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Recent progress in the chemistry of β-aminoketones

Mohamed M. Hammouda[ab] and Khaled M. Elattar *[c]

The β-aminoketone moiety has been found to be the basic skeleton of several drugs such as the amine salts "tolperisone (vasodilation)" and "oxyfedrine (therapeutic coronary disease)", and fluoroaryl derivatives such as "sitagliptin (antidiabetic)". The objective of this review is to summarize and highlight the chemistry of compounds reported with a β-aminoketone core in the last five years regarding their synthetic strategies, chemical reactivity, and mechanistic synthetic pathways. In the different sections, we categorize the synthesis of β-aminoketones by Mannich reactions *via* catalytic, non-catalytic, and one-pot procedures. Also, the synthesis of the investigated compounds is accomplished by condensation reactions, from propargylic alcohols, reductive hydroamination, alkylation, carbonylative coupling, and acid hydrolysis of metal complexes. The aim of this review is to provide details for the synthesis of piperidines, morpholinones, piperazinones, dihydroxy-2-oxopyrroles, spirocyclic systems, imidazolines, indolizines, pyrido-isoindoles, aminoalcohols, metal complexes, fluoxetine, sotolon, (*S*)-ketamine, indolines, and benzoazepinones.

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[a]*Department of Chemistry, College of Science and Humanities in Al-Kharj, Prince Sattam Bin Abdulaziz University, Al-Kharj, 11942, Saudi Arabia*
[b]*Chemistry Department, Faculty of Science, Mansoura University, El-Gomhoria Street, Mansoura, 35516, Egypt*

[c]*Unit of Genetic Engineering and Biotechnology, Faculty of Science, Mansoura University, El-Gomhoria Street, Mansoura, 35516, Egypt. E-mail: khaledelattar2@yahoo.com; Fax: +201010655354; Tel: +201010655354*

Dr. Mohamed M. Hammouda was born in Mansoura, Egypt, 1983. He received his BSc in 2004 from the Faculty of Science, Mansoura University, Egypt, and his MSc in 2008 from the Faculty of Science, Mansoura University, Mansoura, Egypt. He obtained his PhD in Organic Chemistry in 2013 from the Faculty of Science, Mansoura University, Egypt (PhD thesis Synthesis and Reactions of some New Isatin Mannich Bases and Related Compounds of Expected Biological Activity). In 2013 he joined the Erasmus Mundus Postdoctoral Fellowship, Laboratory of Organic and Bio-Organic Synthesis, Gent University, Belgium and conducted post-doctoral research on the development of new types of chiral catalysts for a wide variety of enantioselective reactions. In 2017 he joined the Chemistry Department, Faculty of Science, Mansoura University as a Lecturer of Organic Chemistry, "Synthesis of nitrogen-containing compounds for antioxidant activity". In 2021 he joined the Department of Chemistry, College of Science and Humanities in Al-Kharj, Prince Sattam Bin Abdulaziz University, Saudi Arabia as an Assistant Professor of Organic Chemistry.

Dr. Khaled M. Elattar was born in Menyet Sammanoud, Aga, El-dakahlia, Egypt (1979). He received his BSc in 2002 from the Faculty of Science, Mansoura University, Egypt, and MSc in 2006 from the Faculty of Science, Benha University, Benha, Egypt. He obtained his PhD in Organic Chemistry in 2011 from the Faculty of Science, Mansoura University, Egypt (PhD supervisors: Prof. A. A. Fadda and Prof. A. S. Fouda). He was a Lecturer in Organic Chemistry, at the Faculty of Education of the Sert University, Sert, Libya from 2012 to 2015. He is a member of the Egyptian Chemical Society. He is a reviewer for some scientific international journals. His main research interests are in the field of organic synthesis, the synthesis of heterocyclic compounds of the pharmaceutical interest, and medicinal chemistry. He joined the editorial board of OA Journal – Pharmaceutics (2018). https://oa.enpress-publisher.com/index.php/Pha/about/editorialTeam. Currently, he is on the Editorial Board of the following journals: Journal of Applied Science, Asian Journal of Textile, Asian Journal of Applied Science, International Journal of Chemical Technology, and Current Research in Chemistry. Recently, he joined the Asian Council of Science Editors (ACSE).

1. Introduction

The class of β-aminoketones plays an important role in heterocyclic synthesis as one of the most vital skeletons employed in the preparation of various synthetic molecules and are extensively present in natural products, drugs, and bioactive molecules.[1–4] As demonstrated in Fig. 1, proroxan acts as a nonselective α-adreno-blocker with peripheral and dominant action to delight and inhibit hypertonic predicaments and other types of sympathetic adrenal pathologies.[5] Also, they are prevalent in native anesthetics such as propipocaine in pharmaceutical synthesis and medical treatment.[6,7] In addition, the incorporation of β-aminoketones in drugs such as amine salts "tolperisone (vasodilation)" and "oxyfedrine (therapeutic coronary disease)", and fluoroalkyl derivatives such as "sitagliptin (antidiabetic)". Drugs derived from the β-aminoketone moiety are known to exhibit remarkable biological potency.[8–10] Accordingly, many methods have been applied for the synthesis of β-aminoketones by amination at the β-position of fluoroalkyl.[11,12] Furthermore, β-amino acids are a sub-class of β-aminoketones that have attracted considerable attention for the synthesis of bioactive peptides.[13–16] The integral compounds with a β-amino acid skeleton display pharmaceutical active characters such as sitagliptin for the treatment of "diabetes mellitus type 2", as influenza virus inhibitors and protein kinase inhibitors (Fig. 1).[2–4,17]

Many recent studies have focused on the development of different ways to prepare β-aminoketones with new technologies to obtain products with higher yields, improved reaction rates, and lower cost. Consequently, these strategies have been adopted for the synthesis of compounds with unique β-aminoketone skeletons. Compounds with β-aminoketone moieties were synthesized through the Mannich reaction[18–20] from accessible enolates and imines with the formation of a C–C bond. Nevertheless, this reaction involved the use of a base with equimolar amounts for the synthesis of enolates, and frequently employed harsh reaction conditions with long reaction times.[21] In another route, β-aminoketones were prepared *via* an aza-Michael reaction involving the addition of amines to α,β-unsaturated ketones,[22–24] given that these reactions have a greater economic advantage than Mannich-type reactions. However, Michael reactions commonly require basic conditions,[25,26] the utility of either stoichiometric or catalytic amounts of Lewis acids (*e.g.*, $Bi(NO_3)_3$,[27] $CeCl_3 \cdot 7H_2O$,[28] ad $SmI_2(THF)_2$ ref. 29), and frequently (toxic) organic solvents, and thus subsequent purification steps are necessary. Another methodology identified from previous research involved the utility of micellar solutions.[30] Also, β-aminoketones can be

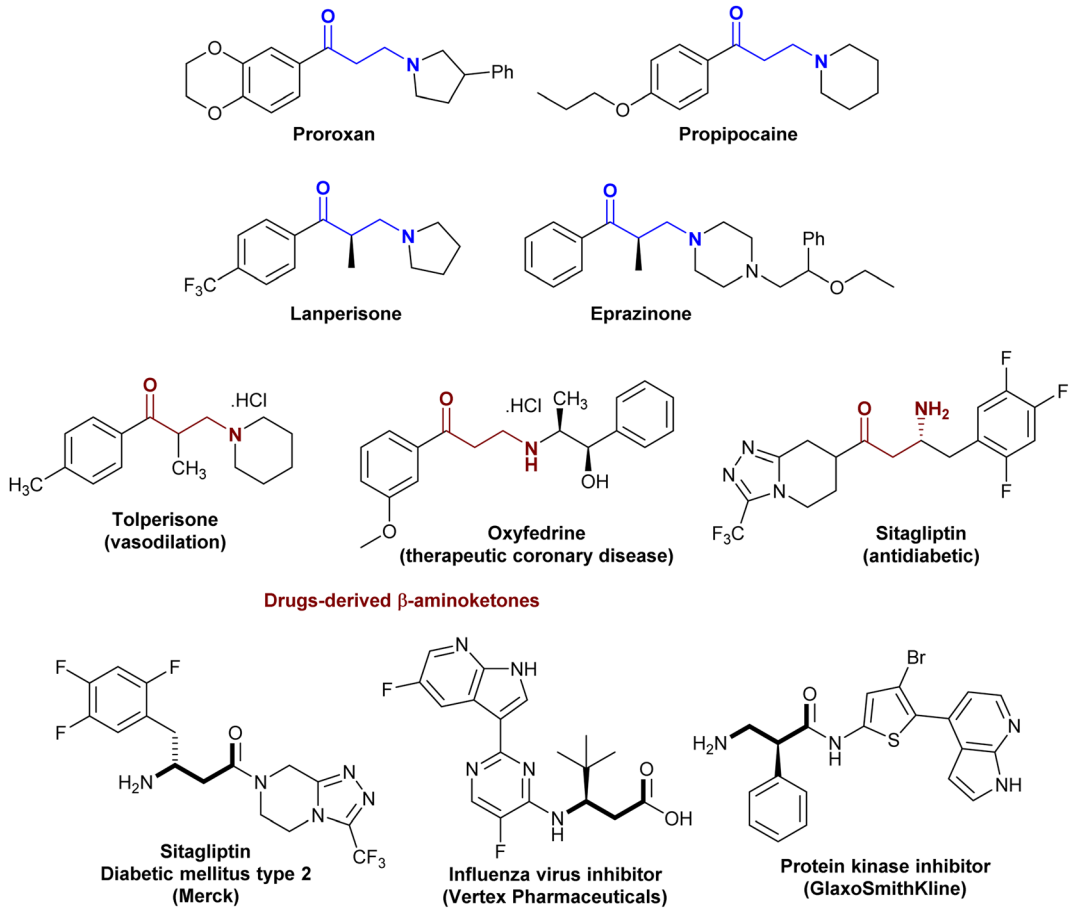


Fig. 1 Drug molecules consisting of β-aminoketone fragments.

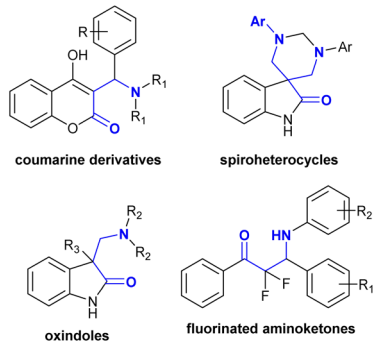


Fig. 2 Variety of versatile compounds with a β-aminoketone core.

prepared *via* the reduction of enaminones.[31,32] The alternative synthetic routes also involved the direct reductive hydroamination of carbonyl alkynes through the chemo- and regioselective synthesis of enamines with the hydroamination of terminal alkynes under catalytic conditions.[33–38] β-Aminoketones were efficiently prepared under mild, green, and catalyzed conditions.[39–41] Specifically, Mannich reactions were further applied in the synthesis of a variety of adaptable compounds incorporating a β-aminoketone motif in water following green approaches, comprising coumarins,[42] Betti bases,[43] spiro heterocycles,[44] oxindoles,[45] and fluorinated aminoketones[46] (Fig. 2).

This study is in continuation of our preceding plans and reports on emphasizing the chemistry of heterocycles with active moieties in the synthesis of heterocyclic compounds with varying biological activities and their impact in the fields of pharmaceutical and medicinal chemistry.[47–61] The literature survey deals with the scope of synthetic approaches applied for the synthesis of β-aminoketones and ascertaining their reactivity against reactions with diverse reagents.

2. Literature patents

The literature reports indicate that many patents focused on the synthesis and reactivity of β-aminoketones, for instance, asymmetric hydrogenation,[62] synthesis of amides,[63] and chelation of metals.[64] The synthesis of β-aminoketones has attracted attention from researchers in the field of organic synthesis, in which many reports highlighted the synthesis of β-amino alcohols,[65] N-mono-substituted amino alcohols,[66] β-aminoketones, and β-amino alcohols with optically active characters,[67–70] and catalytic synthesis of β-aminoketones.[71,72] Subsequently, the work on this moiety was extended to include the assessment of the biological features of β-aminoketones as anti-diabetic agents.[73]

3. Synthetic approaches

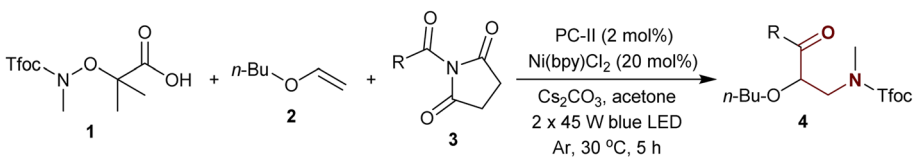
3.1. Multicomponent synthesis

Jiang *et al.*[74] designated three-component-type coupling reactions to synthesize a series of β-aminoketones **4**. Specifically, the reaction of N-protected acid **1** with vinyl ether **2** and acyl succinimides **3** in acetone containing cesium carbonate under catalytic conditions gave the desired β-aminoketones **4** in moderate to low yields (37–61%) (Scheme 1). In these reactions, succinimides **3** act as electrophiles with N–C bond cleavage, and compound **1** acts as a radical source after N–O bond cleavage. The reactions were deliberated as the aminoacylation of the alkene-ether type as a route for the synthesis of β-aminoketones.

Hadizadeh *et al.*[75] developed the synthesis of β-aminoketones **7** under 2-(sulfamoyloxy)ethyl hydrogen sulfate catalytic conditions. Therefore, the reactions of aldehydes **5** with ketones **6** in the enol form and acetonitrile in the presence of acetyl chloride afforded a series of β-aminoketones **7** in 85–95% yield (Scheme 2). This protocol is proficient to prepare these compounds without the formation of by-products and the yield of the products depends, in general, on the type of substituents linked to the aldehyde moiety using a recyclable catalyst. The catalyst activated the aldehyde carbonyl group for interaction with acetonitrile and acetyl chloride to generate intermediates **A-1**. Next, the interactions of the generated intermediates **A-1** with the corresponding enolized ketones generated intermediates **B-1**, as described in the proposed reaction mechanism sequence.

3.2. Catalyzed Mannich reactions

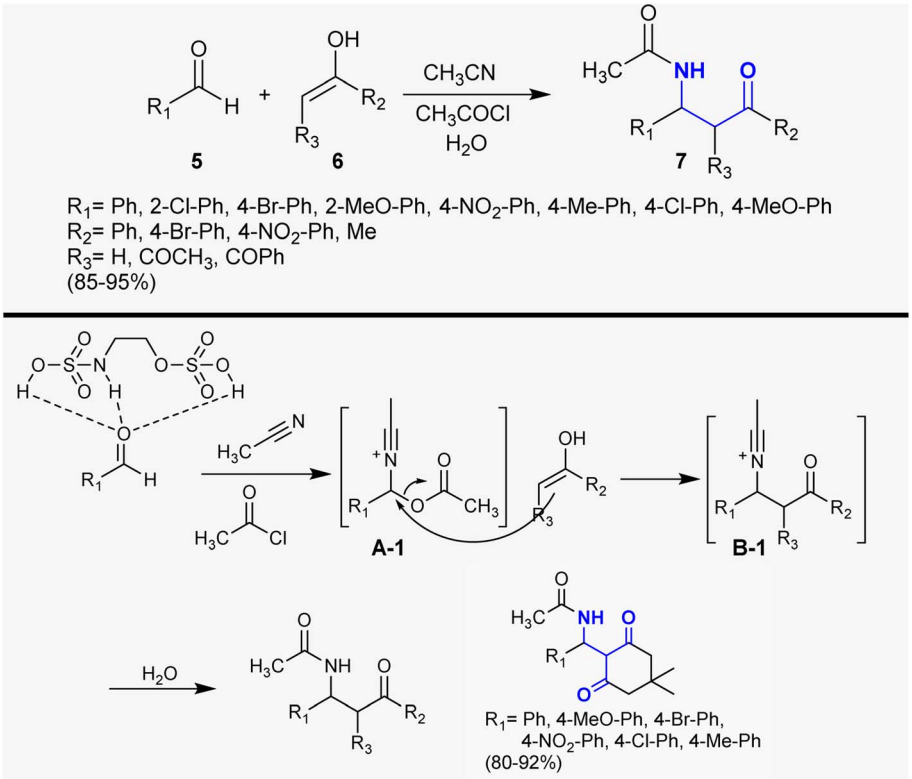
The Mannich reaction was adopted to prepare the asymmetric β-aminoketone series **8a–j** in the presence of an organocatalyst, *e.g.*, aryl pyrrolidine-carboxamide. Predominantly, the Mannich reaction of arylamines with aryl aldehydes and acetophenones in acetonitrile containing a catalyst gave the desired asymmetric β-aminoketone series **8a–j**. The products obtained by this method possessed excellent properties (82–90%) depending on the nature of their substituents, which was preferable to have electron-withdrawing characters to achieve enantioselective β-



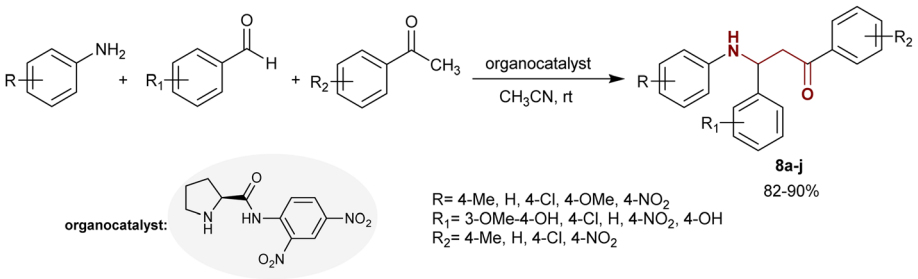
R= *n*-Pr, -CH_2CH_2Ph, cyclohexyl, -$CH_2CH_2CO_2Me$, Ph, 4-Cl-Ph, -$(CH_2)_8CH{=}CH_2$

(37-61%)

Scheme 1 Aminoacylation of 1-(vinyloxy)butane.



Scheme 2 Synthesis of β-aminoketones through multicomponent reactions.

