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Cloke–Wilson rearrangement: a unique gateway to access five-membered heterocycles

Usman Nazeer,[ab] Aqsa Mushtaq,[a] Ameer Fawad Zahoor, *[a] Freeha Hafeez,[ac] Irum Shahzadi[a] and Rabia Akhtar[ad]

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Cyclopropanes are of great synthetic value in heterocyclic chemistry due to their highly reactive nature. They are widely employed to synthesize various biologically active organic compounds. Generally, vinyl, carbonyl, imine, and alkylidene cyclopropanes are utilized as efficient synthetic precursors in organic synthesis. The Cloke–Wilson rearrangement of these activated cyclopropanes is carried out to achieve the synthesis of diverse heterocyclic scaffolds. Various oxygen, nitrogen, and sulfur-containing heterocyclic compounds have been synthesized employing this rearrangement. With time, Cloke–Wilson rearrangement has evolved into a high yielding enantioselective and diastereoselective approach utilizing integrated novel methods. Our review focuses on the recent approaches for Cloke–Wilson rearrangement to synthesize several five-membered heterocycles and its applicability towards the natural product syntheses reported during 2000–2020.

1. Introduction

Cyclopropanes are the smallest carbocycles that possess an affluent position in synthetic organic chemistry.[1] Cyclopropanes are widely utilized as useful synthetic building blocks owing to the presence of the high π character, intrinsic torsional, and angle strain of about 115 kJ mol^{-1}, which enable them to undergo ring-opening reactions to give diversely functionalized target molecules[2,3] Regardless of the ring strain, cyclopropanes are relatively stable and chemically unreactive towards C–C bond cleavage unless polarized and get activated by the introduction of activating groups on the ring.[4] Mostly, vinyl, carbonyl, imine, and alkylidene substituents are introduced to enhance the reactivity of cyclopropanes.[1,5] The substituted cyclopropanes undergo ring-opening/cyclization reactions to generate five-membered heterocycles, such as vinylcyclopropane to cyclopentene,[6] cyclopropyl-carbonyls to dihydrofurans,[7] cyclopropylimines to pyrroline,[8] and cyclopropyl thioketones to dihydrothiophenes.[9] Neureiter was the first chemist to report the synthesis of dichlorocyclopentene by the thermal rearrangement of dichlorovinylcyclopropane above 400 °C.[10] After one year, in 1960, vinylcyclopropane was transformed to cyclopentene by thermal rearrangement at 325–500 °C.[11] A decade later, Woodward and Hoffman called this rearrangement an example of a [1,3]-sigmatropic reaction.[12] Later on, reaction kinetics,[13] substituents effect,[14] reaction stereochemistry,[15] and theoretical calculations[16] were thoroughly investigated in organic synthesis.[15c] The vinylcyclopropane rearrangement is widely applicable in the total synthesis of various organic compounds, such as aphidicolin,[17a] zizaene,[17b] hirsutene,[17c] specionin,[17d] and salviasperanol.[18] Cyclic imines, such as pyrrolines have been employed to synthesize various biologically active organic compounds.[19] In 1929, Cloke reported the synthesis of 2-phenylpyrroline hydrochloride by the Cloke–Wilson rearrangement of cyclopropylimine–pyrroline.[8a] After forty years, Stevens applied it to the synthesis of a variety of alkaloids, such as mesembrine, nicotine, ipalbidine, and septicine.[20] In 2011, the synthesis of crispine A and harmicine alkaloids was accomplished *via* cyclopropylimine rearrangement by Saha and coworkers.[21] Many other research groups published the synthesis of pyrrolidine-based alkaloids by this rearrangement.[22] Since then, this rearrangement is considered to be an efficient synthetic route to generate several five-membered N-containing heterocycles.[23,72–74] In 1947, Wilson reported the thermal rearrangement of cyclopropylcarbaldehyde to dihydrofuran.[7a] Besides its application in the synthesis of diverse heterocycles,[24] this rearrangement is also involved in the total synthesis of various natural products.[25] The [3 + 2] cycloaddition reaction of cyclopropanes with aldehydes results in the synthesis of furans,[26a] but the synthetic route to the furan moiety *via* the rearrangement of cyclopropyl ketone is a highly efficient and cost-effective protocol.[26b] The transition metal-catalyzed synthesis of functionalized furans by the ring-opening/closure of cyclopropanyl ketones is another

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[a] *Department of Chemistry, Government College University Faisalabad, 38000-Faisalabad, Pakistan. E-mail: fawad.zahoor@gcuf.edu.pk*

[b] *Department of Chemistry, University of Houston, 3585 Cullen Boulevard, Texas 77204-5003, USA*

[c] *Department of Chemistry, Riphah International University Faisalabad, 38000-Faisalabad, Pakistan*

[d] *Department of Chemistry, The Superior University Lahore, Faisalabad-Campus, Faisalabad, Pakistan*

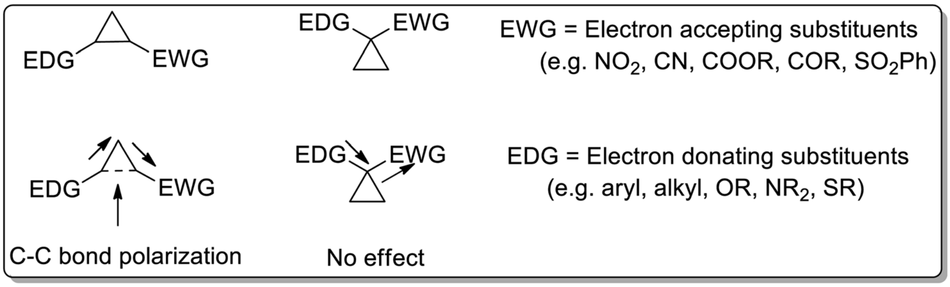


Fig. 1 Comparison of position of the attached substituents for the activation of the cyclopropyl ring.

facile and efficacious synthetic pathway.[27] The objective of this review is to provide a broad overview of recent methodological development of Cloke–Wilson rearrangement to furnish five-membered O-, N-, and S-heterocycles and its applications in the total synthesis of natural products. To date, no specific review has been published on this particular topic.

2. Chemistry of cyclopropanes

Cyclopropanes are the center of attraction in organic chemistry because of their high π character, intrinsic torsional, and angle strain, which enable them to undergo ring-opening reactions to attain several heterocyclic organic compounds.[3] Cyclopropanes are relatively stable and chemically inert towards C–C bond cleavage unless activated.[4a] The cyclopropane ring gets activated by attaching electron-donating groups (D) and electron-withdrawing groups (A) on the ring. For the activation of the C–C bond, there are two ways of attaching electron-donating groups and electron-withdrawing groups: vicinal positioning and geminal positioning. The push and pull effect (as a result of attached donor and withdrawing substituents at the vicinal position) is responsible for induced polarization between two adjacent C–C atoms. Comparably, electron donating and withdrawing substituents at the geminal position have no effect on C–C bond polarization (Fig. 1).

Cyclopropane ring opening is promoted by induced polarization, which gives rise to the zwitterionic intermediate. Being highly reactive, the generated dipole demonstrates distinctive properties like electrophilic addition reactions, nucleophilic addition reactions, cycloaddition reactions, and rearrangement reactions.[28]

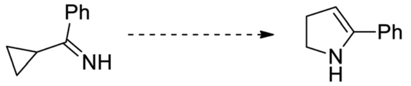
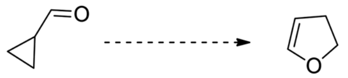
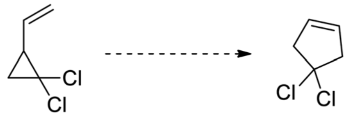
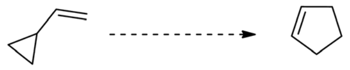
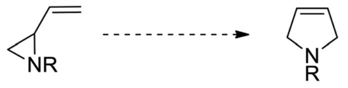
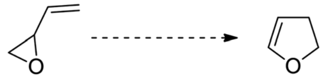
3. Biological importance of cyclopropanes and five-membered heterocycles

Cyclopropanes are highly reactive three-membered heterocyclic rings, which are structural constituents of various biologically active organic compounds and drugs. For example, tranylcypromine is a cyclopropyl constituting anti-anxiety drug, which is used to relieve stress.[29] Similarly, (+)-curacin A,[30], (+)-ambruticin S,[31] andgrenadamide[32] are some of cyclopropyl-based medicinally important naturally occurring compounds that exhibit anti-cancer, anti-fungal, and cannabinoid receptor-binding activities, respectively. The five-membered heterocycles (obtained as a result of Cloke–Wilson rearrangement) are also of significant importance in medicinal chemistry.[33a] For example, suvorexant is an oxazole-based drug (oxygen containing five-membered heterocycle), which is used to treat sleep disorder.[33b] A nitrogen-containing five-membered heterocycle, *i.e.*, imidazole, has been found to be active against fungus, bacterial, viral, and cancer cell lines.[34a] Similarly, purine derivatives have also been found to exhibit cytotoxic potential.[34b] Moreover, thiophene and its derivatives are sulfur-containing heterocycles that have found applications as anti-bacterial, anti-viral, anti-inflammatory, and anti-cancer agents.[35]

4. Chronological discovery of cyclopropanes and their heteroatom variants

The chronological discovery of cyclopropanes and their varied heteroatomic rearrangement is of great significance. In 1929, Cloke[8a] reported the synthesis of 2-phenylpyrroline

Table 1 Chronological discovery of cyclopropane and its heteroatom variants rearrangement

Entry	Main conversion	Scientist
1		Cloke[8a]
2		Wilson[7a]
3		Neureiter[10]
4		Vogel, Overberger and Borchert[11]
5		Atkinson, Rees[36] and Lwowski[38]
6		Paladini and Chuche[37]

hydrochloride by cyclopropylimine–pyrroline rearrangement *via* the vacuum distillation of phenyl cyclopropyl ketimine hydrochloride (Table 1, entry 1). In 1947, Wilson[7a] reported the heat-catalyzed rearrangement of cyclopropylcarbaldehyde to yield dihydrofuran (Table 1, entry 2). In 1959, Neureiter[10] reported the synthesis of dichlorocyclopentene by the rearrangement of dichlorovinylcyclopropane at more than 400 °C (Table 1, entry 3). After a year, in 1960, vinylcyclopropane was found to give cyclopentene *via* thermal rearrangement[11] (Table 1, entry 4). Atkinson and Rees[36] reported the thermal rearrangement of vinylaziridines to attain pyrrolines in 1967 (Table 1, entry 5). In 1971, Paladini and Chuche[37] reported the synthesis of dihydrofurans *via* the rearrangement of vinyloxirane (Table 1, entry 6) and, after one year, Lwowski and co-workers[38] reported this rearrangement by treating singlet and triplet nitrenes with dienes.

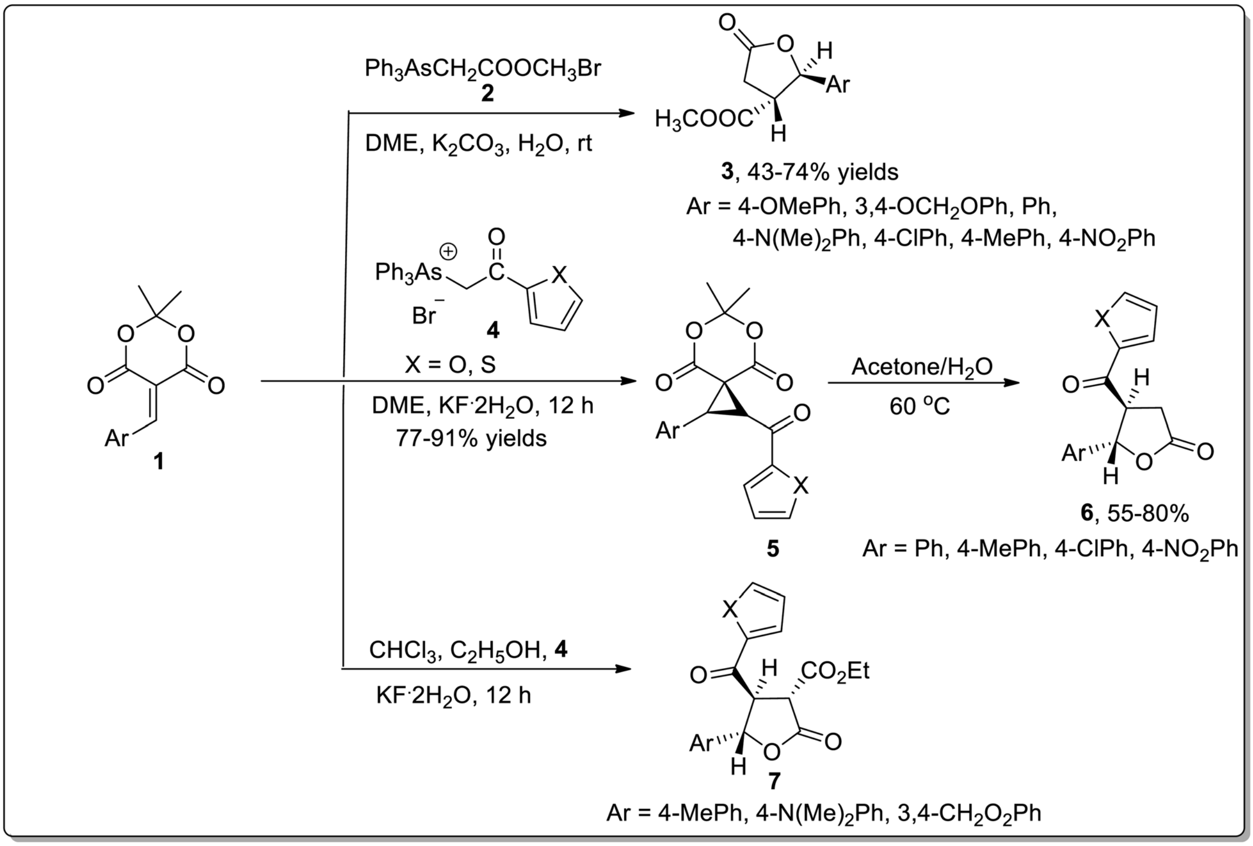
5. Cloke–Wilson rearrangement

The highly strained cyclopropyl ketones, cyclopropylimines, and cyclopropyl thioketones are processed *via* Cloke–Wilson rearrangement to synthesize stable functionalized five-membered heterocycles. This rearrangement proceeds without the addition of an external nucleophile by involving the ring-opening/closing reaction.[9,28,39] In 1929, Cloke[8a] treated cyclopropyl substituted ketones with NH_4Cl by applying heat to attain dihydropyrroles. In 1947, a similar kind of transformation was reported by Wilson[7a] to synthesize dihydrofuran from cyclopropyl carboxaldehyde in the presence of heat. Owing to the requirement of high temperature (200–500 °C) for this strategy, its scope and applications are limited.[40] However, many activation methods have been developed including transition metal catalysis,[8b,41] photocatalysis,[40d,42] cyclopropylcarbaldehyde-promoted activation,[43] organocatalysis,[44] Lewis acid catalysis,[25,54–65] Brønsted acid catalysis,[66–74,89,90,93] and Brønsted base catalysis[68] to carry out this transformation. Cloke–Wilson rearrangement also finds applications in the total synthesis of natural products.[21,25,91–94] Thus, the construction of five-membered O-, N-, and S-heterocycles can be easily achieved *via* Cloke–Wilson rearrangement.

