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A Novel Approach to the Palladium catalyzed the one-step design asynthesis of alpha ketoamide.

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ABSTRACT- The acyclic keto-amide has multiple reactive centers with electrophilic and nucleophilic characteristics. This methodology has a broad substrate scope (aromatic amines and aliphatic amines) and opens up an exciting and appealing avenue for synthesizing a-ketoamide derivatives. Alpha ketoamide is produced in a single step from Aromatic derivatives and amines amidated using palladium catalysis. This review concentrates on synthesizing alpha ketoamide in a single step and its mechanistic studies**.**

Keyword- Palladium catalysis, amidation of amines and mechanistic studies.

I. INTRODUCTION-

α-Keto amide is an essential building block in biology and synthetic organic chemistry. Based on the potential biological properties of α-keto amide-containing molecules, one of the main components of natural products and biologically significant compounds is alpha-keto amides and their derivatives ([1]anti-viral including anti-HIV anti-tumor, anti-inflammatories including anti-IBD,[2] anti-bacterial5)—the creation of synthetic preparation techniques for alpha-keto amides and their use in organic compounds and medicinal chemistry.[3,4] Several processes, such as alkylation, arylation, acylation, nucleophilic addition at the carbonyl group, chemo-selective reduction (hydrogenation), and oxidation, are carried out on alpha-keto amides. The amide can be a handle for asymmetric catalysis Michael reaction [5,6]and a reactivity moderator.[7] Additionally, appropriately substituted α-keto amides engage in many classical reactions, including Michael[8-10]iso-Pictet-Spengler,[11]Mannich, Stetter, and others, to produce a wide range of valuable intermediates and finished compounds.[12] The varied reactivity of α-keto amides has been further studied to synthesize various compounds. Numerous research articles on the synthesis of α-keto amides can be found after thoroughly investigating the scientific literature. However, when we began this research, we only found one review paper that dealt with the synthesis of α-keto amides.[13] A thorough overview of the synthesis of keto amides was just published—recently discovered aerobic oxidative processes using molecular oxygen present particularly alluring methods for dealing with α-keto amides. The oxidative amidation-diketonization of terminal alkynes,[14] the coupling of aryl acetaldehydes and aryl methyl ketones with amines, the oxidative amidation-diketonization of terminal alkynesarylacetamides directly oxidized,oxidative aminations of hetero aryl[15] and 2,2-dibromo-1-aryl ethanes compunds[16-18] alpha-arylamino amides undergo oxidative cleavage in Aerobic oxidative coupling of aryl methyl ketones with formamides[19]. Aerobic oxidative cross dehydrogenative coupling (CDC) of amines with alpha-carbonyl aldehydes[20], and C=C bond activation of enaminones Even though, Cu(I) catalyzed synthesis of α-Ketoamides in neat conditions[21] was reported previously, versatile organic compounds, and are easily transformed to different functional groups. Ketones can undergo oxidative transformations by Pd[22], and photocatalysis [23]. Due to the ready availability of the starting materials, the use of carbon monoxide as a direct source of carbonyl functionalities, and the use of molecular oxygen (O2) or air as the alkene terminal oxidant, the following two approaches, namely double amino-carbonylation and oxidative amidation, have received much more attention and have been extensively studied among the various catalytic methods of alpha-ketoamide formation.

Scheme. 1 single-step synthesis of alpha-ketoamide. Drug molecules [24,25] contain α-keto amide moieties thrombin inhibitor[26,] cathepsin k inhibitor[27],[28] HIV protease inhibitor[29,30]telaprevir[31], Cytokine inhibitor[32], Varespladib[33,]histone

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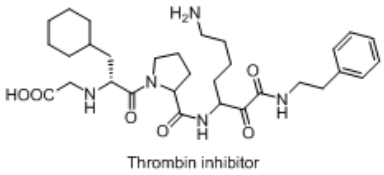
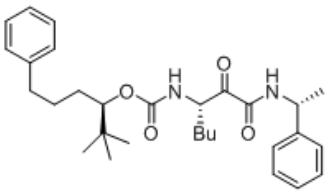
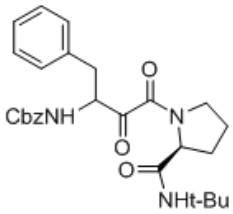
deacetylase inhibitor[34], and Boceprevir35.And Inhibitors of Coronavirus and Enterovirus Replication[36].



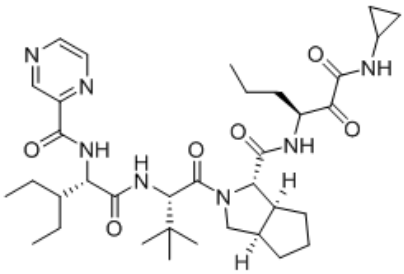
Thrombin inhibitor

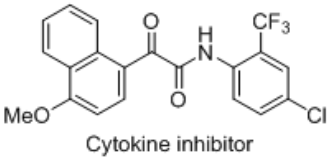


cathepsin K inhibitor

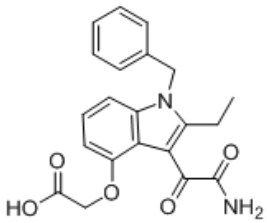


HIV protease inhibitor

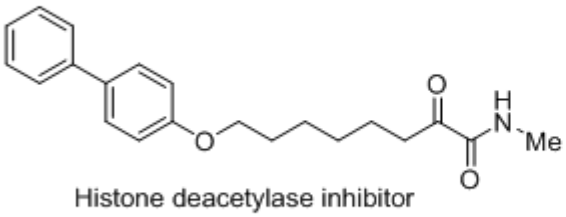

Telaprevir



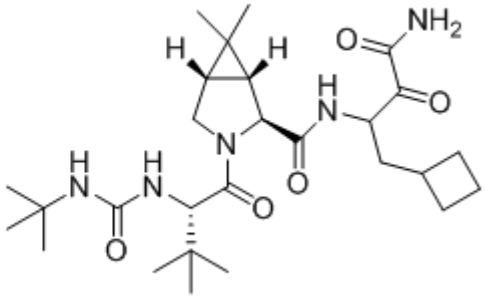
Cytokine inhibitor



Varespladib



Histone deacetylase inhibitor



Boceprevir

It is used to synthesize organic compounds; copper catalysis has earned a reputation as a potent tool. It is one of the most affordable and plentiful metals and has a variety of oxidation states that can be used in catalytic cycles. These include Cu(0), Cu(I), Cu(II), and Cu (III) enable, ing one-electron or two-electron processes for its action. As a result, strong two-electron reactions and radical pathways are feasible to produce bonds are possible. Bond-forming pathways could take place. These characteristics enable copper to catalyze the oxidationnumber of substrateoxidation and oxidative coupling remarkable range of applications.Direct C-Hfunctionalization is possible through copper-catalyzed aerobic oxidative cross-coupling, which can also effectively create an effective method for creating C-C and C-X (X = N/O/S) bonds. With oxygen acting as a stoichiometric oxidant, reactions can occurinn the open air or in an O2 atmosphere. O2 is reduced to water or H2O2, which is less toxic than other oxidants**.**

α-Ketoamides syntheses under palladium catalysis

Palladium-catalyzed double carbonylation is a prominent catalytic strategy for the production of alpha-ketoamides. It works as a catalyst in palladium-catalyzed cross-coupling. Individual carbon atoms are "encouraged" and "allowed" to react. Catalysts are used to initiate or accelerate a wide range of chemical reactions, running from manufacturing processes to chemical reactions in our bodies. Pd-Pd-catalyzed doss-coupling methods

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have emerged as critical catalysts for the creation of bonds between carbon atoms and heteroatoms.Cross-coupling chemistry has been extensively used in the discovery, development, and marketing of novel medications during the last three decades. Completion among several Pd-catalyzed cross-coupling procedures, as well as decarboxylative, carbonylative, alpha-arylative, and carbon-nitrogen reactions. These include Heck reaction Negishi, Sonogashira, Suzuki, and Stille reactions.

Palladium catalysis plays a crucial role in the synthesis of Active Pharmaceutical Ingredients (APIs). It enables the construction of complex molecular structures with high efficiency and precision. Cross-coupling reactions, a common application of palladium catalysis, facilitate the creation of key bonds in the synthesis of drug molecules. This method allows chemists to assemble diverse building blocks, contributing to the development of novel and targeted pharmaceuticals. Suzuki-Miyaura cross-coupling, palladium catalysis enables the coupling of boron-containing compounds with aryl or vinyl halides. This reaction is widely utilized for synthesizing biaryl compounds, a common structural motif in pharmaceuticals.

Heck coupling involves the palladium-catalyzed coupling of aryl or vinyl halides with olefins. This versatile reaction is valuable for constructing carbon-carbon bonds in the synthesis of complex molecules, including many pharmaceuticals

palladium-catalyzed synthesis of alpha-keto amides, the use of isocyanides and amines as starting materials provides a versatile platform for constructing diverse molecular structures. The process is often employed in the context of multicomponent reactions, allowing for the simultaneous incorporation of different functional groups into the final product.Key steps in this synthesis include:

Activation of Isocyanide:
The palladium catalyst activates the isocyanide, making it reactive towards nucleophilic attack.
Amination:The amine reacts with the activated isocyanide, forming an amidine intermediate. This step is crucial for introducing the nitrogen functionality.
Oxidative Insertion:The amidine undergoes oxidative insertion into the palladium center, forming a palladium amidinate complex.
Reductive Elimination:Reductive elimination from the palladium amidinate complex results in the desired alpha-keto amide and regenerates the palladium catalyst in organic synthesis.
The Buchwald-Hartwig amination, a palladium-catalyzed process for carbon-nitrogen bond formation, has several key features:

Catalyst System:Typically employs a palladium(II) source, a phosphine ligand, and a base. Common ligands include triphenylphosphine (PPh3) and biaryl phosphines such as BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl).

Reaction Mechanism:
Oxidative Addition: Palladium inserts into the aryl halide, forming a Pd(II) complex.
Transmetallation: The amine coordinates with the Pd(II) complex, leading to the formation of a Pd(II) amido intermediate.
Reductive Elimination: The carbon-nitrogen bond is formed, and the palladium catalyst is regenerated.
Scope and Selectivity:Compatible with a wide range of aryl halides and amines, providing access to various aryl amines.Exhibits excellent regioselectivity and chemoselectivity.
Applications:
Widely used in the synthesis of pharmaceuticals, agrochemicals, and other fine chemicals.
Enables the efficient construction of complex molecules due to its versatility and efficiency.
Mild Reaction Conditions:Typically conducted at moderate temperatures and under relatively mild conditions, allowing for the incorporation of various functional groups.
Overall, the Buchwald-Hartwig amination is a powerful tool in organic synthesis, contributing to the rapid and selective formation of carbon-nitrogen bonds. Its broad applicability has made it a cornerstone in the development of diverse organic compounds.
applications in the synthesis of various organic compounds. Some notable applications include:
Pharmaceuticals:
Crucial in the synthesis of pharmaceutical intermediates and active pharmaceutical ingredients (APIs).
Enables the efficient construction of aryl amine motifs, which are prevalent in many drug molecules.
Agrochemicals:
Used in the synthesis of agrochemicals and crop protection agents.