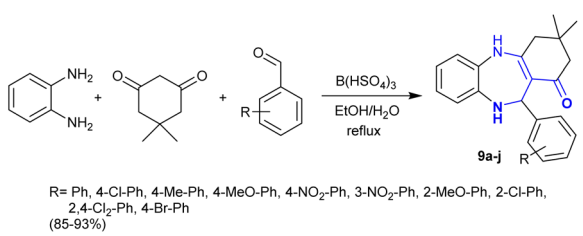


Scheme 3 Synthesis of β-aminoketones through Mannich reaction.

aminoketones with the best yields under mild reaction conditions (Scheme 3).[76]

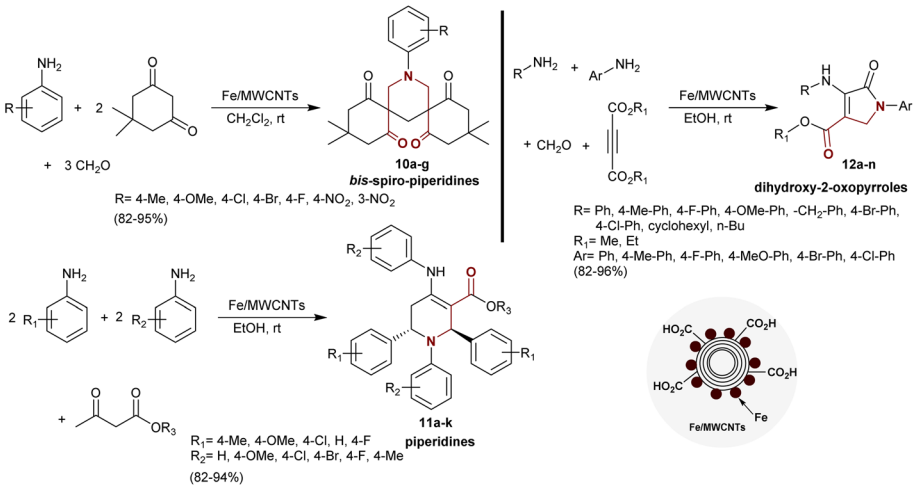
Heterocycles with a benzodiazepine skeleton are a privileged class in the fields of medicinal and applied chemistry. Benzodiazepines are safe and effective drugs for the treatment of anxiety, insomnia, agitation, seizures, muscle spasms, *etc.*[77–80] Thus, Karimi-Jaberi *et al.*[81] developed the synthesis of hexahydro-1*H*-dibenzo[1,4] diazepinones **9a–j** through one-pot multicomponent reactions utilizing a green approach. In this sequence, *o*-phenylenediamine reacted with dimedone and aryl aldehydes in a one-pot three-component procedure under reflux and catalytic conditions to afford the desired benzodiazepines **9** (Scheme 4). The use of boron hydrogen sulfate as an efficient catalyst in an ethanol/water mixture improved the yields and the rate of the reactions.

Sharghi *et al.*[82] developed a method for the synthesis of *bis*-spiro-piperidines **10a–g**, piperidines **11a–k**, and dihydroxy-2-oxopyrroles **12a–n** under nano catalytic conditions. Thus, multicomponent reactions of dimedone with aryl amines, and formaldehyde using Fe/MWCNTs as an effective and recyclable

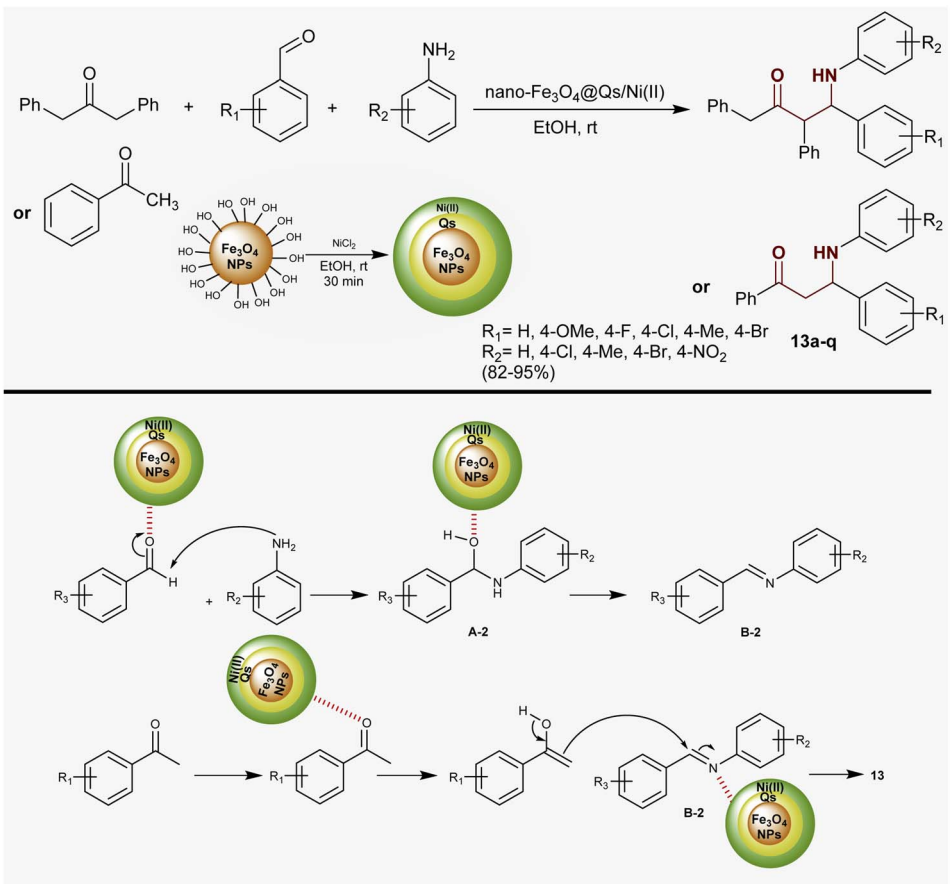


Scheme 4 Synthesis of benzo[1,4] diazepinones.

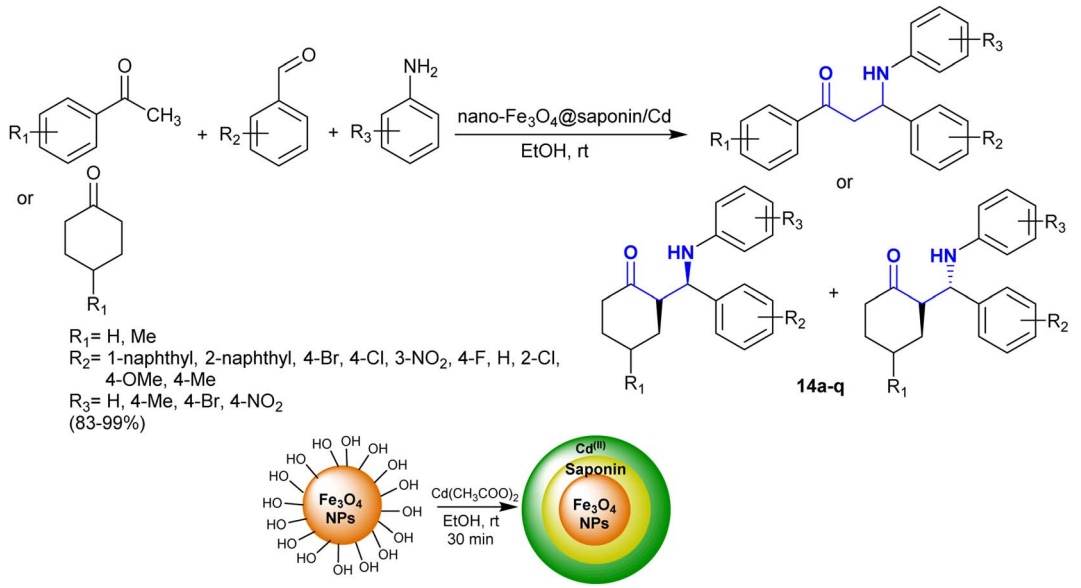
nano-catalyst gave the respective *bis*-spiro-piperidines **10a–g** in excellent yields (82–95%). Also, multicomponent one-pot reactions of aryl amines (2 equiv.) with other aryl amines (2 equiv.) and β-ketoesters afforded the desired piperidines **11a–k.** The previous reactions could be also applied using the same aryl amine with four equivalents in the reactions with β-ketoesters. Four-component reactions of alkyl-, aryl amines with formaldehyde, and alkyne diesters under the same reaction conditions gave the corresponding dihydroxy-2-oxopyrroles **12a–n.** The yields of the products prepared from this protocol were excellent and the produced compounds with β-aminoketone moieties were simply separated (Scheme 5).



Scheme 5 Synthesis of β-aminoketones under nano-catalytic conditions.



Scheme 6 Synthetic route and proposed mechanism for the formation of β-aminoketones.



Scheme 7 Synthesis of β-aminoketones under catalytic conditions.

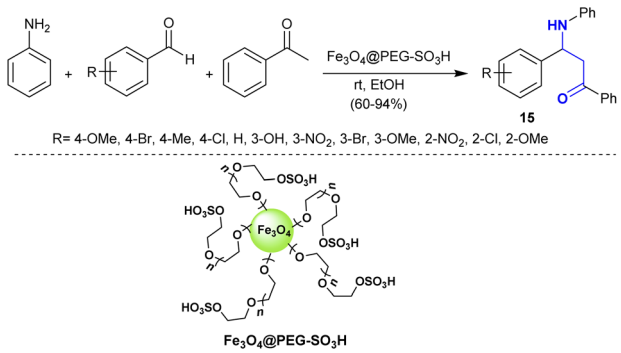
Heidarpour *et al.*[83] developed a route for the synthesis of two series of β-aminoketones in remarkable yields through Mannich reactions under catalytic conditions. Therefore, multi-component one-pot reactions of aryl aldehydes and amines with aryl/alkyl ketones such as acetophenone and 1,3-diphenylpropan-2-one catalyzed by nanomagnetic Fe_3O_4@Qs/Ni(II) in ethanol at room temperature yielded the anticipated β-aminoketones **13a–q** (82–95%). In this method, the nano-catalyst was prepared and utilized with ease of separation and recyclability with good efficiency. The nano-catalyst activated the nucleophilic attack of amino groups at the aldehydic carbonyl group of aryl aldehyde to generate intermediates **A-2**. Condensation of **A-2** formed intermediates **B-2**, which reacted with ketones after enolization by the action of the nano-catalyst to give the target products (Scheme 6).

Kiani *et al.*[84] developed the synthesis of Fe_3O_4@saponin/Cd as an efficient magnetic nanocatalyst for the synthesis of β-aminoketones with exceptional yields (83–99%) and reduced reaction time. In this route, the nanocatalyst is recyclable and prepared by the treatment of nano-Fe_3O_4@saponin with cadmium acetate. Thus, one-pot three-component reactions of aryl or cycloalkyl ketones with aryl aldehydes and aryl amines in ethanol at room temperature under catalytic conditions yielded the respective β-aminoketones **14a–q** (Scheme 7).[85–92] The sequence of these reactions is related to Mannich-type reactions in a green protocol. The nanocatalyst activated the aldehyde ketone to nucleophilic attack by the amine group, and consequently enabled the enolization of the aryl or cycloalkyl ketones in the condensation.

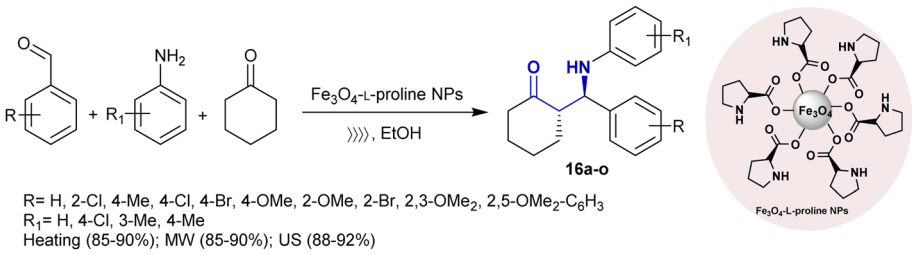
Maleki *et al.*[93] developed the synthesis of β-aminoketones through Mannich reaction under nano catalytic conditions. Consequently, three-component one-pot reactions of aryl amines with aryl aldehydes, and acetophenone catalyzed by Fe_3O_4@PEG-SO_3H yielded the target β-aminoketone compounds **15** (Scheme 8). This method involved the co-precipitation technique and characterization of the nano-catalyst for amended reaction yields and increased rates. This is a green technique given that the reactions were performed in ethanol at room temperature and the nanocatalyst is recyclable with high efficiency and easy preparation.

Safaei-Ghomi *et al.*[94] developed the asymmetric synthesis of β-aminoketones **16a–o** under magnetic nanoparticles, conventional, ultrasonic, and microwave irradiation conditions. Subsequently, the Fe_3O_4-L-proline nanoparticles catalyzed the Mannich reactions of aryl aldehydes with aryl amines and cyclohexanone to produce the preferred β-aminoketones with improved reaction yields under ultrasonic conditions than other conventional or microwave irradiation conditions (Scheme 9). The probable mechanism for the asymmetric Mannich reaction was previously reported using the same nanocatalyst under altered reaction conditions.[95]

Mannich reactions of active methylene, *i.e.*, cyclohexanone with primary amines, *i.e.*, aniline and aldehydes, in water as an aqueous medium at room temperature yielded the desired β-



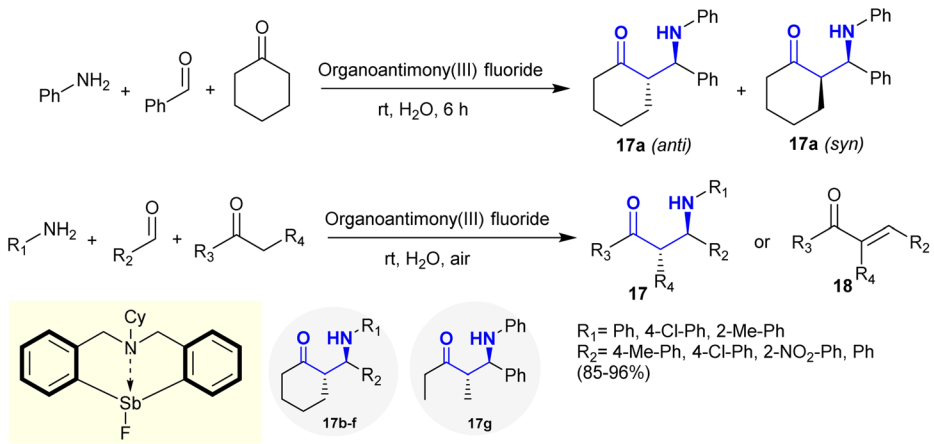
Scheme 8 Nanocatalytic synthesis of β-aminoketones.



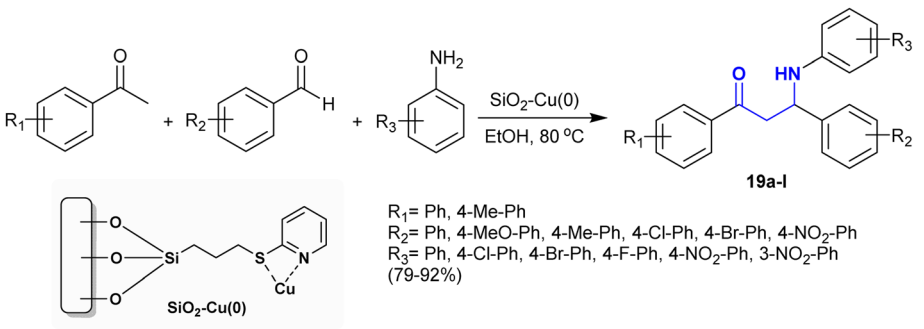
Scheme 9 Mannich reaction for the catalyzed synthesis of β-aminoketones.

aminoketones **17**. The reaction is stereoselective under catalytic conditions using organoantimony(III) halides as a Lewis acid catalyst tolerant to water with the possible formation of *anti* and *syn* products. The best yield in the preparation of compound **17** was accomplished using organoantimony(III) fluoride with 98% yield (*anti*/*syn*: 98/2). The Sb–F moiety acts as a hydrogen bond acceptor in this reaction through the proposed catalytic pathway with the generation of a six-membered cyclic transition state. A series of β-aminoketones **17** was synthesized under the optimized conditions by Mannich-type reactions, which involved the reactions of amines with aldehydes and active methylene components. Cross condensation reactions may take place in the case of aliphatic amines with the formation of condensation products **18** in moderate to good yields (Scheme 10).[96]

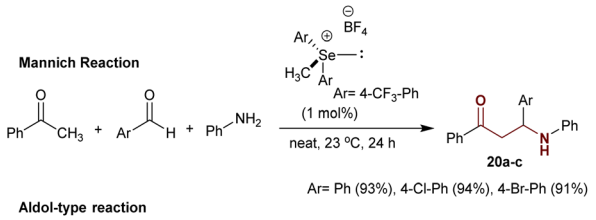
The synthesis of β-aminoketones was investigated by Gupta *et al.*[97] applying a Mannich reaction under catalytic conditions. In this route, the Mannich reactions were catalyzed efficiently by catalytic silica-functionalized copper(0) nanoparticles. This procedure involved reactions of acetophenones with aryl aldehydes and aryl amines under the optimized conditions to afford the desired products of β-aminoketones **19** (Scheme 11). Heating at 80 °C was necessary for improved the reaction rate. The generation of product **19** was accomplished through C–C and C–N bond formation. The catalyst was recyclable for six runs of



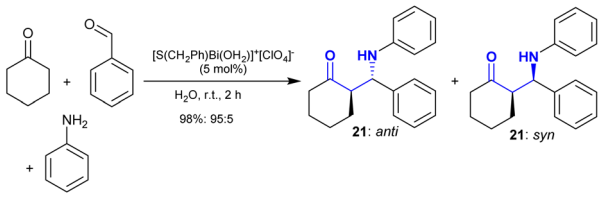
Scheme 10 Mannich reactions under Lewis acid catalytic conditions.



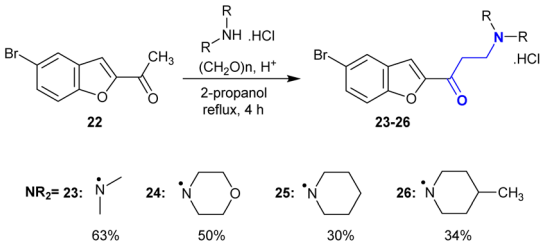
Scheme 11 Mannich reactions catalyzed by catalytic copper nanocluster.



Scheme 12 Mannich reaction for the synthesis of β-aminoketones.



Scheme 13 Stereoselective Mannich-type reaction.



Scheme 14 Synthesis of Mannich bases.

reusability and proficiently produced the products with excellent yields.

