CHEMICAL REVIEWS

Review

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Recent Developments in General Methodologies for the Synthesis of α-Ketoamides

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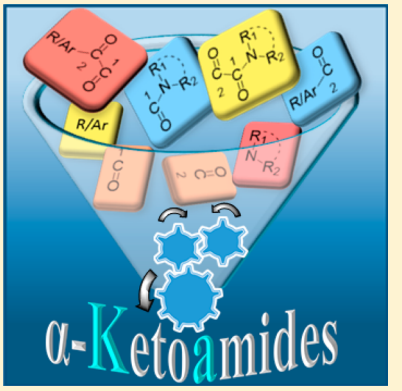
ABSTRACT: The α-ketoamide motif is widely found in many natural products and drug candidates with relevant biological activities. Furthermore, α-ketoamides are attractive candidates to synthetic chemists due to the ability of the motif to access a wide range of functional group transformations, including multiple bond-forming processes. For these reasons, a vast array of synthetic procedures for the preparation of α-ketoamides have been developed over the past decades, and the search for expeditious and efficient protocols continues unabated. The aim of this review is to give an overview of the diverse methodologies that have emerged since the 1990s up to the present. The different synthetic routes have been grouped according to the way the α-ketoamide moiety has been created. Thus, syntheses of α-ketoamides proceeding via C(2)-oxidation of amide starting compounds are detailed, as are amidation approaches installing the α-ketoamide residue through C(1)−N bond formation. Also discussed are the methodologies centered on C(1)−C(2) σ-bond construction and C(2)−R/Ar bond-forming processes. Finally, the literature regarding the synthesis of α-ketoamide compounds by palladium-catalyzed double-carbonylative amination reactions is discussed.



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1. INTRODUCTION

1.1. Natural and Non-Natural α-Ketoamides

The α-ketoamide structural moiety represents the key framework of many natural and non-natural products displaying a broad spectrum of biological activities. For instance, these include members isolated from several *Streptomyces* species, such as the immunosuppressant drugs FK506, a 23-membered macrolide from *Streptomyces tsukubaensis*,[1] and rapamycin, isolated from *Streptomyces hygroscopicus*,[2] which are T-cell proliferation blockers (Figure 1).

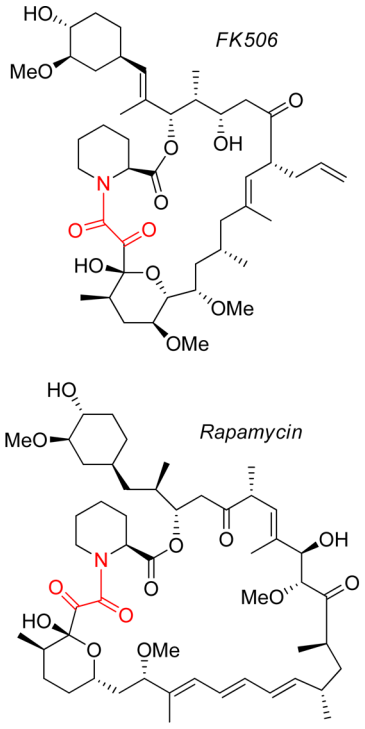

Figure 1. Structure of T-cell proliferation blockers FK506 and rapamycin.

Complestatin (chloropeptin II), originally isolated from the mycelium of *Streptomyces lavendulae* SANK 60477,[3] and its isomer chloropeptin I, obtained from *Streptomyces* sp. WK-3419[4] (Figure 2), are proven to inhibit HIV replication, and studies on their total synthesis, modification, and activity attracted the efforts of many chemists.[5−7]

Moreover, eurystatins A and B, produced by *Streptomyces eurythermus* R353-21,[8] and the pentapeptide poststatin (H-Val-Val-Pos-D-Leu-Val-OH), isolated from *Streptomyces viridochromogenes*,[9] have been shown to inhibit prolyl endopeptidase (Figure 3).

Notably, poststatin incorporates an unusual α-keto-β-amino acid residue, namely, (*S*)-3-amino-2-oxopentanoic acid (L-postine, Pos), between valylvaline and D-leucylvaline dipeptides. Similarly to poststatin, a number of naturally occurring α-

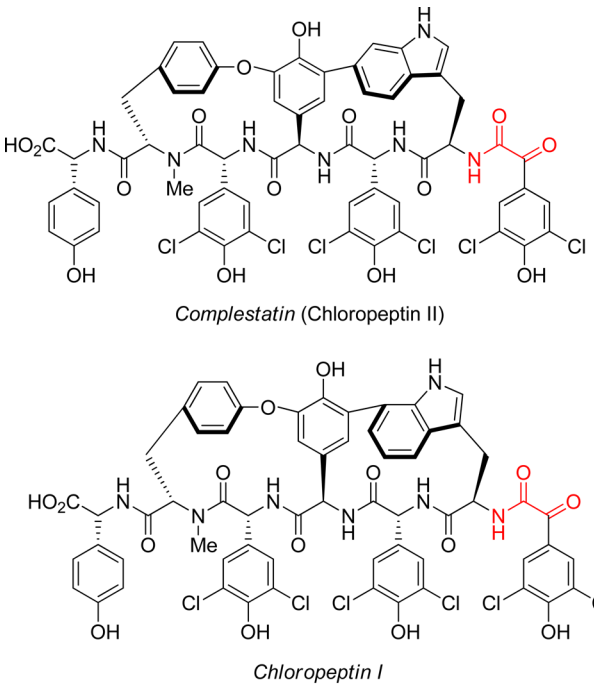

Figure 2. Structure of HIV inhibitors complestatin and chloropeptin I.

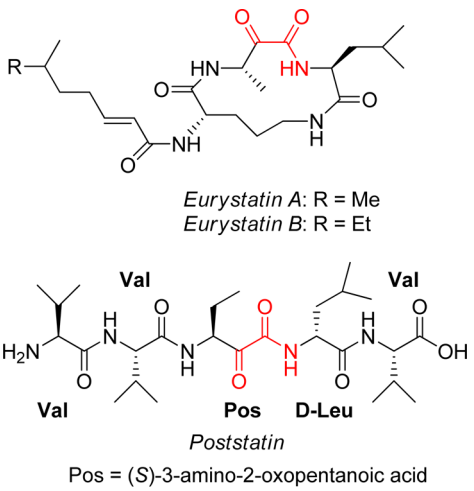

Figure 3. Structure of prolyl endopeptidase inhibitors eurystatin A and B and poststatin.

ketoamide-containing compounds incorporate nonconventional α-keto-β-amino acids. As an important case in point, α-ketohomoarginine (k-Arg) is present in cyclotheonamides (Ct, Figure 4), a family of macrocyclic pentapeptides isolated from the Japanese marine sponge *Theonella swinhoei* that have been shown to be potent inhibitors of serine proteases, such as thrombin and trypsin.[10−12]

Structurally, the two major forms, CtA and CtB, contain a vinylogous tyrosine (V-Tyr) fragment, while CtC is appended with a dehydrovinylogous tyrosine (D-V-Tyr). Derivative CtD features a Leu residue in place of the D-Phe one, while CtE has a phenylacetylalanyl side chain. Further modifications in the *N*-acyl group of the alanyl side chain differentiate derivatives CtE2 and CtE3. In 2002, two new tryptase inhibitors, cyclotheonamides E4 and E5, were isolated from a marine sponge of the genus *Ircinia*.[13] The former showed potent inhibitory activity against human tryptase, paving the way to its possible

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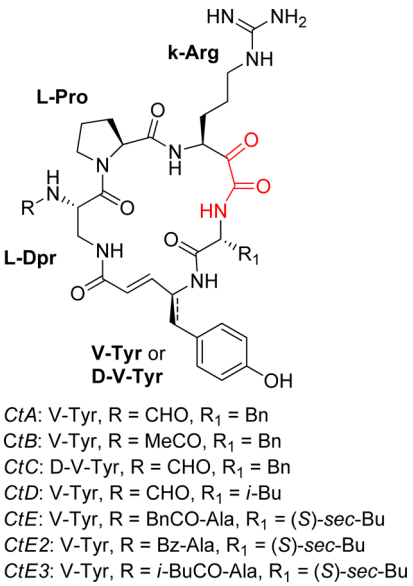

Figure 4. Structure of serine proteases inhibitors cyclotheonamides A–D, E, E2, and E3.

use as a therapeutic agent in the treatment of allergic diseases, including asthma.

Importantly, it has been demonstrated that the α-ketoamide moiety, harbored with the k-Arg unit, is responsible for the unique mode of action of cyclotheonamides, with the α-keto group taking part in the formation of a reversible tetrahedral adduct with a hydroxyl group of the enzyme's active site.[14,15]

The cyclic peptides jahnellamides A and B, recently isolated from the terrestrial myxobacterium *Jahnella* sp., contain a number of unusual non-proteinogenic amino acids, including α-keto-β-methionine (k-Met) (Figure 5).[16] f5

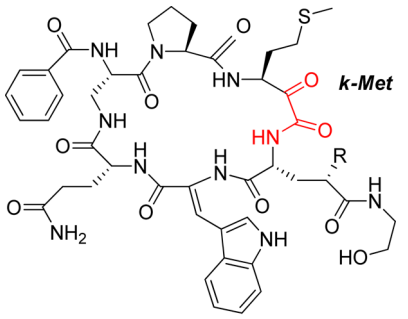

Figure 5. Structure of jahnellamides A and B.

A combination of feeding experiments and in silico analysis suggested that jahnellamides A and B are assembled through a modular mixed nonribosomal peptide synthetase (NRPS)–polyketide synthase (PKS) pathway, with the α-keto functionality being formed in a similar fashion to that proposed for the α-ketoserine-containing peptide myxoprincomide.[17] At present, there are only a few biological data on jahnellamides showing that janellamide A shows neither antifungal activity nor cytotoxicity toward HCT-116 cells, but predictably further evaluation will be pursued to evaluate the biological meaningfulness of this new class of natural products.

The macrocyclic depsipeptide aplidine (Figure 6), also known as dehydrodidemnin B, was isolated in 1990 from the f6

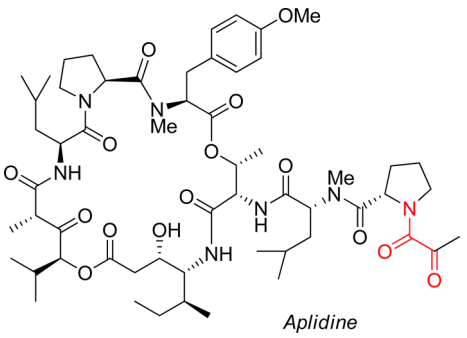

Figure 6. Structure of aplidine.

Mediterranean invertebrate *Aplidium albicans*.[18] It has stood out as a potent antitumoral and is currently in multiple phase II and III trials for the treatment of various cancers.[19]

Non-natural molecules incorporating the α-ketoamide motif have attracted interest in connection with their wide range of biological activities. For example, peptide α-ketoamides proved to be active as cysteine proteases inhibitors.[20−22] In the case of calpain I inhibitors, it is likely that an initially formed reversible enzyme–inhibitor complex suffers attack of the active site cysteine residue (Cys115) on the keto carbonyl group of the α-ketoamide compound, giving rise to a stable but reversible tetrahedral hemithioketal adduct linking the active site histidine residue (His272) via a hydrogen bond (Figure 7). f7

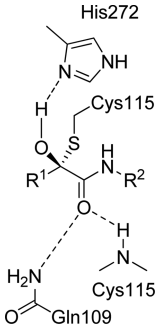

Figure 7. Proposed mechanism of calpain I inhibition by α-ketoamide peptides.

α-Ketoamides have been also used in developing inhibitors of thrombin,[23] HIV protease,[24,25] norovirus 3CL protease,[26] cathepsin K,[27,28] histone deacetylase (HDAC),[29] peptidyl-prolyl isomerase (PPIase),[30,31] phospholipase A_2 (PLA_2),[32−35] leukotriene A4 (LTA_4) hydrolase,[36] epoxide hydrolase,[37] and orexin receptor antagonists[38] (Figure 8). f8

It is worthy of note that among the NS3 serine protease inhibitors from the slow-binding reversible α-ketoamide class under clinical trials or in the market, boceprevir[39] and telaprevir[40] (Figure 9) have been approved by the FDA (U.S. Food and Drug Administration) as therapy for chronic hepatitis C virus (HCV) genotype 1 in May, 2011. Further detailed investigations culminated in the discovery of narlaprevir, with improved potency (~10-fold over boceprevir), pharmacokinetic profile, and physicochemical characteristics.[41] f9

Recently, a systematic comparison of proteasome inhibitors based on a peptidic backbone endowed with an electrophilic C-

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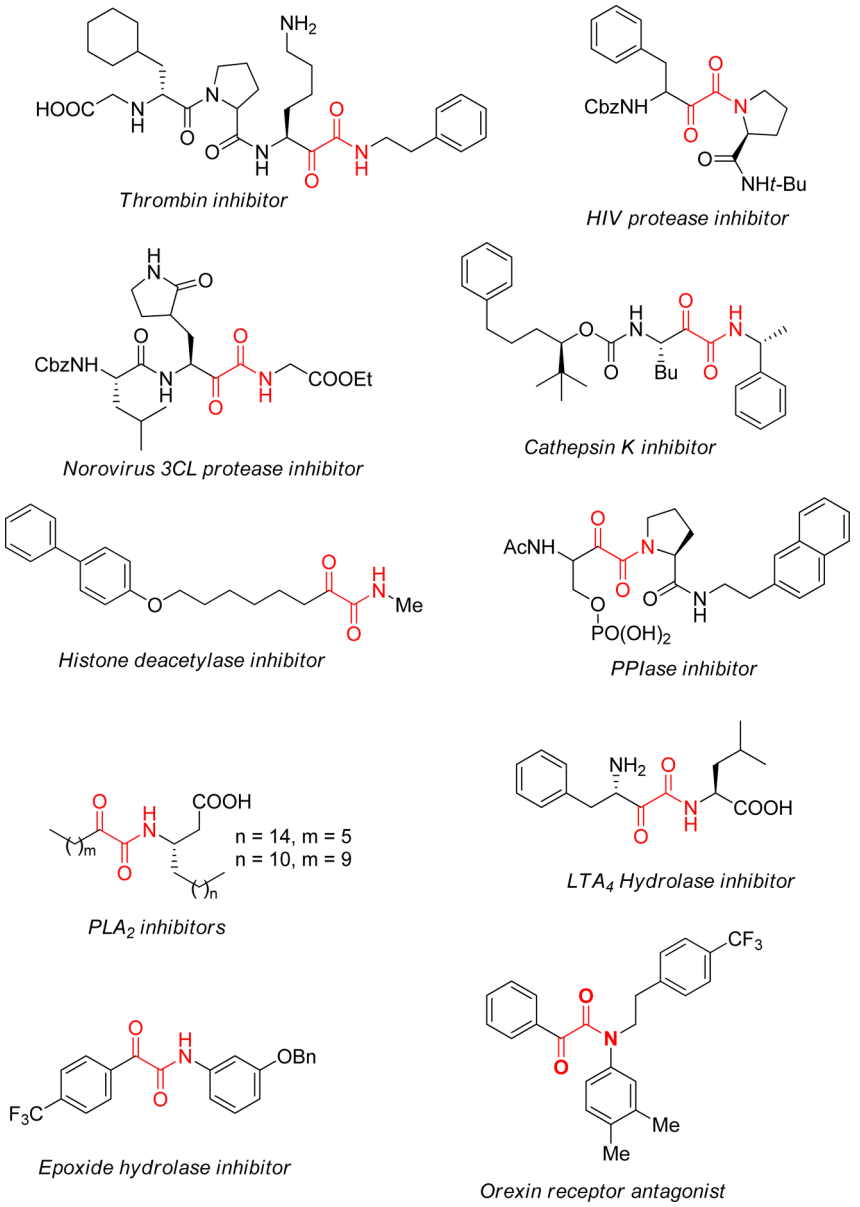

Figure 8. Non-natural biologically active α-ketoamides.

terminus including aldehyde, α-ketoaldehyde, α,β-epoxy ketone, boronic acid, vinyl sulfone, and α-ketoamide moieties has been reported. This study highlighted peptides featuring the α-ketoamide warhead as the most potent reversible inhibitors, with possible applications for the therapy of solid tumors as well as autoimmune disorders.[42]

1.2. Applications of α-Ketoamides

α-Ketoamides may serve as useful precursors for a variety of transformations in organic synthesis. As 1,2-dicarbonyl compounds, they are ambident pronucleophiles,[43−45] with the presence of adjacent multiple reactive centers allowing for selection of specific activation modes to enhance their reactivity. Actually, α-ketoamides display two potential nucleophilic reaction sites, besides two electrophilic centers (Figure 10).

Recently, both the nucleophilicity and electrophilicity of α-ketoamides have been successfully used in single-bond- or multibond-forming asymmetric processes leading to the synthesis of polyfunctionalized acyclic and cyclic architectures. For example, α-ketoanilides were applied as synthetic equivalents of homoenolates in catalytic asymmetric Mannich-type[46,47] and Michael reactions[48−50] with *N*-sulfonyl imines and nitroalkenes, respectively. Importantly, the pronucleophilic character and the presence of the electrophilic ketone moiety have been simultaneously exploited in the diastereo- and enantioselective synthesis of hexasubstituted cyclohexane derivatives by a Michael−Michael−Henry cascade reaction.[49,51]

The organocatalytic asymmetric synthesis of pyrrolidin-2-one derivatives has been successfully achieved from α,β-unsaturated aldehydes and α-ketoamides by aza-Michael/aldol domino reaction[52] and aza-Michael/aldol condensation/vinylogous Michael/aldol condensation[53] cascade sequence. Furthermore, highly enantioselective Pictet−Spengler reaction[54] of ketimines derived from α-ketoamides leading to optically active quaternary α-amino acid derivatives has been reported.[55]

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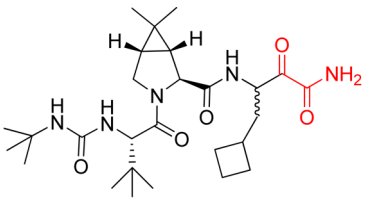
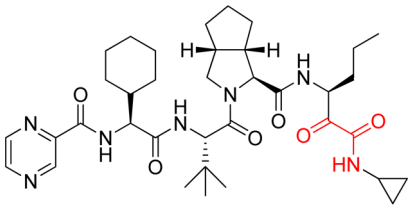
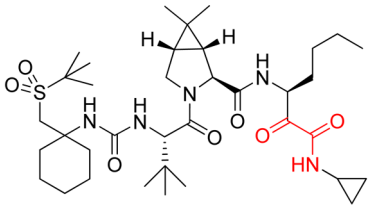


Boceprevir (SCH 503034)



Telaprevir (VX-950)



Narlaprevir (SCH 900518)

Figure 9. Structure of HCV NS3 serine protease inhibitors boceprevir, telaprevir, and narlaprevir.

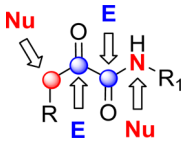


Figure 10. Potential reaction sites in α-ketoamides. Nu = nucleophilic, E = electrophilic.

1.3. Aim of the Review

In view of both the peculiar structural features and the important biological roles of α-ketoamides, it is not surprising that a plethora of different methods for their efficient synthesis have been and continue to be proposed. However, no comprehensive reviews dealing with the synthesis of α-ketoamides have appeared hitherto in the literature, unlike α-keto acids[56−58] and α-keto esters.[59−61]

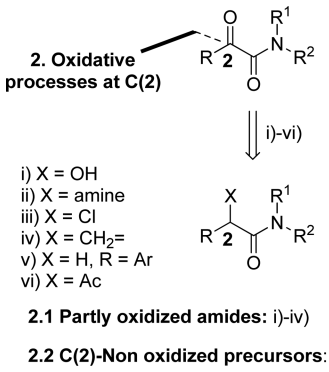
The aim of this review is to cover the important progress that has been made for the preparation of α-ketoamides from the 1990s up to the present. The synthetic routes to α-ketoamides have been grouped according to the way the α-ketoamide architecture has been assembled. Thus, syntheses of α-ketoamides occurring via C(2)-oxidation of amide starting compounds are discussed in section 2, while examples of amidation approaches are detailed in section 3. Methodologies for α-ketoamides preparation centered on the C(1)−C(2) σ bond construction are covered in section 4, and section 5 is dedicated to C(2)−R/Ar bond forming processes. Finally, section 6 contains the literature dealing with the palladium-catalyzed double-carbonylative amination reactions.

2. OXIDATIVE PROCESSES AT C(2)

In this section, synthetic approaches to α-ketoamides occurring via C(2)-oxidation of amide starting compounds are discussed.

In particular, subsection 2.1 deals with syntheses that make use of partly oxidized amides, such as α-hydroxy, α-amino, and α-chloroamide derivatives, while methods providing α-ketoamides from C(2)-nonoxidized amide precursors have been collected in subsection 2.2 (Scheme 1).

Scheme 1. Oxidative Processes at C(2)



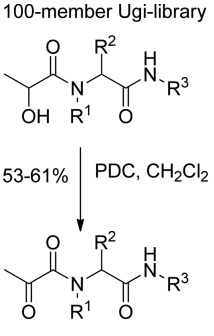
2.1. Partly Oxidized Amides

2.1.1. Oxidation of 2-Hydroxyamides. The oxidation of an alcohol to the corresponding carbonyl compound is a common transformation in synthetic organic chemistry, and several methods to accomplish this fundamental functional group manipulation are reported in the literature.[62] Not surprisingly, α-ketoamides have been conveniently obtained by oxidation of previously prepared α-hydroxyamides.

In search for cysteine protease inhibitors, Nakamura and co-workers[63] were able to prepare a combinatorial library of α-hydroxyamides by reaction of DL-lactic acid with a set of five aldehydes, five amines, and four isocyanides under parallel solution-phase conditions. The resulting 100-member Ugi-library was oxidized with PDC in the same reaction vessel to give *N*-pyruvoyl amino acid derivatives in moderate yields (Scheme 2).

Xu et al.[64] prepared an Ugi-library of 32 α-hydroxyamides through liquid-phase combinatorial synthesis using four carboxylic acids, two amines, two aldehydes, and two isocyanide/α-hydroxyamide hybrids. In the second step, DMP was used as oxidant, giving peptidomimetic α-ketoamides

Scheme 2. Oxidation of 2-Hydroxyamides Reported by Nakamura et al.[63]



R^1 = pyrrolidin-2-one-*N*-$(CH_2)_3$, Pr, Bn ,$Ph(CH_2)_2$, $Ph(CH_2)_3$
R^2 = H, $Ph(CH_2)_2$, $(Ph)_2CH$, Cy, *i*-Pr
R^3 = *t*-Bu, Cy, Bu, *t*-BuOCOCH$_2$

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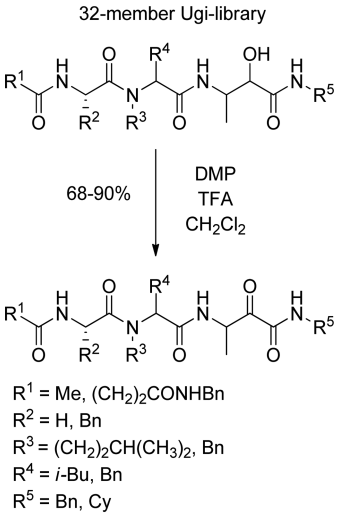
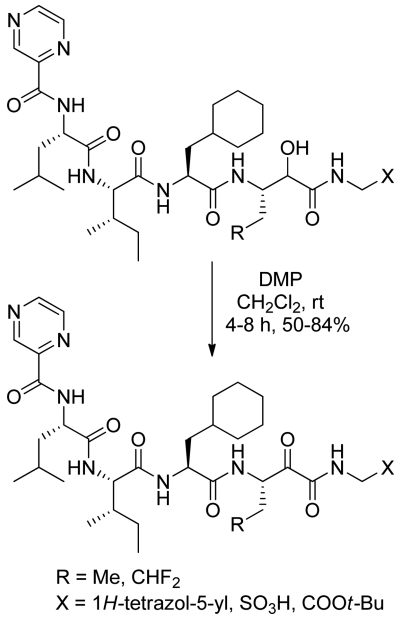
designed to inhibit the human cytomegalovirus protease (Scheme 3).

Scheme 3. Oxidation of 2-Hydroxyamides Reported by Xu et al.[64]



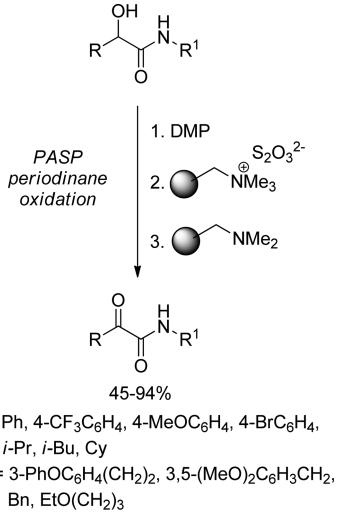
Incorporation of a β-amino-α-hydroxy acid moiety in a peptide chain followed by DMP oxidation allowed researchers at the Bristol-Myers Squibb Co.[65] to obtain glycine α-ketoamide oligopeptides active as HCV NS3 protease inhibitors (Scheme 4).

Scheme 4. Oxidation of 2-Hydroxyamides Reported by Han et al.[65]



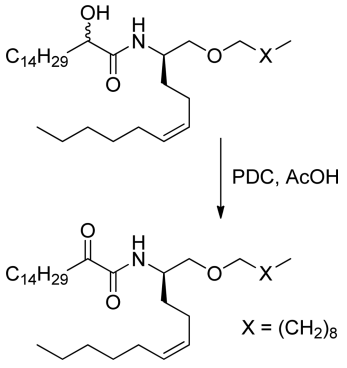
Parlow and co-workers.[66] prepared a chemical library of α-ketoamides using polymer-assisted solution-phase synthesis both to couple α-hydroxy acids with amines and oxidize the resulting α-hydroxyamide derivatives using an excess of DMP (Scheme 5). After completion of the reaction, the mixture was sequentially treated with a thiosulfate resin, in order to reduce the excess of DMP, and Amberlyst A-21 resin, to sequester the resulting 2-iodobenzoic acid. Filtration, rinsing with dichloromethane, and concentration afforded the expected α-ketoamides in moderate to high yield. The method was revealed to be compatible with a variety of aryl and alkyl moieties on both diversity sites of the α-ketoamide.

Scheme 5. Oxidation of 2-Hydroxyamides Reported by South et al.[66]



Kokotos and co-workers[67] prepared a pancreatic lipase inhibitor featuring the α-ketoamide moiety incorporated into a lipophilic ether backbone (Scheme 6). The PDC oxidation of diastereomeric α-hydroxyamides was selected as the final synthetic step to set up the reactive functional group.

Scheme 6. Oxidation of 2-Hydroxyamides Reported by Kokotos and Co-Workers[67]



Later, the same research group applied a hydroxyamidation−oxidation strategy to the synthesis of potent and selective inhibitors of the human cytosolic phospholipase A_2 (GIVA PLA_2).[68] Thus, the coupling of DL-α-hydroxypalmitic acid with glycine, β-alanine, and γ-aminobutyric and δ-aminovalerianic acid esters gave the expected α-hydroxyamides, which were easily transformed to the designed PLA_2 inhibitors by NaOCl−TEMPO oxidation (Scheme 7).

The same oxidation system proved suitable for the preparation of lipophilic 2-oxoamides shown in Figure 11.

The simultaneous C(2)-oxidation of a α-hydroxyamide moiety and a phenyl ring by using the $NaIO_4$−$RuCl_3$ system[33] was envisaged as the successful strategy for the enantioselective synthesis of β- and δ-norleucine-based inhibitors (Scheme 8).

The oxidation of a 2-hydroxyamide under Moffatt conditions was the last step along the synthesis of the serine protease

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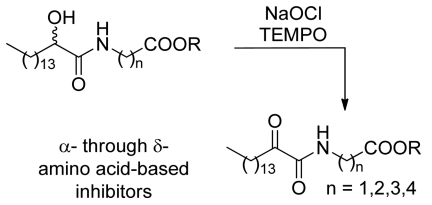
Scheme 7. Oxidation of 2-Hydroxyamides Reported by Kokotos and Co-Workers[68]



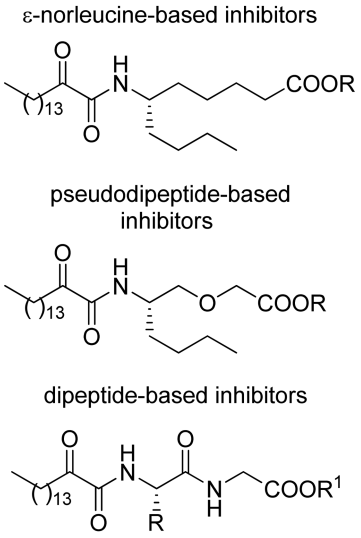
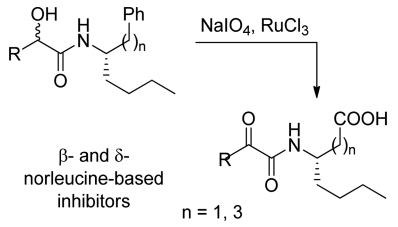


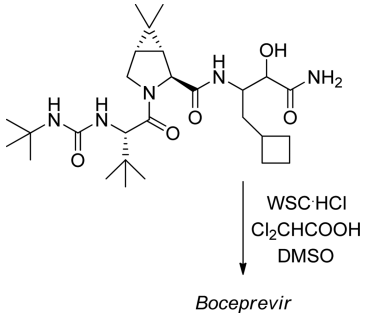
Figure 11. Lipophilic 2-oxoamides incorporating (*S*)-configured amines.

Scheme 8. Oxidation of 2-Hydroxyamides Reported by Dennis and Co-Workers[33]



s9 inhibitor boceprevir (Scheme 9).[69] Recently, this oxidation was performed with DMP in ethyl acetate,[70] thus avoiding the displeasing odor of dimethyl sulfide, which represents an important drawback on the industrial scale.[71]

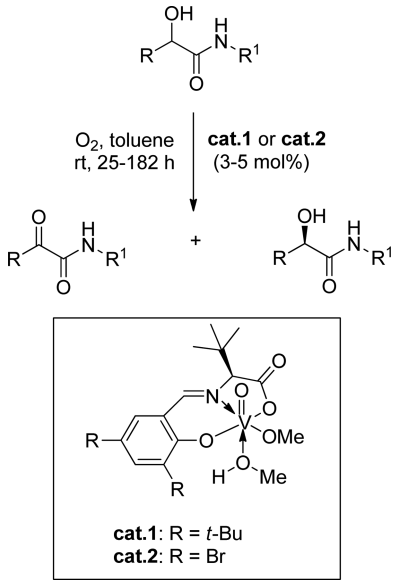
Scheme 9. Oxidation of 2-Hydroxyamides Reported by Venkatraman et al.[69]



Several methodologies for the oxidation of alcohols with stoichiometric dioxygen by using metal oxides as well as homogeneous or heterogeneous metal complexes as the catalysts have been developed in the last two decades. Furthermore, in recent years the asymmetric variants of the aerobic catalytic processes have attracted a lot of attention.

In this context, Chen and co-workers[72] reported the asymmetric aerobic oxidation of α-hydroxy esters and α-hydroxyamides promoted by chiral *N*-salicylidene vanadyl carboxylate catalysts (Scheme 10). Thus, the kinetic resolution s10

Scheme 10. Oxidation of 2-Hydroxyamides Reported by Chen and Co-Workers[72]



of racemic α-hydroxyamides afforded the achiral α-ketoamides together with the target chiral nonracemic α-hydroxyamides. The vanadyl(V)−methoxide complexes **cat.1** and **cat.2**, derived from *N*-salicylidene-L-α-amino acids and vanadyl sulfate, served as efficient catalysts for the asymmetric aerobic oxidation of a variety of α-hydroxyamides at ambient temperature in toluene. An array of α- and N-substituents were tolerated, with **cat.1** being recommended for the oxidation of α-aryl-α-hydroxyamides, while **cat.2** was used to oxidize α-alkyl-α-hydroxyamides.

2.1.2. Oxidation of 2-Aminoamides. The oxidation of α-aminoamides to the corresponding α-ketoamides has been less frequently utilized in comparison to the same operation on α-hydroxyamides, and only a few synthetic approaches are described in the literature.

The solid-phase synthesis of new protease inhibitors entailed a selective conversion of the *N*-terminal α-amino group of peptides into a α-ketocarbonyl moiety (Scheme 11).[73] Thus, s11 the tetrapeptide Leu-Phe-Leu-Gly was assembled through solid-phase peptide synthesis (SPPS), and the resulting resin-bound peptide was oxidized under transamination conditions with sodium glyoxylate in the presence of sodium acetate and catalytic copper sulfate.

Actually, an efficient and quantitative enzyme-free transfer of the amine group from the *N*-terminal amino acid to the electron-deficient aldehyde of glyoxylate smoothly took place in an aqueous buffer at pH 5.5−6.0 to give resin-bound 4-methyl-2-oxopentanoyl-Phe-Leu-Gly, which eventually detached upon saponification (Scheme 11).

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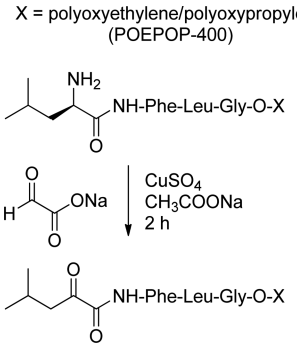
Scheme 11. Oxidation of 2-Aminoamides Reported by Meldal and Co-Workers[73]

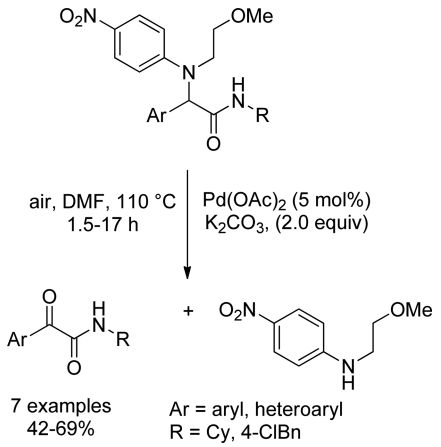


The ample scope of the method was demonstrated by submitting to the transamination conditions the pentapeptides obtained through elongation of the resin-bound tetrapeptide Leu-Phe-Leu-Gly with 10 different N-terminal amino acids, namely, Gly, Leu, Thr(*t*-Bu), Cys(Trt), Glu(*t*-Bu), Gln, Lys(Boc), Trp, Arg(Pmc), and His. In all the cases but one, the corresponding α-ketocarbonyl peptides were formed as confirmed by a combination of HPLC and MALDI-MS analyses. The cuprate binding to the histidine residue was assumed to be responsible for the failure of the transamination reaction. Importantly, the resin-bound α-ketocarbonyl peptides have been used in on-bead assays for the identification of protease inhibitors structures.

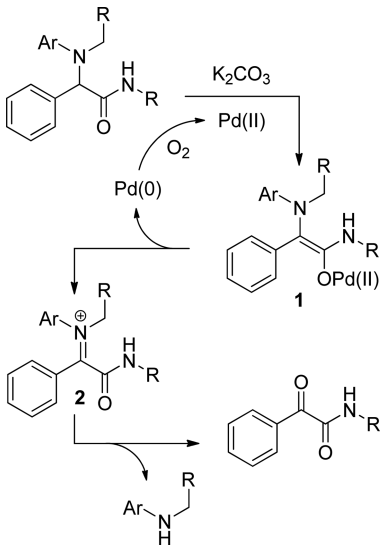
In 2005, El Kaïm and co-workers reported an efficient strategy for the N-arylation of primary amines via an Ugi–Smiles four-component reaction leading phenols, amines, aldehydes, and isocyanides to condense with formation of α-aryl-α-arylaminoacetamides.[74] Later on, the multicomponent process was envisioned as a straightforward synthetic entry to compounds suitable for Pd-catalyzed postcondensation transformations providing polycyclic derivatives.[75] Contrary to this expectation, the α-aminoamides underwent fragmentation under Heck-like reaction conditions to give aryl α-ketoamides together with the *p*-nitroaniline derivative (Scheme 12).

Only α-aryl-α-aminoacetamides bearing an acidic α-proton were suitable substrates for the Pd-mediated oxidative cleavage. Accordingly, the formation of the Pd(II) enolate **1** was assumed as the starting step. Then, discharge of Pd(0) gave the iminium intermediate **2**, which was hydrolyzed to the target α-ketoamide (Scheme 13).

Scheme 12. Oxidation of 2-Aminoamides Reported by El Kaïm et al.[75]

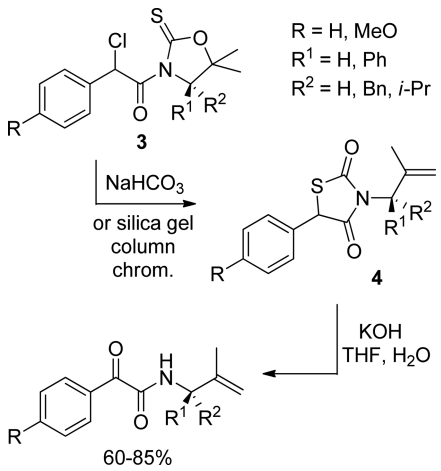


Scheme 13. Mechanism Proposed for the Pd-Promoted Fragmentation of α-Arylaminoamides[75]



2.1.3. Oxidation of 2-Chloroamides and α-Substituted Acryloyl Amides. A nonobvious method for the synthesis of chiral α-ketoamides entailed exposure of *N*-acyloxazolidine-thiones **3** to basic media.[76] Thus, the heterocyclic compounds, easily accessible via condensation of amino acid-derived chiral auxiliaries with α-chlorophenylacetyl chloride compounds, underwent a $NaHCO_3$-promoted elimination of HCl, triggering a tandem heterocyclic ring-opening/ring-forming process (Scheme 14). The resulting diastereomeric mixture of 5-phenylthiazolidine-2,4-diones **4** suffered an unexpected KOH-promoted carbon monosulfide expulsion reaction, providing chiral nonracemic α-ketoamides in good yields.

Scheme 14. Oxidation of 2-Chloroamides Reported by Ortiz and Co-Workers[76]



Hon et al.[77] prepared α-ketoamides of 2-oxononanoic acid by ozonolysis of α-substituted acryloyl amides, in turn prepared by amidation of 2-methylenenonanoic acid with ammonium hydroxide, valine methyl ester, and pyrrolidine, respectively (Scheme 15).