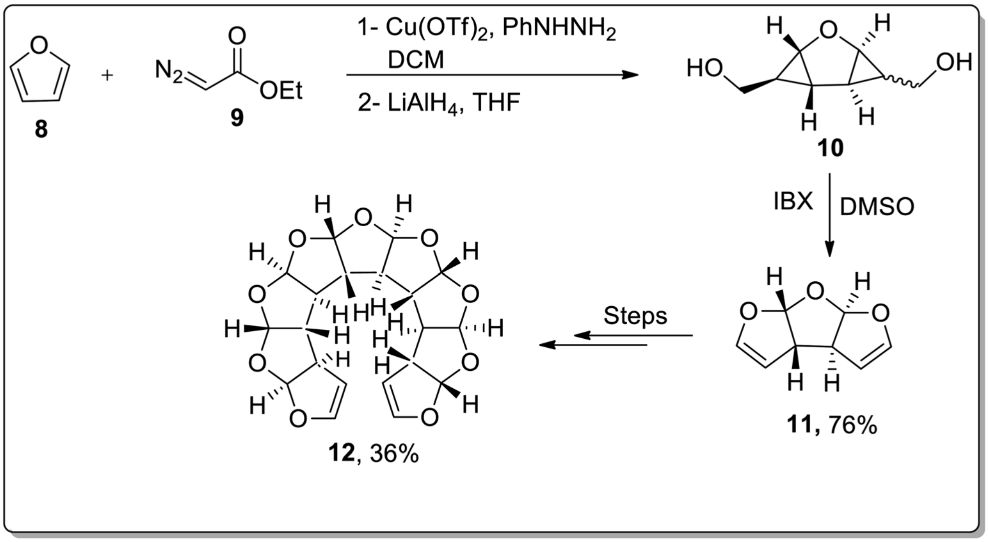
6. Synthesis of O-heterocycles

6.1. Thermal rearrangement

The wide significance of γ-butyrolactones has attracted great interest towards their synthesis. In 2002, Chen[45a] *et al.* carried out one-pot reaction between arsonium ylides **2** and substituted electron-deficient olefins **1** to synthesize substituted cyclopropanes or β,γ-disubstituted-γ-butyrolactones **3**. In 2008, Wu[45b] *et al.* further utilized this rearrangement by reacting arsonium ylides **4** having furoyl or thienoyl functional group with substituted olefins **1** for the synthesis of β,γ-disubstituted butyrolactones **6** and α,β,γ-trisubstituted butyrolactones **7**. Elecctron-donating groups bearing olefins **1** (on aryl ring) gave β,γ-disubstituted γ-butyrolactones **6** in good yields *via* one-pot



Scheme 1 Synthesis of substituted butyrolactones 3, 6, and 7 *via* Cloke–Wilson rearrangement.



Scheme 2 Synthesis of oligoacetal **12** *via* Cloke–Wilson rearrangement.

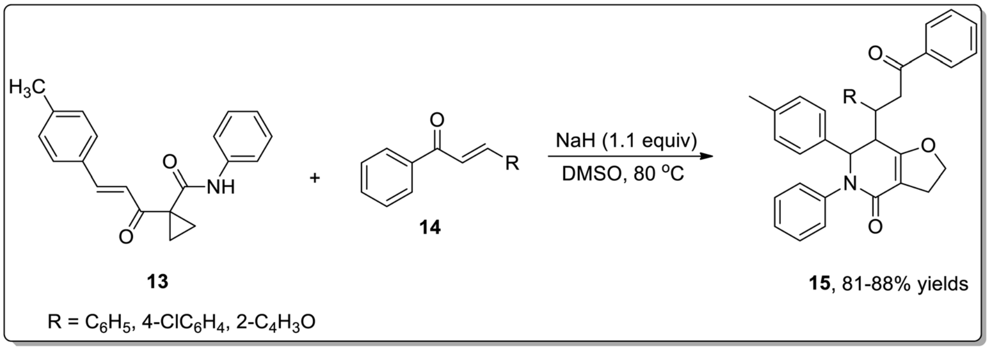
reaction in moderate reaction conditions. However, a similar reaction resulted in the formation of spirocyclopropyl Meldrum's acids **5** by employing weak electron-donating or electron-withdrawing groups bearing olefins **1**. These acids were further transformed to β,γ-disubstituted butyrolactones **6** in the presence of acetone and water at 60 °C. Electron-donating substituents bearing olefins also led to the synthesis of α,β,γ-trisubstituted butyrolactones **7** using chloroform as a solvent in the presence of ethanol. Triphenylarsine was obtained as a by-product and can be reused (Scheme 1).[45]

In 2009, the synthesis of anti-fused oligoannelated tetrahydrofuran moieties was carried out by Werz and coworkers from *in situ*-generated donor–acceptor cyclopropanes as a result of the cyclization reaction. The cyclization was initiated from the Cu(OTf)$_2$-catalyzed double cyclopropanation of furan **8** with ethyl diazoacetate **9** to give a tricyclic bis-cyclopropane. The cyclopropanation reaction was followed by LiAlH$_4$-mediated reduction, which resulted in diol **10**. The diol moiety **10** was further subjected to oxidation in the presence of IBX to afford tricyclic bisacetal **11**. In order to generate oligoacetal **12** up to a nonacyclic system, this three-step reaction array was repeated thrice (Scheme 2).[46]

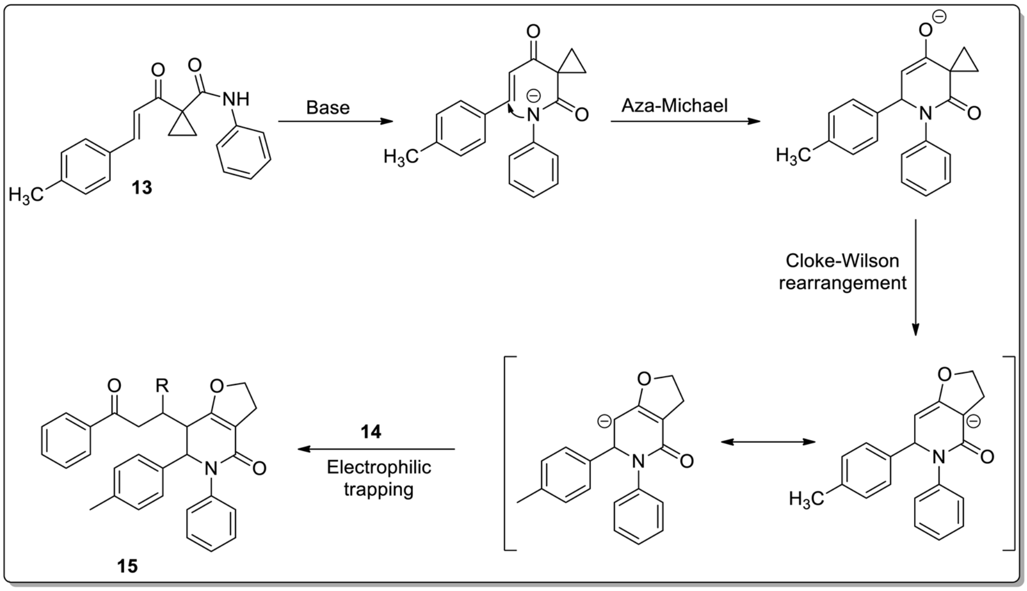
In 2011, Liang and co-workers reported the synthesis of furo[3,2-*c*]pyridinones **15** by the reaction of 1-cinnamoylcyclopropanecarboxamides **13** with various electrophiles **14** by an aza-oxy-carbanion relay *via* cascade the aza-Michael addition/Cloke–Wilson rearrangement/transfer of the carbanion and electrophile-confined reactions. This novel and facile synthetic strategy proceeded *via* non-Brook rearrangement pathway for the synthesis of medicinally important furo[3,2-*c*]pyridinones **15** in high yields (Schemes 3 and 4).[47]

The synthesis of 2,3-dihydrofuro[3,2-*c*]pyridines **17** (in moderate yields) by employing Cloke–Wilson rearrangement was reported by Dong and coworkers in 2012. The synthesis of target molecules was achieved by treating 1-acyl-1-[(dimethylamino)alkenoyl]cyclopropanes **16** as the electrophilic source, which proceeded *via* one-pot annulation and ring-expansion reaction. The mechanism of their one-pot synthesis involved the intermolecular addition of ammonia, regioselective thermal Cloke–Wilson rearrangement of cyclopropylketone, intramolecular aza-nucleophilic addition/elimination, and dehydration reaction (Scheme 5).[48]

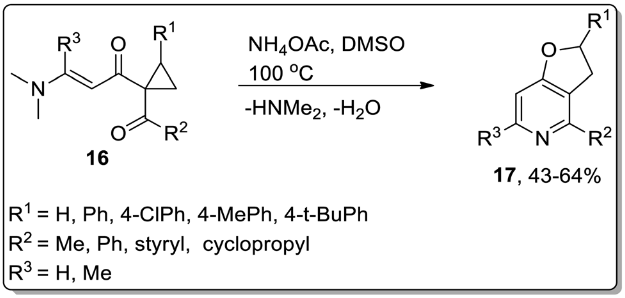
In 2013, the synthesis of substituted dihydrofuroquinolines **20** was established by Ren and co-workers, which proceeded by treating azido-cyclopropyl ketones **18** with a reducing agent,



Scheme 3 Synthesis of furo[3,2-c]pyridinones **15** *via* Cloke–Wilson rearrangement.



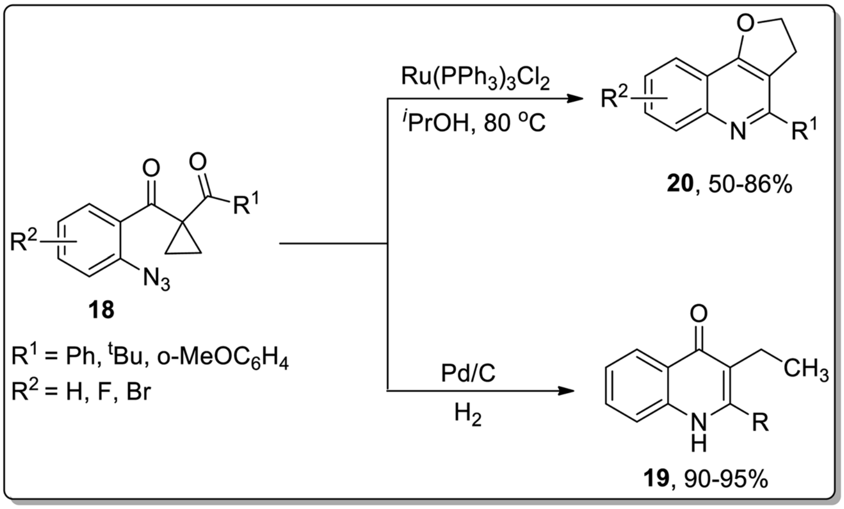
Scheme 4 Mechanism for the synthesis of furo[3,2-c]pyridinones **15** *via* Cloke–Wilson rearrangement.



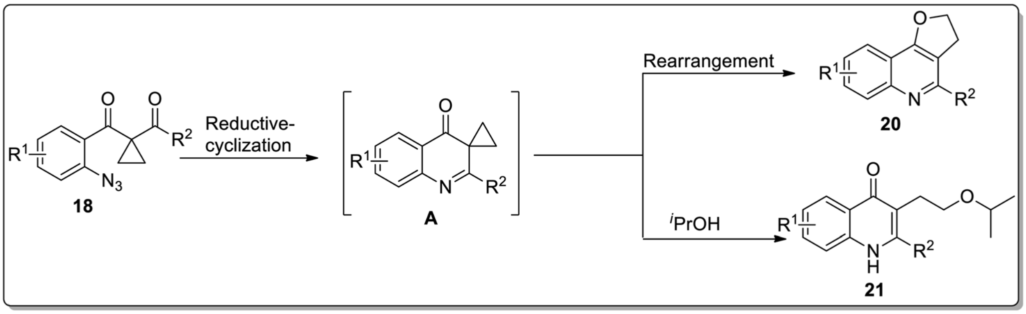
Scheme 5 Synthesis of 2,3-dihydrofuro[3,2-c]pyridines **17** *via* Cloke–Wilson rearrangement.

followed by cyclization and rearrangement. The Ru-catalyzed regioselective transformation commenced with the reduction of the azide group upon heating in the presence of the Ru-catalyst in ^{i}PrOH to an amine, which was later condensed with a ketone to generate intermediate **A.** Intermediate **A** further resulted in the synthesis of dihydrofuroquinolines **20** by Cloke–Wilson rearrangement, while ring-expansion, that took place as a result of the attack of solvent ^{i}PrOH on the intermediate **A,** led to the generation of by-product **21** (Scheme 6).[49] Meanwhile, cyclopropyl-substituted scaffolds **18** afforded quinolone derivatives **19** by carrying out the reaction in the presence of hydrogen atmosphere and palladium (supported on charcoal) (Scheme 7).