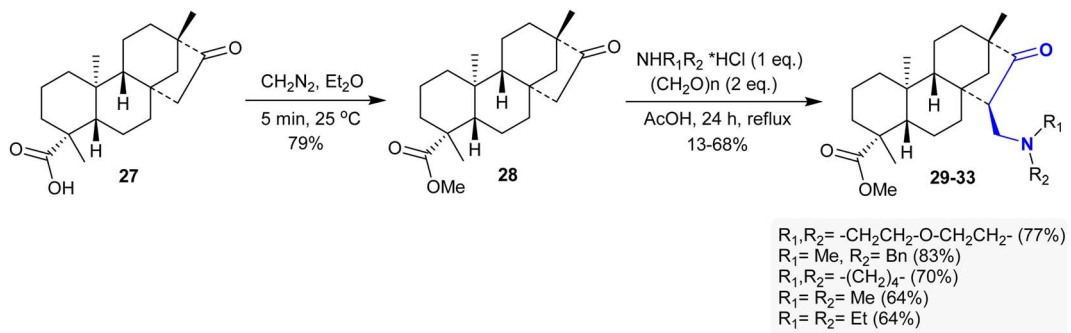
Precisely, the solvent-free reaction of acetophenone with aryl aldehydes and aniline under efficient catalytic conditions of chalcogenide (1 mol%), which was "prepared from diaryl selenium reaction with methyl iodide in the presence of $AgBF_4$", gave the anticipated β-aminoketones **20a–c** in exceptional yields of 91–94%.[98] In this case, the multicomponent reactions proceeded through a Mannich-type reaction (Scheme 12).[99]

Iwanejko *et al.*[100] reviewed the green approaches for the synthesis of β-aminoketones through the Mannich reaction. Particularly, Qui *et al.*[101] recently developed the synthesis of β-aminoketones **21** through a green protocol under catalytic conditions. Therefore, the three-component one-pot reaction of benzaldehyde with cyclohexanone and aniline in water gave the desired Mannich adducts. The reaction is stereoselective with the formation of *anti*: *syn* adducts with (95 : 5) in a brilliant yield of 98% (Scheme 13). The Brønsted acid-surfactant enables the dispersion of the organic reactants in water to improve the product yield and reaction rate with high efficiency. The literature reports are rich with the utility of Brønsted acid-surfactants with free ionic liquids as catalysts, *e.g.*, (BASCILs), ([TMBSA]HSO_4), and ([DDPA]HSO_4), in addition to quaternary ammonium salt surfactants, and BASCILs with Tos^- and $CH_3SO_3^-$ organic ions.[90,92,102,103]

3.3. Non-catalyzed Mannich reactions

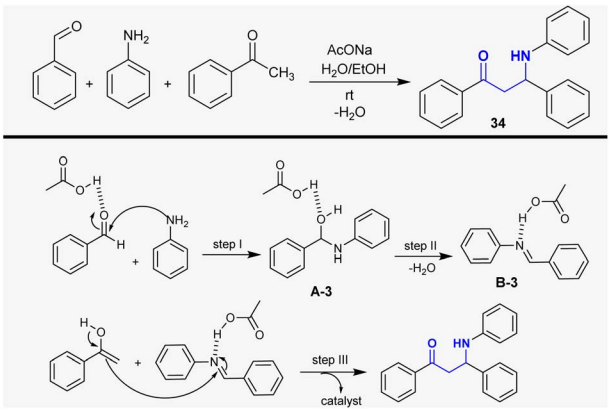
In another route, 1-(5-bromobenzofuran-2-yl)ethan-1-one (**22**) was subjected to Mannich reactions with hydrochloride salts of secondary amines and formaldehyde to give Mannich bases **23–26** (Scheme 14). The reactions were processed in *iso*-propanol under reflux conditions. The amine salts were prepared *in situ* by the addition of a catalytic amount of hydrochloric acid. Mannich base **23** produced a better yield (63%) through the aminomethylation step of compound **22** by reaction with dimethyl amine. This procedure efficiently produced the products after a short time. The products tended to decompose in solutions of water and DMSO with the loss of the amine group, which was the opposite for their solid state.[104]

The methyl ester of isosteviol **28** was efficiently synthesized by treatment with diazomethane in diethyl ether, as reported by Coates *et al.*[105] Particularly, the Mannich reaction of compound **28** with diverse secondary amine hydrochloride salts and paraformaldehyde in glacial AcOH yielded a series of β-aminoketones **29–33** in 64–83% yield (Scheme 15) following the method of Szakonyi *et al.*[106] The products were stereo-selectively prepared with the formation of a diastereoisomer that has a structured 7*R*-configuration at the generated C15 stereocenter. The stereoselectivity in these reactions depended on the nature of the reacted amine salts. The cytotoxic results of β-aminoketones **29–33** demonstrated moderate to weak cytotoxic behaviors on A2780, SiHa, HeLa, MCF-7, and MDA-MB-231 human tumor cell lines (nearly IC_{50}= >20 μM).[107]



Scheme 15 Synthesis of β-aminoketones **29–33** *via* Mannich condensation.

Habibi-Khorassani *et al.*[108] developed the synthesis of β-aminoketone **34** through the Mannich reaction of benzaldehyde with acetophenone and aniline in a mixture of water and ethanol-containing sodium acetate. The kinetic parameters were studied for this reaction under catalytic conditions of sodium acetate. The reaction is second order based on its rate constant. The activation of the carbonyl group of the aldehyde proceeded by the action of the catalyst to initiate the reaction by amino group attack at the carbonyl group in the first step. Next, the condensation step was accomplished to give the Schiff base, which reacted with acetophenone to generate the β-aminoketone (Scheme 16).



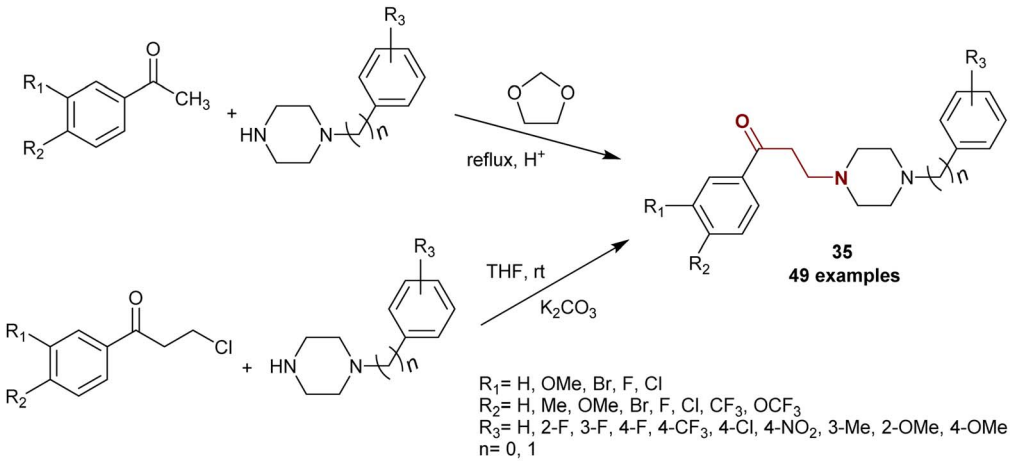
Scheme 16 Proposed mechanism for the synthesis of β-aminoketone through the Mannich reaction.

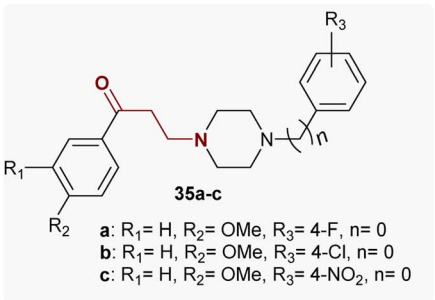
3.4. One-pot Mannich reaction

Martin-Escolano *et al.*[109] reported an efficient, inexpensive, and fast technique for the preparation of a series of β-aminoketones. Thus, the synthesis of β-aminoketones **35** was accomplished by Mannich reactions of acetophenones with piperazines in the presence of 1,3-dioxolane as a source of formaldehyde under reflux conditions or by condensation of piperazines with β-halo ketones in THF containing potassium carbonate at room temperature (Scheme 17). The mechanism in the second route proceeded by aliphatic nucleophilic substitution for the investigated β-halo ketones by the piperazines. Most of these β-aminoketones **35** were prepared by Mannich reaction[110] or by the method reported by Martinez-Esparza *et al.*[111] to prepare the analogous product of β-aminoketone ($R_1 = R_2 = H$, $R_3 = 4$-F, $n = 0$). Compounds **35a**, **35b**, and **35c** revealed potent cytotoxic activities against epimastigote-type *Trypanosoma cruzi* strains with selective potency, as shown in Scheme 1.

3.5. The addition to imines and unsaturated compounds

Mazzeo *et al.*[112] utilized the enolizable feature of 1,3-dicarbonyl analogs **37** in an effortless reaction sequence with trifluoroacetaldimines **36** as effective electrophilic types. The different selectivity of the Mannich-type adducts **38a–e** prepared by reactions of (*S*)–*N*-*tert*-butane-sulfinyl-trifluoro-acetaldimine

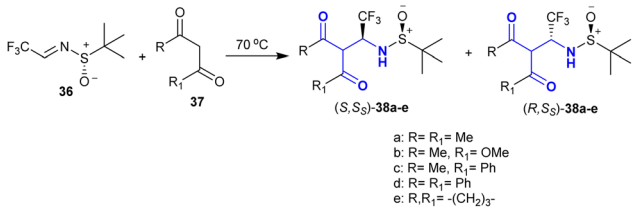




Cytotoxicity for Compounds on the Epimastigote Form of *Trypanosoma cruzi* Strains

T. cruzi Arequipa strain: IC_{50}; **a**: 1.4±0.1; **b**: 9.5 ± 0.8; **c**: 31.6 ± 0.3 μM
T. cruzi SN3 strain: IC_{50}; **a**: 2.0 ± 0.1; **b**: 6.3 ± 0.5; **c**: 22.0 ± 0.2 μM
T. cruzi Tulahuen strain: IC_{50}; **a**: 1.8 ± 0.2; **b**: 7.3 ± 0.6; **c**: 37.4 ± 0.4 μM
Toxicity IC_{50}; **a**: 55.0 ± 4.9; **b**: 300.0 ± 24.1; **c**: 587.2 ± 37.6 μM

Scheme 17 Routes for the synthesis of β-aminoketones through one-step reaction.



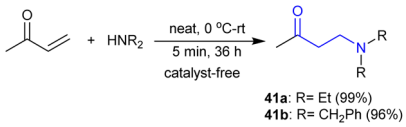
Scheme 18 Stereoselective synthesis of β-aminoketones.

with 1,3-dicarbonyl analogs depended on the reaction conditions and the structural nature of the reacted 1,3-dicarbonyl analogs. The reactions progressed under solvent-free conditions with tremendous yields and stereoselectivity. These reactions also have high synthetic potential for the preparation of chiral β-aminoketones. The same reactions may also proceed under DBU basic catalytic conditions in dichloromethane at a lower temperature but the yields of the products may be reduced, and also the stereoselectivity may be opposite to the free-solvent conditions for the same analog. The steric factor of the substituents completely affected the stereochemical of the obtained product (Scheme 18).

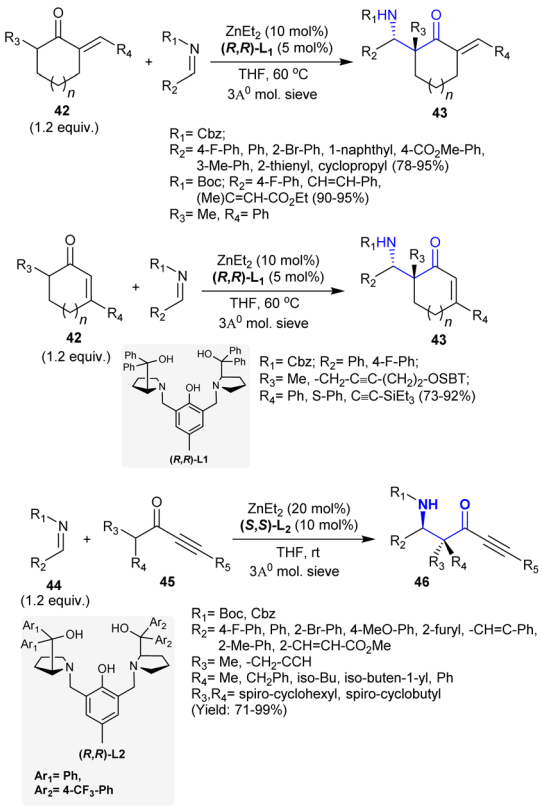
Rassukana *et al.*[113] developed the synthesis of optically active *O*,*O*-dimethyl α-iminotrifluoro-ethyl-phosphonates **40**. Thus, the reaction of NH-iminophosphonate (+)-**39** with acetone under proline catalytic conditions enabled the synthesis of optically active β-aminoketones with a phosphonate moiety and the anticipated phosphonic acids. The reaction is diastereoselective reduction, leading to the preparation of chiral synthons under proline-catalyzed conditions (Scheme 19).

Fischer *et al.*[114] reported an efficient method for the synthesis of β-aminoketones **41a** and **b** in exceptional yields through the addition of secondary amines to α,β-unsaturated carbonyl compounds. This process involved the addition of an alkene double bond with C–N bond formation under catalyst-free conditions (Scheme 20).

Owing to the biologically privileged impact of the β-aminoketone core, which is located in the basic skeleton of common biologically active alkaloids, Trost *et al.*[115] developed the enantioselective synthesis of β-aminoketones **43** and **46** through Zn-ProPhenol-supported Mannich reactions. Thus, the reactions of *N*-carbamoyl imines with unsaturated ketones gave either cyclic or acyclic β-aminoketones **43** with quaternary stereocenters (Scheme 21). Significantly, the unsaturation presented through the nucleophile provided a convenient platform for structural variations. This method is a chemoselective and diastereoselective synthetic route for the synthesis of the target products with the aid of sustainable substrates and low catalyst



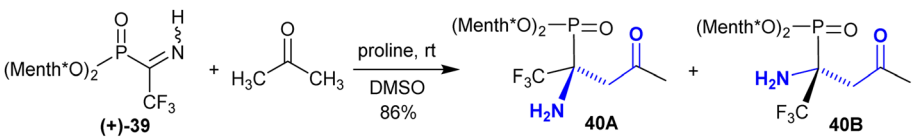
Scheme 20 Synthesis of β-aminoketones by addition to unsaturated ketones.



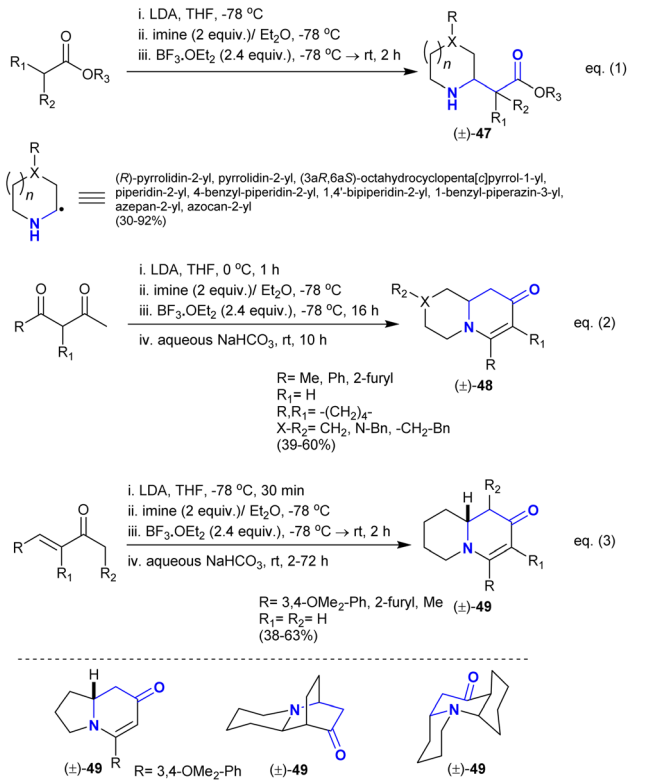
Scheme 21 Catalytic synthesis of cyclic and acyclic β-aminoketones.

packing, which does not affect its competence. Concisely, Mannich adducts including quaternary stereogenic centers were proficiently synthesized under Zn-ProPhenol catalytic conditions from reactions of exocyclic enones **42** as potential pronucleophiles with imines. Correspondingly, the reactions of imines **44** with alkynyl ketones **45** under catalytic conditions yielded the acyclic β-aminoketones.

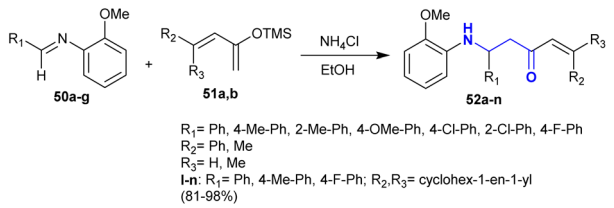
Kim *et al.*[116] reported the α-alkylation of alicyclic imines with the nucleophilic enolate esters to synthesize a series of mono- and poly-cyclic β-aminoketones **47** with high diastereoselectivity (eqn. (1)). This method provided the modification



Scheme 19 Reaction of amino phosphonate (+)-**1** with acetone.



Scheme 22 Catalytic synthesis of piperidines, pyridopyrazinones, and quinolizinones.



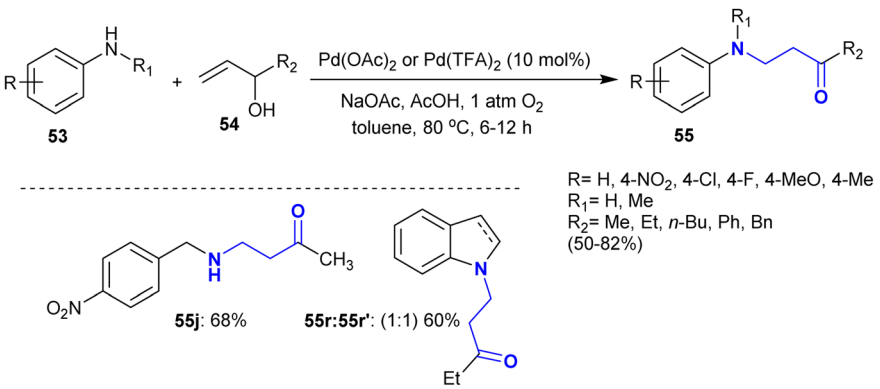
Scheme 23 Synthesis of β-aminoketones *via* Mannich-type reactions.

of simple amines through C–H bond functionalization (Scheme 22). It also assisted the synthesis of natural target products such as (±)-myrtine. The esters were firstly treated with lithium diisopropylamide as a strong base before the addition of imines. The catalytic boron trifluoride etherate was the source of boron trifluoride, which acted as a Lewis acid catalyst to increase the nucleophilicity of esters. Alternatively, the use of 1,3-dicarbonyl compounds "dianions" as substrates instead of enolate esters tended to result in the preparation of a series of enaminones "pyridopyrazinones and quinolizinones" **48** (eqn. (2)). In this route, the base treatment supported the intramolecular condensation after the addition step with the annulation of the products. Also, the reactions of α,β-unsaturated ketones with *in situ* prepared imines under the same conditions yielded the bicyclic quinolizinones **49** (eqn. (3)). The mechanism of these reactions was proposed as the basic catalyst supported the nucleophilic addition and intramolecular heteroconjugation addition.

