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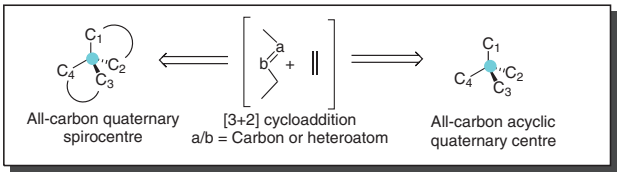
Recent Progress on the [3+2] Cycloaddition Route for the Synthesis of All-Carbon Quaternary Stereocentres

Ani Deepthi*
Maneesh Mohan
Meenakshy C. Balachandran

Department of Chemistry, University of Kerala, Kariavattom campus, Thiruvananthapuram 695581, Kerala state, India
anideepthi@gmail.com



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Crowd-Reviewed

Abstract Construction of all-carbon quaternary centres is an important task in organic synthesis. In spite of the challenges associated with Csp^3–Csp^3 bond construction in a sterically constrained environment, significant advances have been made in this area. Among the latter, both catalytic and noncatalytic [3+2] cycloaddition approaches have gained wide attention recently. This short review summarizes the [3+2] cycloaddition reactions reported during the period 2016–2022 for the synthesis of molecules possessing one or more all-carbon quaternary stereocentres.

Key words all-carbon, quaternary, stereocentres, [3+2] cycloaddition, cyclization

1 Introduction

All-carbon quaternary centres refer to stereogenic carbon centres attached to four different neighbouring carbons.[1,2] Such carbon centres have a special importance owing to their ubiquitous presence in natural products and to their specificity in biological systems due to their structural diversity and enhanced conformational constraints, which makes them suitable targets for protein binding. For example, spirocyclic compounds have found increased utility in drug discovery because of their three-dimensional structural uniqueness.[3] Figure 1 shows some examples of biologically active molecules containing all-carbon quaternary spiro-centres. Fredericamycin A,[4a] first isolated from *Streptomyces griseus* ATCC49344, is known for its potent activity against P388 mouse leukaemia, CD8F mammary tumours and B16 melanoma *in vivo*; whereas coleophomone D,[4b] isolated from *Stachybotrys parvispora Hughes*, is known for its antibacterial and antihypertensive properties. Elatol displays antibiofouling, antibacterial and antifungal properties and is also cytotoxic against HeLa and Hep-2-human carcinoma cell lines.[5a] Colletoic acid is an inhibitor of human 11β-hydroxy steroid dehydrogenase type I (11β-HSD1 inhibition is a new therapeutic approach for type I diabetes mellitus),[5b] and horsfiline, an oxindole alkaloid, is a therapeutic agent.[5c]

Given the importance of generating quaternary stereogenic carbon centres, especially as spirocyclic molecules, numerous efforts have been made for developing efficient methods for their stereocontrolled synthesis.[6–11] Asymmetric [3+2] cycloadditions have created a niche in organic chemistry.[12] Recently Wang and Liu catalogued all-carbon [3+2] cycloaddition methods for natural product synthesis in which they invoke the importance of the strategy to create complex scaffolds of biological interest.[13] In this review, we present selected [3+2] cycloaddition reactions that lead to formation of one or more all-carbon quaternary stereocentres reported during the period 2016–2022. These have been classified into different categories (i) based on the substrate used to generate the 1,3-dipolar species, (ii) those involving allyl-palladium intermediates, (iii) those involving phosphine-allenoate zwitterionic intermediates, and (iv) those involving radical pathways, nitrones, nitrile oxides and nitronate salts, although certain examples can be included in more than one group in this classification.

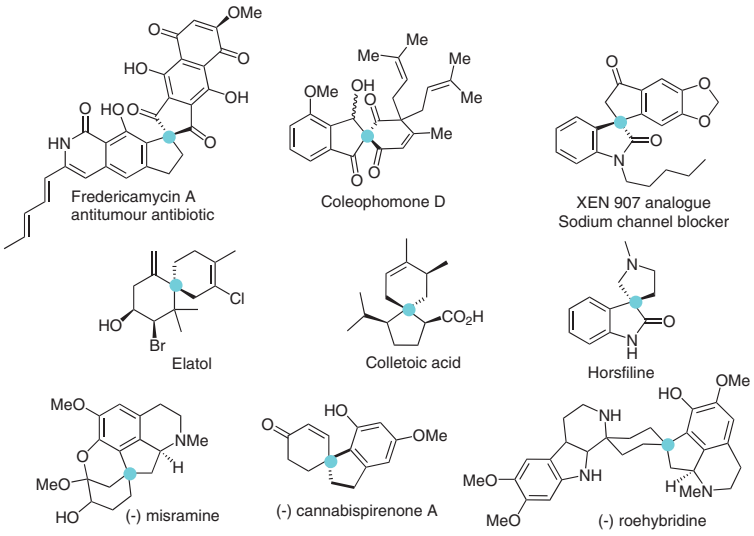


Figure 1 Some biologically active molecules containing all-carbon quaternary stereocentres

Biographical Sketches

Ani Deepthi was born in Kerala, India. After securing an MSc degree in Applied Chemistry from Cochin University of Science and Technology, she undertook her PhD degree working under the guidance of Dr Vijay Nair in CSIR-NIIST, Thiruvananthapuram and carried out post-doctoral studies at the National University of Singapore with Prof. Suresh Valiyaveettil. Currently, she is an Assistant Professor at the Department of Chemistry, University of Kerala. Her research interests include synthesis of small molecules possessing bioactive or photoactive properties, chemosensors, and isolation and semisynthetic modification of natural products. She has 32 publications in-peer reviewed journals and two students have secured their PhD under her guidance.

Maneesh Mohan was born in Alappuzha, Kerala, India. He received his BSc. degree in 2011 from Sree Narayana College, Cherthala and MSc. degree in 2016 from Sree Narayana College, Chengannur. He then worked as a Government Guest Lecturer at Sree Narayana College, Kollam and later worked as a Project Assistant II at CSIR-NIIST, Thiruvananthapuram, Kerala. He secured his MPhil. degree from the Department of Chemistry, University of Kerala and is currently pursuing his Ph.D under the guidance of Dr. Ani Deepthi. His research interests include synthesis and *in vitro* anticancer evaluation of beta carboline-based spiroheterocycles.

Meenakshy Chandrika Balachandran was born in Kuzhithurai, Tamil Nadu, India. She received her B.Sc. degree in 2018 from University College, Palayam, Thiruvananthapuram and M.Sc. Degree in 2020 from H.H. The Maharaja's College for Women, Vazhuthacaud, Thiruvananthapuram. She qualified in the joint CSIR-UGC NET in 2020 and is currently carrying out her doctoral research under the guidance of Dr. Ani Deepthi at the Department of Chemistry, University of Kerala, Kariavattom. Her research focuses on the synthesis of dispiro-heterocyclic compounds and their anti-cancer properties.

2 Classification based on Substrate used to Generate the 1,3-Dipole

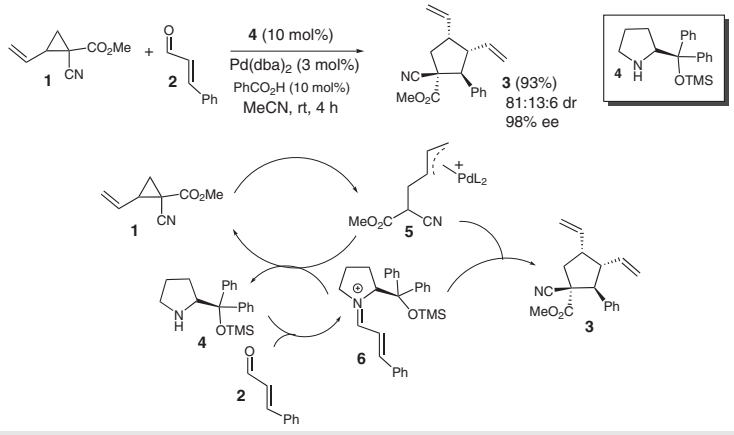
2.1 Suitably Substituted Cyclopropanes

Previous studies have shown that vinyl cyclopropanes (VCPs), when catalytically activated by palladium or by other transition metals, generate a 1,3-dipolar intermediate that can, in turn, form five-membered rings with various dipolarophiles via [3+2] cycloaddition reactions.[14] However, due to the challenges associated with the short lifetime of the intermediate in the presence of phosphine ligands, asymmetric versions of these reactions have great significance.[15] In this context, recently developed synergistic catalysis proved to be advantageous, wherein the vinyl cyclopropane is activated by a palladium catalyst while the dipolarophile is activated by a second catalyst. For instance, Jørgensen and co-workers in 2016 developed a protocol in which the activated vinyl cyclopropane reacts with the dipolarophile that is, in turn, activated by an organocatalyst. The methodology resulted in the synthesis of densely substituted cyclopentanes with up to four contiguous stereocentres in high yields and with excellent stereoselectivities. For example, vinyl cyclopropane **1** reacted with cinnamaldehyde **2** in the presence of benzoic acid in acetonitrile to yield the product **3** (Scheme 1). Here, the vinyl cyclopropane is activated by palladium while the α,β-unsaturated aldehyde is activated as the iminium ion formed by reaction with the organocatalyst **4**. More specifically, oxidative addition of Pd(0) catalyst facilitates ring opening of the vinyl cyclopropane, yielding a π-allyl palladium intermediate **5** and, in parallel, condensation of catalyst **4** and cinnamaldehyde **2** leads to the formation of the iminium ion **6**. Intermediates **5** and **6** combine to generate the [3+2] cycloadduct **3**.[16]

