuric acid (H_2SO_5) by using primary or secondary alcohols as solvent has been reported to afford esters in high yields.[6] Aliphatic aldehydes react smoothly at room temperature via formation of a hemiacetal, which is then oxidized by a Baeyer–Villiger-type reaction with oxone. By contrast, ester synthesis from electron-deficient aromatic aldehydes can only be accomplished upon heating and the introduction of electron-donating groups to the benzaldehyde



Scheme 2. Mild oxidative esterification in the presence of iodine.

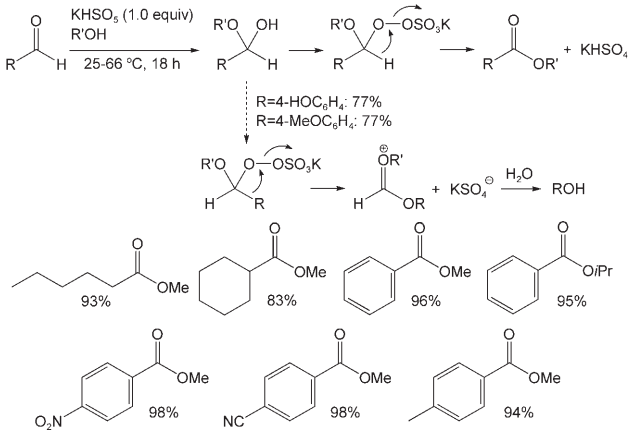


Scheme 3. Oxidative esterification using I_2/PhI(OAc)$_2$ in methanol.

scaffold favors migration of the aryl group over that of hydrogen, thus leading to phenols upon hydrolysis (Scheme 4).

The direct formation of esters from aldehydes through the oxidation of intermediate hemiacetals formed in situ has gained wide popularity and has also been accomplished with several other oxidizing agents, including chromic–sulfuric acid,[7] pyridinium dichromate,[8] hydrogen peroxide,[9] ozone,[10] *N*-iodosuccinimide,[11] sodium hypochlorite,[12] silver carbonate on Celite,[13] 2,3-dichloro-5,6-dicyanobenzoquinone in the presence of amberlyst,[14] sodium metaperiodate,[15] 1,2-dimethylindazolium,[16] and mixtures of methanesulfonic acid and aluminum oxide (Figure 1).[17] A photochemical oxidative esterification that proceeds under an oxygen atmosphere, aerobic oxidation in the presence of supported gold nanoparticles,[18] and an *N*-bromosuccinimide (NBS) oxidation of acetals formed in situ from aldehydes and stannylated alcohols have also been reported.[19]

Similarly, esters are readily available by oxidation of intermediate acetals and several one-pot procedures are known.[20] Rhee and Kim developed a procedure that combines conversion of aldehydes to dimethyl acetals with trimethyl orthoformate and subsequent in situ oxidation of the



Scheme 4. Oxone-mediated conversion of aldehydes to esters by means of a Baeyer–Villiger oxidation.

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Christian Wolf was born in Hamburg, Germany in 1968. He received his Ph.D. under the direction of Prof. Wilfried A. König from the University of Hamburg in 1995. After working as a postdoctoral Feodor-Lynen Fellow with Prof. William H. Pirkle at the University of Illinois in Urbana, he accepted an R&D position at SmithKline Beecham Pharmaceuticals in 1997. In 2000, he began his academic career as Assistant Professor in the Chemistry Department at Georgetown University in Washington, DC, where he was promoted to Associate Professor with tenure in 2006. His research interests comprise stereodynamics of chiral compounds, asymmetric synthesis, stereoselective sensing, chiral recognition, transition-metal-catalyzed cross-coupling reactions, development of antimalarial drugs, and chiral chromatography.

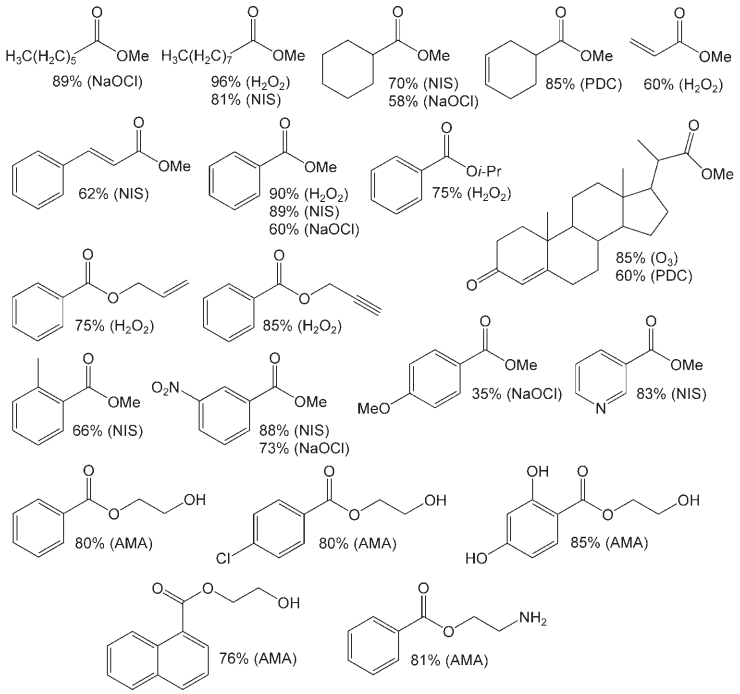
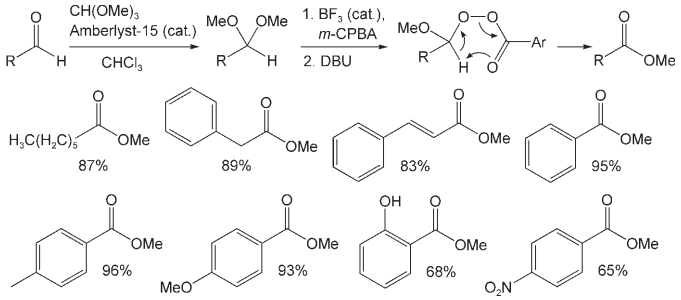
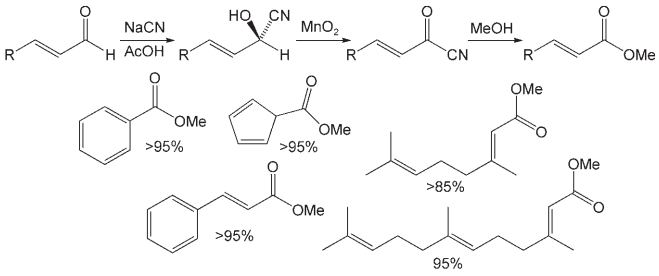


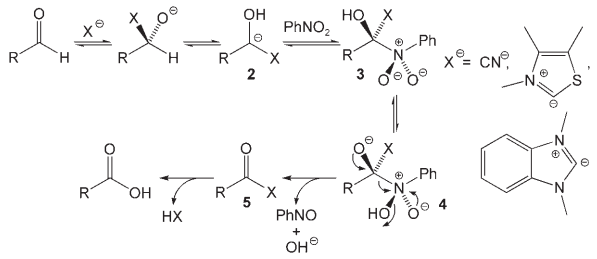
Figure 1. Structures and yields of esters prepared from aldehydes via oxidation of intermediate hemiacetals. The oxidizing agents used are given in parenthesis.