Fukumoto *et al.*[117] reported a green protocol for the synthesis of Mannich-type products. Thus, the reactions of *N*-(2-methoxyphenyl)-1-arylmethanimine **50** with ((butadienyl)oxy) trimethylsilane **51** in the presence of ammonium chloride gave the respective β-aminoketones **52** (Scheme 23). The reactions are stereoselective for the formation of products **52** in excellent yield (81–98%). The mechanism of these reactions is projected as a Mannich-type reaction that involved the formation of β-aminoketones instead of a cyclization step followed by ring cleavage processes.

Kumar *et al.*[118] developed the synthesis of cyclic β-aminoketones **55** through an exceptional and convenient procedure. Therefore, the oxidative coupling supported by catalytic palladium acetate of allyl alcohol derivatives **54** with aryl amines **53** gave moderate to worthy yields of the desired β-aminoketones **55** (Scheme 24). In these reactions, the N-alkylation is more favorite than the N-allylation process, in which the conjugate addition is preferable to the allylic amination as the suggested reaction mechanism.

Many studies have focused on the preparation of fluorocarbon compounds, especially those containing trifluoromethyl, mono fluoro, and difluoromethyl groups. The advantage of the difluoromethylene group is that it is not a terminal group, and therefore, it is difficult to apply modern strategies from the last stage of fluoridation easily. Stunningly important compounds that contain a difluoromethylene group



Scheme 24 Conjugate addition of the aryl amines to allyl alcohols.

are difluoro-β-amino acid and α,α-difluoro-β-amino carbonyl groups.[119] These basic skeletons were found to constitute the chemical composition of some vital compounds applied as drugs[120,121] or inhibitors of enzyme activity such as rhodopeptin, docetaxel analogs, human plasma renin, and HIV-1 protease inhibitors (Fig. 3).[122–124]

Accordingly, Nguyen *et al.*[119] developed the synthesis of β-aminoketones incorporating a difluoromethylene group using magnesium iodide and organic bases. The addition reactions of fluorinated *gem*-diol **56** "difluoroenolates" as extremely α-fluorinated *gem*-diols with "unactivated imines" in THF containing triethylamine and lithium bromide yielded the desired α,α-difluoro-β-aminoketones **57–59**. The reactions of fluorinated *gem*-diol **56**, and **60–64** with imines "*N*-benzylidenebenzylamine" in THF containing magnesium iodide yielded the α,α-difluoro-β-aminoketones **65**, and **66–70**. The reaction of diol **56** with imine in the presence of lithium bromide or lithium chloride failed to provide product **65**. Also, the addition of fluorinated *gem*-diol **56** to imines in the presence of magnesium iodide gave the desired α,α-difluoro-β-aminoketones **71–77**

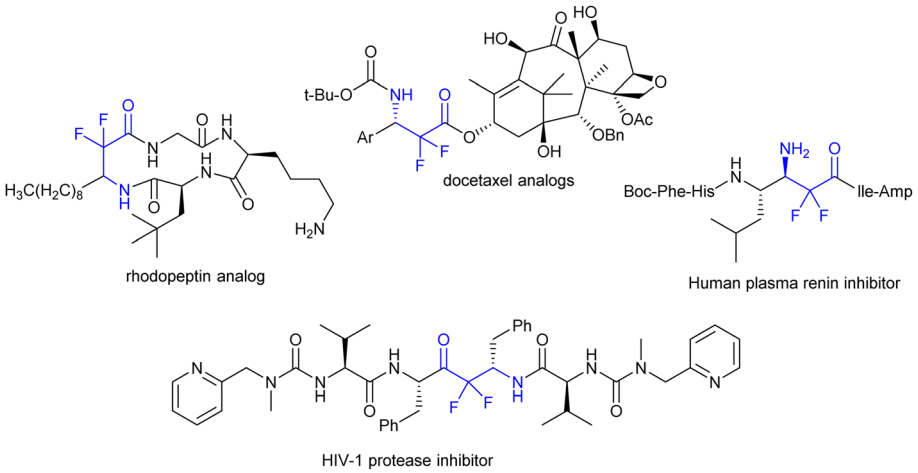
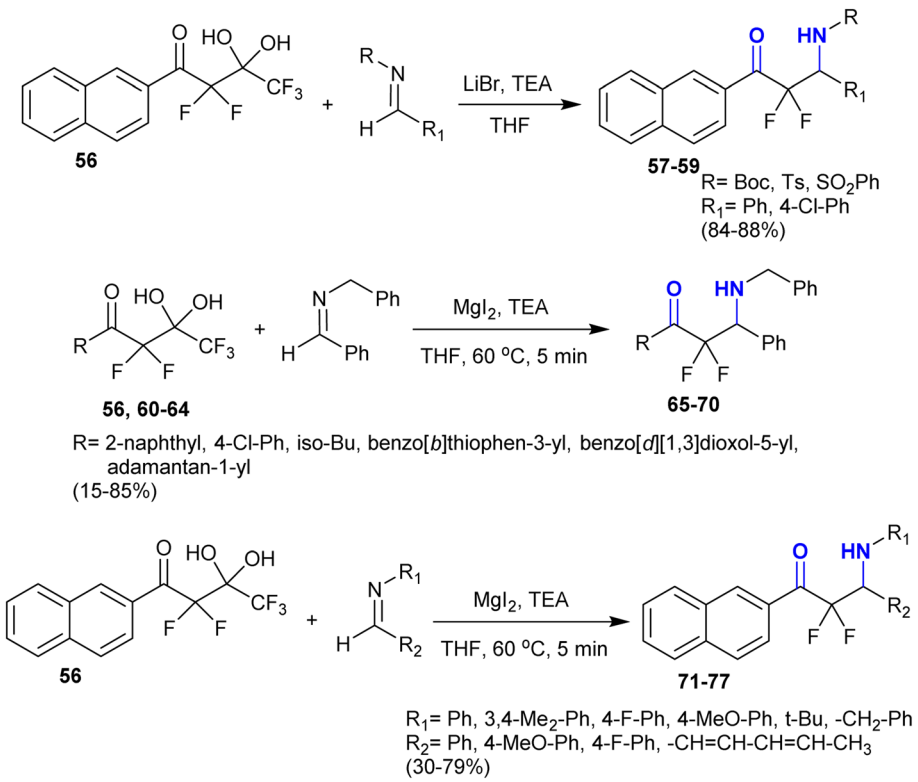


Fig. 3 Examples of privileged bioactive structures of compounds incorporating a difluoromethylene group.



Scheme 25 Synthesis of α,α-difluoro-β-aminoketones.

(Scheme 25) under mild conditions through the iminoaldol reaction model. This protocol provided the challenging preparation of the products without the need for the protection of groups or activation of the imines.

This strategy was extended to the addition reactions of fluorinated *gem*-diol **56** "difluoroenolates" to 5-bromo-3,4-dihydroisoquinoline **78** under the same previous conditions using magnesium iodide to prepare 2,2-difluoro-1-(naphthalenyl)ethanone **79** with excellent yield. Alkylation of **79** with vinyl trifluoroborate[125] through Suzuki–Miyaura cross-coupling reaction in the presence of palladium(II) chloride, triphenyl phosphine, and cesium carbonate afforded the corresponding tetrahydroisoquinoline **80** in moderate yield (40%) (Scheme 26). This protocol verified that the structural divergence of tetrahydroquinolines can be rapidly constructed.[119]

3.6. Condensation reactions

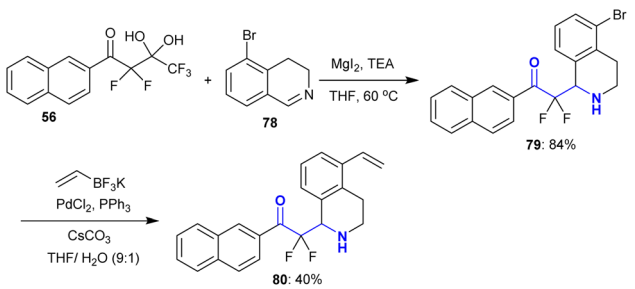
Treatment of 1,3-dicarbonyl compounds with cyclic *N*-acyl ketimines under Brønsted acid-catalyzed conditions in *p*-xylene afforded the anticipated 3-oxoisoindolines **81** in 58–98% yield (Scheme 27). The reactions progressed to yield the products by asymmetric Mannich-type addition type. Also, the products bearing stereocenter chiral carbon were obtained with exceptional yield (up to 98%) and reasonable to excessive enantioselectivity (up to 95% ee). The suggested mechanism of this reaction type involved dehydration of the desired 3-hydroxyisoindolinone to *in situ* generate *N*-acyl ketimines. Subsequent dual activations were attained for *N*-acyl ketimine ions in the transition state together with 1,3-dicarbonyl compounds by the influence of the bifunctional catalytic phosphoric acid. Lastly, nucleophilic attacks took place on the *re*-face of the planar ketimine through the construction of ten-membered transition-states to furnish oxoisoindolines with the (*S*) configuration.[126]

A series of β-aminoketones **82** was efficiently synthesized by Miao *et al.*[127] through a catalytic coupling of aryl amines with β-hydroxyketones (Scheme 28). Hence, the reactions were catalyzed by iodine at room temperature, providing a facile procedure for the synthesis of the target compounds with relatively good yields based on the structural nature of the substituents. The iodine acts as an oxidant and metallic catalyst, enabling the oxidation of the hydroxyl group to the respective aldehyde with the release of HI molecules through the condensation with the amino group. This reaction is selective without the involvement of aza-Michael addition. The final step is the formation of the products through the addition of the H_2 molecule "generated by the decomposition of HI to H_2 and I_2 owing to the intensive reducing impact of HI" to the C=N bond of the latter-formed intermediate.

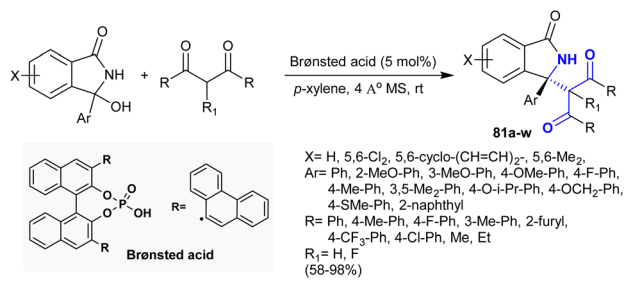
3.7. Synthesis of piperidines

A successful piperidine ring cyclization was achieved by a Mannich condensation reaction from raspberry ketone methyl ether, as demonstrated by Shanthi *et al.*[128] Thus, piperidinone with cyclic β-aminoketone moieties **83** was synthesized by the multicomponent Mannich reaction of methyl ether of raspberry ketone with aryl aldehydes, and ammonium acetate under reflux and catalyst-free conditions (Scheme 29). The stereochemistry of the constructed piperidinones was verified by the perceived coupling constants, in which the chair configuration with the substituents preferred the equatorial orientation, as estimated by 2D-NMR.

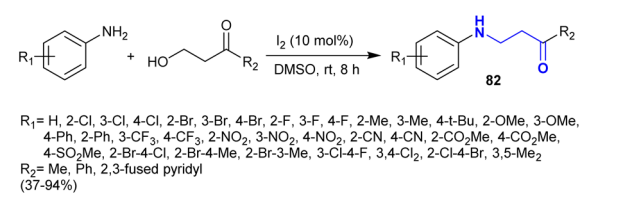
The synthesis of stereoselective bicyclic aza-sugar analogs was recently explored by Yuan *et al.*[129] Subsequently, they[130] interestingly reported a stereoselective synthetic route for the preparation of hydroxy-piperidines and imino-sugar *C*-glycoside



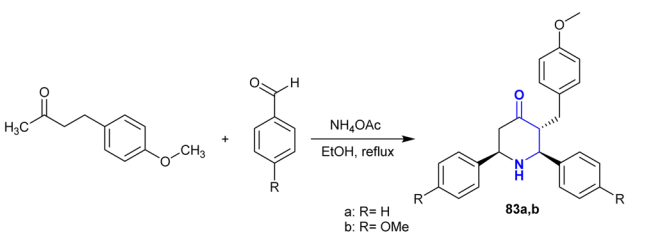
Scheme 26 Synthesis and alkylation of α,α-difluoro-β-aminoketones.



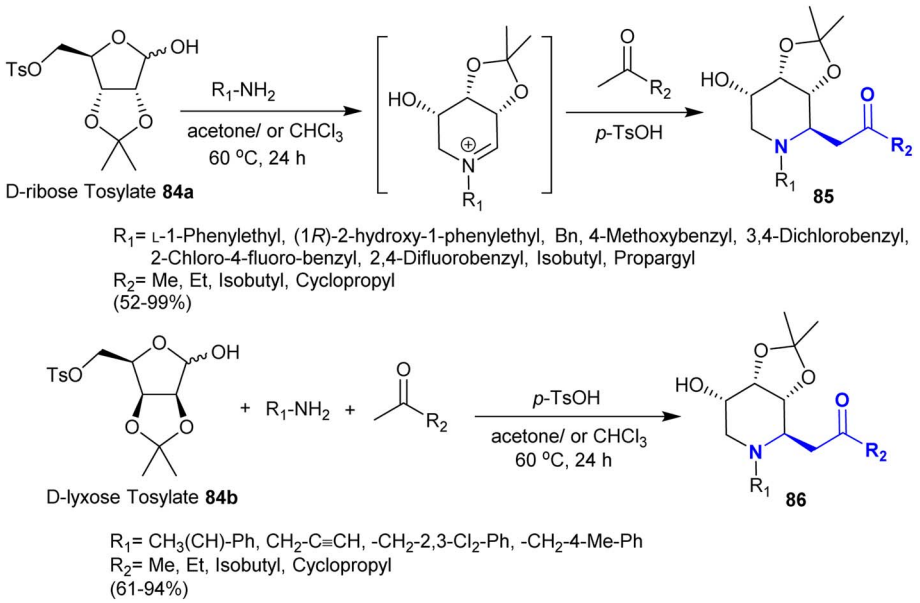
Scheme 27 Synthesis of β-aminoketones through Mannich-type addition.



Scheme 28 Coupling of amines with β-hydroxyketones.



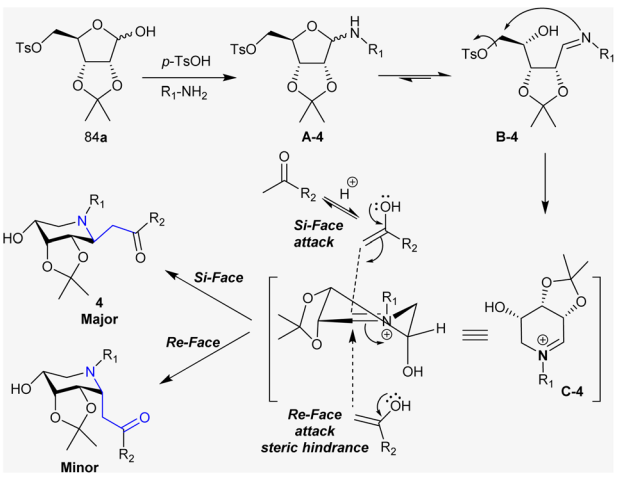
Scheme 29 Mannich reaction for the synthesis of piperidinone compounds.



Scheme 30 Synthesis of β-aminoketones under acid-catalyzed conditions.

analogs. The products in this route are potent glycosidase inhibitors prepared in exceptional yields. Consequently, Mannich reaction of D-ribose- and D-lyxose tosylates **84a** and **84b**, each with substituted amines and ketones in a one-pot procedure yielded the target compounds **85** and **86**, respectively (Scheme 30). The reactions of this type proceeded under *p*-toluenesulfonic acid as a convenient catalyst in acetone for improved yields and reinforced reaction rate.

Under acid-catalyzed conditions, the condensation of amines with D-ribose- and D-lyxose tosylates generated the cyclic hemiaminal (**A-4**). The hemiaminal ring cleavage in intermediate **A-4** generated the imine intermediate **B-4**. Thus, intramolecular nucleophilic substitution attack of the NH group at the C-OTs carbon with the good leaving group character of the OTs group generated the cyclic iminium ion in the form of intermediate **C-4**. The acid catalyst promoted the enolization of the ketone, and hence attack of the α-carbon of the iminium ion carbon (intermediate **C-4**). Accordingly, the two possible products are known as *Si*-face and *Re*-face with the majority of *Si*-face products owing to the steric hindrance factor of the *iso*-propylidene group (Scheme 31).[130]



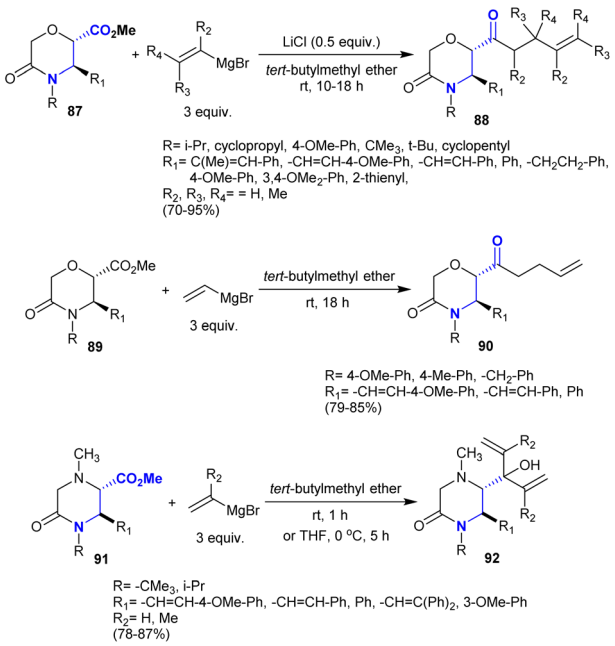
Scheme 31 Projected mechanism for the catalyzed synthesis of β-aminoketones.

3.8. Synthesis of morpholinones and piperazinones

The direct synthesis of β-aminoketones from amides has been applied previously through sequential nucleophilic substitution at the carbonyl group by the reacted Grignard reagent such as vinyl magnesium bromide followed by Michael reaction.[131] Recently, Farah *et al.*[132] also reported the direct synthesis of β-aminoketones **88** from the addition of alkenyl Grignard reagents to methyl (2*S*,3*R*)-3,4-disubstituted-5-oxomorpholine-2-carboxylates "β-aminoketoesters" **87**. The reactions progressed with the addition of lithium chloride in the absence of a transition metal catalyst to produce the desired lactam-bearing homo-allylic ketones. The products were achieved through a regioselective synthetic route with the generation of a new stereocenter carbon but it surprisingly maintained diastereoselectivity. A similar sequence was employed in the reactions of 5-oxomorpholine-2-carboxylates **89** and methyl (2*S*,3*R*)-1,3,4-trisubstituted-5-oxopiperazine-2-carboxylates **91** each with vinyl magnesium bromide reagents in *tert*-butyl methyl ether to give the β-aminoketones **90** and β-amino alcohol derivatives **92**, respectively (Scheme 32).