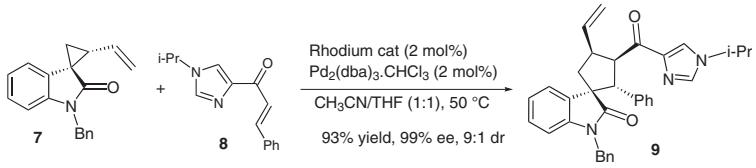
Concurrently, there were also successful efforts by Vitale and co-workers to employ iminium/enamine organocatalysis also with Pd(0) activation of vinyl cyclopropanes for the enantioselective synthesis of polysubstituted cyclopentanes by the formal [3+2] cycloaddition of vinyl cyclopropanes with enals,[17] even though generation of molecules containing all-carbon quaternary centres was not reported.

In 2020, a synergistic bimetallic catalytic system comprising palladium and rhodium catalysts was used by Du and co-workers for the enantioselective synthesis of multisubstituted spirocyclopentane oxindoles containing an all-carbon quaternary stereocentre. In this reaction, α,β-unsaturated 2-acyl imidazole **8** underwent [3+2] cycloaddition with spirovinyl cyclopropanyl-2-oxindole **7** in the presence of palladium and chiral rhodium catalysts to yield the 3-spirocyclopentane-2-oxindole derivative **9** in high yield (Scheme 2). Here, the zwitterionic π-allyl palladium intermediate formed from **7** attacks the *Re*-face of the bidentate *N*,*O*-coordinated intermediate generated by the coordination of rhodium to compound **8**, facilitating the formation of the product **9** as the major isomer (Scheme 2).[18]

Enantioselective ring-openings of other suitably substituted cyclopropanes have also emerged as a powerful strategy for five-membered ring construction.[19] An intramolecular [3+2] annulation reaction of cyclopropanes was report-

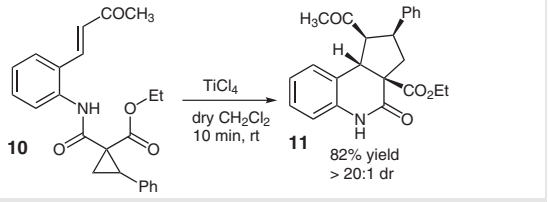


Scheme 1 Combined palladium and organocatalysis to synthesise multisubstituted cyclopentanes containing an all-carbon stereocentres



Scheme 2 Bimetallic catalysis to generate an all-carbon spirocentre

ed by Chen, Yang and co-workers in 2016 (Scheme 3).[20] In this reaction, an amide linker was used for the annulation and $TiCl_4$ was used as the Lewis acid. The coordination of the two carbonyl groups of substrate **10** to titanium(IV) probably facilitates the ring-opening of the cyclopropane, generating a dicarbonyl anion that, in turn, attacks the enone moiety to furnish the six-membered lactam ring and finally leads to dihydroquinolinone **11**.

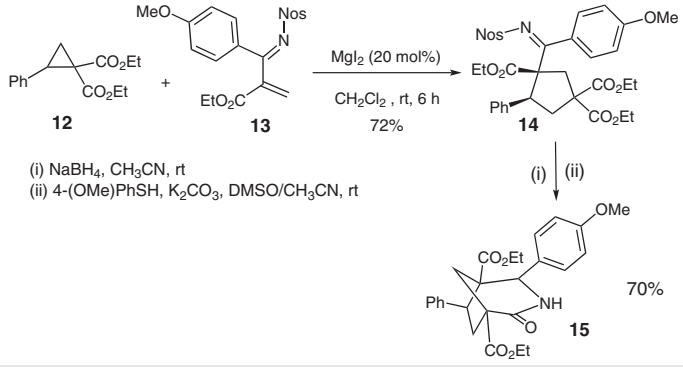


Scheme 3 Synthesis of dihydroquinolinones

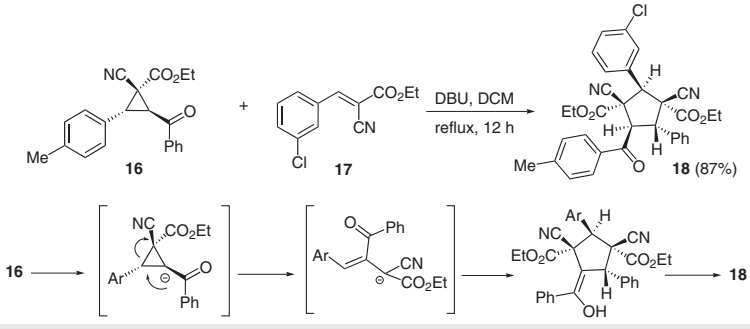
Donor–acceptor cyclopropane **12** was used for the synthesis of pharmaceutically relevant azabicyclo[3.2.1]octane **15**, bearing two all-carbon quaternary stereogenic centres at the bridgehead positions, by reduction of imine **14** and subsequent deprotection and intramolecular amidation. The imine was, in turn, synthesized by MgI_2 catalysed [3+2] cycloaddition of donor–acceptor cyclopropane **12** with azadiene **13** in dichloromethane (Scheme 4).[21]

Wang and co-workers in 2019 used the [3+2] annulation strategy to construct an all-carbon stereocentre by conducting the 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) mediated reaction of cyanocyclopropane carbonate **16** and (*E*)-3-aryl-2-cyano acrylate **17**. The reaction takes place by the initial deprotonation of cyclopropane **16**, which ring opens to form an ylide intermediate. The [3+2] annulation of the ylide to acrylate **17** leads to the cycloadduct **18** after a tautomerization step (Scheme 5).[22]

Aminocyclopropanes have recently emerged as suitable reaction partners that can undergo annulation with alkenes and cyclopropenes under photocatalysis. In 2019, Waser and co-workers reported the [3+2] annulation reaction of cyclopropenes with cyclopropyl aniline **20** using photocatalysis. The catalyst used was 2,4,5,6-tetrakis(diphenylamino)-isophthalonitrile (4DPAIPN). The transformation proved to be highly efficient, and diastereoselectivity was further improved by choosing bulky cyclopropyl aniline and difluorocyclopropenes (Scheme 6).[23] Subsequently, in 2020, a highly diastereoselective and enantioselective [3+2] cycloaddition of cyclopropyl amine with α-alkyl styrenes was reported by Ooi and co-workers using photocatalysis to yield cyclopentanes containing all-carbon quaternary stereocentres. Here, iridium-polypyridyl complexes were used as photocatalysts and the reaction is initiated by capture of the anionic component of the photocatalyst by the cyclopropyl urea **22**,

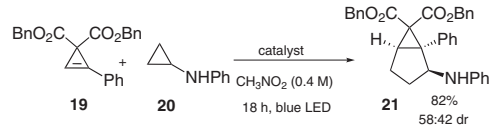


Scheme 4 Synthesis of quaternary bridgehead stereocentres



Scheme 5 DBU-mediated [3+2] cycloaddition to construct cyclopentanes

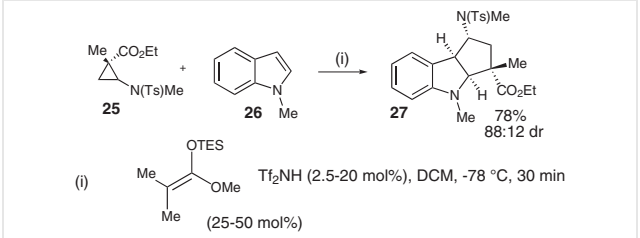
generating a chiral supramolecular ion pair. Under irradiation, single electron transfer (SET) from the substrate to the excited-state cationic iridium generates a radical cation that undergoes stereoselective bond formation with the α-alkyl styrene **23** within the restrictions of the asymmetric environment created by the chiral anion.