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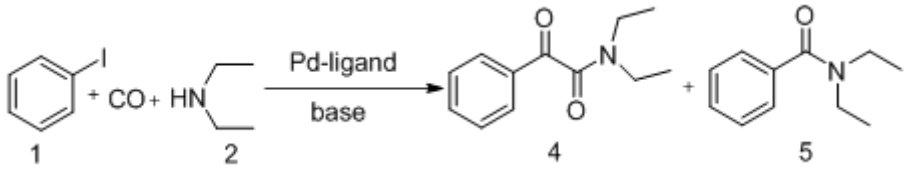
Provides a versatile method for introducing specific nitrogen functionalities into target molecules.
Materials Chemistry:
Valuable in the synthesis of organic materials and polymers.Allows for the creation of functional materials with tailored properties.Fine Chemicals and Specialty Compounds:Applied in the production of various fine chemicals, flavors, and fragrances.Useful for generating compounds with specific structural features required in specialty industries.
Biologically Active Compounds:Facilitates the preparation of biologically active compounds for research and development purposes.Enables the synthesis of molecules with diverse biological activities.

Pd-Catalyst for Amino Di-carbonylation of Aryl Halides for alpha-Ketoamide Synthesis with Hemilabile P, C-Hybrid Ligand[70]Ye Liu, and their group proposed the synthesis of alpha-ketoamide from the amino di-carbonylation of aryl halides 1 affording α-ketoamides with Pd catalysts(Pd (II)-complex).



Scheme 1. Synthesis of alpha-ketoamide from the iodophenyl and amines by Pd.

Scheme 2 illustrates a method for carbonylationof phenyl iodides with an amine group over a Palladium catalyst that contains various phosphines. An active Pd(0)-intermediate is produced by the immediate reaction of PdCl2(MeCN)2 with di-phosphine ligands in the Carbon and Oxygen environment.In process I, complex intermediate 7 is readily formed when L4 is used as a better precursor to a hemilabile P, Chybrid ligand. The P, C-hybrid ligand in question demonstrates the hemilabile "coordination dissociation" property. To create intermediate 6b, which can irreversibly separate the labile PPh2 fragment and enable the amine to produce intermediate 6c after HI scavenging by K2CO3 and concurrent CO-coordination in cycle 2, AriI immediately oxidatively adds the true active catalyst, complex intermediate 7.Following CO incorporation into the Palladium with Aromatic derivative bond and the 2nd carbon mono-oxide coordination, 8 is quickly transformed into the acyl-palladium complex intermediate 10. The desired alpha-ketoamide was created by that of the reductive combination of two carbonyl substituent along with catalyst 7 renewal through continuous migration and formation of the coordinated Carbon mono oxide into the Palladium nitrogen bond. 6 stabilised intermediate 6 is easily added by AriI to yield intermediate B′ when there is a greater concentrate of amine substrate present. In this precursor, the dissociation about one PPh2 remnant as from Palladium canter embraces the amine substrate is found to suppress because of the helpful pincer-type complexation. Due to aa, 7 changes into 6a′, which causes I to transfer ligands with carbon monooxide. When CO is introduced into the Palladium-Aryl bond and the amine substrate is coupled at the same time, 6b is transformed into the acyl-palladium intermediate 6c. 6c eventually yields the amide by reductive elimination because repeated carbon mono-oxide insertion into the Pd-CO bond in 6c is not conceivable

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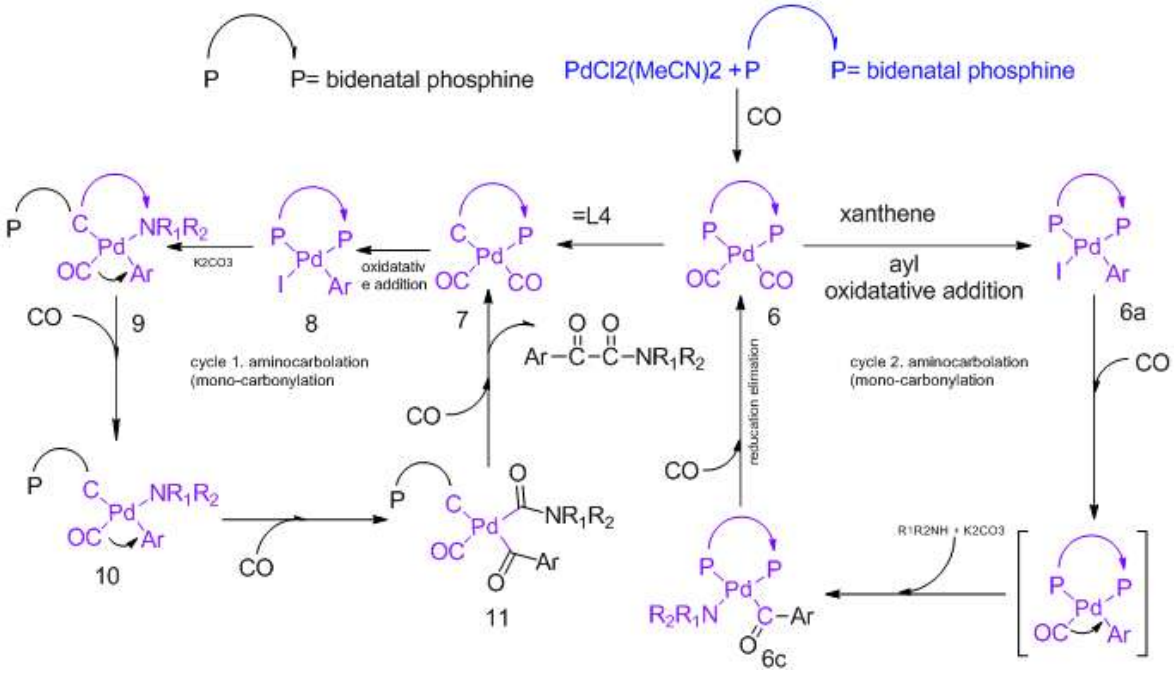
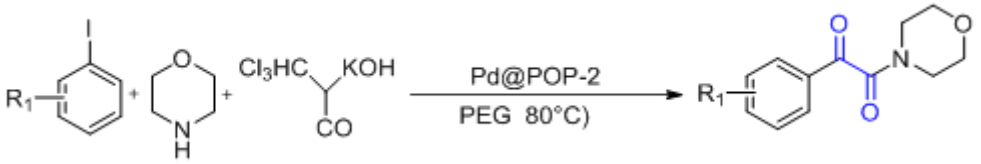


Scheme 2. Phenyl halides were catalyzed to undergo an amino carbonylation reaction with primary amines to create alpha-ketoamides.

Using CHCl3 as the CO, POP-Palladium(II) accelerated simple and secure in-situ carbonylation to produce alpha-keto amides from secondary cyclic amines, Kaushik Ghosh, Manirul Islam[71] and colleagues developed a novel type of catalyst used to manufacture alpha-ketoamide. The reconditioning converts aromatic iodides to their corresponding alpha-keto amides. For the purpose of in situ double carbonylation, KOH was utilised as a standard base and PEG(600) as a solvent. To produce the selective alpha-keto amides, too much base and chloroform were used. The heterogeneous reaction was conducted in a sealed tube for 16 hours at 80 °C with chloroform acting as an external source of CO. scheme 3.



Scheme 3. Synthesis of alpha ketoamide from the aromatic iodides and morpholine by using Pd catalysis.

Preparation of catalyst:

Pd@POP-2 (50 mg/2.3 mol%), 8–20 hours, and Poly-ethylglycol–600 (4 ml). the isolated alpha-ketoamide yield. grafted onto a porous organic polymer (POP-2) catalyst was a novel Pd(II) catalyst. Alpha-keto amides are produced by carbonylation using the reusable heterogeneous catalyst, which has undergone thorough investigation and evaluation.

After mixing toluene imidazole (6.8 gm) and KI (0.1 gm) in 5 mL of Nan 2 atmosphere, the reaction liquid was heated to 400 ° C. After about 30 minutes, CH3ONa (5.4 gramme) in 10 ml of CH3OH was added drop by drop while being constantly stirred to produce imidazole salt.Chloromethylated polystyrene (1.8 gm) was mixed with sodium imidazole solution in 15 ml acetonitrile. After that, the solution was continually agitated at 650°C for 48 hours. The imidazole functionalized polystyrene beads were rinsed with ethanol and dried at 400 degrees Celsius. The reaction mixture was prepared with ml of Nan 2 atmosphere. Heating in a CH3CN (ACN) solvent for two and a half hours at 1100 C degree celsius

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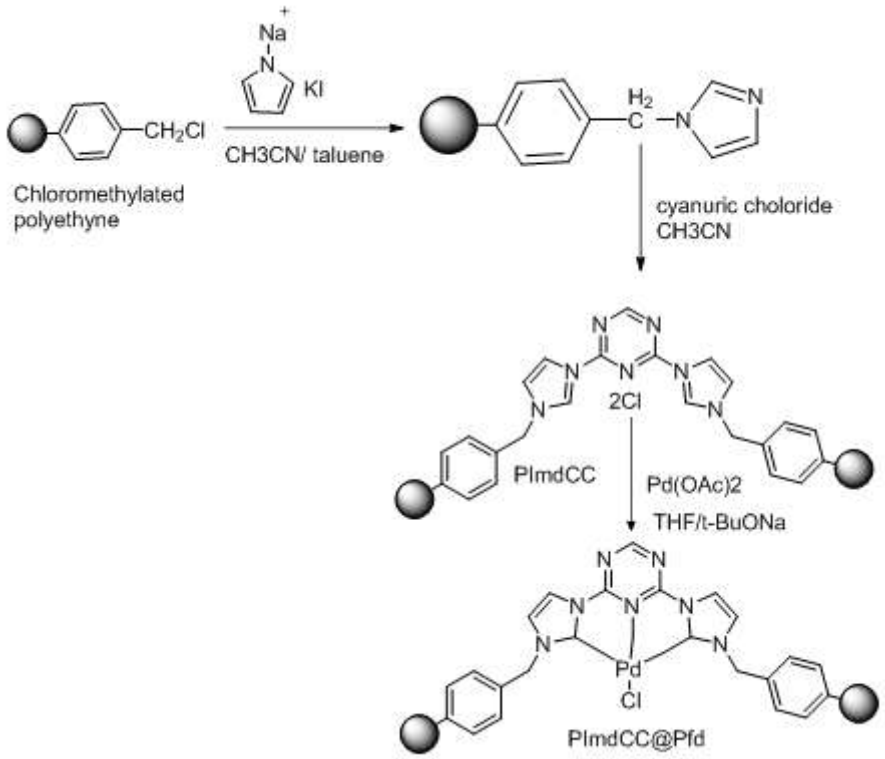
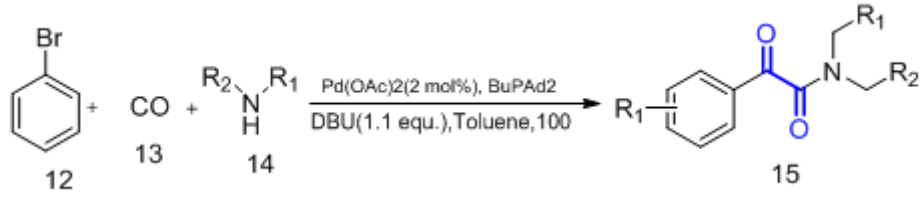
produced the imidazole salt of chloromethyl derivativepolystyrene polymer (0.5 gm) and cyanuric chloride (0.184 gm, 1 mmowasere)

The crystalline product was obtained, and it was then cleaned using ACN and CH3OH. (0.5gm) polymer ligand and The tBuONa (2.2 mmol) in THF (15 mL) was treated for 40 minutes with 9 weight percent palladium acetate while being constantly stirred on this polymer, which supported the PImdCC-ligand (0.5 gm). Then, for one day, the solution was heated to 800 degrees Celsius. The palladium (II) catalyst (PImdCC@Pd) has been subsequently produced, filtered, CH3OH washed, and dried under vacuum at 400 °C.