Scheme 5. Conversion of aldehydes to esters via dimethyl acetals.



Scheme 6. Conversion of α,β-conjugated aldehydes to esters through oxidation of intermediate cyanohydrins.



Scheme 7. Mechanism of the oxidative esterification using cyanide or the conjugate base of 3,4,5-trimethylthiazolium and 1,3-dimethylbenzimidazolium iodide as catalyst.

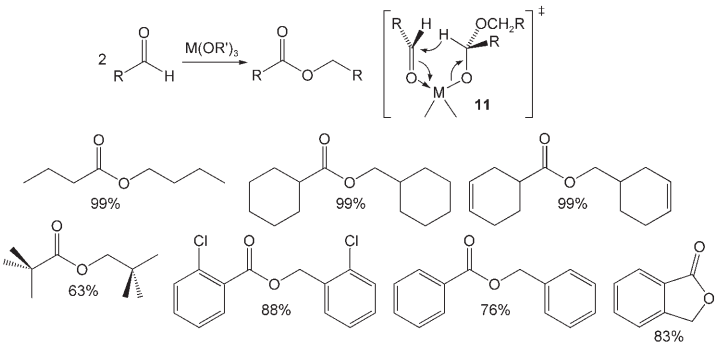
acetal by *m*-chloroperbenzoic acid (Scheme 5).[21] The reaction was found to proceed faster when catalytic amounts of boron trifluoride were used and when a base was added during workup. Noteworthy, this method converts aliphatic as well as electron-deficient and electron-rich aromatic aldehydes to the corresponding methyl esters with 65–96% yield.

Via intermediate cyanohydrins: Corey and co-workers were first to report that conversion of an α,β-conjugated aldehyde to its cyanohydrin with excess of sodium cyanide and acetic acid followed by treatment with manganese dioxide in alcoholic solution provides mild access to the corresponding ester (Scheme 6).[22] This method is not suitable to saturated aldehydes, but it effectively suppresses *cis*/*trans*-isomerization of the conjugated double bond and Corey incorporated this reaction into the synthesis of DL-C18 Cecropia, an insect juvenile hormone.[23]

Castells and Miyashita later showed that this transformation can also be accomplished with catalytic amounts of cyanide,[24] 3,4,5-trimethylthiazolium,[25] and 1,3-dimethylbenzimidazolium salts,[26] respectively. This modified procedure involves oxidation of cyanohydrin-like **2** by nitrobenzene via adducts **3** and **4**; the reaction is accompanied by formation of nitrosobenzene. The resulting strong acylating species **5** then reacts with the alcohol to the desired ester (Scheme 7). The introduction of other acyl halide forming reagents including *tert*-butyl hypochlorite and NBS has further extended the scope of this reaction to aliphatic aldehydes.[27]

Electrocatalytic processes: Electrooxidative transformation of aldehydes to esters has been accomplished in the presence of potassium iodide and sodium cyanide or other mediators.[28] This approach is attractive because it avoids the use

of strong oxidizing agents and sensitive functional groups are generally tolerated under the mild reaction conditions inherent to electrocatalytic oxidation. Following the seminal work of Shinkai,[29] a current-efficient, electrochemical oxidative esterification procedure utilizing catalytic amounts of *N*-benzylthiazolium bromide (**6**) and 3-methyltetra-*O*-acetylriboflavin (**7**) in methanol was described by Diederich and co-workers (Scheme 8).[30] Addition of the thiazolium ylide **8**, which can be generated in situ by deprotonation of **6** with triethylamine, to the aldehyde produces thiazolium-derived intermediate **9**. The electron transfer from **9** to the platinum anode (−0.3 V vs. Ag/AgCl) is then mediated by the acetylated 3-methylflavin **7** and the corresponding 2-acylthiazolium ion **10** finally reacts with methanol to give the desired ester, while **8** is regenerated and available for another catalytic cycle. This procedure was found to furnish methyl benzoates in 54–81% yield under mild conditions, but only up to 20% of aliphatic esters and low turnover numbers were observed when valeraldehyde and cyclohexanecarboxaldehyde were employed. This was attributed to substantial hemiacetal formation which reduces the amount of free aldehyde and thus the rate of aldehyde activation via formation of **9**.



Scheme 9. The Claisen–Tishchenko reaction and products prepared by using aluminum alkoxide catalysts.

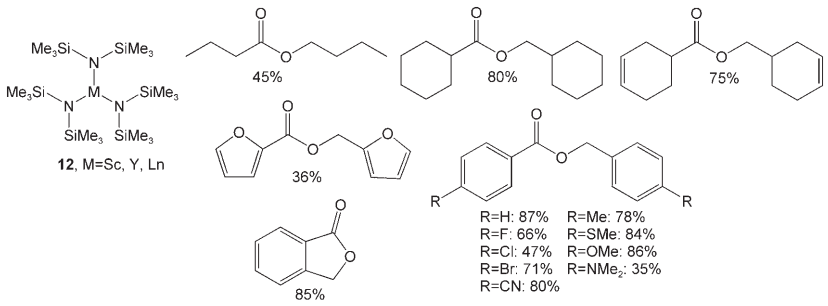


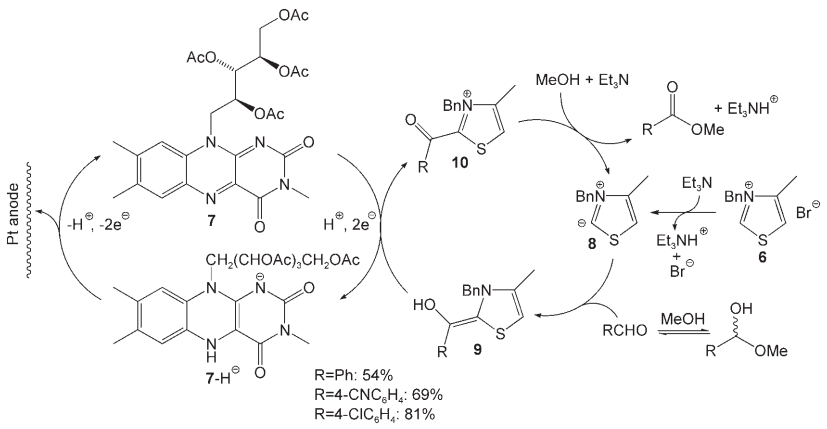
Figure 2. Structures of lanthanide trimethylsilylamide catalysts and esters formed at room temperature.