Scheme 6 [3+2] Annulation of cyclopropene with aminocyclopropane

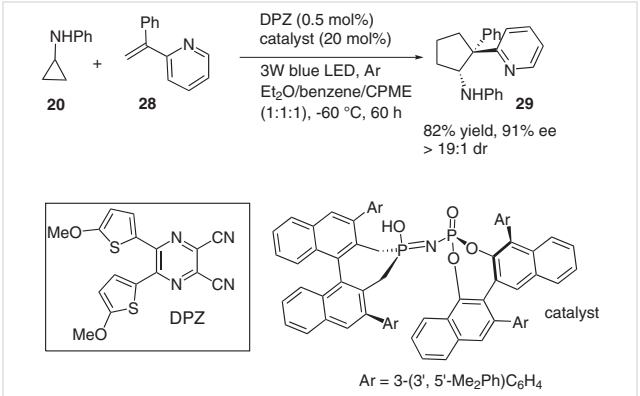
A representative reaction for synthesis of the cyclopentane **24** is depicted in Scheme 7.[24] The Waser group also reported the use of the amino cyclopropane monoester **25** for [3+2] annulation with suitably substituted indoles using silyl bistriflimide as catalyst (Scheme 8). The method was successfully applied for the construction of a non-symmetrical all-carbon quaternary centre at the acceptor position of the cyclopropane in good yield and diastereoselectivity, as exemplified in Scheme 8.[25]

Construction of an all-carbon quaternary stereocentre at the α-position of aza-arenes was reported by Jiang and co-workers by synergistic photoredox and Brönsted acid catalysis. Scheme 9 shows a representative reaction of cyclopropyl aniline **20** with 2-(1-phenylvinyl)pyridine **28** that leads to **29**. It was found that there were remarkable differences in enantioselectivity when using electron-withdrawing or electron-donating substituents on the aromatic ring

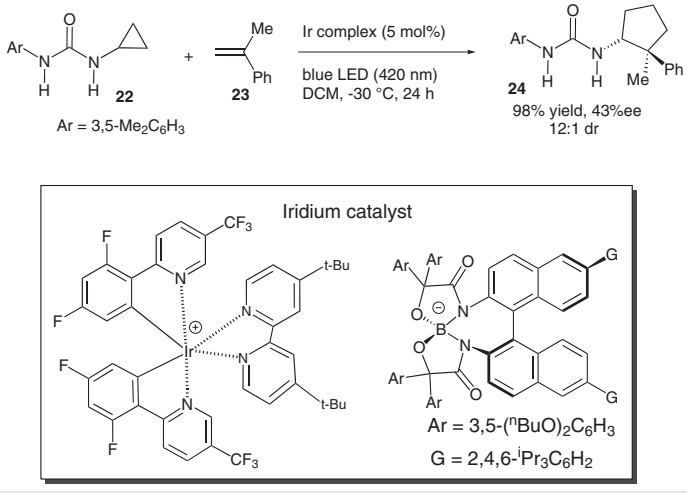


Scheme 8 [3+2] Annulation of indole with aminocyclopropane

of the 2-(1-arylvinyl)pyridine, which led to the proposition of a ternary transition state with the chiral Brönsted acid acting as the bifunctional catalyst. The chiral Brönsted acid catalyst used was an iminodiphosphoric acid that co-catalyses the reaction along with the photocatalyst, dicyanopyrazine (DPZ).[26]



Scheme 9 Photocatalysed enantioselective pyridine tethered cyclopentane synthesis



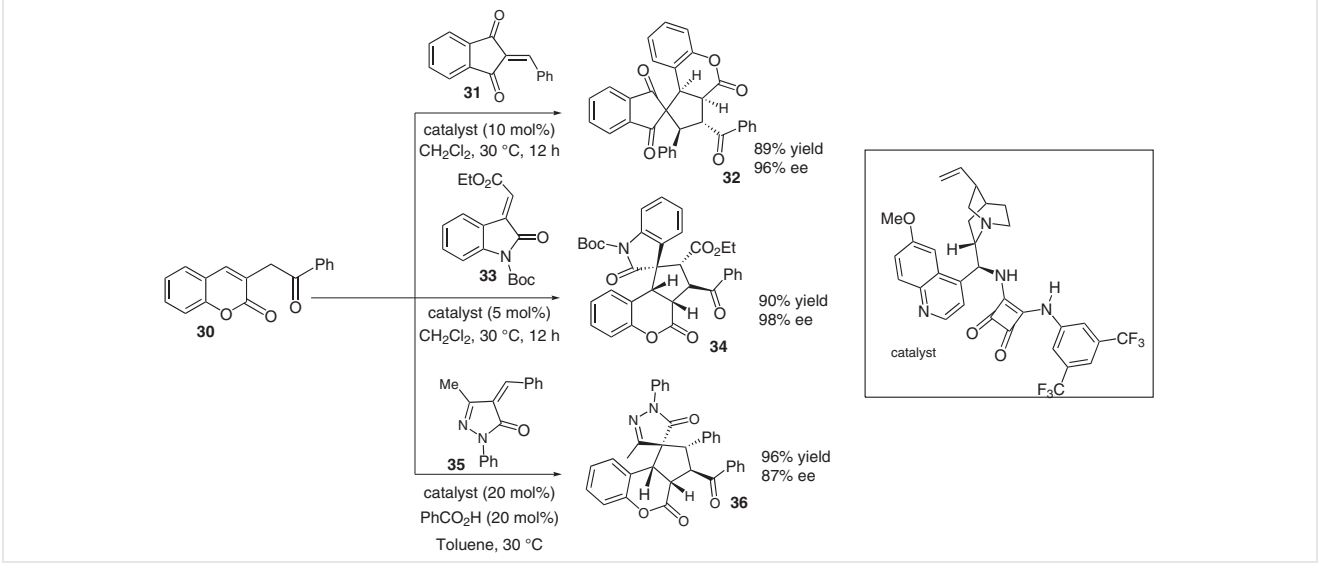
Scheme 7 Photocatalysed enantioselective urea-tethered cyclopentane synthesis

2.2 3-Homoacyl Coumarins

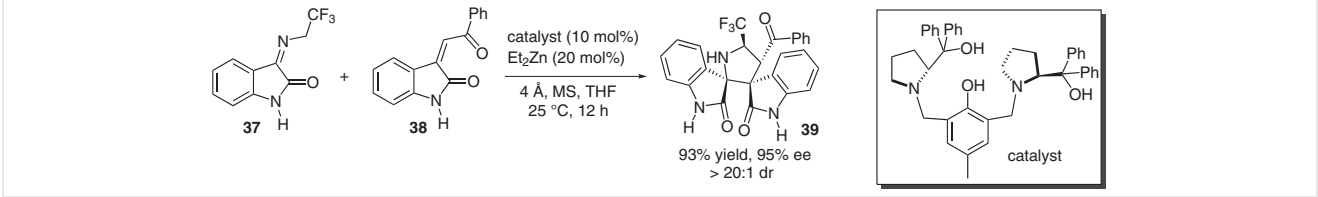
Lin and co-workers have utilized the all-carbon 1,3-dipole precursor 3-homoacyl coumarin **30**, in stereoselective [3+2] cycloaddition reactions in the presence of a squaramide catalyst. Initially indandione alkylidene **31** was used as the dipolarophilic partner, which led to the synthesis of coumarin/indandione fused spirocyclopentanes **32**, bearing four contiguous stereocentres.[27a] Later these workers used alkylidene oxindoles as the dipolarophilic partner to yield a cycloadduct containing five contiguous stereocentres of which one is an all-carbon quaternary spirocentre.[27b] The reaction takes place via initial activation of the homoacyl coumarin **30** by deprotonation to provide a conjugate acid-base pair with H-bonding interactions. The *Re*-face of activated coumarin then adds to the *Re*-face of the alkylidene oxindole **33** to generate a Michael adduct that ultimately leads to product **34** (Scheme 10). Lin's group has also employed the strategy for the enantioselective synthesis of spiropyrazolone fused cyclopenta[*c*]chromen-4-ones.[27c] The reaction occurs by [3+2] cycloaddition of 3-homoacyl coumarin **30** with α,β-unsaturated pyrazolone **35** in the presence of a cinchona alkaloid-derived hydrogen-bonding catalyst and benzoic acid. Excellent yields of spiropyrazolones of the type **36** were obtained in a highly enantioselective manner. All these reactions are summarized in Scheme 10.