Scheme 4.Preparation of polymer-incorporated palladium (II) catalyst.

Versatile Double Carbonylation of Aryl by Palladium Catalysis,Bromides Alpha-ketoamide can be made from morpholine, bromides, and amines using a palladium catalyst, as was demonstrated by Xiao-Feng Wu and colleagues.[72]



Scheme 5

Reductive elimination happened in the hypothesized mechanism amino acylpalladium intermediate 16 Complex 16, on the other hand, is susceptible to reduction elimination reaction, which yields the amide as the main product when additional CO was added to the Palladium-Nitrogen bond (scheme 5, intermediate 16).

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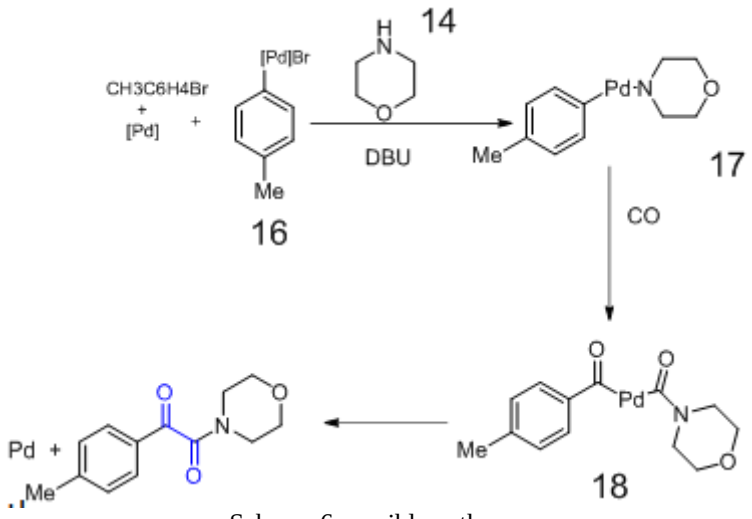
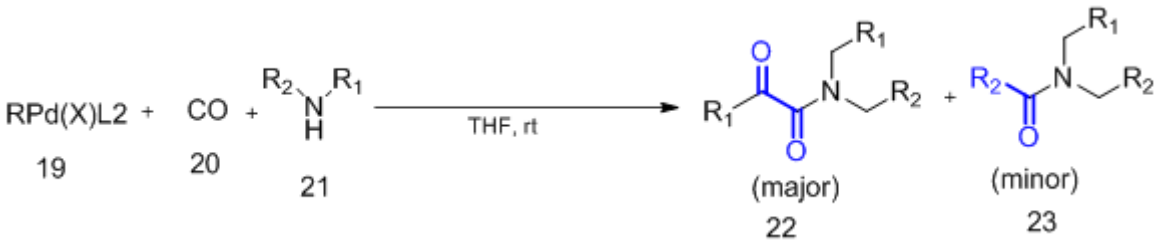


Scheme 6 possible pathway

[73] In 1982, Fumiyuki Ozawa and Akio Yamamoto published the first report on the double carbonylative technique for producing alpha-keto amides. To obtain excellent yields and selectivity, they employed stoichiometric mono-alkyl Pd complexes in a CO environment with secondary amines.Scheme 7.



Scheme 7 Stoichiometric alkyl palladium complexes are used to describe the first double carbonylation pathway to alpha-ketoamides.

[74]In the presence of catalytic Pd-salts, the first catalytic amino de-carbonylation method to alpha-ketoamide synthesis was created, mixing aryl, aryl alkyl, heteroaryl, and vinylic halides. This was a catalytic adaptation of previously documented stoichiometric processes scheme 8.

Scheme 8**.** The first catalytic approach to alpha-ketoamides by amino double carbonylation**.**

Similar to the alpha-keto amides, Kobayashi and Tanaka[75]discovered a catalytic double carbonylative reaction. They also attempted to carbonylate primary amines doubly, but the imine of alpha-keto amides was found to form instead. Scheme 3 depicts a system with two coupled catalytic cycles. When Pd(0) is oxidatively added to an aryl halide, It forms a transitional that is used in both cycles, an organopalladium(II) product 1.It can then be coordinated with another CO to create complex 4 with two mono-carbonylated ligands, which, when reductively eliminated, yields alpha-ketoamide and restores the active Pd(0) catalyst, completing the cycle. A

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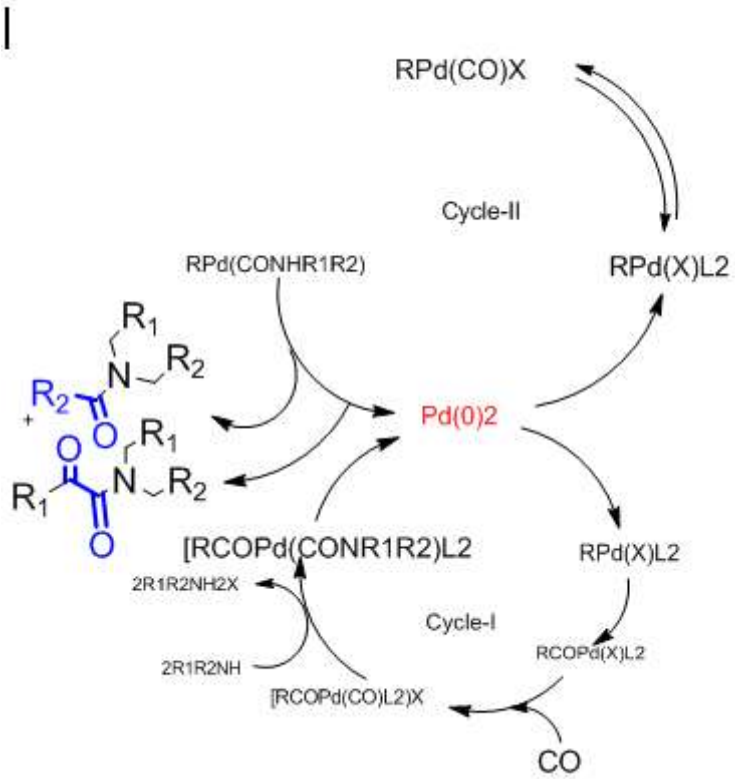
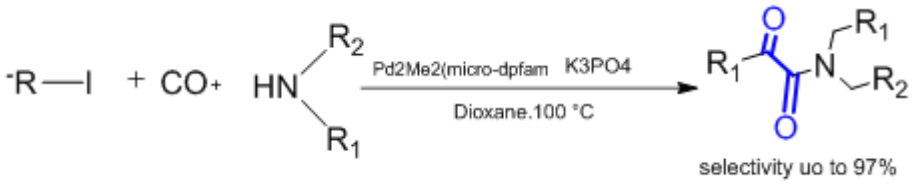
further CO insertion produces acyl-palladium species 2 (cycle I), which may then be coordinated with another CO.As part of catalytic cycle II, palladium and CO combine to generate aryl-carbonyl palladium.



Scheme 9. The catalytic cycle of the amino carbonylative pathway to alpha-ketoamides/amides using Pd as the catalyst

[76]The ideal catalysts during the double-carbonylation process were found to be Pd complexes with tertiary phosphine ligands.However, the phosphines monodentate and bidentate have also been demonstrated to be useful in other cases. Most alpha-keto amides were created by the tertiary phosphine ligand's balanced (not too strong or too weak) coordinating capacity. The Palladium-catalyzed amino-decarbonylation of phenyl iodides with amine nucleophiles was demonstrated to be particularly successful when the bidentate phosphine ligand N, N′ bis-[(diphenylphosphino)phenyl]formamidinate (dpfam) has been used scheme 10.



Scheme 10 Amino carbonylation process mediated by Pd2Me2(-Cl)(-dpfam)

The impact of CuI co-catalyst on the Palladium-catalyzed amino carbonylation procedure has been examined by Nomura and colleagues. The intermediate palladium complex's one phosphine ligand was removed by the copper iodide to create a much more reactive do-bridged heterobimetallic (Pd/Cu) species, which facilitated

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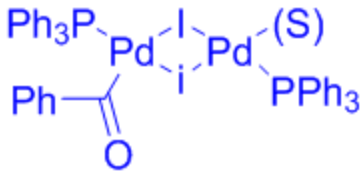
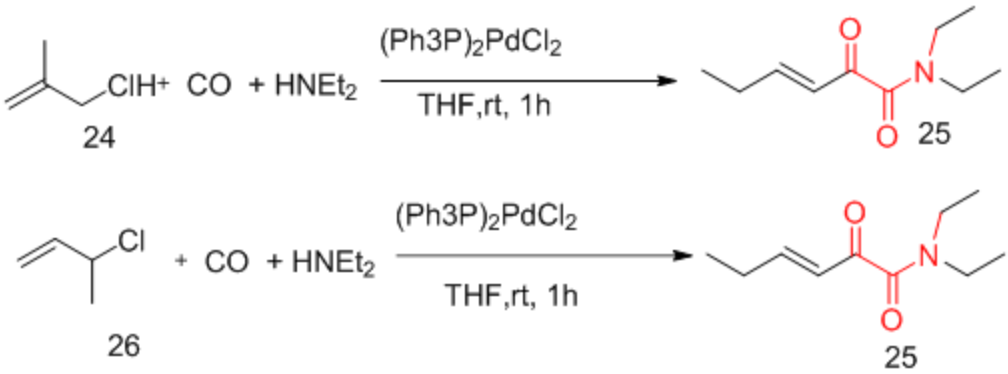
the amino carbonylation process and improved the generation of alpha-ketoamide scheme 11.



Scheme 11. Iodo-bridged heterobimetallic (Pd-Cu) species.

