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New frontiers in the transition-metal-free synthesis of heterocycles from alkynoates: an overview and current status

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Heterocycles are among the well-established classes of compounds, constituting a wide range of organic molecules. These structural motifs not only have a dominant presence in a wide variety of drugs but are also equally present as ubiquitous fragments of numerous vitamins, biologically active natural products, biomolecules, and synthetic drug candidates. Their key role in medicinal chemistry in the design of safe, effective, and efficacious drug molecules gives an impetus to the scientific community to access heterocyclic entities from robust chemical reactions. In this review, we summarize a diverse range of synthetic methods employing alkynoates as key starting materials to furnish useful bioactive heterocyclic frameworks (nitrogen, oxygen, sulfur, fused- and hetero-spirocycles), thus offering new opportunities and expanding the toolbox of synthetic chemistry reactions under transition-metal-free conditions. Several reaction parameters such as the use of easily available starting materials, commercially accessible reagents, and ease of synthesis (moderate temperatures, short reaction times, high yields, limited by-products) are included in the discussion alongside the reaction scope and limitations as well as mechanistic insights. The application of these methodologies in the synthesis of natural products and pharmaceuticals has also been discussed. We hope that the diverse utilities of alkynoates in the delivery of various heterocycles will fulfil the objectives of medicinal chemists in overcoming the formidable challenges associated with drug discovery and development.

1. Introduction

Heterocycles are ubiquitous fragments of numerous natural products, pharmaceuticals, designed bioactive drug candidates and agrochemicals.[1,2] Their significant prevalence in drug candidates improves the solubility and reduces the lipophilic character of the drug molecules.[3,4] In the drug discovery field, heterocyclic entities demonstrate a wide range of biological activities such as anti-inflammatory, antitumor, antidepressant, antibiotic, anti-HIV, antimalarial, antimicrobial, antiviral, and anticancer activities. In addition, these heterocycles also inhibit various enzymes (aldehyde/aldose reductase, α-glucosidase, α-amylase, cholinesterase, monoamine oxidase, urease, β-glucoronidase, alkaline phosphatase) for effective lead identification and the treatment of several chronic disorders.[5–26] These heteroarenes are also well-recognized core structural units in organic chemistry[2] and materials sciences.[27] Fig. 1 shows the representative examples of heterocycles reported in the literature and included in the current review/discussion.

Recognizing the well-established significance of heterocycles in synthetic and medicinal chemistry as well as in the drug discovery arena, their easy, facile and practical synthesis remains a continuous challenge. In this pursuit, several efficient protocols have been established using transition-metal catalysts such as silver,[28,29] gold,[30–33] copper,[34–36] cobalt,[37] iron,[38–40] palladium,[41,42] ruthenium,[43–45] mercury,[46] and rare-earth metals.[47] Several specific transformations such as cycloaddition reactions,[48–52] cycloisomerization reactions,[53,54] Sonogashira reaction,[55,56] C–H bond functionalization processes,[57–59] metathesis reactions[60–62] and multi-component reactions[63–65] have also been reported to produce heterocyclic structures. In addition, various starting materials such as azides,[66–68] α-oxoesters,[69] isocyanides,[70–73] arylglyoxals,[74] and diazo compounds[75,76] have also been employed to deliver a range of heterocycles. Despite these fascinating developments, the generation of molecular/modular complexity in

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the pharmaceutical industry with good atom- and step-economy and broad functional group tolerance from readily available starting materials and commercial feedstock continues to be a driving force for synthetic chemists to develop sustainable methods. In addition, transition-metal-free reactions offer several advantages over transformations involving transition-metal catalysts. For instance, transition-metal-catalyzed protocols are often very sensitive to air and moisture and require very toxic and expensive catalysts and non-commercial supporting ligands. The removal of trace amounts of transition-metal residues from the desired products is quite costly and challenging while crucial, especially in the pharmaceutical industry. In many cases, special additives and cocatalysts are also critical to promote the efficiency and selectivity of transformations. Finally, the large consumption of transition-metal catalysts does not indeed meet the requirement of sustainable synthesis.[77–80] Therefore, alternative approaches to form various bonds particularly in heterocyclic synthesis under transition-metal-free and generally practical and sustainable conditions are highly desirable obviating the need for metal catalysts, ligands, additives and cocatalysts.

In the present review, we summarize and showcase the utility of transition-metal-free approaches for the construction of a variety of heterocycles. These easy, practical and efficient synthetic methods involve the use of alkynoates as cheap, readily accessible and simple feedstock. Alkynoates are significantly important, diverse and powerful building blocks in organic chemistry due to their unique and inherent properties such as the electronic bias on the carbon–carbon triple bond posed by electron-withdrawing groups. A range of chemical reactions could be exploited involving the reactivity of zwitterions derived from activated acetylenic esters with nucleophilic trivalent phosphines such as Wittig reactions,[81] annulations,[82] and cycloadditions.[83] In addition, the reaction between trivalent phosphorus compounds and acetylenic esters in the presence of organic acids such as CH acids, NH acids, OH acids, or SH acids to give a vinyl trivalent phosphonium cation as the important intermediate has also been studied extensively.[84] Other carbon-, nitrogen-, or sulfur-based nucleophiles could be employed as Michael donors while alkynoates act as Michael acceptors. Alkynoates can also undergo isomerization into the corresponding allenes under basic conditions which could be utilized in conjugate addition. Meanwhile, the unusual reactivity of the isocyanide functionality with alkynoates (DMAD) offers opportunities for the generation of complex and diverse drug-like small heterocyclic compounds using the multi-component reaction (MCR) methodology.[85] Thus, this review will consider the use of the triple bond

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Imtiaz Khan received his PhD degree from The University of Nottingham, United Kingdom under the direction of Professor Hon Wai Lam where he developed new synthetic methodologies involving C–H functionalization of inert bonds for the synthesis of carbo- and heterocycles. Later, he worked as a postdoctoral research associate in the same group for one year. He then spent two years (2016–2018) as a Leverhulme Trust research fellow at Cardiff University, before joining The University of Manchester, United Kingdom in 2018. He has a good contribution towards the scientific and academic community with numerous research publications in highly prestigious international journals and various presentations in both national and international conferences. He has published over 60 peer-reviewed articles and reviews with an impact factor of >250 that have been cited over 1800 times. He is serving as an editorial board member of several journals including Current Organic Chemistry, Current Organocatalysis, Mini-Reviews in Medicinal Chemistry, *and* Anti-Cancer Agents in Medicinal Chemistry. *His research interests include the development of novel synthetic methodologies for the efficient synthesis of biologically active heterocycles and carbocycles, frustrated Lewis pair (FLP) chemistry and integrated chemo- and biocatalysis.*

Sumera Zaib

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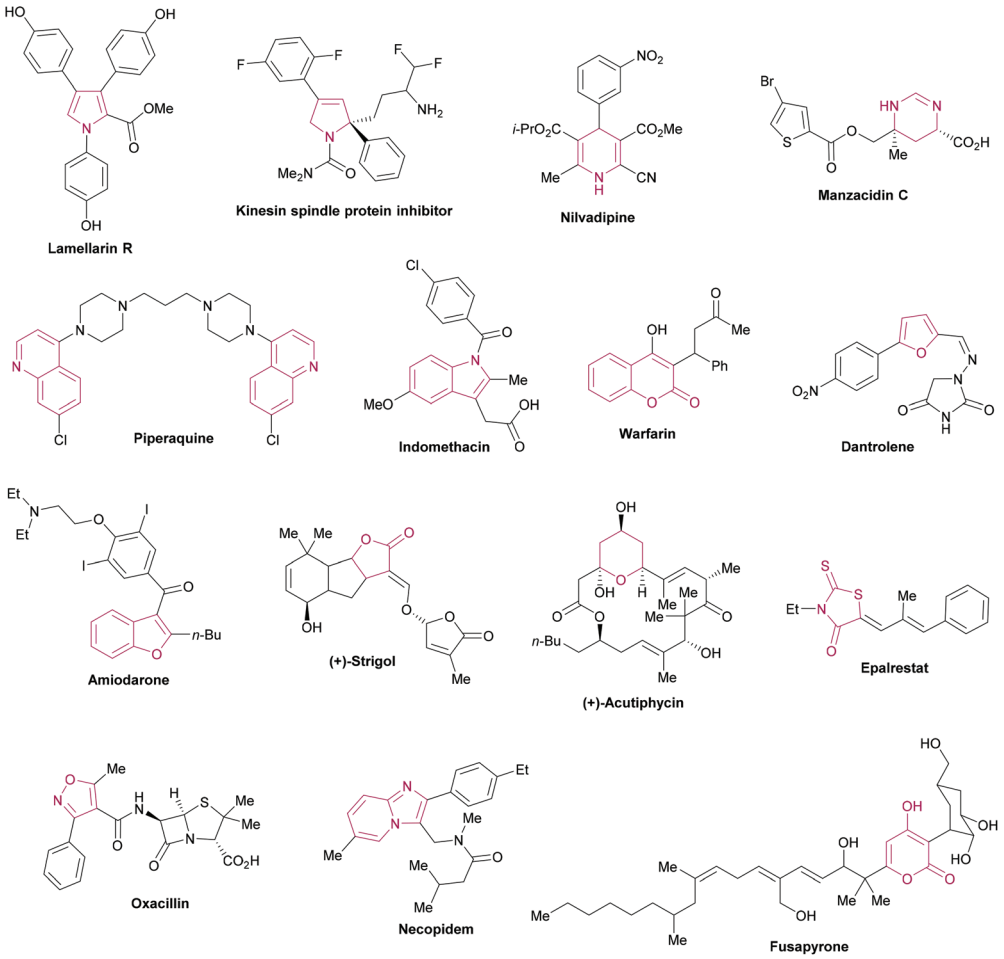


Fig. 1 Selected examples of heterocycles reported in the literature and included in the current review.

Aliya Ibrar

Aliya Ibrar received her PhD degree in organic chemistry from Quaid-i-Azam University, Islamabad, Pakistan under the supervision of Prof. Dr Aamer Saeed, working on the design and synthesis of coumarinyl-based bioactive heterocycles. She is the recipient of the Indigenous 5000 Ph.D. Fellowship from the Higher Education Commission of Pakistan. She has also been a visiting research fellow at the University of Oxford (UK), working in the group of Prof. S. G. Davies. She has also served as an assistant professor of organic chemistry at the COMSATS University, Islamabad, Abbottabad campus, Pakistan, before joining the University of Haripur, Pakistan. Her current research interests include heterocyclic chemistry, focused mainly on the development of new synthetic methodologies, and medicinal chemistry with a particular interest in the discovery and development of bioactive five- and six-membered heterocycles.

directly attached to an electron-withdrawing ester group and its transformation into double or single bonds. The mechanistic details of the selective transformations as well as the post-synthetic manipulations (Suzuki–Miyaura cross-coupling, Buchwald–Hartwig amination, oxidation and hydrogenolysis reactions among many others) have also been included. The robust use of these methods in the synthesis of natural products, pharmaceuticals and bioactive drug candidates has also been discussed. Selected examples of heterocycles accessed by using DMAD and DEAD as coupling units have been reviewed previously;[86–92] thus they have not been discussed exhaustively here and are excluded from the scope of this review except a few representative examples demonstrating the diversity of transformations.

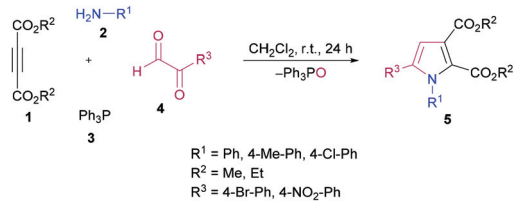
2. Synthetic methods

2.1. Synthesis of nitrogen-containing heterocycles

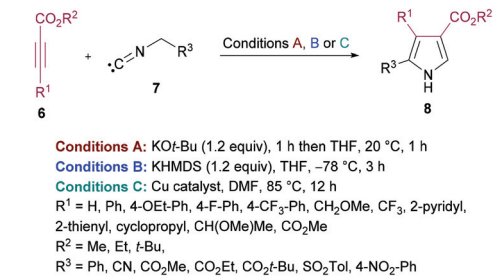
Nitrogen-containing heteroaromatic skeletons are well-recognized structural motifs of numerous pharmaceuticals, natural products and bioactive drug molecules. These heterocyclic

entities also find several useful applications in organic dyes for solar cells and as important building units in organic chemistry.[93] Therefore, environmentally benign and green synthetic approaches to access these N-heterocycles need unlocking under mild reaction conditions.

2.1.1. Synthesis of pyrroles. Anary-Abbasinejad and co-workers[94] developed a facile one-pot multi-component approach to access highly functionalized pyrroles **5** (Scheme 1). The reaction was performed using dialkyl acetylenedicarboxylates **1**, aromatic amines **2**, triphenylphosphine **3**, and arylglyoxals **4** in dichloromethane at room temperature. Various amines and arylglyoxals were tested to broaden the reaction scope and the anticipated products were furnished in good yields.



Scheme 1 Synthesis of highly functionalized pyrroles *via* a multi-component approach.

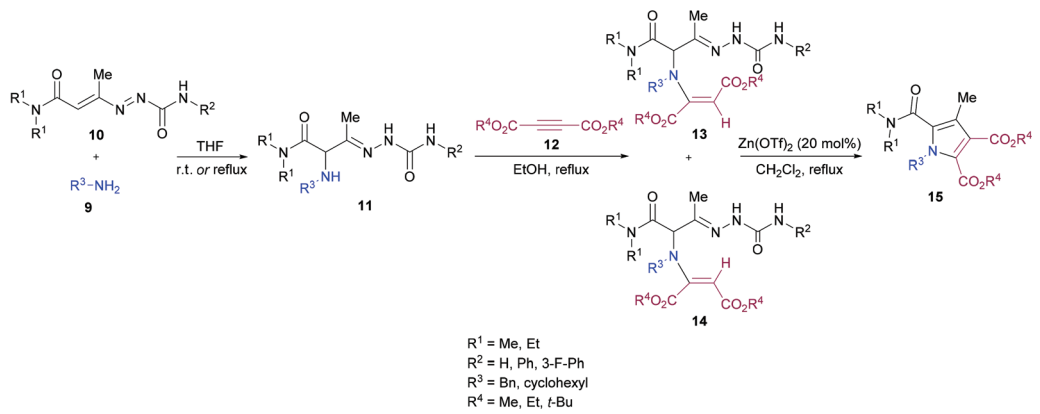


Scheme 2 Synthesis of oligosubstituted pyrroles from substituted methyl isocyanides and acetylenes.

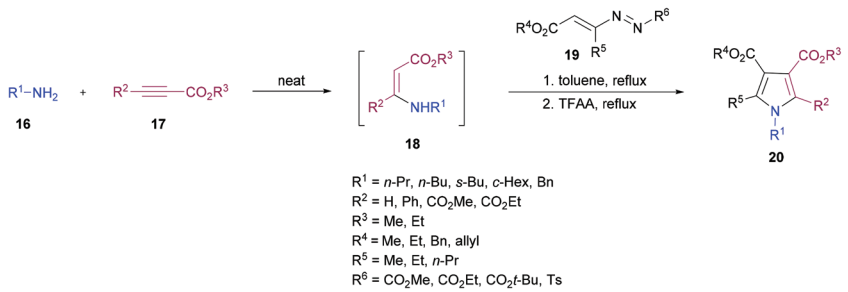
de Meijere and co-workers[95] reported a formal cycloaddition of α-metallated methyl isocyanides **7** and electron-deficient acetylenes **6** to access a range of oligosubstituted pyrroles **8**. The corresponding products were isolated in 25–97% yields (Scheme 2). Three different procedures have been developed. Initially, potassium *tert*-butoxide was employed (method A) which was replaced with potassium bis(trimethylsilyl)amide (KHMDS) added simultaneously with the corresponding acetylene (method B). Lastly, the reactions were performed using a copper catalyst. Several copper sources were employed; however, CuSPh remained the optimal. In all the copper catalysts, the σ-donating character of the counterion was the common property. Using all the three methods, various isocyanides and electron-deficient alkynes were successfully cyclized into the corresponding products.

Mantellini and co-workers[96] established a facile Lewis acid-catalyzed approach for the construction of highly functionalized pyrroles **15** from α-aminohydrazones **11** and dialkyl acetylenedicarboxylates **12** (Scheme 3). α-Aminohydrazones were in turn synthesized from primary amines **9** and 1,2-diaza-1,3-butadienes **10** *via* Michael addition. Initially, various Lewis/Brønsted acid catalysts were screened and the results revealed that $Zn(OTf)_2$ alongside $ZnCl_2$, $Zn(TfO)_2$, $In(TfO)_3$, $Yb(TfO)_3$, $InCl_3$ and $InBr_3$ produces the best conversions; however, in the case of $Zn(OTf)_2$, the reaction time was 0.5 h. Using this catalyst, various pyrrole derivatives were synthesized. This methodology was expedient due to the use of simple and easily accessible starting materials like 1,2-diaza-1,3-butadienes, used as building units in the construction of aza-heterocycles, as well as the mild experimental conditions.

Favi and co-workers[97] introduced a new acid-catalyzed sequential three-component protocol for the rapid assembly of functionalized pyrroles **20** from amines **16**, alkynoates **17** and 1,2-diaza-1,3-dienes **19** (Scheme 4). The reaction proceeds in a regioselective manner with the formation of an enamino ester intermediate followed by Michael addition and subsequent azaheterocyclization. After extensive screening of reaction parameters, suitable conditions were identified. The substrate scope was examined using a model system. Various amines,



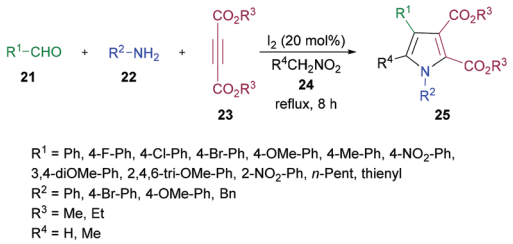
Scheme 3 Lewis acid-catalyzed synthesis of functionalized pyrroles.



Scheme 4 Acid-catalyzed sequential three-component synthesis of substituted pyrroles from amines, alkynoates and 1,2-diaza-1,3-dienes.

alkynoates and 1,2-diaza-1,3-dienes were tolerated to afford the desired pyrrole derivatives. In the case of aliphatic amines, the acid-promoted enamine–azoene cyclization failed due to the reduced nucleophilicity of the amine nitrogen atom. Moreover, DMAD, DEAD, ethyl propiolate and ethyl 3-phenylprop-2-ynoate were successfully coupled delivering the anticipated products in moderate to good yields. The reaction conditions also tolerated various 1,2-diaza-1,3-dienes with a variety of different functional groups.

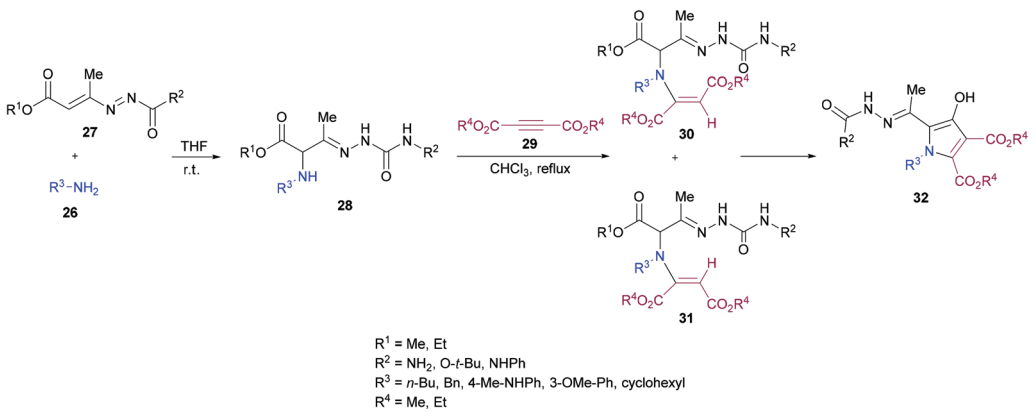
In another study, Das and co-workers[98] demonstrated the synthesis of polysubstituted pyrrole derivatives **25** from an iodine-catalyzed one-pot four-component process involving aldehydes **21**, amines **22**, dialkyl acetylenedicarboxylates **23** and nitromethane **24**. The corresponding tetrasubstituted pyrroles were isolated in good yields (Scheme 5). Using 20 mol% of molecular iodine, the scope of pyrrole formation was examined. A range of aldehydes, amines, and dialkyl acetylenedicarboxylates were tested. Both aromatic and heteroaromatic aldehydes with various functional groups (electron-rich, electron-deficient) participated well in the reaction. However, aliphatic aldehydes remained reluctant to produce the corresponding pyrroles.



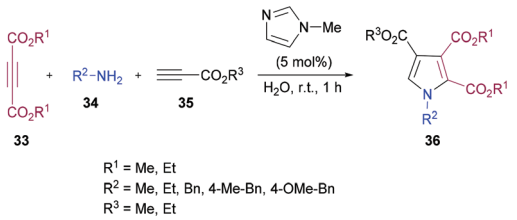
Scheme 5 Iodine-catalyzed four-component synthesis of tetrasubstituted pyrroles from aldehydes, amines, alkynoates and nitromethane.

Building on their previous work,[96] Mantellini and co-workers[99] demonstrated the synthesis of pyrrole derivatives **32** (Scheme 6). The reaction sequence involves the generation of α-aminohydrazones **28** by Michael addition of primary amines **26** to 1,2-diaza-1,3-dienes **27** followed by the coupling with dialkyl acetylenedicarboxylates **29** to produce α-(*N*-enamino)-hydrazones **30**, **31** which were cyclized to the corresponding pyrroles **32**. α-Amino ketones were replaced with α-aminohydrazones in this methodology. Among the different Lewis acids screened for this transformation, $Zn(OTf)_2$ (20 mol%) produced the best results in dichloromethane under reflux. In general, this method was widely applicable for the construction of more complex systems using mild conditions from stable and easily accessible building blocks.

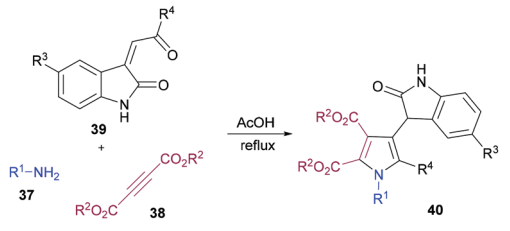
Sayyed-Alangi and co-workers[100] synthesized a range of functionalized pyrroles **36** from a one-pot multi-component methodology using dialkyl acetylenedicarboxylates **33**, primary amines **34** and propiolates **35** in the presence of *N*-methylimidazole in water at room temperature (Scheme 7).



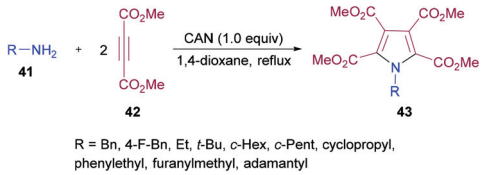
Scheme 6 Zinc(II) triflate-catalyzed divergent synthesis of polyfunctionalized pyrroles.



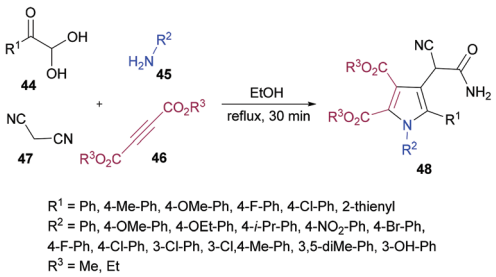
Scheme 7 Synthesis of highly functionalized pyrroles from primary amines and activated acetylenes in water.



Scheme 8 One-pot synthesis of tetrasubstituted pyrroles from arylamines, acetylenedicarboxylates and 3-phenacylideneoxindoles.



Scheme 9 CAN-mediated synthesis of pentasubstituted pyrroles from dimethyl acetylenedicarboxylates and amines.



Scheme 10 Four-component domino synthesis of polysubstituted pyrroles.

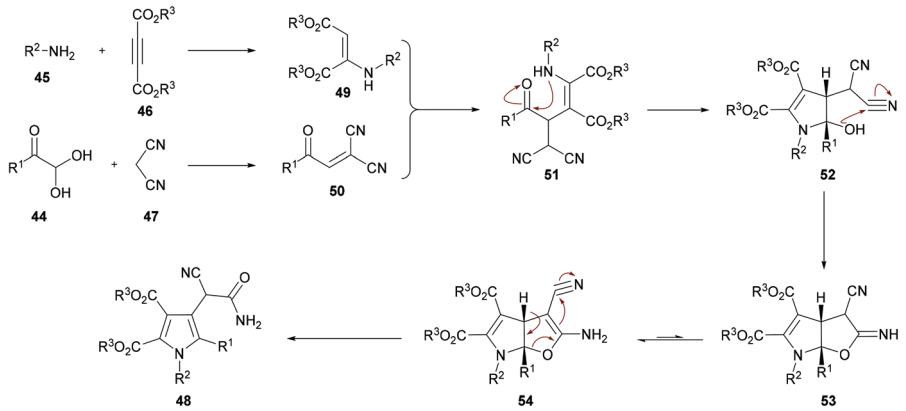
The products were furnished in good yields. The easy availability of the starting materials and their cyclization to pyrrole compounds in water were the key features of this procedure.

Yan and co-workers[101] also utilized a one-pot domino methodology to prepare pentasubstituted pyrroles **40** from arylamines **37**, acetylenedicarboxylates **38**, and 3-phenacylideneoxindoles **39** (Scheme 8). Initially, *p*-methylaniline was treated with dimethyl acetylenedicarboxylate to furnish the β-enamino ester which was coupled with 3-*p*-chlorophenacylideneoxindole in refluxing acetic acid to afford the corresponding pentasubstituted pyrrole in 74% yield. Later, the scope and versatility of the domino reaction were explored with differently substituted arylamines. Benzylamine, α-phenylethylamine and β-phenylamines were used. In addition, 3-phenacylideneoxindoles incorporating both electron-donating (methyl, methoxy) and inductively electron-withdrawing (chloro) substituents participated efficiently under the optimized set of reaction conditions. All the reactions provided smooth cyclization to nitrogen heterocycles in good yields. It is interesting to note that isatinyl substituted products obtained using this method are unusual because under normal circumstances the reaction of isatin and 3-isatinylidene compounds usually provides spirocyclic oxindoles.[102]

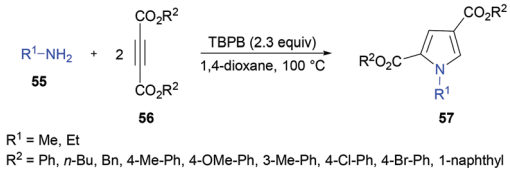
Madabhushi and co-workers[103] reported a facile approach for the preparation of fully functionalized pyrrole derivatives **43** from amine **41** and dimethyl acetylenedicarboxylate **42** using ceric(IV) ammonium nitrate (Scheme 9). The cyclocondensation of two units of DMAD and one unit of primary amine resulted in the formation of a symmetrical pentasubstituted pyrrole. The best results were obtained in 1,4-dioxane using 1.0 equivalent of CAN. A diverse variety of primary amines (benzylamine, α-methyl benzylamine, ethylamine, *t*-butylamine, cyclopropylamine, cyclopentylamine, cyclohexylamine, adamantylamine) were successfully coupled to form the corresponding *N*-alkyl pyrrole compounds in generally good yields.

Huang, Shi and co-workers[104] described a highly efficient metal-free multi-component domino procedure for the construction of multisubstituted pyrroles **48** from the reaction of arylglyoxal monohydrate **44**, aniline **45**, alkynoate **46**, and malononitrile **47** (Scheme 10). Various reaction parameters were screened to obtain the optimal conditions. The results indicated that using equimolar quantities of all the starting materials, the desired product was isolated in 81% yield in ethanol under reflux conditions. Under the optimal conditions, the substrate scope was investigated. Various substituents (methoxy, methyl, fluoro, chloro) on the aryl ring of glyoxal as well as heteroarylglyoxal worked well alongside aliphatic substituents. Similarly, anilines containing electron-rich and electron-deficient substituents were also well endured and the corresponding pyrrole products were obtained in good yields. However, the reaction showed no progress when methyl (or ethyl) 2-cyanoacetate was employed with phenylglyoxal monohydrate, 4-methylaniline, and dimethyl but-2-ynedioate under the optimized reaction conditions.