3.9. Synthesis of spirocyclic β-aminoketones

Ma *et al.*[133] reported the synthesis of a series of *N*-(2-oxo-2′,3′-dihydrospiro[cyclopentane-1,1′-inden]-2′-yl)benzenesulfonamides **95** through the reactions of cycloalkanol-1*H*-indenes with 1-(arylsulfonamido)pyridinium

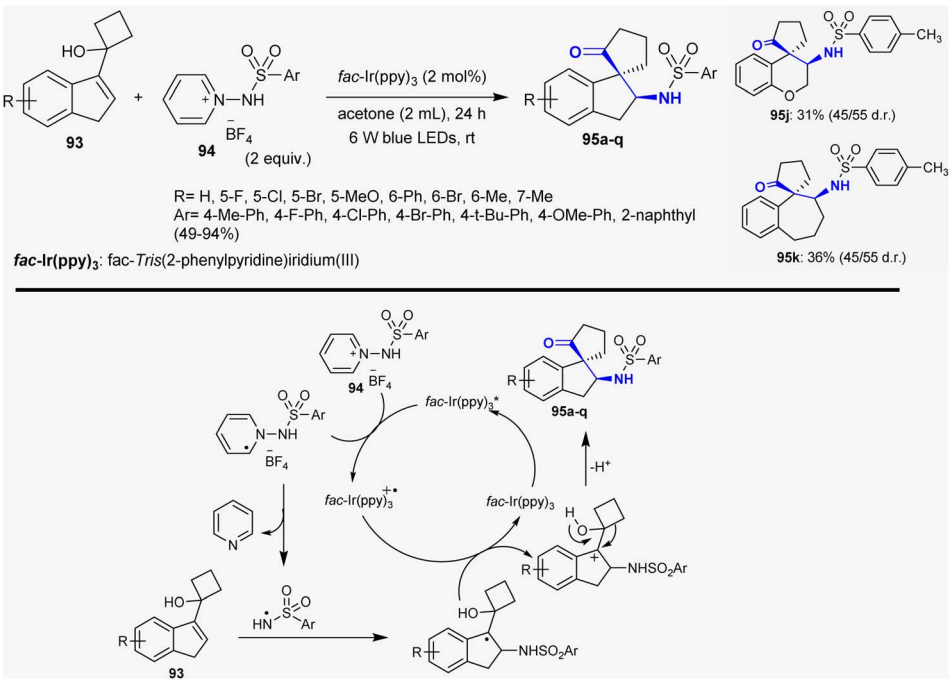


Scheme 32 Synthesis of substituted morpholinones and piperazinones.

tetrafluoroborates. The reactions proceeded under catalytic and mild conditions using visible light photoredox to stimulate N-centered radical addition and semipinacol rearrangement of cycloalkanol with N-protected pyridinium salts. This method efficiently accessed a series of β-aminoketones of the spiro-cyclic type in acetone under *fac*-Ir(ppy)$_3$ (2 mol%) catalytic conditions. The benefits of this performance are to enable extensive scope of substrates, respectable assembly tolerance, and simple synthetic route. The recommended mechanism for this type is a free radical mechanism involving N-centered radical addition and semipinacol rearrangement. Firstly, the reaction was activated by the visible-light-induced SET reduction of pyridinium salt **94** with the generation of radicals. The photo-excitation of the catalyst resulted in the generation of the radical intermediate with the generation of the catalyst in the oxidized form. Cleavage of the N–N bond by hemolytic fission-released pyridine is dependent on the efficiency of the reacted cycloalkanol-1*H*-indenes **93** to rapidly form the greatest stable alkyl radical. Next, oxidation of the previously formed intermediate led to the generation of a carbocation intermediate with the oxidation state of *fac*-Ir(ppy)$_3^{+\bullet}$, and the ground-state *fac*-Ir(ppy)$_3$ was reinforced. Finally, semipinacol rearrangement took place for the intermediate to afford the target compounds **95** (Scheme 33).

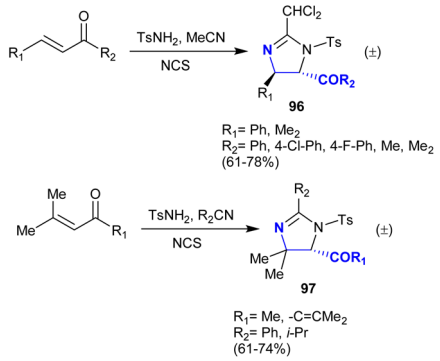
3.10. Synthesis of imidazolines

In another recently developed route, the imidazoline ring was constructed through the one-pot reaction of triflamide with silane in acetonitrile containing *N*-bromosuccinimide accompanied by the dehydrobromination of amidine with the aid of potassium carbonate.[134] One of the most challenging topics in the field of organic synthesis is related to developing novel strategies of regio- and stereoselective approaches to obtain vicinal diamines.[135–139] Timmons *et al.*[140] developed an approach for the direct amination of enones, which is regio-, stereo-, and chemoselective deamination of enones employing electrophiles such as *N*-chlorosuccinimide and tosyl amine. The acetonitrile provided the nitrile group as

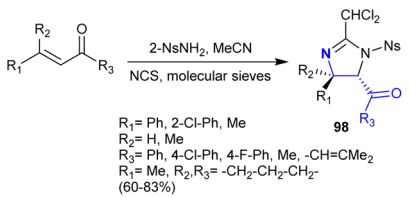


Scheme 33 Synthesis of β-aminoketones with the spiro-cyclic core.

a nucleophile for the nitrogen source. The projected mechanistic route involved the generation of an aziridinium intermediate produced from the reaction of tosyl amine hydrochloride with alkenes followed by [2 + 3] cycloaddition with aziridinium ring cleavage. In particular, α,β-unsaturated ketones reacted with tosyl amine, *N*-chlorosuccinimide, and acetonitrile to produce moderate to good yields of the deamination products **96** with high regioselectivity (>95). The stereoselectivity in the case of the reacted 1,3-di-aryl-prop-2-en-1-ones reached >95 of minor isomer, while no regioisomers of the minor products were formed in the case of the reaction with 1,3-di-alkyl-prop-2-en-1-ones. Furthermore, α,β-unsaturated ketones reacted with tosyl amine, alkyl/aryl nitriles, and *N*-chlorosuccinimide to give the anticipated imidazolines **97** in 61–74% yield (Scheme 34).



Scheme 34 Direct amination of α,β-unsaturated ketones.



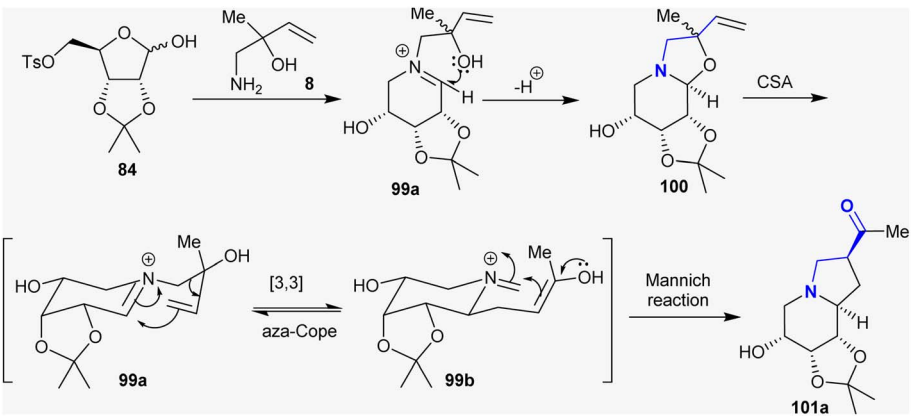
Scheme 35 Synthesis of imidazolidines.

In 2004, Timmons *et al.*[141] also extended their work on the regio- and stereoselective synthesis of imidazoline analogs **98** from the instantly accessible α,β-unsaturated ketones. In these reactions, *N*-chlorosuccinimide and 2-$NsNH_2$ enable nitrogen electrophilic sources. The reactions chemoselectively yielded the products with the formation of side-products such as haloamines (Scheme 35). The reactions of this type involved a mechanism of [2 + 3] cycloaddition, performed in the formation of the deamination products with remarkable regio- and stereoselectivity. The recorded stereoselectivity for this reaction type reached up to >95% in the case of the reactions with α,β-unsaturated ketones that have aryl substituents, while the alkyl substituents tended to have no selectivity. It is worth mentioning that the use of molecular sieves in the reaction of (*E*)-chalcone with 2-$NsNCl_2$ and acetonitrile at room temperature resulted in the formation of the 2-(dichloromethyl)-4,5-dihydro-1*H*-imidazoline analog ($CHCl_2$-imidazolines), while the reaction in the absence of molecular sieves at 50 °C led to the formation of 2-(trichloromethyl)-4,5-dihydro-1*H*-imidazoline (CCl_3-imidazolines).

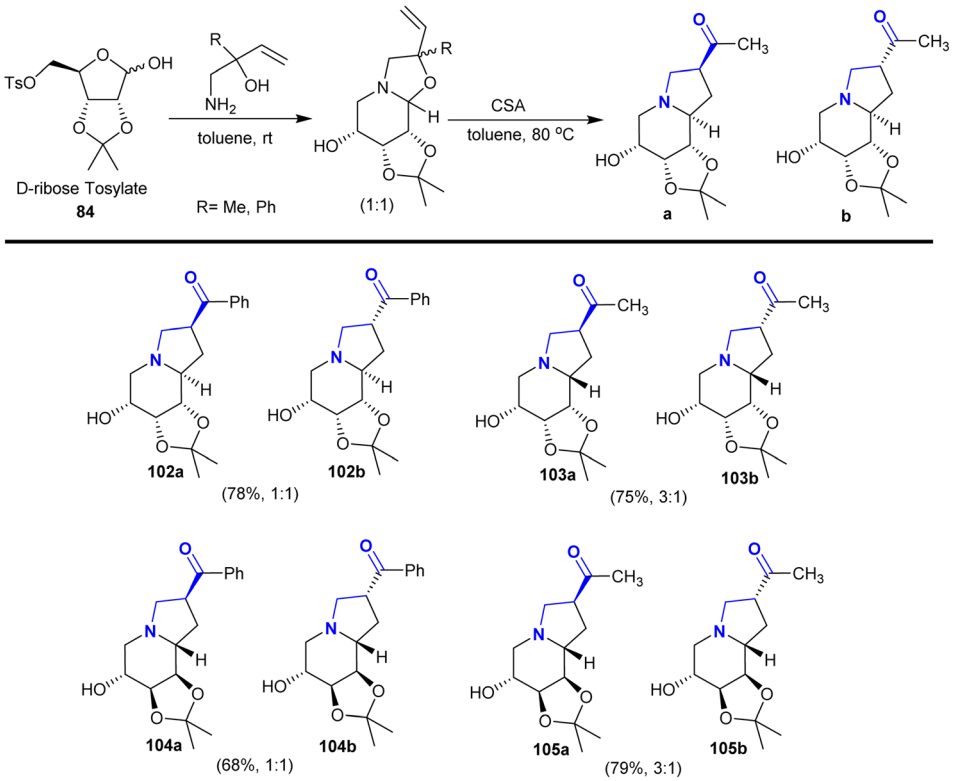
3.11. Synthesis of indolizines

Previously, Chinthapally *et al.*[142] developed a protocol for the stereoselective synthesis of polyhydroxy-2-acyl indolizidines through aza-Cope rearrangement–Mannich cyclization. This approach introduced the conceivable preparation of the prospective indolizidines and tetrahydroindolizidine-based imino-sugars in respectable yields. Camphor–sulfonic acid supported the reaction of substituted amino butanol with sugars such as ribose-tosylate to give the anticipated hydroxy-2-acyl indolizidines (Scheme 36).

Consequently, the reactions of D-ribose tosylate **84** with 1-amino-2-substituted-but-3-en-2-ol derivatives in toluene at room temperature under catalytic conditions of camphor-sulfonic acid (CAS) yielded the anticipated octahydro[1,3] dioxolo-indolizines[142] (Scheme 37). Recently, researchers have focused on employing these reaction approaches to prepare a series of bicyclic aza-sugars **102–105** with glycosidic heteroatoms.[129]



Scheme 36 Estimated mechanistic route for the synthesis of octahydro[1,3] dioxolo-indolizines.



Scheme 37 Synthesis of polyhydroxy-2-acyl indolizidines.

3.12. Synthesis of pyrido-isoindoles

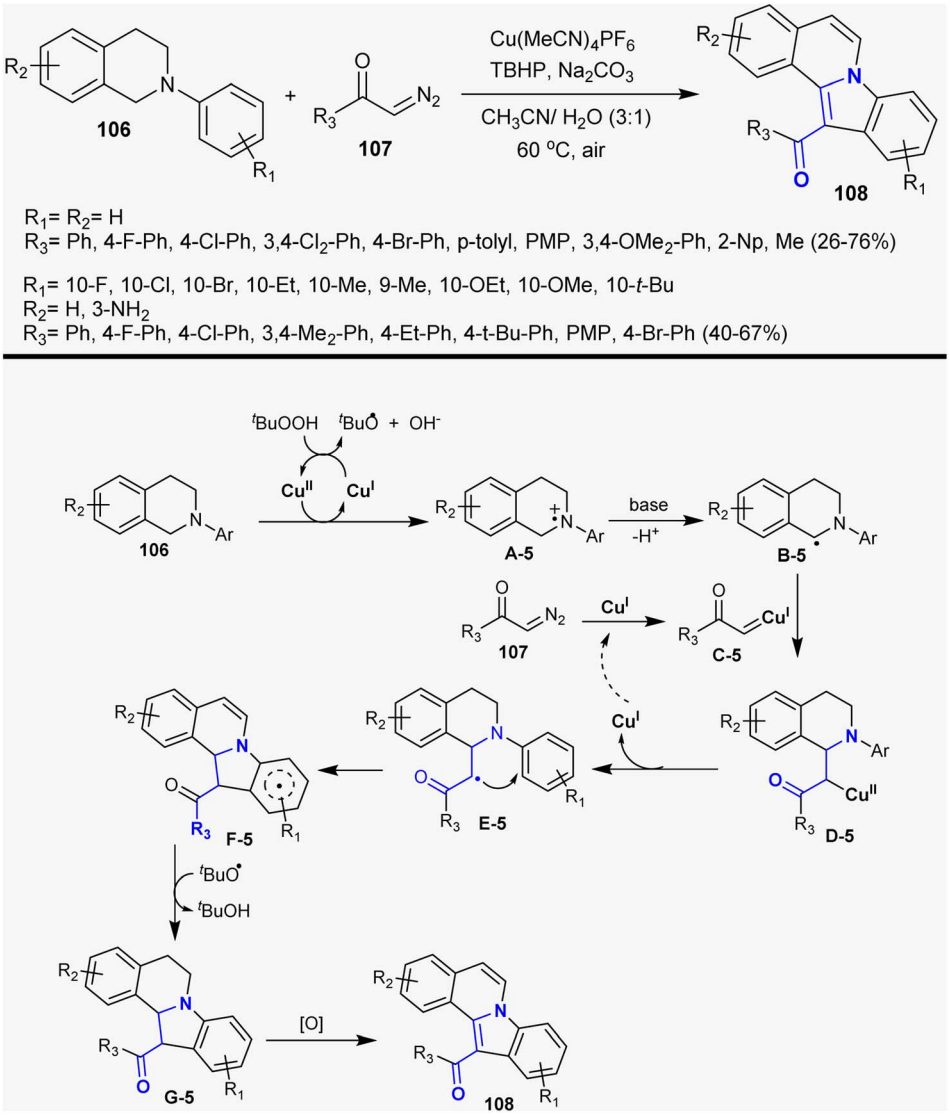
Zhang *et al.*[143] reported the synthesis of indoloisoquinoline series **108** by the reaction of *N*-aryl-1,2,3,4-tetrahydroisoquinolines **106** with α-diazoketones **107**. The reactions proceeded under Cu-catalyzed and oxidative conditions using *tert*-butyl hydroperoxide with the formation of the products in moderate to good yields (26–76%). The reaction sequence involved Cu-catalyzed [4 + 1] annulation, dediazotization of α-diazoketones, and oxidative dehydrogenation. Thus, the Cu(II) complex enabled electron transfer with the *tert*-amines generating amine radical cation intermediate **A-5**. Next, a proton was lost from the formed intermediate **A-5** to generate the aminoalkyl radical **B-5**. Intermediate **B-5** was trapped by carbene **C-5**, which was generated by the interaction of compound **107** with copper Cu(II)complex to generate intermediate **D-5**. Homolytic cleavage of intermediate **D-5** generated intermediate **E-5** with the release of the Cu(I) catalyst. The cyclization of the 5-*endo*-trig type intermediate **E-5** followed by proton abstraction with the assistance of the *t*-BuO˙ base produced intermediate **G-5**. The final step is oxidative dehydrogenation to give the anticipated products **108** as cyclic β-aminoketones (Scheme 38).

A sequence of reactions involving the synthesis of polycyclic isoindolines was efficiently developed by Wang *et al.*[144] Thus, a series of tetrahydropyrido-isoindoles **110** was synthesized by treatment of chalcone-based pyridinium salts **109** with piperidine through ring-opening/ring-closure reactions. Two main factors that may affect the deconstruction of the pyridinium motif were defined as the exceptional binding of unstable in situ-formed cyclic β-aminoketones and the instability of the produced *N*,*N*-ketals. Alternatively, Wittig reactions of the anticipated isoindolines with several phosphorus ylides yielded isoindolines **111** with α,β-unsaturated ketone side chains (Scheme 39).

3.13. Synthesis from propargylic alcohols

Guo *et al.*[145] reported the synthesis of β-aminoketone from the reaction of 3-phenylprop-2-yn-1-ol **117** with N-Ts-substituted hydrazine. Therefore, 1-phenyl-3-(3-phenyl-1*H*-pyrazol-1-yl) propan-1-one **119** was prepared in 83% yield through the nucleophilic addition of the in situ-formed intermediate **118** and hydrazine derivative followed by cyclocondensation. The hydrazine derivative was applied in this reaction as a nucleophilic reagent in the one-pot synthesis for the construction of a pyrazole ring from the propargylic alcohol (Scheme 40).