2.3 Isatin-Based (Trifluoromethyl)imines

Isatin-based (trifluoromethyl)imines were reported to undergo [3+2] annulations with alkenes efficiently in the presence of metal catalysts in conjunction with organocatalysts. A Brönsted base and Lewis acid co-operatively catalysed asymmetric 1,3-dipolar cycloaddition reaction was reported to yield a series of trifluoromethyl substituted 2,3-pyrrolidinyl dispiro-oxindoles with high enantioselectivity. The reaction was initiated by deprotonation of **37** by the complex generated from the organocatalyst and Et_2Zn, accompanied by release of ethane. This was followed by coordination of methylene indolinone **38** to the zinc from the less-hindered face. Michael addition followed by Mannich reaction led to an intermediate complex, from which the final product **39** was released by proton exchange and the catalytic cycle continued (Scheme 11).[28]



Scheme 10 Homoacyl coumarin in [3+2] cycloaddition yielding all-carbon spirocentres



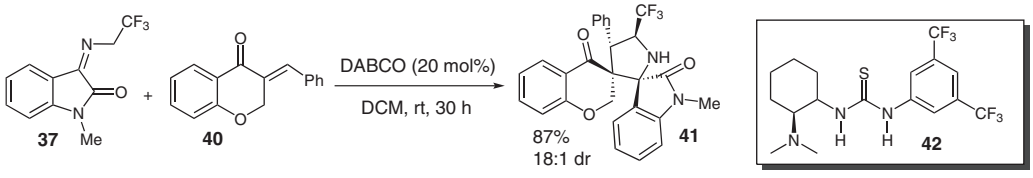
Scheme 11 Zinc complex mediated all-carbon spirocentre formation

In another report, isatin-based (trifluoromethyl)imines were reported to undergo [3+2] cycloaddition with unsaturated 4-benzylidene chromanones **40** promoted by the organocatalyst DABCO. The authors could also achieve up to 69% enantiopurity for the spirooxindole-chromanone hybrid **41** using Takemoto's bifunctional thiourea catalyst **42**, via formation of an '*exo*' transition state (Scheme 12).[29] Concurrently Knipe and co-workers reported the use of cinchona-derived thiourea catalyst **43** for the synthesis of spiropyrrolidine oxindoles with excellent enantioselectivities. Some of the examples reported contained molecules with all-carbon quaternary stereocentres, as exemplified in the synthesis of **45** and **47** (Scheme 13).[30]

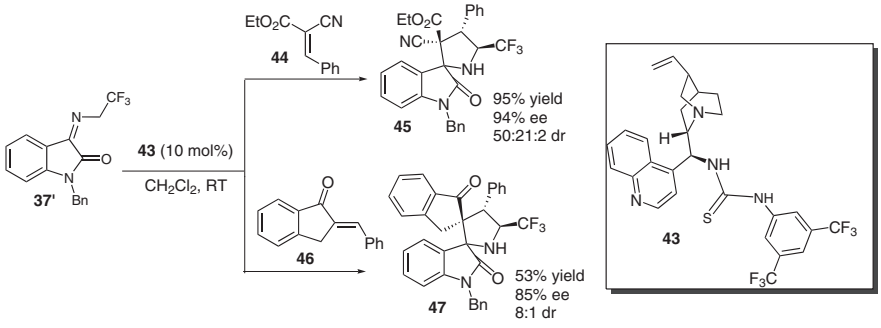
2.4 Iminoesters and Isocyanoesters

Zhang and co-workers in 2017 reported a copper(I) catalysed asymmetric *exo*-selective [3+2] cycloaddition of β-trifluoromethyl β,β-disubstituted enone **49** with azomethine ylides (generated from glycine ketinimine **48**), leading to the synthesis of chiral pyrrolidines bearing a trifluoromethylated quaternary carbon centre. The chiral ligand used in the reaction was (*S*)-MeO-DTBM-Biphep **53** and the copper salt used was $Cu(CH_3CN)_4BF_4$ (Scheme 14). The reaction was found to be general for a wide range of enones and acyclic azomethine ylides. Moreover, the products formed could be oxidized to 3*H*-pyrroles using 2,3-dichloro-5,5-dicyano-1,4-benzoquinone (DDQ) and converted into *N*-hydroxy pyrroles and nitrones using *m*-CPBA in varying efficiencies.[31] Later, the same group reported the Cu(I)-Ming-Phos-catalysed enantioselective [3+2] cycloaddition of glycine ketinimine with β-trifluoromethyl enone **50**, which yielded the highly functionalized pyrrolidine **52** containing an all-carbon quaternary stereocentre in 95% enantiomeric excess (Scheme 14).[32]

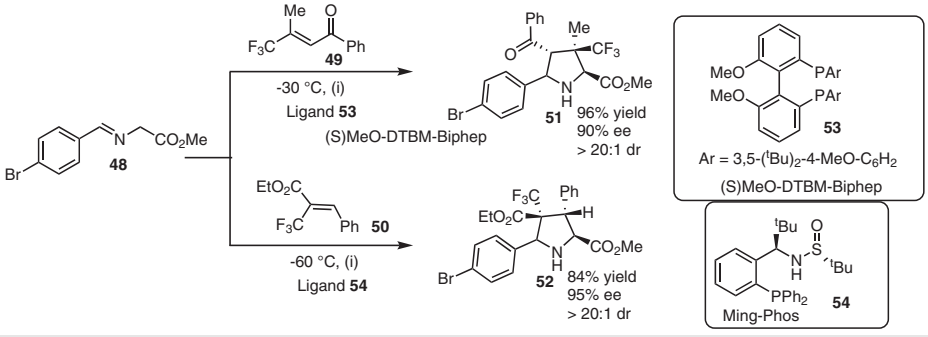
Subsequently, ligand-controlled [3+2] cycloaddition of iminoesters leading to chiral pyrrolidines with adjacent or discrete quaternary stereocentres with at least one all-car-



Scheme 12 DABCO mediated all-carbon spirocentre formation



Scheme 13 Use of thiourea catalyst

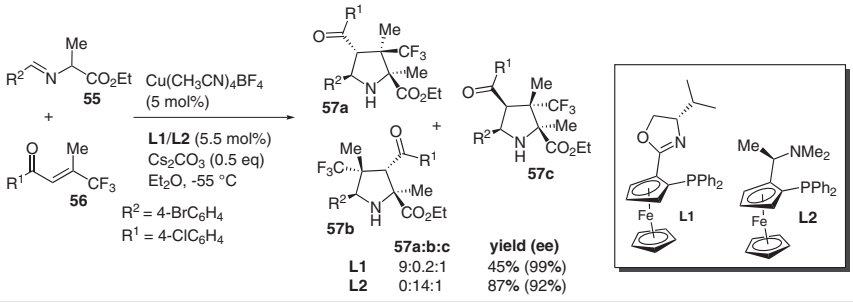


Scheme 14 Copper(I) catalysed [3+2] cycloaddition for synthesis of multi-substituted pyrrolidines. *Reagents and conditions*: (i) $Cu(CH_3CN)_4BF_4$ (5.0 mol%), Ligand (5.5 mol%), Cs_2CO_3 (50 mol%), THF.

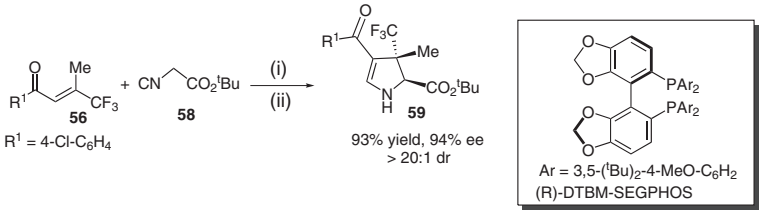
bon stereocentre was reported by the same group. Scheme 15 depicts a representative reaction of α-methyl-iminoester **55** and β,β-disubstituted enone **56** in the presence of a copper catalyst and chiral ligands **L1** or **L2**, yielding **57a** or **57b** as the major product, depending on the ligand. Computational studies provided insights into the regioselective control. When ligand **L1** was used, the phosphorus and nitrogen atoms of the ligand remained coordinated to the Cu(I) throughout the process, yielding **57a** in higher amounts, while a switch in regioselectivity was observed when **L2** was used due to formation of a Cu–O^{enone} bond, with the amine nitrogen atom of **L2** dissociating from Cu(I) centre.[33] The same group has also reported the synthesis of optically active dihydropyrroles containing an all-carbon quaternary stereocentre by copper-catalysed [3+2] cycloaddition of **56** with isocyanoesters of the type **58**, and maximum yields and enantioselectivities were obtained using (*R*)-DTBM-Seg-Phos as catalyst. Scheme 16 shows a representative example for the synthesis of the dihydropyrrole **59**.[34]