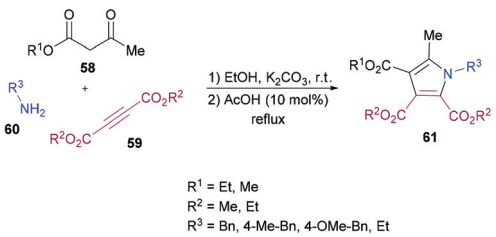
Based on the literature reports (Shu *et al.*, 2013)[105] and the results obtained from this domino process, the proposed mechanism is illustrated in Scheme 11 which starts with the addition of aniline **45** to alkyne **46** to generate intermediate **49**. Simultaneously, Knoevenagel condensation of arylglyoxal monohydrate **44** and malononitrile **45** produced intermediate **50**. Michael addition of β-enamino ester **49** to intermediate **50** afforded **51**, which was cyclized *via* intramolecular nucleophi-



Scheme 11 Proposed mechanism for the formation of highly substituted pyrroles **48**.



Scheme 12 TBPB-mediated synthesis of trisubstituted pyrroles from alkynoates and amines.



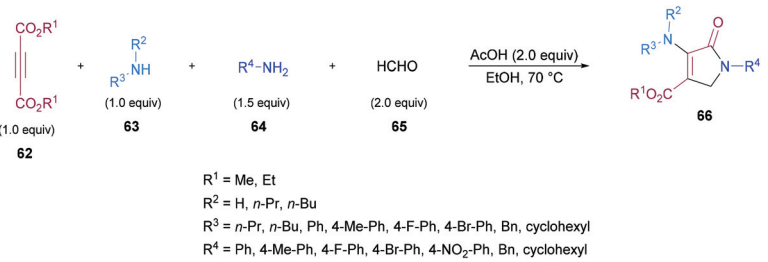
Scheme 13 Synthesis of pentasubstituted pyrroles from alkyl acetoacetates, dialkyl acetylenedicarboxylates and amines.

lic addition to deliver intermediate **52**. Another intramolecular cyclization of **52** produced **53**, which tautomerized to the more stable intermediate **54**. Finally, a ring-opening reaction of intermediate **54** furnished the polysubstituted pyrrole **48**. Furthermore, density functional theory (DFT) calculations were performed at the B3LYP/6-31G level of theory for intermediates **53** and **54** and the results suggested that intermediate **54** could be easily transformed into the more stable pyrrole product **48**.

Liu and co-workers[106] described a tandem cyclization for the construction of heterocycles through the formation of new carbon–carbon and carbon–nitrogen bonds (Scheme 12). 1,2,4-Trisubstituted 1*H*-pyrroles **57** were synthesized from amines **55** and alkynoates **56** in the presence of *tert*-butyl perbenzoate (TBPB). A model reaction was used to develop the optimized reaction parameters using dimethyl but-2-ynedioate and *p*-toluidine in dioxane at 100 °C in the presence of TBHP. Dimethyl 1-*p*-tolyl-1*H*-pyrrole-2,4-dicarboxylate was obtained in 92% yield when 2.3 equivalents of TBHP was employed in dioxane. Using these conditions, the substrate scope was investigated. A diverse range of alkynoates and amines were coupled to generate heterocyclic products. The presence of electronically different substituents on the amine ring imparted a significant effect on the yield of the corresponding product. Substrates bearing electron-rich groups provided superior results whereas those bearing strongly electron-deficient (NO_2) groups did not show reactivity. Aliphatic amines also successfully delivered the corresponding pyrroles in excellent yields. On the other hand, diethyl but-2-ynedioate produced the desired pyrrole in 79% isolated yield. However, other alkynoates such as ethyl but-2-ynoate, ethyl 3-phenylpropiolate, and methyl oct-2-ynoate did not produce any product under the optimized reaction conditions.

Mehrabi and co-workers[107] developed a metal-free one-pot two-step synthetic protocol involving alkyl acetoacetates **58**, dialkyl acetylenedicarboxylates **59** and amines **60** to access a range of pentasubstituted pyrroles **61** (Scheme 13). The reaction sequence produces 4-hydroxypenta-1,3-diene-tricarboxylates in the first step followed by cyclization with amines. The heterocyclic products were isolated in excellent yields. The reaction parameters were mainly optimized for the second step where the solvent, temperature, time, and amount of acid were screened. Although 4-hydroxypenta-1,3-diene-tricarboxylates underwent cyclization successfully at room temperature, a slight increase in the yield was noticed under reflux conditions. With an optimized set of reaction conditions, the possibility of using various starting materials to produce functionalized pyrroles was explored. The results indicated that the reactions proceeded smoothly to furnish the pyrrole product in good to excellent yields. Aromatic amines bearing different substituents as well as alkyl amines were successfully coupled to 4-hydroxypenta-1,3-diene-tricarboxylates which were generated from various alkyl acetoacetates and dialkyl acetylenedicarboxylates.

2.1.2. Synthesis of dihydropyrroles. Jiang and co-workers[108] demonstrated a multi-component methodology to



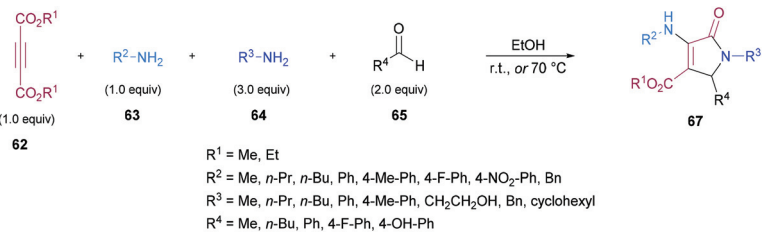
Scheme 14 Multi-component synthesis of polysubstituted dihydropyrroles.

construct tetra- and pentasubstituted dihydropyrroles **66**, **67** in good yields (Scheme 14). This process involves but-2-ynedioates **62**, amines **63**, **64**, and aldehydes **65** as starting materials. Various parameters including solvents, additives, reactant ratios, and temperature were investigated for the identification of the best reaction conditions. Using different starting materials, a range of tetrasubstituted dihydropyrroles were synthesized, no matter whether the same or different primary or secondary amines of aliphatic or aromatic nature were employed. Different substituents (methyl, fluoro, bromo) at the aryl ring were successfully tolerated.

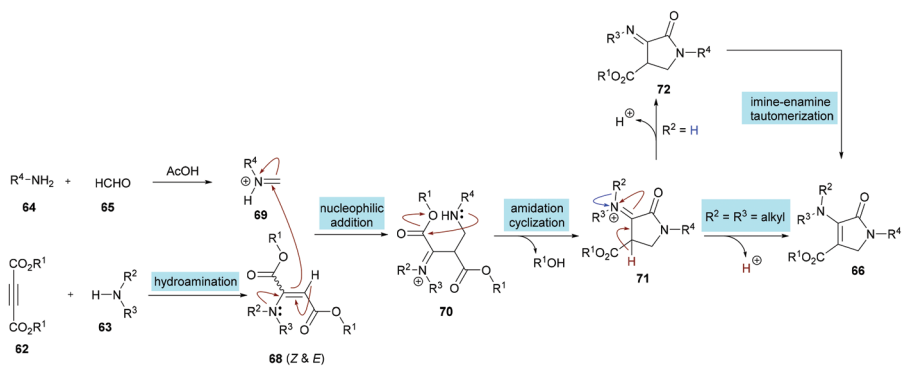
Similarly, some efforts were made to optimize the reaction conditions to produce pentasubstituted dihydropyrroles **67** using alkynoates **62**, amines **63**, **64** and aldehydes **65**; however, the order of the addition of reactants was changed. Again, the compatibility of different functional groups was tested and the corresponding dihydropyrrole products were isolated in good to excellent yields (Scheme 15).

Two different mechanistic approaches were considered for the formation of tetrasubstituted and polysubstituted dihydropyrroles. The first one comprises the domino hydroamination/nucleophilic addition/amidation–cyclization sequence (Scheme 16), whereas the second one involves the hydroamination/amidation/intramolecular cyclization/imineenamine tautomerization sequence (Scheme 17).

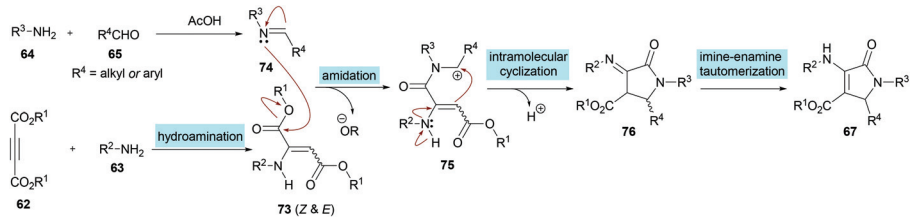
Marinetti and co-workers[109] investigated a [3 + 2] cyclization reaction between allenoates **77** or 2-butynoates **78** and imines **79** using a phosphine catalyst to deliver pyrrolines **80** (Scheme 18). The effect of imine protecting groups on the enantioselectivity was explored by comparing *N*-Ts- and *N*-DPP-imines. Under the optimized reaction conditions, good conversions were obtained when *N*-DPP-imines were used. In addition, the use of a DPP protecting group remains advantageous over the Ts group due to its easy deprotection. In the asymmetric version, good yields and enantioselectivities were observed using the (*S*)-**81** catalyst.



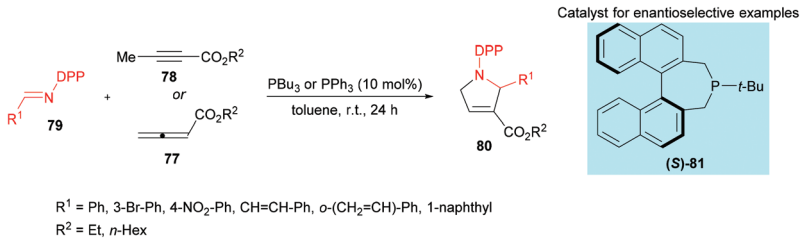
Scheme 15 Synthesis of multisubstituted dihydropyrroles from alkynoates, amines and aldehydes.



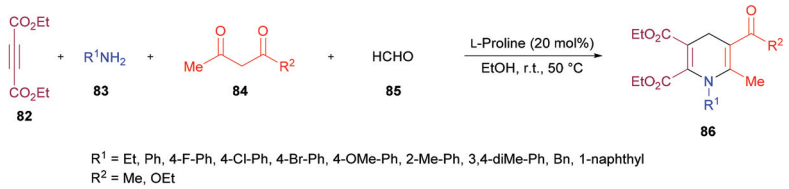
Scheme 16 Proposed mechanism for the formation of polysubstituted dihydropyrroles **66**.



Scheme 17 Proposed mechanism for the formation of polysubstituted dihydropyrroles **67**.



Scheme 18 Phosphine-catalyzed synthesis of pyrrolines from *N*-DPP-imines and allenoates/2-butynoates.

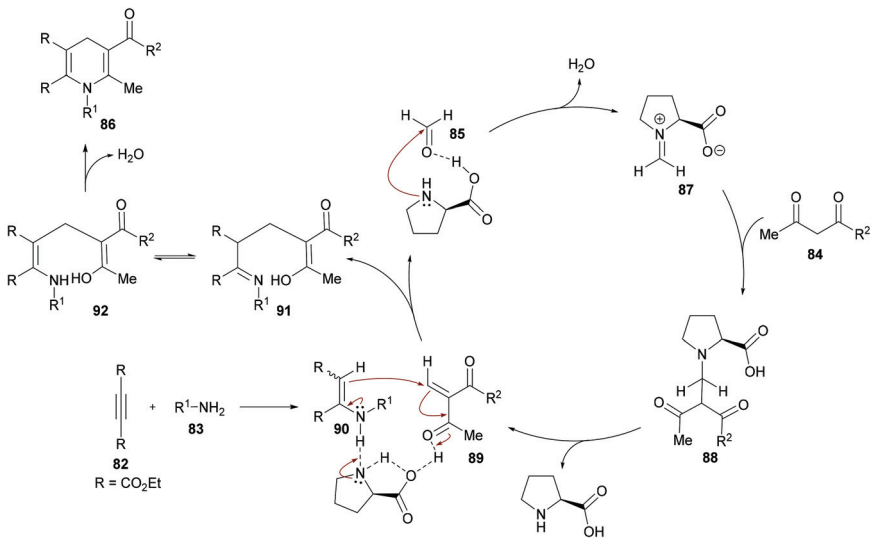


Scheme 19 L-Proline-catalyzed synthesis of highly functionalized 1,4-dihydropyridines.

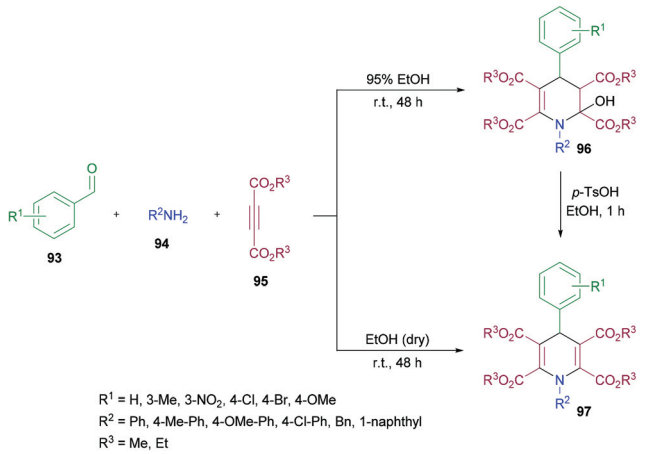
2.1.3. Synthesis of dihydropyridines. Jiang and co-workers[110] developed a new L-proline-catalyzed one-pot four-component reaction methodology for the facile synthesis of densely functionalized 1,4-dihydropyridines **86** from alkynoates **82**, amines **83**, 1,3-dicarbonyl compounds **84** and aldehydes **85** (Scheme 19). The process operates under environmentally benign conditions involving various reactions such as hydroamination/Knoevenagel condensation/Michael-type addition/intramolecular cyclization and delivers 1,4-dihydropyridines in moderate to good yields. After screening various catalysts, L-proline was identified as the optimal. Other reaction parameters including solvents, reactant ratios, and temperature were also considered to obtain the optimized set of conditions. The scope and diversity of 1,4-dihydropyridines were realized where the different electronic nature of the functional groups on the aryl ring of the amines showed a minor impact on the reactivity. As such, electron-rich substituents showed preference over electron-deficient systems producing the anticipated products in higher yields. Sterically hindered amines were also effective coupling partners alongside aliphatic primary amines that showed higher reactivity than the aromatic ones. A limited diversification around the other coupling partners was also investigated.

The authors proposed the reaction mechanism which starts with the activation of aldehyde carbonyl by hydrogen bonding from L-proline and subsequent attack of the proline nitrogen on the activated carbonyl to generate intermediate **87** which on Knoevenagel condensation with 1,3-dicarbonyl compound **84** furnished **88**. Knoevenagel product **89** was obtained with the regeneration of L-proline.[111–113] Meanwhile intermediate **90** was formed by the addition of amines to alkynes which on Michael-type addition to **89** furnished intermediate **91**. The tautomerization of **91** to **92** followed by an intramolecular cyclization provided 1,4-dihydropyridine **86** (Scheme 20).

Yan and co-workers[114] established a one-pot three-component methodology incorporating aldehydes **93**, aromatic amines **94** and acetylenedicarboxylates **95** to afford 2-hydroxyhydropyridines **96** (Scheme 21). Based on the literature reports (Ziyaei-Halimehjani & Saidi, 2008; Glotova *et al.*, 2009; Li *et al.*, 2009; Yavari *et al.*, 2010; Jiang *et al.*, 2010)[115–119] that conjugate addition of aniline to acetylenedicarboxylates smoothly provides 2-(phenylamino)but-2-enedioate, the authors believed that double conjugate addition is possible if another molecule of acetylenedicarboxylates is present in the reaction system. With this idea in mind, they started investigating a range of conditions to identify the optimal parameters for this methodology. The required product was formed in 71% yield in ethanol at room temperature with the presence of an unexpected hydroxyl group at the C-2 position presumably resulting from a hydration step in the reaction process. Other sol-



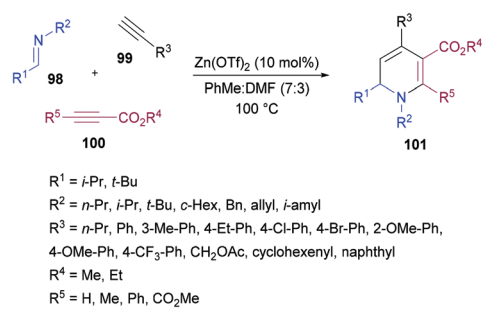
Scheme 20 Proposed mechanism for the formation of 1,4-dihydropyridines **86**.



Scheme 21 Three-component synthesis of 2-hydroxyhydropyridines and 1,4-dihydropyridines from aromatic aldehydes, arylamines and acetylenedicarboxylates.

vents including tetrahydrofuran, acetonitrile, dichloromethane and chloroform retarded the reaction. Similarly, elevated temperatures and the addition of a base to the reaction pot provided a complex mixture of unidentified compounds. The reaction scope was assessed with several aromatic aldehydes as well as amines and the desired dihydropyridine products were isolated in 70–87% yields. Both electron-donating and electron-withdrawing substituents were equally tolerated in the reaction. α-Naphthylamine and benzylamine also provided the corresponding 2-hydroxyhydropyridines in good isolated yields. In addition, the reaction was also performed under inert conditions using absolute ethanol to avoid the formation of 1,4-dihydropyridines **97** bearing a hydroxyl group at the C-2 position and the required products were isolated in 68–81% yields. Similar results were obtained when *p*-toluenesulfonic acid (TsOH) was employed as a catalyst to convert 2-hydroxyhydropyridines **96** to 1,4-dihydropyridines **97** in ethanol under reflux.

Tehrani and co-workers[120] developed a $Zn(OTf)_2$-catalyzed three-component cascade approach to produce less explored 1,6-dihydropyridines **101** from aldimines **98**, terminal alkynes **99** and electron-deficient alkynes **100**. The heterocyclic products were achieved in good to excellent chemical yields (Scheme 22). In a mixture of solvents (toluene and DMF), various reaction parameters such as the catalyst and temperature were screened. Other catalysts including $ZnBr_2$, ZnI_2, $Zn(OAc)_2$, $Cu(OTf)_2$ and $CuBr_2$ were less effective. The reaction scope was explored by testing a range of aldimines and ketimines in the first instance. The anticipated products were isolated in good yields. The variation of the alkyne component was also examined. Both aromatic and aliphatic alkynes were successfully tolerated. The presence of electron-rich and electron-deficient substituents on the aryl ring of alkynes had no influence on the reactivity of this cascade process. The use of electron-deficient propiolates instead of DMAD produced the 1,6-dihydropyridine heterocycle with the regiospecific incorporation of the ester moiety.



Scheme 22 $Zn(OTf)_2$-catalyzed three-component synthesis of highly functionalized 1,6-dihydropyridines from aldimines and two alkynes.

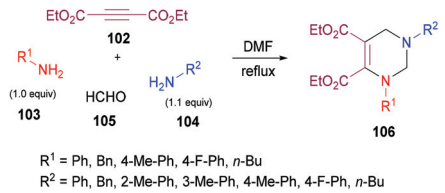
2.1.4. Synthesis of tetrahydropyrimidines. Jiang and co-workers[121] unearthed a facile and convenient one-pot multi-component approach involving alkynoates **102**, amines **103**, **104** and formaldehyde **105** to access a range of diversely functionalized tetrahydropyrimidines **106** (Scheme 23). This domino reaction works smoothly in the absence of a catalyst with the production of nitrogenous heterocycles in high yields. The relay process comprised of hydroamination, Mannich-type reaction and amine-aldehyde dehydration–cyclization sequence. After extensive screening of reaction parameters, including solvent, time and reactant ratios, the best results were furnished when but-2-ynedioic acid diethyl ester **102**/aniline **103**/formaldehyde **105**/benzylamine **104** are used in a ratio of 1 : 1 : 4 : 1.1–1.2 in DMF. Although, both aliphatic and aromatic amines were effective coupling partners, the reaction proceeded much faster with aliphatic primary amines. The reaction was also insensitive to electron-donating and electron-withdrawing substituents present on the aromatic amines. All the tetrahydropyrimidine products were formed in good to excellent yields except the *ortho*-aryl-substituted product which was obtained in a lower yield (62%).

In a subsequent study, Jiang and co-workers[122] developed two multi-component methodologies towards polysubstituted pyrimidine derivatives **111**, **112**. In the metal-free approach, electron-deficient alkynes **107**, amines **108**, **109** and formaldehyde **110** were coupled to obtain the heterocyclic product in an efficient yield (Scheme 24). The product was furnished with high regioselectivity with Markovnikov addition only. Upon the addition of two different amines, the reactivity was in favour of aliphatic amine while no product was formed when aromatic amine was added first. Various aliphatic amines were employed in this method to deliver aza-heterocycles with high yields and regioselectivities. In the second approach where aromatic amines served as potential substrates, extensive catalyst screening was performed to identify the optimized conditions favouring the hydroamination–cyclization reaction sequence. In this pursuit, $AgBF_4$/L-proline was identified as the most effective catalyst. The best working conditions include $AgBF_4$ (5 mol%) and L-proline (5 mol%) in DMF at room temperature, furnishing the desired product in 80% yield in 6 h. Using this set of conditions, various anilines bearing electron-rich (Me, OMe) and electron-deficient (F, Cl, Br, CF_3) substituents were illustrated as suitable coupling partners and the corresponding products were formed in good yields.

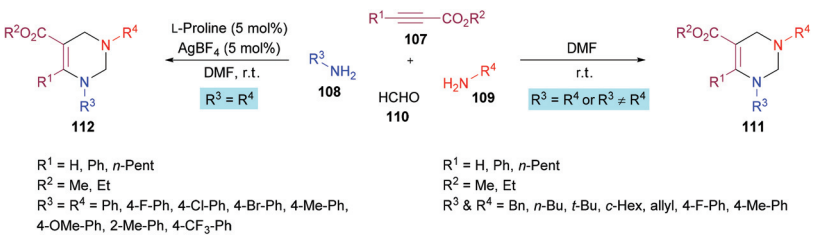
Next, the same group[123] investigated a multi-component methodology to construct functionalized tetrahydropyrimidines **117** from but-2-ynedioates **113**, amines **114**, **115**, and formaldehyde **116** (Scheme 25). After screening of the initial reaction conditions, more ambient conditions were developed, and the results were compared with the heat-promoted MCRs.[124] The products were obtained at much lower temperature and in much shorter time with higher yields.

2.1.5. Synthesis of quinolines. Asghari and co-workers[125] established the synthesis of quinoline derivatives **120** by the addition of acetylenic esters **118** to aromatic amines **119** in the presence of triphenylphosphine (Scheme 26). The initial addition of triphenylphosphine to the acetylenic ester led to functionalized phosphoranes which upon the intramolecular Wittig reaction produced the desired quinoline compounds.

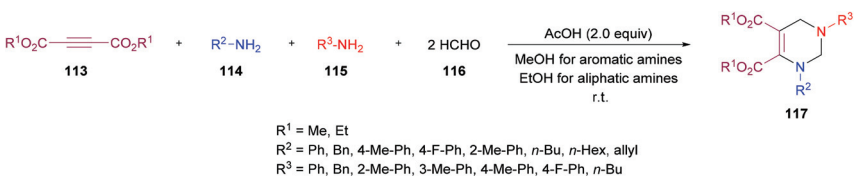
2.1.6. Synthesis of pyrrolidines and indolines. Fu and co-workers[126] demonstrated a straightforward phosphine-cata-



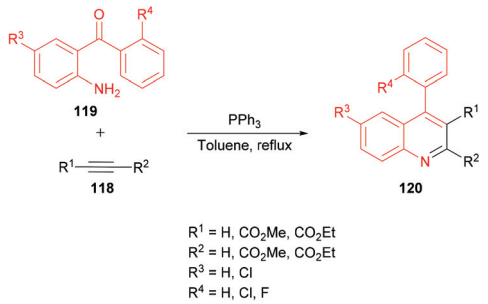
Scheme 23 Catalyst-free one-pot multi-component synthesis of polysubstituted tetrahydropyrimidines.



Scheme 24 One-pot multi-component divergent synthesis of polysubstituted tetrahydropyrimidines.



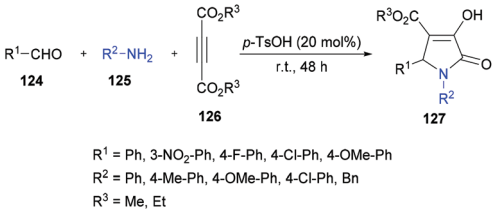
Scheme 25 Multi-component synthesis of polysubstituted tetrahydropyrimidines from alkynoates, amines and formaldehyde.



Scheme 26 Phosphine-catalyzed synthesis of 4-arylquinolines from aromatic aminoketones and alkynoates.

lyzed intramolecular approach to access highly functionalized enantioenriched nitrogenous heterocycles (pyrrolidines and indolines) **123** *via* γ C–N bond formation using alkynoate substrates **121** (Scheme 27). This enantioselective strategy also successfully tolerated various electron-withdrawing and electron-donating functional groups on the aromatic ring delivering indoline products with good enantioselectivity but with insignificant reduction in the yield. The presence of a methyl group *ortho* to nitrogen did not impede the reaction and smooth cyclization was observed towards the corresponding product in 67% yield and 88% ee.

2.1.7. Synthesis of pyrrolidinones. Based on the results obtained from the three-component methodology for the formation of 2-hydroxyhydropyridines or 1,4-dihydropyridines, Yan and co-workers[127] combined the three-component methodology with an acid-catalyzed dehydration step to afford 1,4-dihydropyridines in a convenient fashion. However, the expected product was not furnished; rather 2-hydroxytetrahydroxypyridine was formed and an unexpected pyrrolidinone derivative was generated as the major product (Scheme 28). The result was interesting because there was no literature report to construct pyrrolidinones **127** from electron-deficient alkynes in this manner. The reaction conditions were then optimized and it was revealed that stirring the aldehyde with amine in the presence of 20 mol% of *p*-toluenesulfonic acid for 30 min followed by the introduction of acetylenedicarboxylate provided the desired polysubstituted pyrrolidinone in 62% yield after 24 h. Various amines and aldehydes with dimethyl or diethyl acetylenedicarboxylates were successfully coupled with the generation of the desired pyrrolidinone products in good yields.

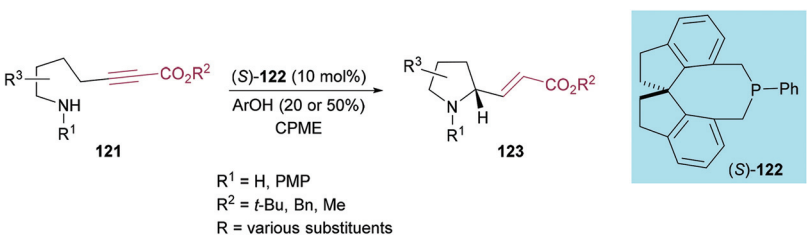


Scheme 28 Three-component synthesis of pyrrolidinones from aromatic aldehydes, arylamines and acetylenedicarboxylates.

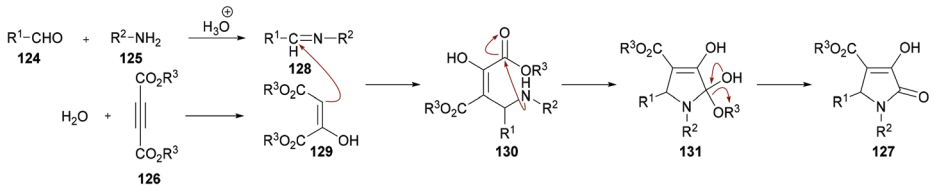
The proposed mechanism for this transformation suggests that the acid-catalyzed condensation of the aromatic aldehyde **124** with arylamine **125** produced imine intermediate **128**. Upon the addition of acetylenedicarboxylate **126** in the presence of water, intermediate **129** was generated by the nucleophilic addition of water to an electron-deficient alkyne. Then, addition of **129** to imine **128** provided intermediate **130** which was cyclized *via* an intramolecular attack of the amine nitrogen on the ester carbonyl resulting in the formation of five-membered ring **131**. Finally, the desired product **127** was delivered by the elimination of protonated alcohol (Scheme 29).

2.1.8. Synthesis of indoles. Nasiri and co-workers[128] synthesized a variety of alkyl 2(1-benzyl-2,4-dioxo-2,3,4,5,6,7-hexahydro-1*H*-indol-3-yl)acetates **134** using enaminones **132** and acetylenic esters **133** as starting materials (Scheme 30). The reactions were catalyzed by triphenylphosphine and the corresponding products were isolated in moderate yields (61–65%).