Tishchenko reactions: The dimerization/disproportionation sequence of aldehydes in the presence of metal alkoxides is generally known as the Claisen–Tishchenko reaction and has been widely used for one-pot synthesis of a wide range of esters.[31] This reaction proceeds via the six-membered transition state **11**, exhibiting a 1,3-hydride shift, and is closely related to the Meerwein–Ponndorf–Verley reduction, the Oppenauer oxidation, and the Cannizzaro reaction (Scheme 9).[32]

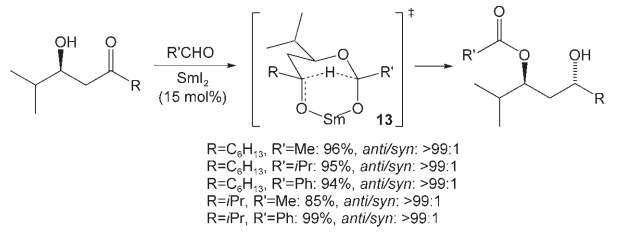
In addition to aluminum and zinc alkoxides,[33] alkaline-earth oxides,[34] lanthanoids,[35] transition-metal complexes,[36] metal hydrides,[37] lithium bromide,[38] lithium tungsten dioxide,[39] and boric acid[40] have been employed as catalysts in the Tishchenko reaction. Lanthanide and alkaline-earth amides **12** show impressive catalytic activity and high turnover under mild reaction conditions albeit isolated yields are low in some cases (Figure 2).[41]

Evans and others have utilized the Tishchenko reaction for diastereoselective samarium-catalyzed preparation of *anti*-1,3-diols from β-hydroxy ketones and aldehydes (Scheme 10).[42] The remarkable asymmetric induction was attributed to efficient chelation control in an activated samarium-derived complex **13** involving coordination of both the aldehyde and the hemiacetal oxygen atoms. The reaction furnishes a series of *anti*-1,3-diol monoesters that proved to be useful precursors of polyketide-derived natural products including (−)-rapamycin.[43]

Because β-hydroxy aldehydes and ketones are readily available aldol condensation products, this reaction has

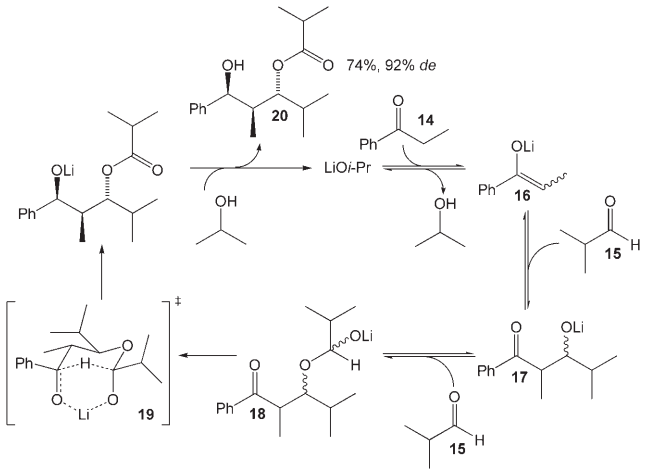


Scheme 8. Electrocatalytic oxidation of aldehydes mediated by a thiazolium ylide and a 3-methylflavin derivative.



Scheme 10. Diastereoselective samarium-catalyzed preparation of *anti*-1,3-diol monoesters.

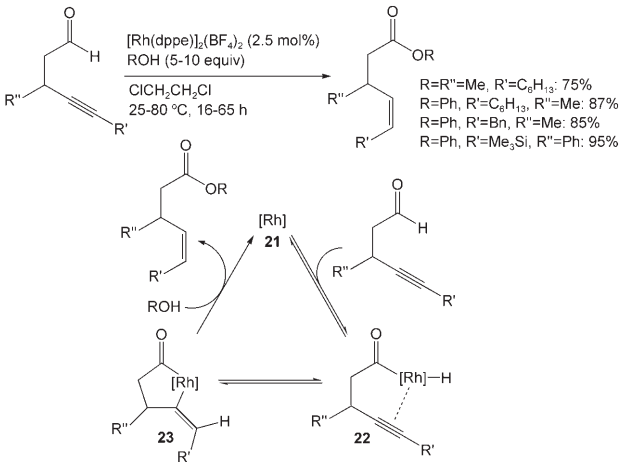
been incorporated into practical crossed-aldol/Tishchenko processes.[44] Morken et al. showed that such a tandem reaction course generates 1,3-diols exhibiting three stereocenters with high stereocontrol when lithium isopropoxide is used as catalyst.[45] A plausible mechanism is shown for the reaction between propiophenone (**14**) and isobutyraldehyde (**15**) (Scheme 11). Initial formation of enolate **16** is followed by



Scheme 11. Mechanism of the tandem crossed-aldol/Tishchenko reaction.

attack at one aldehyde equivalent to form aldol **17**. Acetalization with a second molecule of **15** then gives **18**, which undergoes Tishchenko reaction via transition state **19** to afford diol monoester **20** in 74% yield and 92% diastereomeric excess (*de*).

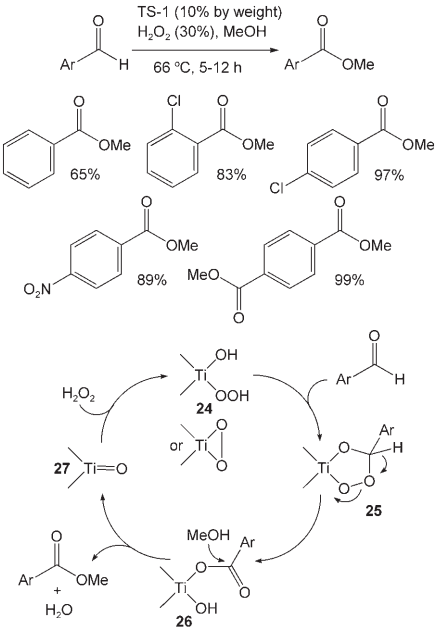
Transition-metal catalysis: In analogy to well-established one-pot procedures for transition-metal-catalyzed dehydrogenation of primary alcohols to esters,[46] a wide range of complexes derived from molybdenum,[47] iron,[48] nickel,[49] ruthenium,[50] rhodium,[51] rhenium,[52] and iridium[53] has been successfully applied to oxidative esterification of aldehydes. An intriguing example is the rhodium-catalyzed conversion of 4-alkynals to alkyl and aryl *cis*-4-alkenoates reported by Tanaka and Fu (Scheme 12).[54] This tandem process couples oxidation of the aldehyde group to a phenol- or methanol-derived ester with stereoselective reduction of the alkyne moiety to a *cis*-alkene. Kinetic studies and deuterium labeling experiments are consistent with a mechanism that involves insertion of rhodium complex **21** into the formyl



Scheme 12. Rhodium-catalyzed formation of methyl and phenyl *cis*-4-alkenoates.

C–H bond of the 4-alkynal. The corresponding rhodium complex **22** then forms the five-membered metallacycle **23**, and irreversible trapping by the alcohol gives the *cis*-4-alkenoate and regenerates **21**.