Zhang *et al.*[146] developed a facile procedure for the synthesis of α-bromo-β-aminoketones **120–122** under catalytic conditions. Consequently, $Bi(OTf)_3$-catalyzed reactions of 3-phenyl(aryl)prop-2-yn-1-ol with sulfonamides and *N*-bromosuccinamide as a source of the halogen yielded the desired series of α-bromo-β-aminoketones **120–122** (Scheme 41). This procedure was achieved in a one-pot reaction of the reacted materials. Tandem Meyer–Schuster-type rearrangements were proposed for these reactions followed by intermolecular Michael addition reactions of α,β-unsaturated ketones with sulfonamides. The substituents at the C4 position of the phenyl



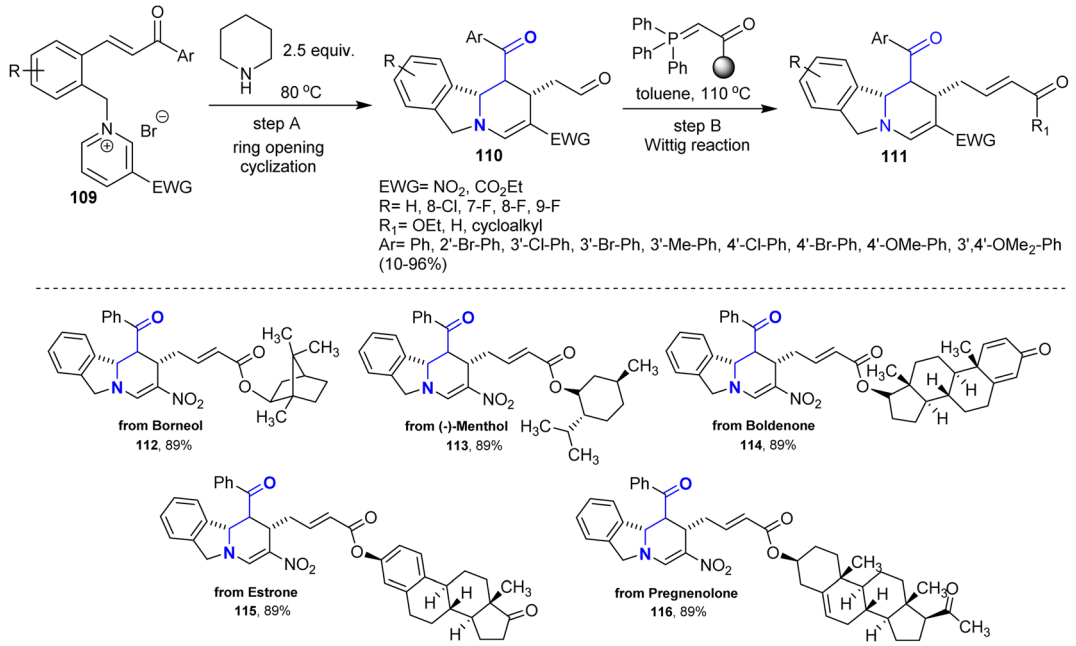
Scheme 38 Synthesis of aza-tetracyclic systems.

ring are preferred to achieve a shortened reaction time and good yields. Substituents with high electron density on the C≡C bond increased the reaction rate. Additionally, the steric hindrance factor of the substituents at the para position of the phenyl ring does not affect the product yield.

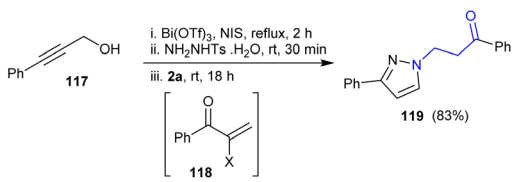
Laserna *et al.*[147] developed gold-catalyzed reactions of hydroxy-alkynes with anilines to efficiently prepare a series of β-aminoketones **123** (Scheme 42). The mechanism of the reactions, in this case, is related to the efficiency of the catalyst to enable the Meyer–Schuster rearrangement[148] of the propargylic alcohols in the first step, and then the conjugated addition of the primary amine to the generated enones. The solvent effect in this reaction type is related to the selectivity of the reaction, and thus a toluene and methanol mixture with a 98 : 2 molar ratio is preferrable. Even though the reactions are tolerant of both electron-deficient and electron-rich aniline substituents, primary and secondary alcohols are appropriate substrates. The nucleophile addition was related to the elimination of the adjacent hydroxyl group.[149] Consistently, the imine reduction after hydroamination provided the analogous amino alcohol in 72% yield as a mixture of diastereomers (85 : 15).

3.14. Reductive hydroamination of ynones

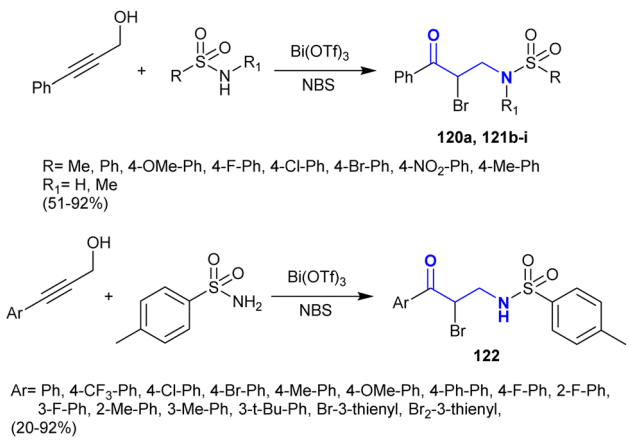
Fu *et al.*[150] employed the reductive hydroamination of ynones for the proficient synthesis of β-aminoketones **124**. In this route, the metal-free reductive hydroamination of alkynones with secondary amines under mild reaction conditions yielded the anticipated β-aminoketones in moderate to good yields. The reactions involved the hydroamination of C≡C bonds through the addition of the amines with the aid of pinacolborane catalyst (Scheme 43). The reaction mechanism may follow the interaction of the amine with the pinacolborane catalyst-generated intermediates that interacted with ynones. Afterward, coordination of the aminoborane with ynones tended to the formation of the reductive complex. The reactions could



Scheme 39 Synthesis of tetrahydropyrido-isoindoles.



Scheme 40 Synthesis of 1-phenyl-3-(3-phenyl-1*H*-pyrazol-1-yl) propan-1-one.

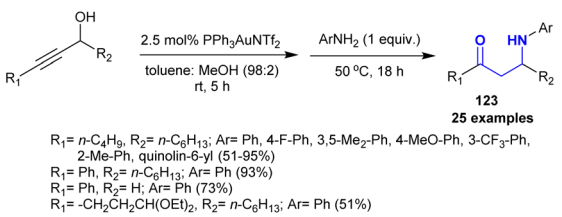


Scheme 41 Synthesis of α-bromo-β-aminoketones.

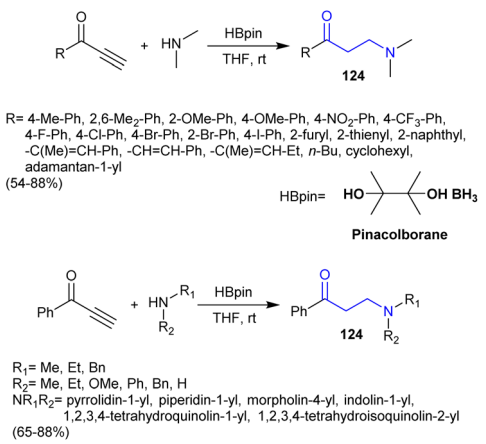
also have followed Michael addition to form the hydroamination product, which was reduced by hydride, enolized, and protonolysis of a carbon–boron bond with the amines to afford the respective ketamine.

3.15. Alkylation of alicyclic imines with β-ketoacids

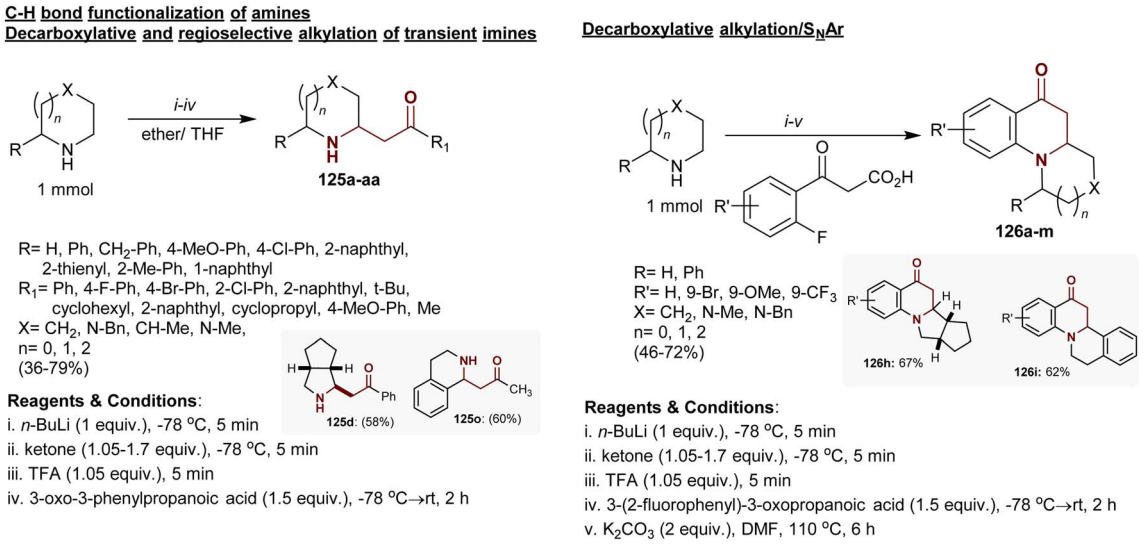
Regioselective alkylation and decarboxylation of alicyclic imines with β-ketoacids yielded the respective β-aminoketones **125** in poor to excellent yields (36–79%). The reactions tended to C–H bond cleavage at the α-position of imines accompanied by C–C



Scheme 42 Addition of amines to alkynols.



Scheme 43 Synthesis β-aminoketones from ynones.

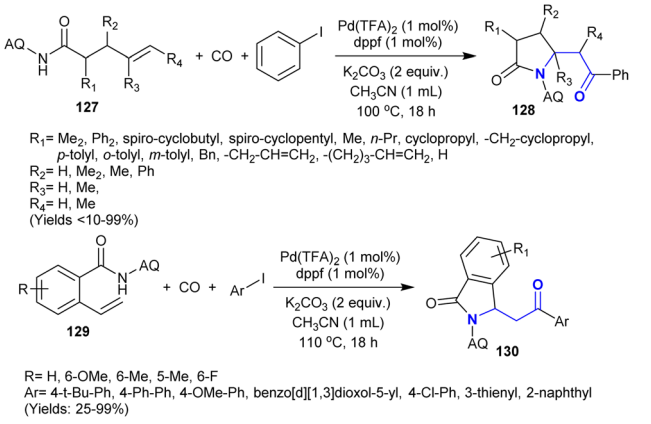


Scheme 44 Regioselective alkylation of alicyclic imines.

bond formation. The reactions enabled the alkylation of imines at the α-position through regioselective substitutions. Ten analogs were obtained as *trans*-diastereomers although the *cis*-isomers were thermodynamically stable with probable interconversion of the products. Also, decarboxylative alkylation of imines with *o*-fluoroaryl-β-ketoacids followed by a nucleophilic substitution step yielded the polycyclic quinolinone products **126a–m** with a β-aminoketone moiety without isolation of the intermediates (Scheme 44).[151]

3.16. Carbonylative coupling

Owing to the difficulties of the reactions intended for the coupling of aryl halides with unactivated alkenes, Peng *et al.*[152] developed a protocol involving these reactions under catalytic conditions. Thus, the carbonylative coupling and amination were developed under palladium-catalyzed conditions to synthesize a sequence of β-aminoketones **128** and **130**. With the support of a leading group (8-aminoquinoline "AQ"), the identity of the olefin to acyl–palladium complex could be improved, thus stimulating the acyl-palladation crosswise of the C=C double bonds. A broad range of β-aminoketones was synthesized in reasonable to exceptional yields with broad regioselectivity employing 4-pentenoic **127** and 2-vinyl benzoic amides **129** as the preliminary materials. This performance involved the generation of two C–C bonds in addition to one C–N bond and delivered a technique for the carbonylative coupling of the desired unactivated alkenes (Scheme 45).



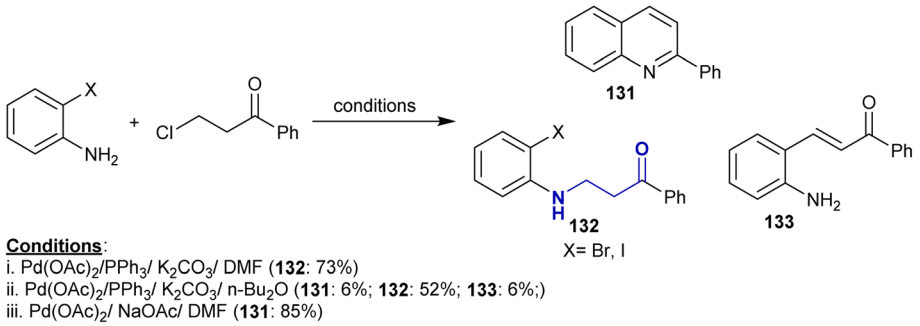
Scheme 45 Synthesis of β-aminoketones *via* carbonylative coupling of unactivated alkenes.

3.17. Coupling of halo ketones with amines

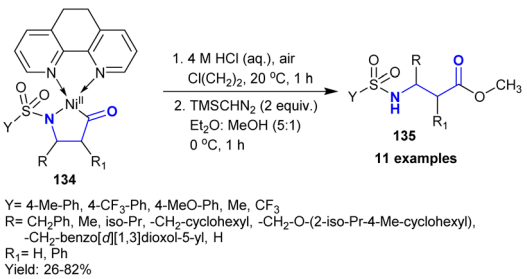
The palladium-catalyzed cascade reactions of *o*-halo-anilines with 3-chloro-1-phenylpropan-1-one were accomplished under different conditions to prepare a series of quinolones. The various conditions led to the formation of side products such as β-aminoketones **132** and arylidene **133**, where the Michael sequence reaction generated β-aminoketones **132** and the Heck reaction generated the desired arylidene **133** *via* β-hydride elimination. The use of palladium acetate and triphenyl phosphine in DMF containing potassium carbonate yielded β-aminoketones **132** as the only product, while the use of *n*-Bu_2O instead of DMF led to the highest yield of β-aminoketones **132**, and the use of sodium acetate as a base in the absence of ligand only gave the aryl quinoline **131** (Scheme 46).[153]

3.18. Acid hydrolysis of metal complexes

Ravn *et al.*[1] developed the synthesis of β-aminoketones **135** in low to good yields (26–82%) through an appropriate and proficient synthetic route for the combination of a single carbon isotope. Thus, the acid hydrolysis of nickel complexes **134** under atmospheric conditions afforded β-aminoketones **135** (Scheme 47). This method enabled easy product purification. The products were formed through the cleavage of M–C and M–N bonds.



Scheme 46 Synthesis of β-aminoketones *via* cascade reactions under palladium-catalyzed conditions.



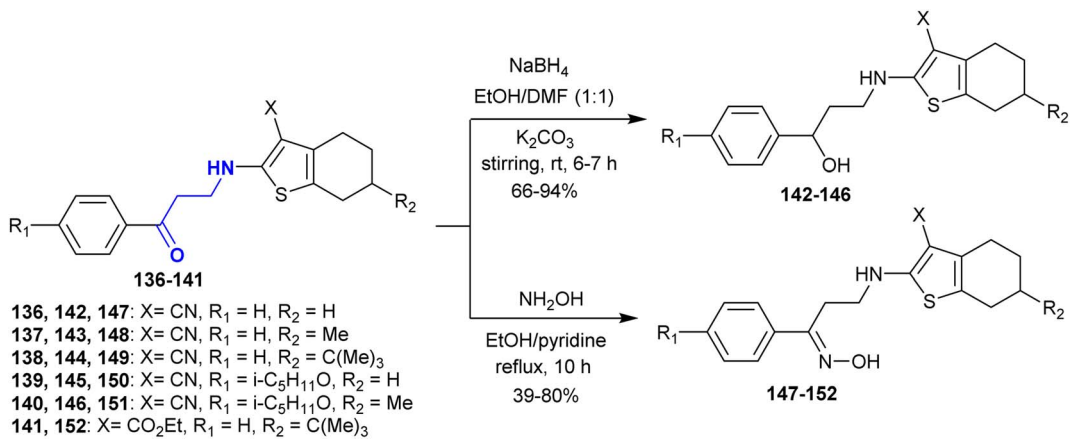
Scheme 47 Synthesis of β-aminoketones under acid hydrolysis conditions.

4. Synthetic applications

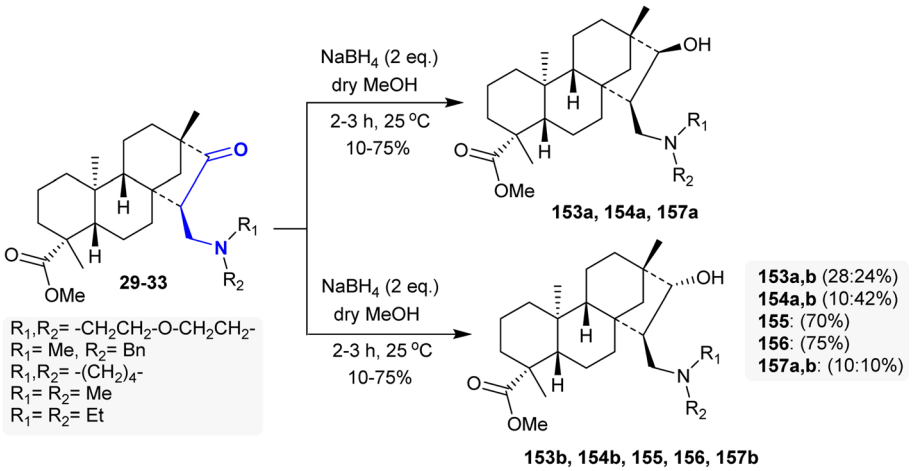
4.1. Aminoalcohol and oxime synthesis

The selective reduction of β-aminoketones **136–141** with sodium borohydride in the presence of potassium carbonate yielded a series of amino alcohols **142–146.** Alternatively, the reactions of β-aminoketones **136–141** with hydroxyl amine hydrochloride gave the corresponding oximes **147–152,** respectively. These reactions proceeded under catalytic conditions of pyridine through nucleophilic attack of the amino group at the carbonyl group followed by condensation (Scheme 48). Compound **149** revealed the most potent antioxidant character given that it can inhibit the oxidation caused by free radicals through the generation of lipid peroxides by about 30%. In addition, compounds **142** and **144** displayed moderate activities, while compound **148** displayed reduced activity. Compounds **145, 146,** and **151** are capable of acting on the free radical oxidation step reactions of lipids in the liver. Among them, compound **142** presented the greatest sensitivity against blood coagulation, while compounds **143, 144,** and **147–151** had reduced activity compounds **145, 146,** and **152** were inactive.[154]

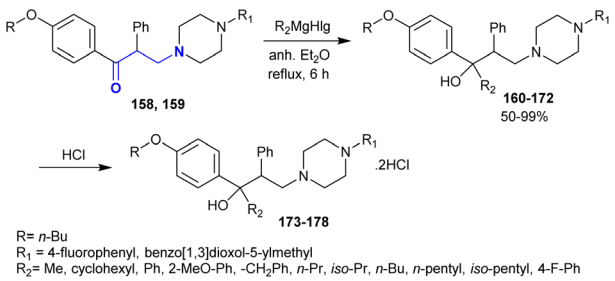
The respective β-aminoketone "methyl esters of isosteviol" **29–33** underwent selective reduction by treatment with sodium borohydride in dry methanol under mild reaction conditions to give 1,3-amino alcohols **153–157** through hydroxy-formylation processes. The 1,3-amino alcohol products are diastereomeric mixtures in some cases. Thus, the reduction of β-aminoketones **31** and **32** yielded products **155** and **156,** respectively, with high stereoselectivity as single diastereoisomers (Scheme 49). Remarkable cytotoxic results were estimated for the 1,3-amino alcohol derivatives against A2780, SiHa, HeLa, MCF-7, and MDA-MB-231 human tumor cell lines. Compounds **154a** and **b** are the most potent cytotoxic agents against HeLa (IC_{50} = 10.17 and 13.65 μM), SiHa (IC_{50} = 12.20 and 14.34 μM), MDA-MB-231 (IC_{50} = 9.20 and 9.26 μM), MCF-7 (IC_{50} = 17.29 and 17.24 μM), and A2780 (IC_{50} = 16.08 and 14.93 μM), respectively. The transformation of the β-aminoketones into 1,3-amino



Scheme 48 Synthesis of aminoalcohols and oximes.