2.5 Aldehydes and Isatins

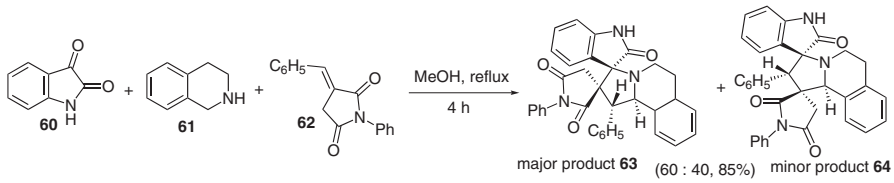
Aldehydes and isatins are versatile substrates to generate azomethine ylides. For instance, construction of an all-carbon spiro quaternary centre was reported by Boudriga and co-workers in 2019 during the diastereoselective synthesis of dispiropyrrolo[2,1-*a*]isoquinoline-fused pyrrolidine-2,5-diones by [3+2] cycloaddition of the cyclic diketone-based tetrahydroisoquinolinium *N*-ylide. In this reaction, the azomethine ylide formed from isatin **60** and 1,2,3,4-tetrahydroisoquinoline **61** approaches the (*E*)-3-arylidene-1-phenyl-pyrrolidine-2,5-dione **62** in an *exo*-manner to yield products **63** and **64**, both containing a spiro quaternary carbon centre, as depicted in Scheme 17.[35] Concurrently, Yan and co-workers reported that acetic acid can act as a catalyst to facilitate the formation of azomethine ylides from aromatic aldehydes and pyrrolidine, which, in turn, undergo [3+2] cycloaddition with 3-arylidene indolin-2-one or with 2-arylidene-1,3-indanedione to yield the corresponding functionalised pyrrolidines containing a spiro all-carbon quaternary stereocentre. In this reaction, the iminium ion **70**, formed from aromatic aldehyde and pyrrolidine, undergoes a [1,3]-hydride shift yielding an enamine intermediate **72**. The latter then undergoes an aldol type reaction with a second molecule of aldehyde **65** followed by dehydration and deprotonation, yielding a conjugated azomethine ylide **67** that finally participates in [3+2] cycloaddition with the alkene **68** to yield cycloadduct **69**, as shown in Scheme 18.[36]



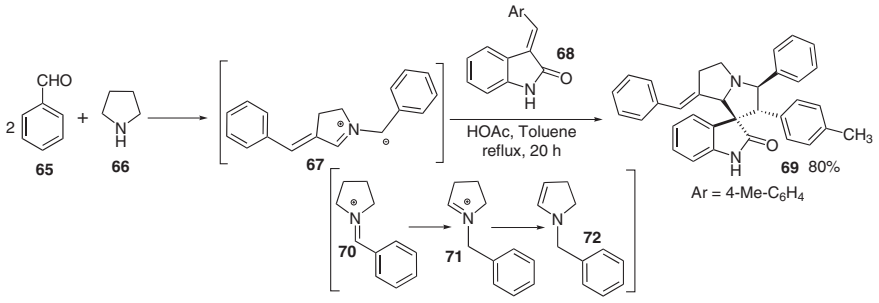
Scheme 15 Ligand-controlled [3+2] cycloaddition of iminoesters leading to chiral pyrrolidines



Scheme 16 Copper-catalyzed [3+2] for synthesis of dihydropyrrole bearing an all-carbon stereocentre. *Reagents and conditions*: (i) $CuBF_4$ $(CH_3CN)_4$ (5 mol%), Ligand (5.5 mol%) (ii) K_2CO_3 (50 mol%), MTBE, –40 °C, 12 h.



Scheme 17 Tetrahydroisoquinoline based azomethine ylide [3+2] to construct an all-carbon quaternary spirocentre

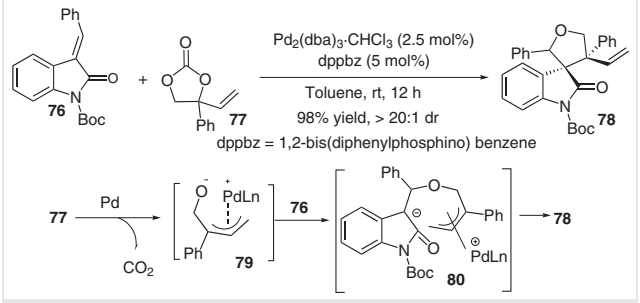


Scheme 18 Construction of an all-carbon quaternary stereocentre by acetic acid catalysis

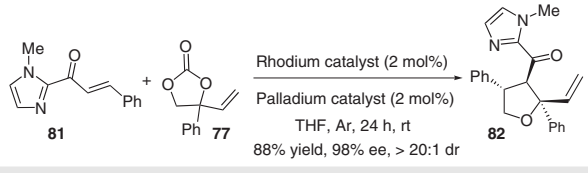
3 Reaction of Allyl Palladium Intermediates

Palladium-catalysed [3+2] cycloaddition of 5-vinyl oxazolidinones and trisubstituted alkenes using chiral ammonium–phosphine ligands was reported by Takashi and co-workers in 2016. The reaction takes place by an initial intermolecular addition of an allyl palladium species to the alkene, generating a zwitterionic intermediate. Subsequent ring closure and bond formation between the two reactive sites of the intermediate yields a product possessing three contiguous stereogenic centres, including two all-carbon quaternary centres. A phosphine ligand incorporating a quaternary ammonium halide component was used to assist Pd-halide contact. A representative reaction of oxazolidinone **73** with (*E*)-ethyl 2-cyano-3-phenylacrylate **74** leading to product **75** is shown in Scheme 19.[37]

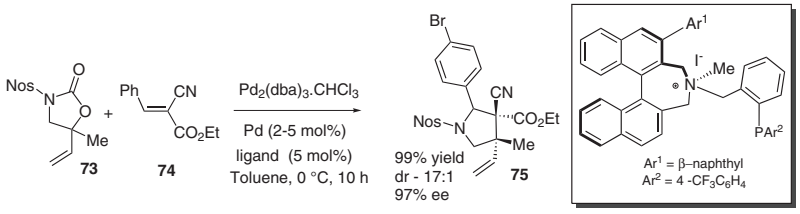
Nucleophilic 1,3-dipolar π-allyl palladium intermediates generated from vinyl ethylene carbonates have been found to be efficient reaction partners. For instance, synthesis of spirooxindoles with two contiguous all-carbon stereocentres was reported by Hu and co-workers by the palladium-catalysed [3+2] cycloaddition of methylene indolinone with vinyl ethylene carbonate. The reaction takes place through the initial formation of the Pd-π-allyl intermediate **79**, which undergoes [3+2] cycloaddition with methylene indolinone **76** by intramolecular nucleophilic attack to yield 3,3′-tetrahydrofuryl spirooxindole **78** (Scheme 20).[38] Recently, the 1,3-dipolar π-allyl palladium intermediate generated from vinyl ethylene carbonate was also reacted with chalcones under rhodium catalysis, leading to formation of tetrahydrofuran derivatives possessing an all-carbon quaternary stereocentre. The asymmetric bimetallic catalysis was achieved using a chiral rhodium complex catalyst along with $Pd_2(dba)_3{\cdot}CHCl_3$ and was demonstrated using α,β-unsaturated 2-acyl imidazole **81** and racemic phenyl vinyl carbonate **77** as cycloaddition partners. The reaction takes place by the activation of the α,β-unsaturated 2-acyl imidazole substrate **81** by the chiral rhodium complex through bidentate coordination. The zwitterionic π-allyl intermediate approaches the double bond of the rhodium complex through its *Si*-face. Subsequent coordination-dissociation and electron neutralization generates an intermediate that undergoes substitution with **81**, releasing the target 1,2,3,4-tetrahydrofuran molecule **82** (Scheme 21).[39]



Scheme 20 Palladium-catalyzed all-carbon spirocentre formation



Scheme 21 Synthesis of tetrahydrofuran containing an all-carbon stereocentre



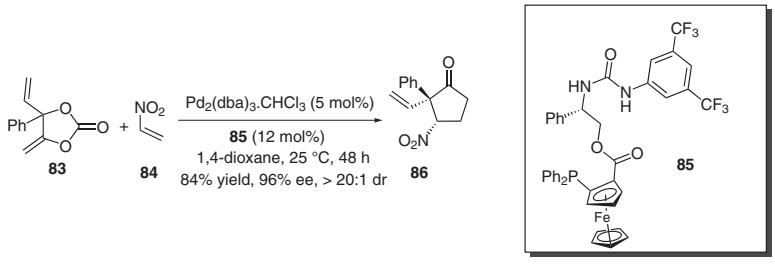
Scheme 19 Synthesis of multisubstituted pyrrolidines via [3+2] cycloaddition of allyl palladium intermediates with acrylates