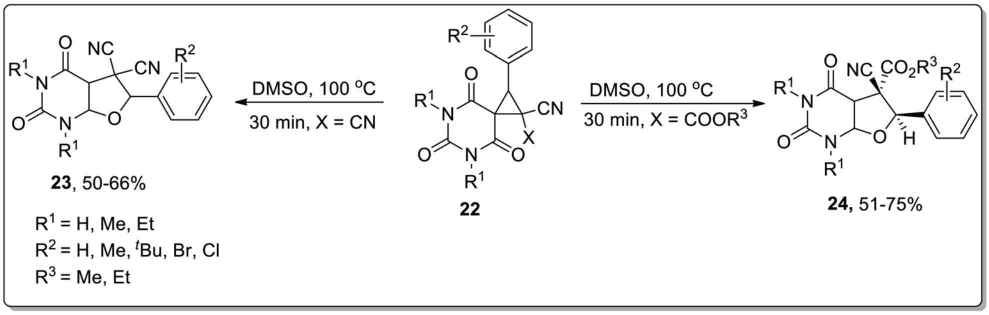
In 2015, Vereshchagin and co-workers carried out thermal Cloke–Wilson rearrangement to synthesize (medicinally essential) substituted furo[2,3-*d*]pyrimidines **23** and **24** in 50–75% overall yields employing spirocyclic barbiturates **22** as precursors in DMSO at 100 °C. The products were obtained directly from the reaction mixture by water-assisted precipitation without requiring any additional catalyst (Scheme 8).[50]



Scheme 6 Synthesis of dihydrofuroquinolines **20** and quinoline derivatives **19** *via* Cloke–Wilson rearrangement.



Scheme 7 Mechanism for the synthesis of dihydrofuroquinolines **20** *via* Cloke–Wilson rearrangement.

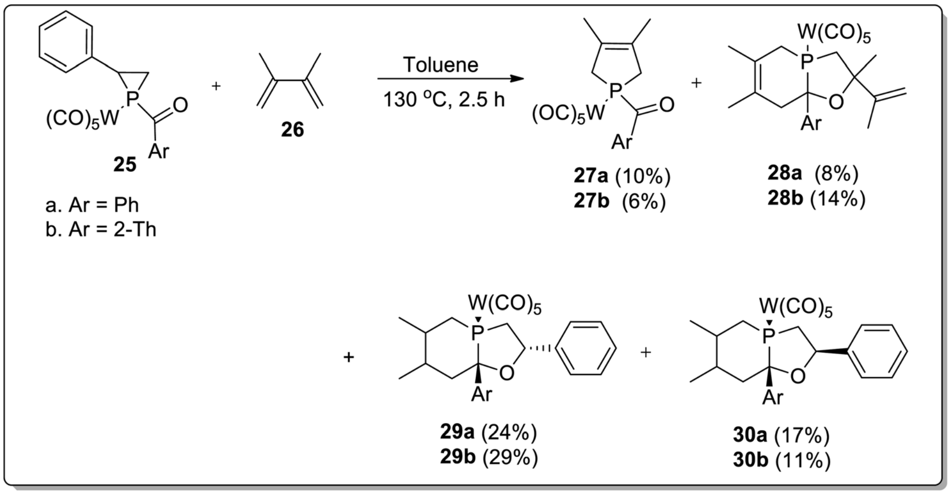


Scheme 8 Synthesis of substituted furo[2,3-*d*]pyrimidines **23** and **24** *via* Cloke–Wilson rearrangement.

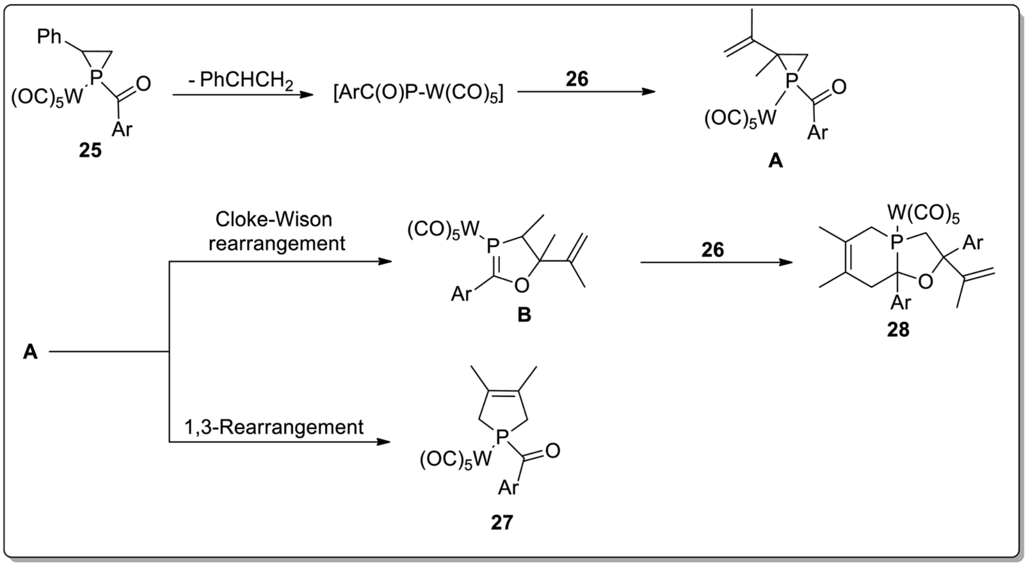
In 2017, Duan and co-workers[51] reported the thermolysis of tungsten pentacarbonyl-substituted 1-acylphosphirane complexes **25** and 2,3-dimethylbutadiene **26** at 130 °C in toluene, which generated different complexes (**27–30**) *via* Cloke–Wilson rearrangement. Complexes **27** and **28** were synthesized by the transformation of the phosphirane ring to the acylphosphinidene complex, which was further made to react with 2,3-dimethylbutadiene to result in a vinylphosphirane intermediate **A.** The vinylphosphirane intermediate **A** was subjected to [1,3] rearrangement to give phospholene **27**; meanwhile, it was also converted to oxaphospholene **B** *via* Cloke–Wilson rearrangement. Oxaphospholene **B** was later treated with 2,3-dimethylbutadiene **26** to afford complex **28** (Schemes 9 and 10).

Furthermore, the tungsten pentacarbonyl-substituted 1-acylphosphirane complex **25** and 2,3-dimethylbutadiene **26** also gave two diastereomeric complexes **29** and **30** by undergoing Cloke–Wilson rearrangement (Scheme 11).[51]

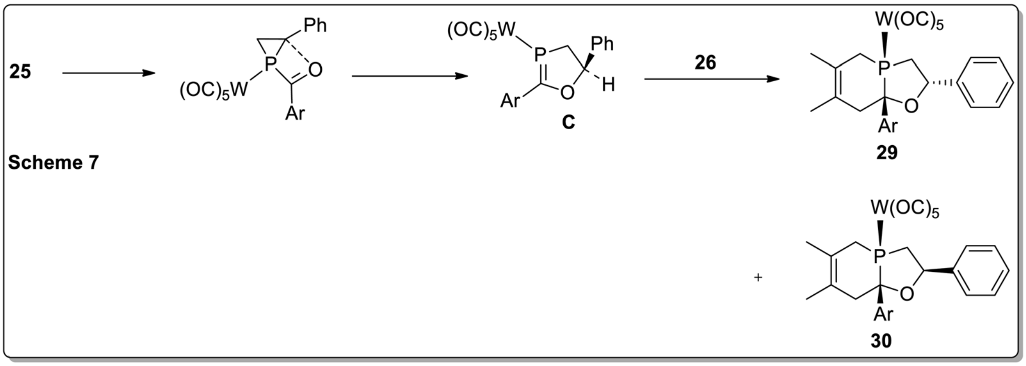
In 2020, Song and co-workers designed the synthesis of *trans*-β,γ-disubstituted-γ-butyrolactones **34** *via* an array of stereocontrolled spirocyclopropanation/Cloke–Wilson ring expansion reactions. The first step of this protocol involved the DBU-



Scheme 9 Synthesis of different complexes **27–30** *via* Cloke–Wilson rearrangement.

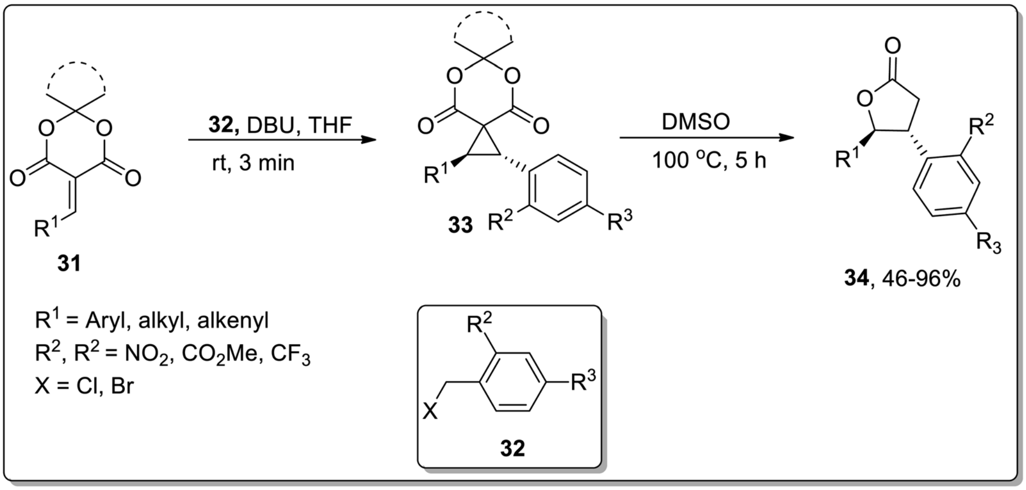


Scheme 10 Synthesis of complexes 27 and 28 *via* Cloke–Wilson rearrangement.

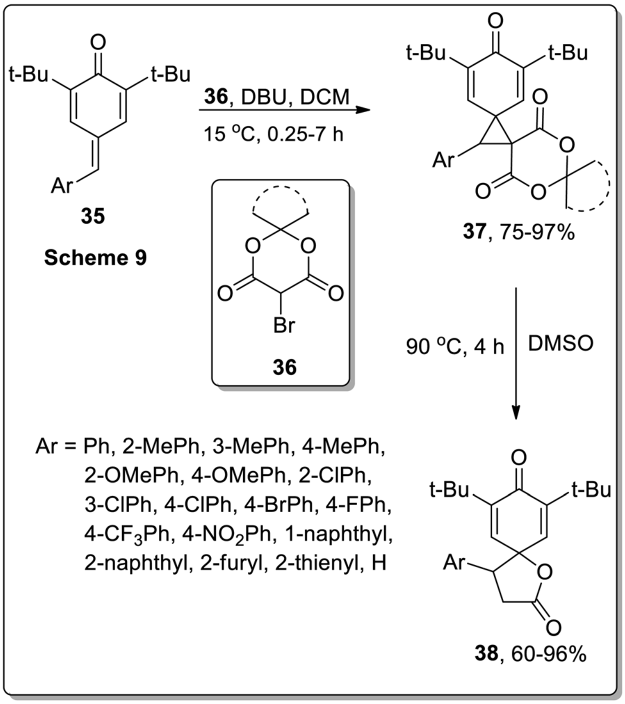


Scheme 11 Mechanism for the synthesis of complexes 29 and 30 *via* Cloke–Wilson rearrangement.

promoted stereoselective spirocyclopropanation of alkylidene meldrum's acids **31** with benzyl halides **32** at room temperature in THF to generate the transisomeric spirocyclopropyl meldrum's acids **33**, followed by DMSO-promoted stereocontrolled thermal decarboxylative Cloke–Wilson ring expansion to result in *trans*-β,γ-disubstituted-γ-butyrolactones **34** in



Scheme 12 Synthesis of substituted *trans*-β,γ-disubstituted-γ-butyrolactones **34** *via* Cloke–Wilson rearrangement.