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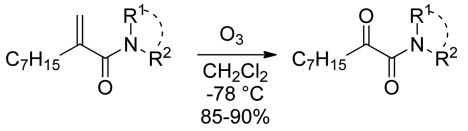
Scheme 15. Oxidation of α-Substituted Acryloyl Amides Reported by Hon et al.[77]

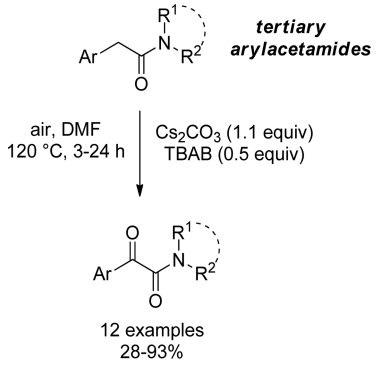


$R^1 = R^2 = H$; $R^1 = H$, $R^2 = CH(i\text{-}Pr)COOMe$
$R^1\text{-}R^2 = (CH_2)_4$

2.2. C(2)-Nonoxidized Amide Precursors

2.2.1. Oxidation of α-Arylacetamides. In 2007, Xu and co-workers[78] reported a simple and efficient entry to N,N-disubstituted aryl α-ketoamides through aerobic oxidation of α-deprotonated arylacetamides, as an adaptation of the DBU-mediated oxidation of phenacyl esters or amides previously applied by Pal et al.[79,80] for the preparation of 3,4-diaryl maleic anhydrides and maleimides. A series of easily available N,N-disubstituted arylacetamides were chemoselectively converted into the corresponding aryl α-ketoamides under mild reaction conditions without using any toxic or expensive reagent. As shown in Scheme 16, the reaction proceeded in DMF at 120 °C

Scheme 16. Oxidation of α-Arylacetamides Reported by Xu and Co-Workers[78]



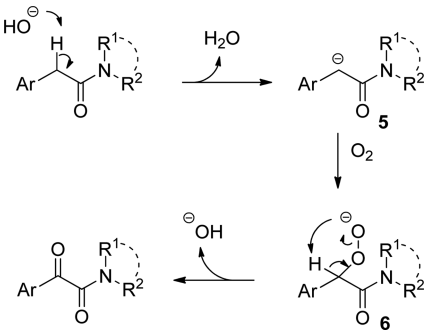
Ar = Ph, 2-BrC_6H_4, 3-BrC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-$NH_2C_6H_4$, 3-Py
$R^1\text{-}R^2 = (CH_2)_5$; $R^1 = R^2 = i\text{-}Pr$; $R^1 = R^2 = Ph$
$R^1 = Me$, $R^2 = Ph$

under air atmosphere employing Cs_2CO_3 (1.1 equiv) as the base in the presence of a catalytic amount of TBAB as an additive. Thus, irrespective of the nature of the aryl group, the C(2)-oxidative process provided the expected α-ketoamides in good to high yields.

The nitro group appeared to be the unique problematic substituent, as the α-ketoamide compound was formed in a modest 40% yield, while the easily oxidizable amino group as well as the pyridine nucleus were well-tolerated. Alkyl groups at the amide nitrogen atom, including bulky isopropyl groups, were suitable, while two phenyl groups produced a considerable drop in the yield of α-ketoamide (28%). The α-ketoamide featuring one methyl and one phenyl group at the nitrogen atom was isolated as a mixture of s-cis and s-trans isomers in 9:1 ratio, which was in agreement with findings by Takahashi et al.[81]

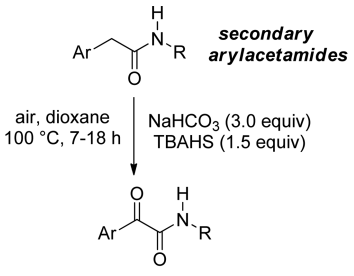
A possible mechanism to explain this transformation involved deprotonation at the benzylic position of the starting amide to give the enolate **5** (Scheme 17). Its reaction with molecular oxygen produced the peroxy anion **6**, which was eventually transformed to α-ketoamide by α-proton abstraction and hydroxyl anion expulsion.

Scheme 17. Mechanism Proposed for the Cs_2CO_3-Promoted Aerobic Oxidation of Tertiary Arylacetamides[78]



Five years later,[82] the same research group developed a synthetic route to *N*-monosubstituted aryl and heteroaryl α-ketoamides entailing an efficient sodium bicarbonate-promoted aerobic oxidation reaction of the corresponding amides in the presence of TBAHS. Thus, the secondary arylacetamides that were not suitable substrates for the Cs_2CO_3-promoted aerobic oxidation could be used as effective starting materials in the new oxidative process. The reactions occurred in open air by refluxing a dioxane solution of arylacetamide in the presence of $NaHCO_3$ (3.0 equiv) and TBAHS (1.5 equiv), providing secondary aryl α-ketoamides (Scheme 18). Clean conversions were observed for arylacetamides with a diverse array of substituents at the amide *N*-atom, provided that they were not electron-poor phenyls or alkyl groups.

Scheme 18. Oxidation of α-Arylacetamides Reported by Xu and Co-Workers[82]



Ar = aryl, heteroaryl; R = aryl, heteroaryl, alkyl

Very recently, α-ketoamides have been conveniently prepared by Cs_2CO_3-promoted DTBP oxidation of α-arylacetamides formed in situ by a radical/radical cross-coupling reaction of methylarenes with *N*,*N*-dialkylformamides (Scheme 19).[83] Under standard conditions, methylarenes were reacted with dialkylformamide compounds in the presence of TBAI (10 mol %), oxidant (8.0 equiv), and Cs_2CO_3 (2.0 equiv) as the base, at 120 °C under Ar atmosphere for 12 h. The process showed a broad substrate scope and functional group tolerance, producing the target α-ketoamides in good yields, with *N*,*N*-dialkylformamides other than DMF giving comparable results.

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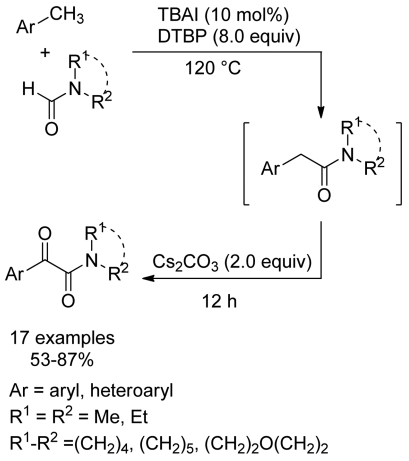
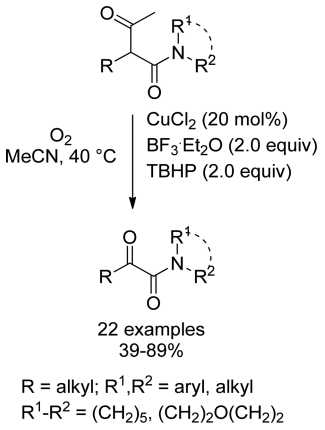
Scheme 19. Oxidation of α-Arylacetamides Reported by Feng and Co-Workers[83]



2.2.2. Oxidation of α-Substituted Acetoacetamides.

In 2013, Li and Yu[84] reported that α-substituted acetoacetamides could be transformed into aliphatic α-ketoamides upon treatment with Cu(II) salts in the presence of Lewis acids under aerobic conditions, well complementing the above protocols for aryl α-ketoamides preparation. A series of control experiments led to the selection of $CuCl_2$ and BF_3 as the most suitable copper catalyst and Lewis acid promoter, respectively, with the latter being necessary for the reaction to take place. Suitable working conditions for the oxidative deacetylation reaction entailed the use of TBHP as an additive oxidant at 40 °C in acetonitrile under an air atmosphere (Scheme 20). A

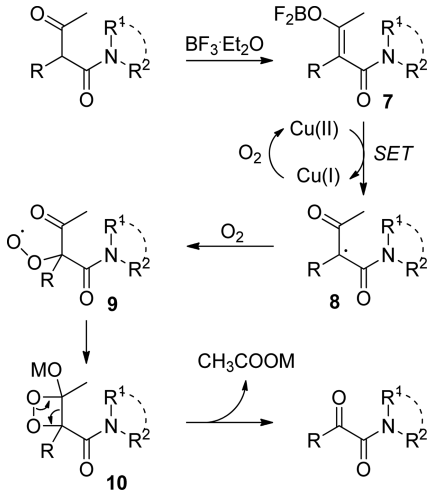
Scheme 20. Oxidation of α-Substituted Acetoacetamides Reported by Li and Yu[84]



variety of α-substituted tertiary acetoacetamides were successfully oxidized to the corresponding α-ketoamides, while both α-unsubstituted acetoacetamides and secondary acetoacetamides were unsuitable substrates.

A free radical mechanism involving the initial single-electron transfer (SET) oxidation of the boro-enolate **7** has been proposed (Scheme 21). The resulting α-carbonyl radical **8** reacted with dioxygen to give the peroxy radical **9**, which cyclized to the 1,2-dioxetane intermediate **10**. The subsequent four-membered ring opening by O−O and C−C bond cleavage accounted for the α-ketoamide formation.

Scheme 21. Mechanism Proposed for the Cu(II)-Catalyzed, BF_3-Promoted Aerobic Oxidation of α-Substituted Acetoacetamides[84]



3. AMIDATION APPROACHES

This section deals with synthetic approaches installing the α-ketoamide motif through C(1)−N bond formation. In detail, subsection 3.1 covers nonoxidative strategies exploiting 2-oxo acids as convenient starting materials. On the other hand, subsection 3.2 is devoted to protocols wherein different substrates undergo simultaneous oxidation and amidation reactions.

3.1. Nonoxidative Amidations

Amide bond formation is one of the most important reactions in organic chemistry, because of the widespread occurrence of amides in modern pharmaceuticals and biologically active compounds.[85,86]

Recently, a comprehensive review has covered a field of emerging importance, namely, amide formation through catalytic and synthetically relevant methods for direct condensation of carboxylic acids and amines.[87]

Moreover, the novel approach to amide synthesis through the decarboxylative condensation of *N*-alkylhydroxylamines and α-ketocarboxylic acids has generated a renewed impetus in developing new synthetic methods for the preparation and manipulation of these compounds.[88,89]

The chemoselective condensation of unprotected peptides in the total synthesis of protein molecules, first reported in 1992,[90] is a rapidly changing field with evolving strategies that overcome some of the limitations of the process. The chemistry of native chemical ligation[91] is now well-established and has recently been reviewed[92,93] and discussed in a feature article.[94]

Analogously, great attention has been devoted to the C(1)−N amide bond formation of α-ketoamides. As detailed in Scheme 22, methods proceeding via the coupling reaction of glyoxylic acid derivatives with primary/secondary amines are treated in subsection 3.1.1. Herein, besides synthetic approaches exploiting traditional amide coupling agents, less common protocols for the amide functional motif installation have also been included. Thus, carboxyl group activation and subsequent amidation reaction have been effected in a one-pot fashion with fluorinating agents, as well as using glyoxylic acids in Ugi four-component reactions (U-4CRs). Subsection 3.1.2 covers methodologies that took advantage of tertiary amines and formamides as nitrogen sources in transition-metal-

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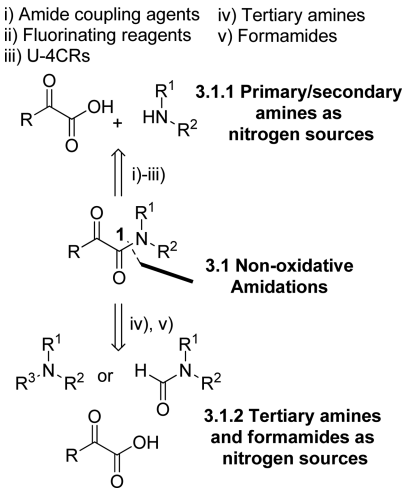
Scheme 22. Nonoxidative Amidations



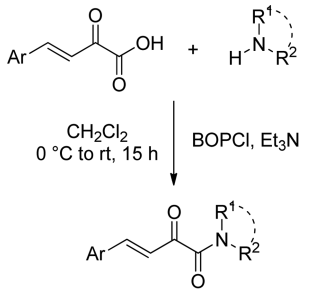
catalyzed amidation reactions of arylglyoxylic acids, with the N-dealkylation and the N-decarbonylation steps being respectively involved prior to the amidation reactions.

3.1.1. Primary/Secondary Amines as Nitrogen Sources. *3.1.1.1. Amide Coupling Agents.* α-Ketoamides have been synthesized by condensation of amines with carboxyl-activated α-keto acid derivatives formed in situ with the assistance of DCC, as well as of other activating reagents.[95,33]

As an example, trans-β,γ-unsaturated α-ketoamides could be selectively prepared by reaction of trans-β,γ-unsaturated α-keto acids and commercially available amines in the presence of classical peptidic coupling agents, such as PyBOP or the less expensive BOPCl. Unlike DCC/DMAP or WSC/HOBt systems, the activation of β,γ-unsaturated 2-oxo acids with BOPCl/Et_3N allowed efficient reactions with an array of amines, providing α-ketoamides (Scheme 23).[96] Interestingly, this methodology was also effective in the preparation of the challenging primary amides by using the system of magnesium nitride/water as a source of ammonia.

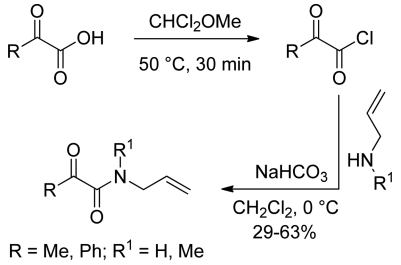
Terminally unsaturated secondary and tertiary α-ketoamides have been prepared as valuable precursors for the generation of a diverse range of heterocycles (Scheme 24).[97] As the starting step, both pyruvic acid and benzoylformic acid were transformed into the corresponding chlorides by employing α,α-dichloromethyl methyl ether as the chlorinating agent.

Scheme 23. Nonoxidative Amidations/Amide Coupling Agents Reported by Rodriguez and Co-Workers[96]



Ar = aryl, heteroaryl; R^1 = H, alkyl; R^2 = aryl, alkyl
R^1-R^2 = $(CH_2)_2O(CH_2)_2$

Scheme 24. Nonoxidative Amidations/Amide Coupling Agents Reported by Heaney et al.[97]



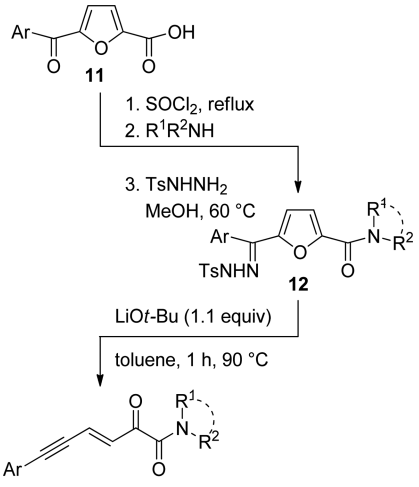
R = Me, Ph; R^1 = H, Me

Nucleophilic substitution with the appropriate allylamines then furnished the corresponding α-ketoamides which were taken to the corresponding α-hydroxyiminoamides, precursors of isoxazolopyrrolidinones and piperazin-5-ones, via thermal-induced cyclization.

The commercial nonavailability of α-keto acids, as well as complexities often involved in their synthesis, can hamper the achievement of α-ketoamides directly through amidation protocols. Thus, more reliable approaches entailing amidation of stable carboxylic acid derivatives, while deferring completion of the α-ketoamide moiety at a late stage of the synthesis, have been proposed.

Recently, Yin and co-workers[98] have reported the preparation of pharmaceutical-relevant enynyl-ketoamides through base-mediated decomposition of the tosylhydrazones **12** (Scheme 25). The latter compounds resulted from amidation

Scheme 25. Nonoxidative Amidations/Amide Coupling Agents Reported by Yin and Co-Workers[98]



Ar = aryl, heteroaryl; R^1 = alkyl; R^2 = alkyl, aryl
R^1-R^2 = $(CH_2)_2O(CH_2)_2$

reaction of 5-aroyl furan-2-carboxylic acids **11** with a series of secondary amines, followed by condensation with toluenesulfonyl hydrazine ($TsNHNH_2$). The pivotal heterocyclic degradation unveiling the enynone moiety occurred by heating compounds **12** in toluene at 90 °C in the presence of lithium *tert*-butoxide (1.1 equiv).

It was assumed that treatment of **12** with base produced the transient furfuryl carbene species **13**, which decomposed to *cis*-

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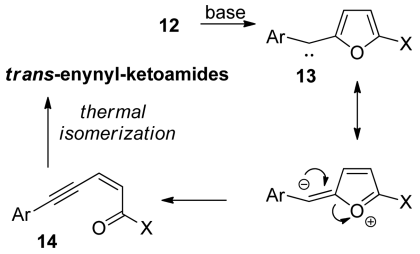
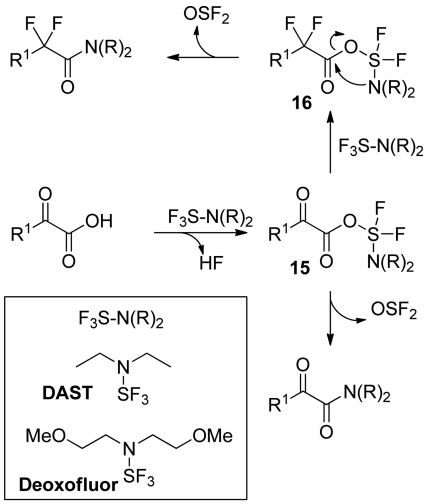
enynyl-ketoamides **14**. These underwent thermal isomerization to give the corresponding trans-isomers (Scheme 26).

Scheme 26. Mechanism Proposed for the Base-Mediated Degradation of Furan Tosylhydrazones[98]



3.1.1.2. Fluorinating Reagents. α-Ketoamides and α,α-difluoroamides, compounds of relevant biological importance,[99] could be obtained as the major products in a one-pot reaction of α-keto acids with the nucleophilic fluorinating reagents bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor) and (diethylamino)sulfur trifluoride (DAST).[100] The product ratio was a function of both reaction time and stoichiometry. Thus, employing a 2-fold molar excess of fluorinating reagents and quenching the reaction after 36 h with aqueous sodium bicarbonate solution, the α-ketoamides were formed along with the corresponding α,α-difluoroamides, which were easily separated by silica gel chromatography (Scheme 27).

Scheme 27. Nonoxidative Amidations/Fluorinating Reagents Reported by Singh and Shreeve[100]



R^1 = Me, Et, Ph, 2-thienyl; R = Et, $(CH_2)_2OMe$

Interestingly, when equimolecular mixtures of benzoylformic acid and fluorinating reagents were reacted in methylene chloride at room temperature for 1 h, the α-ketoamides were isolated in >92% yield together with very small amounts of the α,α-difluoroamides.

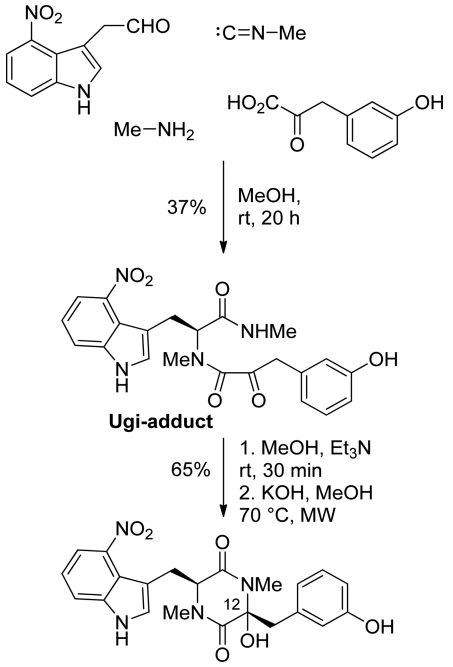
^{19}F NMR spectral analysis during the course of the reaction supported compounds **15** and **16** as intermediates featuring activated carboxyl groups adjacent to carbonyl and CF_2 groups, respectively. Thus, a facile intramolecular nucleophilic acyl substitution by the $N(R)_2$ group provided the corresponding amides with expulsion of volatile SOF_2.

3.1.1.3. Ugi Four-Component Reactions. Multicomponent reactions (MCRs) constitute a formidable tool to generate biologically important scaffolds in a limited number of steps. With the recent emergence of combinatorial chemistry and high-speed parallel synthesis for drug discovery applications, the MCRs have seen a resurgence of interest.

Though the isocyanide-based U-4CR condensation employing α-keto acids gives linear peptide backbones, postcondensation modifications can easily provide pharmaceutical-relevant heterocyclic scaffolds. Actually, 2-oxoamide Ugi adducts have been used as starting materials for successive reactions ranging from simple cyclic imine condensation[101] to aldol[102−104] or Pictet−Splenger-type cyclizations,[105,106] as well as alkaline-mediated ketoamide cyclizations,[107,108] all providing richly decorated mono- and polycyclic nitrogen heterocycles.

In this area, the alkaline-mediated postcondensation modification of the Ugi adduct of 4-nitroindolylacetaldehyde, methylamine, 3-hydroxyphenylpyruvic acid, and methyl isocyanide has been recently used to synthesize the naturally occurring herbicide (±)-thaxtomin A (Scheme 28).[109] In detail,

Scheme 28. Nonoxidative Amidations/U-4CRs Reported by Andreana and Co-Workers[109]



(±)-*Thaxtomin A* (*syn*/*anti* 4:1)

triethylamine-induced cyclization of the Ugi adduct afforded two C(12) epimeric diketopiperazines, with the anti-isomer being predominant (1:10 syn/anti ratio). A subsequent treatment with KOH in methanol at 70 °C under microwave (MW) irradiation led to the modification of the diastereomeric ratio in favor of the syn-isomer (±)-thaxtomin A (4:1 syn/anti ratio).

3.1.2. Tertiary Amines and Formamides as Nitrogen Sources. *3.1.2.1. Tertiary Amines.* In 2013, Wang and coworkers[110] reported a synthetic approach to α-ketoamides entailing the Ag-catalyzed amidation reaction of α-keto acids together with the C−N bond cleavage of tertiary amines. The reaction of 2-oxo-2-phenylacetic acid with Et_3N (3.0 equiv) has been used as a model to optimize the challenging process.

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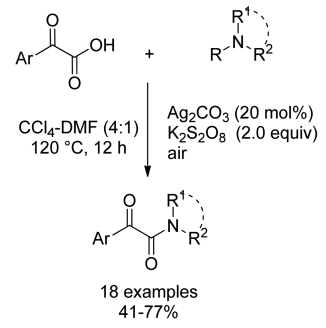
Among the tested transition-metal catalysts, Ag_2CO_3 (20 mol %) showed the highest catalytic activity when combined with the oxidant $K_2S_2O_8$ (2.0 equiv). The reaction conditions included heating at 120 °C for 12 h in CCl_4–DMF (4:1) solvent mixture under air atmosphere (Scheme 29).

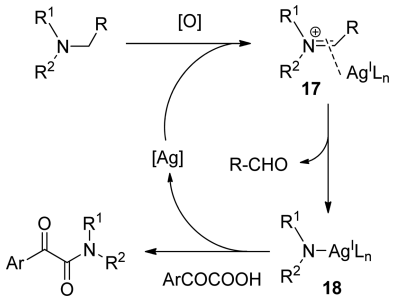
Scheme 29. Nonoxidative Amidations/Tertiary Amines Reported by Wang and Co-Workers[110]



A series of aryl and heteroaryl α-keto acids smoothly reacted with Et_3N to produce the corresponding α-ketoamides in good yields, with both electron-rich and electron-deficient groups on the benzene ring being tolerated. Symmetrical tertiary amines other than Et_3N were suitable nitrogen sources, while disappointing results were given by secondary amines. It is worthwhile noting that nonsymmetrical tertiary amines, such as tetramethylethylenediamine (TMEDA), 1-benzylpiperidine, and *N*,*N*-diethylaniline, reacted with phenylglyoxylic acid via selective C–N bond cleavage.

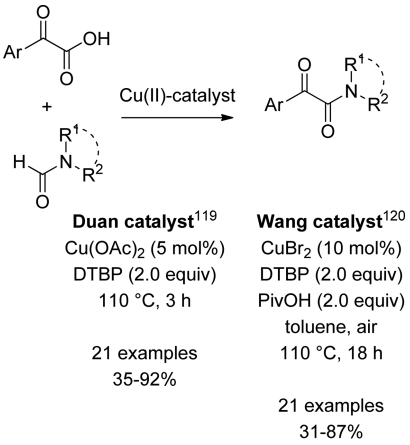
A plausible reaction mechanism entailed the tertiary amine oxidation to give the iminium ion **17**, followed by hydrolytic cleavage and combination with Ag(I) to generate **18**, the key intermediate involved in the amidation of the aryl α-keto acid (Scheme 30).

Scheme 30. Mechanism Proposed for the Ag-Catalyzed Amidation Reaction of α-Keto Acids with Tertiary Amines[110]



3.1.2.2. Formamides. *N*,*N*-Dimethylformamide (DMF) is chiefly used as an effective polar solvent for various chemical reactions. Additionally, DMF can participate in many reactions by serving as a multipurpose building block for various units.[111,112] Indeed, a few reports have appeared describing synthetic approaches to simple amides by using DMF as the amide[83,113−116] and amine source[117,118] under oxidative conditions. Moreover, two papers described almost contemporaneously[119,120] the preparation of α-ketoamides by the coupling reaction of arylglyoxylic acids with formamides in the presence of DTBP as the oxidant and Cu(II) salts as catalysts. Surprisingly, the salt $Cu(OAc)_2$ selected by Duan and co-workers.[119] as the most effective catalyst had been discarded by Wang and co-workers,[120] who employed $CuBr_2$. In detail, Duan's protocol called for heating a mixture of $Cu(OAc)_2$ (5 mol %), arylglyoxylic acids, and DTBP (2.0 equiv) in excess formamides at 110 °C. On the other hand, Wang's amidation conditions required heating a toluene solution of arylglyoxylic acids, formamides (10.0 equiv), $CuBr_2$ (10 mol %), and DTBP (2.0 equiv) at 110 °C under air atmosphere, in the presence of pivalic acid (PivOH, 2.0 equiv) as an additive to inhibit side reactions (Scheme 31).

Scheme 31. Nonoxidative Amidations/Formamides Reported by Duan and Co-Workers[119] and Wang and Co-Workers[120]



Both copper-mediated amidation protocols had similar substrate scope, with a variety of aryl and heteroaryl glyoxylic acids being well-tolerated to provide the expected α-ketoamides in moderate to good yields. Regardless of the protocol applied, the 4-nitrophenyl glyoxylic acid was a problematic substrate, while chloro, bromo, and iodo groups on the phenyl ring were tolerated. Formamides other than DMF were shown to be effective nitrogen sources irrespective of the copper salt employed, while N-monosubstituted formamides gave successful results only under Wang's reaction conditions.

Both research groups envisioned a free radical process for the amidation reaction, even though different mechanistic interpretations were advanced. Thus, Duan and co-workers[119] envisioned formamides as sources of the R_2N unit in the direct coupling with aryglyoxylic acids. Indeed, ^{13}C-labeled experiments proved that the C(1) carbon of *N*,*N*-dimethyl phenylglyoxylic acid amide originated from the corresponding carboxylic acid rather than from DMF (Scheme 32). Accordingly, formamides underwent consecutive C–H bond activation–decarbonylation to give aminyl radicals as the active species.

On the other hand, Wang and co-workers[120] proposed formamides as R_2NCO unit donors. In this case, the decarboxylative acylation of aryglyoxylic acids with formamide radicals generated by hydrogen atom abstraction was postulated. Further support to this mechanism came from recent works on the direct aminocarbonylations of β-keto

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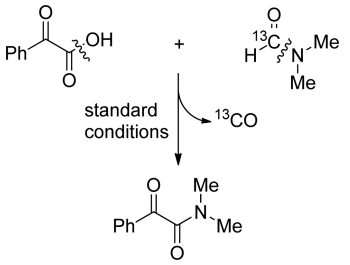
Scheme 32. Duan's ^{13}C-Labeled Experiments[119]



esters,[113] azoles,[114] *N*-alkoxyaryl amides,[115] and methylarenes[83] with *N*,*N*-dialkylformamides.

Very recently, Zhou and co-workers[121] succeeded in preparing aryl α-ketoamides via copper-catalyzed cross-coupling between DMF or *N*,*N*-diethylformamide and aryl glyoxylic acids, in turn produced in situ by oxidation of arylacetic acids. The optimized reaction conditions entailed the heating of aryl glyoxylic acid precursors and formamides at 130 °C for 24 h in the presence of Cu_2O (10 mol %), Phen (20 mol %), DTBP (3.0 equiv), and PivOH (2.0 equiv). A variety of substituted arylacetic acids, including 1-naphthaleneacetic acid, were smoothly transformed into the desired α-ketoamides in moderate to good yields (17 examples, 46−87%). ^{13}C-Labeled experiments proved that the carbonyl group of the products had its origin from the phenylacetic acid, rather than DMF. Moreover, the addition of TEMPO to the reaction mixture suppressed the transformation, supporting the engagement of a free aminyl radical in the reaction pathway, as proposed by Duan and co-workers.[119]

3.2. Oxidative Amidations

This section collects methodologies for C(1)−N amide bond formation through single [C(1)] or multiple [C(1) and C(2)] carbon skeleton oxidation of different substrates and simultaneous amine incorporation.

The oxidative union, usually referred to as *oxidative amidation*, represents a specific topic within the major theme of C−N bond-forming cross-coupling reactions, a very active research area in organic chemistry.[122] A vast array of oxidative amidation procedures has been developed for the preparation of α-ketoamides, allowing for a greater scope in terms of coupling partners and milder approaches.

The different substrates have been ordered according to their oxidative status in a descending order. Thus, glyoxals and 2,2-dibromoacetophenones are followed by α-hydroxy(aryloxy)-acetophenones, aryl acetaldehydes, aryl methyl ketones, β-diketones, and aryl terminal alkynes. Oxidative amidation processes of aryl terminal alkenes, 1-arylethanols, and ethylarenes complete this chapter (Scheme 33). Moreover, strategies depending on the employment of amines or formamides/formamidine as nitrogen sources are discussed separately in subsections 3.2.1 and 3.2.2, respectively.

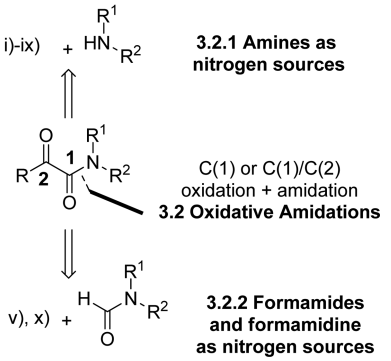
3.2.1. Amines as Nitrogen Sources. *3.2.1.1. Glyoxals.* Hulme and co-workers[123] described the cross-dehydrogenative-coupling (CDC) of commercially available arylglyoxals, attractive precursors of heterocyclic compounds,[124] with secondary amines by exposure to stoichiometric SeO_2 at 100 °C. The reaction could be accelerated by microwave irradiation and allowed one to obtain a series of tertiary aryl α-ketoamides (Scheme 34).

Constrained cyclic amines, such as piperazine and piperidine derivatives, usually gave better performances compared to pyrrolidine and acyclic secondary amines, while primary amines failed to give any appreciable oxidized product.

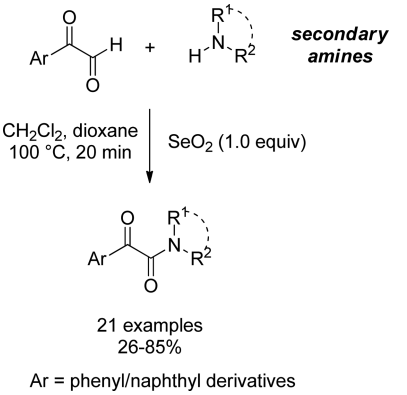
A mechanism has been advanced postulating the reaction of SeO_2 with the amine-arylglyoxal adduct **19** to form intermediate **20**, which afforded α-ketoamides by an internal proton transfer, which took place with concomitant release of $Se(OH)_2$ (Scheme 35).

Scheme 33. Oxidative Amidations

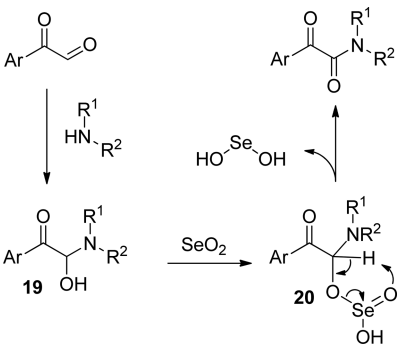
i) Glyoxals
ii) 1-Aryl-2,2-dibromoethanones
iii) 1-Aryl-2-hydroxy(aryloxy)ethanones
iv) Aryl acetaldehydes
v) Aryl methylketones
vi) β-Diketones
vii) Terminal alkynes
viii) Aryl terminal alkenes
ix) 1-Arylethanols
x) Ethylarenes



Scheme 34. Oxidative Amidations/Glyoxals Reported by Hulme and Co-Workers[123]



Scheme 35. Mechanism Proposed for the SeO_2-Promoted Oxidative Amidation of Arylglyoxals[123]



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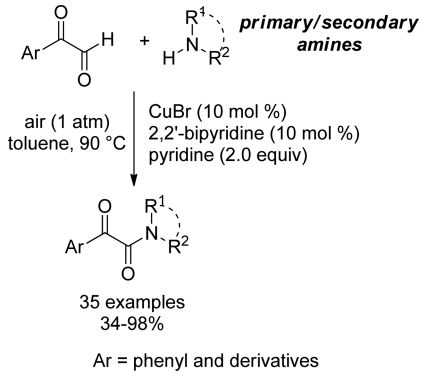
Oxidation is a fundamental operation in organic synthesis, and oxygen is a highly atom-economical, environmentally benign, and abundant oxidant. Moreover, ecofriendly biometals, such as Zn, Cu, and Fe, have begun to attract synthetic chemists due to their biomimetic dioxygen activation properties associated with low cost and abundance. In this context, copper is well-known to catalyze the oxidation and oxidative coupling of many substrates.[125−127] Therefore, it is not surprising that copper-catalyzed oxidative amidation approaches to α-ketoamides have attracted considerable attention within the synthetic organic chemists community.

The group guided by Jiao was very active in this area[128,129] and developed a Cu(I)-catalyzed aerobic oxidative cross-dehydrogenative coupling of amines with α-carbonyl aldehydes.[130] In-depth experimental studies led to the recognition of the optimal conditions in terms of copper catalyst loading, solvent, and reaction temperature. Moreover, it has been demonstrated that the transformation took advantage of the presence of pyridine as a base and 2,2′-bipyridine as a ligand.

Thus, α-ketoamides could be conveniently prepared when a solution of arylglyoxal and amine in toluene was heated at 90 °C under air atmosphere in the presence of CuBr (10 mol %), 2,2′-bipyridine (10 mol %), and pyridine (2.0 equiv), as shown in Scheme 36.

Scheme 36. Oxidative Amidations/Glyoxals Reported by Jao and Co-Workers[130]

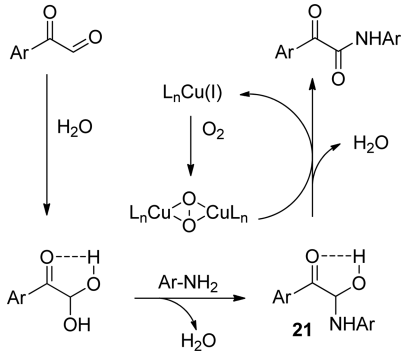


In such a way, the transformation showed broad applicability, as primary/secondary amines and aryl α-carbonyl aldehydes with both electron-donating and electron-withdrawing groups were usable.

Investigations on the mechanism of the copper-catalyzed aerobic oxidative amidation process indicated that the α-carbonyl group of the α-carbonyl aldehyde had the role of a directing group to facilitate the CDC reaction and that molecular oxygen was not only the oxidant but also served to trigger the catalytic process. Accordingly, and taking into account previous information about Cu(I)−dioxygen reactivity, a peroxo−dicopper(II) complex was envisioned as the active catalytic species involved in the oxidation of the in situ formed hemiaminal intermediate **21** (Scheme 37). Thus, formation of the desired α-ketoamide products occurred with the release of the ligand−Cu(I) species from which the active catalyst was derived by dioxygen oxidation.

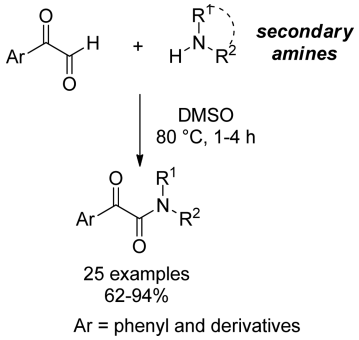
Very recently, a metal-free oxidative amidation of 2-oxoaldehydes has been developed as a facile entry to the correspoding α-ketoamides.[131] The new strategy is based on the unusual role of dimethyl sulfoxide (DMSO) both as solvent

Scheme 37. Mechanism Proposed for the Copper-Catalyzed, Air-Promoted Oxidative Amidation of Arylglyoxals[130]



and oxidant. To find the optimal reaction conditions, the oxidative coupling of phenylglyoxal with pyrrolidine has been carefully investigated. The expected α-ketoamide could be obtained in 94% yield by heating phenylglyoxal and pyrrolidine in DMSO at 80 °C for 1.5 h. On the basis of this result, different sets of experiments were carried out to investigate the scope and limitations of the process. The CDC reaction afforded α-ketoamides in good yields irrespective of the electronic nature and position of substituents on the aromatic ring of the arylglyoxals (Scheme 38).

Scheme 38. Oxidative Amidations/Glyoxals Reported by Vishwakarma and Co-Workers[131]



Interestingly, pyruvaldehyde could also take part in the CDC with piperidine and morpholine, giving the expected α-ketoamides in 63 and 61% yields, respectively. However, the viability of the protocol was restricted to the use of secondary amines, as α-ketoamide products were not formed by employing aliphatic or aromatic primary amines.

The same authors demonstrated that the DMSO-promoted CDC reaction could be extended to acetophenones employed as in situ precursors of 2-oxoaldehydes (see Scheme 65).[131,132]

Investigations demonstrated that DMSO was the sole oxidant and that the electron-withdrawing α-carbonyl group was of fundamental importance. The above findings supported a mechanism pathway in which an oxygen transfer from DMSO to the iminium ion **22** via the intermediate **23** was the key step toward the α-ketoamides (Scheme 39).

One year later,[133] the same research group discovered that the oxidative step could be performed under aerobic conditions by heating toluene solutions of aryl 2-oxoaldehydes and secondary amines at 60 °C, providing α-ketoamides in good yields (Scheme 40).