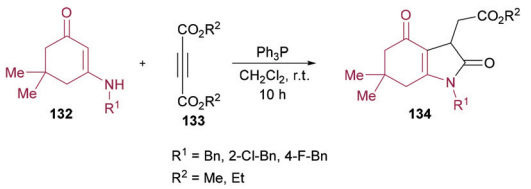
2.1.9. Synthesis of lactams. Based on the previous efforts to use alkynoates for lactone synthesis (Deng & Chuang, 2011),[129] Chuang and co-workers[130] elaborated the approach while using *N*-tosyl aldimines **135**, phosphines **136** and alkynoates **137** to deliver fluorescent γ-lactams **138** (Scheme 31). The highest reactivity was achieved in an aprotic etherate solvent (THF) at 60 °C. The reaction conditions were comparable to those previously developed for lactone synthesis.[129] The scope and generality of the three-component methodology revealed the use of various triarylphosphines and electron-deficient aldimines. A range of γ-lactam products were accessed in 49–79% yields while using different triarylphosphines containing electron-donating and electron-withdrawing substituents and 4-nitrobenzaldimine. The coupling of more nucleophilic tricyclohexylphosphine with 4-cyano aldimine furnished the desired product in a poor yield (22%). Consistent with the pre-



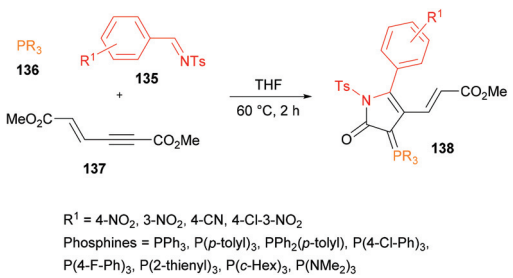
Scheme 27 Phosphine-catalyzed synthesis of pyrrolidines and indolines.



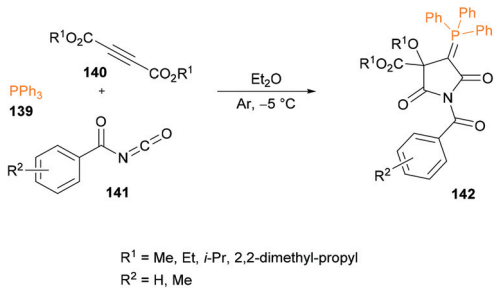
Scheme 29 Proposed mechanism for the formation of pyrrolidinones **127**.



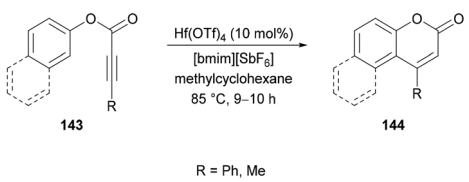
Scheme 30 Phosphine-catalyzed synthesis of alkyl 2(1-benzyl-2,4-dioxo-2,3,4,5,6,7-hexahydro-1*H*-indol-3-yl)acetates from enaminones and acetylenic esters.



Scheme 31 One-pot multi-component synthesis of γ-lactams containing an α-phosphorus ylide moiety.



Scheme 32 Three-component synthesis of highly functionalized triphenylphosphoranylidene succinimides.



Scheme 33 $Hf(OTf)_4$-catalyzed regioselective synthesis of coumarins.

vious report (Deng *et al.*, 2012),[131] electron-withdrawing aldimines were only compatible in the multicomponent reaction.

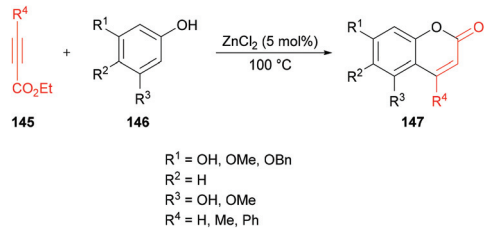
2.1.10. Synthesis of succinimides. Esmaeili and co-workers[132] described a one-pot three-component reaction for the generation of *N*-benzoyl-2-triphenylphosphoranylidene succinimide derivatives **142** from triphenylphosphine **139**, acetylenic esters **140** and aroyl isocyanates **141** (Scheme 32). The reaction performs well under metal-free conditions and the anticipated products were formed in good to high yields. Several properties such as structural, electronic, energetic and mechanistic properties were explored with density functional theory (DFT) calculations using the Gaussian 09 computational package.[133–135]

2.2. Synthesis of oxygen-containing heterocycles

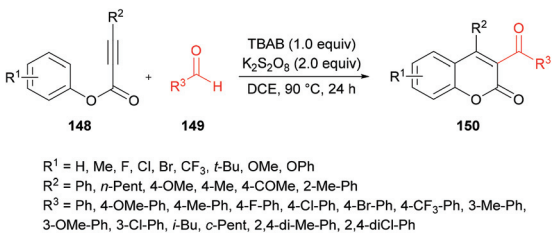
Oxygen-containing heterocycles constitute a privileged class of heterocyclic compounds that contribute enormously to the development of new medicinal and bioactive drug molecules.[136] Therefore, the development of new synthetic methods using mild reaction conditions remains an attractive field.

2.2.1. Synthesis of coumarins. Song and co-workers[137] successfully developed an intramolecular hydroarylation method for the regioselective synthesis of coumarins **144** using aryl phenylpropiolates **143** (Scheme 33). The intramolecular cyclization was catalyzed by $Hf(OTf)_4$ in a mixture of an ionic liquid and methylcyclohexane. The reaction was high yielding at 85 °C for 9–10 h. Aryl 2-butynoate was also tested as a promising substrate and the corresponding coumarin was obtained in 89% yield. However, a lower stabilizing effect of the alkyl group compared to the phenyl group promoted self-oligomerization of the alkynes featuring alkyl substituents. In general, the explored methodology employing an ionic liquid provided an alternative approach to access a diverse variety of products where conventional methods showed a hindered scope.

Costa and co-workers[138] made use of a Lewis acid (zinc chloride) as an efficient catalyst for the construction of coumarins **147** by the hydroarylation of acetylenic esters **145** with oxygenated phenols **146** under solvent-free conditions (Scheme 34). The products were formed in moderate to good yields. The initial reaction of benzene-1,3,5-triol and ethyl propiolate provided the required coumarin in 88% yield. It was worth noting that similar yields were reported by Kaufman and Kelly;[139] however, a stoichiometric amount of the catalyst ($ZnCl_2$) was required, and the reaction time was 12 h. This procedure was improved, delivering the desired coumarins in



Scheme 34 Synthesis of coumarins through zinc chloride catalyzed hydroarylation of acetylenic esters with phenols.



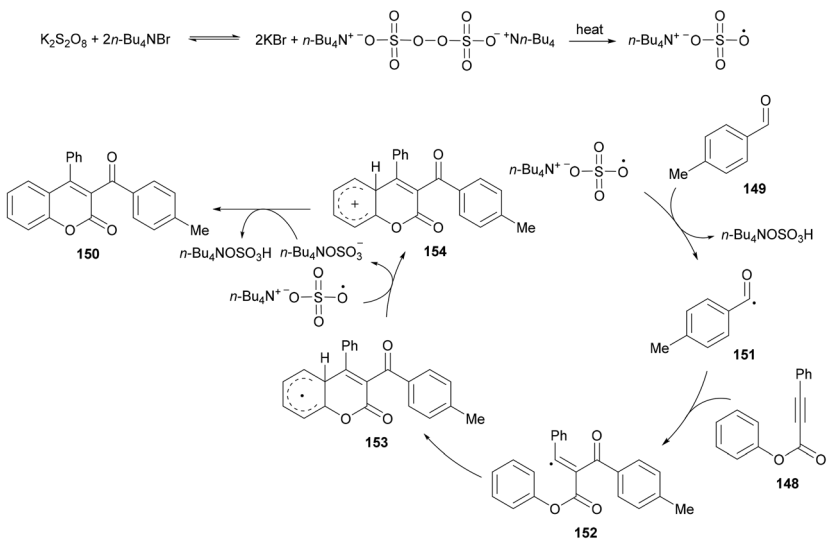
Scheme 35 Synthesis of 3-acyl-4-arylcoumarins *via* metal-free tandem oxidative acylation/cyclization of alkynoates and aldehydes.

pleasing yields after a reaction time of 5–60 minutes in most of the cases.

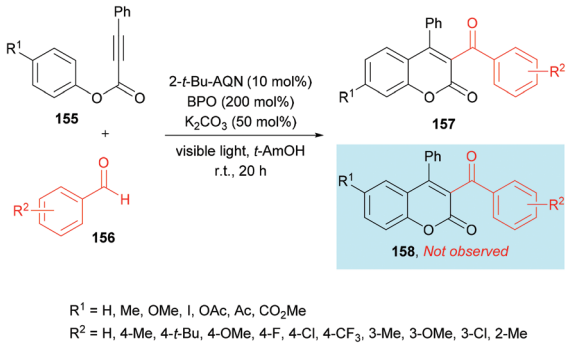
Mi *et al.*[140] developed a metal-free tandem acylation/cyclization method using alkynoates **148** and aldehydes **149** for the generation of substituted coumarins **150** (Scheme 35). This method offers the instantaneous formation of two new C–C bonds *via* C–H functionalization. Regarding the literature methods,[141–148] which suffer several drawbacks including a hindered substrate scope, low atom-economy and toxic reagents, the present protocol realizes a general and direct approach to 3-acylcoumarins. The reaction scope was fairly general, and several functional groups showed great compatibility under the optimal conditions. However, due to a strongly electron-deficient group (CF_3) on the phenoxy ring of the alkynoate, the desired product was furnished in 38% yield. In addition, the steric effect was also quite distinct on the phenoxy ring and in the case of an *ortho*-substituted system, no reactivity was observed. Alkynoates bearing alkyl substituents were also unreactive.

Based on the previous reports (Liu *et al.*, 2011; Shi & Glorius, 2013; Luo *et al.*, 2014),[149–151] the authors proposed a radical mechanism for tandem oxidative acylation/cyclization (Scheme 36). Peroxydisulfate was converted to bis(tetrabutylammonium) peroxydisulfate upon reaction with TBAB which was transformed into tetrabutylammonium sulfate radical anions on heating.[152,153] The reaction of the tetrabutylammonium sulfate radical with **149** produces the acyl radical **151** which adds selectively to the α-position of the C=O bond in **148** producing vinyl radical **152**. Cyclization of **152** then afforded the radical intermediate **153** which subsequently converted into cation **154** *via* single electron transfer (SET). The intermediate **154** was deprotonated to give the desired product **150.**

Similarly, Yamaguchi, Itoh and co-workers[154] developed the synthesis of 3-acyl-4-arylcoumarins **157** using alkynoates **155** and simple aldehydes **156** under radical cyclization conditions (Scheme 37). A photocatalyzed generation of acyl radicals was achieved using aldehydes under metal-free and mild reaction conditions. Based on previous reports (Tada *et al.*, 2011; Tada *et al.*, 2012; Shimada *et al.*, 2013),[155–157] anthraquinone derivatives (AQNs) were employed where an O-centered radical of ^{3}AQN* can trap a hydrogen atom. Phenyl-2-propynate and *p*-tolualdehyde were chosen as model substrates to investigate the reactivity profile of various reaction parameters in the radical addition/cyclization strategy. Photocatalysts including eosin Y, $Ru(bpy)_3Cl_2$ and 2-*tert*-butylanthraquinone (2-*t*-Bu-AQN) were employed alongside a range of oxidants (BPO,



Scheme 36 Proposed mechanism for the formation of 3-acyl-4-arylcoumarins **150**.

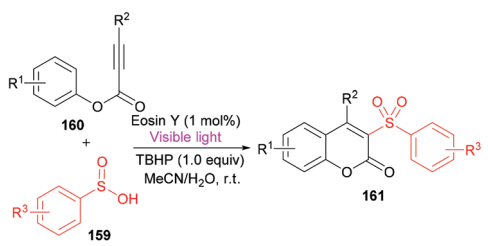


R^1 = H, Me, OMe, I, OAc, Ac, CO_2Me
R^2 = H, 4-Me, 4-*t*-Bu, 4-OMe, 4-F, 4-Cl, 4-CF_3, 3-Me, 3-OMe, 3-Cl, 2-Me

Scheme 37 Synthesis of 3-acyl-4-arylcoumarins from alkynoates and aldehydes under radical cyclization conditions.

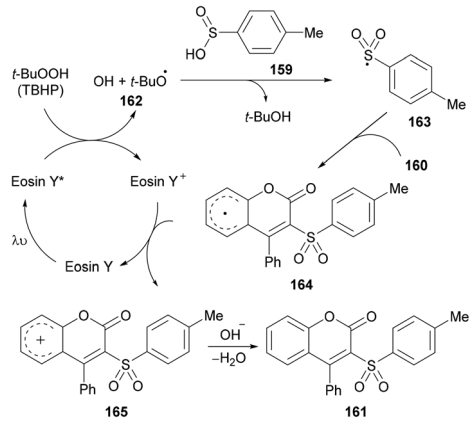
$K_2S_2O_8$, H_2O_2, DTBP) under visible light irradiation. The role of bases (K_2CO_3, Na_2CO_3, KOH, Et_3N) was also investigated. The screening results indicated that acylcoumarins could be furnished in the best isolated yields when the reaction mixture containing 2-*t*-Bu-AQN (10 mol%), BPO (200 mol%), and K_2CO_3 (50 mol%) in *t*-amyl alcohol was irradiated with four 23 W lamps under an argon atmosphere. Benzaldehydes bearing various substituents such as methyl, *tert*-butyl, fluoro, chloro, trifluoromethyl, and methoxy at the 3- and 4-positions of the phenyl ring produced the corresponding 3-acyl-4-arylcoumarins in 47–77% yields. Next, the scope of the reaction was examined with various alkynoates representing structural diversification at the *para*-position of the phenoxy ring. Both electron-donating (methyl, methoxy) and electron-withdrawing (iodo, ester, acetyl, acetoxy) groups were compatible and furnished the desired products in 58–79% isolated yields. With *meta*-substituted alkynoates, two regioisomers were obtained except in the case of methoxy-substituted substrates; however, *ortho*-substituted substrates failed to produce the desired coumarin.

Wang and co-workers[158] utilized sulfinic acids **159**, versatile and readily available intermediates,[159,160] for the formation of coumarin derivatives **161** (Scheme 38). The oxidative cyclization of phenyl propiolates **160** was achieved at room temperature under metal-free conditions. This visible-light induced transformation offered several advantages including broad functional group acceptance, good yields and high regio-



R^1 = H, Me, Et, *i*-Pr, *t*-Bu, Ph, OMe, F, I, Br, Cl, 2,4-di-Me
R^2 = Ph, 4-Me-Ph, 3-Me-Ph
R^3 = H, 4-Me, 4-F, 4-Cl, 4-Br, 2-Cl, 3-CF_3-4-Cl

Scheme 38 Synthesis of coumarins through visible light initiated oxidative cyclization of aryl propiolates with sulfinic acids.

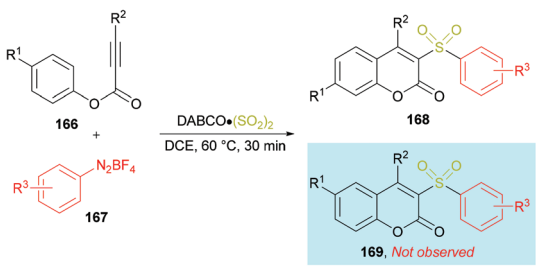


Scheme 39 Proposed mechanism for the formation of 3-sulfonated coumarins **161**.

selectivity except alkyl substituents which were found to be unreactive.

After several control experiments and based on the literature reports (Lu *et al.*, 2013; Luo *et al.*, 2014; Wei *et al.*, 2014; Ouyang *et al.*, 2014),[150,161–163] the authors proposed a mechanism for this photoreaction (Scheme 39). The initial radical formation (*tert*-butoxyl radical **162**) took place by a SET process by the reaction of the excited state of eosin Y* with TBHP. Next, the corresponding sulfonyl radical **163** was produced by the abstraction of a hydrogen radical from 4-methylbenzenesulfinic acid **159** which was transformed into carbocation intermediate **165** *via* radical intermediate **164**. Finally, intermediate **166** was deprotonated to deliver the desired 3-sulfonated coumarins **161**.

Wu and co-workers[164] reported a catalyst-free approach for the efficient synthesis of 3-sulfonated coumarins **168** from aryl propiolates **166** (Scheme 40). Sulfonyl radicals were produced from aryldiazonium tetrafluoroborates **167** in the presence of DABCO·$(SO_2)_2$. This tandem process operates through various reaction sequences such as radical addition, spirocyclization, and 1,2-migration of esters. Phenyl propiolate and phenyldiazonium tetrafluoroborate served as the model substrates whereas DABSO was employed as a sulfonyl radical precursor.

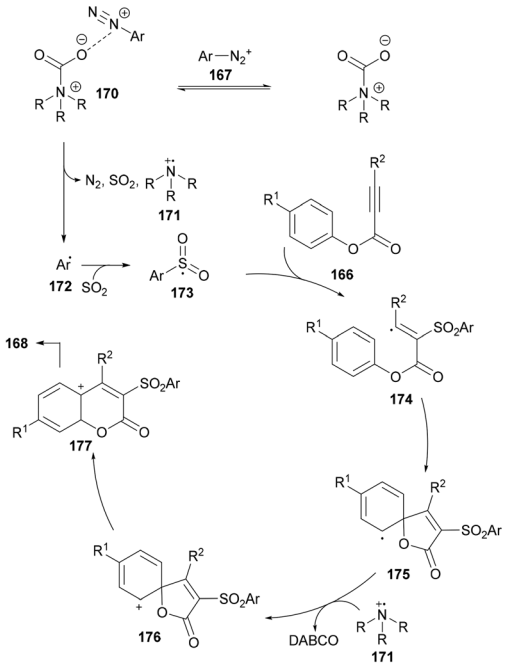


R^1 = H, Me, OMe, F, Ac, Bn
R^2 = Ph, 4-Me, 4-OMe, 4-F, 4-Cl, 2-OMe
R^3 = H, 4-Me, 4-*t*-Bu, 4-OMe, 4-Cl, 4-Br, 4-CO_2Et, 2-Cl, 2-Me, 3-Cl, 3-CO_2Me

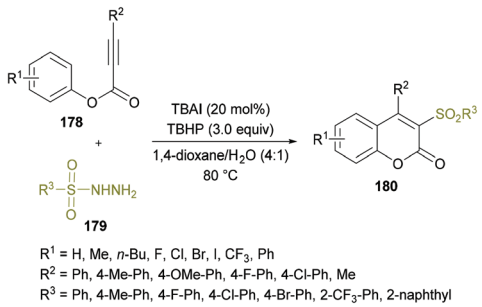
Scheme 40 Synthesis of 3-sulfonated coumarins from aryl propiolates and aryldiazonium tetrafluoroborates in the presence of DABSO.

Various reaction parameters including solvents and temperature were studied to obtain the optimal conditions (aryl propiolate (0.2 mmol), DABCO·$(SO_2)_2$ (0.4 mmol), phenyldiazonium tetrafluoroborate (0.24 mmol), DCE (1.5 mL), under an argon atmosphere, 60 °C, 30 min). Under this set of conditions, aryldiazonium tetrafluoroborates and alkynoates were smoothly cyclized to the desired 3-sulfonated coumarins in good to excellent yields. Several electronically different substituents (methyl, methoxy, *tert*-butyl, chloro, bromo, ester) on the aromatic ring of aryldiazonium tetrafluoroborates showed remarkable tolerance and produced the coumarin products in 60–95% isolated yields. Quinolinyl aryldiazonium tetrafluoroborate was also tolerated, albeit generating the sulfonated coumarin in 31% yield. On the other hand, phenyl propiolates incorporating an aryl group attached to the alkyne component showed similar reactivity. Both electron-rich (methyl, methoxy) and electron-deficient (fluoro, chloro) substituents engendered the sulfonylated heterocycle in 85–92% yields; however, the presence of an alkyl group (*tert*-butyl) completely hindered the reaction. Similarly, substrates containing substituents such as benzyl, methoxy, fluoro, and acetyl at the *para*-position of the phenoxy ring were also examined.

After performing several mechanistic experiments and in line with the literature reports, the authors proposed a possible reaction mechanism which starts with the coordination of arydiazonium cation **167** with DABSO to form the complex **170** *via* electrostatic interaction.[165] Homolytic cleavage of the N–S bond[166] in **170** then furnished the radical cation intermediate **171**, SO_2 and aryl radical **172** which combines with sulfur dioxide to produce the sulfonyl radical **173**. The attack of the radical **173** on the triple bond of the alkynoate generates intermediate **174** which on subsequent spirocyclization provides intermediate **175**. Oxidation by radical cation **171** then affords **176**[167] followed by 1,2-ester migration to intermediate **177**. The desired sulfonylated product **168** was obtained upon aromatization of intermediate **177** (Scheme 41).



Scheme 41 Proposed mechanism for the formation of 3-sulfonated coumarins **168**.

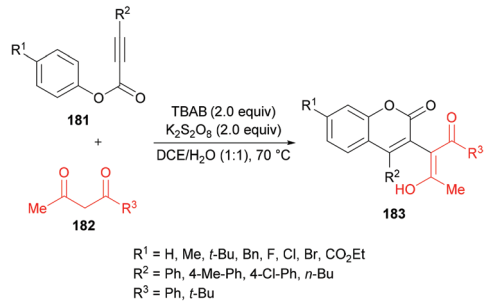


Scheme 42 Synthesis of 3-sulfonated coumarins *via* metal-free arylsulfonylation of alkynoates with sulfonylhydrazides.

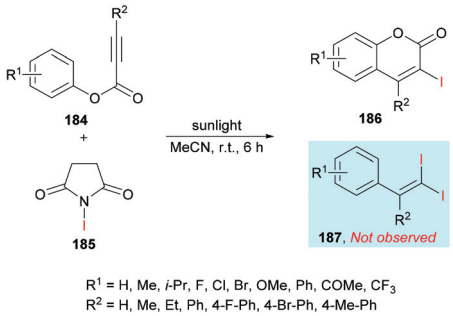
Due to the widespread applications of sulfone functionalities in organic and medicinal chemistry,[168–177] the synthesis of organic molecules with these groups remained an attractive pursuit for many research groups. Recently, Wang and coworkers[178] developed a new metal-free approach to construct structurally diverse 3-sulfonated coumarins **180** (Scheme 42). The easily available starting materials including alkynoates **178** and sulfonylhydrazides **179** were coupled *via* the direct difunctionalization strategy in the presence of TBAI and TBHP as the catalyst and oxidant, respectively. This procedure is generally convenient for the synthesis of 3-sulfonated coumarins as compared to the previously developed methods,[179–183] which possess several limitations including harsh reaction conditions, low chemical yields and tedious work-up procedures. The reaction scope was reasonably broader, tolerating several electron-poor and electron-rich substrates effectively; however, the reactivity was stalled by steric factors leading to trace amounts of the desired compounds. Similar results were afforded when alkyl sulfonylhydrazides, such as methyl sulfonylhydrazide, were used as the substrates. Mechanistically, radical-promoted intramolecular cyclization/oxidation was among the key steps for the formation of the title product.

Liu *et al.*[184] extended the scope of 3-functionalized coumarins **183** by using a range of alkynoates **181** and acetylacetone **182**. The 3-acetonylcoumarins were accessed in moderate yields (Scheme 43). Again, the key step in the mechanistic process was an oxidative tandem 5-*exo* dearomative spirocyclization and ester migration.

In an effort to develop green organic methodologies using photoredox catalysis, Ni *et al.*[185] used alkynoates **184** for the synthesis of 3-iodocoumarins **186** driven by sunlight as a catalyst (Scheme 44). The process operates under catalyst-free conditions and cascade radical iodination and cyclization using *N*-iodosuccinimide (NIS)[186–189] afforded the coumarin products at room temperature. This methodology was different from their previously developed procedure where the iodina-



Scheme 43 Synthesis of 3-functionalized coumarins from alkynoates and acetylacetone.

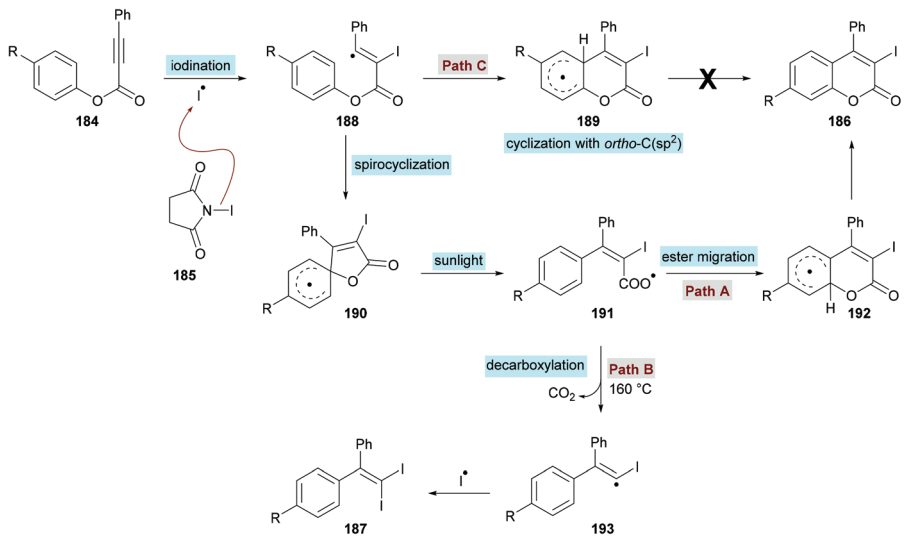


Scheme 44 Synthesis of 3-iodocoumarins *via* sunlight-promoted cyclization of alkynoates with *N*-iodosuccinimide.

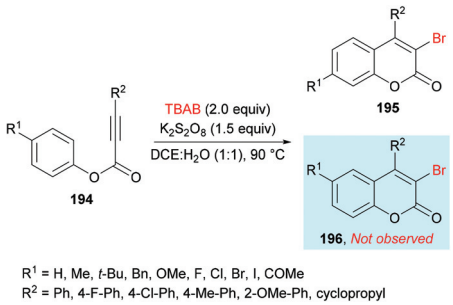
tion triggered cascade radical decarboxylative migration reaction of alkynoates afforded 1,1-diiodoalkenes at elevated temperatures.[190] After extensive screening of reaction parameters, suitable conditions were obtained which were utilized for the exploration of the general applicability of the method. Several sensitive functional groups worked well and delivered iodocoumarins in pleasing yields. It is also notable that the substrates bearing aliphatic substituents such as methyl and ethyl also worked efficiently affording the corresponding coumarins in excellent yields (83–89%). However, no desired product was realized when phenyl propiolate was employed as the substrate. Also, with sterically hindered substrates, only trace amounts of the desired coumarins were achieved.

The proposed catalytic mechanism is illustrated in Scheme 45. The addition of the iodine radical (produced from NIS **185** under sunlight irradiation) to the C≡C bond of the alkynoate provided intermediate **188** which on subsequent intramolecular spirocyclization delivered intermediate **190**. The intermediate **190** provided carboxyl radical **191** by the cleavage of the C–O bond which on cyclization and deprotonation by NIS gave the desired product **186** (path A). However, according to the previous reports (Mendis & Tunge, 2015; Ni *et al.*, 2016),[190,191] intermediate **191** could possibly generate intermediate **193** with the release of a CO_2 molecule. Finally, intermediate **193** reacts with NIS to afford the final 1,1-diiodoalkene product **187**. It is worth noting that **187** was not observed under the current sunlight irradiation experimental conditions.

Qiu, Ding and co-workers[192] developed a tandem radical bromination of alkynoates **194** to furnish a range of 3-bromocoumarins **195** catalyzed by $K_2S_2O_8$ (Scheme 46). This methodology differs from the previous reports where liquid bromine was employed as a bromo source[193–197] using TBAB and $K_2S_2O_8$; thus the bromo radical would undergo addition to the C≡C triple bond of the alkynoate, followed by oxidative spirocyclization and 1,2-migration of the ester group to provide 3-bromocoumarin. Using tolyl alkynoate as a standard substrate with TBAB to develop the optimal conditions, various reaction parameters were investigated. The desired 3-bromo-7-methylcoumarin **195** was isolated, whereas 3-bromo-6-methylcoumarin **196** was not observed as evidenced by Wu and



Scheme 45 Proposed reaction mechanism for the formation of 3-iodocoumarins **186**.

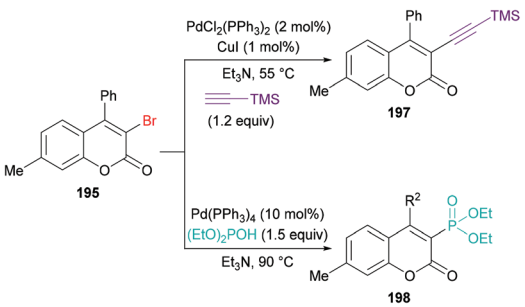


Scheme 46 $K_2S_2O_8$-catalyzed synthesis of 3-bromocoumarins from alkynoates and TBAB.