Scheme 13 Synthesis of spirobutyrolactones **38** *via* Cloke–Wilson rearrangement.

moderate to good yields (46–96%) with excellent diastereoselectivities. These sequential reactions were tolerated by employing various aromatic and aliphatic olefins and diversely substituted benzyl halides (Scheme 12).[52]

A similar strategy was adopted by Song and co-workers to synthesize spirobutyrolactone *para*-dienones **38** *via* the thermal decarboxylative Cloke–Wilson rearrangement of dispirocyclopropanes **37**. The synthesis initiated by the spirocyclopropanation of opara-quinone methides **35** with bromo-Meldrum's acids **36**, that generated dispirocyclopropanes **37** in good yields (75–97%). The resulting dispirocyclopropanes **37** on subsequent DMSO-mediated thermal decarboxylative Cloke–Wilson rearrangement gave spirobutyrolactones **38** in moderate to good yields (60–96%). These sequential reactions were tolerated by a wide range of substrates. The applicability of these sequential reactions was then tested by gram-scale synthesis under the optimized conditions. The resulting spirobutyrolactones yields were obtained in equivalent yields to the sub-millimole-scale reactions (Scheme 13).[53]

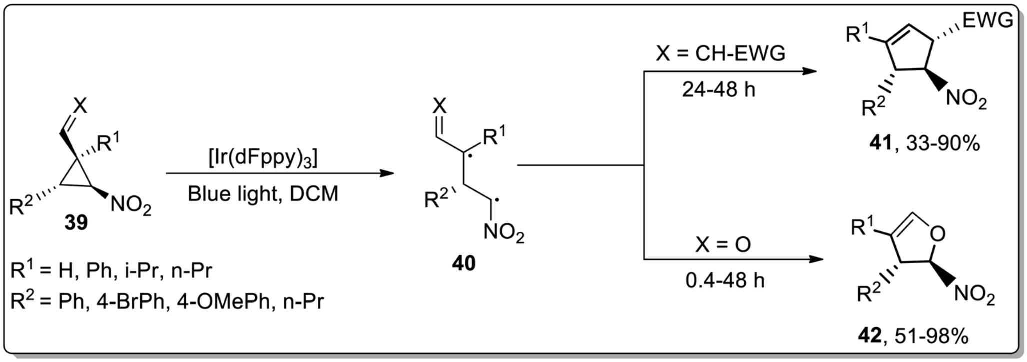
6.2. Photo-catalytic rearrangement

Owing to their applications towards the formation of unusual bonds, photocatalytic reactions have gained remarkable importance. However, these reactions had been rarely employed for the ring-expansion reactions of cyclopropanes. In 2017, Aleman and co-workers utilized a visible-light photocatalyst [Ir(dFppy)$_3$] for the synthesis of enantioenriched dihydrofurans **42** and cyclopentenes **41** *via* an intramolecular ring expansion of cyclopropane **39**. In the presence of heteroatoms such as X = O, the products were obtained as furans derivatives, while cyclopentene derivatives were obtained by treating electron-withdrawing groups bearing cyclopropanes. This methodological development is of great productivity due to the efficient synthesis of products (in good to excellent yields) with excellent enantioselectivity (Scheme 14).[42]

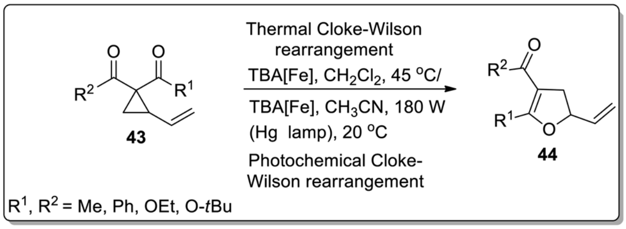
In 2015, Plietker and co-workers demonstrated a base metal complex Bu$_4$N[Fe(CO)$_3$(NO)] (TBA[Fe])-catalyzed Cloke–Wilson rearrangement of substituted cyclopropanes under both thermal and photochemical conditions. The substituted vinyl-dihydrofuans **44** were obtained in good to excellent yields from the corresponding vinyl cyclopropanes **43**. Similarly, the substituted aryldihydrofuans **46** were attained (in good to excellent yields) by reacting cyclopropanes **45** under both thermal (74–99%) and photochemical conditions (40–93%). The iron complex Bu$_4$N[Fe(CO)$_3$(NO)] (TBA[Fe]) showed good reactivity under both the conditions. This iron-catalyst Bu$_4$N[Fe(CO)$_3$(NO)] was observed to exhibit the best conversion at 415 nm (Schemes 15 and 16).[40d]

6.3. Lewis acid-catalyzed/mediated rearrangement

Lewis acids have gained undeniable significance as catalysts in various organic transformations. In 2001, Lewis acid, *i.e.*, TiCl$_4$-mediated Cloke–Wilson rearrangement leading to the synthesis of substituted dihydrofurans **48** was demonstrated by Yadav and Balamurugan in 2001. The synthesis took place by the reaction of electron-withdrawing groups bearing cyclopropanes



Scheme 14 Synthesis of dihydrofurans **41** and cyclopentenes **42** *via* Cloke–Wilson rearrangement.



Scheme 15 Synthesis of substituted vinyldihydrofuans **44** *via* Cloke–Wilson rearrangement.

47 (acceptor) and (*tert*-butyldiphenylsilyl)methyl group (donor) with $TiCl_4$ that split the C–C bond of cyclopropane to generate the substituted dihydrofurans **48** in good to excellent yields (75–96%). The cyclopropanes with two electron-withdrawing groups were transformed into dihydrofurans **48**. It was observed that use of a single ester group did not proceed to target molecule synthesis due to the inadequate activation of the ring. However, the single phenyl ketone group underwent ring activation and ring-splitting to furnish product **49**. In the product, the C–Si bond was retained for further functional group transformations (Scheme 17).[43]

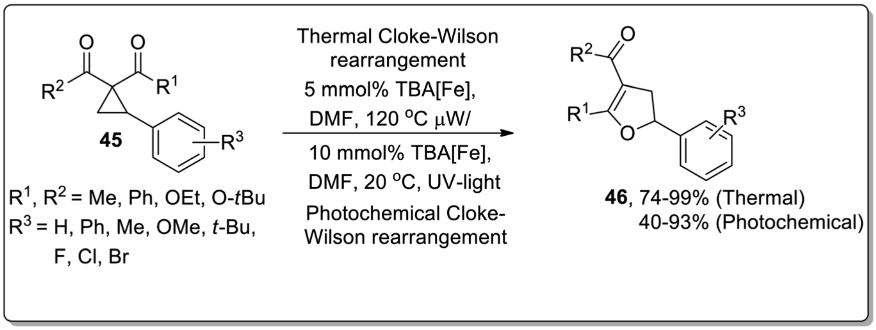
In 2005, Honda and coworkers designed the synthesis of 5-silyl-2,3-dihydrofuran derivatives **51** from cyclopropyl silyl ketones **50** *via* Lewis acid, *i.e.*, trimethylsilyl trifluoromethanesulfonate (TMSOTf)-mediated Cloke–Wilson ring-expansion reaction. The resulting 5-silyl-2,3-dihydrofuran derivatives **51** possess dual active functionalities (cyclic enol ether and vinylsilane) for use in different organic reactions that involve treatment with electrophilic substrates and Heck reaction. 5-Silyl-2,3-dihydrofuran derivatives **51** were obtained in more than 99% yield (maximum yield) by employing phenyl-substituted cyclopropyl silyl ketones **50** (Scheme 18).[54]

In 2007, Zhang and coworkers carried out the synthesis of furoquinoline derivatives **55** from highly-activated cyclopropanes **52**, in which the dihydrofuran moiety was attained by the Lewis acid, *i.e.*, $SnCl_4$-mediated Cloke–Wilson ring-expansion of cyclopropyl ketone. The synthesis initiated with the ring opening, followed by its conversion to a new fused ring, that resulted in intermediate **54**; then, subsequent Combes-type annulation with the elimination of water furnished the furoquinoline derivatives **55**. Easily accessible reagents, broad substrate scope, high chemoselectivity and regioselectivity are the key features of this synthetic strategy (Scheme 19).[55]

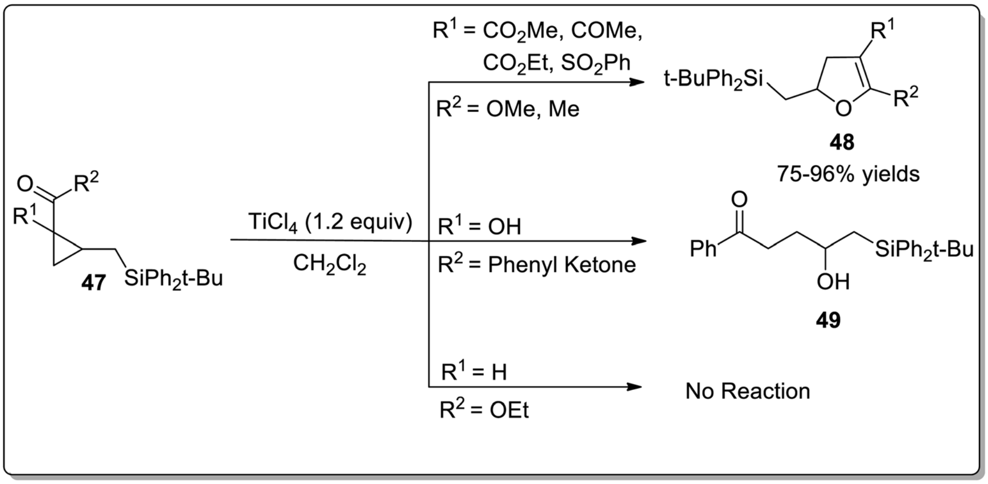
In 2007, Zhang and co-workers designed the synthesis of γ-lactams **59**, γ-iminolactones **60**, and dihydroquinolin-2-ones **61** from β-hydroxymethylcyclopropanylamides **56**. β-Hydroxymethylcyclopropanylamides **56** underwent boron trifluoride diethyl etherate-mediated intramolecular Friedel–Crafts alkylation to produce dihydroquinolin-2-one **59** in 50–83% yields. On the other side, the Lewis acid, *i.e.*, $SnCl_4$/NaI or $TiCl_4$-catalyzed reaction generated intermediate **58** *via* ring opening, which furnished γ-lactams **60** or γ-iminolactones **61** by the employment of either an intramolecular *N*-annulation or *O*-annulation. Bulky groups such as aryl group-bearing reagents preferably proceeded *via O*-annulation, while relatively small groups like methyl, benzyl, and *n*-propyl moved forward by *N*-annulation. Furthermore, *N*-annulation was carried out with great efficacy (even without sodium iodide) due to the more nucleophilic tendency of nitrogen in comparison to oxygen (Scheme 20).[56]

In 2009, Werz and co-workers demonstrated the synthesis of [*n*,5]-spiroketals ($n = 5, 6$) **65** from exocyclic enol ethers **62** by a three-step methodology: Cu-mediated cyclopropanation of exocyclic enol ethers **62** to spiroannelated cyclopropanes formation (bearing an ester group), the reduction of an ester group with $LiAlH_4$ generated respective alcohols **63**, subsequent IBX-oxidation of hydroxyl functionality along with the Lewis acid $Yb(OTf)_3$-catalyzed Cloke–Wilson rearrangement of cyclopropyl ketone moiety **64** afforded [*n*,5]-spiroketals **65**. The product investigation unveiled the instability of the configuration of the spirocenter, synthesized by utilizing only IBX or IBX/$Yb(OTf)_3$-mediated ring expansion. During this transformation, the thermodynamically more stable spiroketal is favored. These results indicated that this reaction did not proceed through a concerted mechanism, while the main reaction pathway was supposed to advance forward through a zwitterionic intermediate formation, which would permit the erosion of stereochemistry at the spirocenter. On the other hand, the use of Dess–Martin periodinane (DMP) preserved the stereochemistry at the spirocenter (Scheme 21).[57]

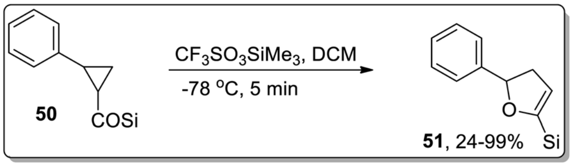
The Lewis acid, *i.e.*, TMSOTf-mediated isomerization of cyclopropanes such as 2-arylcyclopropane-1,1-dicarboxylates **66** was reported by Melnikov and coworkers in 2010. The Lewis-acid promoted ring opening gave rise to three varied



Scheme 16 Synthesis of substituted aryldihydrofuans **46** *via* Cloke–Wilson rearrangement.



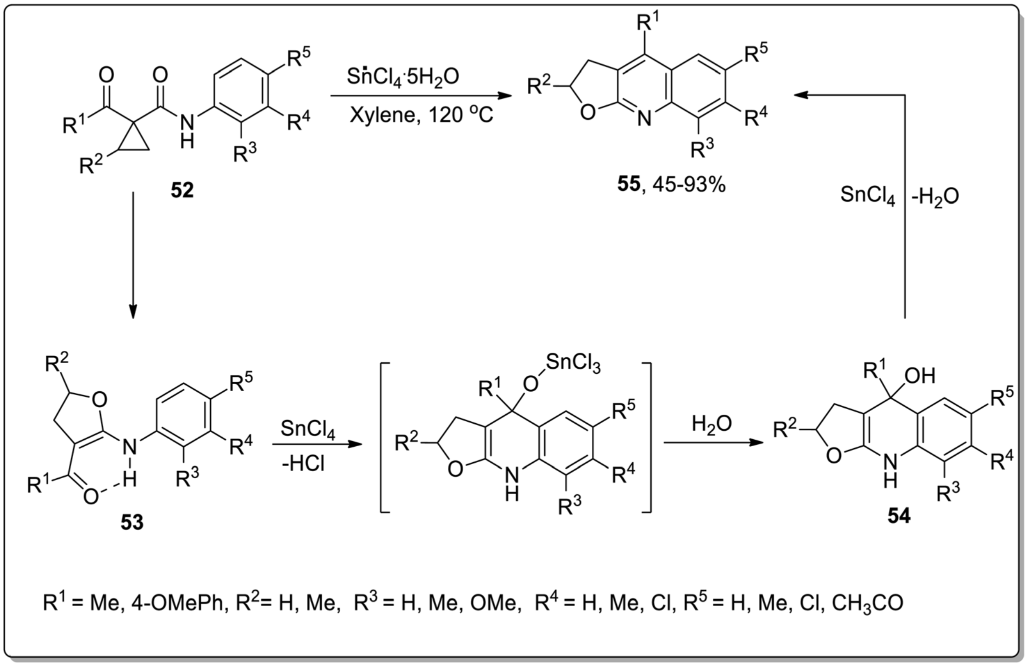
Scheme 17 Synthesis of substituted dihydrofurans **48** *via* Cloke–Wilson rearrangement.