A double carbonylation process that is catalysed by PdIn 1994, Yamamoto,[77] he was described the catalytic amino carbonylation of allylic chlorides 24 at high CO pressure (100 atm) to produce unsaturated 25 alpha-keto amides scheme 12.



Scheme 12 Yamamoto's procedure for allyl choloride amino de-carbonylation using a Palladium catalysis.

The creation of "alpha-allylpalladium complexes" 26 is preceded by Carbon mono oxide to create acyl-Pd species 27 as the process moves forward. Further carbon mono oxide bond formation, an amine assault on 28, and eliminate by reduction of 29 result in the production of the required 25 alpha-ketoamide. in scheme 13.

Scheme 13. Proposed mechanism for Pd-catalysed amino de-carbonylation of allyl chlorides.

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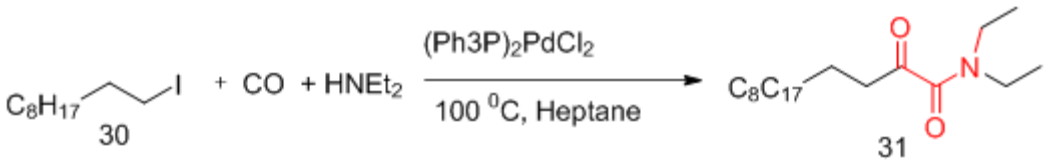
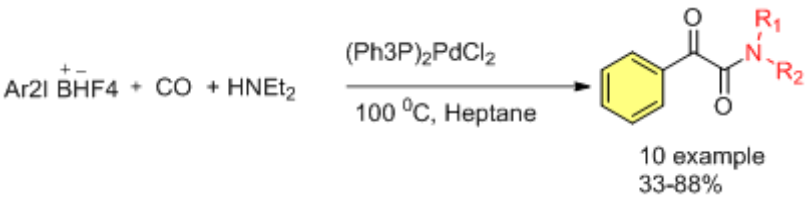
In the presence of a palladium catalyst, Fuchikami [78]and colleagues reported 2-iodoalkanes 30 with perfluoroalkyl substitutions can be amino di-carbonylated with either a primary or secondary amine.



Scheme 14. Fuchikami's method for perfluoroalkyl-containing alkyl iodides to undergo Palladium-catalyzed amino di-carbonylation.

Secondary amines were used by Zhou and Chen[79] to amino di-carbonylate diaryliodonium ions. in the presence of a Pd/Cu-catalyzed system to create alpha-ketoamides with high yields and selectivity under mild reaction conditions.



Scheme 15. The di- & mono-carbonylation of diaryliodonium complexes in the addition of secondary amines is shown in Scheme 16 of Zhou's technique for the Pd-catalyzed amino di-carbonylation of diaryliodonium salt. When intermediate 32 undergoes carbon mono-oxide insertion to create the aroyl Pd species 33, alpha-ketoamide is created. A different way to make the easy amide is to coordinate carbon mono oxideto produce 34 before combining it with an NH2. As a result, the reactivity of NH2 to 33 largely determines the selectivity for alpha-ketoamide production.The specificity for the production of alpha-ketoamide is improved by the rapidity at which amines react with 33. Primary amines are often not good candidates for this reaction since it only forms amides at ideal circumstances. Similar changes were made to the selectivity for the salt used in alpha-ketoamide production by the diaryliodonium. the presence of electron-removing derivatives.

Scheme 16. Mechanism route for diaryliodonium salts to undergo amino di-carbonylation under the influence of Palladium.

Castanet and colleagues [80]evaluated the impact of several Pd-catalysts on the amino di-carbonylation of iodopyridines, both with and without external phosphine ligands. Pd(OAc)2 and PCy3 performed best for simple 2-iodopyridine, but Pd(dba)2 and PPh3 performed best for 6-

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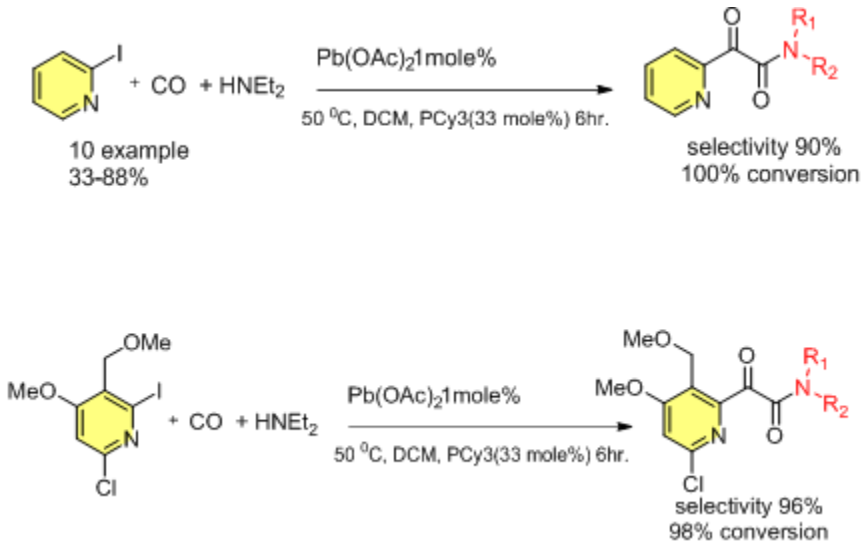
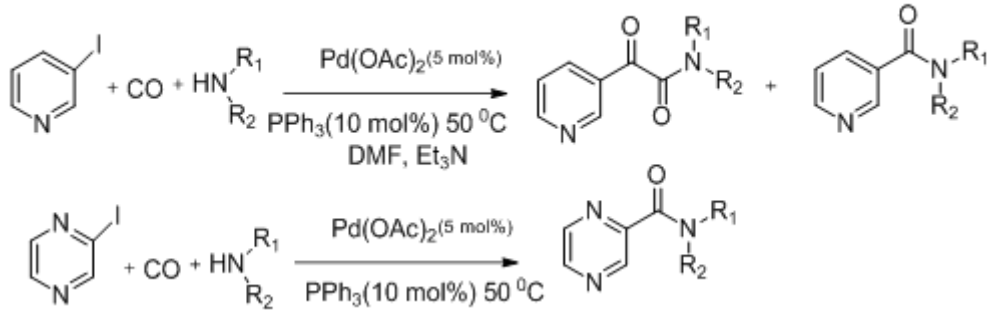
chloro-2-methoxy-3-(methoxymethyl)-4-iodopyridine 17.



Scheme 17 Castanet's approach to iodopyridine amino dicarbonylation using Palladium as the catalyst

Iodo-heteroarenes such as 2-iodopyridine, 3-iodopyridine, and iodopyrazine, as well as a range of primary and secondary amines,were studied by Kollár and co-workers in the amino-decarbonylation process using the Pd(OAc)2/PPh3 catalyst system. When employing 2-iodopyridine and iodopyrazine, an entire generation of N-alkyl/aryl-carboxamides was produced instead of a combination of -ketoamide and carboxamide when using 3-iodopyridine.



Scheme 18.Kollar's method for iodo-heteroarenes' amino di-carbonylation on a Palladium catalyst

The predominant stabilisation of the Pd-arylglyoxyl derivative by chelation of the heteroaryl substituent and the stop of reduction elimination from the acyl-aminocarbonyl-Pd moieties to respective alpha-ketoamide were much more probable the causes of the unique amide creation inside the scenario of 2-iodopyridine scheme 19.

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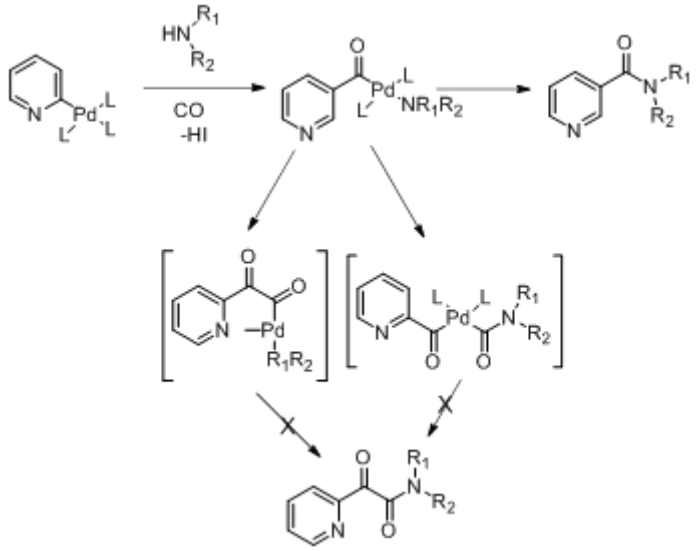
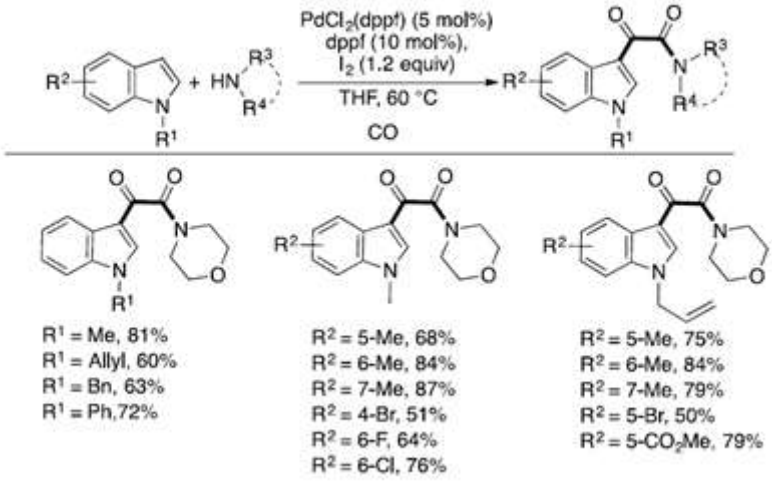


Scheme 19 Possible stages for 2-iodopyridine's aminocarbonylation

[81]Li and colleagues reported the first occurrence of Pd-catalyzed direct inter-aminocarbonylation of indoles, resulting in amides and alpha-keto amides that tolerated both secondary and primary amines (Scheme 15). The amino de-carbonylation of indoles with varied N-protective groups resulted in modest to good alpha-ketoamide yields. Furthermore, indoles with electron-donating groups were more reactive than those with halide moieties. N-methyl indole was used to assess the compatibility of various amines, and as was predicted, secondary amines outperformed primary amines.Furthermore, the double carbonylation method performed well with primary amines such as allylamine and benzylamine, producing the required chemicals at yields that are inadequate.