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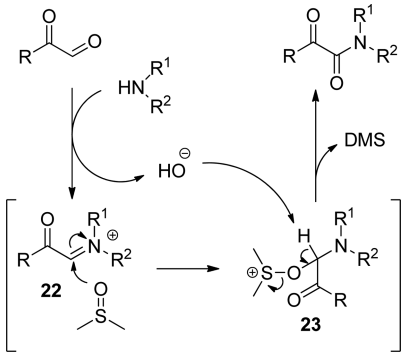
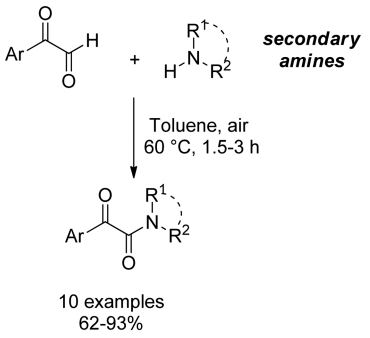
Scheme 39. Mechanism Proposed for the Metal-Free, DMSO-Promoted Oxidative Amidation of Arylglyoxals[131]



Scheme 40. Oxidative Amidations/Glyoxals Reported by Ahmed and Co-Workers[133]



In recent years, gold chemistry has emerged as an important tool in organic synthesis due to the excellent reactivity of catalytic species generated in the orbit of the Au(I)/Au(III) catalytic cycle usually maintained by external oxidants.

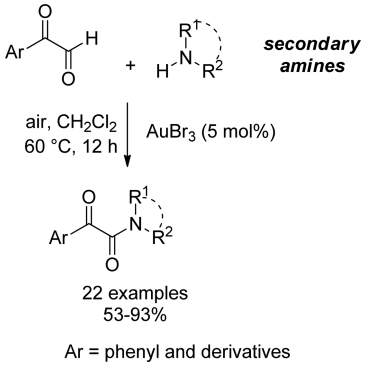
Liu and co-workers[134] disclosed a simple and efficient gold(III)-catalyzed coupling of arylglyoxal derivatives and secondary amines under aerobic oxidative conditions. This protocol, requiring mild conditions and lacking both ligands and additives, was quite appealing for tertiary aryl-substituted α-ketoamides preparation. Optimized conditions for the CDC reactions were found when a mixture of $AuBr_3$ (5 mol %), 2-oxoaldehyde, and secondary amine in CH_2Cl_2 was heated at 60 °C for 12 h (Scheme 41). A wide range of groups at the aromatic moiety of arylglyoxals were well-tolerated, while only secondary amines were effective, with the cyclic ones giving better results.

Investigations about the reaction mechanism demonstrated that dioxygen played the role of oxidant and that radical intermediates were likely involved in the transformation. Thus, it was hypothesized that addition of water to the in situ formed iminium ion **24** could give the hemiaminal **25**, which was eventually transformed into α-ketoamide by the combined action of O_2 and Au(III) (Scheme 42).

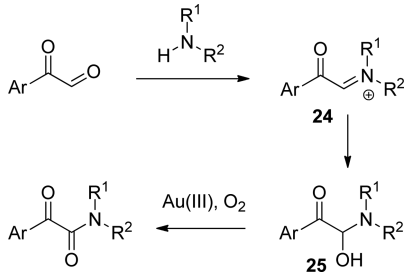
During studies on gold-catalyzed cascade reactions for the preparation of alkenyl-1,2-diketones, Hashmi and co-workers[135] discovered that phenylglyoxal could oxidatively couple with piperidine, provided that O_2 was present in the reaction system. However, no mention has been made about broadening the scope of substrates and mechanism.

3.2.1.2. 1-Aryl-2,2-dibromoethanones. Double bromination of aryl methyl ketones is a longstanding facile process for the

Scheme 41. Oxidative Amidations/Glyoxals Reported by Liu and Co-Workers[134]



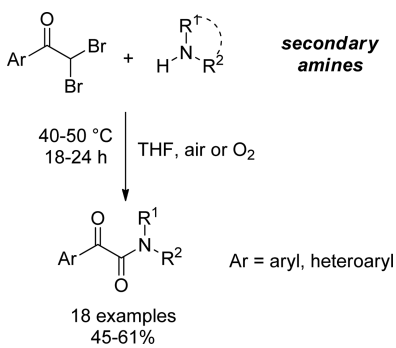
Scheme 42. Mechanism Proposed for the Gold-Catalyzed, Air-Promoted Oxidative Amidation of Arylglyoxals[134]



preparation of aryldibromoethanones, compounds featuring an oxidation state that is equivalent to that of 2-oxoaldehydes.

Thus, Kumar and co-workers[136] demonstrated that aryldibromoethanones could be used as substrates for the oxidative coupling with amines, allowing for a convenient synthetic access to α-ketoamides. As a first achievement, various 2,2-dibromo-1-aryl- and heteroarylethanones were oxidatively coupled with different cyclic and acyclic aliphatic secondary amines. In the optimized reaction conditions, 1:4 molar ratio mixtures of dibromoethanones and secondary amines were heated at 40−50 °C in THF for 18−24 h to provide α-ketoamides (Scheme 43). It was also demonstrated that purging pure oxygen into the reaction mass significantly increased the rate of conversion. In all the cases, the reaction provided α-ketoamides in moderate to good yields, although attempts to employ alkyldibromoethanones were not successful.

Scheme 43. Oxidative Amidations/1-Aryl-2,2-dibromoethanones Reported by Kumar and Co-Workers[136]



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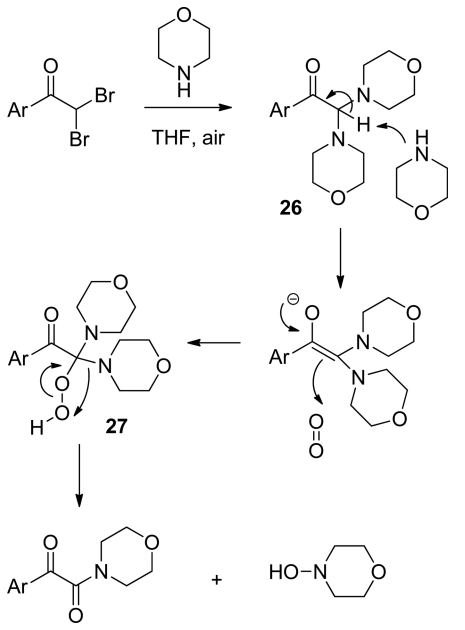
Model studies on the reaction between 1-aryl-2,2-dibromoethanones and morpholine allowed the authors to postulate a reaction mechanism wherein the aryl-2,2-dimorpholin-1-ylethanone **26** was an intermediate and *N*-hydroxymorpholine was a byproduct (Scheme 44). Thus, nucleophilic displacement

Scheme 44. Mechanism Proposed for the Air-Promoted Oxidative Amidation of Aryldibromoethanones[136]



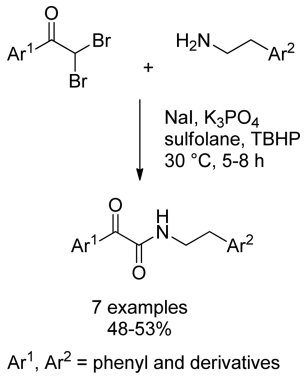
of both bromine atoms by morpholine gave diaminal **26**, which formed the unstable intermediate **27** through base-assisted enolization and reaction with molecular oxygen. A final rearrangement of **27** provided the α-ketoamide compounds through extrusion of *N*-hydroxymorpholine.

The original protocol was later tuned in order to encompass aliphatic primary amines as partners of dibromoethanones in the oxidative amidation reaction.[137] Thus, it was anticipated that better nucleofuge, together with the use of stronger base and stronger oxidizing agent, could be beneficial in the case where sluggish partners were involved in the coupling reaction. Indeed, oxidative amidation in the presence of NaI and K_3PO_4 together with stoichiometric amounts of TBHP in sulfolane at 30 °C (Scheme 45) provided a series of 2-oxo-*N*-phenethyl-2-phenylacetamido derivatives, precursors of isoquinoline alkaloids via Bischler–Napieralski cyclization reaction.

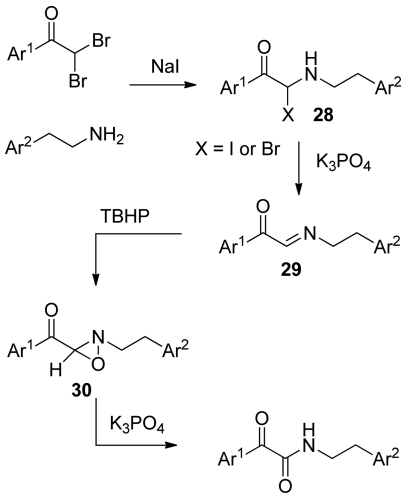
As shown in Scheme 46, a tentative mechanism could be advanced involving a halogen-exchange reaction as a means to accelerate the successive nucleophilic displacement, giving **28**. Further elimination of hydrogen halide generated the imine **29**, which was oxidized to the unstable oxaziridine **30**. The latter underwent a base-assisted ring-opening reaction, providing the α-ketoamide product.

A nice application of the oxidative amidation/Bischler–Napieralski reaction methodology paved the way to a simple and direct synthesis of β-carbolines, as described by Kumar and co-workers.[138] Thus, dibromoethanones and tryptamine could be oxidatively coupled in DMSO by the action of cumene hydroperoxide, in the presence of NaI and triethylamine (Scheme 47). Under optimized conditions, α-ketoamides were prepared in moderate yields accompanied by benzamide impurities.

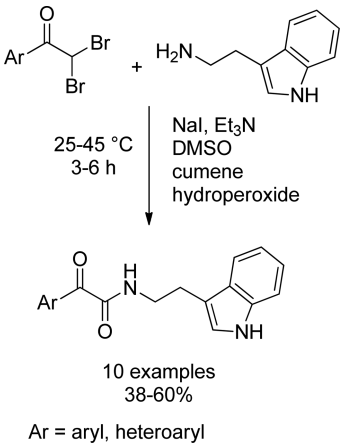
Scheme 45. Oxidative Amidations/1-Aryl-2,2-dibromoethanones Reported by Kumar and Co-Workers[137]



Scheme 46. Mechanism Proposed for the TBHP-Promoted Oxidative Amidation of Aryldibromoethanones[137]



Scheme 47. Oxidative Amidations/1-Aryl-2,2-dibromoethanones Reported by Meruva et al.[138]



3.2.1.3. 1-Aryl-2-hydroxy(aryloxy)ethanones. When substrates taking part in the C(1)–N amide bond formation feature the C(1) at an oxidation state lower than formyl or dibromomethyl, an oxidation must anticipate the CDC reaction with the amine partner.

Sekar and co-workers[139] faced this issue in their economic and environmentally friendly synthesis of α-ketoamides. They

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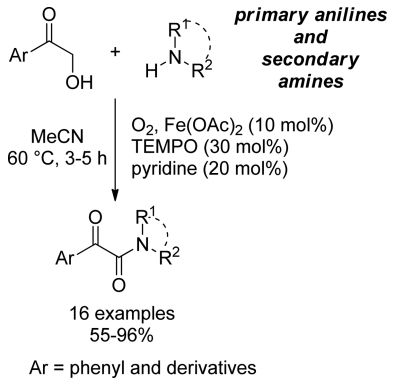
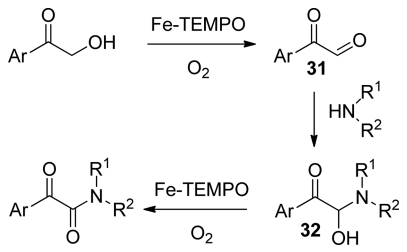
envisaged using the Fe−TEMPO complex as the catalyst and molecular oxygen as the terminal oxidant to perform the oxidative amidation reaction of 2-hydroxyacetophenones with amines. Among iron salts, $Fe(OAc)_2$ afforded the best results, acetonitrile was the solvent of choice, and quite surprisingly, the use of substoichiometric amounts of pyridine resulted in increased yields. In such a way, different α-keto alcohols and amines gave the expected α-ketoamides in good to excellent isolated yields irrespective of the aliphatic or aromatic nature of the amines (Scheme 48).

Scheme 48. Oxidative Amidations/1-Aryl-2-hydroxyethanones Reported by Sekar and Co-Workers[139]



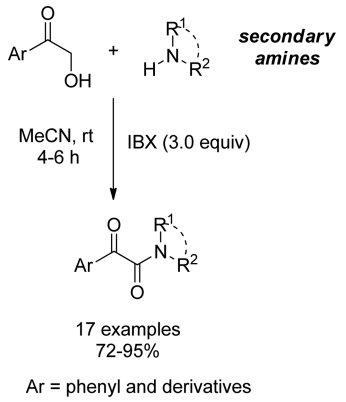
Model studies demonstrated that commercially available phenylglyoxal hydrate and 4-aminobenzonitrile were successfully transformed into the expected α-ketoamide under optimized reaction conditions. Moreover, phenylglyoxal was formed from 2-hydroxyacetophenone when the reaction was performed in the absence of the amine counterpart. These results supported a domino alcohol oxidation/oxidative CDC, where the Fe−TEMPO complex acted both in the initial oxidation of the α-hydroxy ketone to the corresponding α-ketoaldehyde **31** and in the oxidation of the hemiaminal intermediate **32** (Scheme 49).

Scheme 49. Mechanism Proposed for the Fe(II)/TEMPO/O_2 Oxidative Amidation of 1-Aryl-2-hydroxyethanones[139]



About a year after, the same research group disclosed that the hypervalent iodine reagent IBX was an equally good oxidizing agent in the domino alcohol oxidation/oxidative amidation reaction sequence between 1-aryl-2-hydroxyethanones and amines (Scheme 50).[140] Thus, 2-hydroxyacetophenones, amines (4 equiv), and IBX (3 equiv) were reacted in acetonitrile at room temperature for 4−6 h. Actually, 1-aryl-2-hydroxyethanones with both electron-rich and electron-poor groups were good reacting partners of cyclic amines, while the reaction failed with aliphatic/aromatic primary amines. Noteworthy, the metal-free alcohol oxidation/oxidative amidation

Scheme 50. Oxidative Amidations/1-Aryl-2-hydroxyethanones Reported by Kotha and Sekar[140]



protocol was successful on a gram scale, opening the way to an economic, environmentally benign, and practical synthetic approach to α-ketoamides.

Advancement of technologies capable of adding value to biomass has recently emerged as an important research area. Chemists are called to invent processes for obtaining fine chemicals from inexpensive, easily accessible, and renewable natural sources.

In this context, the research group guided by Loh focused special attention on lignin, a disregarded component in lignocellulosic biomass featuring the β-O-4 linkage as a distinctive motif.[141] In particular, they explored the copper-catalyzed oxidative amidation of a model substrate mimetic of the β-O-4 fragment of lignin (Figure 12) with the aim of developing efficient protocols to convert the rigid cross-linked biopolymer into amides and phenols.

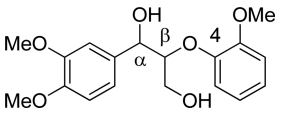


Figure 12. Model substrate mimetic of the β-O-4 fragment of lignin.

The first stage of the chemical investigation called for the Cu(I)-catalyzed aerobic amidation of 2-aryloxyacetophenone derivatives. Their conversion into α-ketoamides was achieved by heating at 70 °C a toluene solution containing a 5 times molar excess of secondary amines and CuI (10 mol %) under an air atmosphere (Scheme 51).

Various secondary amines were tolerated, as well as methoxyl groups at different positions on the phenyl rings, albeit their installation on the C-terminal benzene ring resulted in the concurrent formation of amides (up to 27% yields).

Next, oxidized lignin model substrates were coupled with amines, with removal of the hydroxymethyl group through retro-aldol reaction being the main challenge. Actually, 3-hydroxy-2-aryloxy-1-arylpropan-1-one derivatives (Figure 13) proved to be suitable substrates for the preparation of aryl-α-ketoamides under previously established copper-catalyzed oxidative amidation reaction conditions.

Several control experiments, as well as isotope-labeling reactions, allowed the advancement of the mechanism depicted in Scheme 52. The retro-aldol reaction of the iminium ion **33** produced the enamine **34**, which was taken to the α-imino copper peroxide **35**. The latter underwent degradation to α-

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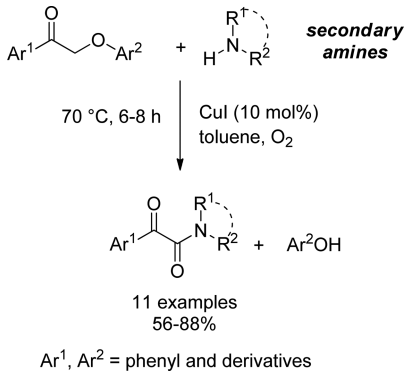
Scheme 51. Oxidative Amidations/1-Aryl-2-aryloxyethanones Reported by Loh and Co-Workers[141]



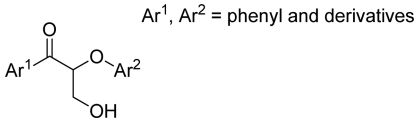
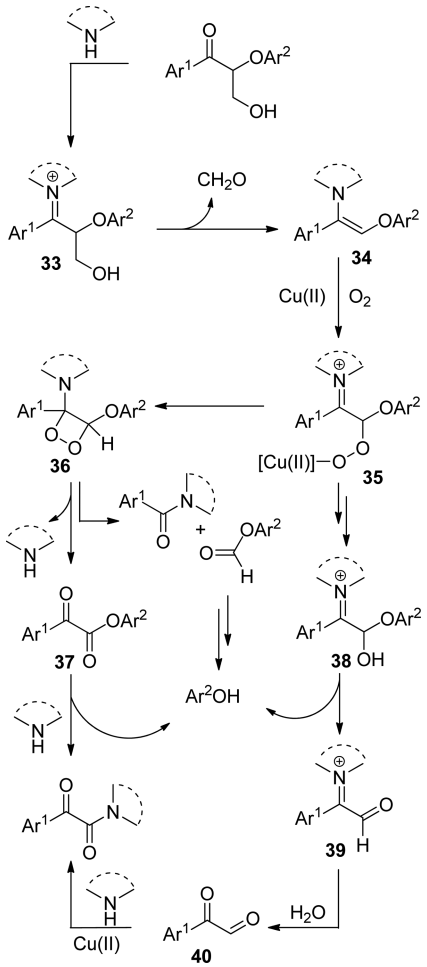


Figure 13. Oxidized lignin model substrates.

Scheme 52. Mechanism Proposed for the Copper/O_2 Oxidative Amidation of Oxidized Lignin Model Substrates[141]

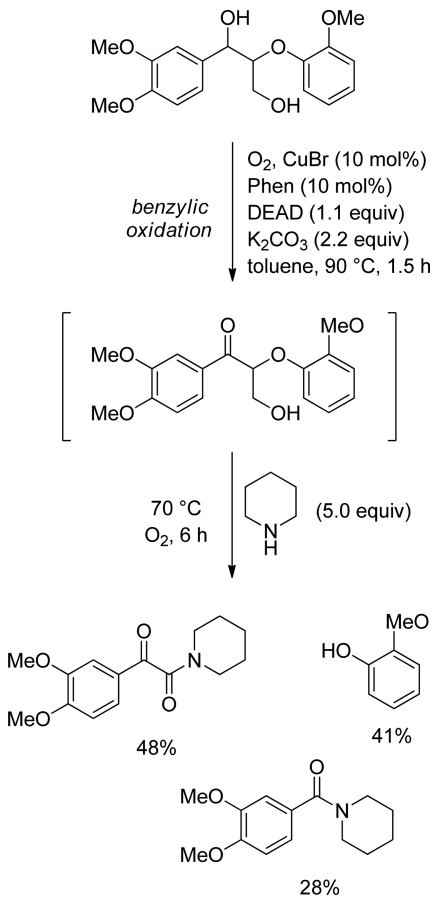


ketoamide, possibly through two pathways. Thus, cyclization to **36** and subsequent fragmentation with elimination of the amine could produce the arylglyoxylic acid aryl ester **37**, which eventually reacted with the amine to give α-ketoamide and phenol products. In some cases, amide side products could be formed together with aryl formates through competitive O—O and C—C bond cleavage of the aminodioxetane intermediate **36**. Alternatively, degradation of the copper peroxide **35** could lead to the arylglyoxal **40** via intermediates **38** and **39**. A copper-mediated CDC of **40** with amine established the 2-oxoamide functional group.

The successful oxidative amidation of oxidized lignin models paved the way to the corresponding reaction of the substrate mimetic of the β-O-4 fragment of lignin, with the chemoselective benzylic alcohol oxidation being required prior to the copper-catalyzed aerobic amide bond formation.

As shown in Scheme 53, the conversion of 1-(3,4-dimethoxyphenyl)-2-(2-methoxyphenyloxy)propane-1,3-diol

Scheme 53. Copper-Catalyzed Oxidative Amidation of a Lignin Model Substrate[141]



was successfully accomplished by combining the Markó aerobic benzylic oxidation [Cu(I), Phen, diethyl azodicarboxylate (DEAD)][142,143] and the Cu-catalyzed aerobic reaction with piperidine. As anticipated, the expected α-ketoamide was produced in 48% yield, together with the corresponding amide and guaiacol in 28% and 41% yields, respectively. Remarkably, the one-pot procedure was also applied to a trimeric lignin β-O-4 model without significant variation in yields and products composition.

3.2.1.4. Aryl Acetaldehydes. Jiao and co-workers[128] performed an unprecedented Cu(I)-catalyzed oxidative coupling process between aryl acetaldehydes and anilines, affording directly α-ketoamide compounds through two C(sp^3)—H, one

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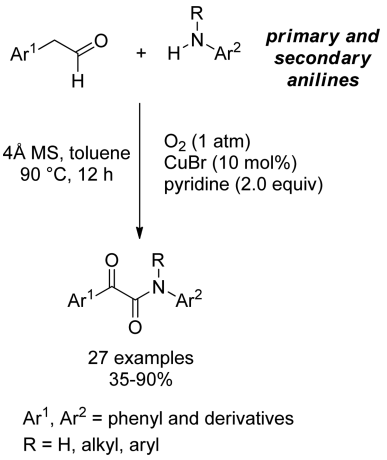
C(sp^2)−H, and one N−H bond cleavage. Thus, heating a toluene solution of aryl acetaldehydes and aromatic primary/secondary amines at 90 °C in the presence of pyridine (2.0 equiv) and CuBr (10 mol %) under O_2 atmosphere gave access to α-ketoamides (Scheme 54).

Scheme 54. Oxidative Amidations/Aryl Acetaldehydes: Jiao et al.[128]



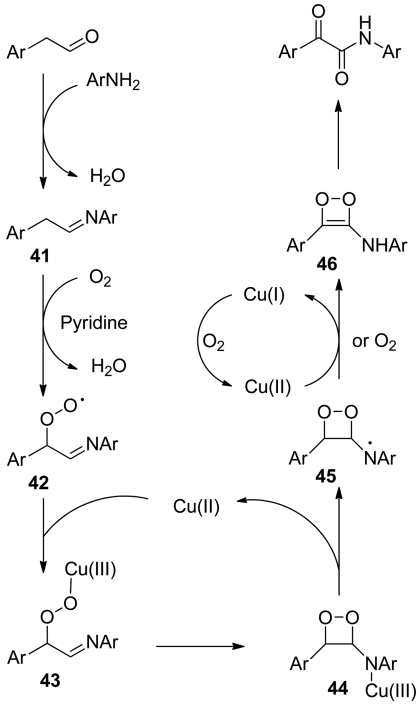
Under optimized conditions, including the presence of molecular sieves (4 Å), the reaction was highly efficient, showing a broad substrate scope. Both electron-rich and electron-deficient aryl acetaldehydes could be smoothly transformed into the desired products. Importantly, halo-substituted aryl acetaldehydes were also good substrates, furnishing products suitable for further chemical manipulations. As far as the amine counterpart is concerned, reactions of anilines as well as of N-substituted anilines bearing both electron-donating and electron-withdrawing groups proceeded well to afford secondary and tertiary α-ketoamides in moderate to excellent yields. However, electron-rich amines sensitive to oxidation to azo compounds gave the expected α-ketoamides in low yield. Moreover, neither alkyl aldehydes nor alkylamines were exploitable under the indicated reaction conditions.

Isotope-labeling experiments with $^{18}O_2$ clearly indicated that both oxygen atoms of the α-ketoamide originated from molecular dioxygen. Further experiments served to establish that 2-phenylacetic acid and the corresponding amide, as well as phenylglyoxal or phenylglyoxylic acid, were in no way intermediates in the copper-catalyzed aerobic oxidative transformation.

Accordingly, a plausible mechanism called for the initial oxidation of the in situ formed imine **41** to give the superoxide radical **42**, which combined with Cu(II) to afford the Cu(III) complex **43**. Subsequent imine intramolecular addition to **44** and N−Cu bond homolysis produced the dioxetane radical intermediate **45**. Cu(II) or dioxygen then transformed **45** into the dioxetene intermediate **46**, which eventually fragmented to the desired α-ketoamide (Scheme 55).

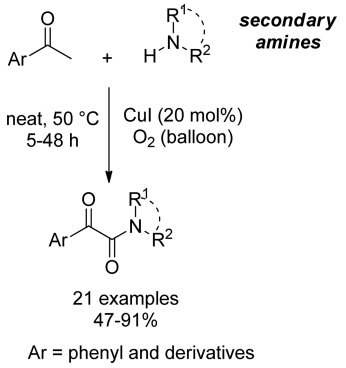
3.2.1.5. Aryl Methyl Ketones. An efficient copper-catalyzed direct oxidative synthesis of α-ketoamides employed stable and readily available aryl methyl ketones, secondary aliphatic amines, and molecular oxygen.[144] After an extensive screening of the reaction parameters, the best conditions for the one-pot transformation were found when the ketone was treated with CuI (20 mol %) in the presence of dioxygen at 50 °C, under

Scheme 55. Mechanism Proposed for the Copper/O_2 Oxidative Amidation of Aryl Acetaldehydes[128]



solvent-free conditions (Scheme 56). Both electron-rich and electron-poor substituents on the aryl ring, including ortho-

Scheme 56. Oxidative Amidations/Aryl Methyl Ketones Reported by Du and Ji[144]



substituents, were tolerated. Higher conversion yields were obtained in the case where electron-withdrawing groups were present on the aryl moiety, while cyclic or acyclic secondary amines were usable in any way. Notably, heteroaryl methyl ketones were compatible with the reaction conditions, while alkyl methyl ketones as well as anilines were not suitable substrates.

Detailed investigations led to establish that (1) both oxygen atoms of the α-ketoamide were derived from dioxygen, (2) arylglyoxals were intermediates in the reaction system, and (3) the superoxide radical ($O_2^{\bullet-}$) must be involved. The above results, together with the acquisition that the use of DABCO as a singlet oxygen inhibitor did not interfere with the process, led to the proposal of the reaction pathway depicted in Scheme 57.

Thus, exposure of the in situ formed enamine **47** to the combined action of Cu(II) and superoxide radical accounted

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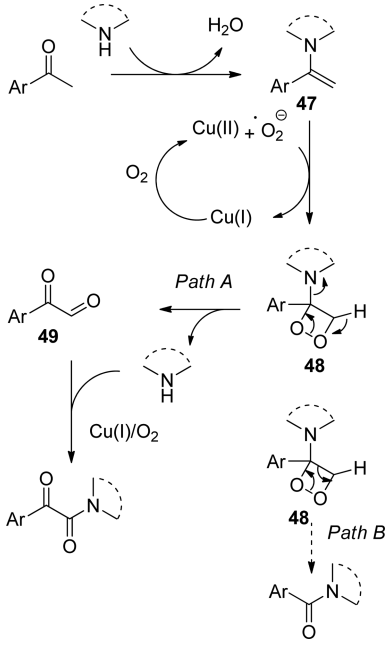
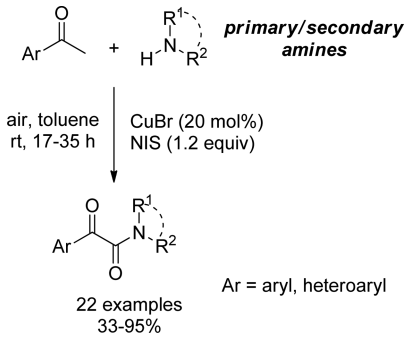
Scheme 57. Mechanism Proposed for the Copper/O_2 Oxidative Amidation of Aryl Methyl Ketones[144]



for the production of the amino dioxetane **48**, an intermediate acting as a fork in the reaction pathway. In fact, its fragmentation via O−O bond cleavage gave arylglyoxal **49** precursor of the α-ketoamide products via copper-mediated CDC with the amine (path A), while concurrent fragmentation of **48** via O−O and C−C bond cleavages gave the amide side products (path B).

Almost contemporaneously, the group led by Liu and Liang[145] discovered the halogen-activated copper-catalyzed aerobic oxidative coupling of aryl methyl ketones with amines making use of NIS. Thus, treatment of aryl methyl ketones and aliphatic primary/secondary amines with CuBr (20 mol %) and NIS (1.2 equiv) in toluene at room temperature under air gave access to α-ketoamides (Scheme 58).

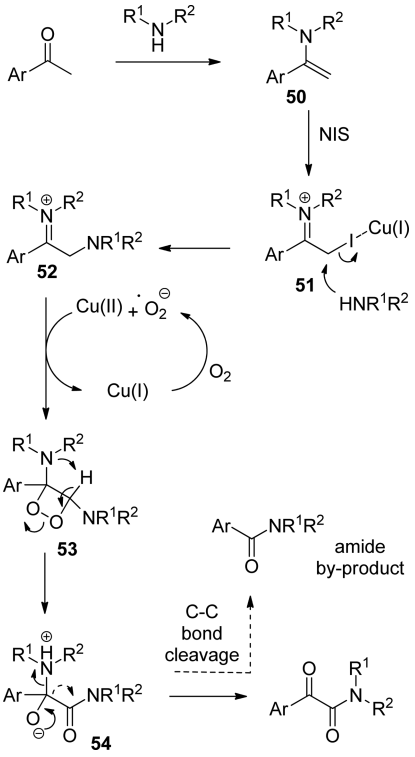
Scheme 58. Oxidative Amidations/Aryl Methyl Ketones Reported by Liu, Liang, and Co-Workers[145]



The process showed a broad substrate scope, with acetophenones bearing functionalities such as nitro and halogen, as well as heteroaryl methyl ketones, being well tolerated. Secondary aliphatic cyclic and acyclic amines performed well, while primary amines gave poor results because of the formation of amide byproducts. Furthermore, reactions with aromatic amines failed to yield the corresponding α-ketoamides.

A possible mechanism for the formation of α-ketoamides and amide byproducts is depicted in Scheme 59. Thus, iodination of

Scheme 59. Mechanism Proposed for the Halogen-Activated Copper/O_2 Oxidative Amidation of Aryl Methyl Ketones[145]



the in situ formed enamine **50** generated intermediate **51**, which underwent iodide displacement by a second equivalent of amine to give the α-amino iminium ion **52**. Its reaction with the superoxide radical and copper-mediated single-electron transfer (SET) process afforded the key aminodioxetane intermediate **53**. Meanwhile, oxidation of Cu(I) into Cu(II) by means of dioxygen in air completed the catalytic cycle. The fragmentation of the dioxetane ring of **53** generated the intermediate **54**, from which both the desired α-ketoamides and the amide byproducts could form through C−N bond cleavage or C−C bond cleavage, respectively.

The urgency of avoiding heavy-metal impurities in drug intermediates encouraged more and more frequently the design of environmentally benign and metal-free synthetic methodologies.

In this context, Lamani and Prabhu[146] developed a user-friendly method for the oxidative amidation of acetophenone derivatives based on the use of NIS as a catalyst and TBHP as a terminal oxidant, in acetonitrile at room temperature (Scheme 60). Optimization of the experiments led to the establishment of a molar ratio of 1:3 for aryl methyl ketone and the amine coupling reagents, as well as the amount of TBHP (3.0 equiv) and iodine source (30 mol %) required to achieve the best yields.

Under standard reaction conditions, several acetophenone derivatives as well as heterocyclic methyl ketones underwent oxidative amidation to provide α-ketoamides in good to excellent yields.

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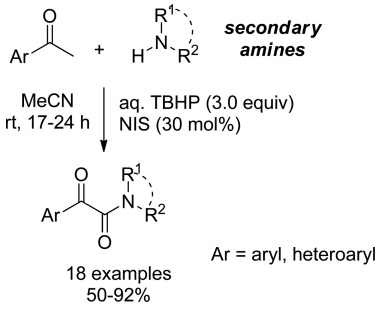
Scheme 60. Oxidative Amidations/Aryl Methyl Ketones Reported by Lamani and Prabhu[146]



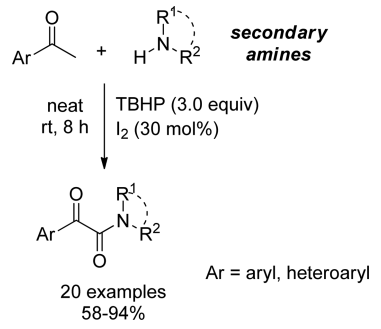
As in the related halogen-activated copper-catalyzed aerobic oxidative amidation protocol,[145] the coupling of 4-methoxyacetophenone with piperidine gave the lowest conversion yield (50%).

Although no detailed mechanism has been proposed, experimental data supported the belief that both phenacyl iodides and α-amino ketones were really intermediates along the pathway to α-ketoamides under standard conditions.

At the same time, two research groups[147,148] independently advanced the idea of shifting from NIS to the TBHP/I_2 system as a convenient source of electrophilic iodine (I^+) to activate the C(sp^3)–H bond.

Zhang and Wang[147] developed the tandem direct oxidative coupling of acetophenones with secondary amines at room temperature under solvent-free conditions (Scheme 61).

Scheme 61. Oxidative Amidations/Aryl Methyl Ketones Reported by Zhang and Wang[147]

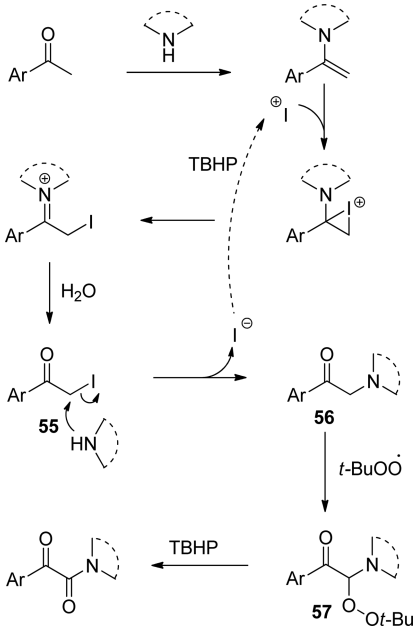


Under the recommended reaction conditions, a variety of aryl/heteroaryl methyl ketones could be oxidatively coupled with secondary aliphatic cyclic or acyclic amines to give α-ketoamides in good to excellent yields.

Some experimental data supported the cascade pathway shown in Scheme 62. Thus, in line with Prabhu's hypothesis,[146] the TBHP/I_2-promoted oxidative coupling reaction of acetophenones with secondary amines likely involved phenacyl iodide **55** and α-amino ketone **56** as key intermediates. The former should derive through α-iodination of aryl methyl ketone via an enamine formation–iodonium addition–hydrolysis sequence. The subsequent iodide displacement by the nucleophilic secondary amine accounted for the formation of **56**. At this stage, a free radical substitution with a *tert*-butyl peroxy radical generated the intermediate **57**, which was eventually transformed to α-ketoamide by TBHP.

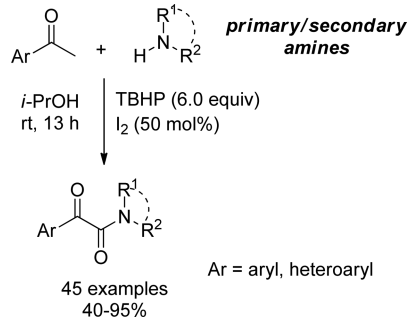
Soon after the report by Zhang and Wang,[147] Wan and co-workers reported the results of research aimed at converting

Scheme 62. Mechanism Proposed for the I_2/TBHP Solvent-Free Oxidative Amidation of Aryl Methyl Ketones[147]



aryl methyl ketones to α-ketoamides through metal-free oxidative amidation conditions.[148] Under optimized conditions, α-ketoamides were prepared by reaction of acetophenones with primary/secondary amines using TBHP (6.0 equiv) and I_2 (50 mol %) in *i*-PrOH at room temperature, as shown in Scheme 63. Noteworthy, this preparation could be scaled up to 100 mmol without significant variation in yield.

Scheme 63. Oxidative Amidations/Aryl Methyl Ketones Reported by Wan and Co-Workers[148]



A vast array of substituents on the aromatic ring were tolerated, including the oxidation-sensitive groups, such as C–C multiple bonds and phenol. Among heteroaryl methyl ketones, the heteroaryl groups thiophene, thiazole, pyrazine, pyridine, and benzofuran were compatible with reaction conditions. With regard to the amines, cyclic amines as well as acyclic secondary/primary amines were effective partners.

Experimental investigations into the mechanism validated previous speculations by the groups of Prabu[146] and Wang[147] about the involvement of both phenacyl iodide **58** and α-amino ketone **59** as synthetic intermediates. Wan advanced that conversion of the latter into α-ketoamides proceeded via intermediates **60**–**62** (Scheme 64).

Thus, α-iodination of **59** provided **60**, which was taken to **62** through iodide expulsion and water addition. Finally, TBHP

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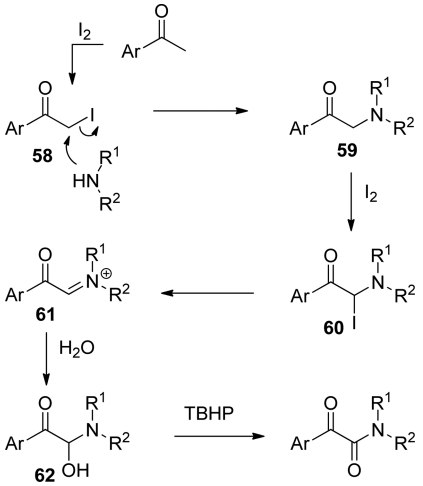
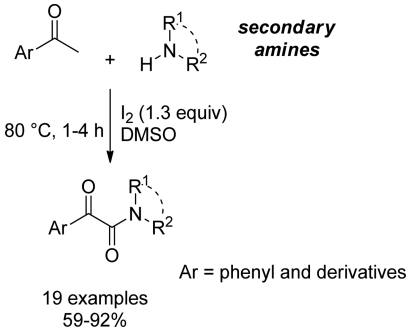
Scheme 64. Mechanism Proposed for the I_2/TBHP Oxidative Amidation of Aryl Methyl Ketones[148]



oxidation gave the α-ketoamide products. Notably, experiments with $H_2{}^{18}O$ showed that the ^{18}O was incorporated into the C(1) carbonyl oxygen.

As previously stated, Ahmed and co-workers[131] succeded in extending to acetophenones the DMSO-promoted oxidative coupling reaction of arylglyoxals with amines by combining the halogen-mediated C(sp^3)−H bond activation of aryl methyl ketones with the Kornblum oxidation.[149] Thus, heating different aryl methyl ketones, cyclic and acyclic secondary amines (1.5 equiv), and iodine (1.3 equiv) in DMSO at 80 °C provided the corresponding α-ketoamides in good to excellent yields, with electronically rich acetophenones being the best substrates.[132] As for the related DMSO-promoted CDC of arylglyoxals with amines,[131] viability of the method was restricted to the use of aliphatic secondary amines (Scheme 65).