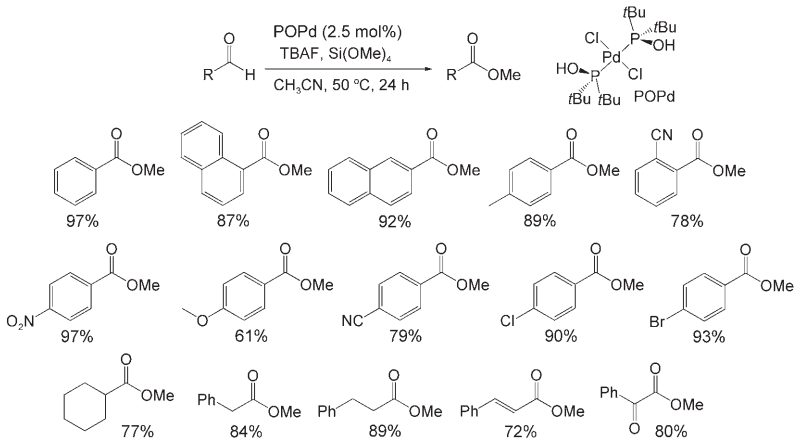
The transformation of aldehydes to esters with hydrogen peroxide in alcoholic solvents can be catalyzed by several agents, including peroxovanadium species[55] and titanium silicates.[56] Chavan and co-workers applied the titanium-containing molecular sieve TS-1 to heterogeneous catalytic oxidation of aromatic aldehydes using 30% H_2O_2 in methanol heated under reflux (Scheme 13). Aromatic esters were isolated in 65–99% yield and the reusable titanium silicate was readily removed by filtration from the product mixture. The use of hydrogen peroxide as the oxidant makes this



Scheme 13. Oxidation of aldehydes using TS-1 and H_2O_2 in methanol (top) and proposed catalytic cycle (bottom).

approach quite attractive because it generates water as the only by-product. However, aliphatic aldehydes produced esters in low yields and anisaldehyde was mainly converted to 4-methoxyphenol, which can be attributed to a side reaction similar to that shown in Scheme 4 for the oxone-mediated transformation of electron-rich benzaldehydes. It was suggested that formation of a titanium hydroperoxide **24** and reaction with the aldehyde generates titanium-derived trioxolane **25** that rearranges to titanium carboxylate **26**. Methanolysis then furnishes the desired aromatic ester and regenerates the titanium silicate **27**.

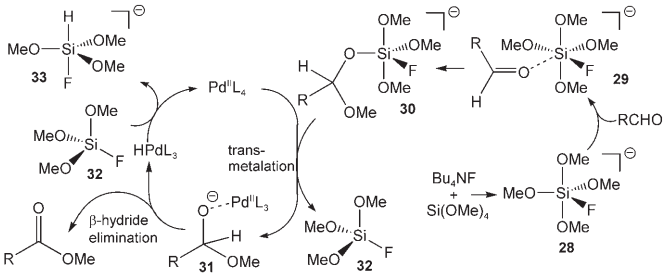
We recently discovered that 2.5 mol% of the palladium-phosphinous acid, POPd, catalyzes formation of methyl benzoate from benzaldehyde in the presence of one equivalent of tetrabutyl ammonium fluoride (TBAF) and phenyltrimethoxysilane at room temperature in 91% yield.[57] Further studies revealed that the reaction proceeds with both aromatic and aliphatic aldehydes in the presence of stoichiometric amounts of less expensive $Si(OMe)_4$ and other orthosilicates in acetonitrile at 50°C (Scheme 14). Under these



Scheme 14. POPd-catalyzed oxidative esterification.

conditions, several aromatic aldehydes gave the corresponding methyl benzoates in up to 97% yield. This procedure is also applicable to aliphatic, α,β-unsaturated and α-keto aldehydes. For example, cyclohexanecarboxaldehyde, 3-phenylpropanal, cinnamaldehyde, and phenylglyoxal were converted to the corresponding methyl esters in 77–89% yield. The POPd-catalyzed oxidative esterification of aldehydes proceeds under mild reaction conditions and has successfully been conducted on the gram scale.

Based on NMR and crystallographic studies, a mechanism for the Pd^{II}-catalyzed one-pot esterification of aldehydes was proposed (Scheme 15). Accordingly, coordination of the aldehyde to a hypervalent silicate species **28** generated from TBAF and tetramethyl orthosilicate facilitates intramolecular transfer of a methoxy group via **29**. The corresponding acetal intermediate **30** then participates in transmetalation to the Pd^{II} catalyst, thus forming fluorotrimethoxysilane and Pd complex **31** that readily undergoes β-hydride elimination

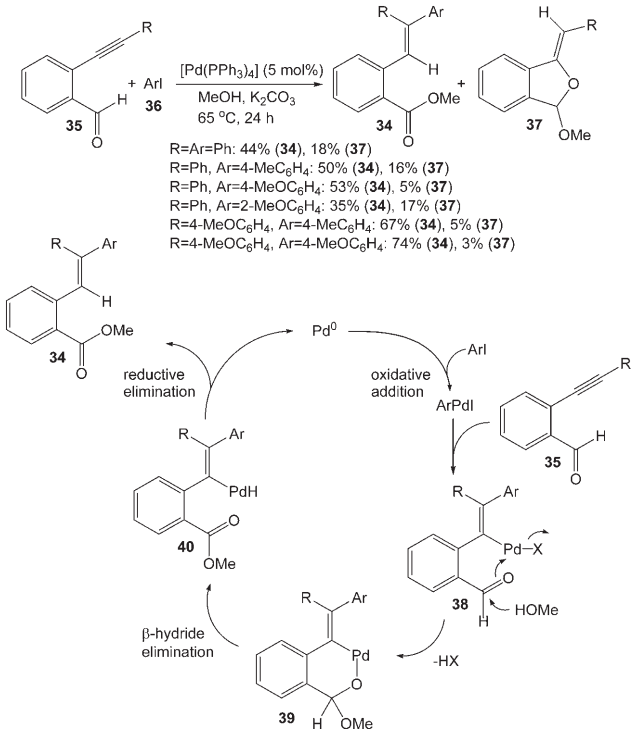


Scheme 15. Pd^{II}-catalyzed oxidative esterification of aldehydes with $Si(OMe)_4$.

to form the desired ester. The hydride is then transferred from the Pd center to fluorotrimethoxysilane **32**, generating $HSiF(OMe)_3$ (**33**) and POPd, which can enter another catalytic cycle. Tetramethoxysilane is apparently involved in several ways in the reaction: it forms a pentavalent siloxane that increases the electrophilicity of the aldehyde substrate, it provides the methoxy group, and it generates the hydride acceptor $SiF(OMe)_3$.

Wu et al. demonstrated that palladium catalysis provides a means to integrate intermolecular C–C bond formation and oxidative esterification into a one-pot procedure.[58] Several methyl 2-vinylbenzoates **34** were prepared through $[Pd(PPh_3)_4]$-catalyzed tandem esterification–hydroarylation of 2-alkynylbenzaldehydes **35** with aryl iodides **36** in methanol. The reaction was found to proceed with high regio- and stereoselectivity, but only moderate to good yields were achieved; this result is partly due to simultaneous formation of isobenzofuran-derived cyclization by-products **37** (Scheme 16). A mechanism that is in agreement with the observed stereochemical outcome and deuterium labeling experiments was proposed. Accordingly, oxidative addition of the aryl iodide to the Pd^0 catalyst is followed by regio- and stereoselective insertion of the alkynylbenzaldehyde to form vinylpalladium species **38**. Addition of methanol to the formyl group, which is probably activated by coordination to the Lewis acidic Pd^{II} center, and deprotonation then generates palladacycle **39**, which undergoes β-hydride elimination to **40**. Finally, reductive elimination of **40** furnishes 2-vinylbenzoate **34** and the free Pd^0 catalyst.