Very recently, Zi and co-workers used vinyl methylene cyclic carbonates of the type **83** to generate vinyl-substituted palladium-oxyallyl species that undergo enantioselective inverse electron-demand [3+2] cycloaddition with electron-deficient nitroalkenes of type **84**. A hydrogen-bond-donating ligand was used to construct the cyclopentanone **86** containing an all-carbon quaternary stereocentre in a highly stereoselective manner. The optimised ligand for achieving maximum enantiomeric excess was found to be Fe-Ur-Phos **85**, which contains a urea moiety. The latter facilitates the hydrogen-bond formation between the chiral catalyst and nitro group of **84**, which imparts the stereocontrol of the reaction (Scheme 22).[40]

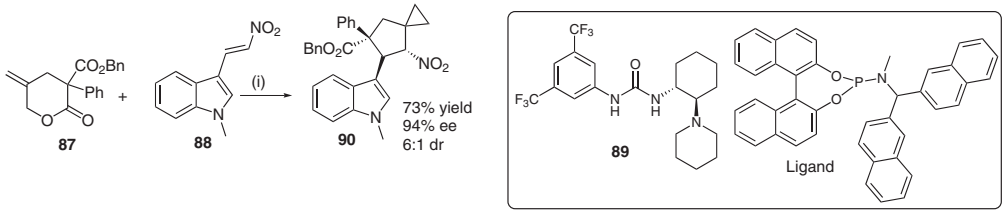
Liu and co-workers recently reported cooperative catalysis mediated by a palladium catalyst and urea-tertiary amine organocatalyst for the [3+2] cycloaddition between γ-methylidene-δ-valerolactones of type **87** and β-nitrostyrene **88**. The reaction occurs by the initial generation of a 1,4-dipole from **87** by oxidative addition of palladium, facilitated by CO_2 release and followed by intermolecular Michael addition to the species generated from the nitro-olefin. The strong hydrogen bonding between the urea-tertiary amine catalyst **89** and the nitro-olefin helps in the *Re*-face attack of the zwitterionic π-allyl intermediate onto the nitro-olefin, providing good control of the stereochemistry of the all-carbon quaternary stereocentre. Subsequent intramolecular cyclisation affords the final product **90** (Scheme 23).[41]

4 Reaction of Phosphine-Allenoate Zwitterionic Species

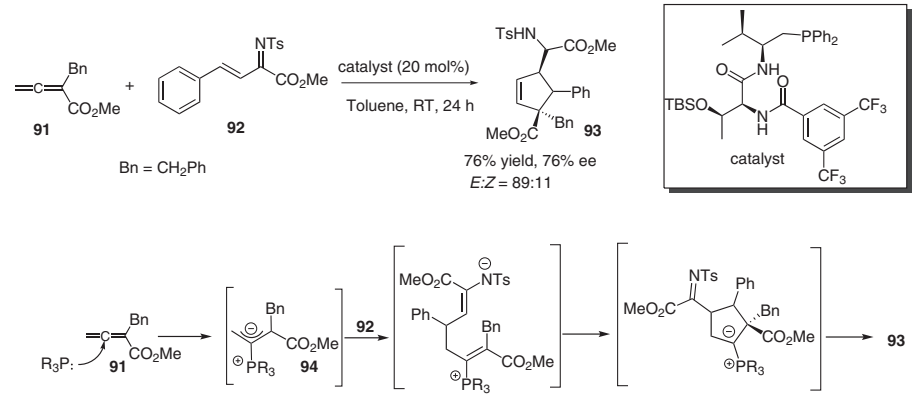
It is well known that phosphines can add to alkynoates and allenoates to generate zwitterions that, in turn, can undergo [3+2] cycloaddition with alkenes and alkynes.[42] Asymmetric versions of such reactions using chiral phosphine catalysts have been widely explored[43] and the strategy has been utilised for the synthesis of all-carbon quaternary stereocentres.[44] An enantioselective [3+2] annulation of α-substituted allenoates of the type **91** with β,γ-unsaturated *N*-tosyl imine **92** in the presence of a phosphine catalyst was reported by Lu and co-workers. The reaction resulted in the formation of cyclopentene **93**, containing an all-carbon quaternary centre. The reaction takes place via initial activation of the allenoate by attack of the phosphine, generating intermediate **94** that then undergoes [3+2] annelation with the *N*-tosyl imine, leading to product **93** after proton shift (Scheme 24).[45] Recently Liu and co-workers used this strategy for the regioselective synthesis of CF_3-substituted quaternary carbon-centred molecules in moderate to good yields. The reaction occurs through initial nucleophilic addition of the phosphine onto the allenoate, yielding the zwitterionic intermediate **98** that undergoes α-addition to the double bond of **96** to yield the anionic intermediate **99**, which, in turn, cyclises to **100**. Final 1,2-proton transfer and β-elimination of the catalyst yields the target cyclopentene **97** (Scheme 25).[46]



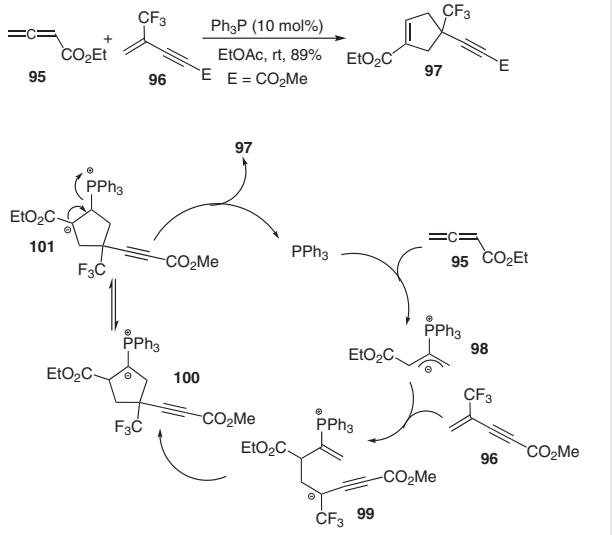
Scheme 22 Ferrocene-based catalyst for enantioselective cyclopentanone synthesis



Scheme 23 Urea-tertiary amine catalysis. *Reagents and conditions*: (i) $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol%), Ligand (22 mol%), **89** (5 mol%), 4 Å MS, THF, –10 °C.

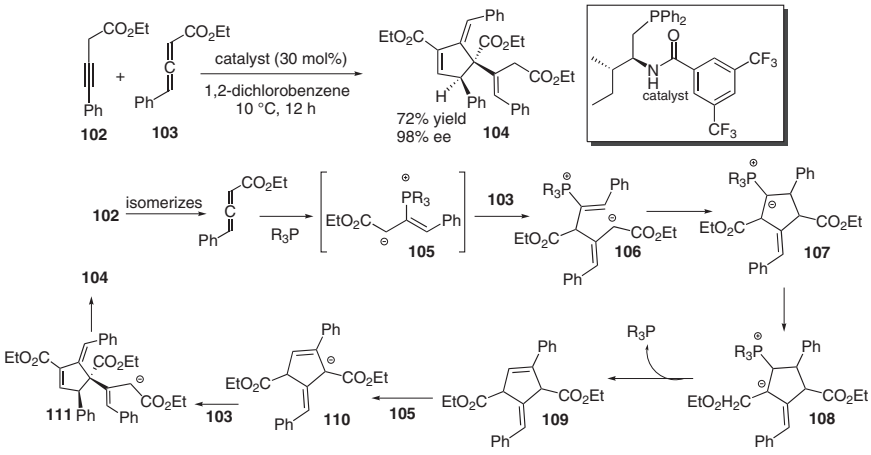


Scheme 24 [3+2] Annulation of *N*-tosylimines with allenoates

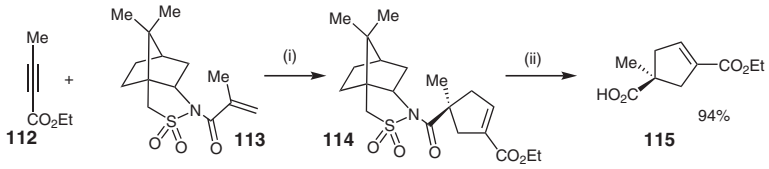


Scheme 25 Phosphine-catalysed cyclopentane synthesis

Yao and co-workers reported a stereoselective and enantioselective trimerization of γ-aryl-3-butynoates catalysed by L-isoleucine-derived amide phosphine to yield cyclopentenones bearing an all-carbon quaternary stereocentre. The reaction occurs by addition of the phosphine to the allenoate (formed by isomerisation of the alkyne **102**) to form zwitterionic intermediate **105**, which, in turn, reacts with another molecule of allenoate to yield intermediate **106** followed by intramolecular Michael addition to yield **107**. After a 1,2-*H* shift and expulsion of the catalyst, **109** is obtained, leading eventually to the final product **104** containing an all-carbon quaternary stereocentre (Scheme 26).[47] Very recently Takao and co-workers also utilised this strategy for the synthesis of cyclopentene molecules possessing all-carbon quaternary stereocentres using Oppolzer's camphor sultam **113** as one of the reaction partners.[48] The camphor sultam acts as a chiral auxiliary in this reaction, which is subsequently removed by chemoselective hydrolysis using alkaline hydrogen peroxide to furnish carboxylic acid **115** in 94% yield (Scheme 27). The high