Scheme 49 Synthesis of amino alcohols.



Scheme 50 Synthesis of amino alcohols and their dihydrochloride salts.

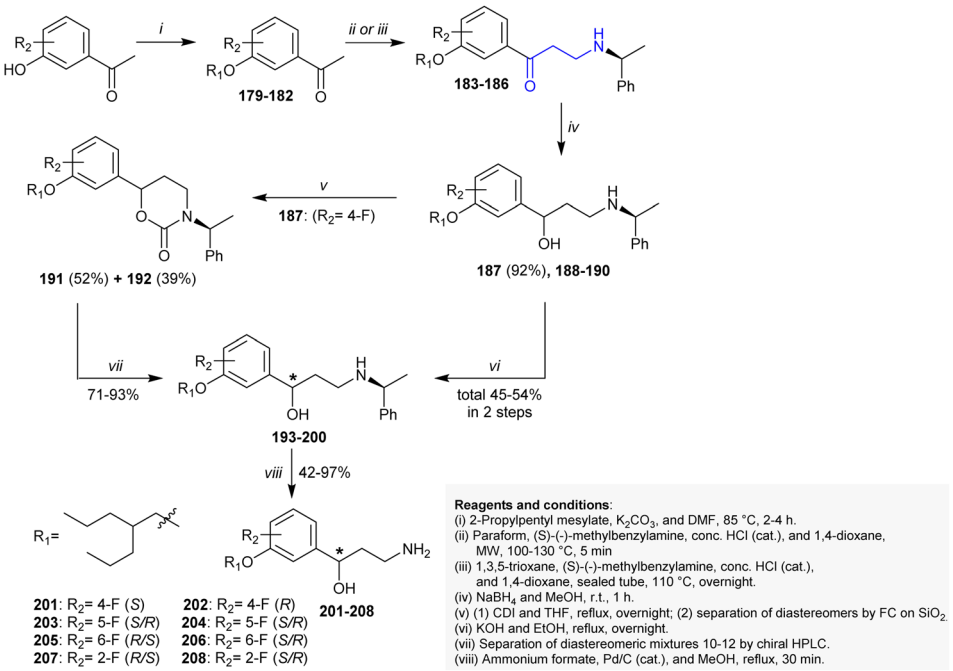
alcohols improved the cytotoxic effects of these compounds. In addition, the incorporation of *N*-benzyl substituents in the amino group is crucial for improved cytotoxic influence and privileged antiproliferative characters.[107]

Owing to the privileged biological potency of tertiary amino alcohols,[155,156] Gevorgyan *et al.*[154] synthesized a series of tertiary piperazinyl amino alcohols **160–172** by the reaction of β-aminoketones **158** and **159** with a Grignard reagent "prepared from metallic magnesium with alkyl(aryl)halide in anhydrous diethyl ether". The dihydrochloride salts of some of these compounds **173–178** were prepared by treatment with hydrochloric acid (Scheme 50). The impacts of the synthesized compounds **162**, **163**, **168**, **170**, **175**, and **178** against C-180 mouse tumor DNA methylation were studied *in vivo*. The incubation step was accomplished for the drug sample with a concentration of 3×10^{-6} M with the tumor cell line at 37 °C for 24 h. The influence of the compounds on inhibiting DNA methylation was estimated. It was found that compound **162** "R = *n*-Bu, R_1 = 4-fluorophenyl, R_2 = phenyl" inhibited DNA methylation by 51.6%. The incorporation of the methoxy group at the o-position of the phenyl group reduced the activity to 37.5%.

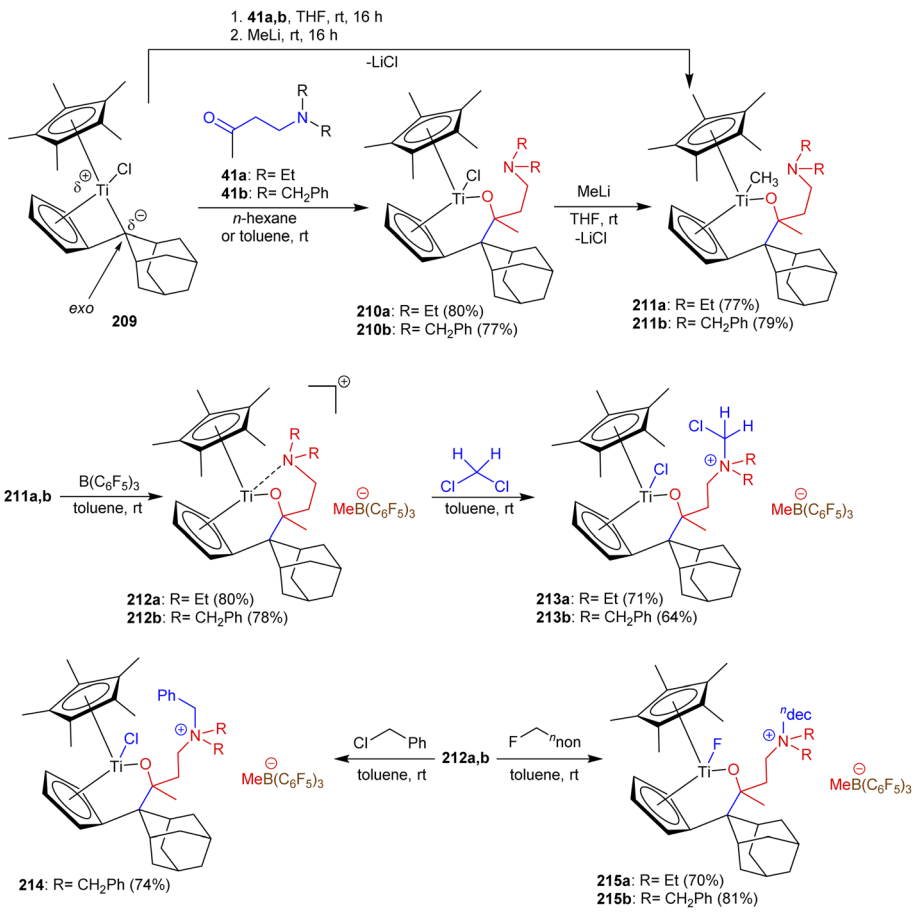
Blum *et al.*[157] developed a synthetic route for the preparation of enantiopure γ-amino alcohols **201–208** from the reactive precursors β-aminoketones **183–186**. Thus, the synthesis of this series is based on the preparation of the reactive precursor β-aminoketones **183–186**. In this route, acetophenones reacted with 2-propylpentyl mesylate in DMF/K_2CO_3 under heating conditions followed by a Mannich three-component reaction with chiral benzylamines under microwave irradiation conditions to yield β-aminoketones **183–186**. The reactions proceeded under HCl catalytic conditions with the preparation of compounds **183** and **185** in moderate yields (47%) together with insufficient yields of compounds **184** and **186** (<20%). Alternatively, a proficient method was applied for the preparation of compounds **184** (34%) and **186** (78%) by heating compounds **180** and **182** with 1,3,5-trioxane in a sealed pressure tube. The reduction of compounds **183–186** with sodium borohydride in methanol gave an analogous diastereomer mixture of N-protected γ-amino alcohols **187–190**. The preparative chiral HPLC technique was applied to separate diastereomeric mixtures of compounds **187–190**, respectively. Nitrogen deprotection of compounds **193–200** was accomplished by reductive hydrogenation with Pd/C in the presence of ammonium formate to yield the enantiomeric γ-hydroxyalkyl amine products **201–208**, respectively (Scheme 51).

4.2. Synthesis of metal complexes

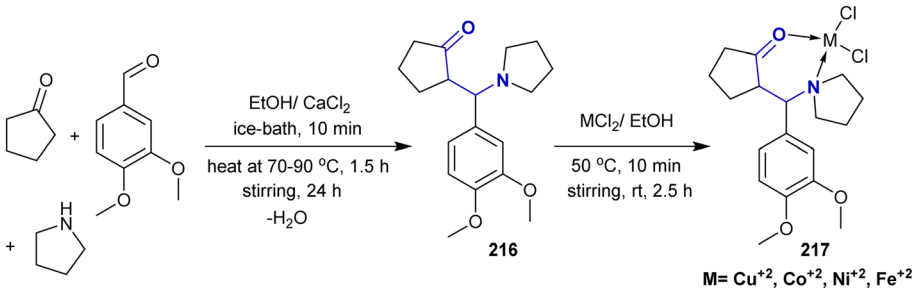
As reported by Fischer *et al.*,[114] β-aminoketones **41a** and **b** were involved in the exceedingly proficient synthesis of titanium complexes. Therefore, the monopentafulvene complex **1** reacted with β-aminoketones **41a** and **b** as bidentate O,N-ligands and yielded the cationic titanium complexes **212a** and **b** through multistep synthesis, respectively. The reactions involved treatment with ligands in n-hexane or toluene at room temperature followed by treatment with methyl lithium and the strong Lewis acid $B(C_6F_5)_3$ for activation. Subsequently, the cationic complexes **213** were prepared by the treatment of **212** with dichloromethane with C–Cl bond cleavage. Besides, treatment of **212a** with benzyl chloride in toluene afforded titanium complex **214** in good yield through the formation of a Ti–Cl bond. Predominantly, treatment of titanium complexes **212a** and **212b** with *n*-fluorodecane under the same previous



Scheme 51 Synthesis of amino alcohols.



Scheme 52 Synthesis of cationic titanium complexes.



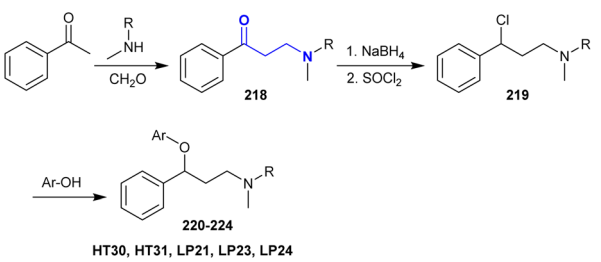
Scheme 53 Synthesis of β-aminoketones and complex formation.

conditions yielded complexes **215a** and **215b**, respectively, over the formation of Ti–F bonds (Scheme 52).

According to Liaqat *et al.*,[158] Mannich base **216** was prepared as a ligand for the synthesis of metal complexes. Thus, the multicomponent reaction of cyclopentanone with 3,4-dimethoxybenzaldehyde and pyrrolidine in equimolar ratios in ethanol containing calcium chloride gave the corresponding Mannich base **216**. Consequently, treatment of the Mannich base ligand with equimolar ratios of the anticipated metal chlorides yielded the respective metal complexes **217** (Scheme 53).

4.3. Synthesis of fluoxetine derivatives

A series of β-aminoketones was synthesized by the Mannich reaction of acetophenone with methyl amines and formaldehyde in ethanol under reflux conditions. Subsequent reduction of β-aminoketones **218** followed by treatment with thionyl chloride in dichloromethane under heating conditions yielded the respective chloro-phenyl propane-amines **219**. Fluoxetine derivatives **220–224** were efficiently synthesized through reactions of amines **219** with 3- or 4-trifluoromethyl phenol, 4-hydroxybenzaldehyde or 4-hydroxybenzonitrile, respectively, under gentle heating in DMF catalyzed by potassium carbonate (Scheme 54).[159]



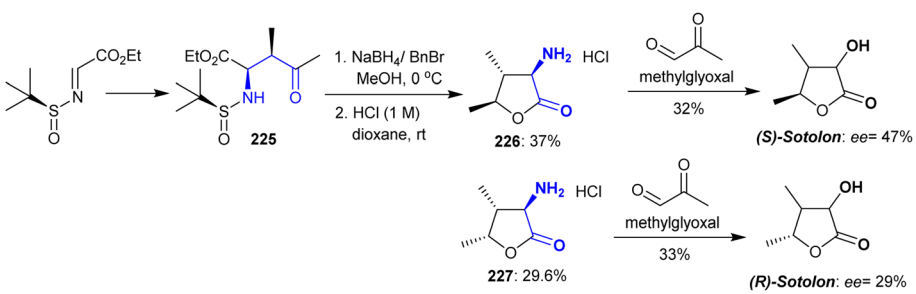
Scheme 54 Synthesis of fluoxetine analogs.

4.4. Synthesis of sotolon

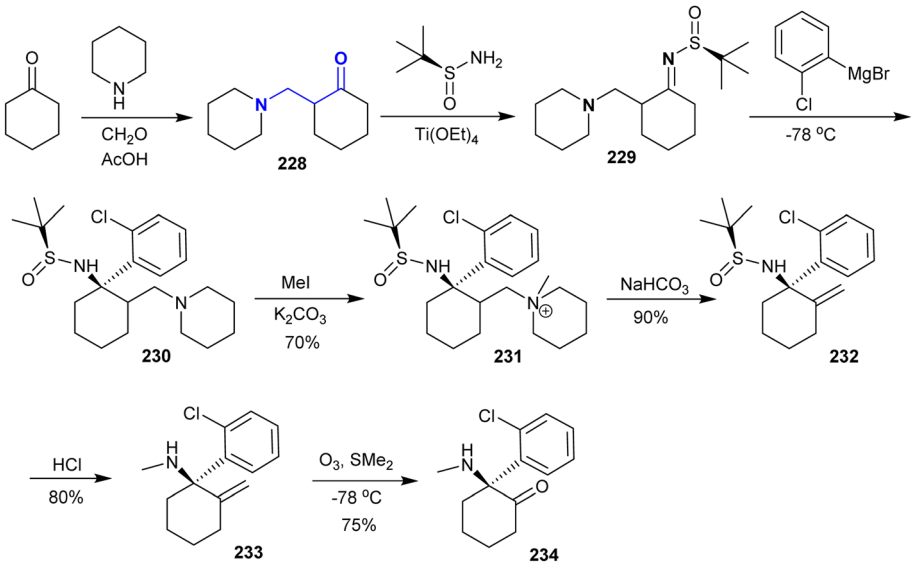
The synthesis of sotolon was developed by Trang *et al.*[160] from cyclic β-aminoketones **226** and **227** through their reactions with methylglyoxal. An auxiliary chiral starting precursor such as (*S*)–*N*-*tert*-butane sulfinimine was incorporated in the synthesis of sotolon as an optically active compound. Consequently, the reduction of ethyl (2*R*,3*R*)-2-(((*S*)-*tert*-butylsulfinyl)amino)-3-methyl-4-oxopentanoate with sodium borohydride in the presence of benzyl bromide, followed by treatment with hydrochloric acid resulted in sulfinyl group cleavage and aminolactone ring closure with the generation of two optically pure products **226** and **227** as a racemic mixture (ee > 99%). The transformation of amine hydrochlorides into the optically active (*S*)- and (*R*)-sotolon was processed in the presence of a phosphate buffer solution (Scheme 55). Hence, the plausible mechanism of this reaction was tandem isomerization-aldolization and isomerization-Mannich reactions.

4.5. Asymmetric synthesis of (*S*)-ketamine

Gohari *et al.*[161] reported the synthesis of (*S*)-ketamine from a multistep reaction sequence. Therefore, the Mannich reaction of cyclohexanone with piperidine and formaldehyde afforded the desired β-enaminone **228**. Subsequently, β-enaminone **228** reacted with (*S*)-2-methylpropane-2-sulfinamide through the



Scheme 55 Synthesis of optically active sotolon.

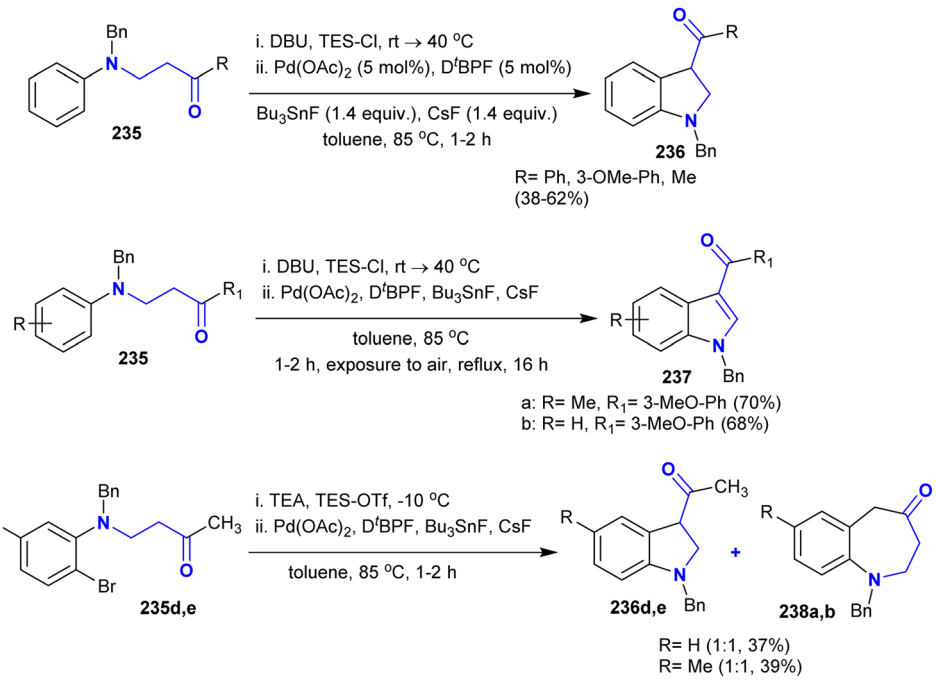


Scheme 56 Multistep synthesis of (*S*)-ketamine.

condensation step under tetraethoxytitanium catalytic conditions to give sulfiniylamin **229** in 85% yield. The reaction of **229** with Grignard reagent gave compound **230** in 80% yield, which was methylated with methyl iodide to produce the quaternary salt **231** (70% yield). Treatment of salt **231** with sodium bicarbonate afforded sulfinamide **232**. Deprotection of the amino group by removal of the *t*-butyl sulfinyl group was achieved by treatment with hydrochloric acid to give (*R*)-1-(2-chlorophenyl)-*N*-methyl-2-methylenecyclohexan-1-amine (**233**). (*S*)-Ketamine **234** was enantioselectively synthesized in 75% (75% ee) yield in the final step through the ozonolysis step (Scheme 56).