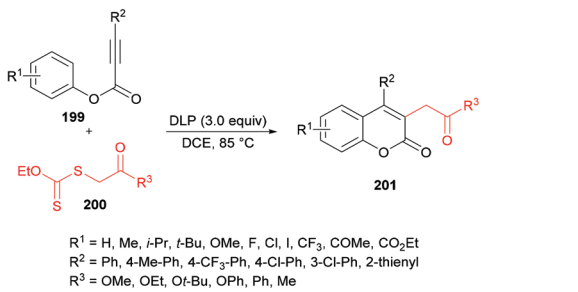
Wang.[198–203] Further optimization of the relevant reaction parameters (oxidant, solvent, temperature) was then performed. A mixture of DCE and water (v/v = 1 : 1) was identified as the best reaction media. The addition of water was critical to hinder the formation of liquid bromine *via* homocoupling. With the identification of the optimized conditions (2.0 equiv. TBAB, 2.0 equiv. $K_2S_2O_8$, in DCE/H_2O (v/v 1 : 1) at 90 °C), the versatility of various alkynoates was explored. The presence of various substituents (R^1) such as methyl, *tert*-butyl, benzyl, methoxy, fluoro, chloro, bromo, iodo, and acetyl at the phenyl ring of the alkynoate was productive in the delivery of the desired products in 63–78% yields. In addition, the scope and versatility of the reaction were further explored using various substituents (R^2). Aryl groups bearing electron-rich (methyl, methoxy) and electron-deficient (halogens) substituents were compatible and produced 3-bromocoumarins in 64–80% yields. However, phenyl 3-cyclopropylpropiolate showed some hindrance in cyclization and gave the corresponding 3-bromo-4-cyclopropylcoumarin in 42% yield. Other halogen sources such as tetrabutylammonium fluoride (TBAF), tetrabutylammonium chloride (TBAC) and tetrabutylammonium iodide (TBAI) were unsuitable to furnish the desired halogenated product under the optimized reaction conditions. Moreover, keeping in view the synthetic utility of bromo compounds to serve as useful building blocks, synthetic functionalization was performed with the successful installation of alkynyl (**197**) and phosphite (**198**) groups onto the coumarin skeleton under palladium catalysis (Scheme 47).

Pan, Yu and co-workers[204] demonstrated the synthesis of substituted coumarins **201** by carboannulation of alkynoates **199** with xanthates **200**. This dilauroyl peroxide (DLP)-promoted process involves radical addition/cyclization using metal-free conditions (Scheme 48). The effect of different oxidants in a variety of solvents was examined. Phenyl 3-phenylpropiolate and methyl 2-((ethoxycarbonothioyl)thio)acetate were employed in the presence of BPO as an oxidant to develop the optimal conditions. Several other oxidants including DTBP, TBHP, DLP, $K_2S_2O_8$, $PhI(OAc)_2$ and H_2O_2 were tested; however, DLP showed superior results and produced methyl 2-(2-oxo-4-phenyl-2*H*-chromen-3-yl)acetate in 74% yield in dichloroethane solvent. The reaction performed in various other solvents (DCM, MeCN, THF, PhCl, acetone) did not demonstrate any increase in the product yield. The scope and generality of this radical cyclization were expanded using different alkynoate substrates bearing both electron-rich (methyl, isopropyl, *tert*-butyl, methoxy) and electron-deficient (trifluoromethyl, halogens) substituents on the aryl ring. The corresponding 4-aryl-3-(2-methoxy-2-oxoethyl) coumarins were isolated in moderate to good yields. However, alkynoates incorporating strongly electron-deficient substituents (ester, acetyl) produced the corresponding products in lower yields. 4-Nitrophenyl 3-phenylpropiolate remained unreactive. Heterocyclic substituents at the alkynoate were also compatible, albeit producing the coumarin in 42% yield. The structural diversity was also realized when different xanthates featuring alkyl ester, ketone, and cyano were employed and the corresponding products were isolated in moderate to good yields.

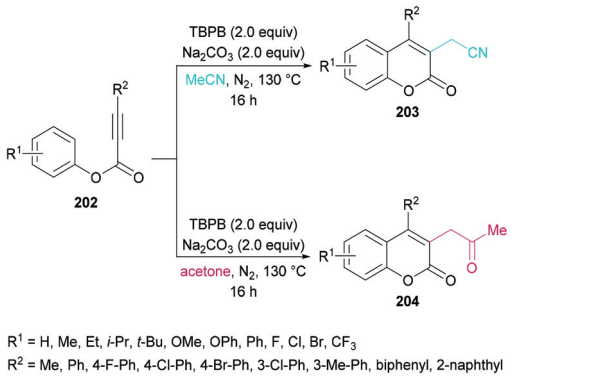
Sun and co-workers[205] reported a facile route for the synthesis of cyanomethylated coumarins **203** *via* cyanomethylation and cyclization of aryl alkynoates **202** (Scheme 49). Acetonitrile was used as a cheap cyanomethyl source in the presence of *tert*-butyl peroxybenzoate (TBPB) under metal-free conditions. Various oxidants, bases and temperatures were screened to optimize the reaction conditions. A variety of alkynoates bearing different substituents on the aromatic (phenoxy) ring were tested. Both electron-donating and electron-withdrawing substituents were compatible. The effect of substituents present on the alkyne was also investigated. No



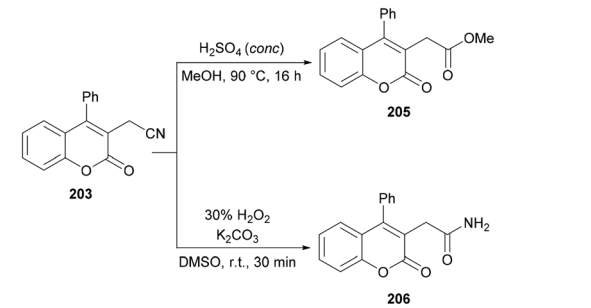
Scheme 47 Palladium-catalyzed synthetic functionalization of 3-bromocoumarin **195**.



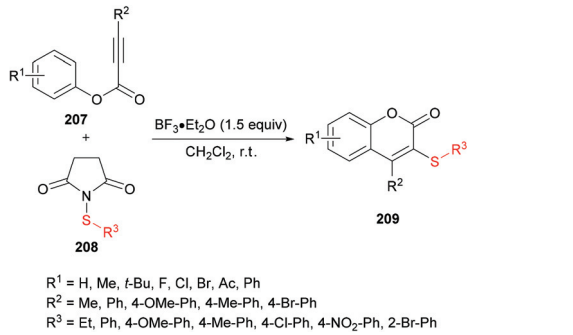
Scheme 48 Dilauroyl peroxide (DLP)-promoted synthesis of 3-(β-carbonyl)coumarins *via* radical addition/cyclization of alkynoates with xanthates.



Scheme 49 Synthesis of 3-functionalized coumarins from aryl alkynoates.



Scheme 50 Synthetic manipulation of the nitrile functionality in cyanomethylated coumarin **203**.



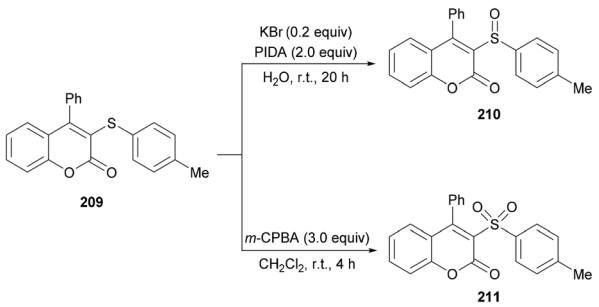
Scheme 51 BF_3·Et_2O-mediated synthesis of 3-sulfenylated coumarins from aryl alkynoates and *N*-sulfanylsuccinimides.

significant electronic influence was observed with differently substituted groups. The alkynes bearing an alkyl group however remained inert under the optimized reaction conditions. They further explored the scope using acetone instead of acetonitrile and the desired products (2-oxopropyl substituted coumarins **204**) were isolated in good yields. The nitrile functionality was further transformed into other functional groups under different conditions to yield the corresponding products (Scheme 50). For instance, 2-(2-oxo-4-phenyl-2*H*-chromen-3-yl)acetonitrile was converted into methyl 2-(2-oxo-4-phenyl-2*H*-chromen-3-yl)acetate **205** and 2-(2-oxo-4-phenyl-2*H*-chromen-3-yl)acetamide **206**.

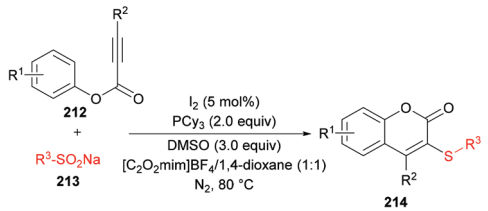
Chang and co-workers[206] described a facile metal-free sulfenylation/cyclization approach involving aryl alkynoates **207** and *N*-sulfanylsuccinimides **208** in the presence of BF_3·Et_2O to produce 3-sulfenylated coumarins **209** in moderate to excellent yields (Scheme 51). Initial screening included the investigation of various parameters to identify the optimal conditions to perform the metal-free transformation. Without the addition of a Lewis acid, no corresponding product was observed, and the electrophilic cyclization furnished the coumarin product in 87% yield when the reaction was performed with 1.5 equivalents of BF_3·Et_2O in dichloromethane at room temperature. Various other Lewis acids ($FeCl_3$, $AlCl_3$) and Brønsted acids (TFA or TfOH), however, led to inferior results. The use of other solvents as well as electrophilic sulfenylating reagents led to diminished reactivity. Under the established reaction conditions, the scope and limitations of the cyclization methodology were explored. A range of substituents on the phenoxyl ring of alkynoates were tested and gave the 3-sulfenylated coumarins in good yields.

Both moderately electron-rich (methyl and *tert*-butyl) and electron-deficient functional groups (fluoro, chloro, bromo, acetyl) at the *para*-position of aryl 3-phenylpropiolates produced similar results. *ortho*-Substituted alkynoates also produced the desired annulated product in good to excellent yields. A sterically bulky naphthyl alkynoate also produced the coumarin product in 81% yield. The reaction scope also included the variation of substituents at the alkynyl functionality. Phenyl arylpropiolates with variable degrees of electronic character were found to be compatible in addition to alkylpropiolates. Moreover, additional sulfenylating reagents bearing different arylthiol partners were also made a part of this study and the desired products were furnished in moderate to high isolated yields. Notably, the *para*-methoxy substituted alkynoate led to the formation of spiro[4.5]triene-2,8-dione, generated *via ipso*-sulfenylcyclization. Keeping in view the applications of sulfinyl and sulfonyl functional groups in organic and medicinal chemistry,[207–210] 3-sulfinylated **210** and 3-sulfonated coumarins **211** were prepared under oxidative conditions using (diacetoxyiodo)benzene (PIDA) and *meta*-chloroperbenzoic acid (*m*-CPBA) as the oxidants (Scheme 52).

Wu, Jiang and co-workers[211] reported an iodine-catalyzed electrophilic cyclization of alkynoates **212** and sodium arylsulfinates **213** to construct 3-sulfenylcoumarins **214** in moderate to good yields (Scheme 53). The optimized reaction conditions were developed using phenyl 3-phenylpropiolate and sodium benzenesulfinate as model substrates. Several oxidants including O_2, H_2O_2, TBHP, $K_2S_2O_8$, DTBP and DMSO and non-metal iodine catalysts such as I_2, NIS, I_2O_5, ICl and TBAI were considered in a variety of solvents. After extensive screening, the optimal conditions were identified and used to explore the generality and scope of this reaction. Sodium arylsulfinates bearing electron-rich phenyl groups and halogens were compatible whereas electron-poor groups at the phenyl ring and heteroaryl and alkyl groups produced only a trace amount of



Scheme 52 Synthesis of 3-sulfinylated and 3-sulfonated coumarins under oxidative conditions.



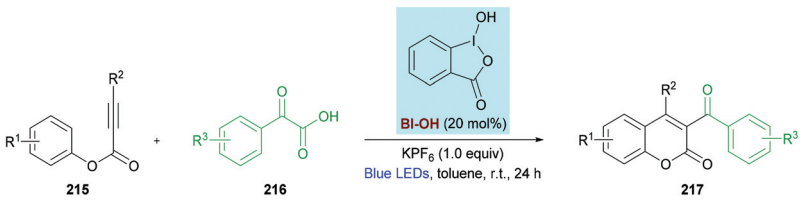
R^1 = H, Me, Et, *i*-Pr, *t*-Bu, F, Cl, Br, CF_3, COMe, CN
R^2 = Ph, 4-OEt-Ph, 4-Cl-Ph, 2,4-diMe-Ph, *n*-Pent-Ph, *n*-Pent, 2-thienyl
R^3 = Et, Ph, 2-Me-Ph, 4-Me-Ph, 4-OMe-Ph, 4-*t*-Bu-Ph, 2-F-Ph, 3-F-Ph, 4-F-Ph, 4-Cl-Ph, 4-Br-Ph, 4-CN-Ph, 4-CF_3-Ph, biphenyl

Scheme 53 Iodine-catalyzed synthesis of 3-sulfenylcoumarins from aryl alkynoates and sodium arylsulfinates.

the desired products. Moreover, various alkynoate substrates with diverse electronic features were tested. Aryl, alkyl, heteroaryl and extended aryl groups were well tolerated with broad functional group compatibility. Mono-, di-, and tri-substituted substrates were successfully cyclized to coumarin products in good yields.

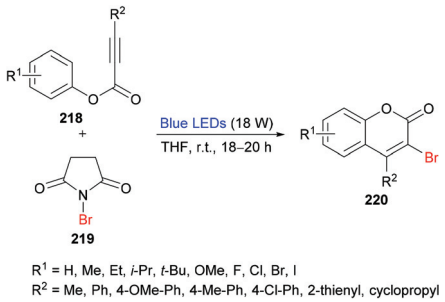
Zhang, Wang and co-workers[212] unearthed a hypervalent iodine reagent (HIR)-catalyzed decarboxylative carbonylarylation of phenylpropiolates **215** with α-oxocarboxylic acids **216**. The reaction proceeds under metal-free conditions generating the desired 3,4-disubstituted coumarins **217** in good yields at room temperature (Scheme 54). An extensive screening of various reaction parameters was performed to identify the optimal conditions. Blue, purple, red, green and white LEDs and sunlight were used as a light source while using eosin Y, $[Ru(bpy)_3]Cl_2$, $PhI(OAc)_2$, [1-hydroxy-1,2-benziodoxol-3(1*H*)-one] (BI-OH), 1,2-benziodoxol-3(1*H*)-one acetate ester (BI-OAc) and BI-C≡C-Ph as catalysts. To enhance the reaction performance, several additives ($PhSO_3Na$, K_2CO_3, Na_2CO_3, TsOH, PivOH, $(NH_4)_2C_2O_4$, KPF_6) were also tested alongside a range of solvents (toluene, benzene, acetone, THF, DMSO, EtOAc, MeCN, DCE, Et_3N). The optimal reaction conditions that were used to explore the scope of the reaction include **215** (0.20 mmol), **216** (0.40 mmol), BI-OH (20 mol%), and KPF_6 (1.0 equiv.) in toluene (1.0 mL) under an air atmosphere. The reaction mixture was irradiated with a 1.5 W blue LED at room temperature for 24 h. Broad functional group tolerance was observed when various aryl 3-phenylpropiolates were reacted with 2-oxo-2-phenylacetic acid. A range of electron-rich substituents (methyl, ethyl, isopropyl, *tert*-butyl) at the *para*-position of the aromatic rings as well as 3,5-$(Me)_2$ substituents produced the anticipated coumarin products in ample yields. Likewise, electron-deficient functional groups (F, Cl, Br, I) also proved to be equally tolerant to standard conditions. Similarly, the reaction scope was further extended by employing various α-oxocarboxylic acids. The electronically different substituents survived under the optimized reaction conditions; however, the *ortho*-substituted substrates showed slow progress and reactivity producing the target product in moderate yields. Notably, 2-(naphthalen-1-yl)-2-oxoacetic acid was successfully coupled to 3-phenyl (4-ethylphenyl)propiolate delivering the substituted coumarin in 67% isolated yield. Heteroaromatic and aliphatic substituted substrates did not produce the desired products, presumably due to the lower stability of the acyl radicals. The radical mechanism was confirmed by using TEMPO or BHT, as a radical scavenger that completely inhibited the reaction.

She and co-workers[213] demonstrated a facile approach for the preparation of 3-bromocoumarins **220** from alkynoates **218** through visible-light-mediated radical cyclization using NBS **219** as the bromo source (Scheme 55). This strategy involves a bromo radical addition/spirocyclization/ester migration cascade sequence and can be performed under very mild reaction conditions in the absence of any catalyst or strong oxidant. Initially, various reaction conditions were screened

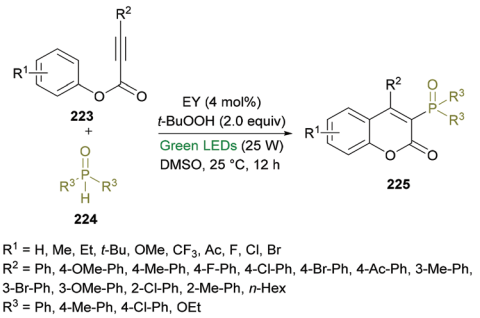


R^1 = H, Me, Et, *i*-Pr, *t*-Bu, F, Cl, Br, I
R^2 = Ph, 4-*n*-Bu-Ph
R^3 = H, 4-Me, 4-Et, 4-*n*-Bu, 4-*t*-Bu, 4-F, 4-Cl, 4-Br, 4-I, 2-Me, 3-Me, 2-Cl, 3-Br, 2,5-diCl, 2,5-diMe

Scheme 54 Hypervalent iodine reagent (HIR)-catalyzed synthesis of 3,4-disubstituted coumarins from phenylpropiolates and α-oxocarboxylic acids.



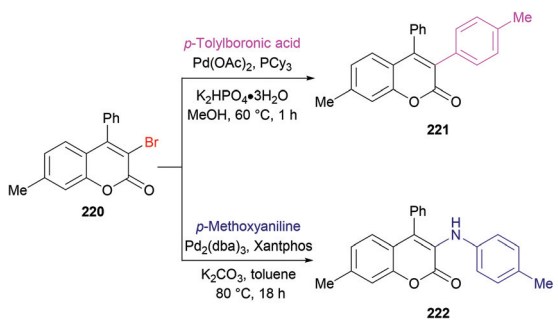
Scheme 55 Visible-light-mediated synthesis of 3-bromocoumarins from alkynoates and NBS.



Scheme 57 Visible-light-promoted synthesis of 3-phosphorylated coumarins from alkynoates and phosphine oxides.

using tolyl alkynoate and NBS with an 18 W blue LED as a visible light source. A range of solvents including MeCN, DCM, DMSO, DMF, THF, and 1,4-dioxane were employed. The best results were obtained in THF. The scope and diversity of the substrates used to prepare coumarins were investigated. Various alkyl groups (methyl, ethyl, *i*-propyl, *tert*-butyl) at the *para*-position of the aryl ring were suitable under the optimized reaction conditions to furnish the desired 3-bromocoumarins in 63–75% yields. In the case of the methoxy substituent, the product was isolated in 52% yield only. Substrates featuring a halogen substituent (fluoro, chloro, bromo and iodo) were also compatible, albeit producing the anticipated products in moderate yields (51–59%). *ortho*-Substituted alkynoate provided a complex mixture without the detection of the desired product. Different substituents at the alkyne carbon were also suitable for this transformation. Moreover, the presence of a bromo substituent at the 3-position of coumarin proved to be a viable functional handle to perform Suzuki–Miyaura cross-coupling[214] and Buchwald–Hartwig amination reactions (Scheme 56). Some 3,4-biphenyl coumarin derivatives having biological significance[215,216] were also synthesized using this methodology.[217]

Xu and co-workers[218] developed a metal-free, visible-light-promoted direct difunctionalization of alkynoates **223** using eosin Y (EY) as the photocatalyst and *tert*-butyl-hydroperoxide (TBHP) as the oxidant (Scheme 57). This process involves a radical tandem phosphorylation/cyclization reaction sequence

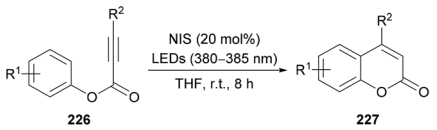


Scheme 56 Synthetic manipulation of 3-bromocoumarin **220** using Suzuki–Miyaura cross-coupling and Buchwald–Hartwig amination reactions.

to afford a range of 3-phosphorylated coumarins **225** in good yields and excellent regioselectivities. Avoiding the use of stoichiometric amounts of radical initiators or high-energy UV light,[219] for the generation of P-centered radicals, visible light photoredox catalysis was employed. The reaction optimization was started with phenyl 3-phenylpropiolate, diphenylphosphine oxide (radical precursor) with TBHP as the oxidant under the influence of an organic photocatalyst and the irradiation of visible light. A survey of various photocatalysts, oxidants and solvents to produce the 3-phosphorylated coumarin was conducted with the identification of EY as the photocatalyst, TBHP as the oxidant, and DMSO as the solvent rendering the heterocyclic product in 87% yield. This set of conditions was further applied to various alkynoates and phosphoryl radical precursors.

The variation of the R^2 substituent at the alkyne component of the alkynoate demonstrated good functional group tolerance. Electron-donating (methyl, methoxy) and electron-withdrawing (fluoro, chloro, bromo, ketone) groups at the phenyl ring showed equal participation in this domino radical cyclization process. Alkyl group substituted alkynoates exhibited no reactivity. Although, other P-centered radical precursors proved to be good coupling partners, diethyl phosphonate furnished the corresponding product in 35% yield only. The next round of structural changes includes the variation of different substituents at the phenoxy ring of alkynoates. Again, various substituents including methyl, ethyl, *tert*-butyl, methoxy, trifluoromethyl, fluoro, chloro, and bromo were successfully tolerated. The extended aromatic system (2-naphthyl) also gave the desired coumarin in 55% isolated yield; however, *ortho*-substituted phenoxy rings were found to be sensitive to standard reaction conditions. Gram-scale synthesis was also performed with the isolation of the target product in 74% yield.

Li and co-workers[220] prepared a library of coumarin derivatives **227** using *N*-iodosuccinimide as a free-radical initiator under photo-irradiation. This metal-free methodology uses readily available starting materials (alkynoates **226**) and involves free radical intramolecular cyclization and ester rearrangement to afford coumarin products at room temperature (Scheme 58). *p*-Tolyl 3-phenylpropiolate served as a model substrate to optimize the reaction conditions. Various iodine

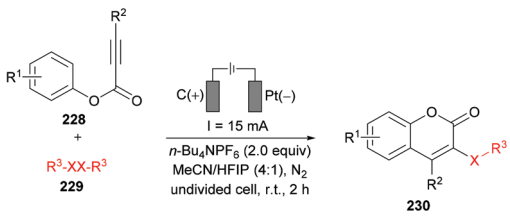


R^1 = H, Me, Et, *i*-Pr, *t*-Bu, OMe, Ph, F, Cl, Br
R^2 = H, Et, *n*-Pr, Ph, 4-OMe-Ph, 4-Me-Ph, 4-Et-Ph, 4-*t*-Bu-Ph, 4-Cl-Ph, 4-Br-Ph, 3-Me-Ph, 3-F-Ph, 2-Me-Ph, 3,5-diMe-Ph, 2-thienyl

Scheme 58 Photoinduced cyclization of alkynoates to coumarins with *N*-iodosuccinimide as a free-radical initiator.

sources (iodobenzene, TBAI, NIS, I_2) in different solvents (PhMe, DCE, MeCN, DMF, DMSO, THF) were investigated. The best results were obtained in THF using 20 mol% of NIS delivering the coumarin product in 91% yield with a trace amount of 3-iodo-4-phenyl-coumarin. The variation of electronically and sterically different groups was introduced at the aryl component of the alkynoate to investigate the substrate scope. Electron-donating (methyl, ethyl, i-propyl, *tert*-butyl, methoxy, phenyl) and electron-withdrawing (fluoro, chloro, bromo) groups were successfully tolerated, However, strongly electron-deficient groups such as nitro, trifluoromethyl and formyl substituted alkynoates failed to show any reactivity under the optimized reaction conditions. Di-halogenated alkynoate also produced the desired coumarin in 77% yield. The reaction did not tolerate *ortho*-substituted and heterocyclic substrates. The scope was further broadened using alkyl and aryl substituents at the C≡C triple bond of the alkynoate. Methyl, ethyl, *tert*-butyl, methoxy, fluoro, chloro, and bromo at the phenyl ring were all compatible. 3-Alkyl-coumarins were successfully accessed from 3-ethyl- and 3-propylpropiolic acids in good yields; however, unsubstituted as well as heteroaryl substituted alkynoates showed no product formation. The mechanistic experiments revealed that the selection of the wavelength of light and the loading of NIS were critical in the construction of de-iodinated coumarins.

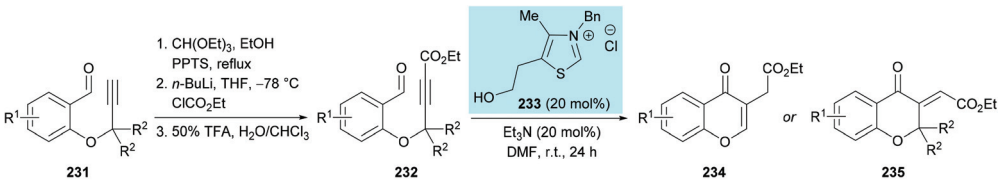
Guo and co-workers[221] reported an electrochemical oxidative annulation of alkynoates **228** with diselenides or disulfides **229** to access a range of coumarins **230** (Scheme 59). In an electrochemical environment, oxidative cyclization generated new chalcogen-substituted coumarins under metal- and oxidant-free conditions. The model reaction was composed of a graphite anode and a platinum cathode to perform electrochemical oxidative cyclization of phenyl 3-phenylpropiolate, thus delivering 3-organoselenyl-2*H*-coumarin. A range of different electrolytes (*n*-Bu_4NBF_4, *n*-Bu_4NPF_6, *n*-Bu_4NI, *n*-Bu_4NBr, Et_4NClO_4) in various solvents (MeCN, DMF, DCE, HFIP) were screened. A variation in the constant current from 15 mA resulted in decreased reactivity. The scope of the electrochemical oxidative reaction includes the investigation of various alkynoates with diselenides or disulfides. The *para*-substituted phenoxy ring bearing both electron-rich (Me, Et, *t*-Bu) and electron-deficient (F, Cl, Br, CF_3, Ac) groups demonstrated complete tolerance under the optimized conditions. In addition, the substrates incorporating alkyl (Me, Et) and aryl substituents at the alkyne moiety also showed high compatibility; however, when R^2 = H, no reaction occurred. Pleasingly, the *ortho*-methyl substituted alkynoate produced the cyclized product in 75% yield. On the other hand, both aliphatic and aromatic diselenides were smoothly coupled to alkynoates. The reaction of 2-naphthyl alkynoate also gave the coumarin product in 75% yield. Furthermore, disulfide also exhibited good tolerance under electrochemical oxidative cyclization conditions to afford the desired products in 53%–56% yields. This green protocol could also be performed at the 5 mmol scale generating the corresponding product in 58% yield.



R^1 = H, Me, Et, *t*-Bu, F, Cl, Br, CF_3, Ac
R^2 = H, Me, Et, Ph, 4-Me-Ph, 4-OMe-Ph, 4-F-Ph, 4-Cl-Ph, 4-Br-Ph, 2-thienyl
R^3 = Me, Et, Ph, 2-Me-Ph, 4-Me-Ph, 3-OMe-Ph, 4-Cl-Ph, 4-Br-Ph
X = Se, S

Scheme 59 Electrochemical oxidative synthesis of functionalized coumarins from alkynoates and diselenides or disulfides.

2.2.2. Synthesis of chromones. Liu and co-workers[222] developed an organocatalytic intramolecular Stetter-type hydroacylation reaction between an aldehyde and activated alkynes to produce chromones **234**, **235** (Scheme 60). A range of parameters including N-heterocyclic carbenes, bases, and solvents were tested to generate the optimized reaction conditions. After careful investigation, carbene (20 mol%), triethyl-



R^1 = H, Me, *t*-Bu, OMe, F, Cl, $OCH_2C{\equiv}CCO_2Et$
R^2 = H, Me

Scheme 60 N-Heterocyclic carbene-catalyzed synthesis of chromones through intramolecular hydroacylation of activated alkynes.