Scheme 26 L-Isoleucine derived amide phosphine catalysed reaction



Scheme 27 Camphor sultam as chiral auxiliary. *Reagents and conditions*: (i) *n*-Bu_3P (30 mol%), toluene, 0 °C (ii) LiOH, aq H_2O_2, THF/H_2O, RT.

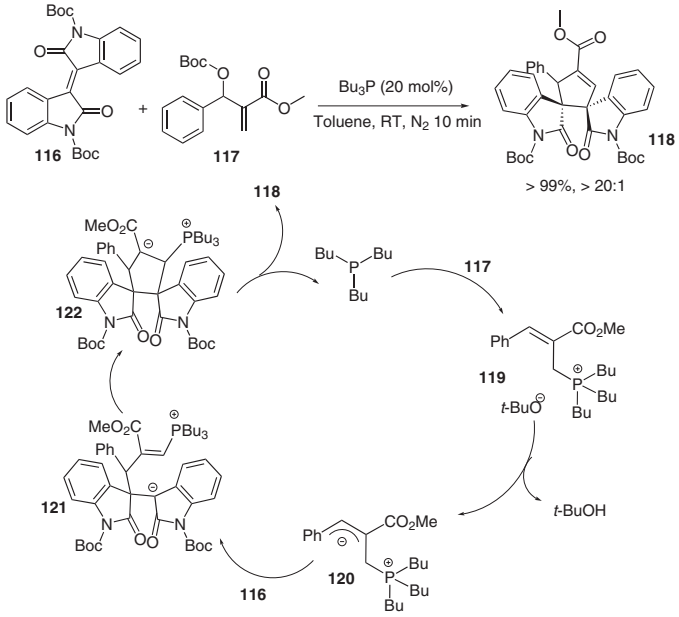
regioselectivity is probably due to the bulkiness of the camphor sultam. The authors have also applied this strategy for the formal synthesis of *R*-(−)-puraquinonic acid.

In another earlier report, Morita–Baylis–Hillman (MBH) carbonates were used instead of allenoates to generate zwitterionic intermediates using nucleophilic phosphines. The latter reacted with MBH carbonate **117** to yield the salt **119** that, in turn, was deprotonated by the *tert*-butoxide to form species **120**. The dispirobisoxindole **118**, containing two all-carbon quaternary stereocentres, was formed by [3+2] cycloaddition of isoindigo **116** with **120** through formation of intermediates **121** and **122** (Scheme 28).[49]

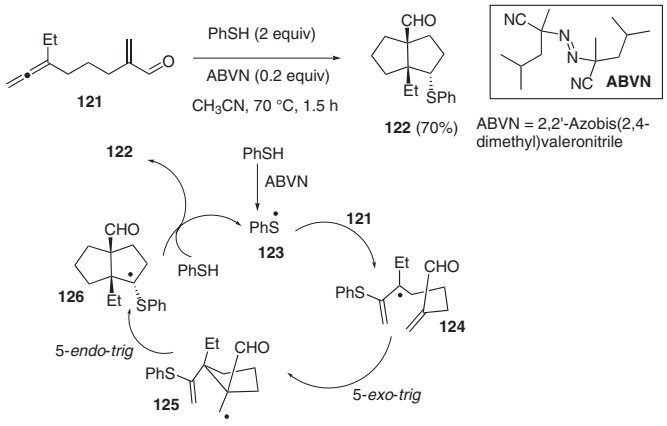
5 Miscellaneous Cycloaddition Reactions

In 2017, Li and co-workers reported that an allene-tethered electron-deficient olefin underwent intramolecular [3+2] cycloaddition in the presence of benzene thiol to yield [3.3.0]bicyclic systems containing *vicinal* quaternary carbon stereocentres. The intramolecular cascade reaction is initiated by an electrophilic benzene thiol radical **123**, affording a thermodynamically stable tertiary radical **124**, by adding to the central sp-carbon atom of the allene **121**. Subsequent attack of this radical to the α,β-unsaturated double bond via a 5-*exo*-*trig*-cyclisation led to radical intermediate **125** that then underwent a 5-*endo*-*trig*-cyclisation to generate **126**. The latter in the next step abstracts a hydrogen atom from the benzene thiol and is converted into the final product **122** (Scheme 29).[50]

An intramolecular silyl-nitronate cycloaddition was reported by Veselovsky and co-workers for the enantioselective synthesis of substituted cyclopentanones containing an all-carbon quaternary stereocentre. Henry reaction of 4-methyl pentenal **127** with nitromethane in the presence of the chiral catalyst **128** yields the unsaturated nitro alcohol **129**. The latter is then converted into silyl ether **130** that, when treated with 1,1,1,3,3,3-hexamethyldisilazane (HMDS), yielded cyclopentaisoxazolidinone **132** through formation of the nitronate **131** by a stereoselective intramolecular cycloaddition with *trans*-disposition of the OTBS substituent relative to the annulated isoxazolidinone ring. Further transformation of **132** by exposure to sodium methoxide led to ring opened oximes **134a** and **134b** (*anti*/*syn* ratio 12:1 by ^1H NMR analysis) through nitroso tautomerism. Final deoximation of the oximes by tritura-



Scheme 28 Reaction of MBH carbonate in the presence of phosphine



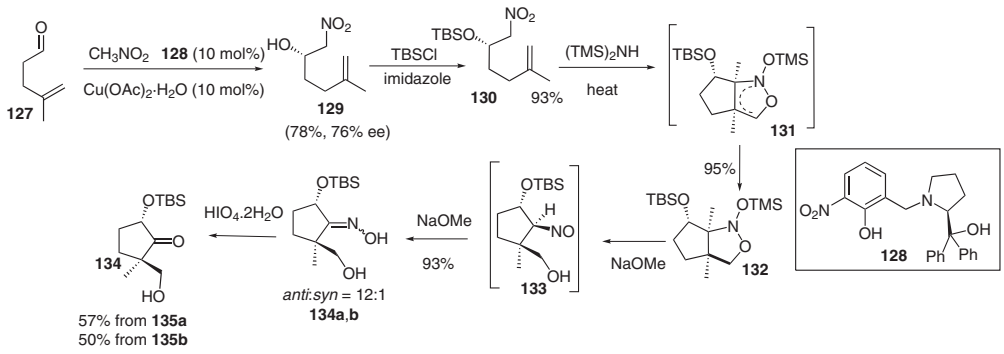
Scheme 29 Synthesis of bicyclic [3.3.0] compounds containing *vicinal* all-carbon stereocentres

tion with periodic acid resulted in the cycloalkanone **135** (Scheme 30).[51]