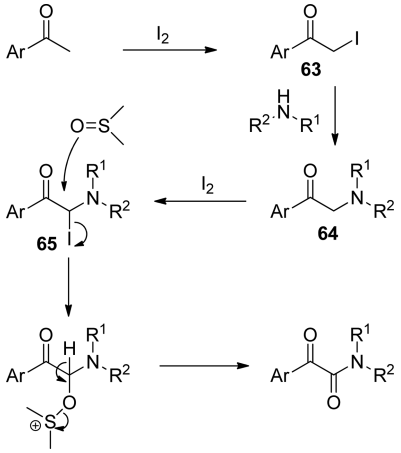
Scheme 65. Oxidative Amidations/Aryl Methyl Ketones Reported by Ahmed and Co-Workers[132]



Results from some control experiments led to postulation of a mechanistic pathway wherein a double oxidation by I_2 and a final one by DMSO are the main steps involved in the one-pot iodination−Kornblum oxidation−CDC sequence of aryl methyl ketones with amines. Thus, phenacyl iodides **63** reacted with amine nucleophiles to generate α-amino ketones **64**, which underwent additional oxidation by I_2 to give intermediates **65**, which was eventualy transformed into α-ketoamides through Kornblum oxidation (Scheme 66).

A very interesting approach has been recently added to the plethora of new methodologies for the synthesis of α-

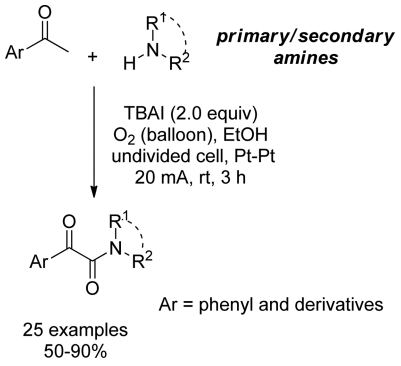
Scheme 66. Mechanism Proposed for the I_2−DMSO Oxidative Amidation of Aryl Methyl Ketones[132]



ketoamides. Thus, the one-pot oxidative amidation of acetophenones with amines was achieved through anodic oxidation by using dioxygen as a reactant.[150]

Optimal conditions for the preparation of α-ketoamides were found when acetophenones, amines (4.0 equiv), and TBAI (2.0 equiv) in ethanol reacted with O_2 in an undivided cell equipped with a platinum anode and a cathode. The oxidative amidations took place at ambient temperature under a constant current of 20 mA (Scheme 67).

Scheme 67. Oxidative Amidations/Aryl Methyl Ketones Reported by Wang and Co-Workers[150]



This method showed broad substrate scope, as both primary and secondary amines were effective partners of either acetophenone and its derivatives, provided that their phenyl ring did not display strong electron-withdrawing groups. As a matter of fact, 4-nitroacetophenone produced the corresponding α-ketoamide in only trace amounts. Tertiary and secondary α-ketoamides were obtained in moderate to good yields regardless of the aliphatic or aromatic nature of the amine coupling partners.

A series of experiments performed under electrochemical conditions clearly indicated that 2-oxoaldehyde **68** was an intermediate and that radical species were involved in the reaction. On these bases, it was assumed that iodine free radical generated at the anode reacted with acetophenone to give the carbon radical **66**, which intercepted dioxygen to form the peroxyradical **67**. Its O−O bond cleavage furnished the 2-oxoaldehyde **68** precursor of the hemiaminal **69**. The latter was oxidized at the anode with formation of the α-ketoamide

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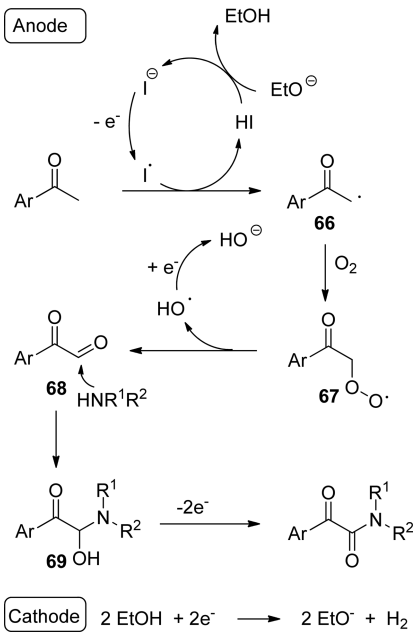
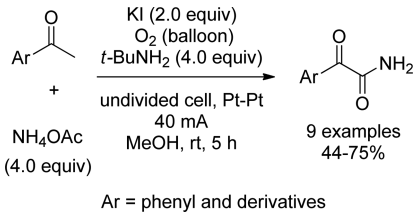
products, while the ethanol cathodic reduction generated H_2 and ethoxide anion.

Scheme 68. Mechanism Proposed for the Oxidative Amidation of Aryl Methyl Ketones through Anodic/O_2 Oxidation[150]



Noteworthy, primary aryl α-ketoamides could be obtained by replacing the amines with ammonium acetate (4.0 equiv), using *t*-BuNH$_2$ as an additive (4.0 equiv) and KI (2.0 equiv) as the electrolyte. Methanol was used as the solvent to increase the solubility of both the ammonium acetate and the electrolyte (Scheme 69). Besides acetophenone, a variety of substituted

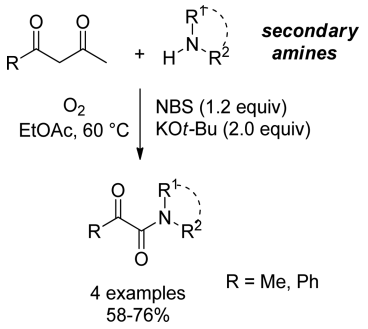
Scheme 69. Oxidative Amidations/Aryl Methyl Ketones Reported by Wang and Co-Workers[150] (preparation of primary aryl α-ketoamides under electrochemical conditions)



aryl methyl ketones were appreciable substrates, furnishing the corresponding primary α-ketoamides in moderate to good yields. Interestingly, a year later, Yu and co-workers[151] reported the preparation of phenylglyoxylic acid amide by oxidative amidation of acetophenone with ammonium iodide and *tert*-butyl hydroperoxide, but the chemical process, however, appeared to be less fruitful than the electrochemical one (40% vs 75% yield).

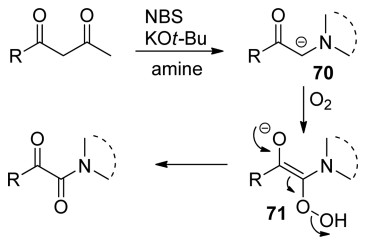
3.2.1.6. β-Diketones. Recently,[152] phenylglyoxylic and pyruvic acid amide derivatives have been obtained by heating equimolar amounts of β-diketones (1-phenylbutane-1,3-dione or acetylacetone) and aliphatic *N*-heterocycles in ethyl acetate, in the presence of KO*t*-Bu (2.0 equiv) and NBS (1.2 equiv), under air (Scheme 70). Interestingly, enhanced yields could be obtained by performing the reaction under O_2 atmosphere.

Scheme 70. Oxidative Amidations/β-Diketones Reported by Chen and Co-Workers[152]



Thus, the mild transition-metal-free deacetylation−oxidative amidation process entailed dioxygen as the actual oxidant under NBS-promoted conditions. As the reaction did not work in the absence of NBS, it has been assumed that an N-electrophilic species, in turn generated from the amine and NBS, was at first captured by the enolate nucleophile (Scheme 71). Then, a

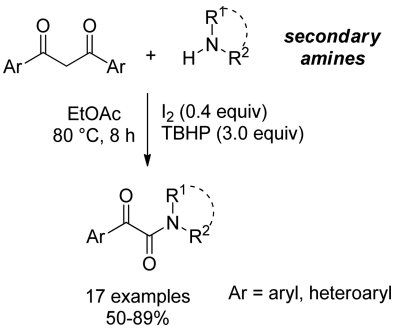
Scheme 71. Mechanism Proposed for the Deacetylation−Oxidative Amidation of β-Diketones[152]



retro-Claisen reaction and deprotonation afforded the anionic species **70**, which intercepted O_2 to give the hydroperoxy intermediate **71**. The latter underwent dehydroxylation to provide α-ketoamide products.

At the same time, Wang and co-workers[153] reported that 1,3-diarylpropan-1,3-diones could undergo C−C bond cleavage and coupling with secondary amines in the presence of I_2 and TBHP. The best results were obtained when ethyl acetate solutions of β-diketones and amines (1:3 ratio) containing I_2 (0.4 equiv) and TBHP (3.0 equiv) were heated at 80 °C for 8 h (Scheme 72). The one-pot, strong-base-free, TBHP/I_2-

Scheme 72. Oxidative Amidations/β-DiketonesReported by Wang and Co-Workers[153]



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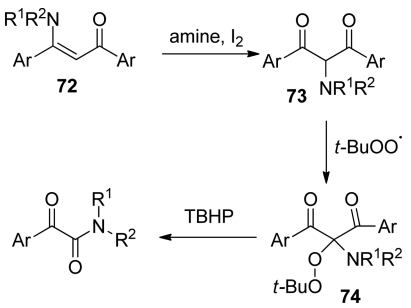
promoted oxidative amidation reaction tolerated a wide range of readily available symmetrical 1,3-diaryl 1,3-diketones. Under standard conditions, the unsymmetrical dicarbonyl compounds 1-phenylbutane-1,3-dione and ethyl 2,4-dioxo-4-phenylbutanoate could be also used as phenylglyoxyl donors. Among the secondary amines tested, 1-methylpiperazine performed better than morpholine, piperidine, and diethylamine.

Possibly, the reaction of the secondary amine with I_2 to give a N-electrophilic species was the first step involved in the tandem C−C bond cleavage/oxidative amidation reaction process (Scheme 73). In the subsequent step, the N-electrophilic

Scheme 73. Mechanism Proposed for the Dearoylation−Oxidative Amidation of β-Diketones[153]

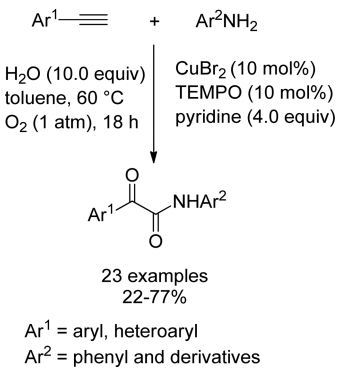


species was captured by the in situ formed enaminone nucleophile **72** to give the α-amino substituted β-diketone **73**. The latter underwent free radical substitution with *tert*-butylperoxy radical, and the resulting intermediate **74** eventually produced the α-ketoamides by TBHP-promoted fragmentation reaction.

3.2.1.7. Terminal Alkynes. The first synthesis of α-ketoamides via diketonization of terminal alkynes has been reported by Zhang and Jiao[129] employing aromatic amines in the presence of catalytic copper(II) bromide and TEMPO under oxygen. Neither alkylacetylenes nor primary alkylamines or N-substituted anilines were suitable starting materials in the amidation−diketonization process.

As shown in Scheme 74, optimized conditions called for heating at 60 °C a toluene mixture of aromatic amines, arylacetylenes (5.0 equiv), and $CuBr_2$ and TEMPO (10 mol % each), in the presence of pyridine (4.0 equiv) and water (10.0 equiv), under O_2 (1 atm). The competitive alkyne homocoupling reaction was difficult to control; hence an excess of alkynes had to be employed. Investigations on the scope of the

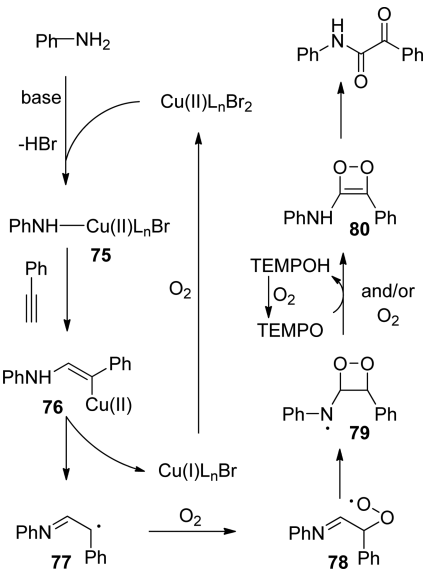
Scheme 74. Oxidative Amidations/Terminal Alkynes Reported by Zhang and Jiao[129]



method showed that both electron-rich and electron-deficient phenylacetylenes were good substrates, while anilines bearing electron-withdrawing groups on the aromatic ring gave scanty conversion yields.

The authors demonstrated that both oxygen atoms in the α-ketoamides originated from molecular oxygen and that a superoxide radical was likely an intermediate. Accordingly, a mechanism in which dioxygen acted both as oxidant and reactant has been advanced, as shown in Scheme 75 for the

Scheme 75. Mechanism Proposed for the Copper/TEMPO/O_2 Oxidative Amidation of Terminal Alkynes[129]



reaction between phenylacetylene and aniline. Alkyne insertion into the initial aniline−copper complex **75** gave a Cu(II) intermediate **76**, from which the imine radical **77** originated through Cu(I) discharge. The subsequent reaction with molecular oxygen gave the intermediate superoxide radical **78**. Further intramolecular cycloaddition to the imine and oxidation of the resulting aminyl radical **79** generated the 1,2-dioxetene intermediate **80**, which eventually collapsed to the desired α-ketoamide through fragmentation.

Interestingly, in 2015 Shah and co-workers[154] revisited Zhang and Jiao's[129] copper-promoted oxidative amidation of terminal alkynes and contributed to the simplification of the original cocktail of reagents. Actually, they prepared 2,*N*-diaryl-2-oxoamides (eight examples, 60−70%) simply by heating a DMSO solution of the terminal alkyne and the aromatic primary amine (2.0 equiv) at 80 °C for 10 h in an air atmosphere, in the presence of $Cu(OTf)_2$ (10 mol %) and TEMPO (15 mol %). Furthermore, aryl tertiary α-ketoamides were easily prepared provided that TEMPO was not added to the reaction mixture. Under revisited conditions, secondary amines, such as pyrrolidine, piperidine, morpholine, piperazine derivatives, and diethylamine, took part in the cross-coupling reaction with terminal alkynes, giving the corresponding aryl tertiary α-ketoamides (13 examples) in moderate to good yields (54−85%).

Sagadevan et al. disclosed a highly atom-efficient green process for the synthesis of α-ketoamides via oxidative amidation/diketonization of anilines with terminal alkynes, in the presence of molecular oxygen and light at room temperature without the use of hazardous chemicals.[155] The

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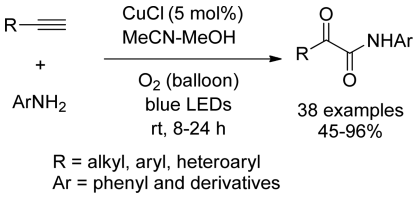
process, based on a light−copper-mediated synergistic double activation of substrates, did not proceed upon exclusion of light or O_2. Optimization studies led to set conditions where a mixture of MeCN−MeOH (1:1 v/v) was the best solvent system and CuCl (5 mol %) the best catalyst, providing α-ketoamides in generally good yields (Scheme 76). The protocol

Scheme 76. Oxidative Amidations/Terminal Alkynes Reported by Sagadevan et al.[155]



was effective for a wide range of anilines and terminal alkynes. However, neither *N*-substituted anilines nor aliphatic amines were suitable substrates. Furthermore, electron-rich phenylacetylenes suffered the concurrent homocoupling process, which was eventually suppressed by dilution. Both electron-rich and electron-neutral substituted anilines were well-tolerated. On the contrary, the coupling reactions became sluggish when employing scarce nucleophilic anilines. Terminal alkynes other than arylacetylenes were also effective partners in the coupling reaction with anilines.

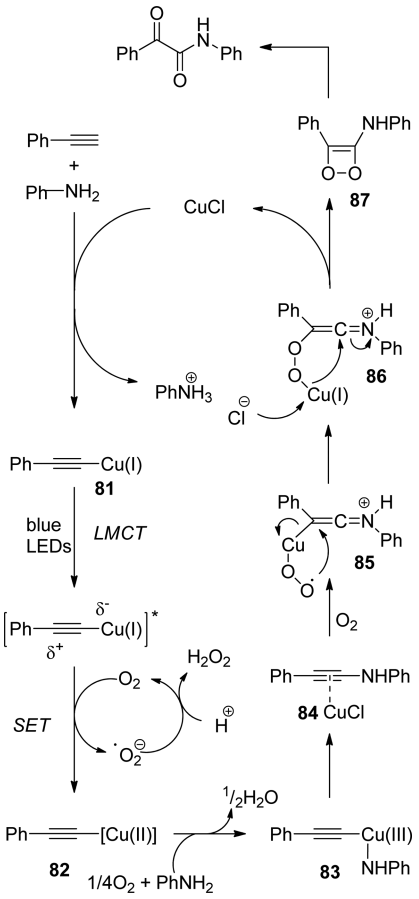
The mechanism proposed for the highly efficient and green process is depicted in Scheme 77. The in situ formed Cu(I)−phenylacetylide **81**, when excited by blue light, experienced a ligand-to-metal-charge transfer (LMCT) that set the stage for a single-electron transfer (SET) to molecular oxygen, providing the Cu(II)−phenylacetylide complex **82**. In the following step, nucleophilic addition of aniline resulted in the formation of the Cu(III) complex **83**, which afforded the electron-rich ynamine **84**, coordinated to Cu(I) ion, through reductive elimination. The subsequent reaction of **84** with O_2 gave the copper(II)−peroxo complex **85**, which first isomerized to the Cu(I) species **86** and then cyclized to the 1,2-dioxetene **87**, precursor of the desired α-ketoamide.

Several reports described the oxidation of ynamides to produce α-ketoimides by using expensive transition-metal catalysts, external oxidants, and harsh conditions that restricted the practical applicability of the methods.[156] In this context, Zhu and co-workers[157] disclosed the validity of *N*-Boc-ynamides as convenient starting materials for the preparation of *N*-monosubstituted α-ketoamides upon exposure to the inexpensive ecofriendly iodine/water/air oxidant system in the presence of TFA as an additive. Thus, the *N*-Boc-ynamides were easily prepared by coupling *N*-Boc-benzylamines or *N*-Boc-anilines with terminal alkynes, including alkylacetylenes, via the corresponding bromoethynyl derivatives, according to a reported procedure.[158,159]

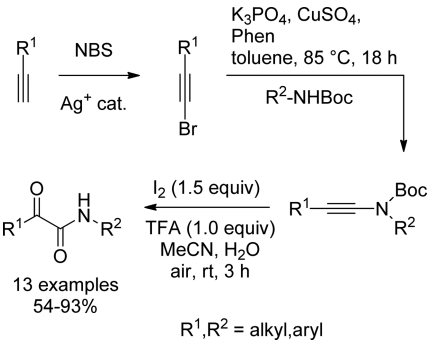
As shown in Scheme 78, the key oxidation reaction simply required stirring the mixture of ynamides and I_2 (1.5 equiv) in MeCN−H_2O at room temperature under air in the presence of TFA (1.0 equiv) to provide α-ketoamides in moderate to good yields.

Control experiments demonstrated that both molecular oxygen and water had an important role and that the oxidation reaction occurred before the *N*-protective group removal. On these bases, a possible starting step was the formation of an iodonium intermediate **88**, followed by regiospecific nucleophilic attack of water to produce the α-iodo ketone **89** (Scheme 79). Homolitic cleavage of its C−I bond generated the carbon radical **90**, which reacted with molecular oxygen to yield the peroxy radical species **91**. Eventually, hydroxyl radical expulsion and TFA-promoted removal of the *N*-Boc protective group gave the *N*-monosubstituted α-ketoamide. Combination of the hydroxyl and iodine radicals resulted in the production of the iodine electrophilic reagent HIO involved in the formation of **88**.

Scheme 77. Mechanism Proposed for the Light/Copper-Mediated, O_2-Promoted Oxidative Amidation of Terminal Alkynes[155]



Scheme 78. Oxidative Amidations/Terminal Alkynes Reported by Zhu and Co-Workers[157]



At the same time, Shah and co-workers[160] developed a metal-free route for the synthesis of α-ketoamides using TMSOTf/I_2/DMSO as a novel catalytic system for the oxidative coupling of terminal alkynes with virtually any primary/secondary amine.

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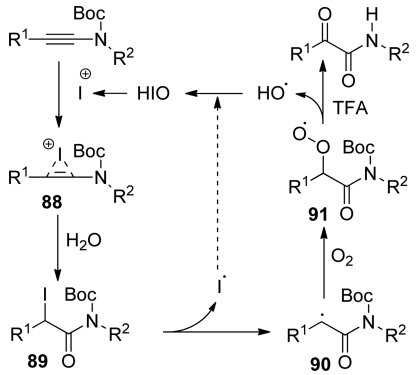
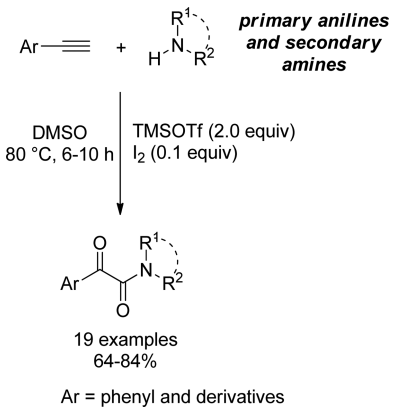
Scheme 79. Mechanism Proposed for the I_2-Promoted Aerobic Oxidative Amidation of *N*-Boc-ynamides[157]



Importantly, the reaction afforded the α-ketoamides in high yields exploiting DMSO both as the solvent and the oxidizing agent, thus circumventing the need of any metal catalysts or external oxidizing agents. Optimal results were observed when the alkyne substrate was treated with TMSOTf (2.0 equiv) and I_2 (0.1 equiv) in DMSO at 80 °C (Scheme 80). Under these

Scheme 80. Oxidative Amidations/Terminal Alkynes Reported by Shah and Co-Workers[160]

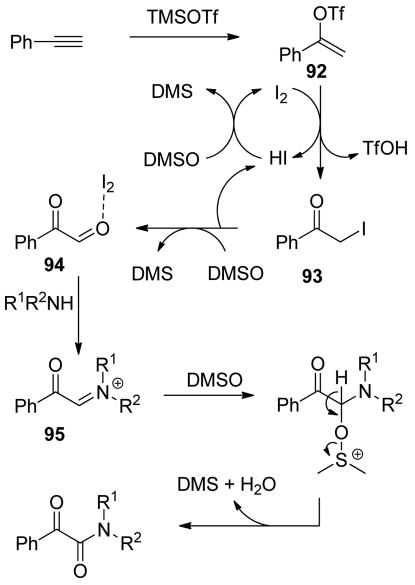


optimized conditions, various substituted phenylacetylenes smoothly reacted with a number of cyclic amines and anilines to give the corresponding tertiary and secondary α-ketoamides in high yields. The method was also successful in reacting diethylamine with phenylacetylene, and *p*-toluidine with 1-ethynylcyclohex-1-ene.

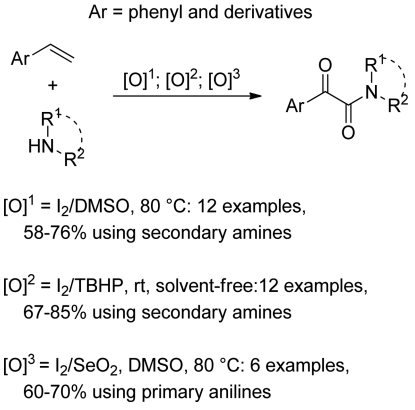
As illustrated in Scheme 81, a plausible mechanism entailed the initial TMSOTf-promoted conversion of the terminal alkyne into vinyl triflate **92**, which reacted with iodine to give the α-iodo acetophenone **93**. The subsequent Kornblum oxidation afforded arylglyoxal **94**, which was first activated by iodine and then attacked by the amine to give the iminium ion **95**. The latter intermediate reacted with the oxidizing agent DMSO to yield the 2-oxoamide products. Notably, DMSO was also involved in the recycling of I_2 through HI oxidation.

3.2.1.8. Aryl-Terminal Alkenes. Aryl α-ketoamides have been recently prepared by Shah and co-workers[161] through the direct oxidative coupling of amines with readily available aryl-terminal alkenes. Three oxidation systems with different scope in substrates or reaction conditions were fit for the purpose (Scheme 82).

Scheme 81. Mechanism Proposed for the I_2-Catalyzed, TMSOTf/DMSO Oxidative Amidation of Terminal Alkynes[160]



Scheme 82. Oxidative Amidations/Aryl-Terminal Alkenes Reported by Shah and Co-Workers[161]



Thus, in the $[O]^1$ system, DMSO solutions of aryl-terminal alkenes and secondary amines were heated at 80 °C in the presence of I_2 (1.0 equiv), while the $[O]^2$ system gave enhanced yields of α-ketoamides by using the I_2/TBHP couple at room temperature under solvent-free conditions. Oxidative amidations performed with $[O]^1$ and $[O]^2$ systems tolerated different styrene derivatives, but only secondary amines, including piperidine with the acid-sensitive *N*-Boc protecting group, were usable. Successive investigations led to the selection of I_2/SeO_2 in DMSO at 80 °C as system $[O]^3$, effective in the oxidative coupling reaction with aromatic primary amines. Thus, a variety of aniline derivatives bearing both electron-withdrawing and electron-donating groups reacted with styrene to afford secondary α-ketoamides.

Intriguingly, just a few months after Shah's report, Ren et al.[162] obtained very similar results in their I_2/TBHP/DMSO-mediated oxidative amidation of unsaturated hydrocarbons.

In the same year, the Sekar research group disclosed its finding on the direct oxidative coupling of styrene derivatives with amines.[163] The metal-free one-pot synthesis of α-ketoamides entailed the use of the inexpensive I_2/IBX system

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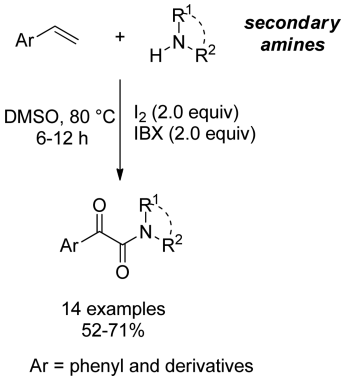
as the additive−oxidant pair in DMSO (Scheme 83). In detail, the styrene compound and I_2/IBX (2.0 equiv each) were stirred

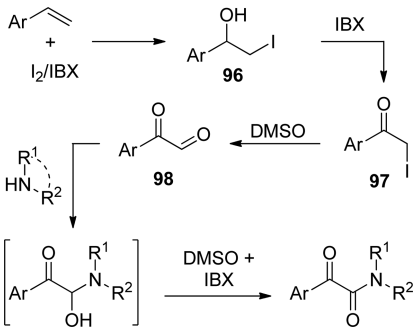
Scheme 83. Oxidative Amidations/Aryl-Terminal Alkenes Reported by Sekar and Co-Workers[163]



in DMSO at 80 °C for 3.5 h, and then amine (4.0 equiv) was added dropwise with stirring until completion of the reaction (3−13 h). As per Shah's [O][1] and [O][2] systems, the I_2/IBX-promoted oxidative amidation tolerated styrenes with substitution at the phenyl ring with electron-withdrawing as well as electron-donating groups. While cyclic amines gave the desired products, neither aliphatic primary amines nor anilines were usable.

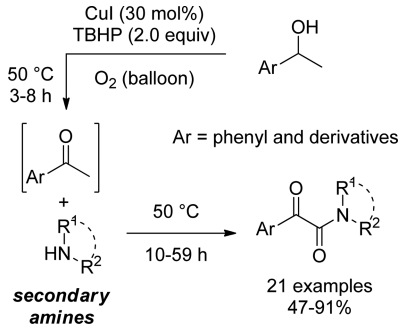
Control experiments established that phenylglyoxal was formed under reaction conditions. Accordingly, a tentative mechanism called for the initial formation of iodohydrin **96**, followed by an oxidative step giving the phenacyl iodide **97**. The latter underwent Kornblum oxidation to phenylglyoxal **98**, which afforded the desired α-ketoamides via DMSO- or IBX-promoted cross dehydrogenative coupling reaction with secondary amines (Scheme 84).

Scheme 84. Mechanism Proposed for the I_2/IBX/DMSO Oxidative Amidation of Aryl-Terminal Alkenes[163]



3.2.1.9. 1-Arylethanols. At the end of 2014, Sekar and co-workers[164] reported that copper(I) iodide was an efficient catalyst for the one-pot transformation of 1-arylethanols and secondary amines into α-ketoamides by using the couple $TBHP/O_2$ as the oxidant system. As shown in Scheme 85, a mixture containing 1-arylethanol, CuI (30 mol %), and TBHP (5−6 M in decane, 2.0 equiv) was heated at 50 °C under an oxygen atmosphere. After consumption of the alcohol (3−8 h), the amine (3.0 equiv) was added and the mixture stirred at 50 °C until completion of the reaction (10−59 h).

Scheme 85. Oxidative Amidations/1-Arylethanols Reported by Sekar and Co-Workers[164]



Control experiments indicated that the copper/TBHP combination was responsible for the alcohol conversion into aryl methyl ketone and that the copper/oxygen system was involved both in the C(sp^3)−H oxidation and in the subsequent oxidative amidation. Importantly, the one-pot multistep process worked only with CuI, while other copper salts provided considerable amounts of the ketones. A wide range of aryl alcohols reacted with cyclic and acyclic secondary amines to yield α-ketoamides, together with small amounts (up to 5%) of the corresponding amides. Importantly, no α-ketoamide formation was observed upon carrying out the reaction under a nitrogen atmosphere or using primary or tertiary amines.

The above observations led to speculate whether the process proceeded via a cleavage reaction of an aminodioxetane intermediate, as previously advanced by Du and Ji[144] for the oxidative amidation of aryl methyl ketones.

3.2.2. Formamides and Formamidine as Nitrogen Sources. In the following, applications of different formamides as amine surrogates in oxidative amidation reactions are detailed. Indeed, the stable C(sp^2)−N bonds of DMF and related N,N-disubstituted formamides may be cleaved under both radical and acid conditions. Notably, formamides show less pollution, odor, and toxicity with respect to the corresponding amines.[83]

3.2.2.1. Aryl Methyl Ketones. In 2012, a novel, environmentally friendly protocol for the direct synthesis of α-ketoamides from aryl methyl ketones and *N,N*-dialkylformamides using TBAI/TBHP[165] oxidation system was reported by the group of Mai and Qu.[166] Typically, the aryl methyl ketone/*N,N*-dialkylformamide mixture (1:2.5 molar ratio) was heated at 100 °C in water in the presence of TBAI (20 mol %) and excess TBHP (5.0 equiv), as shown in Scheme 86. Though water was the solvent of first choice, good transformations were obtained under neat conditions as well. Different aryl methyl ketones and *N,N*-dialkylformamides took part efficiently in the oxidative amidation process. Notably, besides DMF and *N,N*-diethylformamide, piperidine-, morpholine-, and 4-methylpiperazine-1-carbaldehydes were also effective sources of the corresponding amines. TBAI and TBHP were essential for the transformation. Moreover, the formyl group had a crucial role, as none of the desired products were obtained using *N,N*-dimethylacetamide or secondary amines as the nitrogen atom sources. Importantly, the intuition that under current oxidative conditions aryl methyl ketones could be formed from 1-arylethanol precursors led to the extention of the method to comprehend such substrates.

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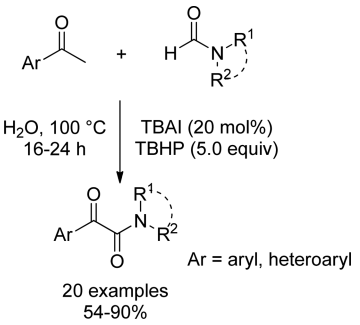
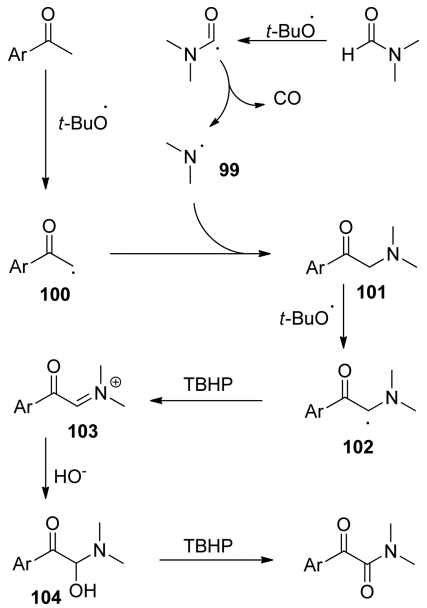
Scheme 86. Oxidative Amidations/Aryl Methyl Ketones (formamides as nitrogen sources) Reported by Qu and Co-Workers[166]



Phenylglyoxylic acid was not a partner of DMF, so the reaction pathway depicted in Scheme 87 was advanced as the

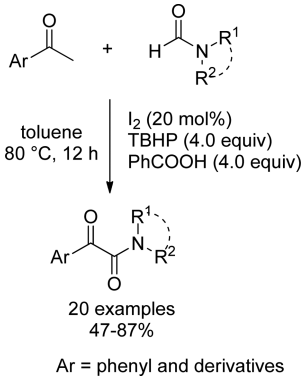
Scheme 87. Mechanism Proposed for the TBAI/TBHP Oxidative Amidation of Aryl Methyl Ketones with Formamides[166]



plausible mechanism through which aryl methyl ketones were coupled with *N*,*N*-dialkylformamides under TBAI-catalyzed conditions. The *tert*-butoxyl radical, catalytically generated in situ from the iodide anion oxidation, reacted with the *N*,*N*-dialkylformamide to produce homolytic C(sp^2)−H bond cleavage followed by decarbonylation to the aminyl radical **99**. Its coupling with **100**, in turn formed by *tert*-butoxyl radical hydrogen abstraction from the aryl methyl ketone, afforded the α-amino ketone **101**. The latter was eventually oxidized to the desired α-ketoamide product, probably via intermediates **102**−**104**.

A very similar approach was reported a year later by Wang and co-workers,[167] who accomplished the aryl methyl ketone/*N*,*N*-dialkylformamide oxidative coupling by using I_2/TBHP,[147] with the addition of benzoic acid as additive to promote the release of amines from formamides. Thus, α-ketoamides were obtained by heating at 80 °C for 12 h a toluene solution containing aryl methyl ketones and formamides (1:4 molar ratio), iodine (20 mol %), and TBHP and the additive benzoic acid (4.0 equiv each) (Scheme 88). To explore the scope and limitation of the reaction, a wide array of acetophenones and

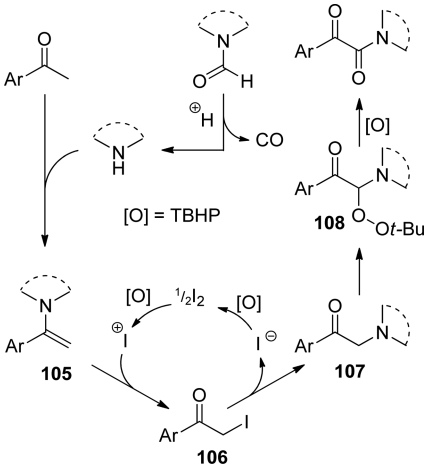
Scheme 88. Oxidative Amidations/Aryl Methyl Ketones (formamides as nitrogen sources) Reported by Wang and Co-Workers[167]



formamides were tested. The results indicated that acetophenones with electron-withdrawing groups were better substrates than the ones bearing electron-donating groups, and that ortho-substituents slightly decreased yields of the corresponding α-ketoamides. With regard to the formamide components, it was observed that DMF was superior to *N*,*N*-diethylformamide and that cyclic formamides were also compatible substrates. Notably, secondary formamides, namely, *N*-methylformamide and *N*-ethylformamide, worked effectively to deliver the corresponding secondary α-ketoamides in moderate yields (55% and 60% yields).

As shown in Scheme 89, the first step along the reaction pathway was the benzoic acid-promoted C−N bond cleavage of

Scheme 89. Mechanism Proposed for the I_2/TBHP Oxidative Amidation of Aryl Methyl Ketones with Formamides[167]



formamides. The resulting amines were then condensed with acetophenones to give enamines **105**, which were transformed into α-ketoamides via phenacyl iodides **106**, α-amino ketones **107**, and *tert*-butyl peroxides **108**, through a cascade process similar to that postulated by the same authors for the related coupling of aryl methyl ketones with amines.[147]

The broadly shared interest in developing copper-catalyzed methodologies suitable for carbon−heteroatom bond formation

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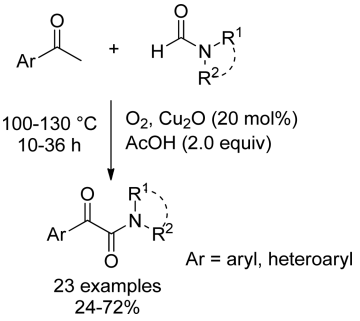
led Zhou and Song to introduce in 2014 a new synthetic approach to α-ketoamides from aryl methyl ketones and dialkylformamides.[168] Thus, the power of the Cu(I)/O_2 system in catalyzing oxidative amidations[144,145] and that of carboxylic acids in releasing amines from formamides[167] could be efficiently combined in order to prepare α-ketoamides from aryl methyl ketones and formamides. Aryl methyl ketones gave tertiary α-ketoamides upon treatment with formamides in the presence of Cu_2O (20 mol %) and acetic acid (2.0 equiv) under oxygen atmosphere at 100−130 °C (Scheme 90). A variety of

Scheme 90. Oxidative Amidations/Aryl Methyl Ketones (formamides as nitrogen sources) Reported by Zhou and Song et al.[168]

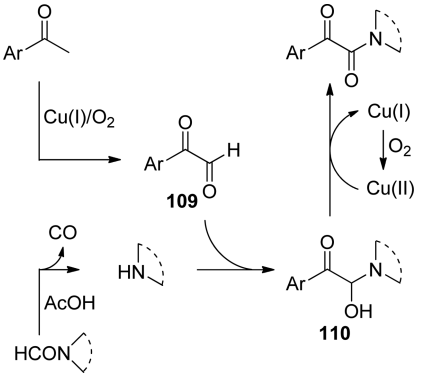


phenyl-substituted as well as naphthyl and thienyl methyl ketones reacted with DMF to give the corresponding *N*,*N*-dimethyl-α-ketoamides in moderate to good yields. *N*-Formyl cyclic amines were also decent amine sources, while a disappointing result was obtained using diethylformamide (<5% yield).

Isotope-labeling experiments demonstrated that molecular oxygen was incorporated in the final α-ketoamide products. Moreover, the partly oxidized compounds phenylglyoxal and 2-hydroxyacetophenone smoothly reacted with DMF under standard conditions. Thus, in line with Du and Ji's report,[144] α-ketoamides are likely to be formed through copper-mediated dioxygen activation followed by C(sp^3)−H bond functionalization and copper-catalyzed aerobic CDC reaction of arylglyoxals **109** with amines via hemiaminals **110** (Scheme 91).