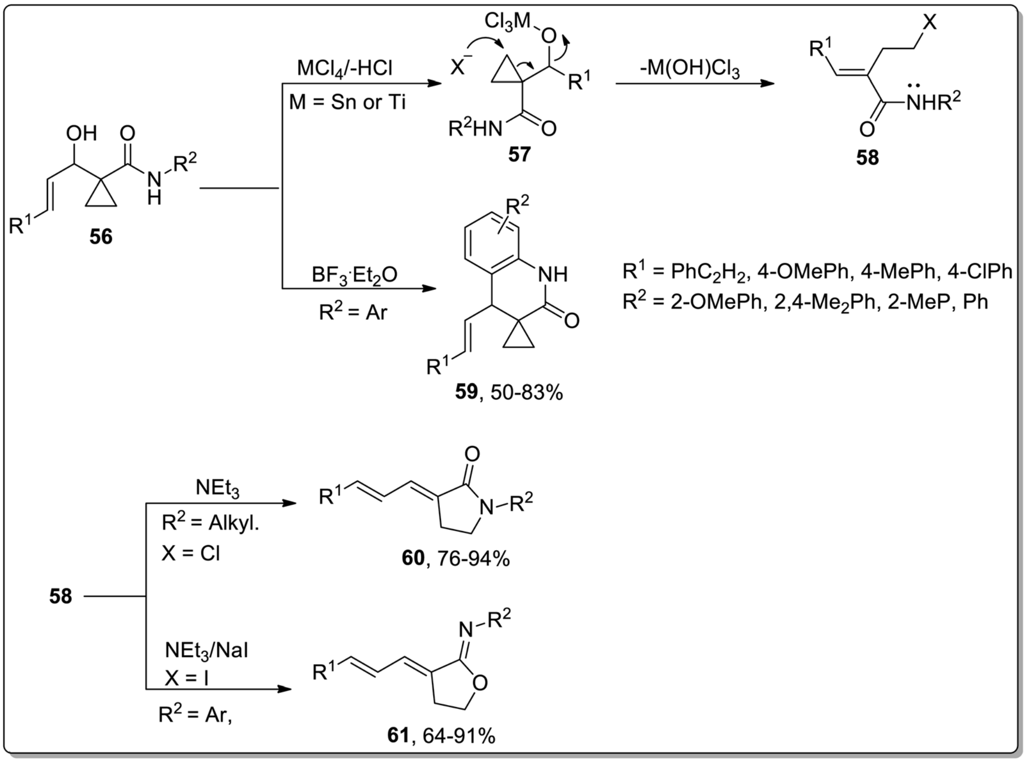
Scheme 18 Synthesis of 5-silyl-2,3-dihydrofuran derivatives **51** *via* Cloke–Wilson rearrangement.

products, *i.e.*, *E*-styrylmalonates **67**, substituted chloropropane **68**, and γ-butyrolactone **69**. Boron trifluoride diethyl etherate-mediated ring expansion resulted in the synthesis of γ-butyrolactone **69** in 78% yield in the presence of phenyl chloride. Meanwhile, 81% yield of γ-butyrolactone **69** was achieved using $SnCl_4$ and dichloromethane; however, $Sn(OTf)_2/CH_3NO_2$-promoted isomerization led to 77% yield of **69**. Cyclopropane **66** resulted in dihydrofuran formation *via* Cloke–Wilson rearrangement, which was subsequently subjected to acetal hydrolysis to afford γ-butyrolactone **69** in 23–78% yields (Scheme 22).[58]

In 2011, Davies and co-workers reported the synthesis of polycyclic benzo-fused dihydrofurans **74** by three sequential rhodium, silver, and gold-catalyzed reactions. The cascade reactions commenced with the generation of cyclopropyl ketones **72** (in fair to excellent yields) by treating alkenes **71** and diazoketones **70** in the presence of rhodium catalyst. The



Scheme 19 Synthesis of furoquinoline derivatives **55** *via* Cloke–Wilson rearrangement.

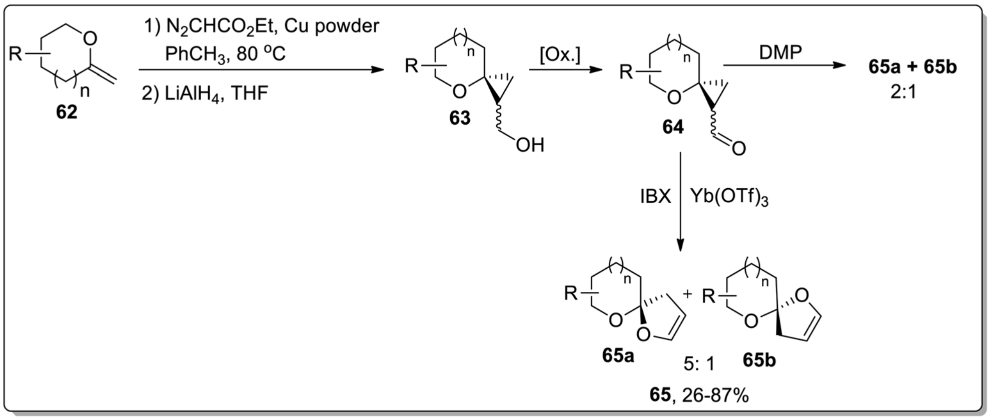


Scheme 20 Synthesis of γ-lactams **59**, γ-iminolactones **60**, and dihydroquinolin-2-ones **61** *via* Cloke–Wilson rearrangement.

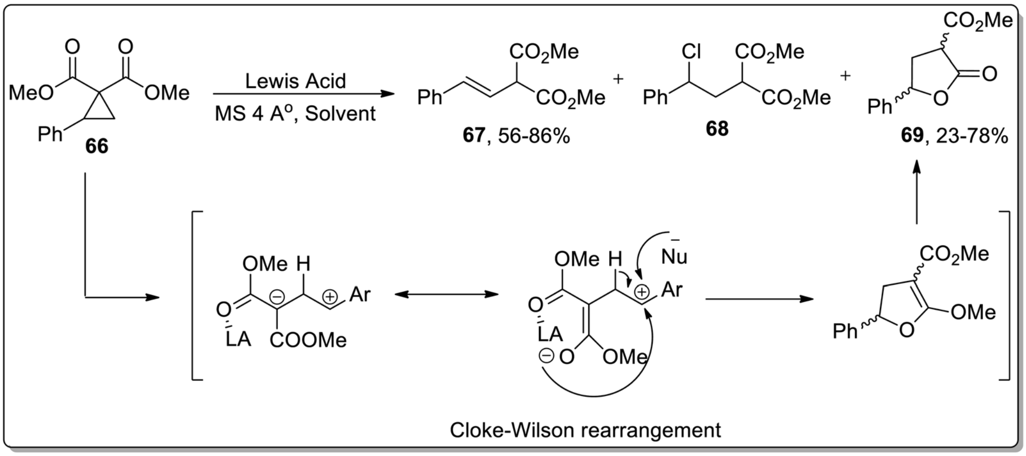
sequential AgOTf-catalyzed ring-expansion of cyclopropyl ketones **72** resulted in the formation of dihydrofurans **73**, followed by Au-catalyzed benzannulation to achieve benzo-fused dihydrofurans **74** in low to excellent yield range (21–99%). For these cascade reactions, a one-pot strategy was also implemented, which involved dichloromethane-involving Rh-catalyzed cyclopropanation. After bringing the solution to room temperature, silver and gold catalysts were then added along with toluene. This one-pot protocol furnished polycyclic benzo-fused dihydrofurans **74** in good yields (Scheme 23).[59]

In 2013, Corey and colleagues demonstrated the synthesis of bislactones **80–81** and ketolactones **82–84** in 61–86% (moderate to good yields) *via* Lewis acid, *i.e.*, TMSOTf-mediated Cloke–Wilson rearrangement of cyclopropyl esters. The donor–acceptor cyclopropanes **75–79** were treated with TMSOTf in aqueous conditions using 2-nitropropane as the solvent within the temperature range of 23–110 °C. The TMSOTf-promoted cleavage of cyclopropane ring was followed by oxygen atom integration to the ester functionality, which ultimately generated the lactones (**80–84**) after subsequent hydrolysis (Scheme 24a and b).[60]

In 2016, Katukojvala and coworkers designed the substituted 2,3-dihydronaphthofurans **86**, employing silver (Ag)-promoted intramolecular transannulation of ((2-alkynyl)aryl)cyclopropyl ketones **85**. This transformation proceeded with the hydration of the alkyne, followed by the regioselective ring-expansion of



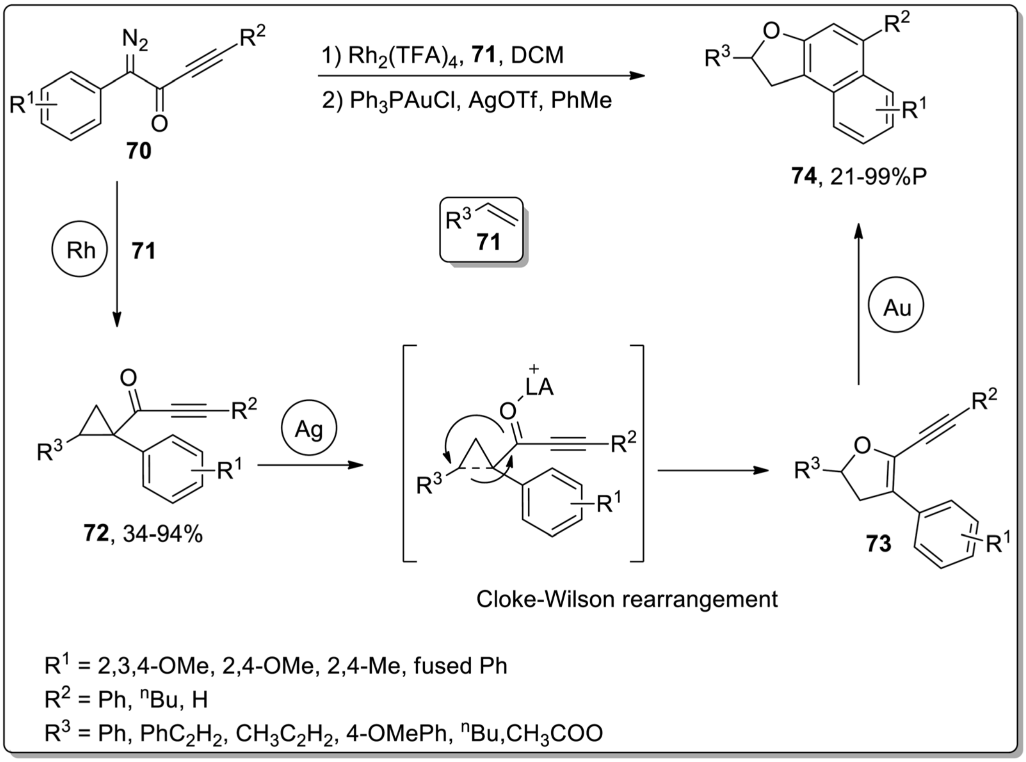
Scheme 21 Synthesis of [*n*,5]-spiroketals (*n* = 5, 6) **65** *via* Cloke–Wilson rearrangement.



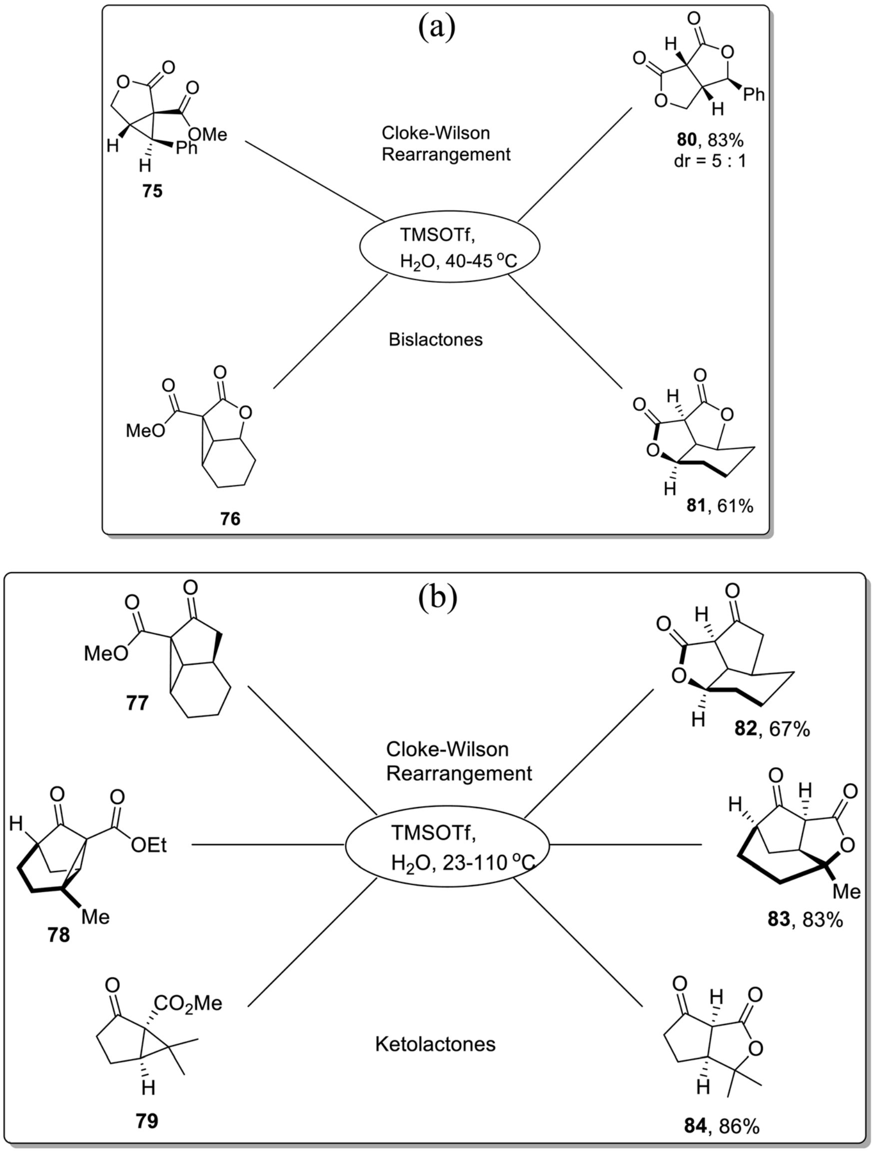
Scheme 22 Synthesis of *E*-styrylmalonates **67**, substituted chloropropane **68**, and γ-butyrolactone **69** *via* Cloke–Wilson rearrangement.

cyclopropyl ketone to yield substituted benzofuran heterocycles **B** *via* Cloke–Wilson rearrangement, and finally benzannulation took place to yield the target molecules **86.** AgOTf (as an efficient Lewis acid) enhanced the −ve inductive effect of carbonyl group and thus carried out the conversion of cyclopropyl ketone into the dihydrofuran skeleton. This transformation could not proceed with terminal alkynes. This is a direct way to synthesize the tricyclic core structures, which are biologically important scaffolds and are main constituents of various natural products (Scheme 25).[61]

In 2017, Wang and co-workers employed Cloke–Wilson rearrangement to synthesize 4-cyanofuran-3-carboxylate derivatives **88** by subjecting 1-cyanocyclopropane-1-carboxylates **87** to iodine and potassium carbonate-promoted ring cleavage, followed by cyclization and subsequent rearrangement. In this transformation, iodine behaved as a Lewis acid and enhanced the electrophilic character of the carbonyl group, thereby generating an iodine–carbonyl complex **A.** Then, the base-mediated opening of ring, followed by tautomerization, gave intermediate **B.** Later on, intermediate **B** was treated with phenylmethylium ion *via* intramolecular nucleophilic coupling to afford intermediate **C**, which upon further intramolecular nucleophilic addition, iodination, tautomerism, and elimination of HI resulted in 4-cyanofuran-3-carboxylate derivatives **89.**



Scheme 23 Synthesis of benzo-fused dihydrofurans **74** *via* Cloke–Wilson rearrangement.