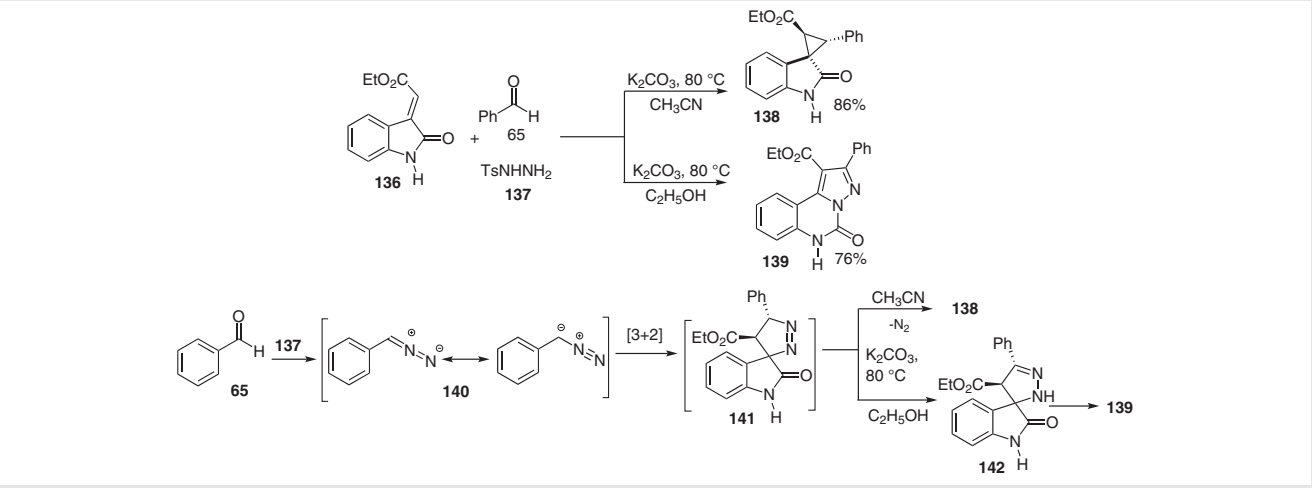
A formal 1,3-dipolar cycloaddition of 3-ylidene oxindoles of the type **136** with aryl diazomethane **140** (generated from benzaldehyde **65** and tosyl hydrazine **137**) was reported by Babu and co-workers in 2018.[52] In this reaction, the intermediate cycloadduct **141** underwent decomposition in the aprotic solvent to deliver 3-spirocyclopropyl-2-oxindole **138**, containing an all-carbon quaternary stereocentre. It was also observed that, in the presence of protic solvent, the cycloadduct **141** tautomerizes to form **142** which, in turn, is oxidised to the corresponding spiropyrazole oxindole. The latter then undergoes spontaneous rearrangement to pyrazoloquinazolinone **139**. Thus, a solvent-controlled switchable product selectivity was demonstrated, as depicted in Scheme 31.

Gao and co-workers, in 2019, reported the application of a [3+2] cycloaddition strategy for the construction of the core skeleton of calyciphylline A alkaloids. Herein, nitrone-induced [3+2] cycloaddition was used for the construction of the *cis*-hydroindole A–C rings containing an all-carbon quaternary centre at C5. Scheme 32 shows a representative construction of the stereogenic C5 centre of an important precursor to himalensine A[53,54] in which a cycloheptene substrate **143** is treated with *N*-benzylhydroxylamine resulting in a nitrone intermediate that, on intramolecular 1,3-dipolar cycloaddition through 6-*exo*-cyclisation with the α,β-unsaturated ester, results in cycloadduct **144**, an important precursor containing the all-carbon quaternary centre of himalensine A **145**.

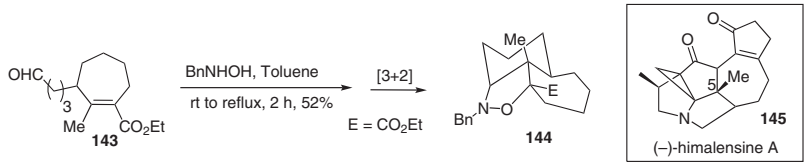
Gao and co-workers, in 2019, reported the asymmetric total synthesis of (–)-viridin and (–)-viridiol (Figure 2), both containing a quaternary all-carbon stereocentre at C-10. The strategy involved the synthesis of compound **146** from L-ribose, which was then transformed into the unsaturated ester **147** by ruthenium-catalysed cross-metathesis. Treatment of **147** with hydroxylamine hydrochloride generated oxime **148**, which was converted into nitrile oxide **149** with chloramine-T. Subsequent intramolecular [3+2] cycloaddition generated isooxazoline **150**, which, on reductive hydrogenolysis and hydrolysis, yielded ketone **151**. Wittig reaction of the latter produced compound **152**, which, on reaction with dimethyl hydroxylamine hydrochloride (DMHH), yielded the Weinrib amide **153**. This reacted with the anion of dihydroindenol **154** to yield **155** as a mixture of diastereomers at C17 (see Figure 2). Compound **155** was



Scheme 30 Synthesis of cyclopentanones via intramolecular silyl-nitronate cycloaddition



Scheme 31 Synthesis of 3-spirocyclopropyl-2-oxindole **138** and pyrazoloquinazolinone **139**



Scheme 32 Intramolecular nitrone-ene [3+2] cycloaddition for construction of a precursor to the himalensine alkaloids

converted into the desired tetracyclic core **156**, containing an all-carbon quaternary stereocentre at C10, using a metal-catalysed hydrogen atom transfer (MHAT) strategy with the help of cobalt-salen catalyst **158** and phenyl silane. Selective removal of the TES group using Dowex resin followed by oxidation with Dess–Martin periodinane (DMP) yielded compound **157**, which was converted into viridin and viridiol (Scheme 33).[55]

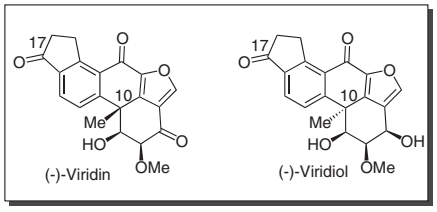


Figure 2 Structures of viridin and viridiol

6 Conclusion

Effective ways of constructing all-carbon stereocentres have been reported in the past five years using [3+2] cycloaddition strategies involving metal-catalysed, organocatalysed, photocatalysed, base/acid-mediated, and thermal [3+2] cycloadditions, leading to products containing one or more all-carbon stereocentres. We believe that this review along with other reviews in this period,[56–61] will provide insight for organic chemists wishing to construct molecules containing all-carbon quaternary stereocentres.

Conflict of Interest

The authors declare no conflict of interest.

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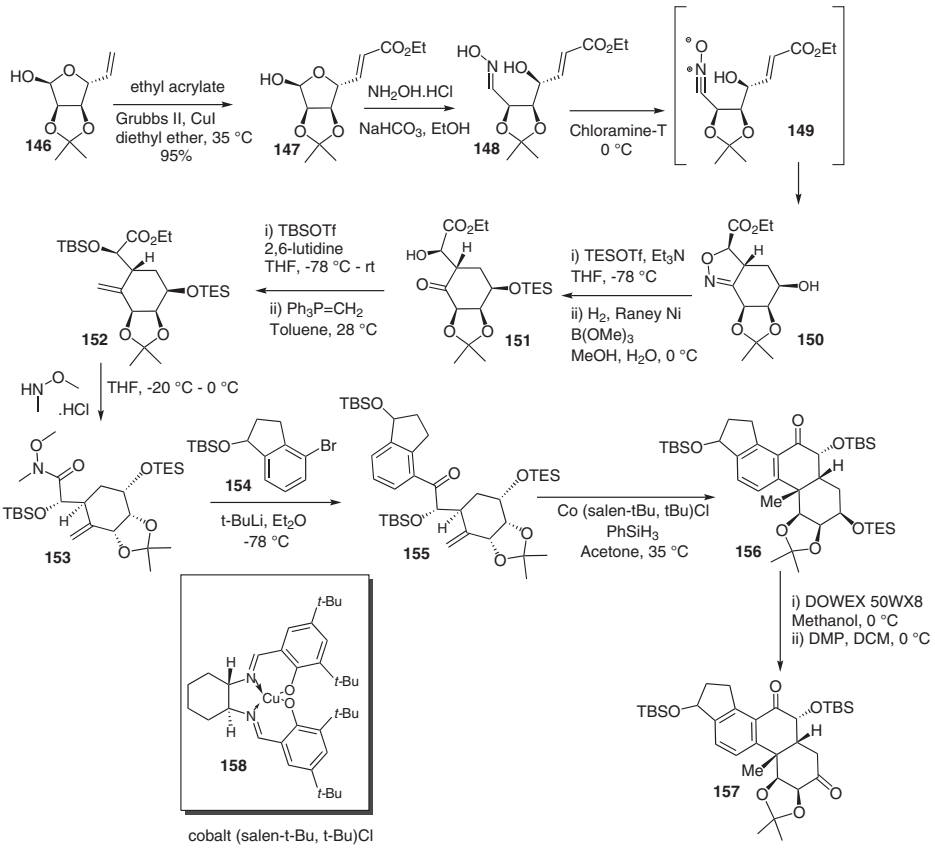

Scheme 33 Sequential synthesis of viridiol precursor

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