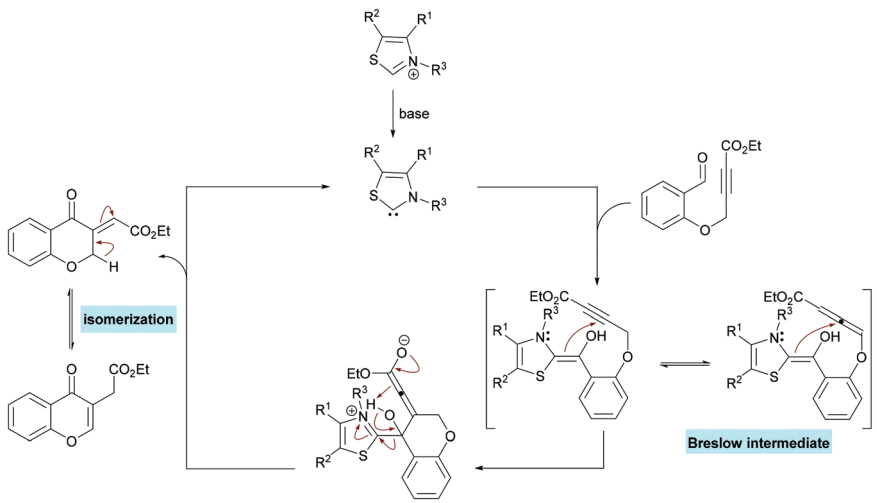
amine (20 mol%) and DMF solvent were identified as the optimized conditions. Using these conditions, the scope and generality of the reaction were tested. A diverse majority of salicylaldehydes incorporating electron-rich and electron-deficient groups delivered the desired chromones in good yields. Halogens at the phenyl ring were also successfully tolerated. On the other hand, alkynes bearing a ketone functionality as the electron-deficient substituents (acetyl, trimethylacetyl, benzoyl, phenylacetyl) were efficiently used, delivering the desired products in 66–74% yields.

The proposed mechanism for this transformation starts with the nucleophilic attack of carbene on the electrophilic carbonyl carbon of the aldehyde which on proton transfer results in an acyl anion equivalent (Breslow intermediate).[223–225] The subsequent attack of a nucleophilic carbon on an activated alkyne thus generates a new carbon–carbon bond. Proton exchange followed by elimination of the catalyst produced the exocyclic kinetic product which underwent isomerization to afford the aromatized product (Scheme 61).

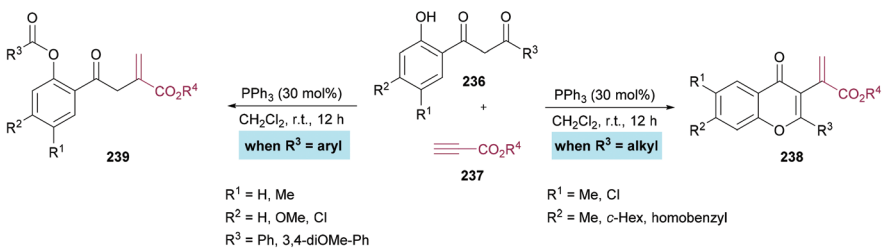
Xue and co-workers[226] demonstrated the synthesis of chromones while investigating the phosphine-catalyzed α-addition reaction of 1,3-diketones **236** with terminal alkynoates **237** (Scheme 62). 1,3-Dicarbonyl substrates containing an alkyl group provide chromone derivatives **238** whereas aromatic substituents lead to the formation of vinylesters **239**, important building units in the construction of nitrogen-containing heterocycles and other functionalized molecules.[227–233]

Based on the literature reports,[234,235] the authors proposed the reaction mechanism which starts with the nucleophilic addition of PPh_3 to the electron-deficient alkyne **237** to form zwitterion **240**. 1-(*o*-Hydroxyaryl)-1,3-diketone was deprotected to produce **241** and **242**. Subsequent proton transfer in **242** produced **243** which then adds to **241** to furnish **244**. A second proton transfer gave **245** which was cyclized *via* an intramolecular nucleophilic addition to produce **246**, a key divergent intermediate for both products. In the first case, when R^3 is an aryl group, a carbon–carbon bond cleavage in intermediate **246** led to **247**, which on elimination of the phosphine catalyst furnished product **237**. However, when R^3 is an alkyl group, another proton transfer followed by the elimination of PPh_3 gave **249**. The corresponding heterocyclic product **238** was furnished on dehydration of **249**. Notably, the divergent reactivity towards the formation of different products was possibly dependent on the stabilization of the intermediate **246** (Scheme 63).

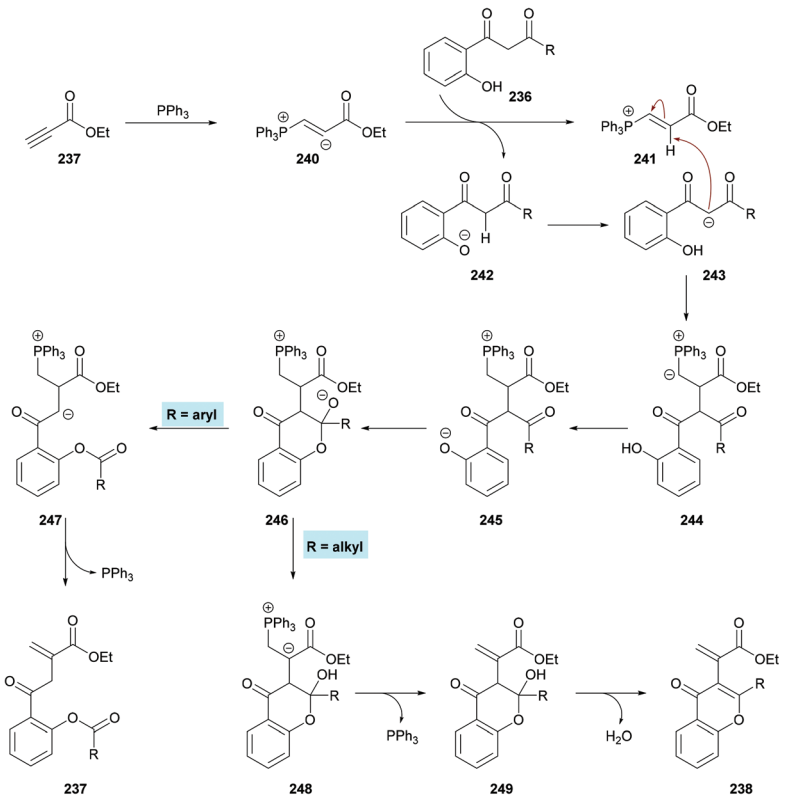
2.2.3. Synthesis of chromanones. Xue and co-workers[236] developed a DABCO-catalyzed condensation method for the synthesis of chromanones **252** from *ortho*-acylphenols **250** and terminal alkynoates **251** where KO*t*-Bu was employed in the



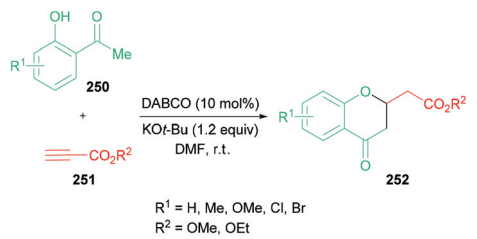
Scheme 61 Proposed mechanism for the formation of chromones **234**.



Scheme 62 PPh_3-catalyzed synthesis of chromones through the α-addition reaction of 1-(*o*-hydroxyaryl)-1,3-diketones with terminal alkynoates.



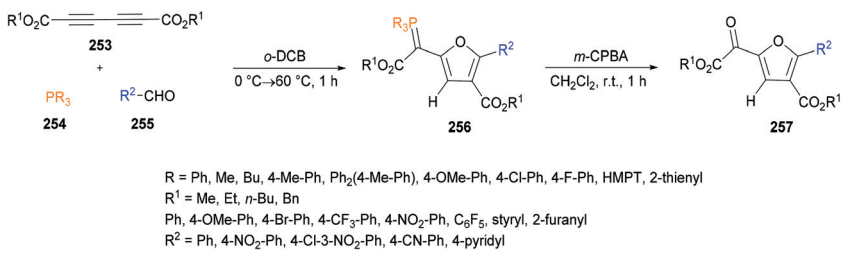
Scheme 63 Proposed mechanism for the formation of chromones **238**.



Scheme 64 DABCO-catalyzed synthesis of 2-alkyl-substituted chromanones from *ortho*-acylphenols and terminal alkynoates.

second step of this one-pot process for intramolecular cyclization (Scheme 64). During the course of reaction optimization, the addition of DABCO and KO*t*-Bu in two subsequent steps was found to be critical as a trace amount of the product was observed when both were added simultaneously. A diverse range of chromanone products were furnished using various *ortho*-acylphenols bearing different functional groups. Substrates endowed with electron-rich substituents on the aromatic part performed better compared to electron-deficient substituted *ortho*-acylphenols. Notably, the multi-substituted *ortho*-acylphenols were also found to be viable substrates producing the corresponding products in moderate yields.

2.2.4. Synthesis of furans. Deng and Chuang[237] developed a multi-component approach involving diynedioates **253**, phosphines **254** and aromatic aldehydes **255** delivering a range of multisubstituted furans **256** bearing phosphorus ylides in good yields (Scheme 65). The reaction sequence involves the nucleophilic attack of phosphine on diynedioates generating a 1,5-dipolar species which undergoes addition to aromatic aldehydes followed by 5-*endo-dig* cyclization. Various reaction con-

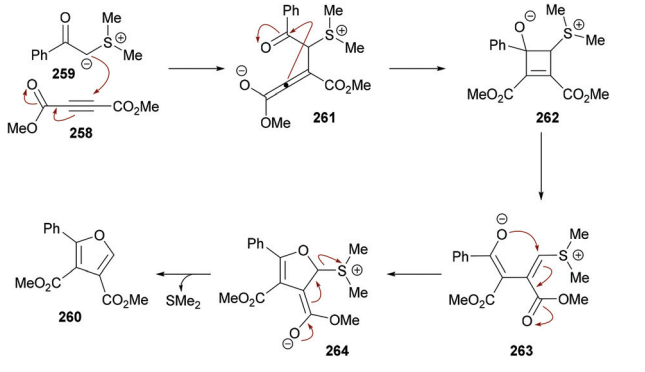


Scheme 65 Multi-component synthesis of furans containing phosphorus ylides from phosphines, diynedioates and aryl aldehydes.

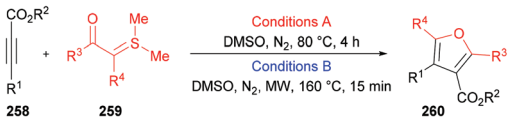
ditions were screened, and the desired product was isolated in an optimal yield when *o*-dichlorobenzene was employed as a solvent at 60 °C. The scope of the reaction was examined using various phosphines, diynedioates, and aldehydes. Electron-rich phosphines performed better producing the corresponding furans in 81–85% yields compared to electron-deficient phosphines. Furan products were also isolated in comparable yields when heteroaromatic phosphines were employed. Various substituted benzaldehydes and 4-pyridinecarboxaldehyde also participated generating the anticipated heterocyclic products in remarkable yields. Moreover, di-*n*-butyl hexa-2,4-diynedioate, diethyl hexa-2,4-diynedioate, and dibenzyl hexa-2,4-diynedioate delivered the furans in good yields. Notably, the highly nucleophilic phosphines (PMe_3 or PBu_3) were unreactive under the optimized conditions in addition to electron-rich aldehydes. The furan products were further functionalized under oxidative conditions using *m*CPBA (2.4 equiv.) to afford α-keto esters **257**.

Xu and co-workers[238] highlighted a simple and straightforward synthetic approach to access a series of structurally diverse polysubstituted furans **260** from sulfur ylides **259**[239–245] and alkyl acetylenic carboxylates **258**. This process involves a tandem sequence of Michael addition, intramolecular nucleophilic addition, 4π ring opening, intramolecular Michael addition, and elimination to afford dialkyl furan-3,4-dicarboxylates in moderate to good yields (Scheme 66).

The model reaction was performed using dimethyl acetylenedicarboxylates and dimethylsulfonium benzoylmethylide in 1,2-dichloroethane. Further optimization of the reaction conditions included the variation of the starting material ratios in a variety of solvents (DMF, MeCN, DMSO) at different temperatures. The desired product was isolated in 79% yield when the reaction was conducted in DMSO at 80 °C under a nitrogen atmosphere (Scheme 67). Subsequent experiments were performed using these conditions to demonstrate the versatility of the protocol using various sulfonium ylides and alkynoates. Furan-3,4-dicarboxylates were isolated in moderate to good yields. A range of substituents (methyl, methoxy, fluoro, chloro, bromo, trifluoromethyl, cyano, nitro, dichloro) at the



Scheme 66 Proposed mechanism for the formation of polysubstituted furans **260**.

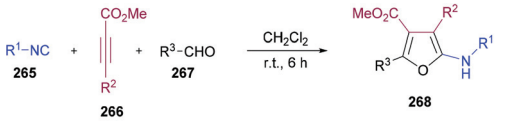


R^1 = CO_2Me, CO_2Et
R^2 = H, Me, Et
R^3 = H, CO_2Me, CO_2Et
R^4 = Ph, 4-Me-Ph, 4-OMe-Ph, 4-F-Ph, 4-Cl-Ph, 4-Br-Ph, 4-CN-Ph, 4-CF_3-Ph, 3,4-diCl-Ph, 1-naphthyl, 2-naphthyl

Scheme 67 Regiospecific synthesis of polysubstituted furans from sulfonium acylmethylides and acetylenic esters.

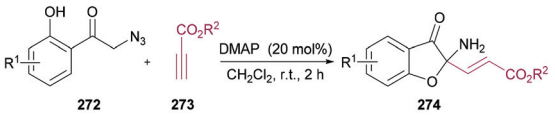
phenyl ring of sulfonium ylides were compatible. 1-Naphthyl and 2-naphthyl bearing sulfonium ylides also produced the desired products in 85% and 75% yields, respectively. Diethyl acetylenedicarboxylate was also successfully reacted with different dimethylsulfonium 2-aryl-2-oxoethylides. The scope was further extended to alkyl 2-substituted furan-3-carboxlyates using alkyl propynoates and the desired 4-trifluoromethyl-furan-3-carboxylates were constructed in 44–57% yields; however, methyl propynoate remained less reactive and delivered the corresponding furan-3-carboxylate product in 15% yield. This method was also useful to deliver trialkyl furan-2,3,4-tricarboxylates when the reactions were performed at 160 °C under microwave irradiation conditions.[246–251] Furthermore, dialkyl furan-2,4-dicarboxylates were prepared; however the regioselectivity was different from those reported in the literature.[252]

In view of the significant influence of the trifluoromethyl or perfluoroalkyl group on the lipophilicity, metabolic stability and permeability[253–261] of biologically active molecules, trifluoromethylated or perfluoroalkylated furans have gained central importance due to their anti-HIV, antibacterial and antiparasite activities.[262–264] To access these scaffolds, Zhang, Cao and co-workers[265] developed a one-pot multi-component methodology using isocyanides **265**, methyl perfluoroalk-2-ynoates **266**, and aromatic aldehydes **267**. The process operates at room temperature providing an easy access to a diverse range of 2-amino-3-perfluoroalkylfurans **268** in good to excellent yields (Scheme 68). Based on previously developed conditions for the synthesis of perfluoroalkylated cyclopentadienes, the optimization investigation was started using isocyanides, 2-isocyano-2-methylpropane, methyl 4,4,4-trifluorobut-2-ynoate and 2-nitrobenzaldehyde as model substrates in dichloromethane. Other solvents such as THF, $CHCl_3$ and toluene produced poor results. The reaction scope survey revealed the compatibility of all the three components. Both aliphatic and aromatic aldehydes incorporating electron-donating and electron-poor groups were employed. The electronic nature of the substituents displayed significant influence on the reactivity with electron-withdrawing groups being more productive in terms of the product yields. Electron-deficient heterocyclic aldehydes (picolinaldehyde) also turned out to be good coupling units. Moreover, various perfluoroalk-2-ynoates were also included in the multi-component reaction.



R^1 = *t*-Bu, *c*-Hex, trimethylphenyl
R^2 = CF_3, C_2F_5, *n*-C_3F_7
R^3 = 2-NO_2-Ph, 4-NO_2-Ph, 2-NC-Ph, 4-NC-Ph, 2-Cl-Ph, 2,3-diCl-Ph, 2,3-diF-Ph, 2-Br-Ph, 2-CF_3-Ph, 2,4,5-triF-Ph, 2,4,6-triF-Ph, pentafluorophenyl, 2-pyridyl, homobenzyl

Scheme 68 Multi-component synthesis of 2-amino-3-perfluoroalkylfurans from isocyanides, methyl perfluoroalk-2-ynoates and aldehydes.



R^1 = Me, OMe, Cl, diMe
R^2 = Me, Et, Ph, Bn, 4-Me-Bn, 4-Cl-Bn, 4-Me-Ph, 4-Cl-Ph

Scheme 70 Dimethylaminopyridine-catalyzed synthesis of 2-aminobenzofuran-3(2*H*)-ones from 2-azido-1-(2-hydroxyphenyl)ethanones and alkynoates.

Alkynoates with CF_3, C_2F_5, and *n*-C_3F_7 groups were well tolerated delivering the desired products in high yields. The scope was further expanded to isocyanides bearing *tert*-butyl, cyclohexyl and 2,4,6-trimethylphenyl groups displaying high reactivity and furnishing the corresponding 2-amino-3-perfluoroalkylfurans in good to excellent yields.

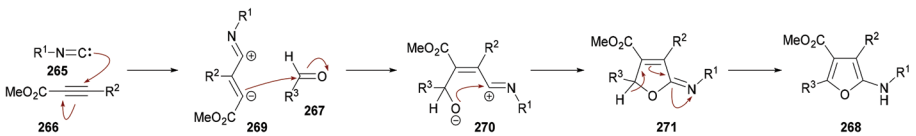
Mechanistically, this multi-component methodology starts with a regioselective Michael addition of isocyanide **265** to methyl 2-perfluoroalkynoate **266** generating 1,3-dipolar intermediate **269** which on nucleophilic addition to aldehyde **267** produced the zwitterionic intermediate **270**. Subsequent cyclization followed by a [1,5]-*H* shift delivered the aminofuran product **268** [266–268] (Scheme 69).

2.2.5. Synthesis of benzofurans. Wang and co-workers[269] demonstrated a 4-dimethylaminopyridine-catalyzed cyclization of 2-azido-1-(2-hydroxyphenyl)ethanones **272** with alkynoates **273** to afford a diverse range of 2-aminobenzofuran-3(2*H*)-one derivatives **274** in moderate yields (Scheme 70). Various reaction parameters were screened for the identification of the optimized conditions. The versatility of the reaction was examined under the optimal reaction conditions revealing that a variety of azido ketone substrates **272** were successfully cyclized to the corresponding 2-aminobenzofuranones in modest yields. Different substitution patterns incorporating electron-donating and electron-withdrawing groups were tolerated. Moreover, the reaction scope encompassing various electron-deficient alkynes was also evaluated. Ethyl, methyl, benzyl and phenyl substituted alkynes were successfully converted to the desired 2-aminobenzofuran-3(2*H*)-ones in moderate to good yields.

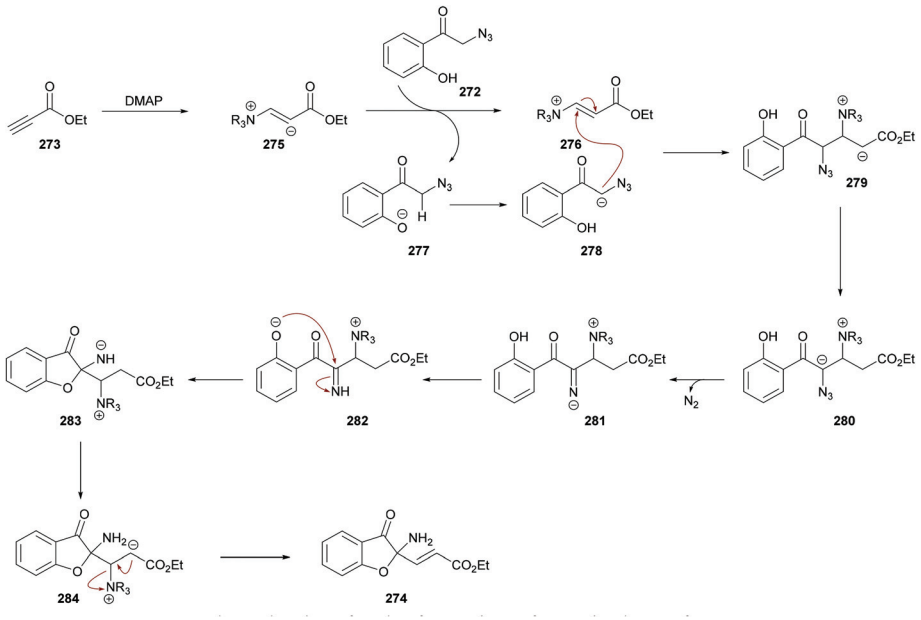
The proposed mechanism is illustrated in Scheme 71 which starts with the addition of DMAP to the electron-deficient alkyne **273** to generate zwitterion **275**. Deprotonation of **272** followed by proton transfer afforded intermediate **278** which on Michael addition to **276** furnished compound **279**. Another proton transfer followed by the loss of N_2 delivered intermediate **281** [270,271] which underwent another proton transfer to form **282**. Intramolecular nucleophilic addition of **282** produced intermediate **283**, followed by proton transfer and elimination of DMAP to afford the heterocyclic product **274**.

2.2.6. Synthesis of dioxanones and benzodioxinones. Taran and co-workers[272] introduced a one-step phosphine-catalyzed method for the preparation of 1,4-dioxane-2-one **288** and 1,4-benzodioxine-2-one derivatives **289** from 1,2-diol starting materials **286**, **287** (Scheme 72). A range of diols were efficiently converted to the desired products at room temperature. The methodology was further extended to the synthesis of 1,4-benzodioxin-2-ones using the phosphine-catalyzed α-*O*-addition and transesterification reaction. The title products were obtained as *Z*-isomers in acceptable yields. The reactivity of the reaction was found to be highly dependent on the pK_a of the diol and/or the nucleophilicity of the corresponding catecholate. Electron-rich catechols furnished the best results compared to electron-deficient catechols.

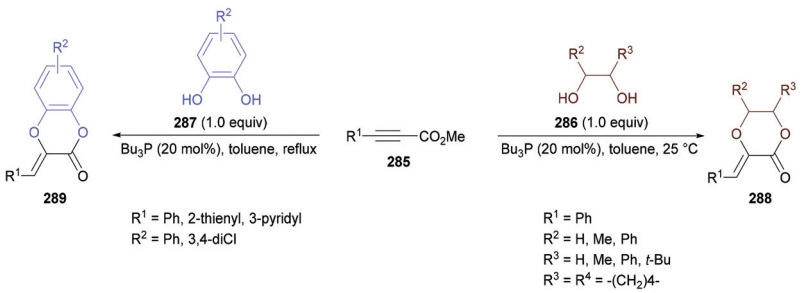
2.2.7. Synthesis of lactones. Yu, Pu and co-workers[273] discovered a convenient protocol for the asymmetric synthesis of 4-amino-2(5*H*)-furanones **293** involving alkynes **290**, aldehydes and amines **292** (Scheme 73). The reaction can be performed at room temperature producing the heterocyclic products with high enantioselectivity (84–90% ee). The investigation is based on their previous reports where γ-hydroxy-α,β-acetylenic esters[274–278] were synthesized from an enantioselective reaction of methyl propiolate and aldehydes using 1,1′-bi-2-naphthol (BINOL) in combination with $ZnEt_2$, $Ti(O^iPr)_4$, and HMPA. In the present approach, these esters were subsequently cyclized with aliphatic amines to produce amino furanones. Various conditions were tested for this two-step process to establish the optimized protocol. Under the optimal reaction conditions, different aldehydes were initially coupled to methyl propiolate followed by the addition of benzylamine to afford 4-amino-2(5*H*)-furanones. Moderate to good isolated yields were obtained with high enantioselectivity. Linear and branched aliphatic aldehydes were efficiently tolerated along-



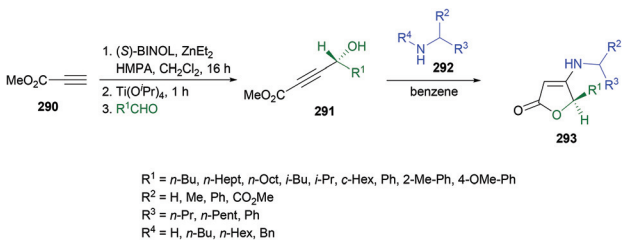
Scheme 69 Proposed mechanism for the formation of 2-amino-3-perfluoroalkylfurans **268**.



Scheme 71 Proposed mechanism for the formation of 2-aminobenzofuran-3(2*H*)-ones **274**.



Scheme 72 Phosphine-catalyzed synthesis of 1,4-dioxane-2-ones and 1,4-benzodioxine-2-ones from 1,2-diols and alkynoates.

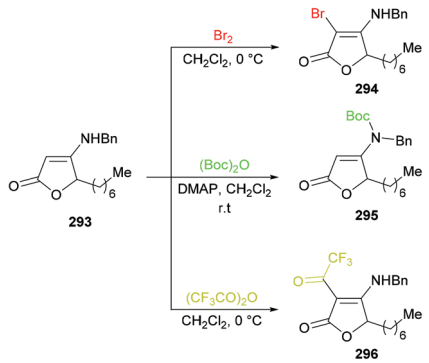


Scheme 73 Asymmetric synthesis of 4-amino-2(5*H*)-furanones from alkynoates, aldehydes and amines.

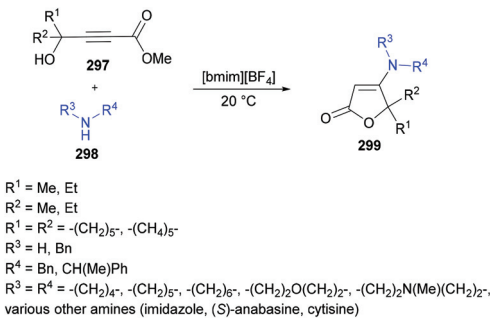
side cyclic and few aromatic amines. Moreover, the use of racemic alkyl- and aryl-substituted acetylenic esters were also investigated for the addition reaction of primary and secondary amines. The corresponding products were isolated in good yields. The synthetic modification of the products illustrated that 3-brominated heterocycle **294** could be accessed when treated with Br_2, although bromination and iodination of 4-amino-2(5*H*)-furanones using NBS[279] and ICl or $I(py)_2BF_4$[280–282] were previously known. Similarly, *C*-acylated product **296** was isolated in an excellent yield (95%) instead of an *N*-acylated product using trifluoroacetic anhydride at room temperature; however, *N*-protected product **295** was furnished in 99% yield when the reaction was performed with $(Boc)_2O$ using DMAP at room temperature (Scheme 74).

Zlotin and co-workers[283] investigated the reaction of methyl 4-hydroxyalk-3-ynoates **297** and amines **298** to afford 4-aminofuran-2(5*H*)-ones **299** in ionic liquids (Scheme 75). The reaction rate was accelerated many fold while reducing the time and improving the product yield. Several examples were synthesized, and the data were compared with the literature showing the supremacy of the reaction conditions employing ionic liquids. Additionally, the recyclability of IL [bmim][BF_4] was demonstrated in the synthesis of butenolides. Reaction rates and product yields remained unaffected over at least five reaction cycles.

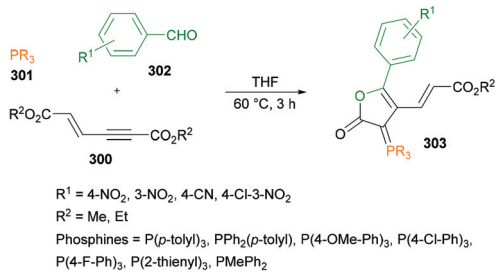
Deng and Chuang[284] reported a series of γ-lactones **203** bearing an α-phosphorus ylide functionality from hex-2-en-4-ynedioic acid dialkyl esters **200**, phosphines **201** and aldehydes



Scheme 74 Synthetic modification of 4-amino-2(5*H*)-furanone **293**.



Scheme 75 Synthesis of 4-aminofuran-2(5*H*)-ones from methyl 4-hydroxyalk-3-ynoates and amines in ionic liquids.

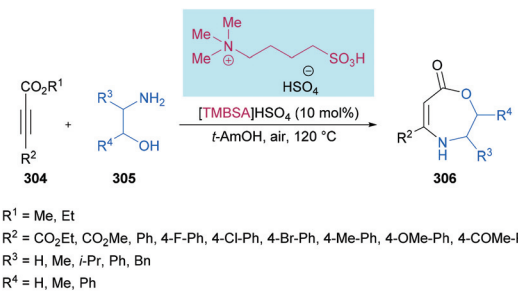


Scheme 76 Multi-component synthesis of γ-lactones featuring α-phosphorus ylides from enynes, phosphines and aldehydes.