4.6. Synthesis of indolines and benzoazepinones

The procedure reported by Kumar *et al.*[118] was extended to the synthesis of a series of indolines and benzoazepinones. Thus, the annulation of *N*-aryl-β-aminoketones under palladium-catalyzed conditions gave the target products **236–238** through intramolecular α-arylation with one-pot annulations (Scheme 57). The treatment of β-aminoketones with chlorotriethylsilane in the presence of DBU led to the *in situ* generation of the respective silylenol ethers, which were annulated by the Pd-catalyst with high selectivity. The reactions yielded azepinones



Scheme 57 Synthesis of indolines and benzoazepinones.

and 3-acylindolines by the use of triethylamine and triethylsilyl trifluoro-methane-sulfonate for the enolization of β-aminoketones.

5. Miscellaneous approaches

The reactions of oximes **239** with quinuclidine as an electron-donor in the presence of Togni's reagent in acetonitrile under argon at 25 °C followed by hydrolysis *via* HCl gave the desired hydrochlorides of β-aminoketones **240** (Scheme 58). The amine was necessary for this conversion, where its absence led to no reaction. The effects of the substituents on the product yield were noticed clearly through the reactions using 4-MeO-Ph, Ph, and fluorenyl substituents instead of 3-CF_3-Ph, which led to reduced yields of β-aminoketones **240**. The mechanism of this type of reaction involved the addition of fluoroalkyl radicals on the alkene C=C double bond with the radical formation in the C2 position. The fluoroalkyl radicals were produced from a complex of electron donor–acceptor of Togni's reagent II or fluoroalkyl iodides and quinuclidine. Subsequently, 5(6)-*exo-trig* cyclization of C2 radical on the nitrogen atom of ketoxime ethers followed by N–O bond cleavage with the formation of π bond between C–N. Other examples of radical sources can be applied using this protocol instead of Togni's reagent II and fluoroalkyl iodides.[162]

6. Reactivity

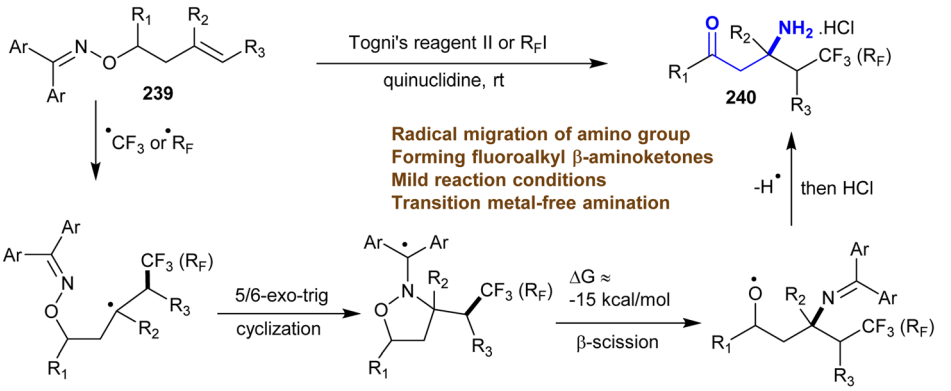
6.1. Amino group substitution

The reactivity of Mannich base **23** was investigated against a variety of nucleophiles, in which the product type depended on the reacted nucleophiles. Thus, Mannich base **23** reacted with 4-chlorothiophenol to give β-(arylmercapto)ketone **241**, while its reaction with piperazine "aliphatic" in a 2 : 1 molar ratio yielded the symmetric *bis*(1-(5-bromobenzofuran-2-yl) propan-1-one) **7**. Particularly, the reaction of Mannich base **23** with an acyclic aromatic amine such as 4-amino-benzenesulfonamide and cyclic 3,5-dimethyl-1*H*-pyrazole yielded the corresponding β-aminoketones **243** and **244**, respectively. The reactions involved nucleophilic substitutions through the attack of the sulfur or amine nucleophiles at the β-carbon. Alternatively, the reaction of Mannich base **23** with phenyl hydrazine tended to the ring closure product **245** in moderate yield (Scheme 59). The first step was the nucleophilic substitution of the NH group of phenyl hydrazine followed by cyclocondensation.[104]

Gevorgyan *et al.*[154] also developed the synthesis of a series of β-aminoketones **136–141** in a mixture of water and alcohol after a short time. Thus, 3-(diethylamino)-1-(aryl)propan-1-one hydrochlorides **246** reacted with tetrahydrobenzo[*b*]-thiophenes **247** under free-catalyst conditions to afford the desired β-aminoketones **136–141** (Scheme 60). The antioxidant evaluation assay demonstrated that compounds **136** and **139** displayed moderate activities for inhibiting the free radical reactions, while lower activities were recorded for compounds **137** and **140** and the active character for compound **141**. Compounds **136, 137**, and **139–141** presented the most sensitive shifts for the activation of the blood coagulation system.

6.2. Reactivity of substituents

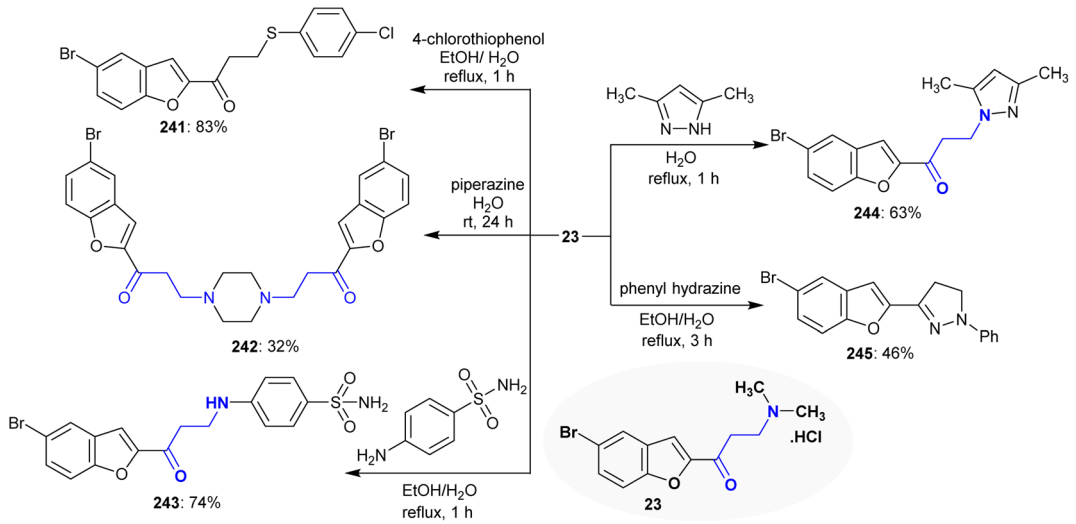
Under optimized conditions, tetrahydropyrido[2,1-*a*]isoindo-line **250** was prepared by the reaction of acetyl acetone with



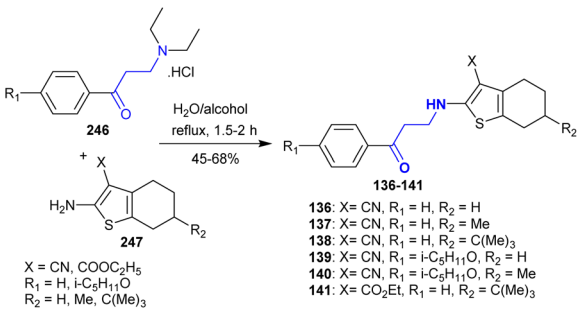
Ar= 3-CF_3-Ph
R_1= Ph, 4-CF_3-Ph, 4-CN-Ph, 4-F-Ph, 4-Cl-Ph, 4-Br-Ph, 4-Me-Ph, 4-Ph-Ph, 4-OMe-Ph, 3-Cl-Ph, 3-Br-Ph, 3-Me-Ph, 2-Cl-Ph, 2-Br-Ph, 2-Me-Ph, 2,4-Me_2-Ph, 3,4-O-CH_2-O-Ph, 2-naphthyl, 3-pyridyl, 3-thienyl, CH_2CH_2-Ph, $CH_2CH_{2\text{-}3}$-CF_3-Ph, n-hexyl, iso-Bu, CH_2CH_2-cyclohexyl, 4-Cl-but-1-yl
R_2= H, Ph, 4-Me-Ph,
R_3= H,
R_2,R_3= cyclohex-1,2-diyl
RF= n-C_3F_7, n-C_4F_9, n-C_5F_{11}, n-C_6F_{13}, n-C_8F_{17}, n-$C_{10}F_{21}$, -C(F)$(CF_3)_2$, -CF_2-CF_2-Cl, -$(CF_2)_2$-O-$(CF_2)_2$-SO_2-O-Ph, -$(CF_2)_2$-O-$(CF_2)_2$-$SO_{2\text{-}4}$-morpholinyl

Reagents and condiions:
Togni's reagent II (1.5 equiv.)/ Quinuclidine (3 equiv.)/ MeCN, Ar, rt, 12 h then HCl/MeOH, 2 h
R_F-I (2 equiv.)/Quinuclidine (3 equiv.)/ MeCN, white CFL/Ar, rt, 12-24 h then HCl/MeOH, 2 h
FG-LG (3 equiv.)/Quinuclidine (4 equiv.)/ LED light/ MeCN /Ar, rt, 12-24 h then HCl/MeOH, 2 h

Scheme 58 Synthesis of β-aminoketones through amination and radical migration of amino group.



Scheme 59 Substitution reactions of β-amino group.



Scheme 60 Synthesis of β-aminoketones.

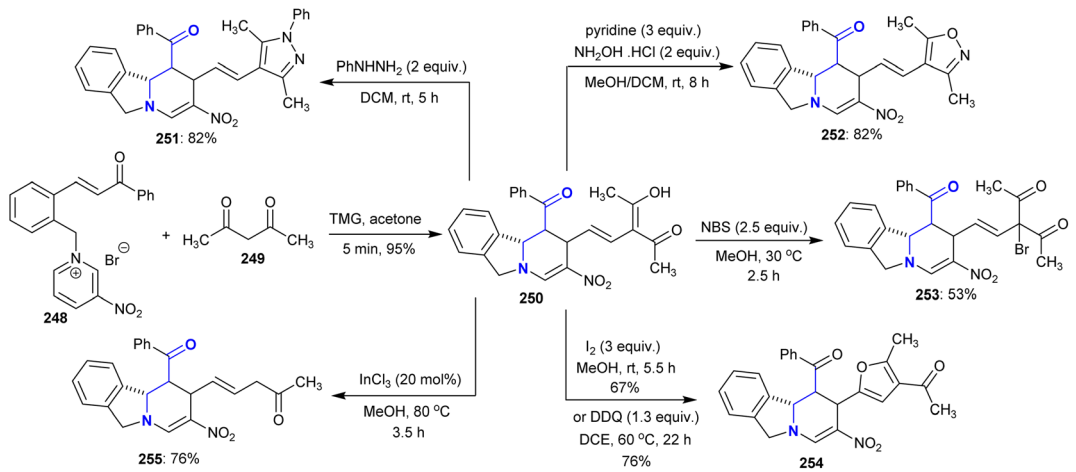
chalcone-based pyridinium salt in acetone with excellent yield (95%). The reactivity of compound **250** was investigated through reactions with phenyl hydrazine, hydroxylamine hydrochloride, and *N*-bromosuccinimide to yield binary heterocycles and branched halides **251–253**, respectively. Also, the oxidative cyclization in the presence of iodine gave the acetyl furan analog **254**, and deacetylation of one acetyl group in the presence of $InCl_3$ catalyst gave compound **255** in 76% yield (Scheme 61).[144]

6.3. Synthesis of imines

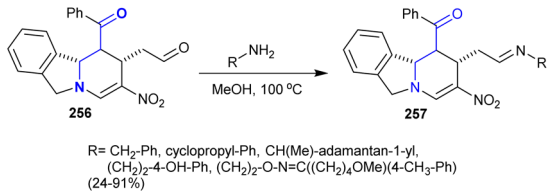
In this case, tetrahydropyrido[2,1-*a*]isoindole **256** reacted with various amines in methanol under reflux conditions to give the desired imines **257** in 24–91% yield (Scheme 62). These imines are assumed to have potential biological and pharmaceutical interest.[144]

6.4. Reductive cyclization

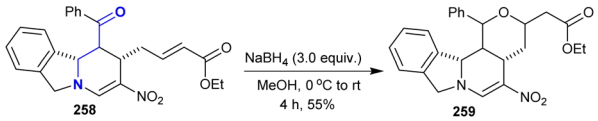
Treatment of tetrahydropyrido[2,1-*a*]isoindol-2-ylbut-2-enoate **258** with sodium boron hydride in methanol led to the formation of hexahydro-1*H*-pyranopyrido[2,1-*a*]isoindole **259** in a moderate yield (55%). Product **259** was obtained through the



Scheme 61 Reactivity of tetrahydropyrido[2,1-*a*]isoindoline.



Scheme 62 Synthesis of imines.



Scheme 63 Reductive cyclization.

reduction process followed by Michael addition in a sequence of reductive cyclization (Scheme 63).[144]

7. Concluding remarks

Formerly, Gevorgyan *et al.*[163] reviewed the same topic regarding the advances in the chemistry of β-aminoketones and published an update in 1985 regarding the chemical reactivity of this type of moiety. In 2008, Simplício *et al.*[164] reviewed the amine prodrugs including the significance of β-aminoketones as the privileged motif of many drugs. Alternatively, Verkade *et al.*[165] reviewed the utility of organocatalysts in asymmetric Mannich reactions, which was accompanied by the study of Allochio Filho *et al.*[166] in 2017, where they reported multicomponent Mannich reactions including their various applications. The present study highlighted the synthetic importance of the preparation of β-aminoketones and their applications given that this type of core is the basic structure of many drugs. The various synthetic strategies for β-aminoketones included multicomponent synthesis, *e.g.*, Mannich reactions under catalytic and non-catalytic conditions, addition to imines and unsaturated compounds, and condensation reactions of alcohols with amines. The multicomponent synthesis is a beneficial route for the synthesis of piperidines, while morpholinones, and piperazinones are prepared from alkenyl Grignard reagents with the corresponding ester. The spirocyclic systems are prepared from reactions of cycloalkanol-1*H*-indenes with 1-(arylsulfonamido)-pyridinium tetrafluoroborates. Also, imidazolines are synthesized by applying regio-, stereo-, and chemoselective deamination of enones employing electrophiles such as *N*-chlorosuccinimide and tosyl amine. Furthermore, indolizine-based β-aminoketones are efficiently synthesized through aza-Cope rearrangement–Mannich cyclization with high stereoselectivity. These protocols were extended to include the synthesis of pyrido-isoindoles from reactions of *N*-aryl-1,2,3,4-tetrahydroisoquinolines with α-diazoketones under catalytic conditions. Besides, propargylic alcohols are beneficial substrates for the synthesis of β-aminoketones and their reactions with N-Ts substituted hydrazines. Other methods are applied for the synthesis of β-aminoketones such as reductive hydroamination of ynones, alkylation of alicyclic imines with β-ketoacids, carbonylative coupling, coupling of halo ketones with amines, and acid hydrolysis of metal complexes. The synthetic applications of β-aminoketones covered the synthesis of amino alcohol and oxime derivatives, metal complexes, fluoxetine, sotolon, (*S*)-ketamine, indolines, and benzoazepinones. The compounds with β-aminoketone fragments underwent tertiary amino group substitutions. The reactions of substituents were extended to include the synthesis of imines and reductive cyclization.

8. Future prospective

N-Mannich bases have been extensively employed as prodrugs of amine drugs. The corresponding *C*-Mannich bases (β-aminoketones) have attracted much less interest perhaps because they are not appropriately liable to undergo *in vivo* elimination at the biological pH.[167] In addition, β-aminoketones were firstly observed to be inhibitors of TR coactivator interaction through the utility of high-throughput screening employing a library of 138 000 compounds in an *in vitro* fluorescence polarization assay.[168] Although researchers are interested in preparing many compounds that contain the β-aminoketone nucleus to explore the multiple biological properties of these compounds, many researchers have focused on developing and finding different preparation approaches instead of exploiting these compounds by including them in various biological assessments.

Conflicts of interest

The authors state no conflict of interest.

Abbreviations

Polycarbonates	(PC);
2,2′-Bipyridine	(bpy);
Argon	(Ar);
Room temperature	(rt);
Boron hydrogen sulfate	($B(HSO_4)_3$);
Iron-doped multi-walled carbon nanotubes	(Fe/MWCNTs);
Sulfonated-polyethylene glycol-coated Fe_3O_4 nanocomposite	(Fe_3O_4/PEG-SO_3H);
Tri-methylammonium-butane sulfonate	(TMBSA) ionic liquid (IL);
3-(*N*,*N*-Dimethyldodecylammonium) propanesulfonic acid hydrogen sulfate	([DDPA][HSO_4]);
Human ovarian cancer cell line	(A2780);
A cell line isolated from fragments of a primary uterine tissue	(SiHa);
An immortal cell line	(HeLa);
An epithelial cell line isolated from the breast tissue	(MCF7);
An epithelial, human breast cancer cell line	(MDA-MB-231);
Lithium diisopropylamide	(LDA);
Trifluoroacetic acid palladium(II) salt	(Pd(TFA)2);
2-Nitrobenzenesulfonamide	(2-$NsNH_2$);
Bismuth(III) trifluoromethanesulfonate	($Bi(OTf)_3$);

1,1′-Ferrocenediyl-*bis*(diphenylphosphine) (dppf); Human ovarian cancer cell line (A2780); 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU); and *N*-Bromosuccinimide (NBS)

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