Scheme 20 Direct inter-amino di-carbonylation of indoles under Palladium catalysis

Pd-catalyzed double carbonylation reaction Pd is a very versatile accelerator for dual carbonylation processes. However, the expensive price of Palladium-catalysts and the poor recovery of conventional homogeneous Palladium-catalysts prompted the use of easily separable solvents to overcome the challenges Green reaction mediums are used in amino de-carbonylation. Ionic

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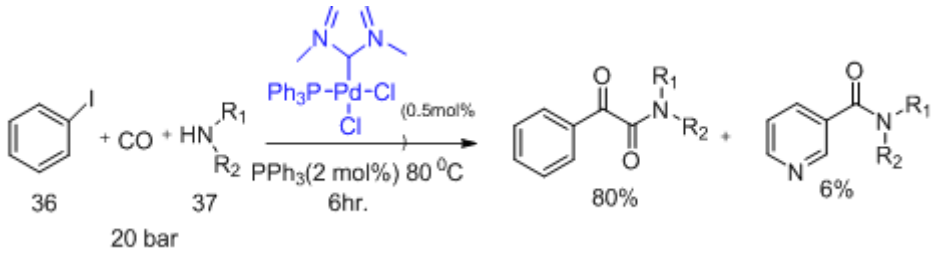
liquids(ILs), water, supercritical fluids, and other greener solvents have developed as future solvents to lessen the environmental impact of volatile organic solvents.They make it easier to separate compounds from catalysts as well.

Hexafluorophosphate, as well as 1-butyl-3-methylimidazolium tetrafluoroborate, are two instances of phenyl halides that Tanaka,[82] as well as collaborators, initially disclosed carbamylated with amines 37 in an ionic liquid using a customary Pd catalyst with precise for the production of alpha-keto amides 38 scheme 21. When the compounds were isolated using ether, the process enables the catalyst/ionic liquid mixture to really be recovered.

Scheme 21 aryl iodide is amino dicarbonylated utilizing an ionic liquid as the reaction media.

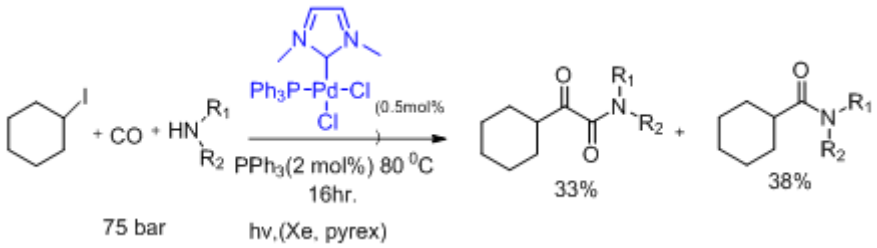
Scheme 22 Reaction procedure the mixture of ionic solution PPh3 (2 mol%), (2 ml),PhI (2.66 mmol), and NEt2H (13.3 mmol) Pd(OAc)2 (0.5 mol%) were used in the reaction, which took place at 80 °C for three hours. The internal standard used in the Gas chromatographic was n-decane.

[83]Ryu and colleagues achieved long-term amino di-carbonylation using ionic liquid as the reaction media.In comparison to the conventional batch method, they described the effective employing of microflow system for Palladium-catalyzed amino di-carbonylation operations in ionic liquids at low carbon mono oxide pressures with greater selectivity and better productivity figure Subsequent research revealed that the selectivity percentage in a batch process was limited by CO penetration into the ionic liquid at reduced pressure.



Scheme 22. Iodophenyl is amino di-carbonylated using Ryu's technique in an ionic liquid medium.

Using ionic solution like [bmim][PF6] and [bmim][NTf2] as well as a catalytic quantity of a Pd-carbene complex, Ryu and colleagues have demonstrated photo-induced amino di-carbonylation reactions with alkyl halides to create amides and alpha-ketoamides. Unfortunately, alpha-ketoamide production showed low selectivity and yields. Reusing the Pd-catalyst and ionic liquid for product extraction with cyclohexane is an option figure.



Scheme 23. Ryu's method for the microflow-enabled Palladium-catalyzed amino dicarbonylation of cyclohexyl iodide in ionic liquid media.

Uozumi and colleagues[84] discovered that in scheme 24 aryl halides38 might be carbonylated twice using a palladium-catalyzed method at atmospheric CO pressure and room

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temperature (25 °C) (1 atm). Due to the fact that earlier combinations of ligands, bases, and solvents DNSO etc. as well as 2-bis(diphenylphosphino)ethane and n-Bu3P, significantly decreased selectivitytriphenylphosphine was used as a ligand in the presence of THF and 1,4-and DABCO. As a result, an efficient catalytic system with substantially improved selectivity for the double carbon was developed.

Scheme 24.

In a uniquely designed sealed 2-chamber glass reactor53 operating on room temp, Skrydstrup and associates came up with a clever strategy in 2012. They used COgen (9-methylfluorenecarbonyl chloride) as a solid source of CO (Scheme 25). There has been much research done on the 13C-isotope tagging of norepinephrine, mescaline, and clenbuterol. Alpha-amino alcohols, phenethylamines, 2-oxazolidinones, and other new 13C and 2H phenethylamine derivatives have all been produced using this double carbonylation process.

Scheme 25. Using 9-methylfluorenecarbonyl chloride as a solid source of Carbon mono oxide, Palladium catalyses the amino carbonylation of phenyl iodide.

[85]To create aryl iodides and amines via a practical, all-purpose process with high selectivities and conversions at atmospheric CO pressure, sergio Castillo created a phosphine-free Pd/DBU catalyst.

Scheme 26. Castillo's method for the phosphine-free, Palladium-catalyzed amino di-carbonylation of phenyl iodide.

At room temperature and atmospheric CO pressure, Han and colleagues have recently reported double carbonylation of PhI with either secondary or primary amines to create alpha-ketoamides. At ambient carbon mono oxide pressure and ambient temperature, Han and colleagues recently reported double carbonylation of aryl iodides with primary or secondary amines to create alpha-ketoamides scheme 27.

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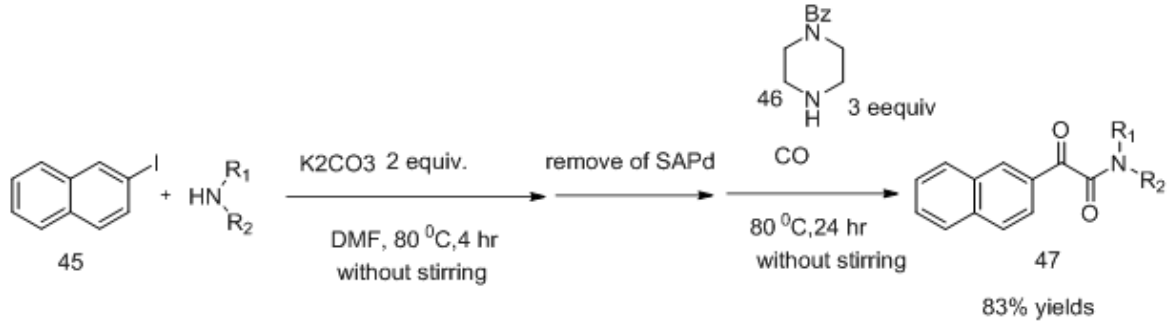
Scheme 27. Han's method for the Palladium-catalyzed double carbonylation of PhI without the need of a ligand or additives.

Palladium-catalyzed heterogeneous amino dicarbonylation

In a two-step procedure, Sato and colleagues[86] employed palladium nanoparticles (PdNPs). Sato and colleagues utilised nanoparticles (PdNPs) in a two-step approach to amino dicarbonylate aryl iodides with amines while working at atm pressure. The nanoparticle have probably absorbed from a sulfur-treated gold-supported Pd substance (SAPd). Excellent to good alpha-ketoamide yields were achieved after the process scheme 28.

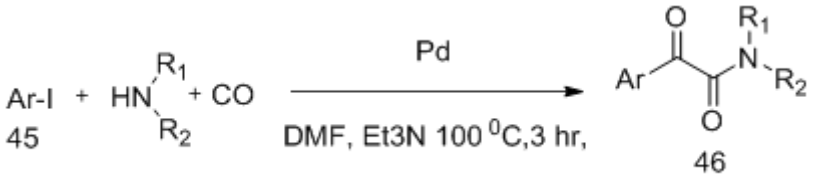
Scheme 28 Sato's method for amino dicarbonylating PhI when SAPd is present.

A potent anti-HIV medication was produced in one step by doubly carbonylating 2-iodonaphthalene 45 with N-benzoylpiperazine 46 (Scheme 29).With outstanding yields (85%), they subsequently showed a large-scale reaction utilizing SAPd.



Scheme 29 double carbonylation in the addition of SAPd to create an anti-HIV molecule in a single step.

Zhang and colleagues [87] discovered a covalent triazine framework-supported palladium (Pd/CTFs) for selective double carbonylation of aryl iodides 45 at room temperature. This ligand-free technique was used to synthesize46 alpha-keto amides with high selectivity (Scheme 30).



Scheme 30.Zhang's protocol for the amino-di-carbonylation of aryl iodides using covalent triazine framework-supported palladium (Pd/CTFs).

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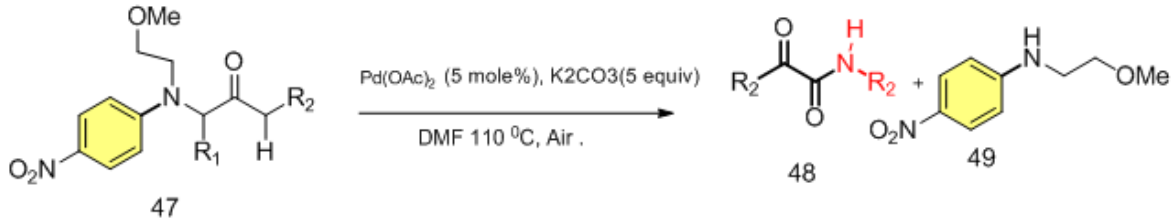
alpha-arylamino amides are oxidatively broken down in an aerobic reaction by Palladium to produce alpha-ketoamides, Laurent[88]As a novel method of producing alpha-keto amides, Kaim presented a unique Pd-catalyzed aerobic oxidative cleavage of alpha-arylamino amides.



Kaim's method for the Palladium-catalyzed aerobic oxidative cleavage of alpha-arylamnio amides to alpha-ketoamides is shown in scheme 31.

Nevertheless, under similar circumstances, scheme 32, the alkyl substituents lost reactivity and were unable to produce the necessary alpha-keto amides.Pd is produced as a Pd enolate, which transforms into an iminium derivative, or 49.and It is most likely related to the substrate's need for an acidic proton under these circumstances because the reaction creates alpha-keto amides when water or peroxides are present in the aqueous. This clarifies why alkyl derivatives are unable to produce alpha-keto amides.

Scheme 32 Pathway of the aerobic oxidative cleavage of pheylamnio amides to alpha-ketoamide by Palladium.

Decarboxylative coupling of alpha-oxo carboxylic acids with cyanamides under the influence of Palladium.[89] The preparation of N-monosubstituted alpha-keto amides using a new decarboxylative technique was reported by Patel and colleagues using a Pd(II)-catalyzed reaction of alpha-oxo carboxylic acid 51 with cyanamides 52.by chemo-selective aroyl addition in a unique 1,2-palladium migration from Nitrogen to Carbon, which is created from alpha-oxocarboxylic acid by decarboxylation.