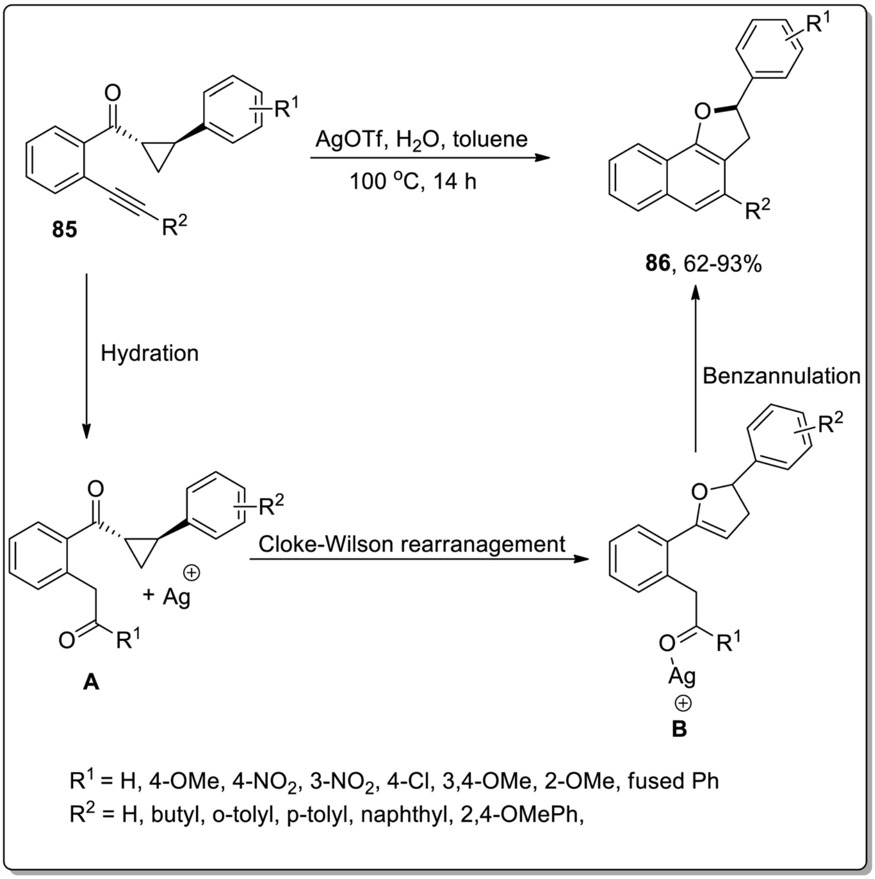


Scheme 24 (a) Synthesis of bislactones **80–81** *via* Cloke–Wilson rearrangement. (b) Synthesis of ketolactones **82–84** *via* Cloke–Wilson rearrangement.

This protocol can be immensely employed for the synthesis of diverse organic compounds owing to easily accessible starting reagents and high yields of target molecules. Moreover, various medicinally important polysubstituted furancarboxylates are envisioned to be synthesized utilizing this protocol (Scheme 26).[62]

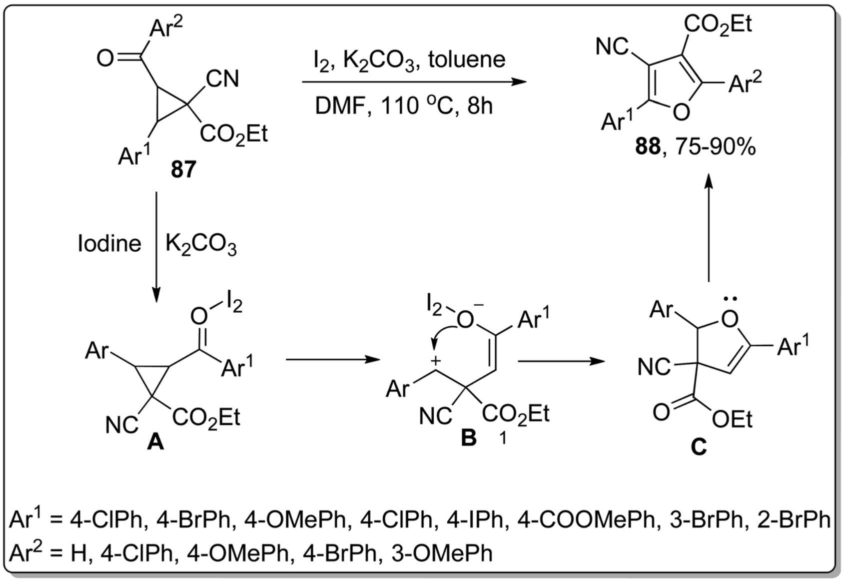
In 2019, Song *et al.* demonstrated the DBU-mediated stereospecific expansion of spirocyclopropyl compounds to synthesize spirobarbiturate-cyclopropanes **92** obtained by treating barbiturate-based olefins **90** with substituted benzyl chlorides **91** at room temperature in tetrahydrofuran. As a result, moderate to high yields (45–95%) of spirobarbiturate-based cyclopropanes **92** were afforded with remarkable diastereoselectivity ratio (dr > 20 : 1). The next step involved the procurement of dihydrofuran-based pyrimidinedione frameworks **93** in 99% yield *via* $AlCl_3$-mediated Cloke–Wilson rearrangement. This synthetic protocol proceeded with the retention of anti-configuration, entailing a wide substrate scope, thereby providing a series of diversely-substituted target molecules (Scheme 27).[63]

Another Lewis acid, *i.e.*, $AlCl_3$-mediated Cloke–Wilson rearrangement, was established by Song and coworkers (in 2019) to generate substituted 5,6-dihydrofuro[2,3-*d*]pyrimidines **94** from spirocyclopropyl barbiturates **93**. A wide range of diversely-substituted spirocyclopropanes were endured by treating them at room temperature. The efficiency of the reaction was observed to be unaltered due to the electronic properties and place of attachment of various substituents on the phenyl ring. In consequence, 69–98% (good to excellent yields) of furan-based pyrimidines **94** were achieved with the retention of *anti*-configuration (Scheme 28).[64]

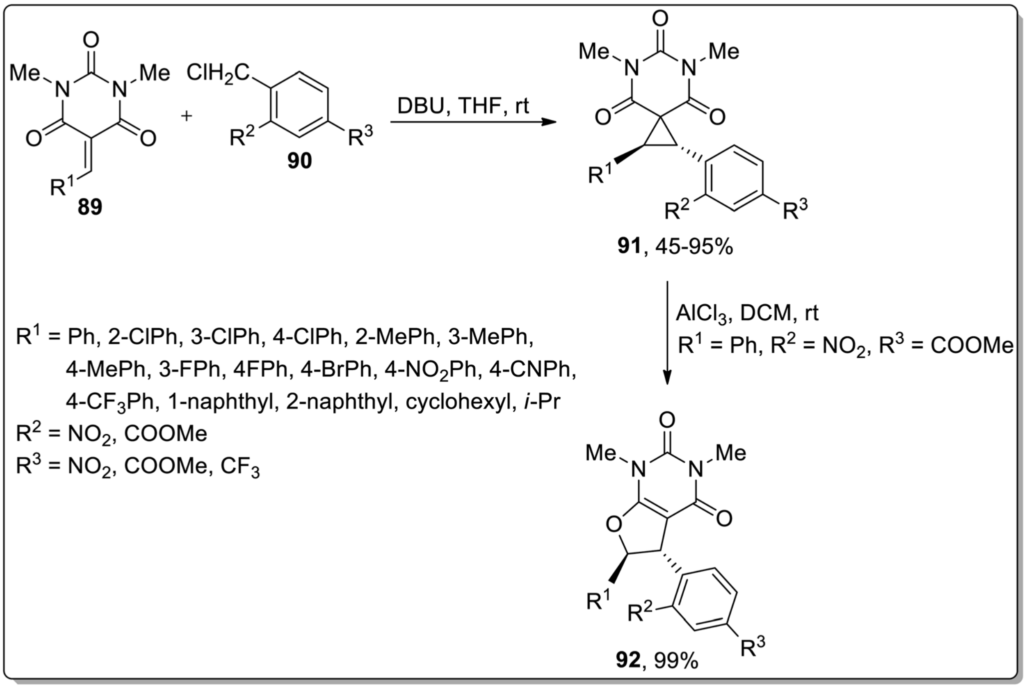


Scheme 25 Synthesis of substituted 2,3-dihydronaphthofurans **86** *via* Cloke–Wilson rearrangement.

In 2020, Namboothiri and colleagues illustrated the synthesis of fused furans **97** from alkylidenecycloalkanones **95** by utilizing cyclopropanation reaction and Cloke–Wilson rearrangement in their sequential two-step methodology. Initially, substituted alkylidenecycloalkanones were made to react *via* diastereoselective dibromocyclopropanation using magnesium and tribromomethane in THF at room temperature to synthesize dibromocyclopropyl ketones **96.** Cyclopropyl ketone **96** was further subjected to acidic Al_2O_3-mediated regioselective ring expansion by Cloke–Wilson rearrangement reaction by



Scheme 26 Synthesis of 4-cyanofuran-3-carboxylate derivatives **88** *via* Cloke–Wilson rearrangement.

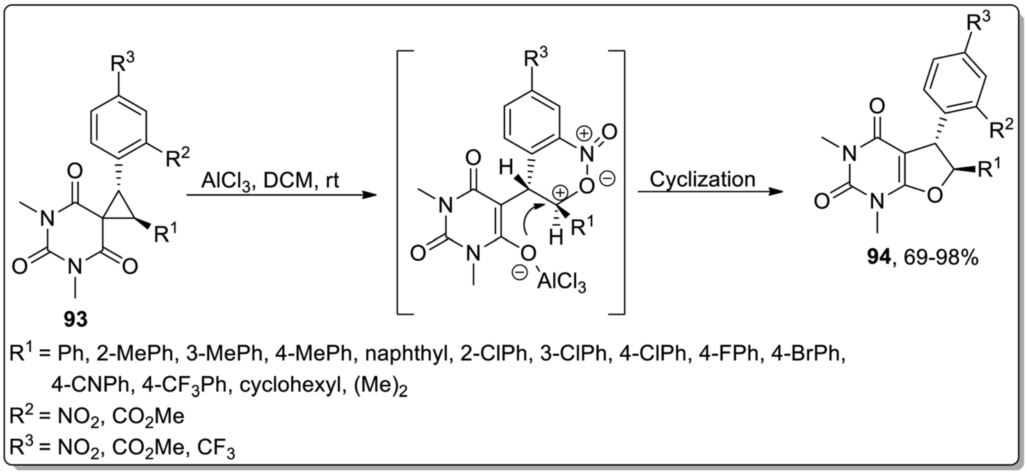


Scheme 27 Synthesis of spirobarbiturate-cyclopropanes **92** *via* Cloke–Wilson rearrangement.

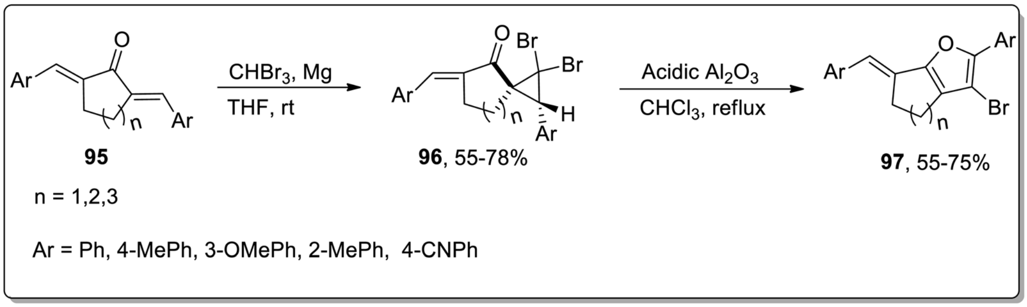
refluxing in chloroform. The regioselective fused furan derivatives **97** were furnished in 55–75% yields. Various alkylidenecycloalkanones derived from tetralone, indanone, and benzosuberone were subjected to the optimal conditions that produced 2-aryl-3-bromofurans in good yields, validating the wide substrate tolerant nature of this protocol (Scheme 29).[65]

6.4. Brønsted acid-catalyzed/mediated rearrangement

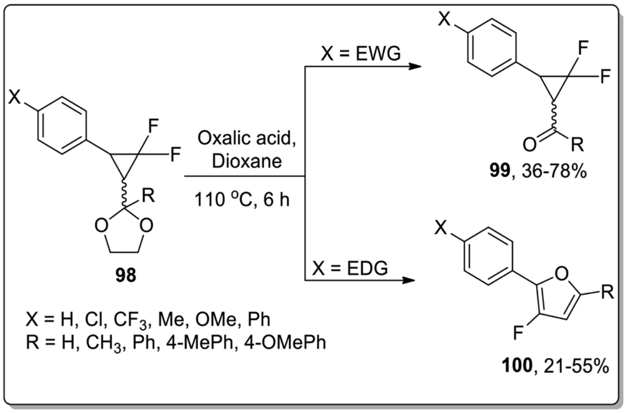
Since the advent of the 21st century, Brønsted acids have been efficiently employed as catalysts to synthesize numerous organic compounds.[66a] In 2003, Chen and Xu reported the synthesis of substituted cyclopropyl ketones **99** and substituted fluorofurans **100** from *gem*-difluorocyclopropyl acetals and ketals **98**, which were obtained by the [1 + 2] cycloaddition of difluorocarbene and α,β-unsaturated aromatic aldehydes and ketones. These fluorinated scaffolds **98** were further subjected to acidic hydrolysis to give fluorofuran derivatives **100** *via* Brønsted acid-mediated intramolecular Cloke–Wilson ring rearrangement. However, the electron withdrawing-substituted compounds furnished substituted cyclopropyl ketones **99**. The product ratio was observed to be dependent on the electronic properties of the substituent on the β-phenyl ring, *i.e.*, the electron-donating groups bearing reagents resulted in the synthesis of furan derivatives **100** *via* Cloke–Wilson rearrangement, while electron-withdrawing groups-bearing compounds gave normal ketones **99** (Scheme 30).[66b]



Scheme 28 Synthesis of substituted 5,6-dihydrofuro[2,3-*d*]pyrimidines **94** *via* Cloke–Wilson rearrangement.