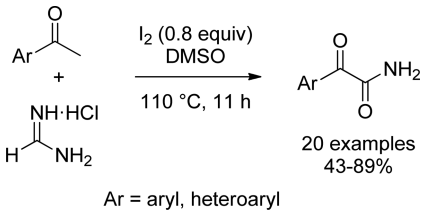
A variety of primary aryl α-ketoamides were prepared through a molecular iodine-catalyzed oxidative cross-coupling of aryl methyl ketones with formamidine hydrochloride as a

Scheme 91. Mechanism Proposed for the Cu(I)/O_2 Oxidative Amidation of Aryl Methyl Ketones with Formamides[168]



free ammonia surrogate.[169] Aryl methyl ketones bearing electronically neutral, electron-donating, and electron-withdrawing substituents smoothly reacted with equimolar amount of formamidine hydrochloride in DMSO at 110 °C in the presence of I_2 (0.8 equiv), as shown in Scheme 92. Aryl and

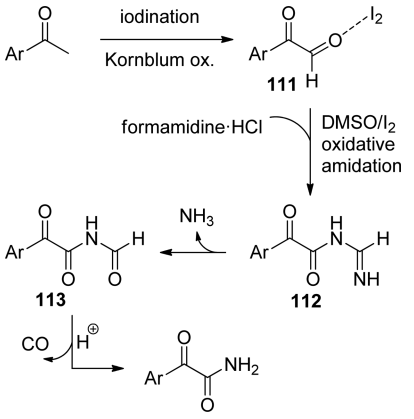
Scheme 92. Oxidative Amidations/Aryl Methyl Ketones (formamidine as nitrogen source) Reported by Wu and Co-Workers[169]



heteroaryl primary α-ketoamides were prepared in moderate to excellent yields, while aliphatic primary α-ketoamides could not be prepared from alkyl methyl ketones and the ammonia surrogate.

Control experiments indicated that the direct release of ammonia was not involved in the process and that *N*-formyl-2-oxo-2-arylacetamides **113** were formed as intermediates. Thus, in line with Vishwakarma's proposition,[131] an iodination/Kornblum oxidation sequence accounted for the formation of 2-oxoaldehydes **111**, which underwent CDC reaction with formamidine by I_2 activation (Scheme 93).

Scheme 93. Mechanism Proposed for the I_2/DMSO Oxidative Amidation of Aryl Methyl Ketones with Formamidine[169]



Hydrolysis of the resulting intermediates **112** furnished the imides **113**, which were eventually transformed into the desired α-ketoamides via an acid-catalyzed decarbonylation process.[167]

3.2.2.2. Ethylarenes. In 2014, Sun and co-workers[170] reported the oxidative amidation of ethylarenes with *N*,*N*-dialkylformamides in the presence of TBAI as a catalyst and TBHP as the oxidant. The unprecedented transformation entailed the sequential dehydrogenation of the five inert C(sp^3)−H bonds of the ethyl group followed by the CDC reaction with amines, in turn derived through radical cleavage of formamides.

The environmentally friendly, mild, and metal-free process gave access to α-ketoamides when mixtures of ethylarenes and dialkylformamides (1:6 molar ratio) were heated at 80 °C

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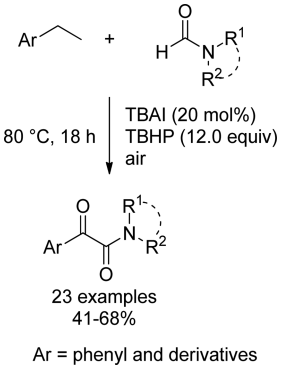
under air atmosphere in the presence of TBAI (20 mol %) and TBHP (12.0 equiv) (Scheme 94). Irrespective of both the

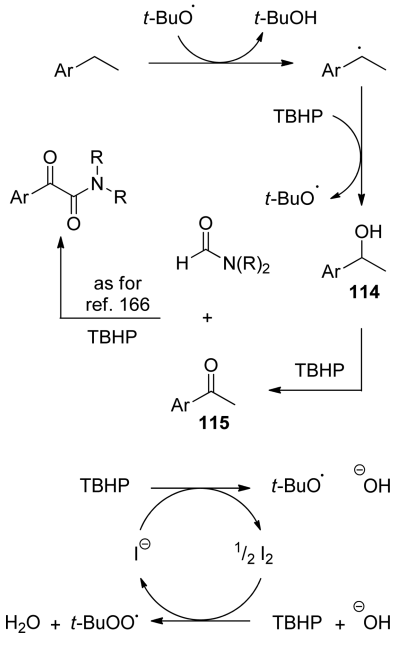
Scheme 94. Oxidative Amidations/Ethylarenes (formamides as nitrogen sources) Reported by Sun and Co-Workers[170]



nature and the position of substituents on the phenyl ring, *N*,*N*-dimethyl-α-ketoamides were prepared in moderate yields by using DMF as the amine source. Diethylformamide as well as *N*-formyl cyclic amines were also suitable coupling partners to prepare tertiary α-ketoamides, while *N*,*N*-diisopropylformamide unexpectedly furnished secondary α-ketoamides, showing that cleavage of an alkyl C−N bond was also possible under the reaction conditions.

Unlike phenylacetaldehyde, both 1-phenylethanol and acetophenone were suitable substrates under standard conditions. Moreover, dimethylamine was ineffective as a nitrogen source, and importantly, the addition of the radical scavenger TEMPO stopped the oxidative amidation process. Accordingly, a *tert*-butoxyl-promoted radical process at the benzylic C−H bond of ethylarenes was envisioned to produce 1-arylethanols **114**, which were oxidized by TBHP to the corresponding aryl methyl ketones **115** (Scheme 95). Eventually, the latter reacted with formamides along the steps already described for the

Scheme 95. Mechanism Proposed for the TBAI/TBHP Oxidative Amidation of Ethylarenes with Formamides[170]

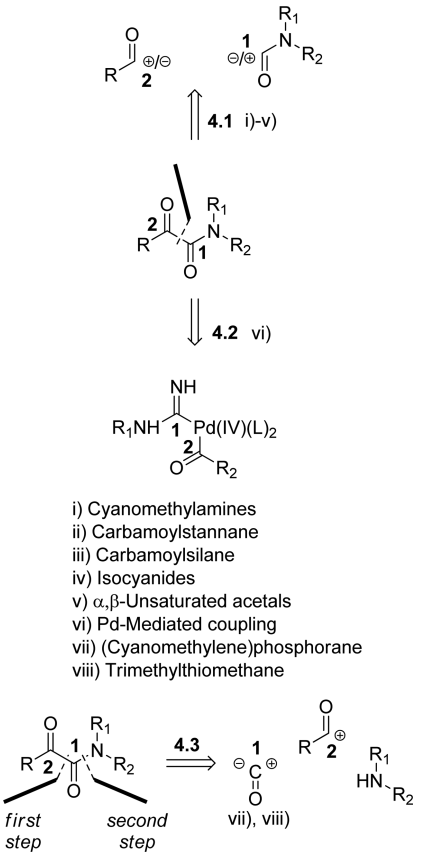


TBAI/TBHP oxidative coupling of aryl methyl ketones with dialkylformamides,[166] wherein the iodide/iodine catalytic cycle generated the *tert*-butoxyl radical species involved both in the activation of the C(sp^3)−H benzylic bond and in the decarbonylation of formamides.

4. C(1)−C(2) BOND-FORMING PROCESSES

This section includes methodologies for α-ketoamides preparation centered on the C(1)−C(2) σ-bond construction. This operation has been accomplished for the most part through carbon−carbon retrosynthetic ionic disconnection devising C(1)-carbamoyl or C(2)-carbonyl umpoled synthons to react with normal polarized C(2) and C(1) carbonyl derivatives, respectively (Scheme 96).

Scheme 96. C(1)−C(2) Bond-Forming Processes



Thus, cyanomethylamine, carbamoylstannane, carbamoylsilane, and isocyanide reagents have been used as equivalents to C(1)-carbamoyl anions, while α,β-unsaturated acetals masked umpoled C(2) carbonyls (subsection 4.1). A Pd-mediated C(1)−C(2) coupling is accommodated in subsection 4.2. Eventually, strategies allowing for the sequential C(1)−C(2) and C(1)−N bond formation are discussed in subsection 4.3. Actually, (cyanomethylene)phosphorane and trimethylthiomethane acted as C(1)-carbonyl 1,1-dipole synthons, with the inverse and normal polarity accounting for C(1)−C(2) and C(1)−N sequential bond construction, respectively.

4.1. C(1)−C(2) Ionic Disconnections

4.1.1. Cyanomethylamines. The use of KH-deprotonated cyanomethylamines as C(1) umpolung reagents, originally introduced by Takahashi et al.[171] to prepare α-ketoamides by

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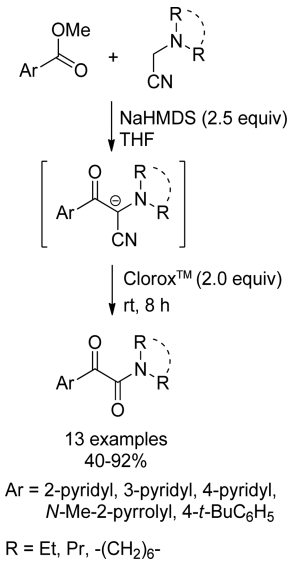
reaction with benzoic ester followed by oxidation with $Cu(OAc)_2$, was revisited by Wang and co-workers[172] 20 years later, providing a great improvement of the procedure. In detail, the safe base NaHMDS was added to a THF solution of cyanomethylamines and methyl esters of aryl carboxylic acids in order to produce the corresponding acylated cyanomethylamine sodium salts, which were directly oxidized by adding 5.25% NaOCl solution (Clorox) at room temperature (Scheme 97). This procedurally simple, one-pot operation provided aryl and heteroaryl α-ketoamides in good overall yields.

Scheme 97. C(1)−C(2) Bond-Forming Processes/ Cyanomethylamines Reported by Wang and Co-Workers[172]



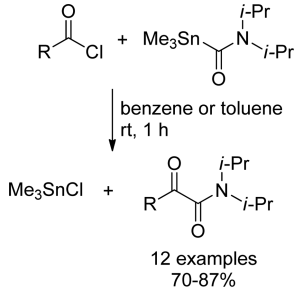
13 examples
40-92%

Ar = 2-pyridyl, 3-pyridyl, 4-pyridyl, *N*-Me-2-pyrrolyl, 4-*t*-BuC_6H_5

R = Et, Pr, -$(CH_2)_6$-

4.1.2. Carbamoylstannane. The electrophilic substitution reaction at the Sn−C bond of (*N*,*N*-diisopropylcarbamoyl)-trimethylstannane by acid chlorides opened a convenient and general route to α-oxoamides, including some members that were not easily prepared via other methods.[173] As shown in Scheme 98, benzene or toluene solutions of acyl chlorides and carbamoylstannane (1.1 equiv) were stirred at room temperature for 1 h, producing the corresponding *N*,*N*-diisopropyl-2-oxoamides. Methyl, isobutyryl, phenylacetyl, methacryloyl, and cinnamoyl chlorides were suitable electrophiles. Not surprisingly, chloroacetyl chloride and perfluorobutanoyl chloride displayed lower reactivity than the foregoing acid chlorides; hence, heating of the reaction mixtures was required. Aromatic and heteroaromatic acid chlorides were also shown to be sluggish partners of the carbamoylstannane, with prolonged reaction times being required at room temperature. Importantly, this method had a major drawback, since the preparation of the toxic organotin reagent required handling hazardous carbon monoxide.

Scheme 98. C(1)−C(2) Bond-Forming Processes/ Carbamoylstannane Reported by Tanaka and Co-Workers[173]

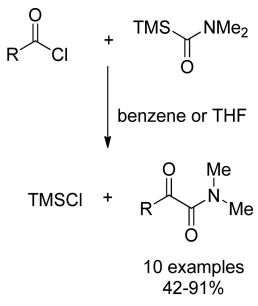


12 examples
70-87%

R = alkyl, aryl, heteroaryl

4.1.3. Carbamoylsilane. Almost contemporaneously, Chen and Cunico[174] achieved the preparation of α-ketoamides by coupling (*N*,*N*-dimethylcarbamoyl)trimethylsilane with acyl chlorides in benzene or THF solution under anhydrous conditions (Scheme 99). Side products were formed by protonolysis of carbamoylsilane, with consequent production of DMF, and over-reaction of the formed α-ketoamides. However, tuning the amount of carbamoylsilane (1.1 equiv) and the reaction temperature (room temperature or below) usually allowed one to minimize these side processes.

Scheme 99. C(1)−C(2) Bond-Forming Processes/ Carbamoylsilane Reported by Chen and Cunico[174]

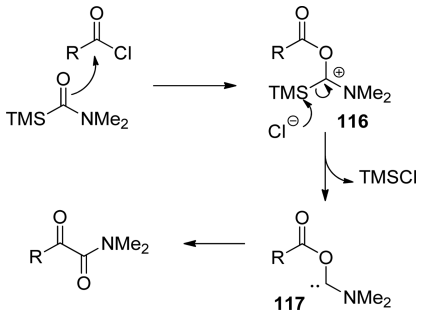


10 examples
42-91%

R = alkyl, phenyl and derivatives, cinnamyl, phenylethynyl, methoxycarbonyl

As shown in Scheme 100, the O-acylation of the carbamoylsilane was assumed to give transient isoimidium salt **116**, which underwent trimethylsilyl chloride (TMSCl) expulsion, generating the acyloxy(amino)carbene **117**. The latter eventually underwent rearrangement to the α-ketoamide products.

Scheme 100. Mechanism Proposed for the Carbamoyltrimethylsilane Coupling with Acyl Chlorides[174]



4.1.4. Isocyanides. In 1892, Nef[175] first described the interaction of isocyanides with acyl chlorides followed by hydrolysis of the resulting imidoyl chlorides to form α-ketoamides.[176] These findings remained largely ignored and were rediscovered by Ugi and Fetzer[177] more than 50 years ago with the successful preparation of 15 α-ketoamides by decomposition of the so-called α-adducts with water or formic or acetic acid.

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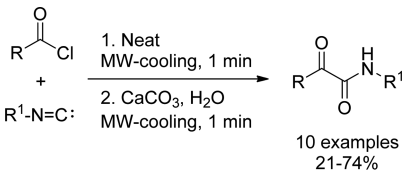
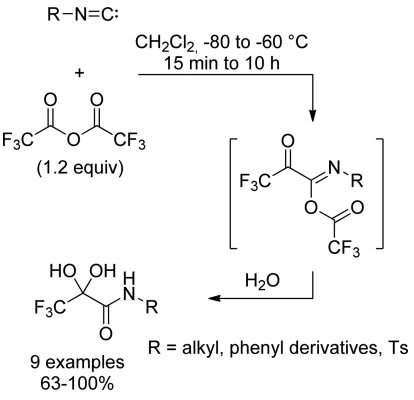
Along their studies on the development of a practical and straighforward methodology for the preparation of α-ketoamides, Chen and Deshpande[178] exploited microwave technology to accelerate both formation and hydrolysis of imidoyl chloride α-adducts. Thus, α-ketoamides were prepared in moderate to good yields by applying 100 W irradiation along with air-cooling both to the aromatic/aliphatic acyl chlorides−alkyl isocyanides condensation and to the $CaCO_3$-mediated hydrolysis of the resulting imidoyl chlorides (Scheme 101).

Scheme 101. C(1)−C(2) Bond-Forming Processes/ Isocyanides Reported by Chen and Deshpande[178]



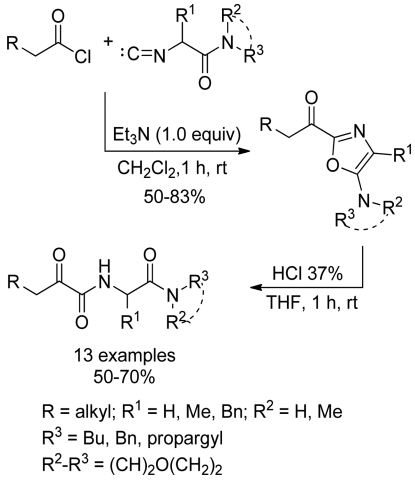
El Kaïm and Pinot-Perigord[179] employed trifluoroacetic anhydride as the electrophilic partner of isocyanides in an efficient preparation of a series of trifluoropyruvamide derivatives that were isolated as the corresponding crystalline and stable hydrates. A careful control of temperature and concentration was required to secure high yields. Thus, trifluoroacetic anhydride (1.2 equiv) was added to a cold (−80 to −60 °C) dichloromethane solution of isocyanides (1.0 equiv, 0.35 M) under argon. After consumption of the isocyanide, water was added and the temperature brought to 25 °C to perform hydrolysis (Scheme 102).

Scheme 102. C(1)−C(2) Bond-Forming Processes/ Isocyanides Reported by El Kaïm and Pinot-Perigord[179]



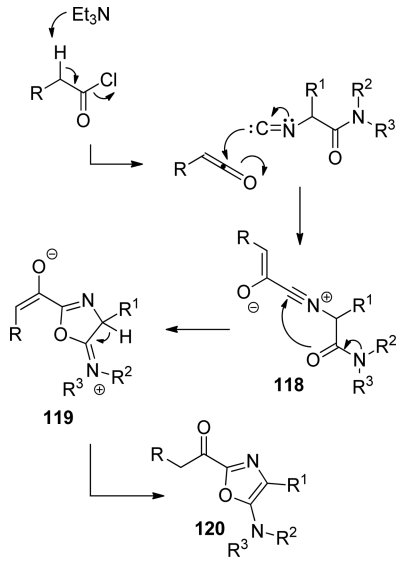
Pirali and co-workers[180] described a novel and reliable methodology to rapidly prepare structurally diverse α-ketoamides based on the reaction of acyl chlorides with α-unsubstituted and α-substituted isocyanoacetamides, easily accessible starting materials. As shown in Scheme 103, acyl chlorides and α-isocyanoacetamides (1.0 equiv) were efficiently coupled in dichloromethane in the presence of triethylamine (1.0 equiv) at room temperature for 1 h. The resulting 2-acyl-5-aminooxazoles were subjected to acid hydrolysis in THF and HCl 37% (100 μL/0.10 mmol) for 1 h to give α-ketoamides in good yields.

Scheme 103. C(1)−C(2) Bond-Forming Processes/ Isocyanides Reported by Pirali and Co-Workers[180]



The observations that the isoxazole intermediate derived from (*S*)-2-phenyl butanoyl chloride and *N*-benzyl isocyanoacetamide was a racemic mixture and that benzoyl chloride was an inadequate partner of isocyanides suggested involvement of a ketene in the reaction mechanism. Thus, the triethylamine-promoted dehydrochlorination of aliphatic acyl chlorides gave ketene electrophilic species promptly intercepted by isocyanides (Scheme 104). The resulting nitrilium ions **118**

Scheme 104. Mechanism Proposed for the Reaction of Acyl Chlorides with α-Isocyanoacetamides[180]



underwent internal attack by the nucleophilic oxygen atom of the proximal carboxamide functional group to release **119**, which suffered a subsequent proton transfer, furnishing heterocyclic compounds **120**, precursors of the α-ketoamides.

One year later, the same group reported that *syn*-chlorooximes could be suitable electrophilic partners of isocyanides in a Passerini-type three-component reaction (P-3CR), providing *syn*-α-oximinoamides.[181]

As a natural extension of these findings, they decided to explore the reaction of α-isocyanoacetamides with chlorooximes envisioned as in situ precursors of nitrile *N*-oxide

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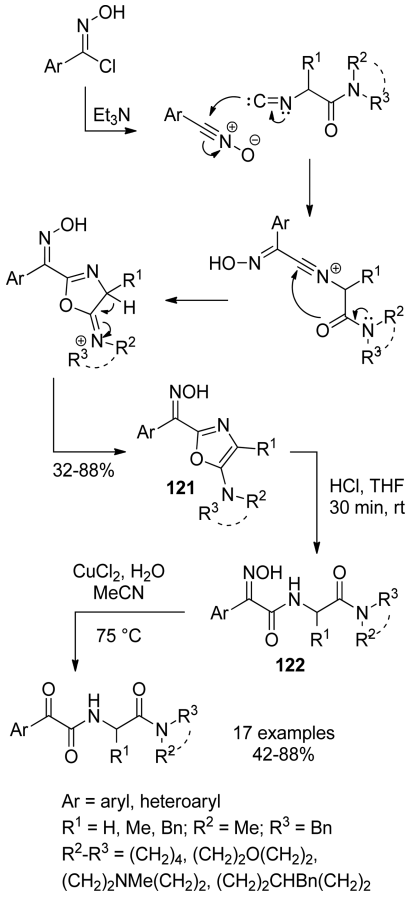
electrophilic species.[182] In such a way, they anticipated that arylchlorooximes could be suitable reagents to overcome the previously established[180] inability of aromatic acid chlorides to give aryl α-ketoamides by reaction with α-isocyanoacetamides. Indeed, a series of 1,3-oxazol-2-oximes **121** were prepared in good yields under the reaction conditions already applied for acyl chlorides (Scheme 105). Treatment of **121** with HCl

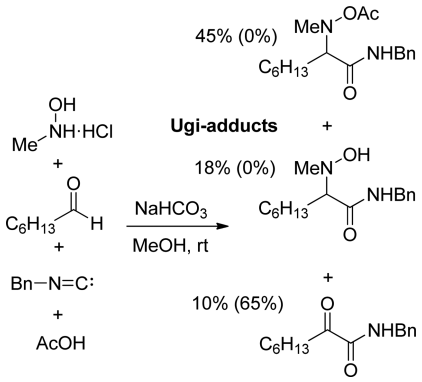
Scheme 105. Mechanism Proposed for the Reaction of Chlorooximes with α-Isocyanoacetamides[182]



afforded compounds **122**, which could be transformed into aryl α-ketoamides by copper(II)-assisted hydrolytic removal of hydroxylamine. The process was quite general as arylchlorooximes bearing both electron-withdrawing and electron-donating substituents reacted smoothly with different tertiary α-substituted or unsubstituted α-isocyanoacetamides.

Looking for novel isocyanide-based multicomponent reactions (IMCRs),[183] Zhu and co-workers[184] disclosed an unprecedented one-pot process to achieve α-ketoamides through a formal oxidative coupling of an aldehyde with an isocyanide. Central to the serendipitous discovery was the careful examination of the products arising from the U-4CR of *N*-methylhydroxylamine, heptanal, benzyl isocyanide, and acetic acid following the directions of Guanti and co-workers (Scheme 106).[185] Surprisingly, the expected Ugi adducts (63% overall yield) were accompanied by 10% of the unexpected α-ketoamide. Subsequent investigations led to the discovery that crucial parameters for α-ketoamide formation were the use of excess acetic acid (9.0 equiv), molecular sieves as additive (4 Å MS, 750 mg/mmol of aldehyde), and methanol as the solvent. Under these optimized conditions, the U-4CR

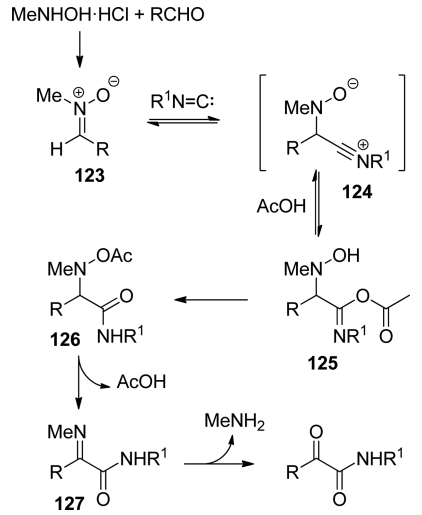
Scheme 106. C(1)−C(2) Bond-Forming Processes/ Isocyanides Reported by Zhu and Co-Workers[184]



adducts were not detected while the α-ketoamide was obtained in 65% yield. This gratifying result led to the study of the scope and limitations of the method. Actually, both aromatic and aliphatic isocyanides, including α-isocyanoacetates, underwent the desired reaction, providing α-ketoamides in moderate to good yields (13 examples, 28−75%). Unlike aromatic aldehydes, simple as well as highly functionalized and suitable protected aliphatic aldehydes were effective substrates.

A plausible reaction sequence for the *N*-methylhydroxylamine-promoted oxidative coupling of aliphatic aldehydes with isocyanides is depicted in Scheme 107. Trapping of the nitrone

Scheme 107. Mechanism Proposed for the Formal Oxidative Coupling of Aliphatic Aldehydes with Isocyanides[184]



electrophile **123** by the isocyanide generated the nitrilium intermediate **124**, which rearranged to the α-acyloxyamino amide **126** via the imidate intermediate **125**, according to an Ugi reaction pathway. The subsequent molecular-sieves-promoted β-elimination of acetic acid furnished the α-iminoamide **127**, which eventually hydrolyzed to α-ketoamide.

Despite the formal oxidative coupling reaction of salicylaldehyde derivatives with isocyanides under oxidant-free conditions having been occasionally used to prepare *N*-alkylated/arylated α-aryl-α-ketoamides,[186,187] Zhu and co-workers[184] found that aromatic aldehydes failed to be effective substrates in the one-pot *N*-methylhydroxylamine-promoted oxidative coupling with isocyanides. Ascribing this failure to the low electrophilicity of

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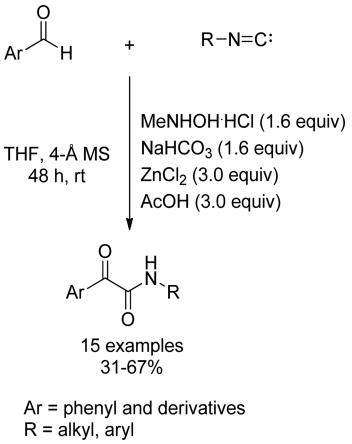
the aromatic nitrone intermediate, they anticipated that the use of a Lewis acid could favor the nitrone−isocyanide coupling to form α-aryl-α-ketoamides. Pleasingly, these compounds were obtained in satisfactory yields by performing the coupling reaction in THF in the presence of $ZnCl_2$ (3.0 equiv) and using both *N*-methylhydroxylamine and acetic acid as shuttle molecules (Scheme 108).[188] The new protocol worked

Scheme 108. C(1)−C(2) Bond-Forming Processes/ Isocyanides Reported by Zhu and Co-Workers[188]



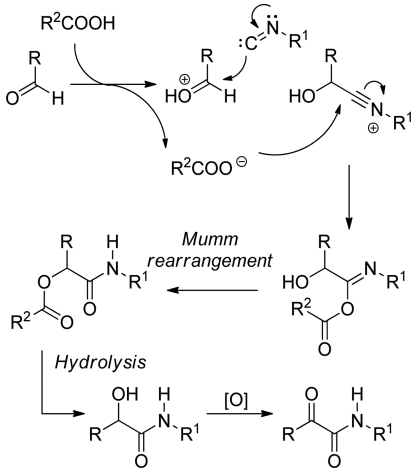
effectively for a variety of representative aromatic aldehydes and isocyanides, well complementing the previous one[184] applicable to aliphatic aldehydes only.

From a retrosynthetic viewpoint, all of the hitherto discussed reactions of isocyanides served to connect electrophilic acyl synthons with carbamoyl anion equivalents, establishing a direct entry to α-ketoamides. However, condensation of isocyanides with carbonyl components, according to Passerini's directions,[189] followed by a late-stage oxidation step, has been extensively used as an alternative two-step synthetic approach to α-ketoamides.

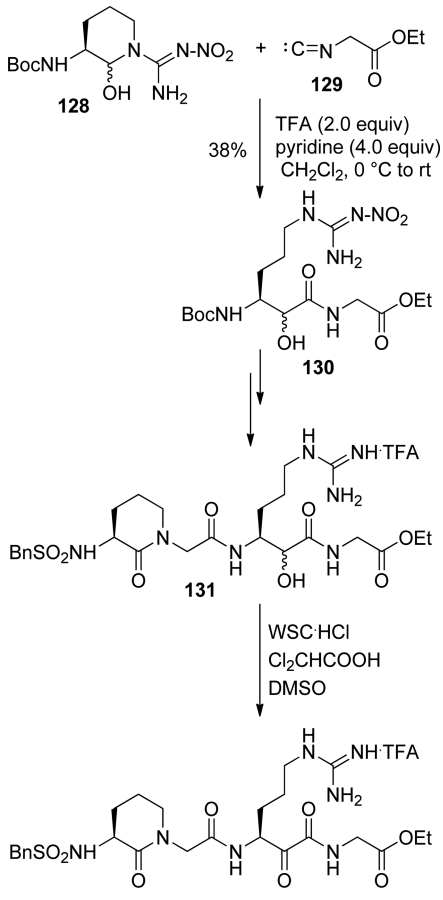
In the original version, the P-3CR was certainly one of the most direct synthetic approaches to α-hydroxyamides, entailing a one-pot combinaton of an isonitrile, an aldehyde (or ketone), and a carboxylic acid in the following sequence: (1) activation of the carbonyl component by a Brønsted acid, (2) nucleophilic addition of isocyanide, (3) trapping of the nitrilium cation by carboxylate anion, and (4) Mumm rearrangement of the acyl imidate, giving α-acyloxycarboxamide (Scheme 109). At this stage, a mild hydrolytic step is required in order to achieve biologically relevant α-hydroxyamides.

Semple et al.[190] developed an efficient P-3CR protocol enabling the direct access to α-hydroxyamides by using TFA (2.0 equiv) in the presence of pyridine (4.0 equiv) to efficiently promote both the initial coupling of isocyanides with *N*-protected α-aminoaldehydes and the final hydrolytic step. As anticipated, the α-trifluoroacetoxycarboxamide intermediates underwent facile hydrolysis during aqueous workup or by silica gel chromatography. The method was successfully applied for the preparation of the α-ketoargininamide thrombin inhibitor (Scheme 110). Thus, the reaction of *N*-α-Boc-argininal derivative **128** with ethyl isocyanoacetate **129** under TFA−pyridine-promoted P-3CR conditions gave compound **130**. Its conversion to the advanced intermediate **131** called for removal of the *N*-protecting group, coupling to a lactam acetic acid moiety, and hydrogenolysis. Eventually, oxidation of the α-hydroxyamide moiety of **131** under Moffatt conditions provided the target compound.

Scheme 109. Mechanism of the Passerini Three-Component Reaction[189]



Scheme 110. C(1)−C(2) Bond-Forming Processes/ Isocyanides Reported by Semple et al.[190]



Interestingly, in 2015, Sunazuka and co-workers[191] reported a Passerini-type reaction exploiting 3,5,6-trifluoro-2-pyridone as an efficient organocatalyst for the α-addition of isocyanides to aldehydes in the presence of water. Remarkably, this method gave access to α-hydroxyamides, avoiding the severe conditions

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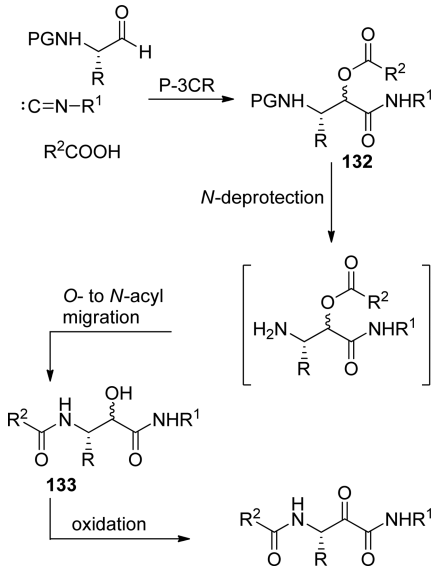
required in mineral acid-catalyzed as well as Lewis acid-catalyzed versions of P-3CR.

Alternatively, α-hydroxyamides could be obtained through a facile *O*- to *N*-acyl shift taking place by orthogonal N-deprotection of the Mumm rearrangement products **132** resulting from *N*-protected α-aminoaldehydes (Scheme 111).[192] Indeed, the stereoconservative Passerini/amine deprotection/acyl migration (PADAM) process delivered the stable adducts **133** featuring two different amide bonds and a central secondary alcohol, potentially oxidizable in a subsequent step to give α-ketoamides.

Scheme 111. Passerini/Amine Deprotection/Acyl Migration (PADAM) Process[192]

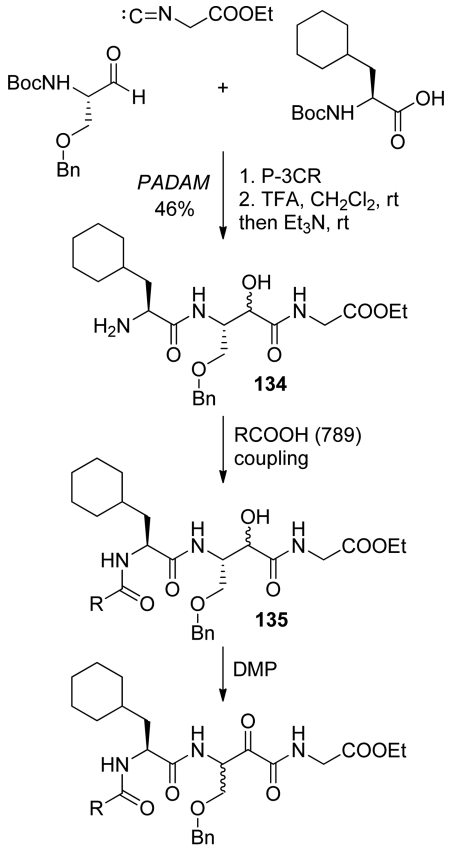


Quite amazingly, a communication by Banfi et al.[185] just a few months before reported the results of a Passerini multicomponent reaction of protected α-aminoaldehydes through a Boc-deprotection/transacylation process. The elegant PADAM strategy served as a concise, atom-economical synthetic entry to complex peptide-like substances, including enzyme inhibitors.

Semple and co-workers applied the PADAM strategy in the total synthesis of eurystatin A,[192] as well as to prepare the N(10)−C(17) fragment of cyclotheonamides.[193] In the first case, a *N*-Fmoc deprotection/transacylation was triggered by Et_2NH in dichloromethane at room temperature while, in the second one, treatment with Et_3N at pH 9 served to promote the *O*- to *N*-acyl migration after *N*-Boc removal with HCl in MeOH.

The PADAM approach has been also used[194] to prepare a library of small molecules bearing an α-ketoamide warhead, evaluated as inhibitors of cathepsin S, a key proteolytic enzyme upregulated in many cancers during tumor progression and metastasis. Thus, P-3CR of a serine-based *N*-Boc-protected α-aminoaldehyde with ethyl isocyanoacetate and *N*-Boc cyclohexylalanine, followed by TFA-promoted *N*-Boc removal and Et_3N-induced acyl migration, generated the α-hydroxy dipeptide **134** in high yield (Scheme 112). Coupling of the latter with 789 different acids generated a library of α-hydroxyl compounds **135**, some of which were taken to the target α-ketoamides upon oxidation using Dess−Martin periodinane reagent.

Scheme 112. C(1)−C(2) Bond-Forming Processes/Isocyanides Reported by Lin and Co-Workers[194]



Banfi and co-workers[195] exploited the PADAM strategy to achieve peptide-mimetic protease inhibitors. The salient steps in this approach were the P-3CR and the sequential treatment with TFA/Et_3N system to trigger acyl migration. The secondary alcohol oxidation was eventually performed with NaOCl, KBr, and catalytic TEMPO.

Later, the same group succeeded in transferring the methodology onto the solid-phase by using solid-supported isocyanides.[196,197] In this manner, libraries of β-acylamino-α-hydroxyamides could be prepared in good yields and purities. The subsequent oxidation with IBX in DMSO delivered the corresponding α-ketoamides, which were recovered almost quantitatively after removal from the resin with TFA or by photoirradiation. The scope of the methodology was also expanded via post-MCR transformations that allowed the rapid access to highly functionalized 2(1*H*)-pyrazinones,[198] important heterocyclic constituents of natural products.

Recently, the homo-PADAM protocol[199] has been introduced to efficiently prepare the diastereomeric α-hydroxy-γ-acylaminoamides **136** by using *N*-Boc β-aminoaldehydes as carbonyl components in the P-3CR (Scheme 113). Stereospecific post-MCR transformations of the separated α-hydroxyamides led to highly substituted C(2) epimeric chromanes, while Dess−Martin oxidation gave enantioenriched α-oxo-γ-acylaminoamides with values of enantiomeric excess (ee) ranging from 92 to >99%.

In 2015, El Kaïm and co-workers[200] reported that the Passerini adducts of cynnamaldehyde and analogues could be efficiently converted into α-ketoamides by a two-step process

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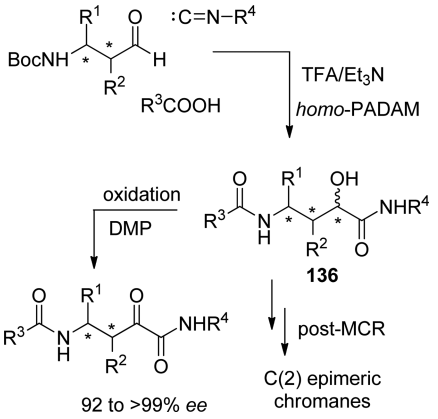
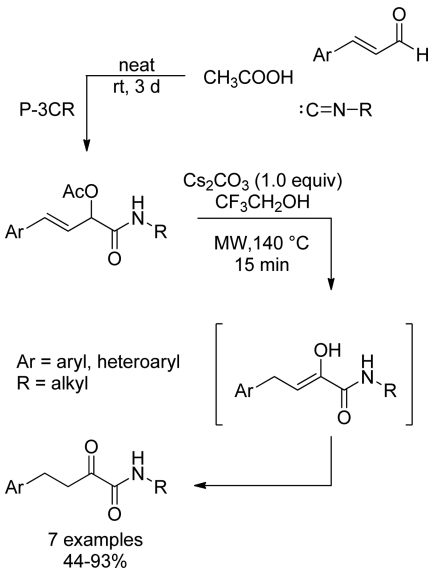
Scheme 113. Homo-PADAM Protocol[199]



involving saponification of the acetyl ester and isomerization of the double bond (Scheme 114). In detail, a suspension of the

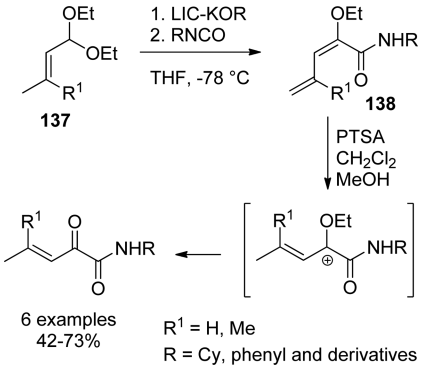
Scheme 114. C(1)–C(2) Bond-Forming Processes/Isocyanides Reported by El Kaïm and Co-Workers[200]



Passerini adducts and Cs_2CO_3 (1.0 equiv) in trifluoroethanol was heated at 140 °C under microwave conditions. The method strongly depended on the nature of the *N*-amide substituent: *N*-cyclohexyl and *N*-*tert*-butyl amides were superior to benzyl amides, while both phenyl and furan were well-tolerated aryl groups. Unlike previously discussed syntheses of ketoamides exploiting P-3CR, the present one did not require any late-stage oxidation step. However, the Passerini–saponification sequence was restricted to the formation of α-ketoamides substituted at the C(4) position by aryl or heteroaryl groups.