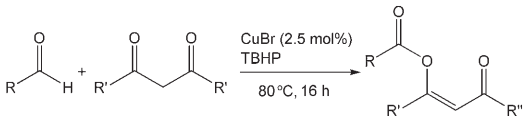
A copper-catalyzed process that utilizes *tert*-butyl hydroperoxide (TBHP) as oxidant to produce esters from aldehydes and β-diketones or β-keto esters, which serve as enolate precursors, has been developed by Yoo and Li.[59] They found that aldehydes undergo stereoselective transformation towards (*Z*)-enol esters in the presence of a β-dicarbonyl



Scheme 16. Palladium(0)-catalyzed synthesis of methyl 2-vinylbenzoates.

compound, 2.5 mol% of CuBr or another copper salt and 1.5 equivalents of TBHP (Table 1). The ability of β-dicarbonyl-derived enolates to form a chelation complex with the

Table 1. Stereoselective CuBr-catalyzed formation of (*Z*)-enol esters.

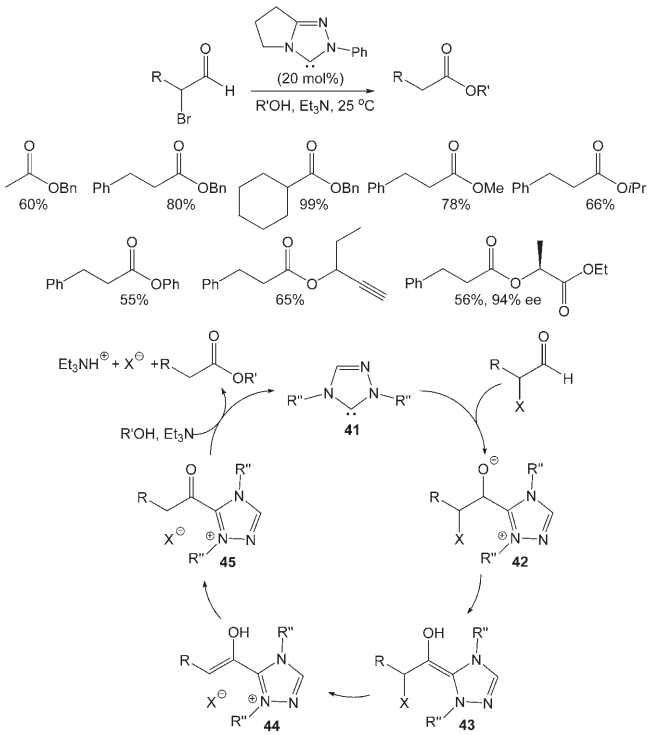


R	R′	R″	Yield
Ph	Me	Me	57 (54)[a]
Ph	Et	Et	80
Ph	Me	OMe	84
Ph	Ph	OEt	86
4-FC_6H_4	Me	OMe	81
4-$MeOC_6H_4$	Me	OMe	81
C_5H_{11}	Me	OMe	72
C_6H_{11}	Me	OMe	80
$CHEt_2$	Me	OMe	89

[a] $CuBr_2$ was used as catalyst.

catalyst proved crucial to the reaction: oxidative esterification using a monodentate cyclic β-diketone was not successful and low yields were obtained with primary alcohols such as *n*-butyl alcohol. Interestingly, the reaction between benzaldehyde and 2,4-pentanedione proceeded with similar yields when CuBr was replaced by $CuBr_2$.

Carbene-catalyzed internal redox reaction and acyl activation of α-functionalized aldehydes: The use of heterocyclic carbenes provides elegant organocatalytic access to esters by means of an internal redox reaction and in situ activation of α-functionalized aldehydes.[60] Rovis' and Bode's groups demonstrated that this approach allows mild conversion of α-halogenated aliphatic aldehydes to the corresponding esters in the presence of catalytic amounts of triazolium-derived carbenes (Scheme 17).[61] It is assumed that this trans-



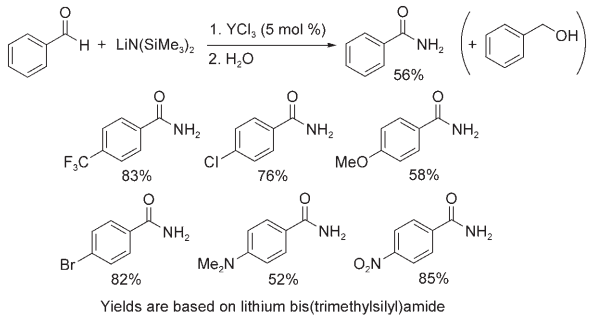
Scheme 17. Carbene-catalyzed conversion of α-bromoaldehydes to esters.

formation involves internal redox reaction of the α-haloaldehyde towards an activated acyl intermediate. The catalytic cycle is initiated by a nucleophilic attack of carbene **41** at the aldehyde, thus generating **42** which forms enol **43**. Subsequent halide elimination then gives enol **44**, which undergoes tautomerization to the activated acyl azolium **45**. Finally, acylating agent **45** is trapped by the alcohol to give the ester, while the catalyst is regenerated. This method produces a wide range of esters derived from either aliphatic alcohols or phenols in good to excellent yields and the reaction generally occurs at room temperature. The same strategy has been applied by several groups to one-pot redox esterification of α,β-unsaturated aldehydes,[62] epoxy aldehydes,[63] and formylcyclopropanes.[64]

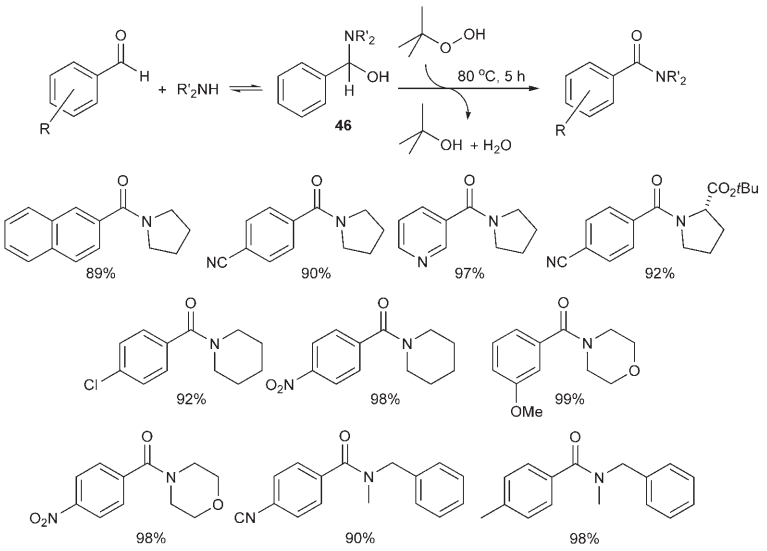
Oxidative Amidation Of Aldehydes

Oxidation of intermediate carbinolamines: In 1966, Nakagawa and co-workers discovered that aromatic and allylic aldehydes can be directly converted to amides in the presence of ammonia and stoichiometric amounts of nickel peroxide.[65] Since then, several groups have developed new methods

suitable to direct conversion of aldehydes to amides using iodine,[66] NBS,[67] and manganese dioxide[68] as oxidizing agents. We recently reported a metal-free oxidative amidation of various aldehydes with secondary amines in the presence of *tert*-butyl hydroperoxide (TBHP) (Scheme 18).[69] In analogy to the oxidative esterification mechanism involving formation of an intermediate hemiacetal discussed above, this reaction probably proceeds via a carbinolamine **46**, which is oxidized by TBHP (Scheme 1). Our procedure avoids the use of additives and expensive transition-metal catalysts and it provides convenient access to a wide range of electron-rich and electron-deficient benzamides in very high yields within 5 h.