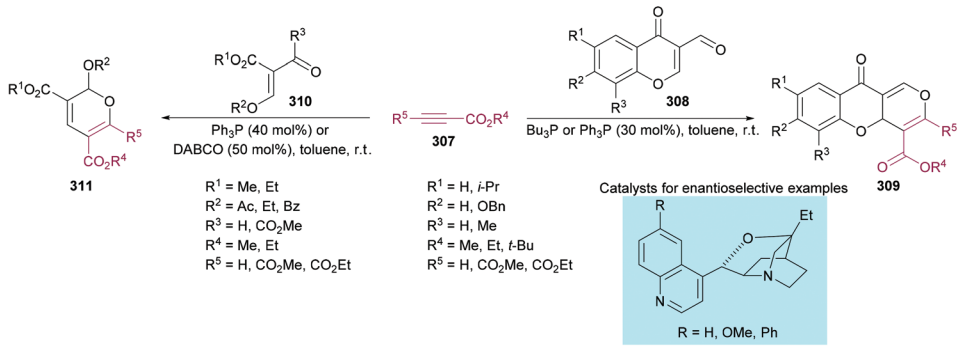
202 (Scheme 76). The authors investigated various reaction conditions including solvents (THF, DCE, DCM) at different reaction times and temperatures. Chlorinated solvents were found to be less effective compared to THF. Initially, the reactivity of different phosphines was tested. Triarylphosphines produced the desired lactones in moderate to good yields (55–79%). Electron-donating aryl bearing phosphines generally performed better compared to the electron-withdrawing one whereas heteroaryl phosphine was also a smooth coupling partner, albeit producing the lactone in a lower yield (55%). Moreover, phosphine endowed with an alkyl substituent could only produce the desired product in 38% yield. On the other hand, substituted aldehydes were explored to expand the reaction scope. Electron-deficient aldehydes containing nitro, chloro and nitrile functional groups generally produced efficient results; however, attempts to use alkyl and electron-rich substituted aldehydes remained unproductive.

Chen, Li and co-workers[285] demonstrated a task-specific acidic ionic liquid-catalyzed synthesis of β-enaminolactones **306**. Alkynoates **304** and β-amino alcohols **305** were successfully cyclized to the desired products in ample yields (Scheme 77). The formation of a seven-membered ring involves tandem intermolecular hydroamination and intramolecular transesterification reaction sequences. Diethyl but-2-ynedioate and 2-amino-2-phenylethanol were chosen as model substrates. Initially, various Lewis acid catalysts ($AlCl_3$, $ZnCl_2$, $FeCl_3$, $Yb(OTf)_3$, $Cu(OTf)_2$, $Zn(OTf)_2$) were tested and the results indicated that $Cu(OTf)_2$ and $Zn(OTf)_2$ exhibit good reactivity. As the role of the acid catalyst was found to be critical, the sulfonic-functionalized ionic liquid[286–288] (TSFIL-1 : [TMBSA]HSO_4) was tested due to its many advantages[289–295] and it showed an excellent reactivity and produced the desired lactone in 94% yield. Other parameters including variation of solvents and temperature exhibited inferior results. Under the established reaction conditions, the flexibility of this protocol was assessed. Both alkynoates and β-amino alcohols bearing different groups were employed. Two-point structural diversity was present in each component of this methodology. Substrates with various alkyl and aryl substituents were smoothly converted to their corresponding lactones in moderate to good yields. Primary and secondary alcohols also produced promising results. In general, this method showed a broad substrate scope with good functional group tolerance and operational simplicity.

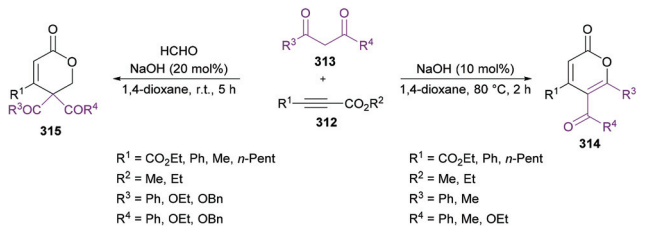
Waldmann, Kumar and co-workers[296] developed organocatalyzed tricyclic benzopyrones **309** involving a [4 + 2] annulation reaction of 3-formylchromones **308** with electron-deficient alkynes **307** (Scheme 78). Under the optimized reaction conditions, a varied range of substituents were endured at the chromone ring and alkynoates. Unsubstituted, alkyl- and alkoxy-substituted chromones and alkynoate esters were efficiently coupled to produce pyran-fused chromones in good yields. Moreover, acyclic oxadienes **310** were also employed as substrates with acetylene carboxylates to generate [4 + 2] annulation products that underwent a subsequent Claisen



Scheme 77 Task-specific acidic ionic liquid-catalyzed synthesis of β-enaminolactones from alkynoates and β-amino alcohols.



Scheme 78 Asymmetric organocatalyzed synthesis of tricyclic benzopyrones.



Scheme 79 Synthesis of polysubstituted 2*H*-pyran-2-ones from alkynoates and activated methylenes.

rearrangement to afford dehydropyrans **311**. A range of different substituents on both starting materials were successfully tolerated. Next, the asymmetric version of this transformation was explored by employing a β-isoquinidine catalyst.

2.2.8. Synthesis of pyrones. Jiang and co-workers[297] developed a multi-component methodology involving the hydroalkylation of alkynoates **312** and activated methylenes **313** for the preparation of functionalized 2*H*-pyran-2-ones **314** (Scheme 79). The target products were obtained in ample yields. Various reaction parameters including temperature, alkaline additives and solvents were screened to obtain the appropriate reaction conditions. The use of 1.0 equivalent of sodium hydroxide in 1,4-dioxane solvent at 80 °C proved to be the optimal conditions producing the desired heterocycle in 89% yield; however, the further experimentation was conducted using 10 mol% of sodium hydroxide as 88% yield was observed. Using these conditions, the scope of the methodology was examined. Several active methylene compounds were successfully coupled to alkynoates to generate six-membered oxygen heterocycles in good yields. Moreover, when ethyl 3-phenylprop-2-ynoate and diethyl propanedioate and formaldehyde were coupled in one pot, diethyl 6-oxo-4-phenyl-2*H*-pyran-3,3(6*H*)-dicarboxylate **315** was obtained in 82% isolated yield. Trisubstituted 2*H*-pyran-2-ones were only obtained when dibenzoylmethane, 1-phenyl-1,3-butanedione, 2,4-pentanedione, and ethyl acetoacetate were used as activated methylene partners.

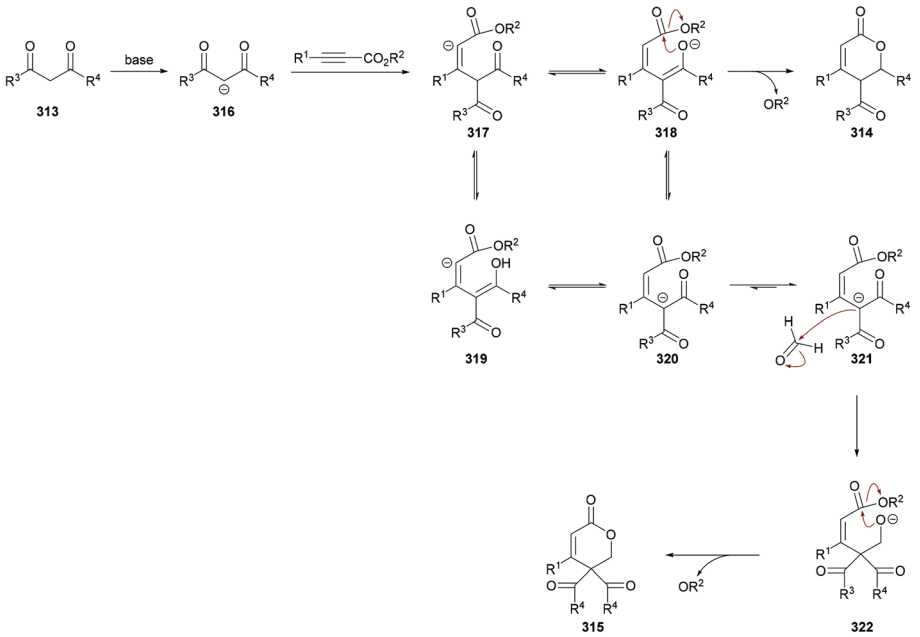
Scheme 80 illustrates the possible mechanistic pathway which starts with the activation of 1,3-dicarbonyl compound **313** to form **316**. Nucleophilic addition of **316** to alkynoate **312** produced intermediate **317** which could possibly be present in different resonance structures, such as **318**, **319**, and **320**. Nucleophilic attack on the carbonyl carbon delivered product **314**. In the presence of an aldehyde, intermediate **320** was converted to intermediate **322**. An intramolecular oxygen nucleophilic cyclization furnished the desired product **315**.

2.3. Synthesis of saturated oxygen-containing heterocycles

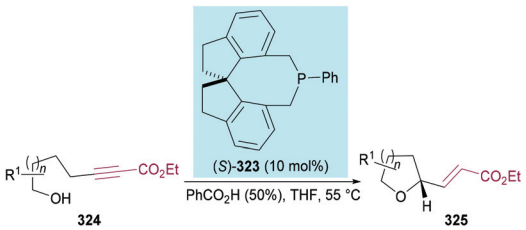
Chung and Fu[298] established that chiral spiro phosphepine ligand **323** can transform a variety of hydroxy-2-alkynoates **324** into various saturated oxygen heterocycles **325** (tetrahydrofurans, tetrahydropyrans, dihydrobenzopyrans) with good enantioselectivity (Scheme 81). Using the optimized reaction conditions, a variety of substrates were converted to products with high enantioselectivity and good yields.

In the same year, Pedduri and Williamson[299] reported a phosphine-catalyzed reaction to access various functionalized tetrahydrofurans **328**, **329** using electron-deficient propargyl alcohols **326** and Michael acceptors **327** as starting materials (Scheme 82). Several reaction conditions were investigated to identify the suitable conditions. Under the optimized conditions, alkylidene-, arylidene-, and heteroarylidene malonate/Meldrum's acid-based alkene derivatives were included to assess the diversity of the reaction. The corresponding heterocyclic products were furnished in good yields as a separable *E* : *Z* mixture.

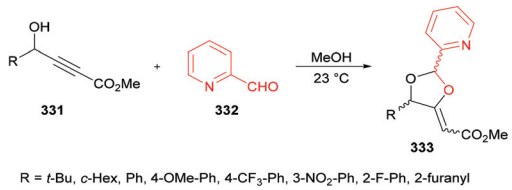
Osman and Koide[300] developed a new synthetic route for the synthesis of functionalized cyclic acetals **333** using 2-pyridinecarboxyaldehyde **332** and γ-hydroxy-α,β-acetylenic esters **331** (Scheme 83). The methodology operates under mild reaction conditions avoiding the need for any additive. After optimizing the suitability of various solvents, methanol was identified to produce the highest conversion and was chosen for subsequent experiments to explore the reaction scope. Various acetylenic esters bearing cyclohexyl, *tert*-butyl, aromatic and hetero-aromatic substituents were successfully tolerated. The post-synthetic functionalization of the products was also performed under hydrogenolysis conditions[301] (Scheme 84).



Scheme 80 Proposed mechanism for the formation of pyranones **314**, **315**.



Scheme 81 Phosphine-catalyzed enantioselective synthesis of oxygen heterocycles.

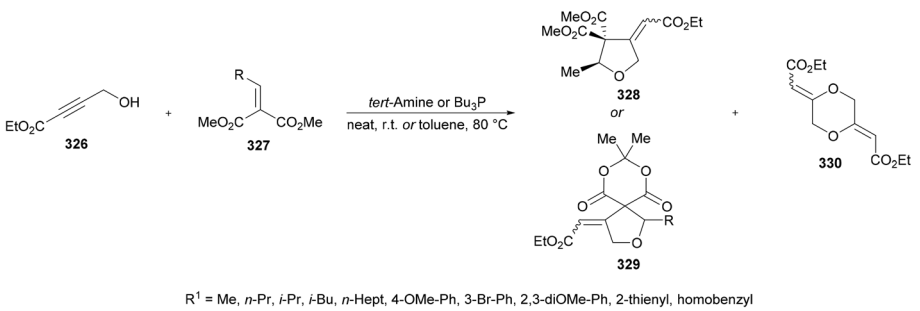


Scheme 83 Cyclic acetal formation between 2-pyridinecarboxaldehyde and γ-hydroxy-α,β-acetylenic esters.

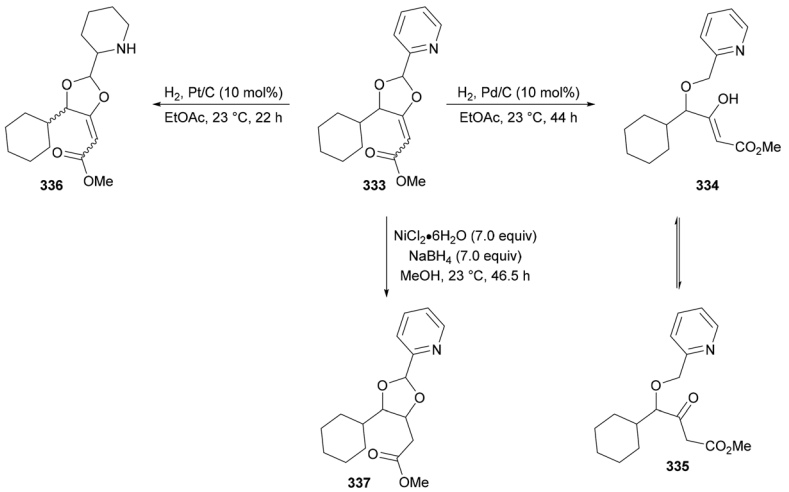
2.4. Synthesis of sulfur-containing heterocycles

Sulfur-containing heterocycles constitute the core structure of various pharmaceuticals, natural products and bioactive pharmacophores. These heterocycles also find wide applications in synthetic organic chemistry.[302] Due to their widespread utility, facile and efficient synthetic methods are always required to meet the requirements in several drug discovery programs.

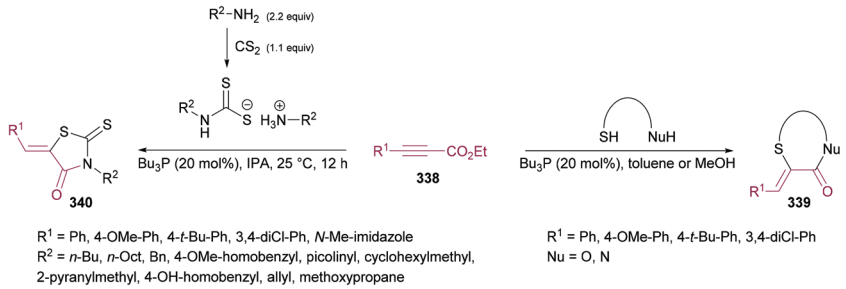
2.4.1. Synthesis of iminothiazolidin-4-ones and 2-thioxo-4-thiazolidinones. Taran and co-workers[303] developed an efficient and facile phosphine-catalyzed approach for the construction of sulfur heterocycles (Scheme 85). This methodology involves a tandem umpolung addition and intramolecular cyclization of bifunctional sulfur pronucleophiles on aryl propiolates **338**. The method appeared to tolerate a diverse range



Scheme 82 Phosphine-catalyzed synthesis of functionalized tetrahydrofurans using electron-deficient propargyl alcohols and Michael acceptors.



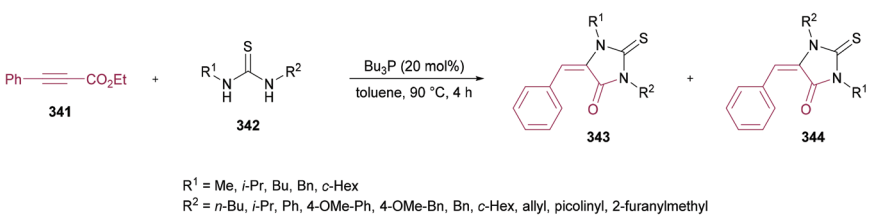
Scheme 84 Synthetic modification of cyclic acetals **333**.



Scheme 85 Phosphine-catalyzed synthesis of sulfur heterocycles.

of substrates (sulfur–oxygen or sulfur–nitrogen pronucleophiles) leading to 5- and 6-membered sulfur-containing heterocycles **339**, **340**. Mercapto alcohols, amines, and amides all worked well to provide the desired arylidene heterocycle *Z* isomers in moderate to good yields. Moreover, thioureas can also be employed as bifunctional *S*,*N*-pronucleophiles producing 2-iminothiazolidin-4-one compounds. Finally, the synthesis of rhodanine (2-thioxo-4-thiazolidinone) was accomplished using dithiocarbamates and aryl propiolates under similar reaction conditions. A variety of amines were reacted with carbon disulfide to generate dithiocarbamates *in situ* which were used to afford the desired cyclized product.

2.4.2. Synthesis of thiohydantoins. Loreau, Taran and co-workers[304] made use of arylpropiolates **341** and thioureas **342** for the synthesis of thiohydantoins **343**, **344** (Scheme 86). The present methodology operates *via* phosphine-catalyzed tandem umpolung addition and an intramolecular cyclization process. This method is different from the classical approach which involves two-step synthesis, aiming at the preparation of the thiohydantoin moiety followed by a Knoevenagel condensation with aldehydes.[305,306] This concept originates from the dual reactivity of thioureas where α-*N*-addition occurs at aryl propiolates under Bu_3P catalysis followed by cyclization to produce thiohydantoins. With the optimized reaction conditions in hand, a range of thioureas were employed as coupling partners



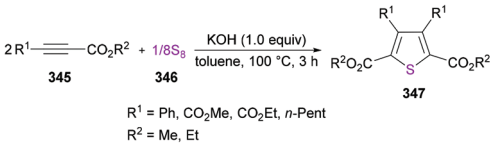
Scheme 86 Phosphine-catalyzed synthesis of thiohydantoins from thioureas and arylpropiolates.

with aryl propiolates to afford numerous 5-arylidene-2-thiohydantoins. The regioselectivity was dependent on the nature of the substituents present in the thiourea functionality. Alkyl, aryl and hetero-aryl bearing thioureas participated efficiently. However, there is a competition in the α-*N*-addition step between the two nitrogen atoms of the thiourea functionality and the reactivity of the NH groups is influenced by steric hindrance, nucleophilicity and pK_a. Despite some limitations (poor yield and a mixture of regioisomers in certain cases), this method presents some advantages over the reported methods.

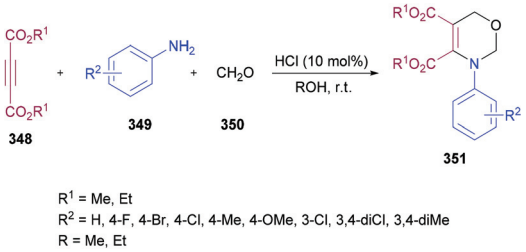
2.4.3. Synthesis of thiophenes. Liu and co-workers[307] demonstrated a facile and convenient approach to access a small library of decorated thiophenes **347** *via* the [2 + 2 + 1] cycloaddition reaction. A variety of alkynoates **345** and elemental sulfur **346** coupled together to generate the title products (Scheme 87).

2.5. Synthesis of O,N-heterocycles

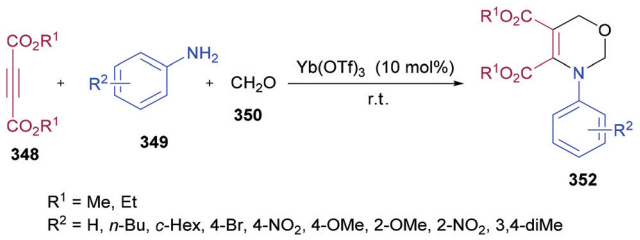
2.5.1. Synthesis of oxazines. Jiang and co-workers[308] described a multi-component one-pot synthetic route for the synthesis of 3,4,5-trisubstituted-3,6-dihydro-2*H*-1,3-oxazines **351** from readily available starting materials (alkynoates **348**, anilines **349**, formaldehyde **350**). The formation of a six-membered N,O-heterocyclic scaffold occurs *via* a Brønsted acid-catalyzed reaction sequence involving domino hydroamination/Prins reaction/cyclization/dehydration (Scheme 88). After successful identification of the optimized reaction conditions, the scope of the multi-component methodology was explored. A range of anilines and electron-deficient alkynes were employed alongside formaldehyde delivering the desired oxazines in good to excellent yields. Substituents at different positions of



Scheme 87 Synthesis of polysubstituted thiophenes *via* the base-induced [2 + 2 + 1] cycloaddition reaction of alkynes and elemental sulfur.



Scheme 88 Brønsted acid-promoted domino one-pot three-component synthesis of 3,4,5-trisubstituted-3,6-dihydro-2*H*-1,3-oxazines.



Scheme 89 Ytterbium triflate promoted one-pot three-component synthesis of 3,4,5-trisubstituted-3,6-dihydro-2*H*-1,3-oxazines.

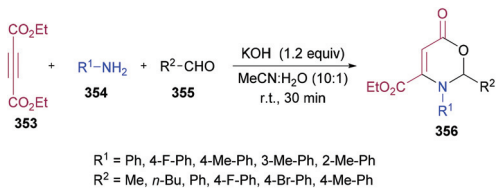
anilines were successfully tolerated; however, *ortho*-substituted anilines remained reluctant to produce the desired products.

Curini and co-workers[309] described the same methodology and produced 3,4,5-trisubstituted-3,6-dihydro-2*H*-1,3-oxazines **352** *via* the ytterbium triflate promoted reaction sequence (Scheme 89). This methodology differs from the previous report in the use of both aliphatic and aromatic amines while avoiding excess formaldehyde and strong mineral acids like HCl.

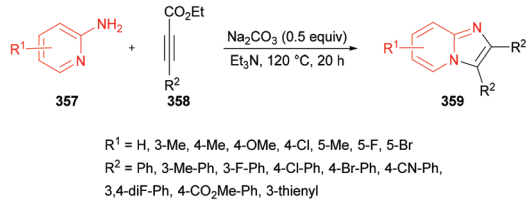
2.5.2. Synthesis of oxazinones. Jiang and co-workers[310] developed a highly efficient three-component methodology involving but-2-ynedioic acid diethyl esters **353**, amines **354** and aldehydes **355** to furnish polysubstituted ethyl 2,5-dihydro-2*H*-1,3-oxazine-6-one-4-carboxylates **356** in good to excellent isolated yields (Scheme 90). A range of solvents (MeCN, PhMe, Et_2O, DCM, THF, EtOH, H_2O) and bases (Na_2CO_3, Et_3N, NaOH, KOH) were screened. A mixture of MeCN and H_2O (10 : 1) was the best choice with the isolation of the heterocyclic product in 78% yield. A variety of amines and aldehydes were utilized to explore the reaction scope. In the case of aliphatic aldehydes, the corresponding products could be isolated in less than three minutes and in excellent yields. Both electron-rich and electron-deficient substituents at the aryl rings of both amines and aromatic aldehydes were also successful coupling partners.

2.6. Synthesis of fused heterocycles

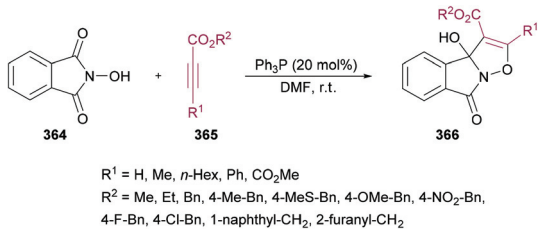
2.6.1. Synthesis of imidazo[1,2-*a*]pyridines. Chen, Wang and co-workers[311] developed a highly efficient transition-metal-free cyclization methodology for the preparation of 2,3-diarylimidazo[1,2-*a*]pyridines **359** involving 2-aminopyridines **357** and alkynoates **358** (Scheme 91). These starting materials were found to be compatible under the optimal conditions.



Scheme 90 Three-component synthesis of polysubstituted 2,5-dihydro-1,3-oxazin-6-ones from alkynoates, amines and aldehydes.



Scheme 91 Synthesis of 2,3-diarylimidazo[1,2-α]pyridines from 2-aminopyridines and alkynoates.



Scheme 93 Phosphine-catalyzed synthesis of 3*a*-hydroxyisoxazolo[3,2-*a*]isoindol-8(3a*H*)-ones *via* [3 + 2] annulation of electron-deficient alkynes with *N*-hydroxyphthalimide.

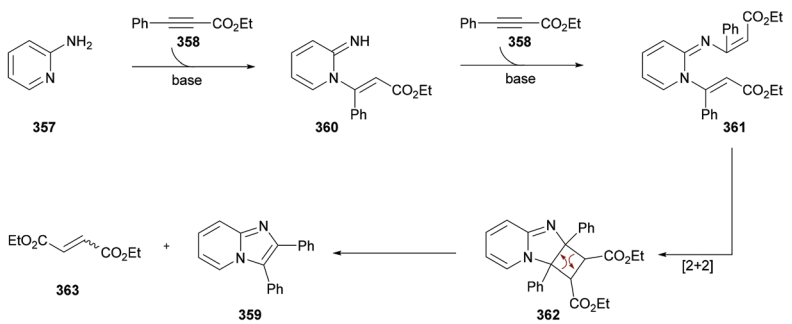
The scope and limitations of the one-pot methodology were explored using a variety of both components. Electron-donating and electron-withdrawing groups were successfully tolerated on the alkynoate. In addition, the effect of different groups at various positions of the 2-aminopyridine moiety was also tested. Halogens including fluoro, chloro, and bromo substituents were also well tolerated. Alkynoates bearing a heteroaryl ring also gave the desired product in good yields; however, in certain cases, a longer reaction time was required.

Mechanistically, 2-aminopyridine **357** was reacted with alkynoate **358** to produce intermediate **361** through **360** *via* intermolecular Michael addition which upon an intramolecular [2 + 2] cycloaddition reaction produced intermediate **362**. The desired product **359** was furnished on cleavage of the carbon–carbon bond of the cyclobutene ring *via* a ring-opening reaction. Diethyl but-2-enedioate byproduct **363** was detected with GC-MS (Scheme 92).

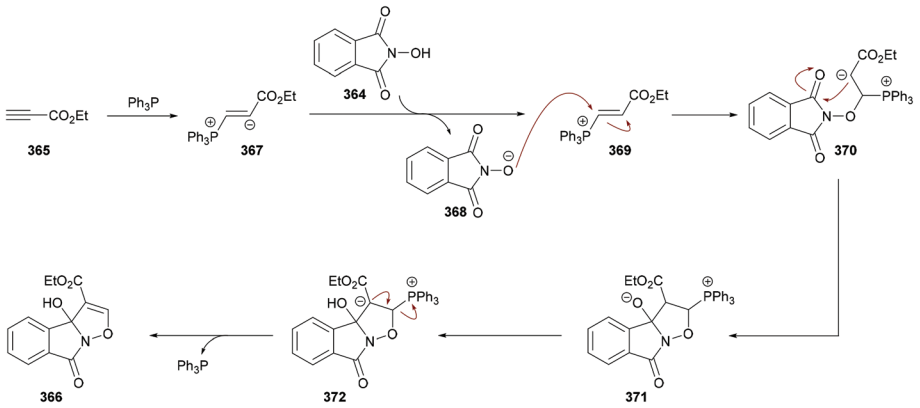
2.6.2. Synthesis of isoindolin-1-ones. Zhou, Lu and co-workers[312] demonstrated a phosphine-catalyzed [3 + 2] annulation reaction involving electron-deficient alkynes **364** and *N*-hydroxyphthalimide **365** to provide a facile access to 3*a*-hydroxyisoxazolo[3,2-*a*]isoindol-8(3a*H*)-ones **366** (Scheme 93). The target fused products were isolated in remarkable yields. Various phosphines, solvents and temperatures were screened. Isoindolin-1-one products were isolated in excellent yields using triphenylphosphine (20 mol%) in DMF at room temperature. Under the optimized conditions, the scope of the reaction was explored delivering a variety of fused products in high yields. Initially, various terminal alkynoates were tested. A variety of ester substituents participated efficiently. The aromatic ring of benzyl propiolates bearing electron-donating and electron-withdrawing functional groups was found to be compatible. A long aliphatic chain (*n*-hexyl) substituted alkynoate showed no reactivity; however, ethyl 2-butynoate and ethyl 3-phenylpropiolate furnished the corresponding 3*a*-hydroxyisoxazolo[3,2-*a*]isoindol-8(3a*H*)-ones in 55% and 99% yields, respectively. These reaction conditions produce different results to those observed in the literature[313] when the reaction was performed using DMAD and a stoichiometric amount of triphenylphosphine at room temperature in dichloromethane and a pyrroloisoindole compound was isolated.

The authors proposed the mechanism of this transformation which was initiated by the nucleophilic addition of PPh_3 to the electron-deficient C≡C bond of alkynoate **365** to form zwitterion **367**, which was used to deprotonate *N*-hydroxyphthalimide **364** generating intermediates **368** and **369**. Michael addition of **368** to **369** produced intermediate **370**.[314–316] Intramolecular nucleophilic cyclization furnished the cyclized intermediate **371** followed by proton transfer to give **372**. Subsequent elimination of PPh_3 produced the desired fused product **366** (Scheme 94).