4.1.5. α,β-Unsaturated Acetals. A nonconventional synthetic approach for α-ketoamides preparation through C(1)–C(2) σ bond construction entailed the use of deprotonated α,β-unsaturated acetals **137** as C(2) umpolung reagents.[201] Thus, metalation of **137** with Schlosser's base generated a nucleophilic species that intercepted electrophilic *N*-alkyl/aryl isocyanates to give the *E*-stereodefined α-ethoxydienamides **138** after mild acidic workup (Scheme 115). The subsequent treatment with a stoichiometric amount

Scheme 115. C(1)–C(2) Bond-Forming Processes/α,β-Unsaturated Acetals Reported by Prandi and Co-Workers[201]

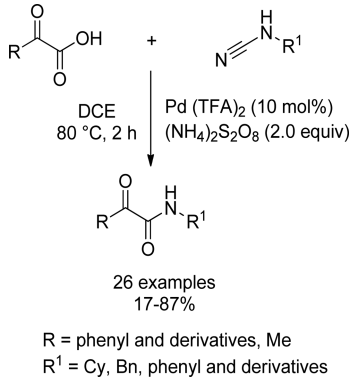


of PTSA monohydrate in CH_2Cl_2/MeOH solvent mixture promoted a facile, selective hydrolysis of the vinyl ether moiety with formation of the β,γ-unsaturated secondary α-ketoamides.

4.2. Pd-Mediated Coupling

Recently, a palladium(II)-catalyzed chemoselective insertion of an acyl moiety into organic cyanamides has been conveniently utilized for the synthesis of *N*-monosubstituted α-ketoamides.[202] Under optimized reaction conditions, heating equimolar amounts of organic cyanamides and glyoxylic acids in the presence of $Pd(TFA)_2$ (10 mol %) and ammonium persulfate (2.0 equiv) in dichloroethane (DCE) at 80 °C for 2 h produced α-ketoamides (Scheme 116). Both pyruvic acid and

Scheme 116. C(1)–C(2) Bond-Forming Processes/Pd-Mediated Coupling Reported by Patel and Co-Workers[202]



alkylcyanamides gave unsatisfactory results, while *N*-phenylcyanamides and phenylglyoxylic acids bearing halides, methyl, and methoxy groups on the phenyl rings were well-tolerated. Indeed, the reaction resulted in a convenient preparation of *N*-aryl monosubstituted aryl α-ketoamides, although difficulties emerged at a 5.0 mmol scale. Interestingly, the Pd-promoted acyl insertion process occurred exclusively at the cyanamide functional group, while other cyano groups were unaffected.

Results from a series of control experiments supported the mechanism outlined in Scheme 117, involving a Pd(II)/Pd(IV) cycle based on the dual role of ammonium persulfate as a radical initiator and oxidant. Thus, the Pd(IV) complex **139** bearing carbodiimide and acyl ligands was formed by reaction of a Pd(II) species with organic cyanamides, ammonium persulfate, and acyl radicals, in turn generated by oxidative decarboxylation of glyoxylic acids. The subsequent isomerization of **139** to the complex **140** via Pd-1,2 migration,

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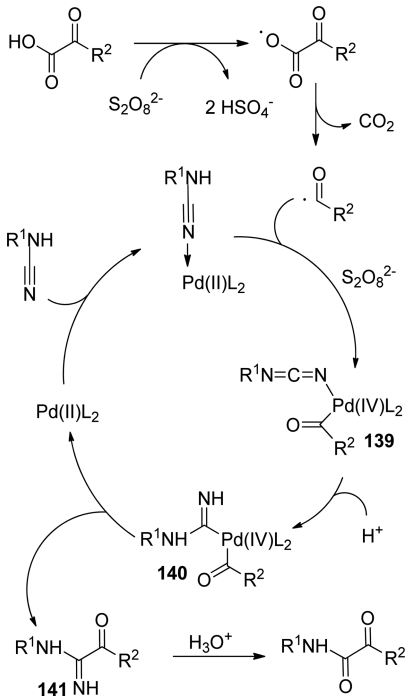
Scheme 117. Mechanism Proposed for the Pd(II)-Catalyzed Chemoselective Insertion of an Acyl Moiety into Organic Cyanamides[202]

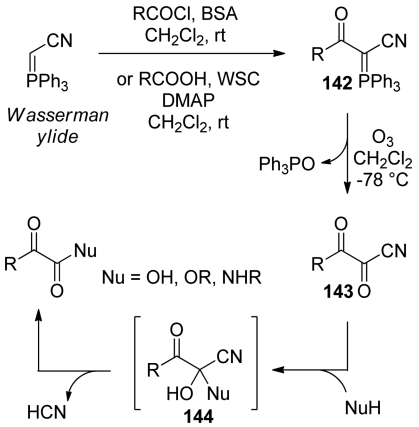


followed by reductive elimination, released the acyl amidines **141**, which were promptly hydrolyzed to α-ketoamide compounds.

4.3. Formation of Sequential C(1)−C(2) and C(1)−N Bonds

4.3.1. (Cyanomethylene)phosphorane. Wasserman and co-workers[203−206] developed a very important and general methodology to prepare α-keto acid, ester, and amide derivatives entailing ozone-mediated oxidative cleavage of cyanoketophosphoranes **142** (Scheme 118). The latter could be efficiently prepared by reaction of (cyanomethylene)-triphenylphosphorane ($Ph_3P{=}CHCN$) with acyl chlorides in the presence of the proton sponge *N,O*-bis(trimethylsilyl)-acetamide (BSA). As an alternative way, carboxylic acids were directly coupled with the Wasserman ylide in the presence of WSC. The ozonolysis of compounds **142** at low temperature

Scheme 118. Wasserman's Approach to α-Keto Acid, Ester, and Amide Derivatives

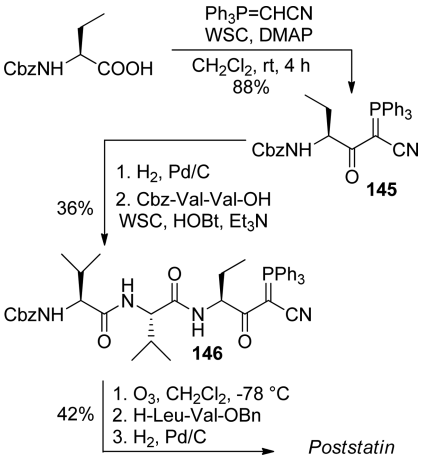


gave labile, highly electrophilic α,β-diketo nitriles **143**, which intercepted nucleophiles such as water, alcohols, or primary amines to give unstable cyanohydrins **144**, eventually providing α-keto acids, esters, and secondary amides, respectively. Dimethyldioxirane was selected in place of ozone as a milder oxidant to perform the carbon−phosphorus double bond cleavage of substrates bearing sensitive functional groups.[207]

The ylide reagent, acting first as a nucleophile and later as a powerful electrophile, served as a carbonyl 1,1-dipole equivalent for the installation of the electrophilic, biologically active α-diketo functional group at the C-terminal of peptides as well as internal to a peptide motif.

Application of the acyl cyanophosphorane methodology to the synthesis of biologically relevant molecules containinig α-ketoamide moieties has been discussed in an account by Wasserman and Parr.[208] As an example, the synthesis of the prolyl endopeptidase inhibitor poststatin entailed coupling of *N*-Cbz-protected (*S*)-2-aminobutanoic acid with (cyanomethylene)triphenylphosphorane, as outlined in Scheme 119. The resulting acyl cyanophosphorane **145** was trans-

Scheme 119. C(1)−C(2) Bond-Forming Processes/ (Cyanomethylene)phosphorane Reported by Wasserman and Parr[208]



formed into compound **146** by N-deprotection and reaction with *N*-Cbz-protected valylvaline under standard peptide-coupling conditions. At this stage, ozonolysis served to generate the electrophilic diketonitrile intermediate that reacted in situ with D-leucylvaline *O*-benzyl ester. Eventually, hydrogenolytic N,O-deprotection afforded the pentapeptide poststatin together with about 15% of its epimer, as revealed by NMR analysis.

The Wasserman protocol was also successfully employed for the preparation of verongamine, hemibastadin-2, and aerothionin (Figure 14), a group of antibiotic marine metabolites containing vicinal dicarbonyls in the form of α-oximino amides.[209]

Moreover, the versatility of the method allowed the synthesis of eurystatins A and B,[210] in addition to cyclotheonamides E2 (CtE2), E3 (CtE3),[206] and C (CtC).[211]

In the synthesis of eurystatins A and B, salient features were represented by the carbonyl-extended tripeptide assembly by application of the acyl cyanophosphorane methodology and the subsequent macrocyclization using DPPA as carboxyl-activating system under conditions of high dilution (Figure 15).

Synthetic approaches to CtE2 and CtE3[206] by Wasserman and to CtC[211] by Aitken exploited the Arg-derived

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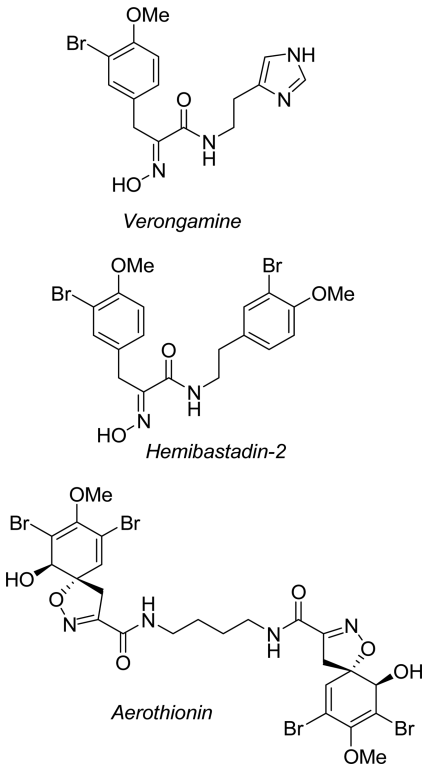

Figure 14. Antibiotic marine metabolites prepared by the Wasserman protocol.[209]

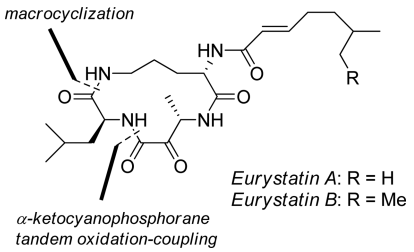

Figure 15. Salient features of the synthesis of eurystatins A and B.[210]

f16 cyanophosphorane shown in Figure 16 as a suitable synthon, giving linear pentapeptides ready for the macrolactamization.

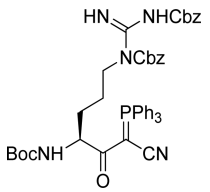

Figure 16. Arg-derived cyanophosphorane.[206,211]

Wasserman reported a successful macrocyclization of a vinylogous L-tyrosine derivative (V-Tyr) via carboxylate activation with the DCC/PFP−OH system, while Aitken used a fully conjugated substrate (D-V-Tyr) in combination f17 with TBTU and a catalytic amount of HOBt (Figure 17).

Besides applications toward the synthesis of peptide mimetics containing the α-ketoamide linkage, the cyano ylide coupling methodology was also fruitful to prepare the related naturally occurring aminopeptidase inhibitors phebestin, probestin, and bestatin. In these approaches, the featured α-

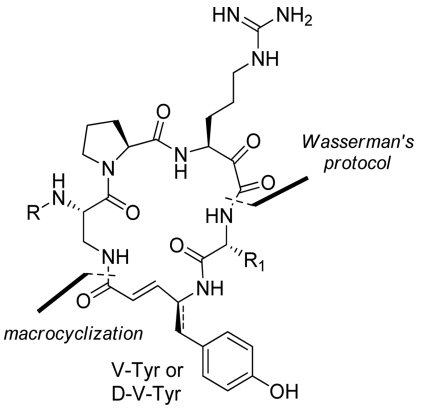

Figure 17. Salient features of the synthesis of CtE2, CtE3, and CtC.[206,211]

hydroxyamide functional motif resulted from the $Zn(BH_4)_2$ diastereoselective reduction of the α-ketoamide precursors at −78 °C.[210]

Wasserman's elegant and convergent methodology has been applied also to the synthesis of a series of potent lipase inhibitors featuring the electrophilic 2-oxoamide functionality attached to a lipophilic domain. Thus, Lee and co-workers prepared the γ-amino acid based inhibitors[212] as well as triacylglycerol-based inhibitors[213] (Figure 18) following the f18 Wasserman protocol.

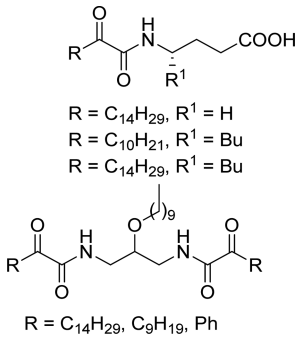

Figure 18. γ-Amino acid-based inhibitors (top) and triacylglycerol-based inhibitors (bottom) prepared by the Wasserman protocol.[212,213]

The HCV NS3 protease inhibitor, featuring a glycine α-ketoamide pentapeptide skeleton (Scheme 120), was obtained s120 at Bristol-Myers Squibb Co. by use of the Wasserman ylide.[214] Its coupling with the *N*-CBz-protected cyclopropane α-aminocarboxylic acid **147** gave the cyano keto ylide **148**, which underwent ozonolysis and in situ trapping with glycine *tert*-butyl ester. The resulting glycine ketoamide was transformed into the biologically active target through a five-step sequence involving $NaBH_4$ reduction of the α-carbonyl group, to prevent interference with subsequent coupling reaction, and restoration of the α-ketoamide functional group at a late stage via Dess−Martin oxidation of the secondary alcohol.

As reported in subsection 2.1,[73] α-ketocarbonyl peptides have been prepared via selective conversion of the *N*-terminal α-amino group of peptides into a α-ketocarbonyl moiety on a solid phase through a copper ion-catalyzed transamination reaction.

Later, the same research group devised a different synthetic strategy useful to produce internal α-ketoamide peptide

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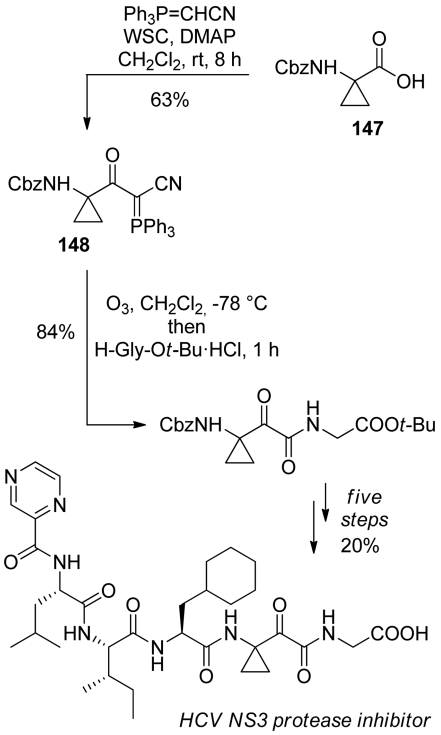
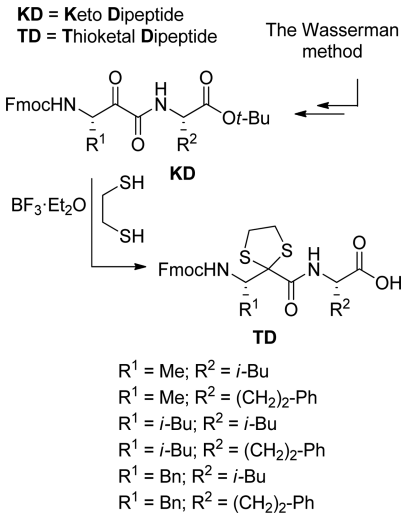
Scheme 120. C(1)−C(2) Bond-Forming Processes/(Cyanomethylene)phosphorane Reported by Han et al.[214]



libraries suitable for protease inhibitor screening on a solid support.[215] The Wasserman method, broadly employed in solution-phase synthesis to introduce the α-ketoamide moiety into peptide backbones, was suitably adjusted to achieve a series of model peptides through solid-phase organic and combinatorial chemistry (SPOCC). Thus, the *N*-Fmoc-protected, stereodefined α-ketoamide dipeptidyl compounds **KD** were prepared according to the cyanophosphorane methodology (Scheme 121). At this stage, the highly electrophilic dicarbonyl moiety of **KD**, incompatible with SPPS conditions, was masked to give thioketal derivatives **TD**. Pleasantly, the reaction with

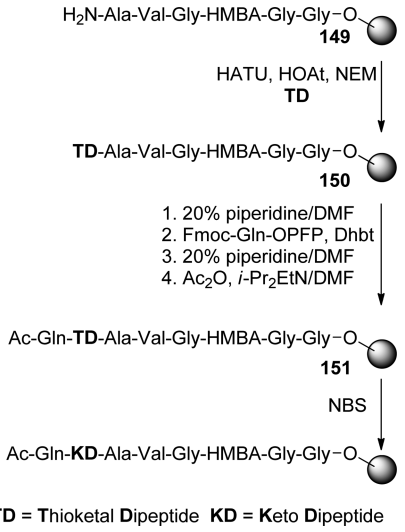
Scheme 121. C(1)−C(2) Bond-Forming Processes/(Cyanomethylene)phosphorane Reported by Papanikos and Meldal[215]



1,2-ethanedithiol in the presence of $BF_3{\cdot}Et_2O$ occurred with simultaneous deprotection of the *tert*-butyl ester functional group.

The *N*-Fmoc-protected dipeptidyl compounds **TD** were attached to resin-bound peptide **149** using HATU, HOAt, and *N*-ethylmorpholine (NEM) as the coupling agent system (Scheme 122). The resulting peptides **150** were converted

Scheme 122. SPOCC Approach to Resin-Bound Peptide Isosteres[215]



into **151** by introduction of glutamine as the *N*-terminal amino acid under standard SPPS protocols. Eventually, reaction of **151** with NBS unmasked the α-ketoamide functional group, addressing pure resin-bound peptide isosteres for protease inhibitor screening on solid support.

Lee[216,217] used the original Wasserman ylide to develop a cyanoketophosphorane reagent suitable for olefination reactions with carbonyl compounds. Thus, the new Horner−Wadsworth−Emmons reagent **152** has been obtained either by coupling diethylphosphonoacetic acid with Wasserman's cyanophosphorane in the presence of WSC or in a two-step procedure entailing the condensation of chloroacetyl chloride with the cyanophosphorane reagent followed by Arbuzov reaction (Scheme 123). Actually, the new cyanoketophosphorane reagent **152** reacted with aryl/aliphatic aldehydes to give (*E*)-configured β,γ-unsaturated α-ketocyanophosphoranes **153** in good yields. The subsequent hydrogenation over Pd/C 10% afforded the cyanoketophosphoranes **154** suitable for installation of the α-diketo functional group according to Wasserman's procedure.

An alternative, easy, high-yielding, one-pot synthesis of **153** entailed the alkylation of **155** with primary alkyl bromides in the presence of NaH or BuLi followed by thermal phenylsulfenic acid elimination (Scheme 123).[218] The stable solid sulfinyl compound **155** was readily prepared by coupling the cheap phenylsulfinylacetic acid and Wasserman's cyanophosphorane in the presence of WSC/DMAP. It is noteworthy that the synthetic strategies to cyanoketophosphoranes devised by Lee widen the scope of Wasserman's approach to α-ketoamides.

4.3.2. Trimethylthiomethane. Lithiotrismethylthiomethane has been used as a reagent equivalent to a carbonyl 1,1-dipole, allowing the two-step synthesis of α-hydroxyamide

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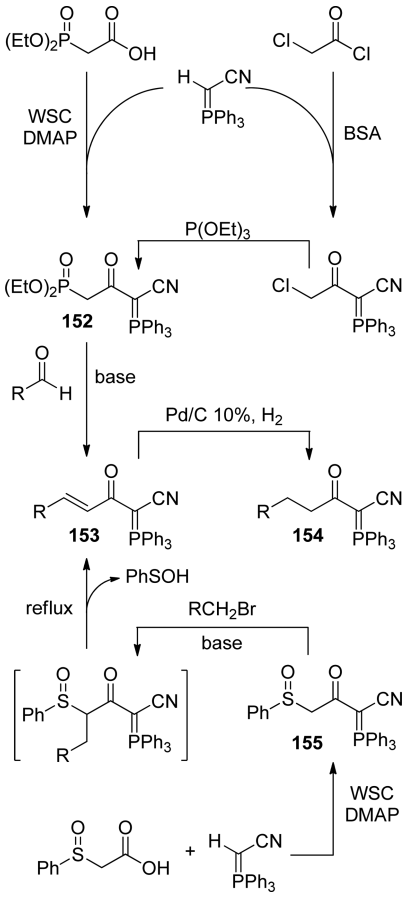
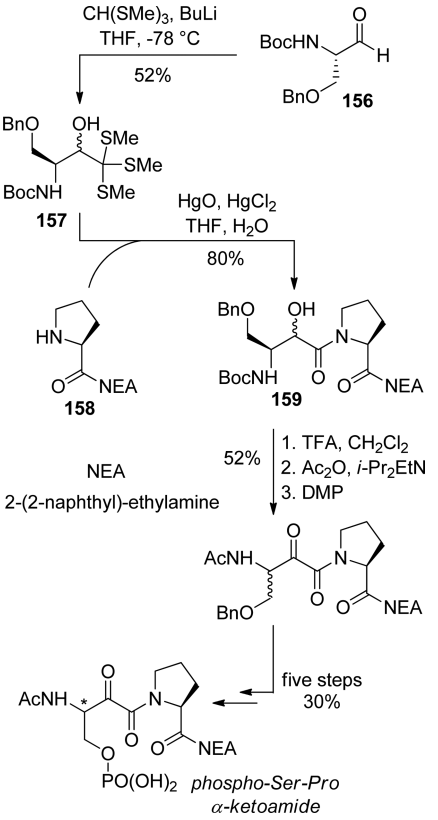
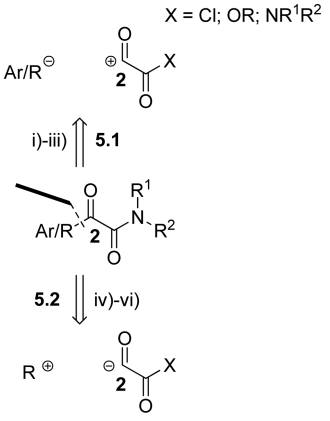
Scheme 123. Synthetic Strategies to Cyanoketophosphoranes Suitable for Olefination Reactions[216−218]



Scheme 124. C(1)−C(2) Bond-Forming Processes/ Trimethylthiomethane Reported by Xu and Etzkorn[31]



Scheme 125. C(2)−R/Ar Bond-Forming Processes



i) Oxalyl chloride
ii) Monooxalyl chlorides
iii) Oxamides
iv) Enolate of ethyl diethoxyacetate
v) Enolate of cyanoacetylpiperidine
vi) NHC-Glyoxamide systems

s124 **159** (Scheme 124). The latter was an advanced intermediate toward the phospho-Ser-Pro α-ketoamide, designed as inhibitor of Pin 1, a peptidyl prolyl isomerase involved in many cellular events and playing an important role in oncogenesis.[31] Actually, the umpoled reactivity provided with the organometallic reagent served the purpose of forming the carbon−carbon bond with the serine-derived aminoaldehyde **156** to give the orthothioester **157**. Reaction of the latter with the proline-amide derivative **158** under $HgO/HgCl_2$ catalysis allowed the C(1)−N bond formation, giving the diastereomeric α-hydroxyamides **159**. Interestingly, the DMP oxidation, while removing chirality at the α-carbon, produced epimerization of the adjacent stereogenic center, providing the corresponding α-ketoamide as a 1:1 diastereomeric mixture. Noteworthy, a five-step sequence was required to get phosphorylation of the serine side-chain of the target molecule.

5. C(2)−R/Ar BOND-FORMING PROCESSES

In this section, two strategies for the preparation of α-ketoamides through C(2)−R/Ar σ bond formation are discussed, with either C(2)-electrophilic or C(2)-nucleophilic species being involved.

s125 As summarized in Scheme 125, in subsection 5.1 we report methods using oxalyl chloride, monooxalyl chlorides, and oxamides as C(2)-electrophile partners of both aryls and metalated alkyl/aryl reagents. The processes applying the complementary approach, namely, the use of C(2)-umpoled glyoxylic acid derivatives, are discussed in subsection 5.2. Herein, starting materials were the enolates derived from ethyl diethoxyacetate or cyanoacetylpiperidine, as well as N-heterocyclic carbene−glyoxamide systems.

Obviously, synthetic approaches making use of oxalyl chlorides, monooxalyl chlorides, and oxamides required a supplementary step in order to complete the α-ketoamide functional group installation, as all of these reagents lack of the amide functional motif.

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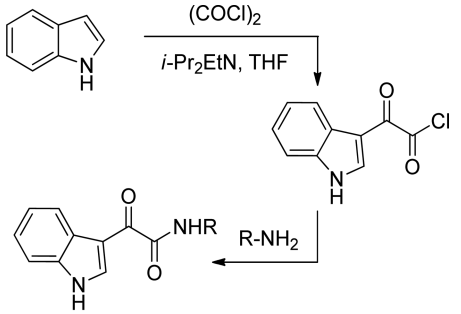
5.1. C(2)-Electrophilic Oxalic Acid Derivatives

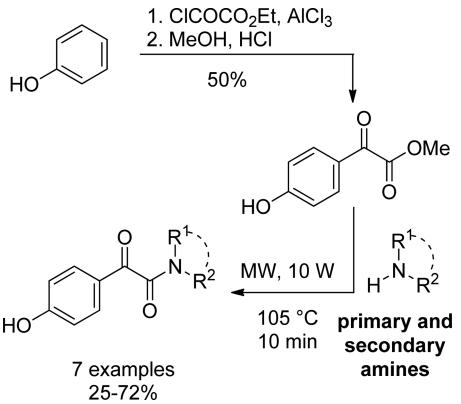
5.1.1. Oxalyl Chloride. *N*-Methylindole as well as *N*-benzyl derivatives have been functionalized at C(3) by reaction with oxalyl chloride (2.0−3.0 equiv) in diethyl ether at 0 °C followed by treatment with ammonium hydroxide solution or HMDS. The resulting indole-3-glyoxylamides served as starting materials both to prepare indolylaryl- and bisindolylmaleimides,[219] biologically active heterocyclic compounds, and synthesize an indole inhibitor of phospholipase A_2, respectively.[220] Similarly, a one-pot three-component general approach for the synthesis of a variety of indole-3-glyoxylamides entailed treatment of the crude indole-3-glyoxyl chlorides with aliphatic or aromatic primary amines (Scheme 126).[221]

Scheme 126. C(2)−R/Ar Bond-Forming Processes/Oxalyl Chloride Reported by Stefani et al.[221]



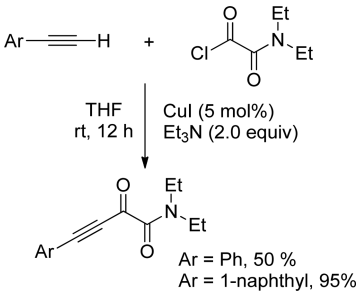
5.1.2. Monooxalyl Chlorides. Phenol has been used as an activated aryl nucleus for acylation with ethyl chlorooxoacetate under Friedel−Crafts conditions.[222] The resulting 4-hydroxyphenylglyoxylic acid was converted into a series of estrogen-mimicking α-ketoamide derivatives via esterification under standard conditions, followed by heating in the presence of an amine partner in a CEM microwave synthesizer, without the need for protection of the reactive phenol (Scheme 127). The two-step sequence proved to be general for both primary and secondary amines, although the expected α-ketoamides were formed in poor to moderate yields.

Scheme 127. C(2)−R/Ar Bond-Forming Processes/ Monooxalyl Chlorides: Reported by Tomkinson and Co-Workers[222]



Zhang and co-workers[223] reported a cross-coupling reaction of phenylacetylene or 1-naphthylacetylene with diethylamino-oxalyl chloride (1.2 equiv) in the presence of CuI (5 mol %) and Et_3N (2.0 equiv) in THF at room temperature for 12 h (Scheme 128). The reaction likely involved alkynylcopper

Scheme 128. C(2)−R/Ar Bond-Forming Processes/ Monooxalyl Chlorides Reported by Zhang and Co-Workers[223]

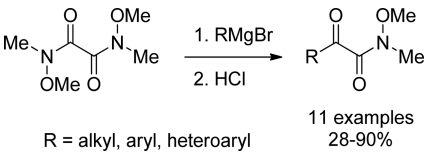


intermediates formed in situ by reaction of aryl-terminal alkynes with cuprous iodide. Importantly, the process allowed a simple and direct entry to 2-oxo-3-butynamides, which otherwise are difficult to obtained by an amidation reaction, because of competitive amine addition to the Michael acceptor substrates.

5.1.3. Oxamides. Symmetrically N-tetrasubstituted amides, derived from oxalyl chloride, have been used as electrophilic counterparts of organometallic reagents. Adams et al.[224] demonstrated that only one of the carbonyl groups of dimethyloxanilide underwent an acyl substitution reaction in the presence of a large excess of Grignard reagent, providing the corresponding α-ketomethylanilide.

Later, symmetric oxamides were combined with aryl lithio reagents to provide α-ketoamides in low to good yields.[225,226] Interestingly, *N*,*N*′-dimethoxy-*N*,*N*′-dimethylethanediamide, a stable crystalline compound easily prepared by reaction of oxalyl chloride with *N*,*O*-dimethylhydroxylamine hydrochloride, reacted with Grignard reagents (1.1−1.5 equiv) in THF at 0 °C for 1−4 h to provide α-ketoamides in moderate to excellent yield (Scheme 129).[227] Importantly, the N-demethoxylation of the formed compounds was the main undesired reaction. Primary and secondary aliphatic, aromatic, and heterocyclic organomagnesium reagents gave the expected α-ketoamides without formation of overaddition products (tertiary alcohols).

Scheme 129. C(2)−R/Ar Bond-Forming Processes/ Oxamides Reported by Sibi et al.[227]



5.2. C(2)-Umpoled Glyoxylic Acid Derivatives

5.2.1. Enolate of Ethyl Diethoxyacetate. Sequential amine-promoted ring-opening reaction of N-substituted 3,3-diethoxy-azetidin-2-ones **163** and hydrolysis of the resulting ketal intermediates **164** were envisioned as a useful means for the preparation of racemic β-amino-α-ketoamides (Scheme

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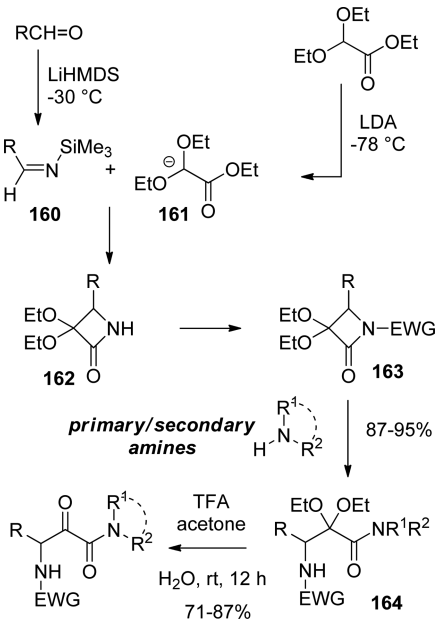
130).[228] Thus, the condensation of silyl imine **160** with lithium ethyl diethoxyacetate **161** provided the N-deprotected

Scheme 130. C(2)−R/Ar Bond-Forming Processes/Enolate of Ethyl Diethoxyacetate Reported by Khim and Nuss[228]



azetidinones **162**. At this stage, introduction at the nitrogen atom of electron-withdrawing groups, such as *p*-toluenesulfonyl (*p*-Ts) and allyloxycarbonyl (Alloc), was required in order to make heterocyclic substrates **163** ready for the nucleophilic ring-opening reaction.

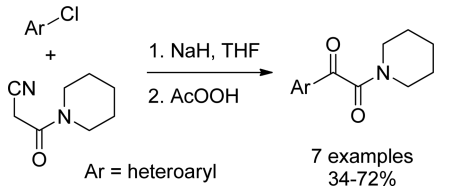
Various primary and secondary amines were suitable nucleophiles, including the Wang resin-bound phenylalanine. The resulting α-ketal amides **164** were produced in excellent yields at room temperature, regardless of the substituents on the nitrogen of the azetidinone. Interestingly, sluggish ring-opening reactions such those with L-phenylalaninol and L-valine methyl ester (L-Val-OMe) could be efficiently performed by using cyanide catalyst. Eventually, hydrolysis of intermediates **164** was performed in a mixture of TFA, acetone, and H_2O (9:1:0.1 ratio) at room temperature for 12 h, giving rise to the racemic β-amino-α-ketoamides in good yields.

It is worthy of note that the methodology was successfully applied to the synthesis of poststatin on a solid support. The ketal pentapeptide was recovered in ca. 14% overall yield after resin cleavage, although its hydrolysis turned out to be extremely sluggish (ca. 7 days).

5.2.2. Enolate of Cyanoacetylpiperidine. In 2005, Wang and co-workers[229] exploited the 1-cyanoacetylpiperidine anion as an umpolung-type equivalent of a glyoxamide moiety. Actually, several heteroaryl chlorides cleanly reacted by the S_NAr path with the aminocarbonylacetonitrile in the presence of NaH. The resulting stabilized anions were in situ oxidized by peracetic acid at room temperature, providing labile cyanohydrins that were promptly transformed by aqueous workup into α-ketoamide derivatives (Scheme 131).

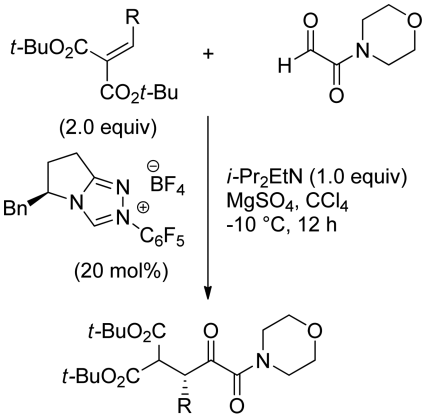
5.2.3. NHC−Glyoxamide Systems. N-Heterocyclic carbenes (NHCs) are versatile organocatalysts for carbonyl reversal of polarity through formation of the nucleophilic Breslow intermediate.[230]

Scheme 131. C(2)−R/Ar Bond-Forming Processes/Enolate of Cyanoacetylpiperidine Reported by Wang and Co-Workers[229]



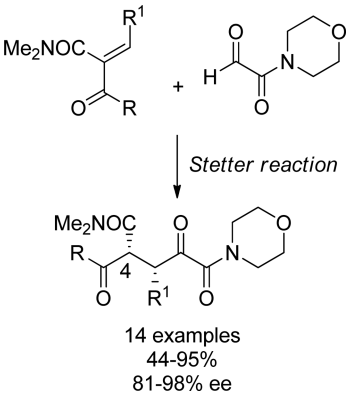
Rovis and co-workers[231] reported the intermolecular Stetter reaction of morpholino-glyoxamide and symmetrically esterified alkylidenemalonates. The resulting α-ketoamides were prepared in good yields and enantioselectivities by using the phenylalanine-derived triazolium salt precatalyst under mild conditions (Scheme 132).

Scheme 132. C(2)−R/Ar Bond-Forming Processes/NHC−Glyoxamide Systems Reported by Rovis and Co-Workers[231]



Similarly, Michael addition products containing two adjacent stereogenic carbon centers could be obtained from alkylidene ketoamides (Scheme 133).[232] The reaction tolerated a variety of functional groups, providing α-ketoamides suitable for further transformations into useful chiral nonracemic building blocks for synthetic applications.

Scheme 133. C(2)−R/Ar Bond-Forming Processes/NHC−Glyoxamide Systems Reported by Liu and Rovis[232]



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Importantly, the Michael adducts proved to be configurationally stable at the epimerizable C(4) carbon, owing to a strong $A_{1,3}$ strain effect in the corresponding enolic form (Figure 19).

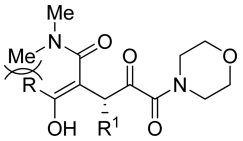
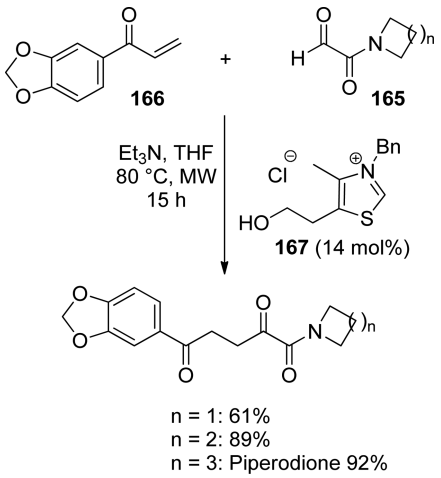


Figure 19. The $A_{1,3}$ strain effect.

A recent application served to prepare piperodione, a physiologically active secondary metabolite isolated from the Javanese pepper plant *Piper retrofractum*.[233,234] The key synthetic step was the microwave-assisted Michael addition of C(2)-umpoled glyoxamides **165** to the aryl vinyl ketone **166** (Scheme 134). These reagents, easily prepared from

Scheme 134. C(2)−R/Ar Bond-Forming Processes/NHC−Glyoxamide Systems Reported by Csuk and Co-Workers[234]



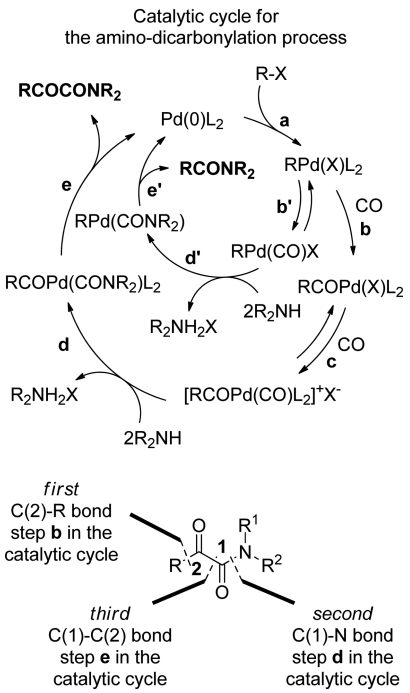
commercially available and cheap starting materials, smoothly coupled in the presence of Et_3N and catalytic amounts of thiazolium chloride **167**, providing the natural target and analogs. Notably, the convergent and efficient synthesis afforded piperodione in 92% yield, avoiding complex extractive procedures from the plant material, which contains the active substance in very small amounts (0.0002%).