Scheme 19. Primary amides prepared by yttrium(III)-catalyzed Cannizzaro disproportionation of aromatic aldehydes.



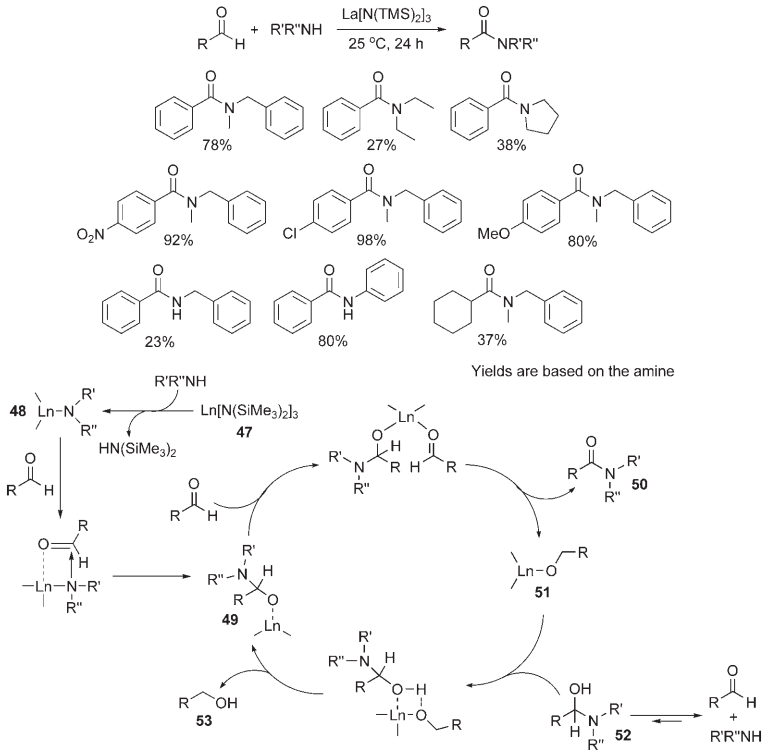
Scheme 18. Metal-free oxidative amidation of aromatic aldehydes with TBHP.

Cannizzaro reactions: The Cannizzaro reaction provides another practical tool for the one-pot transformation of aldehydes to amides and several procedures are known.[70] Excellent results have been accomplished with benzaldehyde derivatives simply by treatment with alkaline amides, but yields are usually low when enolizable aldehydes are used. In particular, lanthanide complexes have been found to catalyze the Cannizzaro reaction. For example, Wang and coworkers showed that yttrium trichloride catalyzes the oxidative amidation of aldehydes at room temperature and primary amides were obtained in good yields from electron-deficient benzaldehyde derivatives (Scheme 19).[71] A major drawback of this disproportionation reaction is the inherently low atom economy, because only 50% of the aldehyde substrate is oxidized and incorporated into the amide structure, while the other half is concurrently reduced to the corresponding primary alcohol. Yields reported in the literature are therefore generally based on the amine source used.

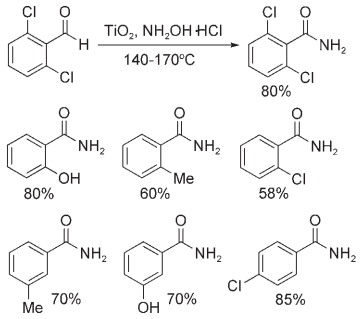
Very recently, Seo and Marks discovered that lanthanide amido complexes effectively catalyze the formation of secondary and tertiary amides (Scheme 20).[72] It was suggested that protonation of $[Ln\{N(Si(Me_3)_2\}_3]$ (**47**) by a primary or secondary amine generates complex **48**, which reacts with the aldehyde to the carbinolamine-derived lanthanide complex **49**. Coordination of a second aldehyde then results in disproportionation to amide **50** and alkoxide **51**, which undergoes ligand exchange with carbinolamine **52** to produce one equivalent of the primary alcohol **53**, while **49** is regenerated. This reaction proceeds with 5 mol% of the catalyst at room temperature, but lanthanide amido complexes are very water-sensitive. Low yields were obtained when diethylamine, pyrrolidine, or benzylamine were used and with cyclohexanecarboxaldehyde, which may be attributed to competing aldol and Tishchenko reactions.

Beckmann rearrangements: The Beckman rearrangement of ketoximes has been known for a long time and utilized for the formation of amides and lactams. When aldehydes and hydroxylamine are employed, this reaction provides an interesting alternative to other one-pot syntheses of primary amides, albeit harsh conditions are generally required. Sharghi et al. demonstrated that aldehydes and hydroxylamine hydrochloride undergo Beckmann rearrangement in the presence of zinc oxide,[73] alumina sulfuric acid,[74] and titanium dioxide.[75] A range of primary benzamides has been obtained in good to excellent yields using two equivalents of TiO_2 at 140–170°C under solvent-free conditions (Scheme 21). In comparison to *ortho*- and *meta*-substituted benzaldehydes, *para*-substituted substrates give superior results, which can be explained by the faster rearrangement rates of the corresponding aldoximes.[76]

A different mechanism is probably involved when aldehydes and hydroxylamine hydrochloride are treated with



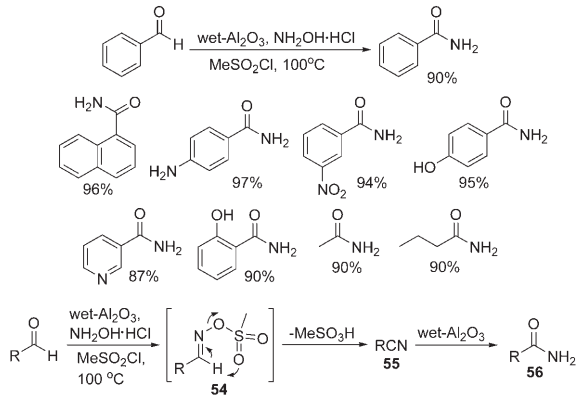
Scheme 20. Scope and mechanism of the oxidative amidation catalyzed by a lanthanide amido complex.



Scheme 21. Titanium dioxide-catalyzed Beckmann rearrangement.

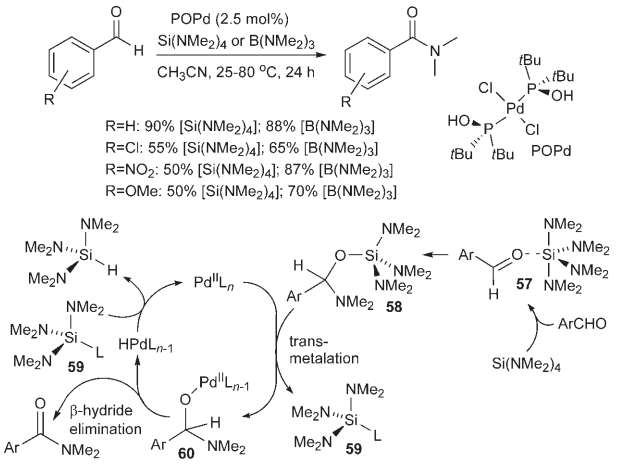
methanesulfonyl chloride and wet alumina.[77] This reaction proceeds at 100 °C and affords aliphatic, aromatic, and heterocyclic primary amides in high yields (Scheme 22). Initial aldoxime formation is probably followed by reaction with methanesulfonyl chloride to adduct **54**. This intermediate then undergoes thermal elimination via a six-membered transition state to nitrile **55**, which shows rapid hydration in the presence of wet alumina to give amide **56**. The reaction provides convenient and efficient access to primary amides and amino, hydroxyl and nitro groups are tolerated.