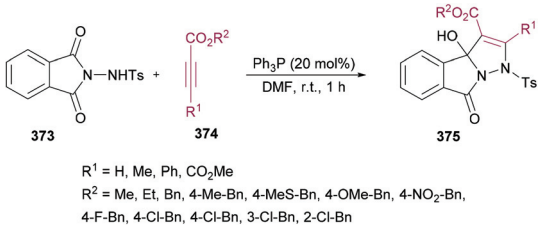
In a subsequent study, the same group[317] reported a metal-free approach to access highly functionalized pyrazolo[5,1-*a*]isoindol-8(3a*H*)-ones **375** through a phosphine-catalyzed tandem Michael addition/intramolecular Morita–Baylis–Hillman reaction sequence involving alkynoates **374** and *N*-amino substituted phthalimide **373** (Scheme 95). Using the optimized reaction conditions, various alkynoates were tested producing the title products in moderate to good yields. Terminal alkynoates were compatible; however, methyl and phenyl substituted derivatives were unreactive. Various elec-



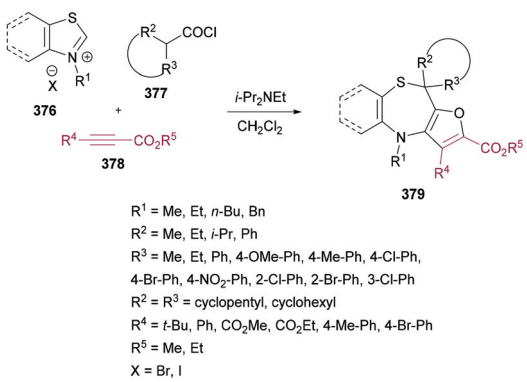
Scheme 92 Proposed mechanism for the formation of 2,3-diarylimidazo[1,2-α]pyridines **359**.



Scheme 94 Proposed mechanism for the formation of 3*a*-hydroxyisoxazolo[3,2-*a*]isoindol-8(3a*H*)-ones **366**.



Scheme 95 Phosphine-catalyzed construction of pyrazolo[5,1-*a*]isoindol-8(3a*H*)-ones from electron-deficient alkynes and *N*-amino substituted phthalimide.

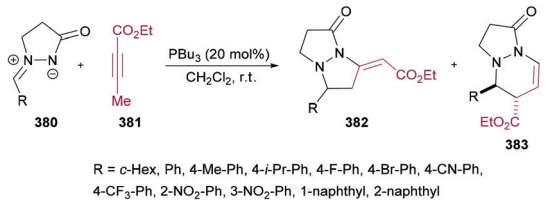


Scheme 96 Multi-component synthesis of highly substituted furan-fused 1,4-thiazepines.

tron-rich and electron-deficient groups at the benzyl ring of propiolates appeared to be well tolerated. However, the presence of a strongly electron-withdrawing nitro group impeded the reaction, producing the corresponding product in 27% yield.

2.6.3. Synthesis of furo-thiazepines. Ma and co-workers[318] developed a three-component method involving thiazole or benzothiazole carbenes **376**, substituted acetyl chloride **377** and electron-deficient alkynes **378** resulting in the formation of the polysubstituted heterocyclic scaffold furo[2,3-*c*]thiazepine **379**. The title products were isolated in good yields using these simple and readily available starting materials (Scheme 96). Based on the previous efforts on the use of thiazole carbenes,[319–325] the authors investigated a domino approach to construct a fused heterocyclic skeleton.[326] For the investigation of reaction conditions, a thiazolium salt and α-methyl phenylacetyl chloride were used that generated thiazole carbene and ketene *in situ*. The effect of several typical bases such as NEt_3, *i*-Pr_2NEt, DBU, and NaH was also studied. *i*-Pr_2NEt in dichloromethane provided the best result. Using the optimized reaction conditions, a diverse range of disubstituted acetyl chlorides were reacted with the thiazolium salt. The corresponding products were isolated in good to excellent yields. Substrates incorporating electron-rich and electron-deficient functional groups participated efficiently; however, the electron-poor system produced sluggish yields. The size of the alkyl group was also important as the isopropyl substituted substrate did not produce any product whereas methyl and ethyl substituents were completely productive. Dialkyl substituted substrates were also equally reactive producing the desired compounds in good yields. The reaction scope was further extended using various thiazolium salts and similar reactivities were observed in terms of the yields of the fused products. Furthermore, two different procedures were developed to investigate various electron-deficient alkynes and in most of the cases better yields were observed where ketenes were used. The authors also tested the benzothiazole carbenes and tricyclic heteroaromatic compounds were furnished in moderate yields. The synthetic utility of the selected derivatives was investigated in the Diels–Alder reaction with arynes to deliver 1,4-thiazepine-fused 7-oxanorbornadienes in excellent yields.[327–329]

2.6.4. Synthesis of tetrahydropyrazolopyrazolones and tetrahydropyrazolopyridazinones. Zhong, Guo and co-workers[330] unveiled a facile approach for the preparation of tetrahydropyrazolopyrazolones **382** and tetrahydropyrazolopyridazinones **383** *via* phosphine-catalyzed [3 + 2] and [3 + 3] annulation reactions of azomethine imines **380** and ethyl 2-butynoate **381** (Scheme 97). This coupling reaction was optimized by using ethyl 2-butynoate with 1-(*p*-nitrobenzylidene)-3-oxopyrazolidin-



Scheme 97 Phosphine-catalyzed [3 + 2] and [3 + 3] annulations of azomethine imines with ethyl 2-butynoate.

1-ium-2-ide in the presence of different phosphine catalysts. Although the best results were achieved when dimethylphenylphosphine was employed with the isolation of **382** and **383** in 65% and 14% yields, respectively, the authors were interested to isolate both products due to their biological significance;[331–335] therefore, the subsequent experimentation was performed with tributylphosphine as the catalyst. A range of azomethine imines were annulated with ethyl 2-butynoate in dichloromethane at room temperature. Tetrahydropyrazolopyrazolone and tetrahydropyrazolopyridazinone derivatives were obtained in moderate to good yields. Both electron-rich and electron-deficient substituents at the phenyl ring were compatible. Strongly electron-deficient groups (nitro, cyano) at the *ortho*- or *para*-position of the phenyl ring provided the target products in relatively much higher yields compared to electron-rich and weakly electron-withdrawing substituents, albeit with poor chemoselectivities toward the [3 + 2] annulation product. Moreover, azomethine imines bearing 1-naphthyl, 2-naphthyl and cyclohexyl groups also underwent a smooth reaction with 2-butynoate, producing the corresponding pyrazolidinone derivatives.

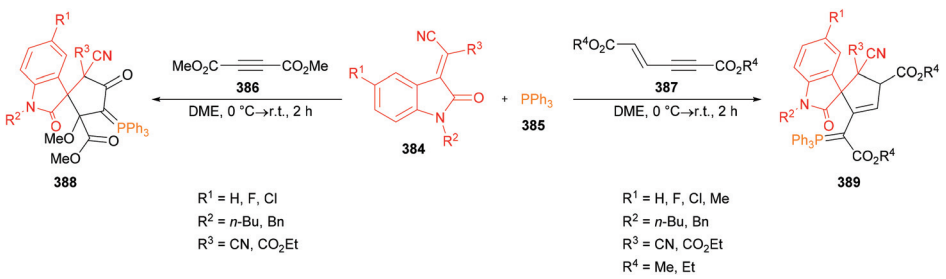
2.6.5. Synthesis of spirooxindoles. Yan and co-workers[336] developed a divergent three-component approach using isatylidene malononitrile (ethyl cyanoacetate) **384** and triphenylphosphine **385** (Scheme 98). Depending upon the addition of the third component (but-2-ynedioate **386** or hex-2-en-4-ynedioate **387**) in dimethoxyethane, triphenylphosphanylidene spiro[cyclopentane-1,3′-indolines] **388** and spiro[cyclopent[2]ene-1,3′-indolines] **389** were furnished in moderate to good yields. Using the optimized conditions, DMAD (1.2 mmol), isatylidene malononitrile (ethyl cyanoacetate, 1.0 mmol), and PPh_3 (1.0 mmol) in DME (10 mL) at 0 °C → r.t. for 2 h, various spirocyclic compounds were accessed. Similarly, dialkyl hex-2-en-4-ynedioates were also employed to expand the substrate scope and the relevant products were isolated in good yields.

The mechanism for the formation of spiro[cyclopentane-1,3′-indolines] **388** is illustrated in Scheme 99. Intermediate **390** was furnished *via* a 1,4-dipolar addition reaction of PPh_3 **385** and DMAD **386**[337–339] which then added to isatinylidene malononitrile **384** and delivered the intermediate **391**. Subsequently, an intramolecular nucleophilic substitution reaction of the carbanion to alkoxide in the ester furnished the cyclic intermediate **392** which on 1,3-arrangement of the triphenylphosphanyl cation led to carbonium intermediate **393**. The desired product was obtained by the coupling of carbonium **393** with methoxide in solution.

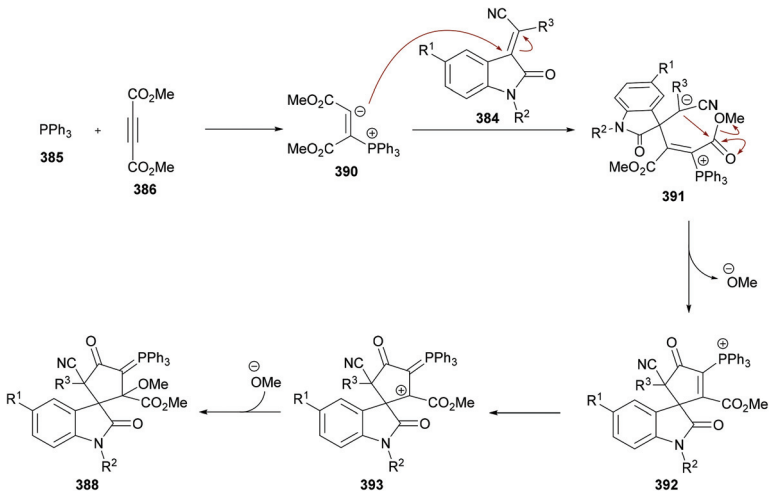
Scheme 100 illustrates the mechanistic pathway for the formation of product **389** in line with the literature precedents.[340–343] Addition of PPh_3 **385** to hex-2-en-4-ynedioate **387** furnished 1,3-dipolar zwitterionic intermediate **394** followed by the addition to isatinylidene malononitrile **384** leading to the formation of adduct **395**. Subsequently, an intramolecular Michael addition of the carbanion to the 1,3-diene holding a stronger electron-deficient triphenylphosphanyl cation afforded the cyclized intermediate **396**. Next, intermediate **397** was formed from **396** by allylic arrangement of the carbanion. Finally, the target product **389** was obtained *via* phosphorus ylide transfer.

In a subsequent study, isatin-derived α,β-unsaturated ketones **398** were cyclized with alkynoates **399** providing access to various cyclopentene spirooxindole compounds **400** using the previously[344] optimized conditions (Scheme 101). The title products were isolated in good to excellent yields with high regioselectivity and moderate to high diastereoselectivities (up to 20 : 1 dr). This methodology provides biologically active spiro-(cyclopentene) oxindoles featuring three contiguous stereocenters, including the quaternary stereogenic center joining the two rings. Similar to previous efforts, good functional group tolerance and structural diversity were observed.[345]

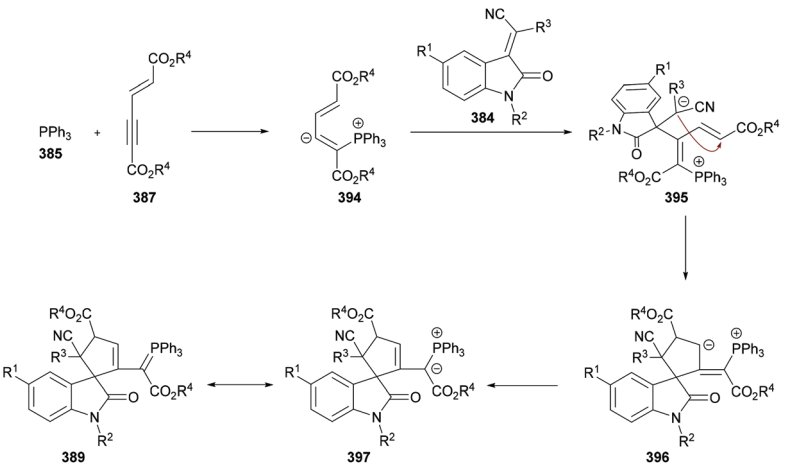
2.6.6. Synthesis of spirocyclic oxindole-butenolides. Li, Jia and co-workers[346] explored a multi-component methodology to produce spirocyclic oxindole-butenolides **404** *via* intermolecular [2 + 2 + 1] cycloaddition involving easily accessible



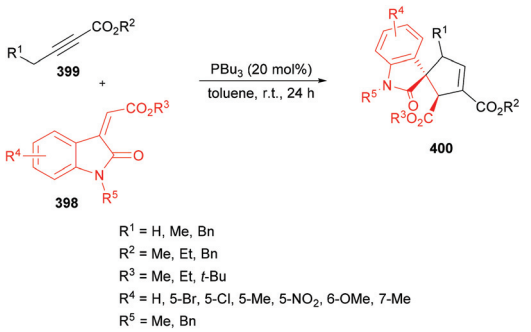
Scheme 98 Three-component synthesis of triphenylphosphanylidene spiro[cyclopentane-1,3′-indolines] and spiro[cyclopent[2]ene-1,3′-indolines].



Scheme 99 Proposed mechanism for the formation of spiro[cyclopentane-1,3′-indolines] **388**.



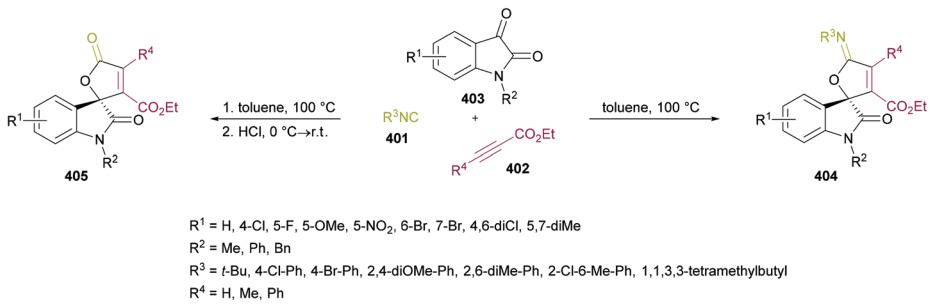
Scheme 100 Proposed mechanism for the formation of spiro[cyclopent[2]ene-1,3′-indolines] **389**.



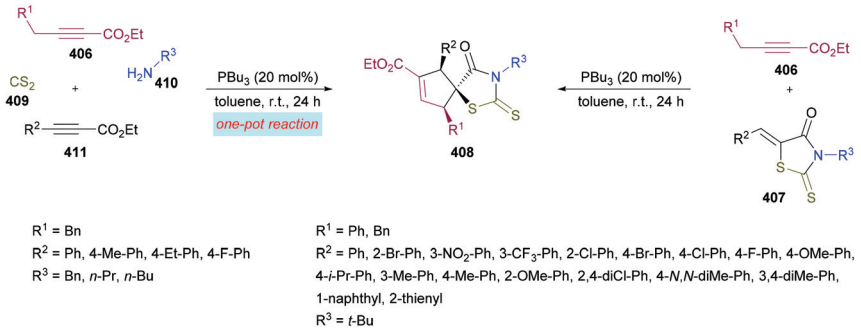
Scheme 101 Regio- and diastereoselective construction of spirocyclopenteneoxindoles through phosphine-catalyzed [3 + 2] annulation of methyleneindolinones with alkynoates.

starting materials (isocyanides **401**, alkynoates **402** and isatins **403**). This atom-economical approach operates through a Michael addition–nucleophilic addition–intramolecular cyclization sequence delivering the title products with good stereoselectivity (Scheme 102). After identifying the suitable conditions, the scope of the reaction with regard to all the three components was envisioned. The first point of variation includes the use of various aromatic isocyanides where sterically encumbered isocyanides were found to be less potent. Next, the scope of various isatins was examined carrying electron-neutral, electron-poor and electron-rich substituents on the aryl component. Moreover, a range of protecting groups on the indole nitrogen also proved to be viable and remained critical for the good conversion to the products. Furthermore, the coupling of [2 + 2 + 1] cycloaddition with a hydrolysis sequence led to the insertion of CO in a one-pot fashion obviating the need to achieve carbonylation under metal catalysis (product **405**).

2.6.7. Synthesis of spirorhodanines. Miao and coworkers[344] developed a diastereoselective phosphine-catalyzed [3 + 2] cycloaddition cascade reaction to generate a series of



Scheme 102 Three-component synthesis of highly functionalized spirocyclic oxindole-butenolides.

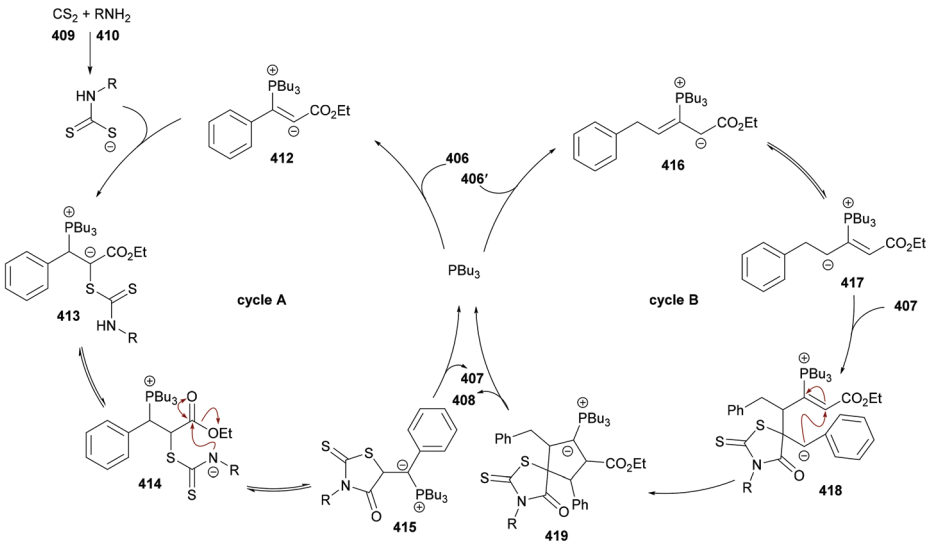


Scheme 103 Phosphine-catalyzed diastereoselective synthesis of cyclopentene spirorhodanines containing three contiguous stereocenters.

cyclopentene spirorhodanine derivatives in high yields and excellent enantioselectivities using alkynoates **406** and 5-arylidene-3-(*tert*-butyl)-2-thioxothiazolidin-4-ones **407** in the presence of PBu_3 (Scheme 103). Ethyl 5-phenylpent-2-ynoate[347] and 5-phenylidene-3-(*tert*-butyl)-2-thioxothiazolidin-4-one[348,349] were chosen as model substrates to perform the optimization studies. The reactions were carried out using various phosphine catalysts (PPh_3, PPh_2Me, PBu_3, DPPE, DPPP, DPPB) in different solvents (PhMe, DCM, THF, $CHCl_3$, MeCN, MTBE) at room temperature. However, tributylphosphine (PBu_3) produced the cycloaddition product cyclopentene 5-spirorhodanine with 95% yield and excellent diastereoselectivity (dr: >20 : 1) in toluene after 24 h. Further attention was paid to explore the scope of this spirocyclization using the optimized reaction conditions. A range of different alkynoates and 5-arylidene-3-(*tert*-butyl)-2-thioxothiazolidin-4-ones were coupled. The aryl component of rhodanine bearing electron-rich and electron-deficient substituents at various positions was tolerant to the optimized conditions. Disubstitution at the aryl ring was also compatible. In all cases, the desired products cyclopentene 5-spirorhodanines were isolated in good to high yields with excellent diastereoselectivities (>20 : 1 dr). 5-Arylidene rhodamine substrates containing naphthyl and thienyl groups also provided the corresponding products with smooth sequential cyclization in 87% and 99% yields and with excellent diastereoselectivities (>20 : 1 dr). However, when the benzyl group in the alkynoate was changed to a phenyl substituent, the reaction outcome was excellent in terms of the yield (81–93%) but with poor diastereoselectivities, signifying that the benzyl group in the alkynoates remains critical for achieving a high diastereoselectivity.

The scope was further extended using the one-pot multicomponent methodology. Cyclopentene 5-spirorhodanine compounds **408** were accessed *via* phosphine-catalyzed one-pot sequential [3 + 2]/[3 + 2] cycloaddition. Ethyl 5-phenylpent-2-ynoate, phenylethylpropiolate[350] benzylamine and carbon disulfide were used to optimize the reaction conditions. As the alkynoate bearing a homobenzyl group was critical for high diastereoselectivity, it was kept unchanged with carbon disulfide while changing the structural diversity on the other two components of the four-component methodology. Methyl, ethyl and fluoro substituents at the *para*-position were tolerated whereas benzylamine, *n*-butylamine and *n*-propylamine were employed. The corresponding products were obtained in 74–92% yields with excellent diastereoselectivities (>20 : 1 dr) except *para*-fluoro substituted spirocyclic rhodanine that was furnished with low diastereoselectivity (6 : 1 dr).

In line with the literature findings (Gabillet *et al.*, 2007; Yang *et al.*, 2013; Gabillet *et al.*, 2014),[351–353] the authors proposed the reaction mechanism for this spirocyclization methodology as shown in Scheme 104. Initially, a nucleophilic attack of the phosphine on phenylethylpropiolate produced the phosphonium salt **412** (zwitterionic intermediate) followed by the addition of an amine and carbon disulfide adduct to generate intermediate **413**. Proton transfer followed by intramolecular cyclization delivered intermediate **415**. Subsequent β-elimination of the catalyst furnished the phenylidene rhodanine **407** (cycle A). On the other hand, the nucleophilic attack



Scheme 104 Proposed mechanism for the formation of cyclopentene spirorhodanines **408**.

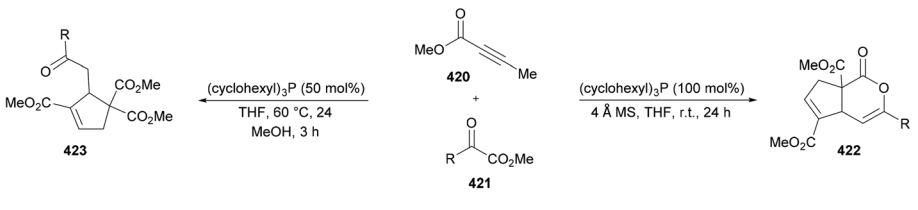
of the regenerated catalyst PBu_3 on ethyl alkynoate gave monozwitterion **416**, which is in equilibrium with intermediate **417**. The addition of phenylidene rhodanine **407** to **417** generated intermediate **418**. Intramolecular cyclization led to phosphorane **419** which on elimination of the catalyst furnished the desired product **408** (cycle B).

2.7. Divergent reactivity of alkynoates

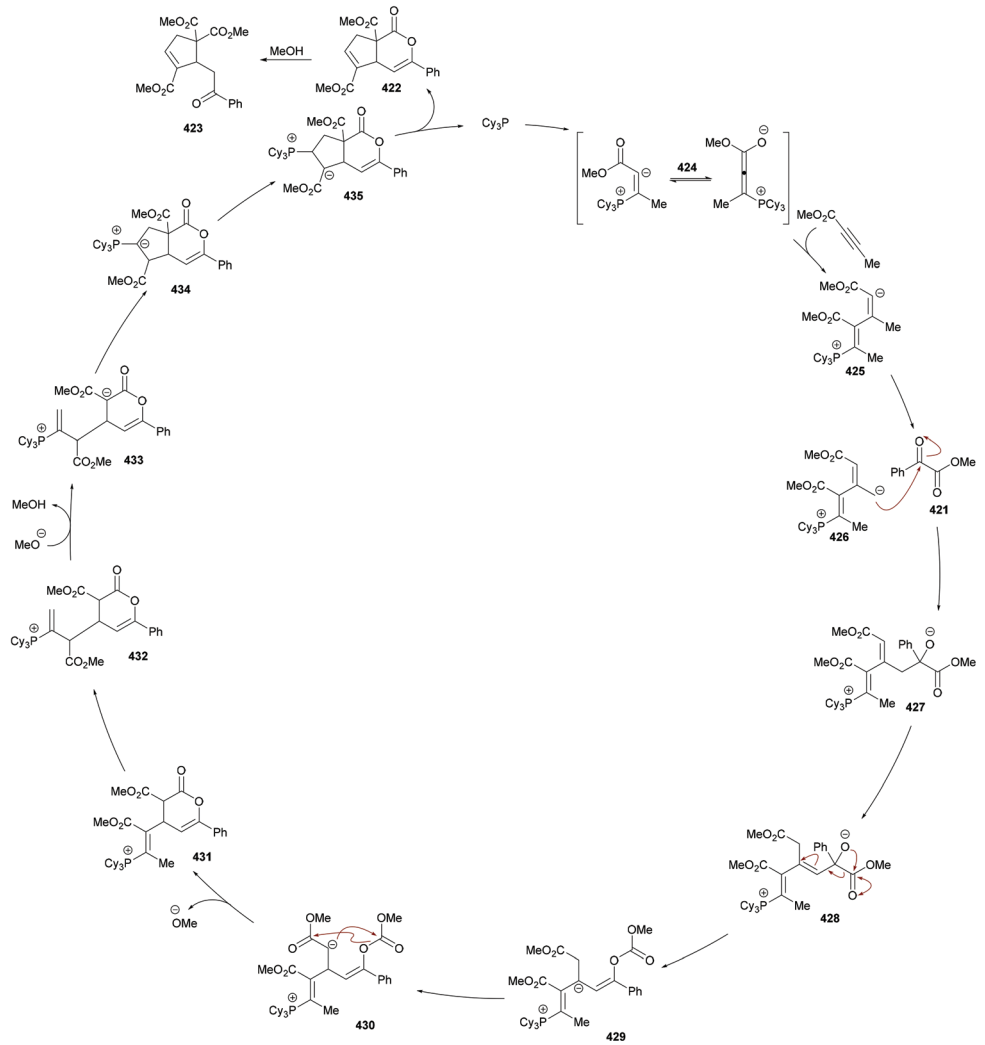
Mbofana and Miller[354] reported a phosphine-catalyzed annulation methodology involving 2-alkynoates **420** and α-keto esters **421** to generate substituted cyclopentene products **422**, **423** (Scheme 105). Initially, a range of phosphines were tested to obtain the desired products in optimal yields. Tricyclohexylphosphine was identified as the lead catalyst. The addition of 4 Å molecular sieves to the reaction mixture (to remove the methanol byproduct) led to the formation of the cyclopentene fused product in 76% yield whereas the addition of methanol after 24 h followed by stirring for 3 h generated cyclopentene exclusively in 74% yield. With two different sets of conditions, the scope of monocyclic and bicyclic products was investigated. A range of α-keto esters were employed under the optimized reaction conditions. Electron-donating (methyl, methoxy) and electron-withdrawing (chloro) groups were tolerated efficiently; however, methoxy-substituted products were isolated in low yields. Substituents at the *para*- and *meta*-positions were also cyclized successfully; however, the monosubstituted substrate remained unreactive. With a naphthyl ester, both products were isolated in 68% and 65% yields, respectively.

Based on the literature reports and initial mechanistic experiments, the authors proposed a catalytic cycle for this divergent methodology (Scheme 106). Phosphine coordination to methyl 2-butynoate generated zwitterionic intermediate **424** which on addition of another molecule of methyl 2-butynoate delivered intermediate **425**.[355] Proton transfer followed by an addition reaction with a keto ester led to intermediate **427**. Subsequent isomerization and rearrangement produced intermediate **429**.[356–358] Another proton transfer alongside concerted ester group migration and cyclization furnished intermediate **431**. Isomerization to **432** followed by deprotonation gave intermediate **433** which underwent cyclization to form intermediate **434**. Proton transfer followed by catalyst elimination furnished the desired cyclopentene fused dihydropyrone heterocycle **422**. Methanolysis of **422** generated the monocyclic five-membered product **423**.