6. PALLADIUM-CATALYZED DOUBLE-CARBONYLATIVE AMINATION

In 1982, Ozawa and Yamamoto[235] reported the transformation of preformed methyl- and phenylpalladium complexes into α-ketoamides under a carbon monoxide atmosphere, in the presence of secondary amine nucleophiles. Soon after, they[236] and others[237] disclosed that the double carbonylation of organic moieties also occurred when the organopalladium complexes were originated catalytically in situ by the action of palladium species onto aryl, heteroaryl, and alkenyl halides, thus establishing a new direct entry into α-ketoamides. Typically, dicarbonylations took place at 60−100 °C and 10−40 bar of carbon monoxide employing excess amine, often acting as the solvent, and Pd(II) complexes as precursors of the catalytically active Pd(0) species. The precatalysts tested were both mono- and bidentate phosphine−palladium(II) complexes containing moderately basic tertiary phosphine ligands. Among them, $PdCl_2(PMePh_2)_2$ and 1,4-bis(diphenylphosphino)butane-$PdCl_2$ were the most effective.

Thanks to extensive experimental studies performed in the 1980s by Yamamoto and co-workers,[238−241] it was established that elementary steps in the amino-dicarbonylation process were (a) oxidative addition of an in situ formed Pd(0) species at the C−halogen bond of organic halides to give organopalladium(II) species; (b) CO insertion into the Pd−C bond to give acylpalladium species; (c) further coordination of CO to give an acyl(carbonyl)palladium species, which may be neutral or ionic depending on the nature of both the ligand and solvent used; (d) nucleophilic attack of the amine on the CO ligand, affording a complex bearing two monocarbonylated ligands; and (e) reductive elimination, giving rise to the C(O)−C(O) chaining with formation of α-ketoamides and restoration of the active Pd(0) species, as depicted in the catalytic cycle shown in Scheme 135.

Scheme 135. Palladium-Catalyzed Double-Carbonylative Amination



Meanwhile, removal of the organopalladium(II) species from the original cycle by sequential coordination with CO and reaction with the amine nucleophile (steps b′, d′) could afford an alkyl(carbamoyl)palladium species that eventually undergoes reductive elimination. Thus, step e′ accounted for both the catalytically active Pd(0) species regeneration and amide products formation. Ultimately, monocarbonylative amination and double-carbonylative amination processes compete each other, and the faster the rate of step d, the better the selectivity for α-ketoamide formation.

Additional efforts were mainly devoted to examine the manifold aspects controlling the reaction rates and selectivity of α-ketoamide versus amide production. Thus, aryl iodides were generally excellent substrates, with para electron-withdrawing groups increasing the reactivity but favoring amides production

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(acceleration of step a and deceleration of the irreversible step b). An opposite trend was observed for aryl iodides bearing para electron-donating substituents, which gave preferentially α-ketoamides as a result of step a deceleration and step b acceleration. For these substrates, the preferential attack of the amine nucleophiles on the CO ligand in $[RCOPd(CO)L_2]^+X^-$ (step d in Scheme 135) explained α-ketoamides production, while the less competitive attack on the acyl group attached to palladium accounted for the collateral formation of amide products.

Besides aryl and heteroaryl halides, vinyl bromides and iodides, as well as allylic chlorides, were suitable substrates for Pd-mediated amino-dicarbonylations.[242,243] Alkyl iodides bearing perfluoroalkyl groups were also used as substrates in a $PdCl_2(PPh_3)_2$-catalyzed amino-dicarbonylation reaction,[244] while, more recently, a variety of alkyl iodides have been employed in a $Pd(PPh_3)_4$-accelerated atom transfer radical carbonylation reaction with diethylamine using photoirradiation conditions.[245]

The use of strongly basic, and within a certain limit, sterically demanding secondary amines was essential for α-ketoamide formation. Thus, the Pr_2NH showed the highest activity for the double-carbonylation, preferring to attack the coordinated CO ligand in $[RCOPd(CO)L_2]^+X^-$ (step d), while the compact amine pyrrolidine gave the highest selectivity for the monocarbonylation by attacking the coordinated CO in RPd(CO)X (step d′). Weaker nucleophilic amines, such as aromatic amines, were more appropriate for the amino monocarbonylation process. In fact, different from strongly basic amines, anilines could give acyl(amido)palladium species $RCOPd(NR_2)L_2$, from which amides were formed on coupling of the amido ligand with the acyl group. Low yields were obtained with all but t-$BuNH_2$ primary amines, because of their tendency to form Schiff bases by condensation with the electrophilic carbonyl group of the formed α-ketoamides.

Curiously, little attention had been paid to the amino-dicarbonylation technique as a synthetic tool to fine chemicals until the arrival of the new millennium, when the reaction disclosed 20 years before has been applied to the synthesis of commodity chemicals.

In this section, the copious literature produced has been grouped in subsections according to the main features of the used protocols. Thus, subsection 6.1 describes the approaches using Pd−phosphine homogeneous catalysts under high CO pressure, while applications of ionic liquid solvents and heterogeneous Pd materials are detailed in subsection 6.2. Besides, Pd−phosphine-catalyzed processes under atmospheric pressure of CO or with CO generated ex situ are reported in subsection 6.3. The final subsection 6.4 deals with synthetic methodologies entailing Pd-DBU, Pd-NHC, and ligand-free Pd catalysts.

6.1. Pd−Phosphine Homogeneous Catalysts under High CO Pressure

Efficient and selective double-carbonylation of iodobenzene with diethylamine has been reported by Miura and co-workers[246] using $PdCl_2(PPh_3)_2$ (3.0 mol %) in combination with CuI (10 mol %) as cocatalyst. An iodo-bridged heterobimetallic (palladium−copper) species (Figure 20) was the plausible reactive intermediate facilitating α-ketoamide formation.

Inoue and co-workers[247] found that the same reaction could be efficiently carried out using the chloro-bridged homobimetallic (palladium) complex $Pd_2Me_2(\mu\text{-Cl})(\mu\text{-dpfam})$ (Figure 21).

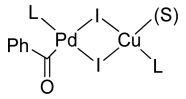


Figure 20. Iodo-bridged heterobimetallic (palladium−copper) species.[246]

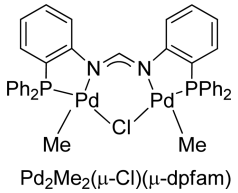
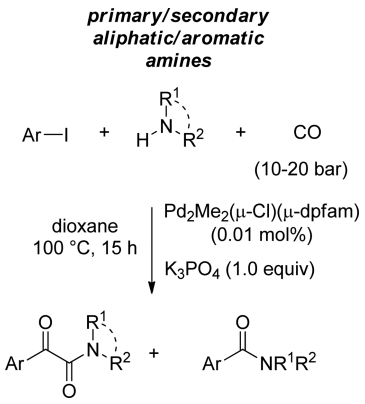


Figure 21. Chloro-bridged homobimetallic (palladium) complex.[247]

Actually, the complex featuring *N*,*N*′-bis[(diphenylphosphino)phenyl]formamidinate (dpfam) as the bidentate phosphine ligand of Pd nuclei was effective also in catalyzing amino-dicarbonylation of different aryl iodides with amine nucleophiles. Optimized conditions entailed the use of the aryl iodide, amine (1.5 equiv), $Pd_2Me_2(\mu\text{-Cl})(\mu\text{-dpfam})$ (0.01 mol %), K_3PO_4 as base (1.0 equiv), and 1,4-dioxane as the solvent, under 10−20 bar of CO pressure at 100 °C for 15 h (Scheme 136).

Scheme 136. $Pd_2Me_2(\mu\text{-Cl})(\mu\text{-dpfam})$-Catalyzed Double-Carbonylative Amination Reported by Inoue and Co-Workers[247]



Although the trends were similar to those obtained under mononuclear catalysis,[240] both reaction efficiency (total yield) and selectivity (di/monocarbonylation products ratio) were improved. Thus, acyclic secondary amines were suitable for the reaction, while pyrrolidine and piperidine showed high reactivity with moderate selectivity (Table 1). Primary amine $BuNH_2$ gave also a good result with negligible formation of Schiff base, while aromatic amines gave exclusively amide products. As observed under mononuclear catalysis, introduction of an electron-withdrawing group on the aryl iodide decreased the selectivity. Moreover, 1-iodonaphthalene as well as 2-iodoheteroarenes were poor substrates in terms of selectivity and/or yields.

Recently,[248] palladium complexes containing phosphorus−nitrogen ligands $\mathbf{L_{1-3}}$ (Figure 22) have been successfully

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Table 1

Ka:a[a]	Ar	R^1	R^2	yield[b] (%)
97:3	Ph	Et	Et	88
93:7	Ph	Et	Pr	75
0:100	Ph	*i*-Pr	*i*-Pr	31
49:51	Ph	$(CH_2)_4$		91
68:32	Ph	$(CH_2)_5$		96
79:21	Ph	H	Bu	95
67:33	Ph	Me	Bn	79
0:100	Ph	H	Ph	68
0:100	Ph	Me	Ph	33
0:100	Ph	Et	Ph	31
96:4	4-$MeOC_6H_4$	Et	Et	69
97:3	4-MeC_6H_4	Et	Et	70
89:11	4-ClC_6H_4	Et	Et	95
24:76	4-$NO_2C_6H_4$	Et	Et	87
64:36	1-naphthyl	Et	Et	11
81:19	2-naphthyl	Et	Et	73
56:44	3-pyridyl	Et	Et	78
4:96	2-pyridyl	Et	Et	45
0:100	2-furyl	Et	Et	25
2:98	2-thienyl	Et	Et	91
62:38	3-thienyl	Et	Et	89

[a]Ketoamide/amide ratio. [b]Isolated total yield.

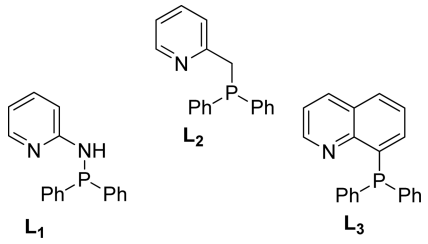


Figure 22. Phosphorus−nitrogen ligands.[248]

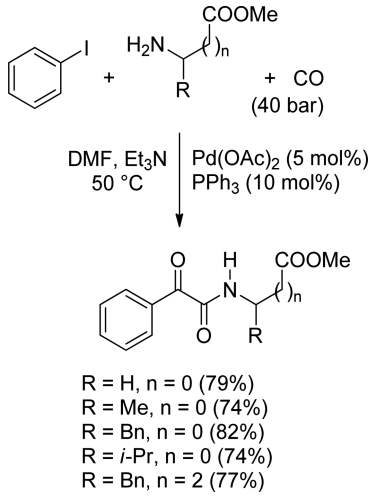
exploited in homogeneous double-carbonylation of iodobenzene with diethylamine under 30 bar of CO pressure in Et_3N/DMF at 90 °C. The selectivity for α-ketoamide formation was reported to be higher than with the classic system using Pd(II)/PPh_3.

The double-carbonylation of iodobenzene with amino acid methyl esters has been reported by using $Pd(OAc)_2/PPh_3$ as the precatalyst.[249] The reaction was performed in DMF/Et_3N at 50 °C under 40 bar of CO pressure (Scheme 137) and afforded α-ketoacylated amino acid derivatives accompanied by a surprisingly low amount of the simple carboxamides (less than 5%).

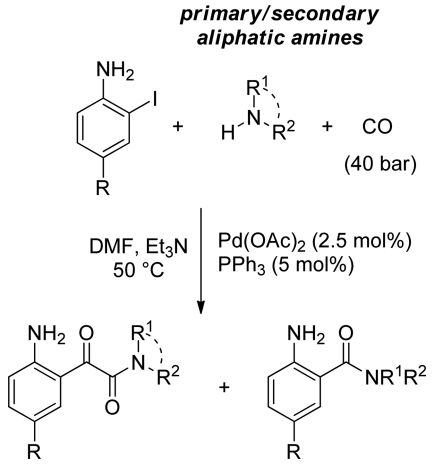
Exploratory studies by Yamamoto and co-workers[250] demonstrated that the Pd-catalyzed dicarbonylation of *o*-haloacetanilides was an effective synthetic strategy to obtain isatin and quinoline derivatives.

Twenty years later, Kollár's group reported results of the catalytic carbonylation of *N*-unprotected 2-iodoaniline derivatives carried out in the absence or in the presence of external basic amines.[251] In the former case, monocarbonylation reactions with trapping of the aromatic amine group accounted for the formation of benzo-fused heterocycles. Conversely, α-ketoamides were almost exclusively formed in the presence of aliphatic primary or secondary amines, in DMF/Et_3N at 50 °C under 40 bar of CO pressure (Scheme 138 and Table 2). The Pd-catalyzed amino-dicarbonylation process was shown to be

Scheme 137. $Pd(OAc)_2/PPh_3$-Catalyzed Double-Carbonylative Amination of Iodobenzene with Amino Acid Esters Reported by Kollár and Co-Workers[249]



Scheme 138. $Pd(OAc)_2/PPh_3$-Catalyzed Double-Carbonylative Amination of 2-Iodoanilines Reported by Kollár and Co-Workers[251]



halogen-selective, with 2-iodo displacement occurring while both 4-Cl and 4-Br substituents remained untouched.

Table 2

Ka:a[a]	R	R^1	R^2	yield[b] (%)
100:0	H	H	*t*-Bu	78
62:38	Me	H	*t*-Bu	72
95:5	Cl	H	*t*-Bu	80
100:0	Br	H	*t*-Bu	83
100:0	CN	H	*t*-Bu	68
100:0	NO_2	H	*t*-Bu	86
95:5	H	H	CH_2COOMe	46
100:0	H	H	CH(Me)COOMe	48
100:0	H	H	CH(*i*-Pr)COOMe	48
100:0	H		$(CH_2)_3CHCOOMe$	68
100:0	Me		$(CH_2)_3CHCOOMe$	71
100:0	Cl		$(CH_2)_3CHCOOMe$	65
100:0	NO_2		$(CH_2)_3CHCOOMe$	58

[a]Ketoamide/amide ratio. [b]Isolated yield of ketocarboxamides.

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The homogeneous $Pd(OAc)_2/PPh_3$ precatalyst has been also reported to effect amino-dicarbonylation of 2-iodoanisole by using *t*-$BuNH_2$ as well as amino acid esters as N-nucleophiles (Scheme 139 and Table 3).[252] Good selectivity for aryl α-ketoamides was achieved under high carbon monoxide pressure (40−60 bar) at 50 °C.

Scheme 139. $Pd(OAc)_2/PPh_3$-Catalyzed Double-Carbonylative Amination of 2-Iodoanisole Reported by Kollár and Co-Workers[252]

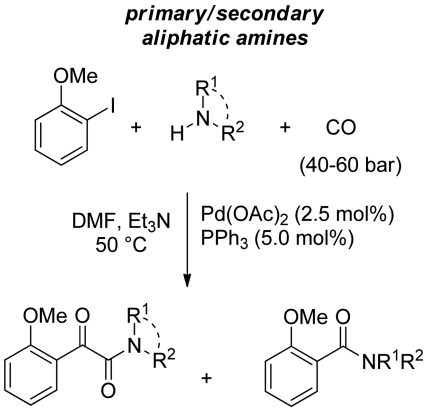


Table 3

Ka:a[a]	R^1	R^2	yield[b] (%)
62:38	H	*t*-Bu	51
80:20	$(CH_2)_5$		67
85:15	$(CH_2)_2O(CH_2)_2$		73
83:17	H	CH_2COOMe	70
95:5	$(CH_2)_3CH(COOBn)$		74

[a]Ketoamide/amide ratio. [b]Isolated yield of ketocarboxamides.

Pd-catalyzed carbonylative amination was chosen as a highly tolerant and straightforward method for the rim functionalization of a cavitand scaffold, resulting in derivatives that could act as flexible binding pockets in "host−guest" chemistry.[253] Both ketocarboxamidocavitands and carboxamido analogs were prepared by reacting the tetraiodo-cavitand Cav-I (Figure 23) with amine nucleophiles (18.0 equiv) in the presence of $Pd(OAc)_2/PPh_3$ catalytic system under 30 bar of CO pressure at 60 °C in toluene or DMF (Scheme 140 and Table 4).

Generally, both an excess of the amine and high carbon monoxide pressure improved selectivity toward tetrakis(2-

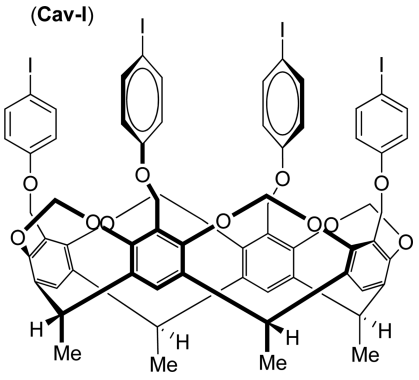


Figure 23. Tetraiodo-cavitand Cav-I.[253]

Scheme 140. $Pd(OAc)_2/PPh_3$-Catalyzed Double-Carbonylative Amination of a Cavitand Scaffold Reported by Kollár and Co-Workers[253]

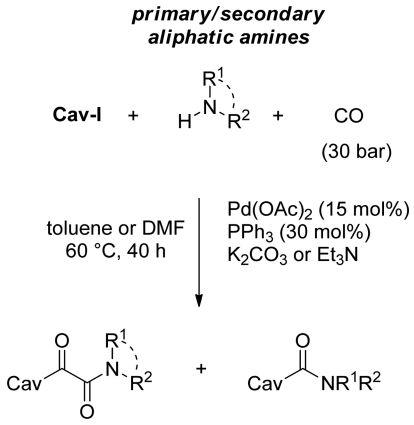


Table 4

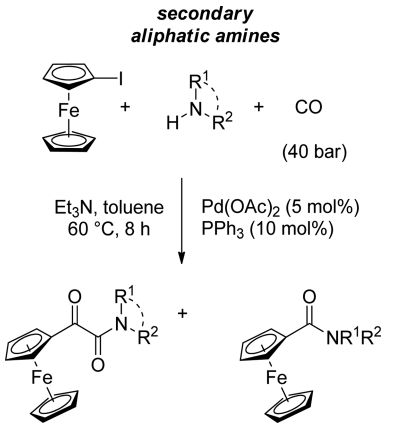
Ka:a[a]	R^1	R^2	yield (%)[b]
100:0	H	*t*-Bu	65
100:0		$(CH_2)_5$	85
91:9	H	CH(Me)COOMe	nd[c]

[a]Ketoamide/amide ratio. [b]Isolated yield of ketocarboxamides. [c]nd = not determined.

ketocarboxamide)cavitands. Unexpectedly, the transformation was shown to be highly chemoselective, as none of the mono-, bi- or trifunctionalized derivatives could be detected in the reaction mixture.

The Kollár research group reported ferrocene α-ketoamides preparation via amino-dicarbonylation of iodoferrocene using the $Pd(OAc)_2/PPh_3$ homogeneous precatalyst (Scheme 141).[254] Thus, iodoferrocene was reacted with the amine

Scheme 141. $Pd(OAc)_2/PPh_3$-Catalyzed Double-Carbonylative Amination of Iodoferrocene Reported by Kollár and Co-Workers[254]



partner in toluene at 60 °C, in the presence of Et_3N, $Pd(OAc)_2$ (5 mol %), and PPh_3 (10 mol %) under 40 bar of CO pressure. Good selectivity for dicarbonylated products has been observed provided that sterically nondemanding secondary amines were employed as nucleophiles (Table 5).

The same authors demonstrated that amino acid esters were less suitable nucleophilic partners of iodoferrocene, although

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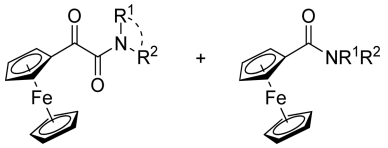
Table 5

Ka:a[a]	R^1	R^2	convrsn[b] (%)
79:21	$(CH_2)_2O(CH_2)_2$		95
70:30	$(CH_2)_5$		89
27:73	$(CH_2)_4CH(Et)$		98
0:100	$CH(Me)(CH_2)_3CH(Me)$		99
82:18	$CH_2CH(Me)CH_2CH(Me)CH_2$		94
69:31	Et	Et	97
73:27	Bu	Bu	97
6:94	Cy	Cy	91

[a]Ketoamide/amide ratio. [b]Determined by GC.

slight selectivity to *N*-ferrocenylglyoxyl amino acid derivatives (Table 6) could be obtained by using DBU in place of Et_3N as the base.[255]

Table 6



R^1	R^2	yield[a] (%)
H	CH_2COOMe	89 (1)
H	$CH(Me)COOMe$	28 (23)
H	$CH(Bn)COOMe$	26 (15)
H	$CH(CH_2)_2SMeCOOMe$	37 (4)
	$(CH_2)_3CHCOOMe$	30 (32)

[a]Isolated yield of ketocarboxamides and, in parentheses, of carboxamides by purification under inert conditions.

1′-Iodoferroceneglyoxylic amide-type products were also prepared via selective monofunctionalization of 1,1′-diiodoferrocene.[256] Thus, compounds having practical importance as starting materials for the synthesis of ferrocene-based biosensors could be prepared in reasonable yields.

Homogeneous catalysts prepared in situ using $Pd(OAc)_2$ and tricyclohexylphosphine (PCy_3) (cat.$_1$) or obtained from fully formed Pd−phosphine complexes (cat.$_2$, cat.$_3$), were successfully employed for the double-carbonylative amination of 4-iodopyridine, 2-iodopyridine, and 2,3,6-trisubstituted 4-iodopyridine with diethylamine.[257] Under optimized reaction conditions, a CH_2Cl_2 solution of the iodopyridil substrate was heated at 40−50 °C in the presence of the amine reagent (5.0 equiv) and the catalyst (1 mol %), under 60 bar of CO pressure (Scheme 142). Pyridylglyoxylic acid amides were thus obtained together with variable amounts of the corresponding amides, which were invariably formed under reaction conditions whatever the Pd-precatalyst employed (Table 7). On the basis of the collected results, 2-iodopyridine was shown to be a less selective substrate for α-ketoamide formation in comparison with the 4-iodo isomer, while a chlorine substituent remained untouched under reaction conditions.

Kollár and co-workers[258] tested the effectiveness of the $Pd(OAc)_2/PPh_3$ system to catalyze the amino carbonylation of 2-iodopyridine, 3-iodopyridine, and iodopyrazine. In line with previous results,[247] a mixture of ketocarboxamides and carboxamides was obtained when 3-iodopyridine was the substrate, while the other heteroaryl iodides formed almost exclusively carboxamides under identical reaction conditions.

Scheme 142. Palladium-Catalyzed Double-Carbonylative Amination of Iodopyridines Reported by Castanet and Co-Workers[257]

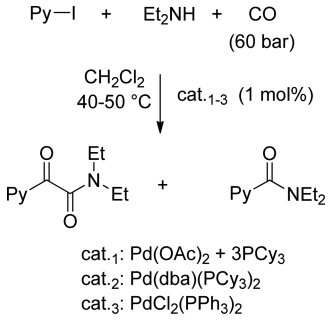


Table 7

Ka:a[a]	cat.	Py	convrsn[b] (%)
95:5	cat.$_1$	4-pyridyl	100
93:7	cat.$_2$	4-pyridyl	100
50:50	cat.$_3$	4-pyridyl	100
54:46	cat.$_2$	2-pyridyl	100
93:7	cat.$_2$	Py[c]	98
75:25	cat.$_3$	Py[c]	100

[a]Ketoamide/amide ratio. [b]Determined by GLC. [c]Py = 6-chloro-2-methoxy-3-(methoxymethyl)-4-pyridyl.

Thus, 3-pyridylglyoxylic acid amides have been obtained by performing amino-dicarbonylation with *t*-$BuNH_2$, piperidine, morpholine, and amino acid methyl esters under 40 bar of CO pressure, in DMF/Et_3N at 50 °C (Scheme 143 and Table 8).

Scheme 143. $Pd(OAc)_2/PPh_3$-Catalyzed Double-Carbonylative Amination of 3-Iodopyridine Reported by Kollár and Co-Workers[258]

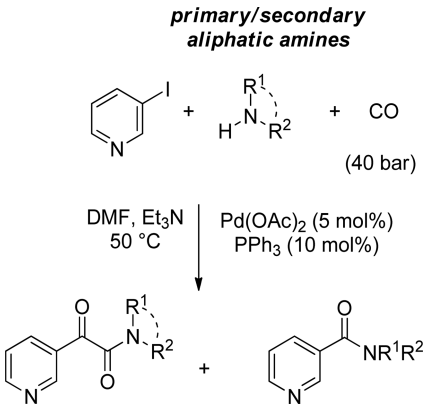


Table 8

Ka:a[a]	R^1	R^2	yield[b] (%)
91:9	H	*t*-Bu	76
31:69		$(CH_2)_5$	22
53:47		$(CH_2)_2O(CH_2)_2$	43
90:10	H	CH_2COOMe	71
80:20	H	$CH(Me)COOMe$	68
30:70		$(CH_2)_3CHCOOMe$	24

[a]Ketoamide/amide ratio. [b]Isolated yield of ketocarboxamides.

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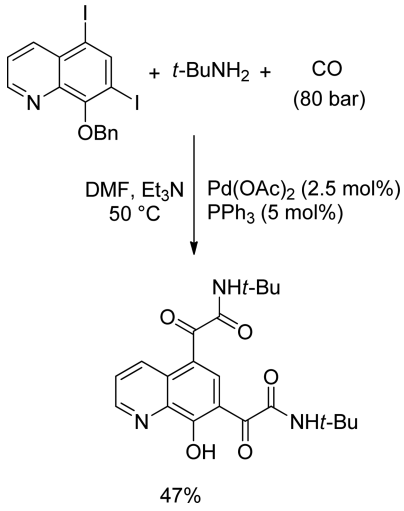
Remarkably, the use of *t*-BuNH$_2$ as N-nucleophile became of high synthetic value since the discovery that *tert*-butyldimethylsilyl triflate was an effective reagent for the selective cleavage of the *t*-Bu group.[259] Importantly, in such a way aromatic primary α-ketoamides became accessible via a two-step reaction sequence overcoming problems associated with the use of ammonia in Pd-mediated dicarbonylation processes.

Amino double-carbonylation of 7-iodoquinoline derivatives was revealed to be a hard process, with amino-monocarbonylation products being formed almost exclusively when 5-chloro-7-iodo-8-methoxy(or 8-benzyloxy)quinoline[253] and 5,7-diiodo-8-benzyloxyquinoline were submitted to the reaction conditions previously employed for the double-carbonylation of simple iodoarenes. However, Kollár and co-workers[260] transformed 5,7-diiodo-8-benzyloxyquinoline into 5,7-bis(*N*-*tert*-butylglyoxylamido)-8-hydroxyquinoline (Scheme 144) by

Scheme 144. Pd(OAc)$_2$/PPh$_3$-Catalyzed Double-Carbonylative Amination of a Diiodoquinoline Substrate Reported by Kollár and Co-Workers[260]

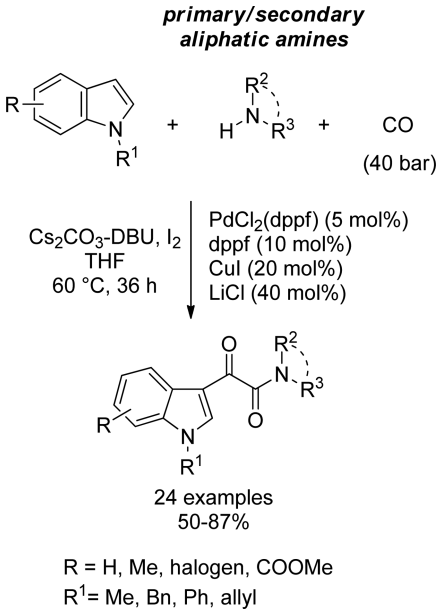


47%

using the Pd(OAc)$_2$/PPh$_3$ precatalyst in the presence of a 6-fold molar excess of *t*-BuNH$_2$ under higher carbon monoxide pressure (80 bar). Almost complete deprotection of the 8-benzyloxy functional group occurred during double functionalization of the arene moiety. Interestingly, the diiodoquinoline substrate underwent regioselective amino monocarbonylation at C(5) when secondary amines as well as aniline were the *N*-nucleophiles in the reaction mixture.

Li and co-workers[261] prepared directly indolyl-3-glyoxylic acid amides through a PdCl$_2$(dppf)-catalyzed double-carbonylation of N-protected indoles with amines. The salient feature of the procedure was the in situ C(3) oxidative functionalization of indole with I$_2$ to give a 3-iodoindole intermediate suitable for the Pd(0) oxidative addition step, required as the starting point of the catalytic cycle. As shown in Scheme 145, standard conditions were found by reacting N-protected indole derivatives and nucleophilic amines (4-fold molar excess) in THF at 60 °C for 36 h under 40 bar of CO atmosphere, in the presence of bases (Cs$_2$CO$_3$–DBU), I$_2$, catalyst [PdCl$_2$(dppf) (5 mol %) + dppf (10 mol %)], and additives [CuI (20 mol %) + LiCl (40 mol %)]. The method showed large substrate scope, both in the indole moiety and amine nucleophiles. N-Protected indole derivatives gave moderate to good yields of indole-3-α-ketoamides, with a variety of substituents on the benzene ring

Scheme 145. PdCl$_2$(dppf)-Catalyzed Double-Carbonylative Amination of N-Protected Indoles Reported by Li and Co-Workers[261]



being well-tolerated. Importantly, halogen substituents exploitable for further transformations could be preserved during the reaction. As expected, indoles bearing electron-donating groups were better substrates for the double-carbonylation, while the presence of electron-withdrawing groups required prolonged reaction time (48 h). HIV-1 inhibitors[262] could be prepared in moderate yields directly from *N*-benzoylpiperazine and *N*-methyl- or *N*-allylindole, respectively, by employing PdCl$_2$(PhCN)$_2$ and Xantphos instead of PdCl$_2$(dppf). Secondary amines gave high yields, but primary amines could be also tolerated, giving rise to the desired products in moderate yields.

6.2. Ionic Liquid Solvents and Heterogeneous Pd Materials

The recovery of the expensive metal catalysts and ligands is one of the problems of homogeneous catalysis, especially for a large-scale synthesis. Many efforts have been directed to circumvent this hurdle. In 2001, Tanaka and co-workers[263] advanced a partial solution by performing the Pd-promoted process in nonvolatile ionic liquid solvents (ILs). Thus, the diethylamine-dicarbonylation of iodobenzene employing the Pd(OAc)$_2$/PPh$_3$ precatalyst in [bmim]$^+$BF$_4^-$ or in the corresponding hexafluorophosphate ([bmim]$^+$PF$_6^-$) was successfully performed under 40 bar of CO pressure at 80 °C. Selectivity for α-ketoamide formation was similar to the one obtained using Et$_2$NH as the solvent, but the method allowed the catalyst/ionic liquid mixture to be recycled after removal of the products by extraction with ether.

Such a result was also achieved by using heterogeneous Pd materials. In 1997, Yan et al.[264] developed a silica-supported polytitazane–palladium complex (Ti–N–Pd) for the double-carbonylation of phenyl halides in the presence of diethylamine. Noteworthy, the supported catalyst could be reused 10 times without noticeable decrease in activity.

In 2001, Alper et al.[265] prepared α-aminoamides via carbohydroamination reaction of various iodoarenes with primary amines under CO and H$_2$ pressure by using Pd on charcoal as the catalyst. The one-pot process involved first a Pd(0)-catalyzed amino double-carbonylation, followed by a

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Pd(0)-catalyzed hydrogenation of the in situ formed α-iminoamide.

More recently, Liu et al.[266] performed amino double-carbonylation reactions in THF by using a catalytic system composed of Pd/C−PPh_3 and DABCO as the base. Unfortunately, catalyst activity dropped, probably because of Pd-leaching phenomena occurring at the active species formed in solution.

Unconventional methodologies, such as a continuous-flow technique using microstructured devices,[267,268] were occasionally reported as an alternative to bench-scale synthesis with moderate results both in terms of yield and selectivity for α-ketoamide formation.

Skoda-Földes and co-workers[269] succeeded in the amino double-carbonylation of iodobenzene with various amine nucleophiles by carrying out the transformation in the flow reactor X-Cube using immobilized $Pd(PPh_3)_4$ catalyst placed in CatCart cartridges (Scheme 146 and Table 9). The highest yields of α-ketoamides were obtained in toluene (flow rate 0.2 mL/min) at 80 °C under 40 bar of CO pressure, using a 2-fold molar excess of amine nucleophiles in the presence of DBU as the base. Unexpectedly, primary amines underwent double-carbonylation better than morpholine.

Scheme 146. Double-Carbonylative Amination with Immobilized $Pd(PPh_3)_4$ Catalyst Reported by Skoda-Földes and Co-Workers[269]

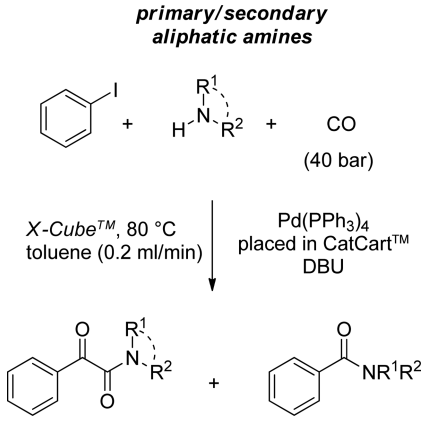


Table 9

Ka:a[a]	R^1	R^2	convrsn[b] (%)
70:30	$(CH_2)_2O(CH_2)_2$		61
87:13	H	Cy	92
91:9	H	allyl	64
96:4	H	Bu	76

[a]Ketoamide/amide ratio. [b]Determined by GC.

An elegant solution allowing efficient catalyst recycling entailed the use of Pd complexes covalently grafted onto mesoporous silica.[270] Postsynthetic grafting of coordinated phosphine−Pd complexes (Figure 24) onto mesostructured SBA-15-type silica support occurred through reaction of the alkoxysilane moieties with surface silanols, giving three hybrid materials referred to as $PdCl_2(PPh_2)_2$@SBA-15, $PdCl_2(PCy_2)_2$@SBA-15, and $PdCl_2$(PNP)@SBA-15.

Optimization of reaction conditions for the double-carbonylation of iodobenzene with diethylamine led to the discovery that superior conversion and selectivity for α-ketoamides

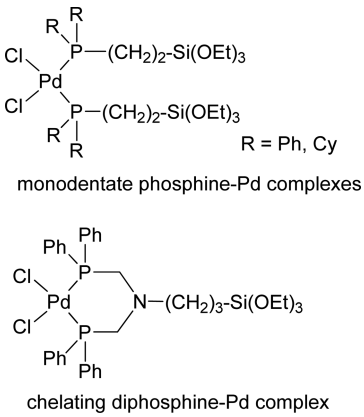
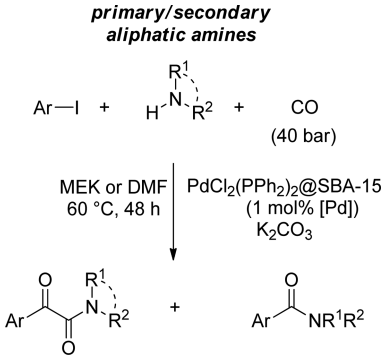


Figure 24. Coordinated phosphine−Pd complexes.[270]

formation were obtained using $PdCl_2(PPh_2)_2$@SBA-15 (1 mol % [Pd]) in methyl ethyl ketone (MEK) or DMF, at 60 °C under 40 bar of CO. After 48 h, centrifugation of the reaction mixture allowed the facile recovery of the solid catalyst, which remained stable and efficient for up to three cycles. Under optimized reaction conditions, the heterogeneous Pd catalyst exhibited high conversion for the amino double-carbonylation of several iodoaromatics with different cyclic and acyclic amines (Scheme 147 and Table 10). Reaction with primary amines was performed in DMF (to avoid Schiff base formation with MEK), and as expected, the weakly basic aniline provided only carboxamide. Among secondary amines, 1,2,3,4-tetrahydroisoquinoline was the best nucleophilic partner for a series of iodoaromatics, including 1-iodonaphthalene.

Scheme 147. Double-Carbonylative Amination with Phosphine−Pd Complexes Covalently Grafted onto Mesoporous Silica Reported by Dufaud and Co-Workers[270]



A related approach combining the advantages of ionic liquid solvents with those of heterogeneous supports has been recently reported by Papp and Skoda-Földes.[271] They prepared a set of supported ionic liquid phase (SILP)−Pd catalysts (Figure 25) either by simple impregnation of silica gel with solutions of Pd precatalysts in ionic liquids (catalysts [Pd]1−3) or by grafting an alkoxysilane-tethered imidazolium ion to silica and adding a solution of $Pd_2(dba)_3$·$CHCl_3$ to the resulting SILP (catalyst [Pd]4).

The silica-supported Pd catalysts exhibited good activity and selectivity for the amino double-carbonylation of iodobenzene with a variety of secondary amines in DMF/Et_3N at 100 °C under 30 bar of CO (Scheme 148). Tertiary α-ketoamides were obtained in good yields, while the amide was the exclusive

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Table 10

Ka:a[a]	Ar	R^1	R^2	yield[b] (%)
85:15	Ph	Et	Et	71
85:15	Ph	Pr	Pr	69
90:10	Ph	$(CH_2)_5$		81
85:15	Ph	$(CH_2)_2O(CH_2)_2$		69
84:16	Ph	Me	Bn	74
0:100	Ph	H	Ph	81[c]
76:24	Ph	H	Bn	63
73:27	Ph	H	Bu	50
91:9	Ph	QCF[d]		81
73:27	2-$MeOC_6H_4$	QCF[d]		58
93:07	3-$MeOC_6H_4$	QCF[d]		86
97:3	4-$MeOC_6H_4$	QCF[d]		80
98:2	2-MeC_6H_4	QCF[d]		84
95:5	4-MeC_6H_4	QCF[d]		83
90:10	1-naphthyl	QCF[d]		77

[a]Ketoamide/amide ratio. [b]Isolated yield of ketocarboxamides. [c]Yield of carboxamide. [d]QCF = 1,2,3,4-tetrahydroisoquinoline carbon framework.