Transition-metal catalysis: Following the pioneering work of Yoshida, several transition-metal-catalyzed transformations of aldehydes to amides and *N*-sulfonylcarboxamides have been reported to date.[78] Similar to the palladium-phosphinous acid catalyzed oxidative esterification of aldehydes in the presence of tetraalkyl orthosilicates described above, we have found that tetrakis(dimethylamino)silane and tris(dimethylamino)borane are suitable for direct oxidative amidation.[69] The reaction occurs in the presence of 2.5 % of POPd at ambient temperatures and produces *N,N*-dimethyl benzamides in good yields when tris(dimethylamino)borane is used. The mechanism for this reaction probably follows that of the POPd-catalyzed oxidative esterification, that is, tetrakis(dimethylamino)silane and tris(dimethylamino)borane serve as both dimethylamino donor and hydride acceptor (Scheme 23). Coordination of the aldehyde to the borane or silicon reagent is expected to produce a hypervalent silicate species, **57**, which undergoes intramolecular transfer of a dimethylamino group to form *N,O*-acetal **58**. Transmetalation to the Pd^{II} catalyst then furnishes silane **59** and Pd complex **60**. Finally, β-hydride elimination forms the benzamide and the hydride is transferred from the Pd center to **59** to regenerate the active catalyst.

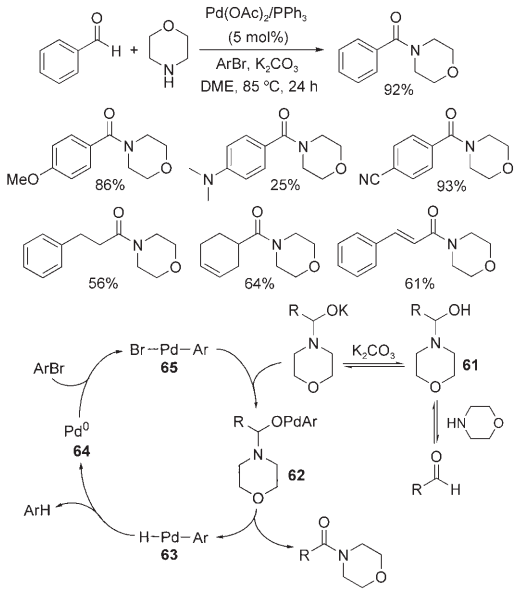


Scheme 22. Solvent-free formation of primary amides.

Another palladium-catalyzed method using an aryl bromide as oxidant was developed by Yoshida's group.[79] Moderate to excellent yields of morpholine-derived aliphatic and aromatic amides were obtained when $Pd(OAc)_2$, triphenylphosphine, and stoichiometric amounts of bromobenzene or 2,4,6-trimethylbromobenzene were employed in 1,2-dimethoxyethane heated under reflux for 24 h (Scheme 24). It was proposed that the aldehyde and morpholine react to carbinolamine **61**, which forms the alkoxypalladium complex



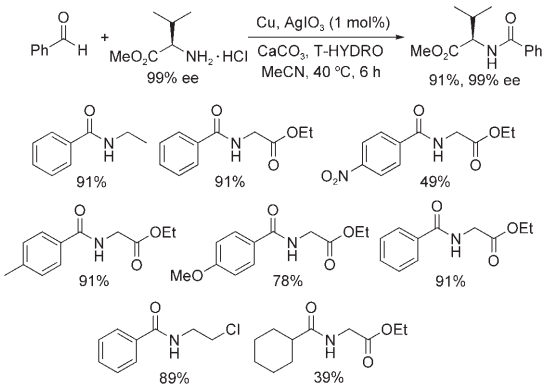
Scheme 23. POPd-catalyzed benzamide formation.



Scheme 24. Pd-catalyzed oxidative amidation using an aryl bromide as oxidant.

62. Elimination of the amide generates hydridopalladium species **63** and reductive elimination gives Pd^0 complex **64** that readily undergoes oxidative addition with the aryl halide oxidant towards **65**. The low yield obtained with 4-dimethylaminobenzaldehyde was attributed to an unfavorable aldehyde–hemiaminal equilibrium and aliphatic aldehydes generally gave lower yields compared to benzaldehyde derivatives due to competing aldol condensation.

More recently, Yoo and Li introduced a copper-catalyzed procedure that is most useful for oxidative amidation of aromatic aldehydes with amine hydrochlorides. Best results were obtained using aqueous *tert*-butyl hydroperoxide (T-HYDRO) in acetonitrile and when catalytic amounts of $AgIO_3$ were added.[80] The reaction proceeds at ambient temperature and the transformation of benzaldehyde with (*R*)-valine methyl ester hydrochloride gave a chiral amide in 91% yield without any sign of racemization (Scheme 25).

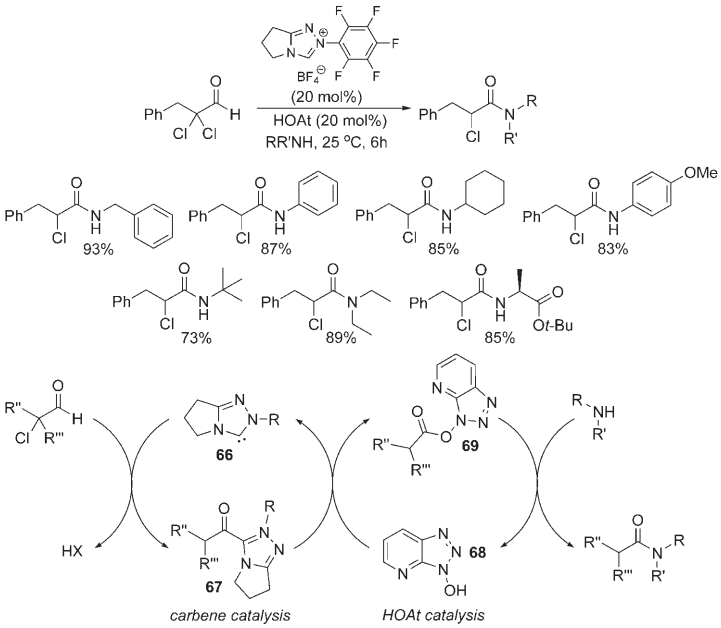


Scheme 25. Copper-catalyzed oxidative amidation of aldehydes with amine hydrochlorides using *tert*-butyl hydroperoxide as oxidant and silver iodate as cocatalyst.