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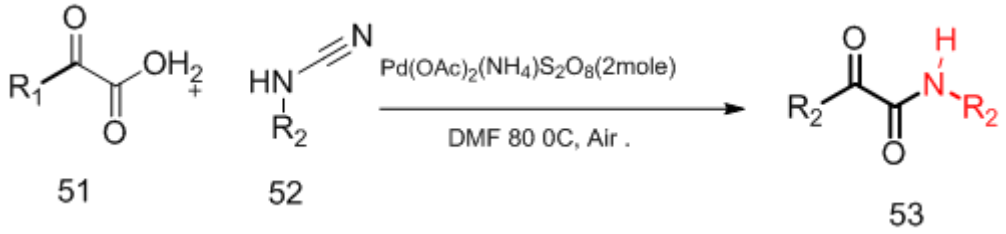
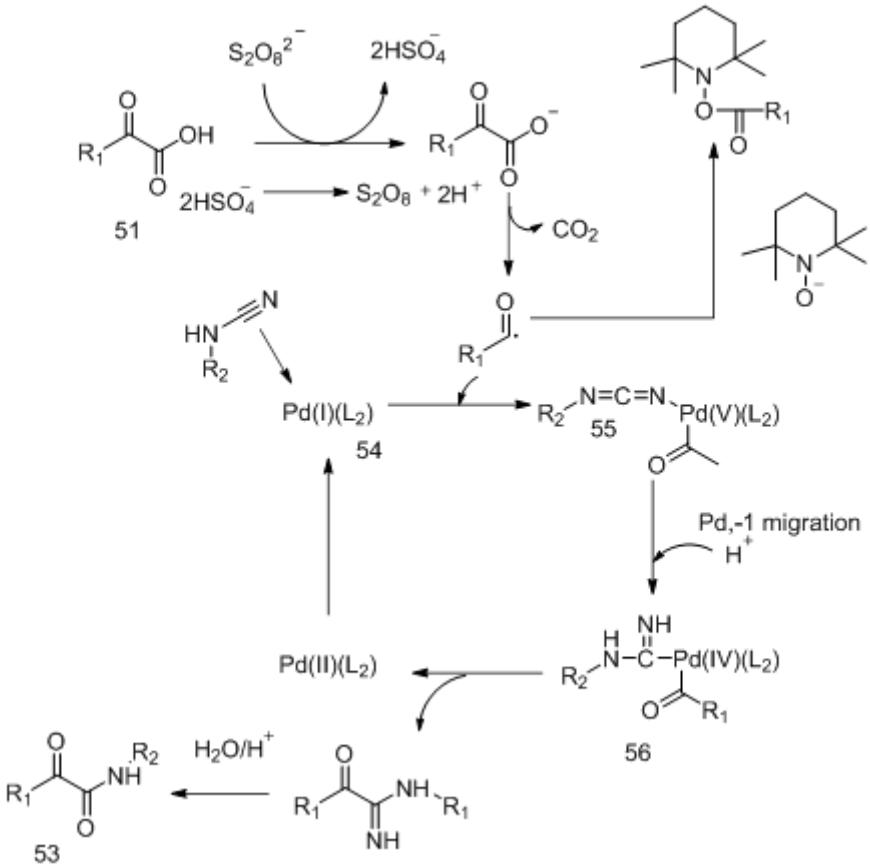


Scheme 33 Patel's method for producing alpha-ketoamides using alpha-oxo carboxylic acids using Pd-catalyzed de-carboxylation.

In terms of physics, transition compound 54 is created when the Palladium(II) first binds on cyanamide. Thus in presence of the oxidant (NH4)2S2O8, the produced acyl radical links to 54 to create a Pd(IV) species, which is represented by 55. Next, 1,2-Pd migrates from nitrogen to Carbon as seen in the image, resulting in transitional compound 56. With the help of the transition complex of alpha-ketimine 53, the subsequent reductive elimination regenerates Pd(II) for another catalytic cycle. Alpha-keto amides are produced in situ by the hydrolysis of this intermediate. As a result, in this reaction, (NH4)2S2O8 serves as a dual oxidizing and a radical activator scheme 34.



Scheme 34 Suggested method by which alpha-oxo carboxylic acids are decarboxylated to produce alpha-ketoamides.

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II. CONCLUSION

In summary, this review briefly summarizes the advances of Palladium catalyzed synthesis of α-Ketoamides from various substrates like aryl methyl ketones, carboxylic acids, α-ketoacids, Aldehydes, β-keto carbonyl compounds, α-azidoketones, benzylimidates, alkynes, and enaminones With suggested reaction mechanism. It is an alternate cost-effective metal in comparison to Other metals like Pd, Ag, Ni etc. There are growing demands for α-ketoamide containing drug Molecules. Starting from antiviral drugs boceprevir and telaprevir (approved in the year 2011) to Antiretroviral drug fostemsavir (year 2020) and snake venom inhibitor Varespladib (year 2022) Several drug molecules bearing α-keto amide moieties have been approved by US FDA

REFERENCE

[1]. H. B. Wedler, T. A. Palazzo, R. P. Pemberton, C. S. Hamann, M. J. Kurth, D. J. Tantillo, Predicting hydration propensities of biologically relevant α-ketoamides, Bioorganic & Medicinal Chemistry Letters 25 (2015) 4153–4157.(a) Venkatraman, S.; Velazquez, F.; Wu, W.; Blackman, M.; Chen, K. X.; Bogen, S.; Nair, L.; Tong, X.; Chase, R.; Hart, A.; Agrawal, S.; Pichardo, J.; Prongay, A.; Cheng,K.-C.; Girijavallabhan, V.; Piwinski, J.; Shih, N.-Y.; Njoroge, F. G. J. Med. Chem. 2009, 52, 336–346. (b) Bogen, S. L.;Pan, W.; Ruan, S.; Nair, L. G.; Arasappan, A.; Bennett, F.; Chen, K. X.; Jao, E.; Venkatraman, S.;Vibulbhan, B.; Liu, R.; Cheng, K.-C.; Guo, Z.; Tong, X.; Saksena, A. K.; Girijavallabhan, V.; Njoroge, F. G. J. Med. Chem. 2009, 52, 3679–3688. © Steuer, C.; Gege, C.; Fischl, W.; Heinonen, K. H.; Bartenschlager, R.; Klein, C. D. Bioorg. Med. Chem. 2011, 19, 4067–4074. (d) Mandadapu, S. R.; Weerawarna, P. M.; Gunnam, M. R.; Alliston, K. R.; Lushington, G. H.; Kim, Y.; Chang, K.-O.; Groutas, W. C. Bioorg. Med. Chem. Lett. 2012, 22, 4820–4826. € Kim, Y.;Lovell, S.; Tiew, K.-C.; Mandadapu, S. R.; Alliston, K. R.; Battaile, K. P.; Groutas, W. C.; Chang, K.-O. J. Virol. 2012, 86, 11754–11762. (f) Kim, Y.; Kankanamalage, A. C. G.; Damalanka, V. C.; Weerawarna, P. M.; Groutas, W. C.; Chang, K.-O. Antiviral Res. 2016, 125, 84–91.

[2]. Q. Liu, S. Perreault, T. Rovis, Catalytic asymmetric intermolecular stetter reaction of glyoxamides with alkylidenemalonates, J. Am. Chem. Soc. 130 (2008) 14066–14067. https://doi.org/10.1021/ja805680z.

[3]. Tomita, K. Yamatsugu, M. Kanai, M. Shibasaki, Enantioselective synthesis of SM-130686 based on the development of asymmetric Cu(I)F catalysis to access 2-oxindoles containing a tetrasubstituted carbon, J. Am. Chem. Soc. 131 (2009) 6946–6948. https://doi.org/10.1021/ja901995a.

[4]. Lu, G.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. Chiral γ- Amino Amide Synthesis by Heterobimetallic Lanthanum/Lithium/ Pybox-Catalyzed Direct Asymmetric Mannich-type Reactions of α- Keto Anilides. Angew. Chem., Int. Ed. 2008, 47, 6847−6850.

[5]. Xu, Y.; Lu, G.; Matsunaga, S.; Shibasaki, M. Direct anti-Selective Catalytic Asymmetric Mannich- Type Reactions of α-Ketoanilides for the Synthesis of γ-Amino Amides and Azetidine-2-amides. Angew. Chem., Int. Ed. 2009, 48, 3353−3356.

[6]. Natarajan, A.; Ramamurthy, V. Org. Biomol. Chem. 2006, 4, 4533–4542. (a) Basle, O.; Raimondi, W.; del Mar Sanchez Duque, M.; Bonne, D.; Constantieux, T.; Rodriguez, J. Org. Lett. 2010, 12, 5246−5249. (b) Schonherr, H.; Leighton, J. L. Org. Lett. 2012, 14, 2610–2613. (c) Xu,Y.; Lu, G.; Matsunaga, S.; Shibasaki, M. Angew. Chem. Int. Ed. 2009, 48, 3353–3356. (d) Liu, Q.; Rovis, T. Org. Lett. 2009, 11, 2856–2859.

[7]. Xu, Y.; Matsunaga, S.; Shibasaki, M. syn-Selective Catalytic Asymmetric 1,4-Addition of α- Ketoanilides to Nitroalkenes under Dinuclear Nickel Catalysis. Org. Lett. 2010, 12, 3246−3249.

[8]. Baslé, O.; Raimondi, W.; del Mar Sanchez Duque, M.; Bonne, D.; Constantieux, T.; Rodriguez,J. Highly Diastereo- and Enantioselective Organocatalytic Michael Addition of α-Ketoamides to Nitroalkenes. Org. Lett. 2010, 12, 5246−5249.

[9]. Acosta, P.; Becerra, D.; Goudedranche, S.; Quiroga, J.; Constantieux, T.; Bonne, D.; Rodriguez,J. Exploiting the Reactivity of

1,2-Ketoamides: Enantioselective Synthesis of Functionalized Pyrrolidines and Pyrrolo-1,4 benzodiazepine-2,5-diones. Synlett 2015, 26, 1591−1595.

[10]. Stöckigt, J.; Antonchick, A. P.; Wu, F.; Waldmann, H. The Pictet-Spengler Reaction in Nature and in Organic Chemistry. Angew. Chem., Int. Ed. 2011, 50, 8538−8564.

[11]. Basle, O.; Raimondi, W.; del Mar Sanchez Duque, M.; Bonne, D.; Constantieux, T.; Rodriguez,J. Org. Lett. 2010, 12, 5246−5249. (b) Schonherr, H.; Leighton, J. L. Org. Lett. 2012, 14, 2610– 2613. (c) Xu, Y.; Lu, G.; Matsunaga, S.; Shibasaki, M. Angew. Chem. Int. Ed. 2009, 48, 3353– 3356. (d) Liu, Q.; Rovis, T. Org. Lett. 2009, 11, 2856–2859.