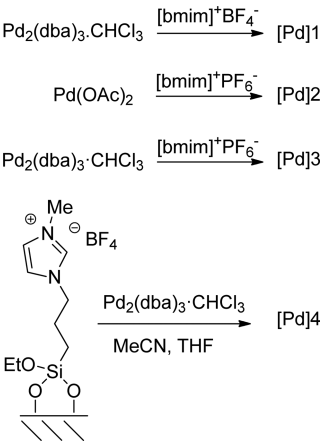
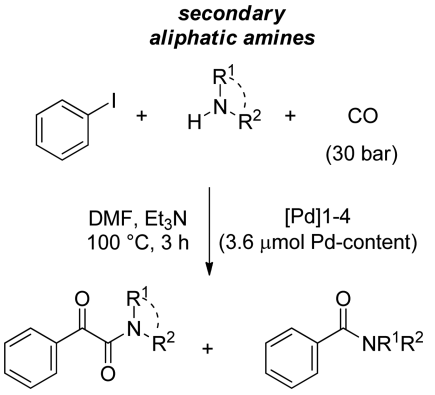


Figure 25. SILP–Pd catalysts.[271]

Scheme 148. Double-Carbonylative Amination with SILP–Pd Catalysts Reported by Papp and Skoda-Földes[271]



product when the bulky *i*-Pr_2NH was the nucleophile, in line with homogeneous reaction (Table 11). Importantly, the methodology allowed efficient catalyst recovery and recycling (at least six times), as well as a significant saving of the expensive ILs. Moreover, it did not require phosphine ligands, an issue we are dealing with in subsection 6.4.

Table 11

Ka:a[a]	R^1	R^2	cat.	convrsn[b] (%)
94:6	$(CH_2)_2O(CH_2)_2$		[Pd]1	88
92:8	$(CH_2)_2O(CH_2)_2$		[Pd]2	100
97:3	$(CH_2)_2O(CH_2)_2$		[Pd]3	95
89:11	$(CH_2)_2O(CH_2)_2$		[Pd]4	100
77:23	Me	Me	[Pd]1	100
69:31	Me	Me	[Pd]4	100
89:11	Et	Et	[Pd]1	100
85:15	Et	Et	[Pd]4	90
0:100	*i*-Pr	*i*-Pr	[Pd]1	73
0:100	*i*-Pr	*i*-Pr	[Pd]4	60
88:12	Bu	Bu	[Pd]1	100
73:27	Bu	Bu	[Pd]4	97
44:56	$(CH_2)_4CH(Et)$		[Pd]1	85
29:71	$(CH_2)_4CH(Et)$		[Pd]4	85
93:7	$(CH_2)_4$		[Pd]1	100
88:12	$(CH_2)_4$		[Pd]4	95

[a]Ketoamide/amide ratio. [b]Determined by GC.

6.3. Pd–Phosphines under Atmospheric Pressure of CO or with CO Generated ex Situ

Academic researchers are reluctant to use highly toxic CO gas, especially when high-pressure equipment is required. For this reason, the double-carbonylation/amine incorporation process has been barely used toward the synthesis of biologically relevant α-ketoamides.

This subsection deals with protocols entailing the use of Pd–phosphines in combination with carbon monoxide at atmospheric pressure (CO balloon) or of stable and easy to handle sources of the hazardous gas. The latter approach (ex situ generation of CO) represents a highly desirable achievement, especially in nonindustrial synthetic applications to perform gram-scale processes based on the use of carbon monoxide reagent (e.g., carbonylative Sonogashira, carbonylative Heck, alkoxycarbonylation, amino monocarbonylation, and amino double-carbonylation).

In 2001, Zhou and Chen[272] disclosed a convenient route for the synthesis of α-ketoamides featuring the $PdCl_2(PPh_3)_2$/CuI catalyst/cocatalyst couple to promote reaction of diaryliodonium salts with secondary amines under 1 atm pressure of carbon monoxide in DMF at room temperature (Scheme 149). As previously observed by Miura amd co-workers,[246] the effect of CuI as cocatalyst was to enhance the palladium catalytic activity, improving both reaction efficiency and selectivity. Actually, both electron-poor and electron-rich phenyliodonium derivatives incorporated nucleophilic secondary amines together with two CO moieties, giving the desired α-ketoamides in good yields. Remarkably, primary amines were not suitable nucleophilic partners of diaryliodonium salts, giving only monocarbonylated amide products.

In the same year, Uozumi et al.[273] reported a practical protocol for the Pd-catalyzed amino-dicarbonylation of aryl iodides with primary amines under atmospheric pressure of carbon monoxide at ambient temperature employing the 1:2 mixture of allylpalladium(II) chloride dimer and triphenylphosphine as the precatalyst system (Scheme 150). Use of THF as the solvent, PPh_3 as the ligand, and DABCO as the base was essential for an efficient catalyst system. Indeed, the reaction with DBU gave exclusively the amide products resulting from the competitive amino monocarbonylation process.

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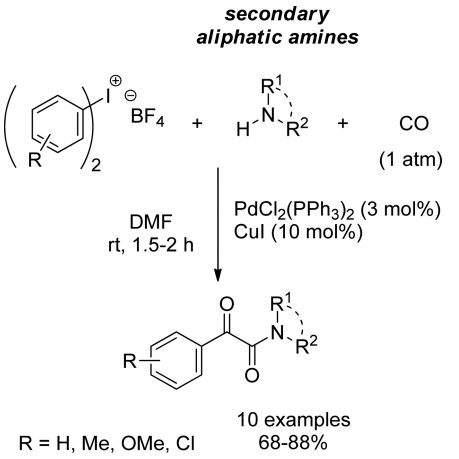
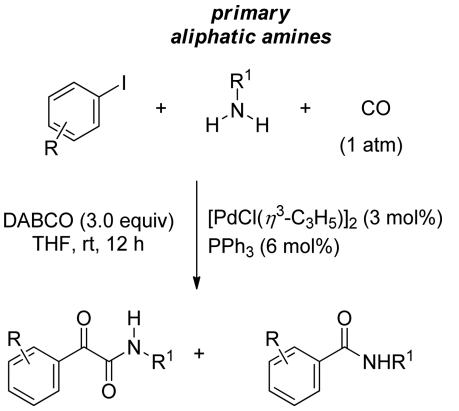
Scheme 149. Palladium-Catalyzed Double-Carbonylative Amination of Diaryliodonium Salts Repoted by Zhou and Chen[272]



Scheme 150. Pd/PPh_3/DABCO-Catalyzed Double-Carbonylative Amination Reported by Uozumi et al.[273]



t12 As shown in Table 12, high conversion yields and selectivity were exhibited by iodobenzene as well as by derivatives bearing electron-donating groups on the aromatic ring, while aryl iodides bearing electron-withdrawing substituents gave mainly amide products.

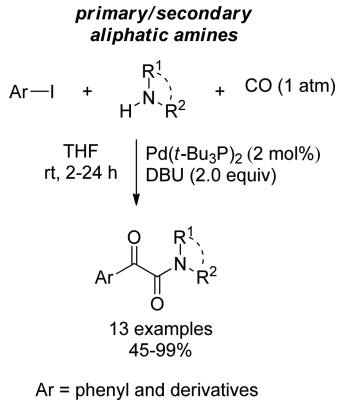
Table 12

Ka:a[a]	R	R^1	yield[b] (%)
93:7	H	*i*-Pr	98
91:9	H	Cy	93
94:6	H	*t*-Bu	69
92:8	H	Bu	86
94:6	4-MeO	Bu	87
92:8	4-Me	Bu	90
89:11	3-Me	Bu	85 (10)[c]
78:22	2-Me	Bu	46 (13)[c]
14:86	3-Cl	Bu	13 (77)[c]
<1:99	4-CF_3	Bu	<1 (98)[c]

[a]Ketoamide/amide ratio. [b]Isolated yield of ketocarboxamides. [c]Yield of carboxamide is in parentheses.

In 2006, Iizuka and Kondo[274] were able to achieve the amino-dicarbonylation of starting materials previously reported[273] to give the amino monocarbonylation process mostly. Thus, excellent yields of α-ketoamides were obtained using phenyl iodide derivatives bearing either electron-withdrawing or electron-donating substituents (Scheme 151). The reaction s151

Scheme 151. Pd(*t*-Bu_3P)$_2$/DBU-Catalyzed Double-Carbonylative Amination Reported by Iizuka and Kondo[274]



occurred under very mild conditions combining iodoarenes, CO (1 atm), and primary or secondary amines in the presence of DBU as the base and Pd(*t*-Bu_3P)$_2$ as the catalyst. The use of DBU was critical, as other organic or inorganic bases gave mainly amide products under identical reaction conditions.

The ligand *t*-Bu_3P was also essential, as other mono- or bidentate phosphines, like PPh_3, PCy_3, dppp, and dppf, switched selectivity toward amide products.

Remarkably, the Pd-catalyzed, *t*-Bu_3P-assisted amino dicarbonylation was also effective when using $Mo(CO)_6$ (1.5 equiv) as a stable and easy to handle source of carbon monoxide. However, its use involved the disadvantage of adding stoichiometric amounts of the transition metal to the reaction mixture.

In 2011, Skrydstrup and co-workers[275,276] disclosed an alternative technique for the ex situ generation of CO by developing in brief succession two crystalline CO-releasing molecules (CORMs), namely, 9-methyl-9*H*-fluorene-9-carbonyl chloride **168** and methyldiphenyl silacarboxylic acid **169** (Scheme 152). As a distinctive feature, compound **168** was s152 activated to release CO via a Pd-catalyzed decarbonylation process, while **169** simply required the intervention of a fluoride source. Both CORMs were crystalline, clean, safe, benchtop-stable sources of carbon monoxide easily accessible on large scale by common synthetic protocols. Importantly, generation of CO from compound **168** could also result in recycling the 9-methylenefluorene precursor, which is produced through palladium decarbonylation/β-hydride elimination. Thus, a system was designed to allow the gaseous carbon monoxide produced in the CO-releasing chamber to be equally distributed above the CO-consuming chamber where the amino double-carbonylation took place according to Kondo's protocol.[274] The two-chamber equipment was used for the preparation of α-ketoamides, including a bioactive carbon-isotope-labeled derivative (Figure 26). f26

6.4. Pd–DBU, Pd–NHC, and Ligand-Free Pd Catalysts

Most of the reported amino-dicarbonylation processes entailed the use of palladium catalysts modified with phosphine ligands, with tri-*tert*-butylphosphine showing remarkable positive effects in terms of overall conversion yields and selectivity.[274] However, the costs and sensitivity to aerial oxidation made

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Scheme 152. Palladium-Catalyzed Double-Carbonylative Amination with CO Generated ex Situ Reported by Skrydstrup and Co-Workers[275,276]

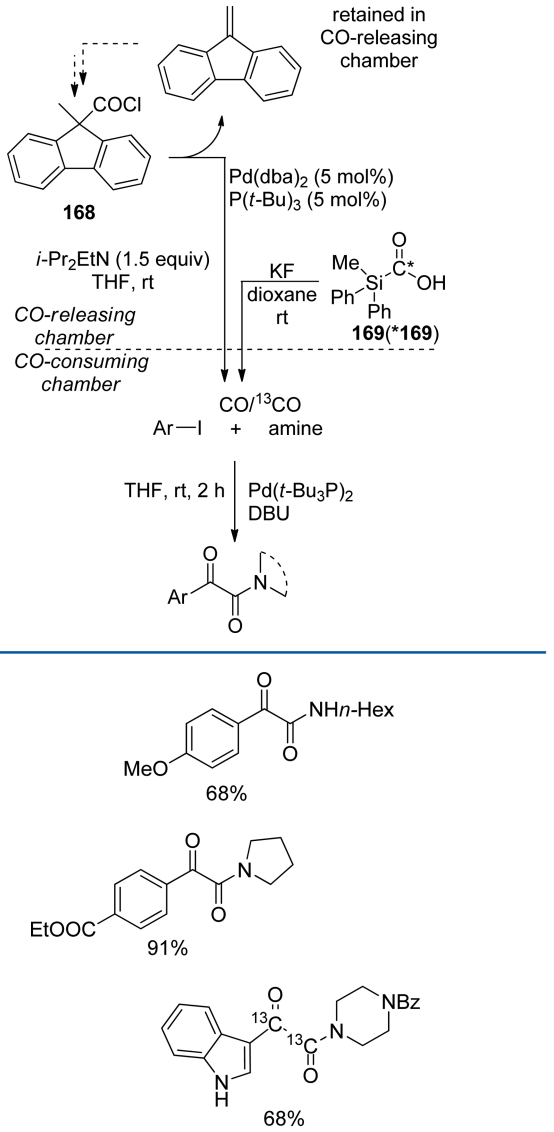

Figure 26. α-Ketoamides obtained by using Pd−phosphines and CO generated ex situ.[275,276]

Scheme 153. $[PdCl(\eta^3\text{-}C_3H_5)]_2$/DBU-Catalyzed Double-Carbonylative Amination Reported by Castillón and Co-Workers[277]

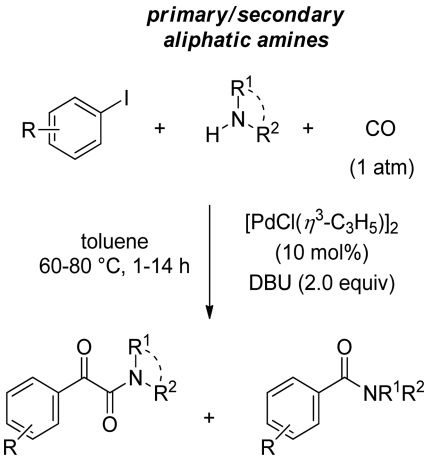

Table 13

Ka:a[a]	R	R^1	R^2	convrsn[b] (%)
98:2	4-MeO	H	Bu	99
65:35	3-MeO	H	Bu	95
2:98	2-MeO	H	Bu	93
8:92	2,4-$(MeO)_2$	H	Bu	95
76:24	H	H	Bu	98
90:10	4-Me	H	Bu	99
91:10	3-Me	H	Bu	97
84:16	2-Me	H	Bu	99
98:2	4-Et	H	Bu	94
97:3	4-*t*-Bu	H	Bu	98
1:99	4-CN	H	Bu	99
1:99	4-NO_2	H	Bu	99
98:2	4-MeO	H	Et	90
94:6	4-MeO	H	Pr	93
98:2	4-MeO	H	*t*-Bu	99
99:1	4-MeO	H	PhCH(Me)	99
96:4	4-MeO	Et	Et	82
91:9	4-MeO		$(CH_2)_4$	93
92:8	4-MeO		$(CH_2)_5$	96
95:5	4-MeO		$(CH_2)_6$	87

[a]Ketoamide/amide ratio. [b]Determined by ^{1}H NMR and GC−MS

the use of basic phosphines quite a problem, especially in large-scale processes. Thus, in recent years the development of stable and effective Pd catalysts resulting from different ligands has become an exciting topical subject.

The first Pd catalyst for the amino-dicarbonylation of aryl iodides involving a nitrogen donor ligand was reported in 2012 by Castillón and co-workers,[277] who used a mixture of allylpalladium(II) chloride dimer and DBU (Scheme 153). The catalytic system proved to be highly efficient and selective for the synthesis of α-ketoamides from several aryl iodides and primary/secondary amine nucleophiles, in toluene at 60−80 °C under atmospheric CO pressure. As observed for the traditional homogeneous Pd catalysts,[273] the substrate scope for the electrophilic phenyl moiety indicated that the electronic properties of para-substituents played an important role in directing the process toward di- or monocarbonylation (Table 13). Thus, the presence of the *p*-methoxyl group favored the almost exclusive formation of α-ketoamide, while electron-withdrawing groups in the para position led to amino-monocarbonylation. The low selectivity for α-ketoamide observed with 2-iodoanisole could not be explained, with steric hindrance not being the only effect involved.

Computational studies on the mechanism of the Pd/DBU-catalyzed amino-carbonylation suggested specific reaction pathways for both di- and monocarbonylation processes that could convincingly explain how the observed ketoamide vs amide selectivity was a function of electron density on the aromatic nucleus.[278]

Steps toward double-carbonylative amination were very similar to those involved in the corresponding Pd−phosphine catalytic system. Thus, formation of the oxidative addition product **170**, coordination of DBU, and migratory insertion of CO accounted for the formation of the aroyl−Pd species **171**, which reacted with a second molecule of CO to give the intermediate **172** (Scheme 154). At this stage, the DBU-

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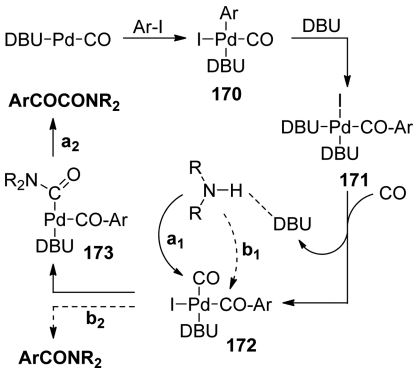
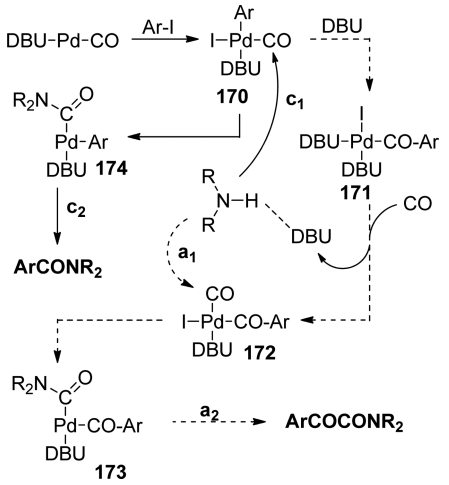
Scheme 154. Mechanism Proposed for the Pd−DBU Double-Carbonylative Amination[278]



assisted amine nucleophilic attack at the terminal CO of **172** (step a_1) produced the palladium−acyl-carbamoyl intermediate **173**, from which α-ketoamides were formed by reductive elimination (step a_2). Accordingly, a para electron-donating substituent directed the process toward double-carbonylation as a result of a facilitated aryl migration to the CO ligand in the step leading to **171**. Moreover, it deactivated amine nucleophilic attack, leading to monocarbonylation product (steps b_1, b_2).

On the other hand, electron-withdrawing substituents on the aryl moiety resulted in slowdown of the aryl migration to the CO ligand (Scheme 155, dashed path), thus allowing the DBU-

Scheme 155. Mechanism Proposed for the Pd−DBU Monocarbonylative Amination[278]



assisted amine nucleophilic attack at the terminal CO of **170** (step c_1). The resulting aryl(carbamoyl)palladium species **174** underwent reductive elimination giving amide products (step c_2).

NHCs are neutral two-electron σ-donors acting as powerful "phosphine mimics" in transition-metal-complex-catalyzed homogeneous reactions. Compared with phosphines, NHCs form stronger bonds with the metal conferring higher thermal tolerance to the active metal complexes. Furthermore, NHCs enhance nucleophilicity of the coordinating metal atom, favoring the oxidative addition step by which transition-metal-mediated reactions, including carbonylative amination of organic halide substrates, are triggered.

In 2009, Xia and co-workers[279] obtained excellent results in the double-carbonylative amination of iodobenzene and derivatives by using a [(NHC)−CuX]-based catalytic system featuring the sterically demanding *N*,*N*′-bis(2,6-diisopropylphenyl)imidazole-2-ylidene (IPr) as the two-electron donor ligand of Cu(I). A 2-fold amount of the imidazolium salt IPr·HCl, precursor of the NHC ligand, was required in order to get the active catalyst. Therefore, a bis-carbene copper complex formed in situ was presumed to be the real active species involved (Figure 27).

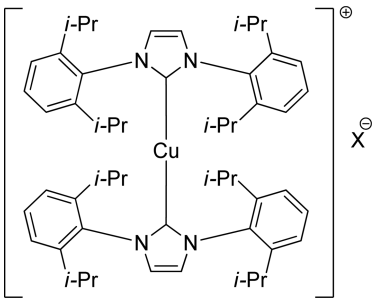


Figure 27. Bis-carbene−copper complex.[279]

Five years later, the same research group described the amino-carbonylation of aryl iodides by using a Pd−NHC catalyst.[280] Among different Pd(II) complexes tested, the precatalyst [Bmim][PdI_2](PPh_3), featuring *N*-butyl-*N*′-methyl-imidazole-2-ylidene (Bmim) and PPh_3 as the neutral ligands of PdI_2, showed the best activity under optimized reaction conditions. Thus, aryl iodide, K_2CO_3, (2.0 equiv), amine (5.0 equiv), and [Bmim][PdI_2](PPh_3) (0.25 mol %) were reacted in dioxane at 90 °C for 5 h under 20 bar of CO pressure to provide α-ketoamides (Scheme 156). As shown in Table 14, secondary amines of high basicity were suitable for the reaction, with the bulky ones giving higher selectivity for the α-ketoamides. On the contrary, $BuNH_2$ was a poor partner of phenyl iodide because of formation of Schiff base side products,

Scheme 156. Double-Carbonylative Amination with [Bmim][PdI_2](PPh_3) Reported by Xia and Co-Workers[280]

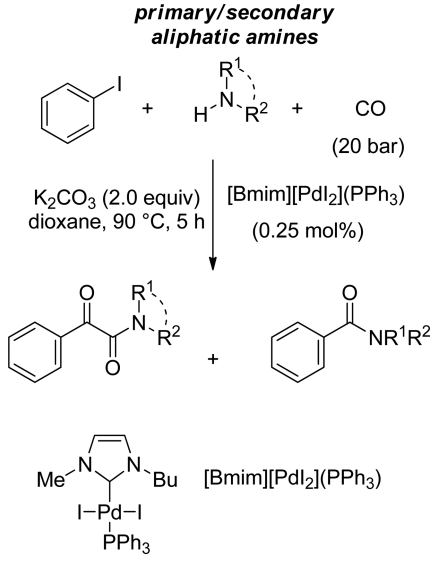


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Table 14

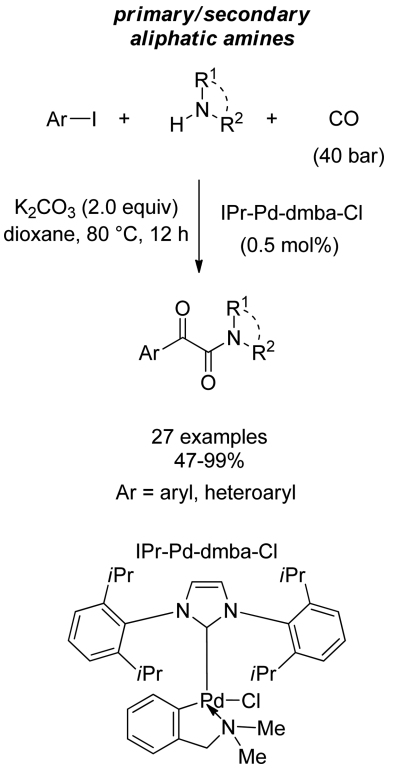
Ka:a[a]	R^1	R^2	convrsn (%)
84:16	Et	Et	75
62:38	Pr	Pr	60
78:22	Bu	Bu	55
94:6	$(CH_2)_5$		41
88:12	$(CH_2)_2O(CH_2)_2$		41
74:26	H	Bu	52
>99:1	allyl	allyl	43
>99:1	Bn	Pr	10
>99:1	Bn	*t*-Bu	43
>99:1	QCF[b]		52

[a]Ketoamide/amide ratio. [b]QCF = 1,2,3,4-tetrahydroisoquinoline carbon framework.

while aromatic amines gave competitive formation of amide products.

The stable NHC−palladacyclic complex IPr−Pd−dmba-Cl containing the sterically demanding IPr and *o*-cyclopalladated *N*,*N*-dimethylbenzylamine (dmba) ligands was an even more efficient and selective precatalyst for the double-carbonylative amination of a variety of aryl iodides with different amines (Scheme 157).[281] Actually, the active Pd(0) catalyst resulted

Scheme 157. Double-Carbonylative Amination with IPr−Pd−dmba-Cl Reported by Xia and Co-Workers[281]

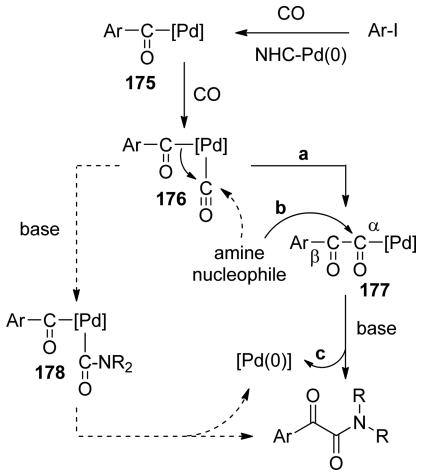


from the in situ controlled decomposition of the non-NHC ligand (dmba). Under optimized reaction conditions, the aryl iodide, K_2CO_3 (2.0 equiv), the amine (5.0 equiv), and the catalyst (0.5 mol %) reacted in dioxane at 80 °C for 12 h under 40 bar of CO pressure to give α-ketoamides.

Exploration of the substrate scope of the amino carbonylation reaction indicated that a series of functional groups on the benzene ring was tolerated, with scanty results being confined to the use of phenyl iodides bearing free phenolic hydroxyl and amino groups. Heteroaryl iodides, with the exclusion of 4-iodopyridine, were also good substrates. Symmetrical acyclic and cyclic secondary amines were suitable nucleophilic partners, with morpholine being the best performer. Primary amine $BuNH_2$ was compatible, while aniline furnished exclusively the amino-monocarbonylated product *N*-phenylbenzamide (31%).

As stated in the introduction to this subsection, the widely accepted mechanism for the Pd-mediated double-carbonylative amination called for the initial formation of the aroyl−Pd species **175** and CO coordination to the metal giving **176** (Scheme 158). Next, amine addition at the terminal CO

Scheme 158. Mechanism Proposed for the Pd−NHC Double-Carbonylative Amination[281]



provided the aroyl-carbamoyl Pd species **178**, eventually taken to the target α-ketoamide by Pd(0) reductive elimination (dashed arrows) (see refs 238−241, 247, 273, 274, 278, and 282). Quite surprisingly, Xia advanced an alternative way for the C(O)−C(O) chaining process in the related Pd−NHC complex-catalyzed transformation (solid arrows). Thus, **176** underwent a carbon monoxide insertion reaction, giving the arylglyoxyl−Pd species **177** (step a) followed by amine nucleophilic attack on the α-carbon of the so-formed Pd ligand (step b). Eventually, a base-promoted reductive elimination (step c) provided α-ketoamide while restoring the catalytically active Pd(0).

In 2015, within the space of a few months, two research groups[283,284] independently disclosed that palladium nanoparticles (Pd NPs), without any specific additives or ligands, were efficient catalysts for the double-carbonylative amination of aryl iodides. Saito and co-workers[283] developed a sulfur-modified Au-supported Pd (SAPd) material that showed remarkable reactivity for a range of Pd-mediated processes, including the amino-carbonylation reaction of aryl iodides under an atmospheric pressure of CO (Scheme 159). The optimal procedure entailed heating at 80 °C for 2 h a DMF solution of aryl iodide in the presence of K_2CO_3 and a sheet of SAPd, under Ar atmosphere without stirring. In this step, Pd NPs of approximately 5 nm in size, leached from the SAPd material, generated the organopalladium(II) species by reaction with aryl iodides. Thereafter, the SAPd sheet was removed from the reaction vessel, while the amine was added and the mixture stirred at 80 °C for 24 h under CO atmosphere.

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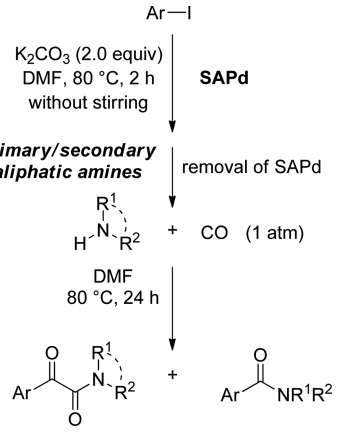
Scheme 159. Double-Carbonylative Amination with Pd NPs Reported by Saitoand Co-Workers[283]



The two-step protocol was successful for various substituted phenyl/heteroaryl iodides and primary/secondary aliphatic amines providing α-ketoamide compounds along with variable amounts of the corresponding amide derivatives (Table 15). As

Table 15

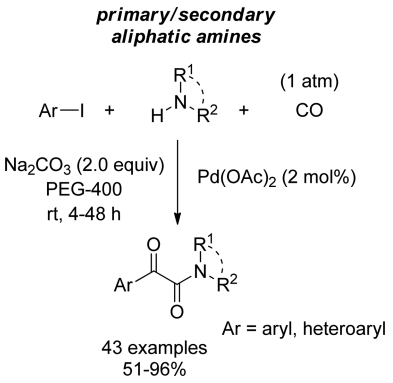
Ar	R^1	R^2	yield[a] (%)
4-$MeOC_6H_4$	$(CH_2)_2O(CH_2)_2$		85 (11)
4-$MeOC_6H_4$	$(CH_2)_4$		82 (10)
4-$MeOC_6H_4$	$(CH_2)_5$		94 (6)
4-$MeOC_6H_4$	$(CH_2)_2NMe(CH_2)_2$		86 (11)
4-$MeOC_6H_4$	$(CH_2)_2X^b(CH_2)_2$		87 (9)
4-$MeOC_6H_4$	QCF[c]		100 (0)
4-$MeOC_6H_4$	H	Bu	74 (22)
4-$MeOC_6H_4$	Pr	Pr	75 (20)
4-$MeOC_6H_4$	Bn	Me	87 (0)
4-$MeOC_6H_4$	$TBSOCH_2CH_2$	Me	70 (0)
4-$MeOC_6H_4$	H	Ph	0 0 (55)
3-$MeOC_6H_4$	$(CH_2)_2O(CH_2)_2$		84 (14)
2-$MeOC_6H_4$	$(CH_2)_2O(CH_2)_2$		29 (55)
3,5-$Me_2C_6H_3$	$(CH_2)_2O(CH_2)_2$		76 (7)
3,4,5-$(MeO)_3C_6H_2$	$(CH_2)_2O(CH_2)_2$		84 (4)
Ph	$(CH_2)_2O(CH_2)_2$		69 (21)
4-ClC_6H_4	$(CH_2)_2O(CH_2)_2$		65 (27)
4-$MeOCOC_6H_4$	$(CH_2)_2O(CH_2)_2$		46 (42)
Ar[d]	$(CH_2)_2O(CH_2)_2$		44 (52)
3-thienyl	$(CH_2)_2O(CH_2)_2$		84 (16)
Ar[e]	$(CH_2)_2O(CH_2)_2$		94 (6)
quinolin-6-yl	$(CH_2)_2O(CH_2)_2$		80 (17)
2-naphthyl	$(CH_2)_2NBz(CH_2)_2$		83 (15)

[a]Yields of α-ketoamides and, in parentheses, of amides. [b]X = C(−OCH_2CH_2O−). [c]QCF = 1,2,3,4-tetrahydroisoquinoline carbon framework. [d]Ar = 2,2-dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-6-yl. [e]Ar = 1-methyl-1*H*-indol-5-yl.

a rule, the reactions of aryl iodides bearing an electron-withdrawing group on the aromatic ring resulted in an increased formation of monocarbonylation products, albeit *o*-iodoanisole gave the amide as the major product. Noteworthy, the SAPd material could be used for at least five reaction cycles without a significant loss of catalytic activity.

Han and co-workers[284] have recently reported a ligand-free palladium-catalyzed double-carbonylation of aryl/heteroaryl iodides with primary or secondary amines using 3.0 ± 0.6 nm Pd NPs, generated in situ from $Pd(OAc)_2$ in PEG-400 (Scheme 160). This transformation proceeded at ambient

Scheme 160. Double-Carbonylative Amination with Pd NPs Reported by Han and Co-Workers[284]



temperature under atmospheric CO, using the Pd(II) precatalyst (2 mol %) in the presence of Na_2CO_3 (2.0 equiv), providing chemoselectively α-ketoamides. Actually, the process allowed the direct three-component coupling of various aryl iodides and amines with CO gas. Thus, besides electron-enriched aryl iodides, the electron-deprived ones were suitable substrates for the reaction with morpholine. Moreover, phenyl iodides bearing free carboxyl and amino groups as well as an acetylated gluco moiety were compatible. Generally, secondary and primary amines, including the bulky amantadine and *tert*-butyl amine, furnished the corresponding α-ketoamides in satisfactory yields with excellent selectivities. Remarkably, the protocol was shown to be adaptable to gram-scale synthesis, with the in situ generated nanocatalyst being recyclable up to five times.

7. CONCLUDING REMARKS

A vast array of synthetic procedures for the preparation of α-keto carboxylic acid amides have been developed over the past decades, and the search of expeditious and efficient protocols for their synthesis continue unabated. In confirmation of this, a new option for α-ketoamide synthesis was reported during the preparation of the present review. The paper entailed an unprecedented cleavage of the C=C double bond in enaminones realized by means of copper catalysis in the presence of hypervalent iodine.[285]

With the aim of highlighting the versatility of synthetic methods for α-ketoamides preparation, we plotted the number of papers within different sections vs two main product families: aryl and alkyl α-ketoamides. The diagram in Figure 28 shows an overall prevalence of papers dealing with the synthesis of aryl α-ketoamides in comparison to alkyl α-ketoamides. In detail, papers collected in subsection 3.1 and section 6 give the largest contribution to aryl α-ketoamides preparation, while the ones included in section 4 provide for the most part alkyl α-ketoamides. Only a limited number of papers describes versatile protocols furnishing both alkyl and aryl α-ketoamides. Importantly, methods for the synthesis of secondary and/or tertiary α-ketoamides are to a great extent predominant, with only four papers describing the preparation of the primary ones.[69,77,150,169]

A different investigation was carried out following the frequency with which papers belonging to different sections

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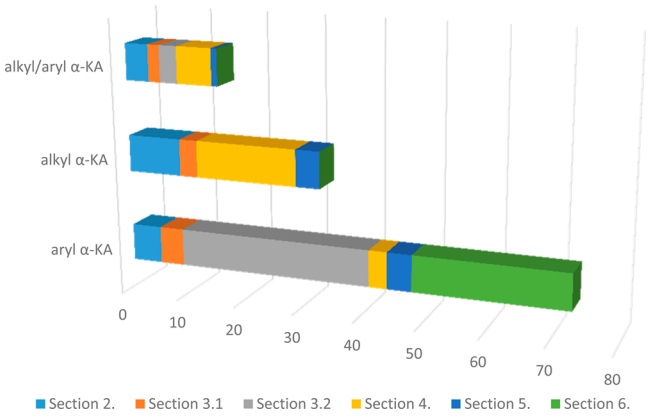

Figure 28. Number of papers vs kind of α-ketoamides.

have been published during the past decade. The diagram in Figure 29 shows that research in the area of oxidative

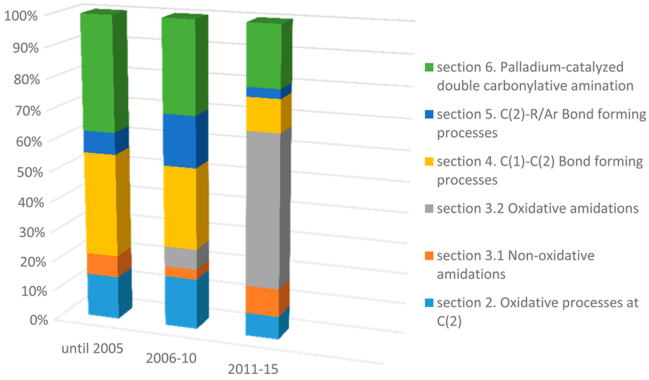

Figure 29. Occurrence of the sections in the past decade.

amidations (subsection 3.2) has known a tumultuous growth, while strategies collected in the other sections have become less and less relevant.

The strategies to access α-ketoamides have been significantly expanded, and important progress has been made in this area, where the developed new procedures have reached a remarkable level of versatility and efficiency. In addition to refined oxidative methods in which molecular oxygen as oxidant greatly improved the efficiency of the methodologies, new protocols have emerged as possible alternatives. Future developments are expected, especially in the interest of green chemistry with development of metal-free protocols using easily available starting materials and mild reaction conditions.

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Notes

The authors declare no competing financial interest.

Biographies

Gian Piero Pollini was born in Genoa, Italy. He graduated in chemistry from the University of Pavia in 1962. Since 1964, he has been an assistant professor, firstly at the Faculty of Sciences of the University of Perugia (1964–1967) and then at the Faculty of Sciences of the University of Ferrara (1968–1981), where, in 1981, he became full professor of organic chemistry. He was chairman of the "Dipartimento di Scienze Farmaceutiche" (1983–1990), dean of the Faculty of Pharmacy (1994–2000), and director of IUSS-Ferrara-1391 (Istituto Universitario di Studi Superiori) (2010–2012). He retired at the end of 2010. His research interests include the development of new methods and reagents and their application to the synthesis of natural and non-natural targets with interesting biological and chemical properties.

Carmela De Risi was born in Ferrara, Italy. She graduated in chemistry at the University of Ferrara in 1992 and obtained the degree of "Dottore in Ricerca" in organic chemistry in 1996. In 1999 she was appointed as researcher of organic chemistry at the Dipartimento di Scienze Farmaceutiche of the University of Ferrara. Her main research interests include the synthesis of biologically active natural and non-natural organic compounds, the chemistry of heterocycles, and the development of general synthetic methodologies.

Born in Fenil del Turco, Italy, Vinicio Zanirato graduated in "chimica e tecnologia farmaceutiche" at the University of Ferrara in 1982 and received the degree of "Dottore in Ricerca" in pharmaceutical sciences in 1987 from the same university. In 1990, he was appointed as researcher at the Dipartimento di Scienze Farmaceutiche of the University of Ferrara. In 1998 he was promoted to the position of associate professor at the University of Siena and in January 2003 he came back to the University of Ferrara, where he was appointed as an associate professor of organic chemistry at the faculty of pharmacy. His research interests include natural product synthesis, developmnet of new reaction methodologies, and design and synthesis of light-driven artificial molecular switches.

ABBREVIATIONS USED

$[bmim]^+BF_4^-$	1-butyl-3-methylimidazolium tetrafluoroborate
BOPCl	bis(2-oxo-3-oxazolidinyl)phosphonic chloride
CDC	cross-dehydrogenative-coupling
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,5-diazabiciclo[5.4.0]undec-5-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DMAP	4-(dimethylamino)pyridine
DMP	Dess–Martin periodinane
DPPA	diphenyl phosphoryl azide
dppf	1,1′-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
DTBP	di-*tert*-butyl peroxide
HATU	1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxybenzotriazole
HMDS	hexamethyldisilazane
IBX	2-iodoxybenzoic acid
NBS	*N*-bromosuccinimide
NHC	N-heterocyclic carbene
NIS	*N*-iodosuccinimide
P-3CR	Passerini-type three-component reaction
PDC	pyridinium dichromate
PFP–OH	pentafluorophenol
Phen	1,10-phenanthroline
PTSA	*p*-toluenesulfonic acid
PyBOP	(benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate
SPPS	solid-phase peptide synthesis

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TBAB	tetrabutylammonium bromide
TBAI	tetrabutylammonium iodide
TBAHS	tetrabutylammonium hydrogensulfate
TBHP	*tert*-tutyl hydroperoxide
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
TFA	trifluoroacetic acid
U-4CR	Ugi four-component reactions
WSC	*N*-(3-(dimethylamino)propyl)-*N*′-ethylcarbodiimide
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

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