Scheme 29 Synthesis of furan derivatives **97** *via* Cloke–Wilson rearrangement.



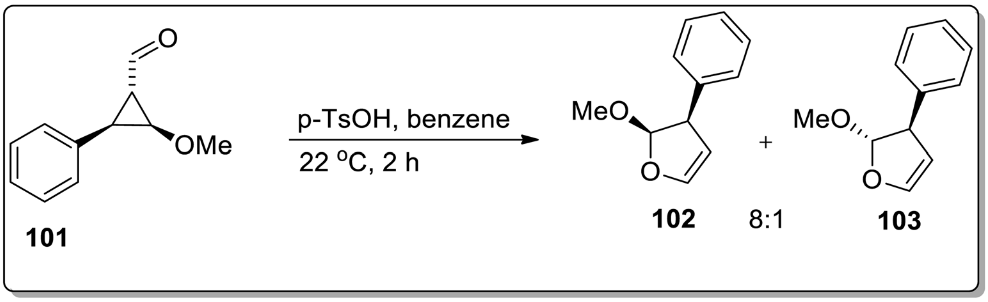
Scheme 30 Synthesis of fluorofuran derivatives **100** *via* Cloke–Wilson rearrangement.

Another Brønsted-acid mediated Cloke–Wilson rearrangement was processed by Baines and co-workers, which resulted in the diastereoselective synthesis of 2-methoxy-3-phenyl-2,3-dihydrofurans **102** and **103**. For this purpose, *trans*-2-methoxy-3-phenylcyclopropane carbaldehyde **101** was subjected to Cloke–Wilson rearrangement in *p*-toluenesulfonic acid and benzene. This transformation afforded a 8 : 1 *cis* and *trans* mixture of methoxy-3-phenyl-2,3-dihydrofuran **102** and **103** (Scheme 31).[67]

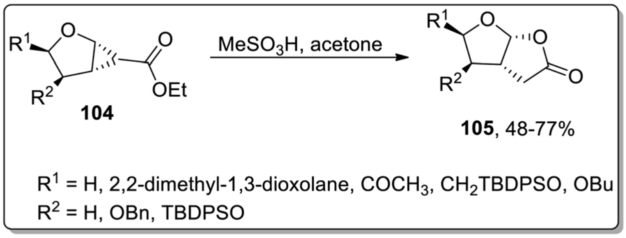
In 2004, Theodorakis and co-workers reported another Brønsted acid, *i.e.*, methanesulfonic acid-catalyzed Cloke–Wilson rearrangement, which led to the synthesis of fused tetrahydrofuran-γ-lactone **105**. This protocol involved the one-pot ring extension of cyclopropanes **104** using acetone as the solvent, which yielded required the bicyclic compounds in moderate to good yields. However, no product formation was observed employing the sp^2 hybridized α-carbon atom bearing cyclopropyl ring as the precursor (Scheme 32).[68]

In 2005, Piras and coworkers designed the synthesis of 2,4,5-tri-substituted 2,3-dihydrofurans **109** and cyclopropyl sulfones **108.** Initially, the reaction of enone **106** with Corey ylide gave cyclopropylsulfides **107**, which upon oxidation with MCPBA (*meta*-chloroperoxybenzoic acid) resulted in the generation of either cyclopropyl sulfones **109** or 2,4,5-tri-substituted 2,3-dihydrofurans **108**. In the formation of 2,3-dihydrofurans, MCPBA has been observed to play the role of an oxidant as well as Brønsted acid, thereby facilitating ring opening and closure. The formation of target molecules was interpreted to be dependent upon the nature of the attached substituents. The cyclopropyl ring with only strong electron-donating substituents favored the formation of 2,4,5-tri-substituted 2,3-dihydrofurans **108** (Scheme 33). Similarly, under the mild reaction conditions (using PTSA in benzene at room temperature), Cloke–Wilson rearrangement of cyclopropyl sulfone **109** furnished 2,3-dihydrofurans **110** (Scheme 33).[69]

In 2006, angular dihydrofuroquinoline derivatives **112** were obtained by subjecting 1-(phenylcarbamoyl)cyclopropane-1-carboxylic acid derivatives **111** to Cloke–Wilson ring-enlargement of cyclopropyl ketone by Su *et al.* In this transformation, phosphoric acid protonated the carbonyl oxygen regioselectively, which facilitated quinolinone ring formation by intramolecular Friedel–Crafts reaction. The synthesis of the furan ring is highly affected by the altered electron density on the involved intermediate. This one-step procedure gave access



Scheme 31 Synthesis of methoxy-3-phenyl-2,3-dihydrofuran **102** and **103** *via* Cloke–Wilson rearrangement.



Scheme 32 Synthesis of fused tetrahydrofuran-γ-lactone **105** *via* Cloke–Wilson rearrangement.

to angular dihydrofuroquinoline derivatives **112** in moderate yields (Scheme 34).[70]

In 2008, Dong *et al.* designed the synthesis of substituted 2,3-dihydrofurans **114** *via* ammonium acetate-mediated Cloke–Wilson ring-enlargement of activated cyclopropanes **113.** This transformation commenced with the N-protonation and H-bonding interaction of ammonium acetate to intermediate **A** formation, which later on gave rise to intermediate **B** by employing oxa-Michael addition and elimination reaction; finally, upon regioselective ring-enlargement, 2,3-dihydrofurans **114** were attained in good yields. These substituted dihydrofurans **114** were then made to undergo an intramolecular annulation reaction to produce the corresponding 5-aryl-2,3-dihydrofuro[3,2-*c*]pyridin-4(5*H*)-ones in efficient yields (Scheme 35).[71]

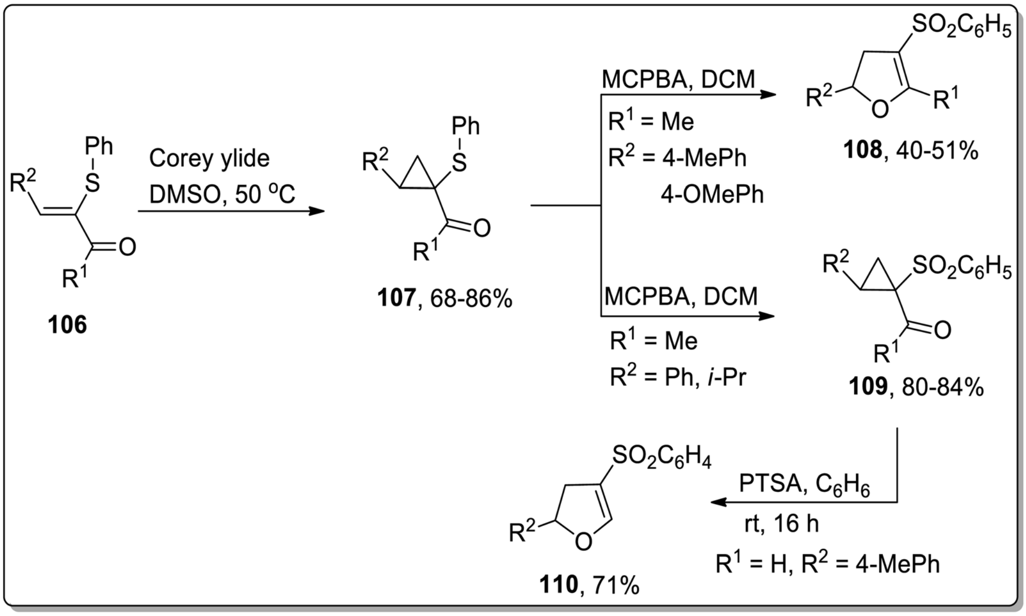
In 2011, Liang and co-workers designed the carboxylic acid-catalyzed synthesis of dihydrofuropyridinones **116** and 3(2*H*)-furanones **117** from 1-alkenoylcyclopropane carboxamides **115** by halonium-initiated tandem reaction. The synthesis initiated with the formation of halonium ion intermediate **A**, which either followed an intramolecular oxa-cyclization (Path a), deprotonation, 1,2-migration, β-hydride elimination, cyclopropane ring opening, and recyclization to produce dihydrofuropyridinones **116** or halo-oxa-cyclization (Path b), cyclopropyl ring opening, and retro-aldol reaction to afford 3(2*H*)-furanones **117**. These products were produced in efficient yields with high chemo- and regioselectivity, and the substituent appended on the enone framework decided the type of the resulting product. The groups with positive inductive effect resulted in dihydrofuropyridinones **116** while 3(2*H*)-furanones **117** were generated by groups with negative inductive effect (Scheme 36).[72]

In 2013, Werz and co-workers designed the synthesis of *N*,*O*-bisacetals **121** from the corresponding pyrrolidine substrate **120** (prepared by treating *N*-Boc protected pyrroles **118** with functionalized imines **119**) *via* Cloke–Wilson rearrangement reaction. The rearrangement was proceeded in the presence of *p*-TsOH (Brønsted-acid catalyst) in THF at 80 °C in fair to efficient yields by substituting R^1 as methyl or phenyl. However, as a result of substituting R^1 as H, the cyclopropane ring-opening and rapid aromatization took place to produce pyrroles **122** in good to excellent yields (Scheme 37).[73]

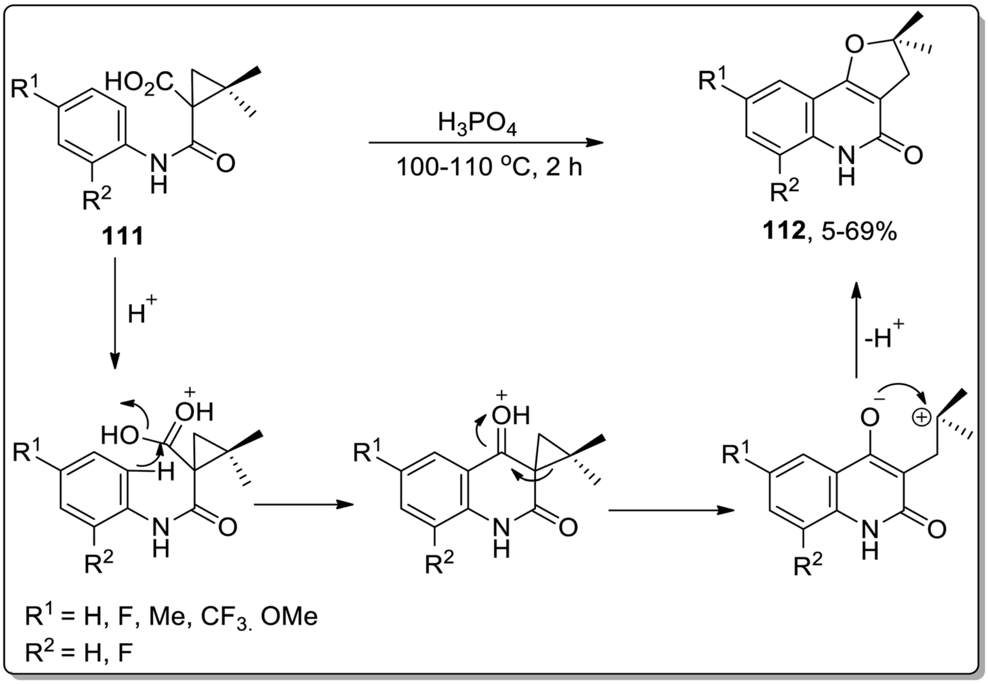
In 2020, Banerjee and coworkers designed the metal-free synthesis of oxybis(2-aryltetrahydrofuran) derivatives **125** from cyclopropane carbaldehydes **123** by a facile three-steps methodology: the Cloke–Wilson rearrangement, which gave **124** intermediate, followed by hydration and finally dimerization. This transformation was accomplished by exploiting inexpensive Brønsted acid-catalyst (PTSA) in an open environment (Scheme 38).[74]

6.5. Brønsted base-mediated rearrangement

In 2012, Dong and coworkers carried out the synthesis of dihydrofuran-based pyridinones **127** by treating functionalized cyclopropanes **126** in the presence of triflic anhydride (Tf$_2$O) in



Scheme 33 Synthesis of 2,3-dihydrofurans **110** and cyclopropyl sulfones **108** *via* Cloke–Wilson rearrangement.