Organocatalysis with *N*-heterocyclic carbenes: The increasing use of *N*-heterocyclic carbenes in organocatalytic reactions has led to the discovery of internal redox processes converting a series of α-functionalized aldehydes to amides, lactams, and imides.[61a,81] Vora and Rovis observed that 2,2-dichloro-3-phenylpropanal and benzylamine give the corresponding amide in 93% yield when catalytic amounts of nucleophilic *N*-heterocyclic carbene **66** are employed in conjunction with 1-hydroxy-7-azabenzotriazole (HOAt) which is a well-known coupling agent commonly applied in peptide synthesis.[82] The reaction proceeds at room temperature and furnishes secondary amides in good to high yields within 6 h. This approach is conceptually similar to the carbene-catalyzed oxidative esterification described above. Accordingly, a mechanism involving the formation of acyl azolium intermediate **67** through an internal redox reaction followed by acyl transfer to HOAt (**68**) and subsequent trapping of **69** with a primary or secondary amine was postulated (Scheme 26). Importantly, this method has been extended to α,β-epoxy and α,β-aziridino, and conjugated aldehydes (Table 2).

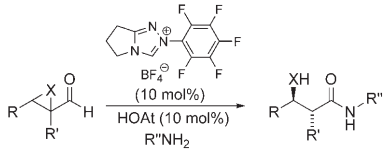
Bode and Sohn applied a similar *N*-heterocyclic carbene and stoichiometric amounts of imidazole to the redox amidation of α,β-conjugated aldehydes and formylcyclopropanes (Table 3).[83] A wide range of substrates bearing nitro, ester, and ketone functionalities was converted to secondary and tertiary amides under mild conditions.

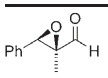
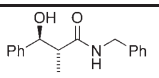
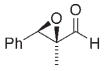
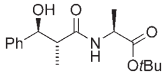
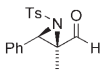
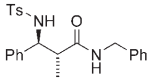
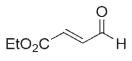
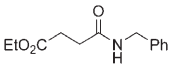
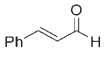
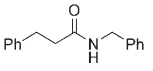
Oxidative homologation: Zhu et al. have shown that primary and secondary amides can be prepared by oxidative one-carbon homologation of both aliphatic and aromatic aldehydes (Scheme 27).[84] This three-component reaction utilizes potassium α-4-methoxyphenyl-α-isocyano acetate (**70**) as the donor of the amide function, while dimethylamine promotes several steps resulting in chain elongation and internal redox reaction. For example, *N*-acyl-α-imino



Scheme 26. Nucleophilic carbene and HOAt relay catalysis.

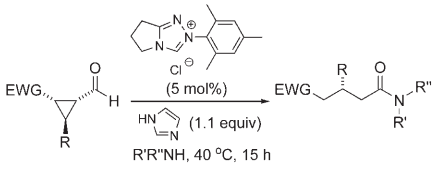
Table 2. Oxidative amidation of α,β-epoxy, α,β-aziridino, and conjugated aldehydes.

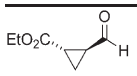
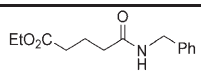
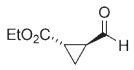
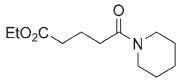
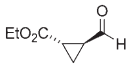
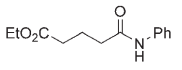
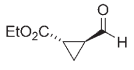
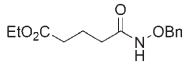
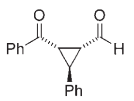
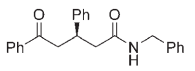
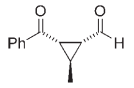
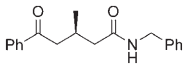
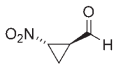
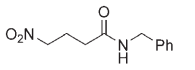


Substrate	Product	Yield	dr
		86	>19:1
		75	15:1
		72	>19:1
		80	/
		82	/

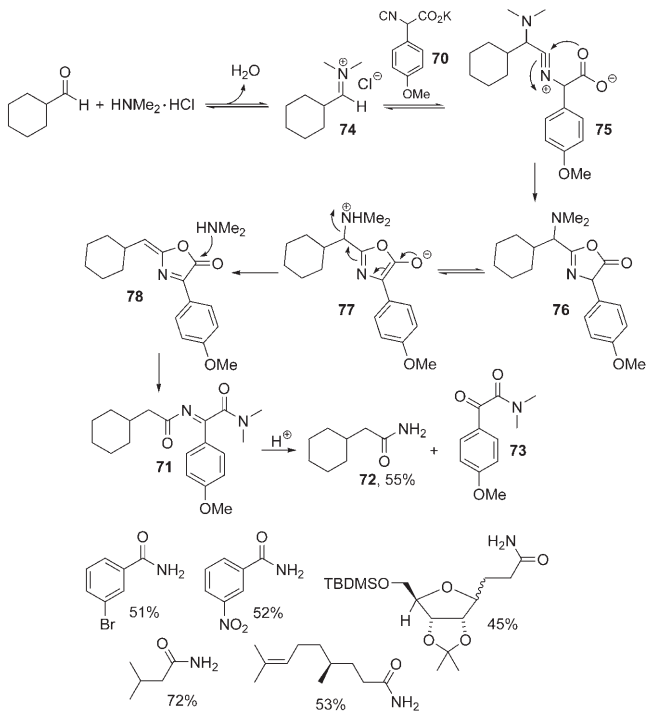
amide **71** was obtained from cyclohexanal and directly converted to amide **72** and keto amide **73** upon acidic workup. It has been hypothesized that nucleophilic attack of isonitrile **70** at iminium **74** gives isonitrilium intermediate **75**, which forms oxazolone **76**. Tautomerization to **77** would then be followed by 1,6-elimination of the ammonium moiety to give **78**. Ring-opening through attack of dimethylamine at the carbonyl function completes the reaction sequence and produces **71**, which undergoes hydrolysis to amides **72** and **73**. It is worth noting that (*S*)-citronellal was transformed to the corresponding primary amide in 53% yield and without any sign of racemization.

Table 3. Oxidative amidation of formyl cyclopropanes.



Substrate	Product	Yield[a]
		88
		74
		70
		53
		81
		83
		54

[a] Based on the amine used.



Scheme 27. One-carbon homologation of aldehydes to amides.

Conclusion and Outlook

Although direct transformations of aldehydes into esters or amides have been known for a long time, the development of one-pot procedures that integrate oxidation and either C–N or C–O bond formation into a single operation has only recently regained significant interest. As a result, a rapidly increasing number of methods exhibiting complementary substrate scope and chemoselectivity is now available. A major advantage of the oxidative amidation and esterification routes developed to date is that they provide efficient and fast access to amides and esters from a wide range of aldehyde substrates under mild conditions, while isolation of carboxylic acid intermediates is unnecessary. This approach is expected to prove invaluable for the synthesis of complex compounds carrying functional groups that are not stable in the presence of carboxylic acids or incompatible with reaction conditions inherent to classical amide and ester formation.

Several groups have realized that oxidative amidation and esterification processes provide unique synthetic opportunities that can be exploited in tandem reactions. A prime example is Zhu's oxidative chain elongation of aldehydes with potassium α-4-methoxyphenyl-α-isocyano acetate in the presence of dimethylamine. The increasing number of transition-metal-catalyzed procedures and the introduction of *N*-heterocyclic carbenes to one-pot conversion of α-functionalized aldehydes towards amides and esters provide intriguing possibilities for the coupling of redox processes with either C–N or C–O bond formation. It is likely that similar methods incorporating oxidative amidation or esterification into multicomponent reactions will emerge in the near future.

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