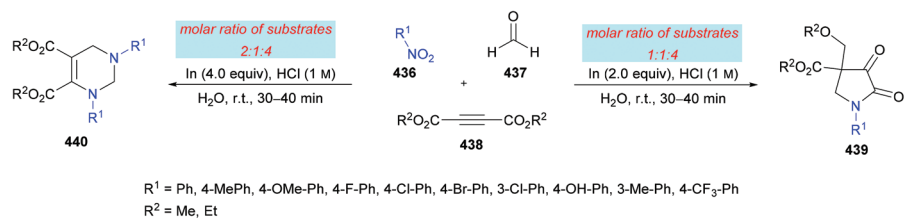
Das and co-workers[359] introduced a distinct multi-component approach utilizing the reactivity of nitroarenes **436**, formaldehyde **437**, and dialkyl acetylenedicarboxylates **438** under



Scheme 105 Phosphine-catalyzed synthesis of cyclopentene derivatives from 2-butynoate and α-keto esters.



Scheme 106 Proposed mechanism for the formation of cyclopentene fused dihydropyrone **422** and monocyclic five-membered product **423**.



Scheme 107 Multi-component synthesis of polysubstituted pyrrolidines and tetrahydropyrimidines in water.

indium catalysis (Scheme 107). The reactions were performed in dilute aqueous HCl at room temperature. Dioxopyrrolidines **439** and tetrahydropyrimidines **440** were formed in good to high yields using 1 : 1 : 4 and 2 : 1 : 4 molar ratios of the substrates. Other metals including Sn, Zn, and Fe were also tested in aqueous HCl; however, indium produced the best results both in terms of the yield and reaction time (30–40 min). The primary point of structural variations includes the use of different nitro compounds. Various nitroarenes were employed alongside electron-deficient alkynes and formaldehyde to deliver the corresponding heterocyclic products in good to high yields. Electron-neutral, electron-rich and electron-deficient substituents were tolerated. Mechanistically, the nitroarenes were reduced to aryl amines[360] in the presence of

an In/aqueous HCl system and were further reacted with electron-deficient alkynes and formaldehyde, respectively.

2.8. Application in the synthesis of natural products and pharmaceuticals

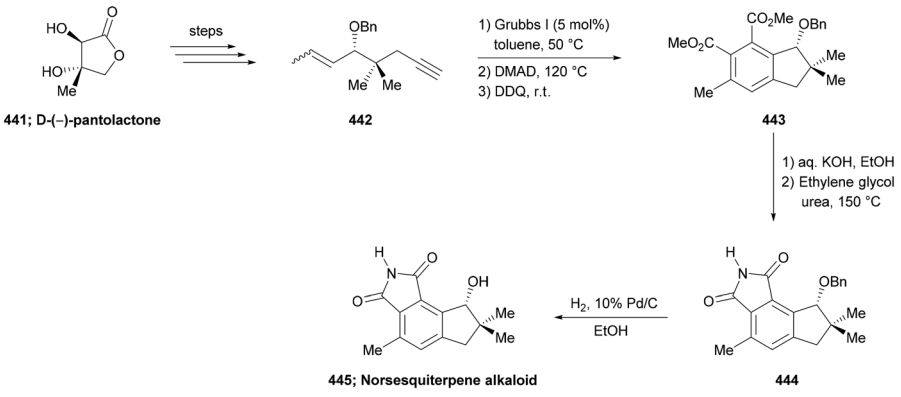
This section highlights the use of alkynoates in the synthesis of natural products and pharmaceuticals. Various methodologies have been employed to construct several key intermediates in the synthesis of bioactive complex molecules.

2.8.1. Total synthesis of a norsesquiterpene alkaloid. Reddy and co-workers[361] reported the first total synthesis of an anticancer norsesquiterpene alkaloid (*R*)-8-hydroxy-4,7,7-trimethyl-7,8-dihydrocyclopenta[*e*]isoindole-1,3(2*H*,6*H*)-dione **445**, isolated from the solid culture of the mushroom-forming fungus *Flammulina velutipes* (Scheme 108). The synthesis of the key enyne intermediate **442** from D-(−)-pantolactone **441** followed by the ring-closing metathesis (RCM) using Grubbs' 1st generation catalyst, the Diels–Alder reaction with dimethyl acetylenedicarboxylate (DMAD) and subsequent treatment with DDQ furnished aromatized compound **443** in a moderate yield (~40%). The hydrolysis of an ester in indane **443** with aqueous KOH followed by heating with urea in ethylene glycol provided compound **444**. Finally, the deprotection of the benzyl group was performed using 10% Pd/C under a hydrogen atmosphere in ethanol delivered the norsesquiterpene alkaloid **445**.

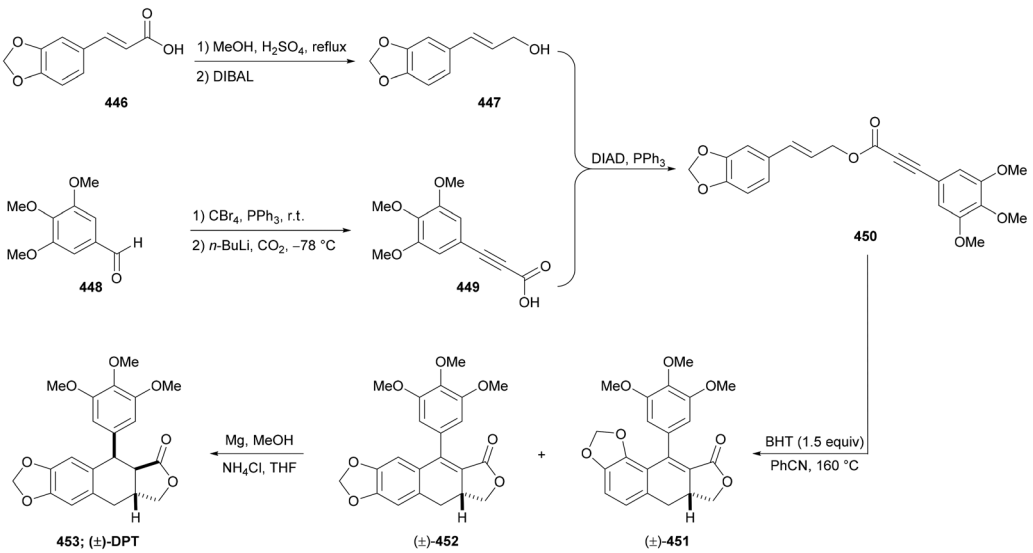
2.8.2. Synthesis of deoxypodophyllotoxin. Andrus, Ess and co-workers[362] developed a short seven-step synthesis of deoxypodophyllotoxin **453**. The ISDA strategy led to the simultaneous formation of the cyclohexyl ring and lactone functionality together with a stereocenter in a single step (Scheme 109). Alcohol **447** was prepared from commercial 3,4-methylenedioxycinnamic acid **446** using Fisher esterification and DIBAL reduction procedures whereas alkyne acid **449** was obtained by the Corey–Fuchs reaction using trimethoxybenzaldehyde **448** followed by trapping with carbon dioxide. Alcohol **447** and alkyne acid **449** were reacted under Mitsunobu coupling conditions to afford the electron-rich alkyne allyl ester intermediate **450**. The ISDA reaction using BHT (1.5 equiv.) in benzonitrile afforded two isomeric products **451** and **452** in 56% overall yield with 1 : 1.6 selectivity. Both structures were confirmed through X-ray crystallography. Finally, the reduction of **452** using Mg/MeOH conditions provided DPT with *cis*-stereochemistry.

2.8.3. Synthesis of (−)-CJ-13,982. Rizzacasa and co-workers[363] reported an efficient and step-economical approach to produce alkyl citrate natural products from a cyclobutene diester (Scheme 110). The enantiospecific synthesis of (−)-CJ-13,982 **459** was started using optically pure lactone **454** [364] (prepared from (*S*)-(+)-γ-hydroxymethyl-γ-butyrolactone) which was transformed into the silyl ketene acetal, and cycloaddition with dimethyl acetylenedicarboxylate (DMAD) afforded the major adduct cyclobutene **455**. Silyl ether and acetal hydrolysis was achieved using HCl in MeOH followed by oxy-Michael addition, and cyclobutene methanolysis afforded the triester as a single stereoisomer in a good yield. Tosyl protection followed by displacement with NaI and zinc-mediated reductive elimination afforded the key alkyl citrate fragment **457**. Cross metathesis (CM) with undecene followed by hydrogenation produced the (−)-CJ-13,982 trimethyl ester **458**. Subsequent hydrolysis using 5.0 equivalents of 1 M aqueous NaOH in dioxane afforded the desired (−)-CJ-13,982.

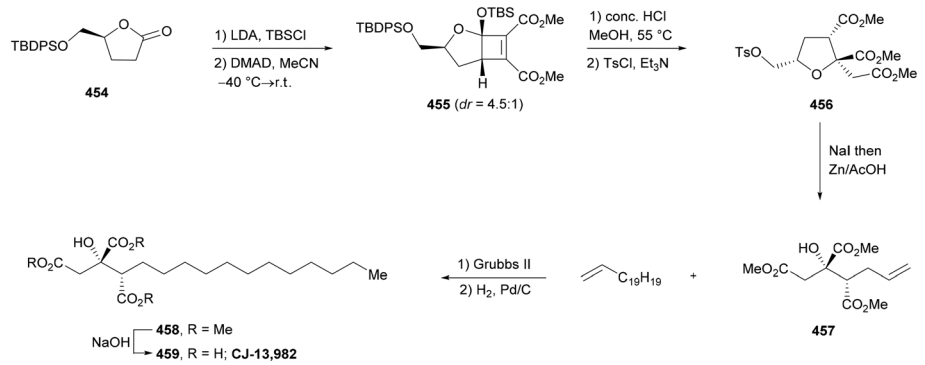
2.8.4. Synthesis of (*R*)-puraquinonic acid. Elmehriki and Gleason[365] developed a stereoselective method for the construction of cyclic α-quaternary stereocenters from biselectrophilic substrates and chiral bicyclic sulfonyl lactam (Scheme 111). Using this method, the total synthesis of (*R*)-puraquinonic acid **470** was achieved in an overall yield of 14%. Vinylation of 3-pentyn-1-ol **460** using catalytic mercury(II) acetate was performed to deliver ethyl vinyl ether **461**. A one-pot sequence involving ene-yne metathesis under Grubbs II conditions forming diene, followed by Diels–Alder cycloaddition with dimethyl acetylenedicarboxylate (DMAD) and oxidation with DDQ afforded arene **462** in 42% yield (3 steps). Reduction of the ester groups using $LiAlH_4$ followed by bromination with phosphorus tribromide produced dibromide **463** in 95% yield (2 steps). Spiroalkylation was performed using **465** to form **466** which was transformed to amide **467** after reduction/alkylation with greater than 95 : 5 dr. The hydrolysis of **467** using sulfuric acid in 1,4-dioxane provided carboxylic



Scheme 108 Total synthesis of a norsesquiterpene alkaloid.



Scheme 109 Synthesis of deoxypodophyllotoxin by the ISDA strategy.



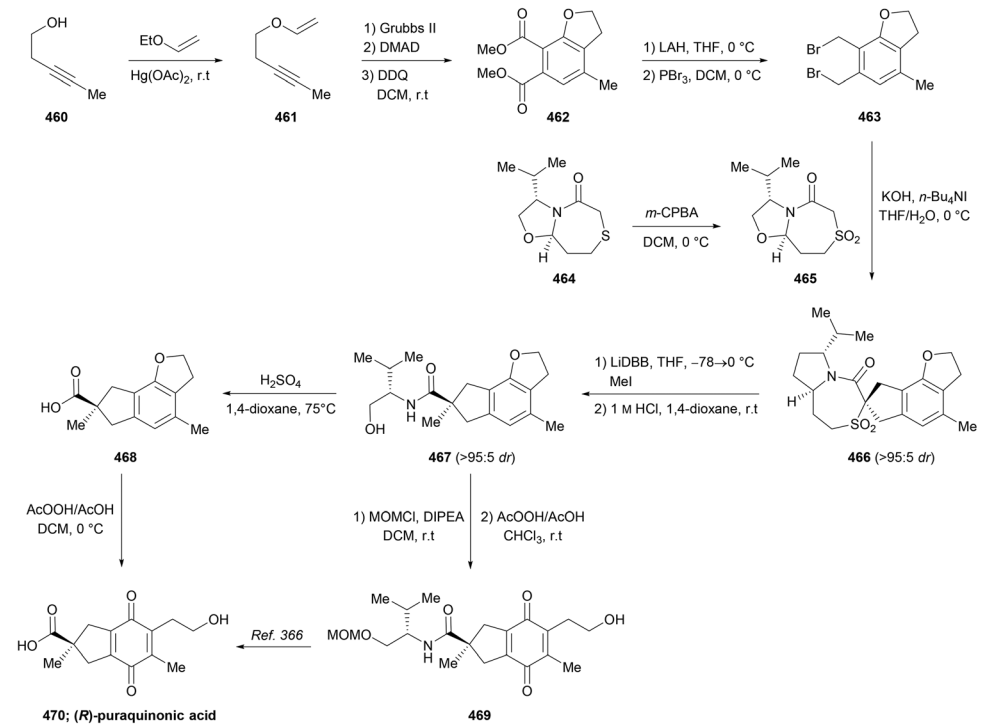
Scheme 110 Synthesis of (−)-CJ-13,982.

acid **468** in 90% yield which was oxidized to puraquinonic acid **470** in 84% yield using a combination of peracetic acid and acetic acid in DCM at 0 °C. On the other hand, protection of alcohol in **467** with a MOM group followed by oxidation using peracetic acid and acetic acid in chloroform at room temperature afforded quinone **469** which was transformed to puraquinonic acid **470** using the literature conditions.[366]

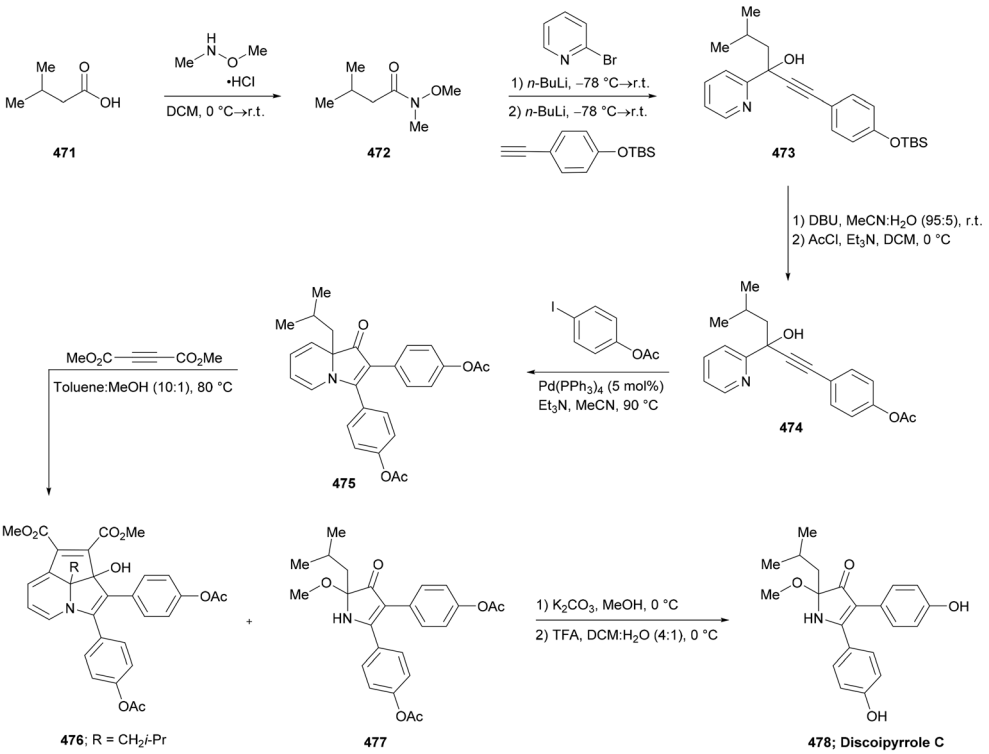
2.8.5. Synthesis of discoipyrrole C. Kurian and Manheri[367] reported the synthesis of 1*H*-pyrrol-3(2*H*)-ones from the reaction of indolizinones with dimethyl acetylenedicarboxylate which was used in the total synthesis of the anticancer discoipyrrole C **478** (Scheme 112). Isovaleric acid **471** was converted to the corresponding Weinreb amide **472** which underwent pyridine *ortho* acylation followed by alkylation to provide intermediate **473**. Deprotection of the TBS group followed by acetylation in the presence of triethylamine afforded **474** which on subsequent tandem amino-palladation, reductive elimination and 1,2-alkyl shift afforded indolizinone **475**.[368] Coupling of **475** with DMAD provided a mixture of tricyclic compound **476** and 1*H*-pyrrol-3(2*H*)-one **477** which on deacetylation delivered the discoipyrrole C **478**.

2.8.6. Synthesis of amlodipine. Kim and co-workers[369] reported the synthesis of amlodipine **486**, a calcium ion channel blocker, using the aza-Diels–Alder reaction between the Knoevenagel adduct **479**, methyl butynoate **480** and benzylamine **481** as the starting point. Debenzylation of the Diels–Alder product **482** was achieved under palladium catalysis followed by a selective allylic bromination with good selectivity (>80 : 20, mono : di) using a buffered solution of pyridinium perbromide. An azidoethanol moiety was introduced[370] which was reduced by Zn/HCl to produce the racemic amlodipine **486** (Scheme 113).

2.8.7. Synthesis of raltegravir. Raltegravir (**496**, isentress) is an important pyrimidine-based anti-HIV drug launched by Merck in 2008.[371] The structural features of this HIV-integrase inhibitor include a functionalized pyrimidone core flanked by an oxadiazole ring with a terminal *para*-fluorobenzyl moiety. The synthesis of the central pyrimidone ring was initiated by the amination of acetone cyanohydrin **487** followed by Cbz-

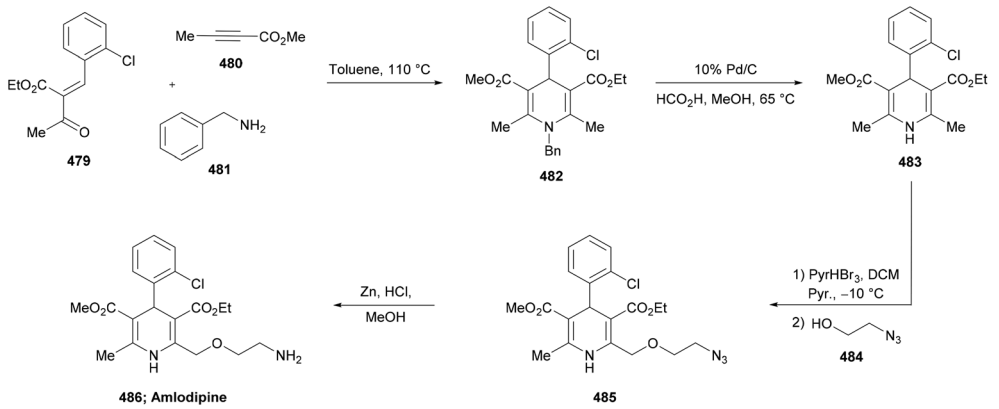


Scheme 111 Synthesis of (*R*)-puraquinonic acid.

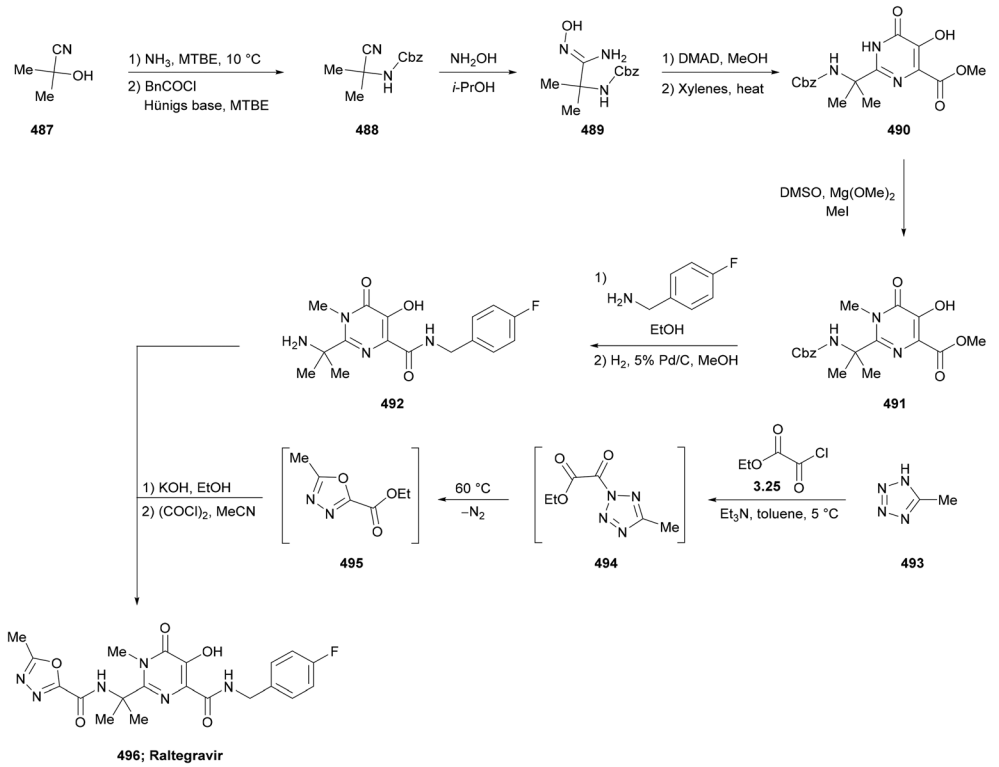


Scheme 112 Synthesis of discoipyrrole C.

protection of the resulting amine and aminolysis of the nitrile with hydroxylamine to give amidoxime **489**. The reaction of **489** with dimethyl acetylenedicarboxylate (DMAD) produced pyrimidine **490** which was *N*-methylated to form **491**. Subsequent amide formation and debenzylation produced **492**. Finally, coupling of **492** with the corresponding acid



Scheme 113 Synthesis of amlodipine.



Scheme 114 Synthesis of raltegravir.

chloride of oxadiazole derivative **495** (prepared *via* a sequence of reactions) afforded the desired raltegravir **496** (Scheme 114).

3. Conclusion and perspectives

Considering the high proportion of heterocycles/heteroaromatics in numerous natural products, synthetic drugs, commercial pharmaceuticals, agrochemicals and designed bioactive pharmacophores, the development of efficient chemical methodologies providing facile access to architecturally complex structures has remained a formidable challenge for both synthetic and medicinal chemists. In the present review, we summarize the remarkable developments in novel synthetic methods allowing the construction of numerous nitrogen-, oxygen-, sulfur-, and fused-heterocycles as well as hetero-spirocycles from alkynoates as simple, readily accessible and commercially available starting materials under transition-metal-free conditions. The discussion focuses on the investigation of the chemical reactivity of the triple bond directly attached to an electron-withdrawing ester group. The unique and inherent properties such as the electronic bias on the carbon–carbon

triple bond posed by electron-withdrawing groups allow a range of chemical reactions (Wittig, annulations, cycloadditions) to occur, exploiting the reactivity of the zwitterions derived from activated acetylenediesters particularly with nucleophilic trivalent phosphines. In addition, the reactions of acetylenic esters in the presence of phosphines with various carbon-, nitrogen-, or sulfur-based nucleophiles were attempted to deliver heterocyclic scaffolds. Organocatalyzed, photocatalyzed, radical, and Lewis and Brønsted-acid-catalyzed reactions of alkynoates were also investigated. Moreover, the alkynoates were also employed in multi-component reactions involving the unusual reactivity of the isocyanide functionality providing ample opportunities for the generation of complex and diverse drug-like small heterocyclic compounds. The investigation of the optimized reaction conditions, viability of the substrates and coupling partners, functional group tolerance and limitations and mechanistic studies as well as post-synthetic functionalization of the heterocyclic products have been performed. Various reaction sequences such as Michael addition/azaheterocyclization, hydroamination/nucleophilic addition/amidation, hydroamination/amidation/intramolecular cyclization/imineenamine tautomerization, hydroamination/Knoevenagel condensation/Michael-type addition/intramolecular cyclization, hydroamination/Mannich-type reaction/amine-aldehyde dehydration–cyclization, nucleophilic addition/intramolecular Wittig reaction, radical addition/cyclization, radical tandem phosphorylation/cyclization, nucleophilic addition/5-*endo-dig* cyclization, Michael addition/intramolecular nucleophilic addition/4π ring opening/intramolecular Michael addition/elimination, intermolecular hydroamination/intramolecular transesterification, umpolung addition/intramolecular cyclization, hydroamination/Prins reaction/cyclization/dehydration, Michael addition/intramolecular Morita–Baylis–Hillman reaction and one-pot sequential [3 + 2]/[3 + 2] cycloaddition reactions were involved to deliver a range of heterocyclic products.

Despite the broad utility of alkynoates leading to various heterocycles over the past decade, there remain several challenges and unexplored opportunities in the demand to develop more general, efficient, sustainable and practical synthetic methods. We present a selection of recommendations for future work. (1) The hindered substrate scope could further be expanded under mild and green reaction conditions. (2) The effect of substitution on the alkyne component could potentially be envisioned from experimental and computational methods. (3) The installation of possibly transformable groups into impactful drugs and pharmaceuticals should be focused. (4) In light of the recent reports on electrochemical oxidative annulation of alkynoates, the field still retains considerable room for synthetic extensions and substantial improvements. (5) It is evident from the literature findings that the development of asymmetric methods to construct enantioenriched heterocycles using alkynoates needs ample attention to further explore the wider chemical space. (6) The strategic combination of efficient chemical synthesis with enzymatic methods to produce small heterocyclic molecules stands as the future goal. Collectively, there is no doubt that the enriched alkynoate chemistry will continue to grow and offer ample opportunities to both synthetic and medicinal chemists in the generation of diverse heterocyclic frameworks of pharmaceutical interest.

Abbreviations

Ac	Acetyl
AQN	Anthraquinone
BHT	2,6-Di-*tert*-butyl-4-methylphenol
Boc	*tert*-Butoxycarbonyl
BINOL	1,1′-Bi-2-naphthol
BI-OH	1-Hydroxy-1,2-benziodoxol-3(1*H*)-one
BI-OAc	1,2-Benziodoxol-3(1*H*)-one acetate
Bmim	1-Butyl-3-methylimidazolidin
Bn	Benzyl
BPO	Benzoyl peroxide
bpy	2,2′-Bipyridine
CAN	Cerium ammonium nitrate
CM	Cross metathesis
CPME	Cyclopentyl methyl ether
DABCO	1,4-Diazabicyclo[2.2.2]octane
DABSO	1,4-Diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCB	Dichlorobenzene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl acetylenedicarboxylate
DFT	Density functional theory
DIAD	Diisopropyl azodicarboxylate
DIBAL	Diisobutylaluminium hydride
DIPEA	*N*,*N*-Diisopropylethylamine
DLP	Dilauroyl peroxide
DMF	*N*,*N*-Dimethylformamide
DMAD	Dimethyl acetylenedicarboxylate
DMAP	Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
DPP	Diphenylphosphinyl
Dppb	1,4-Bis(diphenylphosphino)butane
Dppe	1,2-Bis(diphenylphosphino)ethane
Dppp	Diphenylpropylenediphosphine
DPT	Deoxypodophyllotoxin
DTBP	Di-*tert*-butylperoxide
EDC	*N*-Ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide
EDG	Electron-donating group
Equiv	Equivalent
EWG	Electron-withdrawing group
EY	Eosin Y
Hex	Hexyl
HFIP	Hexafluoroisopropanol
HIR	Hypervalent iodine reagent
HMPA	Hexamethylphosphoramide

HMPT	Hexamethylphosphorous triamide
ICl	Iodine monochloride
IL	Ionic liquid
IPA	Isopropyl alcohol
ISDA	Intramolecular styryl Diels–Alder
KHMDS	Potassium bis(trimethylsilyl)amide
LAH	Lithium aluminum hydride
LED	Light-emitting diode
LiDBB	Lithium 4,4-di-*tert*-butylbiphenylide
MCR	Multicomponent reaction
*m*CPBA	*meta*-Chloroperbenzoic acid
MOMCl	Chloromethyl methyl ether
MTBE	Methyl *tert*-butyl ether
MW	Microwave
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide
Pent	Pentyl
Ph	Phenyl
PIDA	Phenyliodine(III) diacetate
PMP	*p*-Methoxyphenyl
PPTS	Pyridinium *p*-toluenesulfonate
RCM	Ring-closing metathesis
R.T.	Room temperature
SET	Single electron transfer
TBAB	Tetrabutylammonium bromide
TBAC	Tetrabutylammonium chloride
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBHP	*tert*-Butyl hydroperoxide
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
TBPB	*tert*-Butyl perbenzoate
TBSCl	*tert*-Butyldimethylsilyl chloride
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TMBSA	Tri-methylammonium-butane sulfonate
UV	Ultraviolet

Conflicts of interest

There are no conflicts to declare.

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