[12]. Kher, S.; Jirgensons, A. Curr. Org. Chem. 2014, 18, 2240–2269.

[13]. C. Zhang, N. Jiao, Dioxygen activation under ambient conditions: Cu-catalyzed oxidative amidationdiketonization of terminal alkynes leading to a-ketoamides, J. Am. Chem. Soc. 132 (2010) 28–29. https://doi.org/10.1021/ja908911n.

[14]. Aerial Oxidation of 2,2-Dibromo-1Aryl and Heteroaryl Ethanones: A Facile Synthesis of Aryl And Heteroaryl α-Keto Amides http://dx.doi.org/10.1055/s-0028-1087353.

[15]. Raimondi, W.; Bonne, D.; Rodriguez, J. 1,2-Dicarbonyl Compounds as Pronucleophiles in Organocatalytic Asymmetric Transformations. Angew. Chem., Int. Ed. 2012, 51, 40−42.

[16]. Raimondi, W.; Bonne, D.; Rodriguez, J. Asymmetric Transformations Involving 1,2-Dicarbonyl Compounds as Pronucleophiles. Chem. Commun. 2012, 48, 6763−6775.

[17]. Bonne, D.; Constantieux, T.; Coquerel, Y.; Rodriguez, J. Stereoselective Multiple Bond-Forming Transformations (MBFTs): The Power of 1,2- and 1,3-Dicarbonyl Compounds. Chem. – Eur. J. 2013, 19, 2218−2231.

[18]. Synthesis of α-Ketoamides from Aryl Methyl Ketones and N,N-Dimethylformamide via Copper-Catalyzed Aerobic Oxidative Coupling. https://doi.org/10.1002/chin.201503083

[19]. Copper-Catalyzed Aerobic Oxidative Cross-Dehydrogenative Coupling of Amine and α- Carbonyl Aldehyde: A Practical and Efficient Approach to α-Ketoamides with Wide Substrate Scope. https://doi.org/10.1021/ol301130u

[20]. Mhate, M.; Gautam, A.; Kumar, K. N.; Ravichandiran, V.; SWAIN, S. P. Waste-Minimized, Solvent-Free and Continuous Flow Synthesis of A-Ketoamides from Aryl Methyl Ketones Using Recyclable Cubr2 Catalyst, Via Bromo Intermediate. SSRN Electronic Journal 2023. https://doi.org/10.2139/ssrn.4402150.

[21]. G. J. Chuang, W. Wang, E. Lee, T. Ritter, J. Am. Chem. Soc., 133 (2011) 1760–1762. https://doi.org/10.1021/ja108396k

[22]. H. Sunden, M. Engqvist, J. Casas, I. Ibrahem, A. Cordova, Angew. Chem., Int. Ed., 43 (2004) 6532–6535. https://doi.org/10.1002/anie.200460295.

[23]. Perni, R. B.; Almquist, S. J.; Byrn, R. A.; Chandorkar, G.; Chaturvedi, P. R.; Courtney, L. F.; Decker, C. J.; Dinehart, K.; Gates, C. A.; Harbeson, S. L.; et al. Preclinical Profile of VX-950, a Potent, Selective, and Orally Bioavailable Inhibitor of Hepatitis C Virus NS3−4A Serine Protease. Antimicrob. Agents Chemother. 2006, 50, 899−909.

[24]. Malcolm, B. A.; Liu, R.; Lahser, F.; Agrawal, S.; Belanger, B.; Butkiewicz, N.; Chase, R.; Gheyas, F.; Hart, A.; Hesk, D.; et al. SCH 503034, a Mechanism-Based Inhibitor of Hepatitis C Virus NS3 Protease, Suppresses Polyprotein Maturation and Enhances the Antiviral Activity of Alpha Interferon in Replicon Cells. Antimicrob. Agents Chemother. 2006, 50, 1013−1020.

[25]. Adang, A. E. P.; de Man, A. P. A.; Vogel, G. M. T.; Grootenhuis, P. D. J.; Smit, M. J.; Peters, CoM.; Visser, A.; Rewinkel, J. B. M.; van Dinther, T.; Lucas, H.; et al. Unique Overlap in the Prerequisites for Thrombin Inhibition and Oral Bioavailability Resulting in Potent Oral Antithrombotics. J. Med. Chem. 2002, 45, 4419−4432.

[26]. Catalano, J. G.; Deaton, D. N.; Long, S. T.; McFadyen, R. B.; Miller, L. R.; Payne, J. A.; Wells- Knecht, K. J.; Wright, L. L. Design of Small Molecule Ketoamide-Based Inhibitors of CathepsinK. Bioorg. Med. Chem. Lett. 2004, 14, 719−722.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 830-852 www.ijprajournal.com ISSN: 2249-7781

[27]. Barrett, D. G.; Boncek, V. M.; Catalano, J. G.; Deaton, D. N.; Hassell, A. M.; Jurgensen, C. H.; Long, S. T.; McFadyen, R. B.; Miller, A. B.; Miller, L. R.; et al. P2-P3 Conformationally Constrained alpha-Ketoamide-Based Inhibitors of Cathepsin K. Bioorg. Med. Chem. Lett. 2005, 15, 3540−3546.

[28]. Slee, D. H.; Laslo, K. L.; Elder, J. H.; Ollmann, I. R.; Gustchina, A.; Kervinen, J.; Zdanov, A.; Wlodawer, A.; Wong, C.-H. Selectivity in the Inhibition of HIV and FIV Protease: Inhibitory and Mechanistic Studies of Pyrrolidine-Containing α-Keto Amide and Hydroxyethylamine Core Structures. J. Am. Chem. Soc. 1995, 117, 11867−11878.

[29]. Sheha, M. M.; Mahfouz, N. M.; Hassan, H. Y.; Youssef, A. F.; Mimoto, T.; Kiso, Y. Synthesis of Di- and Tripeptide Analogues Containing α-Ketoamide as a New Core Structure for Inhibition of HIV-1 Protease. Eur. J. Med. Chem. 2000, 35, 887−894.

[30]. Perni, R. B.; Almquist, S. J.; Byrn, R. A.; Chandorkar, G.; Chaturvedi, P. R.; Courtney, L. F.; Decker, C. J.; Dinehart, K.; Gates, C. A.; Harbeson, S. L.; et al. Preclinical Profile of VX-950, a Potent, Selective, and Orally Bioavailable Inhibitor of Hepatitis C Virus NS3−4A Serine Protease. Antimicrob. Agents Chemother. 2006, 50, 899−909.

[31]. Recent Advances in the Catalytic Synthesis of α-Ketoamides Dinesh Kumar, Sandeep R. Vemula and Gregory R. Cook . https://doi.org/10.1021/acscatal.6b01116

[32]. Mhate, M.; Gautam, A.; Kumar, K. N.; Ravichandiran, V.; SWAIN, S. P. Waste-Minimized, Solvent-Free and Continuous Flow Synthesis of A-Ketoamides from Aryl Methyl Ketones Using Recyclable Cubr2 Catalyst, Via Bromo Intermediate. SSRN Electronic Journal 2023. https://doi.org/10.2139/ssrn.4402150.

[33]. Wada, C. K.; Frey, R. R.; Ji, Z.; Curtin, M. L.; Garland, R. B.; Holms, J. H.; Li, J.; Pease, L. J.; Guo, J.; Glaser, K. B.; et al. α-Keto Amides as Inhibitors of Histone Deacetylase. Bioorg. Med. Chem. Lett. 2003, 13, 3331−3335.

[34]. Malcolm, B. A.; Liu, R.; Lahser, F.; Agrawal, S.; Belanger, B.; Butkiewicz, N.; Chase, R.; Gheyas, F.; Hart, A.; Hesk, D.; et al. SCH 503034, a Mechanism-Based Inhibitor of Hepatitis C Virus NS3 Protease, Suppresses Polyprotein Maturation and Enhances the Antiviral Activity of Alpha Interferon in Replicon Cells. Antimicrob. Agents Chemother. 2006, 50, 1013−1020.

[35]. A-Ketoamides as Broad-Spectrum Inhibitors of Coronavirus and Enterovirus Replication: Structure-Based Design, Synthesis, and Activity Assessment https://doi.org/10.1021/acs.jmedchem.9b01828

[36]. Stabilized Cu2O nanoparticles on rGO highly catalyzed direct oxidative coupling synthesis ofA-ketoamides with molecular oxygen. 10.1016/j.catcom.2019.105806

[37]. An Approach in Synthesis of 1-Morpholino-2-phenylethane-1,2-dione Catalyzed by Copper (II) Bromide. https://doi.org/10.34311/jics.2020.03.3.145

[38]. Synthesis of α-Ketoamides by Copper-Catalyzed Reactions of Phenylacetic Acids with N,N- Dialkylformamides. https://doi.org/10.1080/00397911.2015.1049273

[39]. Cu(II)-catalyzed decarboxylative acylation of acyl C–H of formamides with α-oxocarboxylic acids Leading to α-ketoamides. https://doi.org/10.1039/C3CC41188E

[40]. Cu-Catalysed oxidative amidation of cinnamic acids/arylacetic acids with 2° amines: an efficient Synthesis of α-ketoamides https://doi.org/10.1039/C9OB02045D

[41]. Copper-catalyzed oxidative condensation of α-oxocarboxylic acids with formamides: synthesis of α- ketoamides. https://doi.org/10.1039/C3OB40787J

[42]. Correction: Copper-catalyzed, hypervalent iodine mediated C C bond activation of enaminones for The synthesis of α-keto amides https://doi.org/10.1039/C6CC90115H

[43]. Copper(II)-Mediated Aerobic Oxidation of Benzylimidates: Synthesis of Primary α-Ketoamides https://doi.org/10.1021/acs.joc.6b01262

[44]. Copper-catalyzed coupling of anthranils and α-keto acids: direct synthesis of α-ketoamides https://doi.org/10.1039/C9OB00822E

[45]. Dioxygen Activation under Ambient Conditions: Cu-Catalyzed Oxidative Amidation−Diketonization of Terminal Alkynes Leading to α-Ketoamides. https://doi.org/10.1021/ja908911n
[46]. Synthesis of α-keto imides through copper-catalyzed oxidation of N-sulfonyl ynamides https://doi.org/10.1039/C7OB02728A
[47]. Diverse Oxidative C(sp2)-N Bond Cleavages of Aromatic Fused Imidazoles for Synthesis of α- Ketoamides and N-(pyridin-2-yl)arylamides. https://doi.org/10.1021/acs.joc.9b00208
[48]. Copper/TEMPO-Promoted Denitrogenation/Oxidation Reaction for Synthesis of Primary α- Ketoamides Using α-Azido Ketones https://doi.org/10.1021/acs.joc.2c01814
[49]. Synthesis of □-Ketoamides from Aryl Methyl Ketones and N,N-Dimethylformamide via Copper-Catalyzed Aerobic Oxidative Coupling DOI: 10.1002/chin.201503083
[50]. Copper-Catalyzed Aerobic Oxidative Coupling of Aryl Acetaldehydes with Anilines Leading to A-Ketoamides. https://doi.org/10.1002/anie.201105285
[51]. Copper-catalyzed aerobic oxidative synthesis of α-ketoamides from methyl ketones, amines and NIS at room temperature https://doi.org/10.1039/c2ob26586a
[52]. Copper-Catalyzed Aerobic Oxidative Coupling of Aryl Acetaldehydes with Anilines Leading to A-Ketoamides. https://doi.org/10.1002/anie.201105285
[53]. Copper-catalyzed direct oxidative synthesis of α-ketoamides from aryl methyl ketones, amines, and molecular oxygen. https://doi.org/10.1039/C1SC00312G
[54]. Copper-Catalyzed One-Pot Synthesis of α-Ketoamides from 1-Arylethanols
[55]. Sever down again search.
[56]. A copper iodide-catalyzed coupling reaction of benzofuran-3(2H)-ones with amines: an approach to A-ketoamides. https://doi.org/10.1039/D1OB00715G
[57]. Copper-catalyzed oxidative cleavage of Passerini and Ugi adducts in basic medium yielding α- ketoamides. https://doi.org/10.1039/C9NJ03533H
[58]. Pending search
[59]. Copper(I) catalyzed oxidative hydrolysis of Ugi 3-component and Ugi-azide reaction products towards 2° α-ketoamides and α-ketotetrazoles. https://doi.org/10.1039/C7OB00881C
[60]. Formamidine hydrochloride as an amino surrogate: I2-catalyzed oxidative amidation of aryl methyl ketones leading to free (N–H) α-ketoamides. https://doi.org/10.1039/C4OB02591A
[61]. Pending search
[62]. I2-Catalyzed Oxidative Cross-Coupling of Methyl Ketones and Benzamidines Hydrochloride: A Facile Access to α-Ketoimides https://doi.org/10.1021/ol501029w
[63]. Pending search
[64]. Metal free one-pot synthesis of α-ketoamides from terminal alkenes. https://doi.org/10.1039/C5RA05671C
[65]. One pot synthesis of α-ketoamides from ethylarenes and amines: a metal free difunctionalization strategy https://doi.org/10.1039/C6OB02361D
[66]. Metal-Free C=C Double Bond Cleavage on Enaminones for the Synthesis of α-Ketoamides by Free-Radical Aerobic Oxygenation https://doi.org/10.1002/ejoc.201900660
[67]. Metal-Free Tandem Oxidative Aryl Migration and C-C Bond Cleavage: Synthesis of α- Ketoamides and Esters from Acrylic Derivatives. https://dx.doi.org/10.1021/ol502834g
[68]. Potassium Iodide/ Tert-Butyl Hydroperoxide Mediated Sequential Oxidative Amidation of Ethylarenes – A Direct Approach to α-Ketoamides and Amides. https://doi.org/10.1002/slct.201803936
[69]. Pd-Catalyst Containing a Hemilabile P,C-Hybrid Ligand in Amino Dicarbonylation of Aryl Halides for Synthesis of α-Ketoamides, https://doi.org/10.1021/acs.organomet.1c00024
[70]. POP-Pd(II) catalyzed easy and safe in situ carbonylation towards the synthesis of α-ketoamides from secondary cyclic amines utilizing CHCl3 as a carbon monoxide surrogate, https://doi.org/10.1039/C9NJ05089B

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[71]. Versatile palladium-catalyzed double carbonylation of aryl bromide. https://doi.org/10.1039/C7CC07412C
[72]. DOUBLE CARBONYLATION REACTIONS OF METHYL- AND PHENYLPALLADIUM(II) COMPLEXES IN THE PRESENCE OF SECONDARY AMINES AFFORDING α-KETO AMIDES https://www.journal.csj.jp/doi/pdf/10.1246/cl.1982.865
[73]. Palladium complexes grafted onto mesoporous silica catalysed the double carbonylation of aryl iodides with amines to give a-ketoamides. DOI: 10.1039/c2cy00516f
[74]. Kobayashi, T.; Tanaka, M. J. Organomet. Chem. 1982, 233, C64–C66.
[75]. Tsukada, N.; Ohba, Y.; Inoue, Y. J. Organomet. Chem. 2003, 687, 436–443.
[76]. Palladium-Catalyzed Double and Single Carbonylation of Aryl Halides and Allylic Compounds, https://doi.org/10.1246/bcsj.68.433
[77]. Palladium-catalyzed double carbonylation of alkyl iodides bearing perfluoroalkyl group. https://doi.org/10.1016/S0040-4039(00)99373-0
[78]. Hypervalent iodine in synthesis 68: palladiumcatalysed double carbonylation of Diaryliodonium salts to give α-keto-amides. DOI: 10.3184/030823401103169180
[79]. A Novel Approach for the One-Pot Preparation of α-Amino Amides by Pd-Catalyzed Double Carbohydroamination. DOI: 10.1016/S0040-4039(99)00596-1
[80]. Palladium-catalyzed mono- and double-carbonylation of indoles with amines controllably leading to amides and α-ketoamides. https://doi.org/10.1039/C2CC36341K
[81]. Palladium-catalysed carbonylation of aryl halides in ionic liquid media: high catalyst stability and significant rate-enhancement in alkoxycarbonylation. https://doi.org/10.1039/B100951F
[82]. Low pressure Pd-catalyzed carbonylation in an ionic liquid using a multiphase microflow system. DOI https://doi.org/10.1039/B600970K
[83]. Double carbonylation of aryl iodides with primary amines under atmospheric pressure conditions using the Pd/PPh(3)/DABCO/THF system. DOI: 10.1021/jo0156924
[84]. A phosphine-free Pd catalyst for the selective double carbonylation of aryl iodides. https://doi.org/10.1039/C2CC17124D
[85]. Double carbonylation of aryl iodides with amines under an atmospheric pressure of carbon monoxide using sulfur-modified Au-supported palladium. https://doi.org/10.1039/C4GC02469A
[86]. Covalent triazine framework-supported palladium as a ligand-free catalyst for the selective double carbonylation of aryl iodides under ambient pressure of CO. https://doi.org/10.1039/C5CC10389D
[87]. New palladium-catalyzed aerobic oxidative cleavage and cyclization of N-aryl peptide derivatives. https://doi.org/10.1039/B716849G
[88]. A Palladium(II)-Catalyzed Synthesis of α-Ketoamides via Chemoselective Aroyl Addition to Cyanamides. https://doi.org/10.1002/adsc.201400011
[89]. Water dispersed gold nanoparticles catalyzed aerobic oxidative cross-dehydrogenative coupling: An efficient synthesis of α-ketoamides in water. https://doi.org/10.1016/j.tetlet.2018.08.042
[90]. (A) Ruthenium-Catalyzed N-Alkylation of Amines and Sulfonamides Using Borrowing Hydrogen Methodology. https://doi.org/10.1021/ja807323a (B) One-Pot Oxidative Esterification and Amidation of Aldehydes. https://doi.org/10.1002/chem.200890128 (C) Palladium-catalyzed oxidative sp2 C-H bond acylation with alcohols. DOI 10.1021/ol200017a
[91]. (D) Palladium-Catalyzed Oxidative sp2 C-H Bond Acylation with Aldehydes. https://doi.org/10.1002/adsc.200900874
[92]. Selective oxidation of ethanol to acetaldehyde on gold. DOI 10.1021/ja805303s (b) Reactivity of the gold/water interface during selective oxidation catalysis. 10.1126/science.1195055 (c) Theoretical study of O-assisted selective coupling of methanol on Au(111). DOI 10.1021/jp110835w.
[93]. Synthesis of α-Ketoamides via Gold(I) Carbene Intermediates.

https://doi.org/10.1021/acs.orglett.2c01489
[94]. Use of Hypervalent Iodine Reagents in Visible Light-Promoted α-Ketoacylations of Sulfoximines with Aryl Alkynes. https://doi.org/10.1021/acs.orglett.0c03338
[95]. Visible-light-mediated direct access to α-ketoamides by dealkylative amidation of tertiary amines with benzoylformic acids. https://doi.org/10.1016/j.tetlet.2019.151191
[96]. Selective amidation by a photocatalyzed umpolung reaction. https://doi.org/10.1039/C9CC01079C
[97]. Visible-Light Mediated Photooxidative Synthesis of α-Keto Amides. https://doi.org/10.1002/adsc.201900279
[98]. Copper(I)-catalysed oxidative C–N coupling of 2-aminopyridine with terminal alkynes featuring a C C bond cleavage promoted by visible light. https://doi.org/10.1039/C6CC05506K
[99]. Electrochemical Synthesis of α-Ketoamides under Catalyst-, Oxidant-, and Electrolyte-Free Conditions. https://doi.org/10.1021/acs.orglett.0c00387
[100]. A two-step continuous synthesis of α-ketoamides and α-amino ketones from 2° benzylic alcohols using hydrogen peroxide as an economic and benign oxidant. https://doi.org/10.1039/C5RA27653E
[101]. Waste-Minimized, Solvent-Free and Continuous Flow Synthesis of A-Ketoamides from Aryl Methyl Ketones Using Recyclable Cubr2 Catalyst, Via Bromo Intermediate. https://dx.doi.org/10.2139/ssrn.4402150
[102]. Simple Catalytic Mechanism for the Direct Coupling of α-Carbonyls with Functionalized Amines: A One-Step Synthesis of Plavix. https://doi.org/10.1021/ja4096472
[103]. (a) Catalytic Dehydrogenative Cross-Coupling: Forming Carbon−Carbon Bonds by Oxidizing Two Carbon−Hydrogen Bonds https://doi.org/10.1021/cr100280d (b) From Oblivion into the Limelight: Iron (Domino) Catalysis https://doi.org/10.1002/anie.200805728 (c) ron- Catalyzed C−C Bond Formation via Chelation-Assisted C−H Activation https://doi.org/10.1002/ijch.201700047 (d) From Oblivion into the Limelight: Iron (Domino) Catalysis https://doi.org/10.1002/anie.200805728
[104]. Selenium Dioxide Promoted α-Keto N-Acylation of Sulfoximines Under Mild Reaction Conditions https://doi.org/10.1002/ajoc.202100298
[105]. DABCO-Catalysed Amidation under Assistance of Aerial Oxidation: Access to α- ketoamides. https://doi.org/10.1002/slct.201801981
[106]. Synthesis of α-ketoamides using potassium superoxide (KO2) as an oxidizing agent. https://doi.org/10.1016/j.tet.2020.131262
[107]. Metal-free oxidative amidation of 2-oxoaldehydes: a facile access to α-ketoamides. Doi: 10.1021/ol5000204.
[108]. Metal-Free Syntheses of α-Ketothioamide and α-Ketoamide Derivatives from Sulfoxonium Ylides. https://doi.org/10.1021/acs.orglett.2c03371
[109]. Structure–Activity Relationship Studies of α-Ketoamides as Inhibitors of the Phospholipase A and Acyltransferase Enzyme Family. https://doi.org/10.1021/acs.jmedchem.0c00522