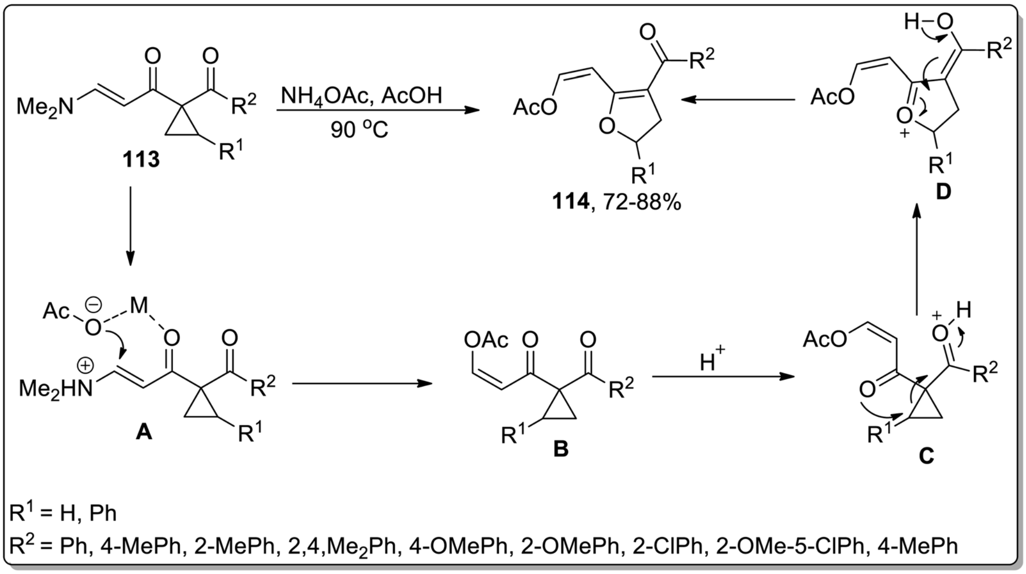


Scheme 34 Synthesis of dihydrofuroquinoline derivatives **112** *via* Cloke–Wilson rearrangement.

dimethylformamide. This reaction commenced from the activation of DMF with TfO_2 to produce Vilsmeier-type reagent that formylated (Vilsmeier-type reaction) substrate **126** to produce iminium salt intermediate **A,** followed by intramolecular cyclization to generate intermediate **B,** which further underwent an intramolecular Cloke–Wilson ring extension promoted by trifluoromethanesulfonate anion (TfO^-) to produce iminium intermediate **C**, which upon treatment with water finally gave target molecules **127** in good to excellent yields (Scheme 39).[75]

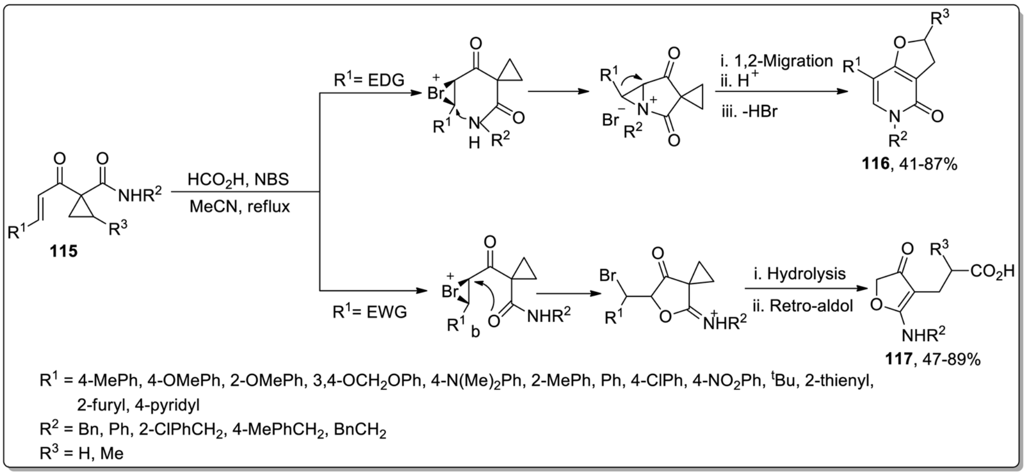
6.6. Transition metals-catalyzed rearrangement

Considering the wide-utilization of catalytic property of transition metals in organic synthesis,[76a–c] Cloke–Wilson rearrangement has also been observed to be carried out employing various transition metals-based catalysts. Palladium-based catalysts are widely employed in numerous organic reactions.[77] In 2003 and 2004, Ma and Zhang reported the synthesis of tetra-substituted furans **130** and polysubstituted 4*H*-pyrans **131** by the isomerization of alkylidene cyclopropyl ketones **129.**

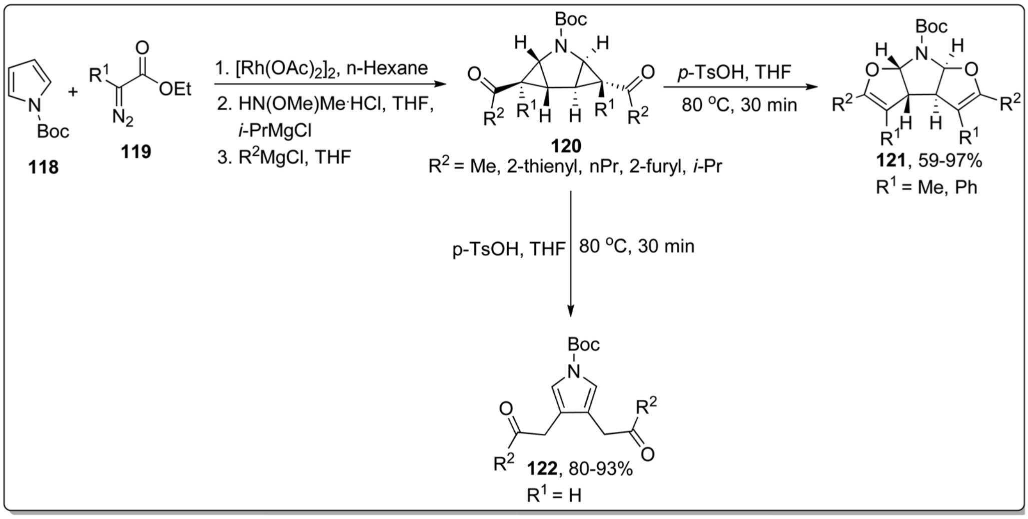


R1 = H, Ph
R2 = Ph, 4-MePh, 2-MePh, 2,4,Me2Ph, 4-OMePh, 2-OMePh, 2-ClPh, 2-OMe-5-ClPh, 4-MePh

Scheme 35 Synthesis of substituted dihydrofurans **114** *via* Cloke–Wilson rearrangement.



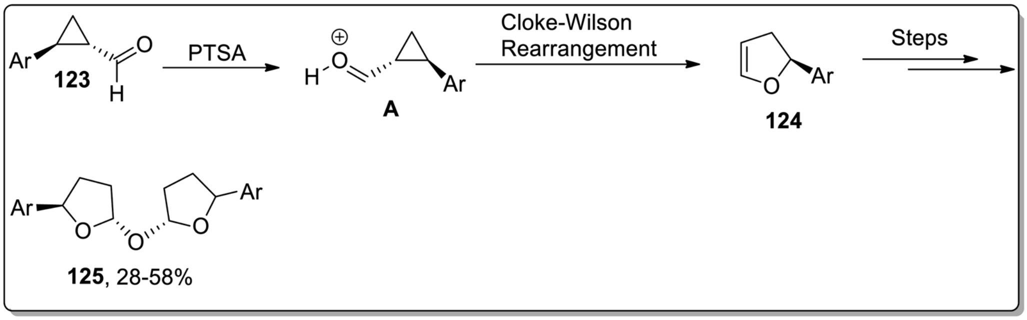
Scheme 36 Synthesis of dihydrofuropyridinones **116** and 3(2*H*)-furanones **117** *via* Cloke–Wilson rearrangement.



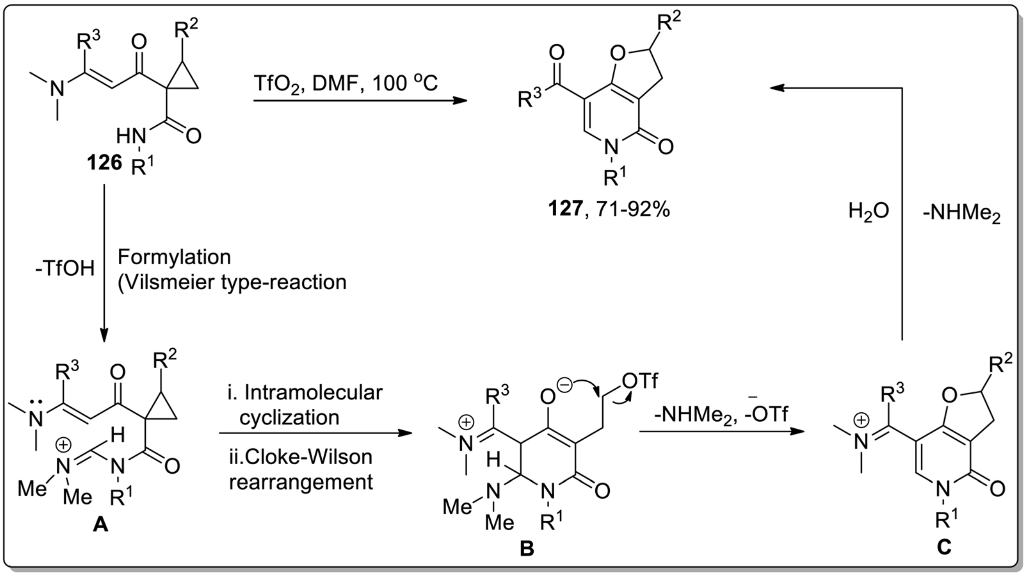
Scheme 37 Synthesis of *N*,*O*-bisacetals **121** and pyrroles **122** *via* Cloke–Wilson rearrangement.

The Cloke–Wilson rearrangement of substituted cyclopropane **129** in the presence of $PdCl_2(MeCN)_2$ yielded the tetra-substituted furans **130.** Meanwhile, 4*H*-pyrans **131** were obtained by carrying out regioselective chloropalladation of alkylidene with $PdCl_2$, followed by β-decarbopalladation, and an intramolecular insertion of double bond with the elimination of $PdCl_2$ (Scheme 40).[41b]

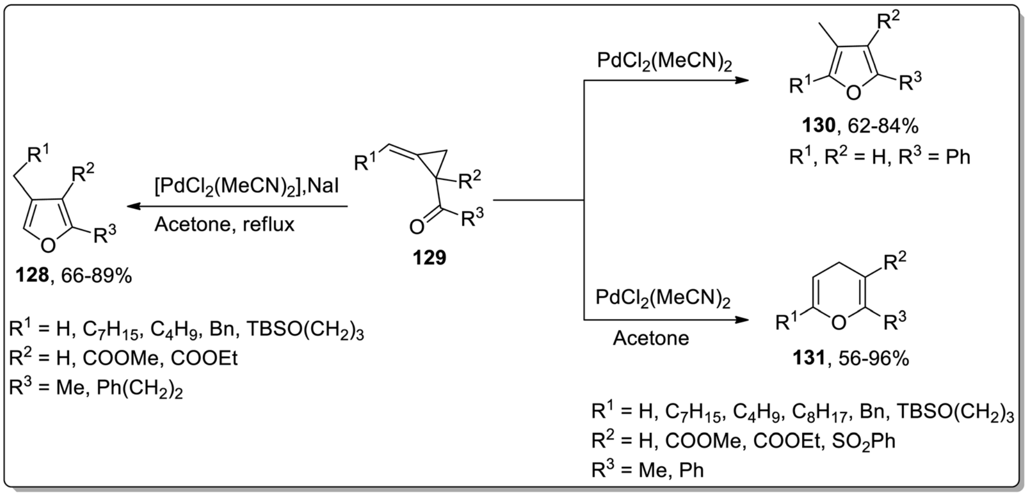
In 2006, Bowman and Johnson reported the Ni-catalyzed Cloke–Wilson ring enlargement of vinyl cyclopropyl ketones **132** to accomplish the synthesis of substituted dihydrofurans **133** in



Scheme 38 Synthesis of oxybis(2-aryltetrahydrofuran) derivatives **125** *via* Cloke–Wilson rearrangement.



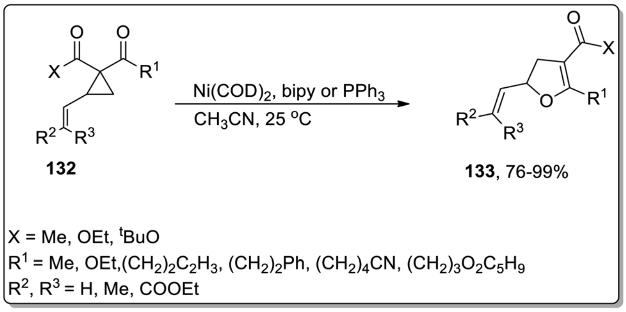
Scheme 39 Synthesis of dihydrofuran-based pyridinones **127** *via* Cloke–Wilson rearrangement.



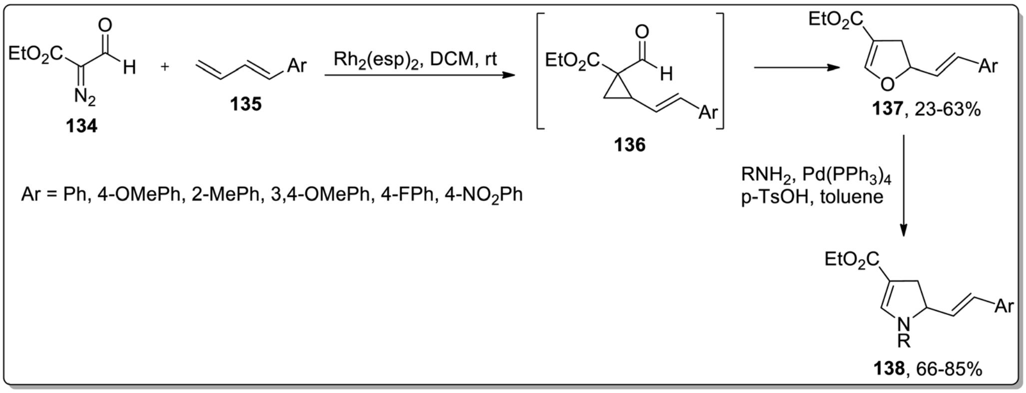
Scheme 40 Synthesis of tetra-substituted furans **130** and polysubstituted 4*H*-pyrans **131** *via* Cloke–Wilson rearrangement.

acetonitrile. The substituted dihydrofurans **133** were obtained in good to excellent yields. In order to ensure the chirality transfer, enantioenriched substituted dihydrofurans were synthesized in excellent yield by keeping the original configuration intact at the vinyl-substituted chiral center. This novel methodology is useful due to low catalyst loading and short reaction time along with various functional groups tolerance (Scheme 41).[7a]

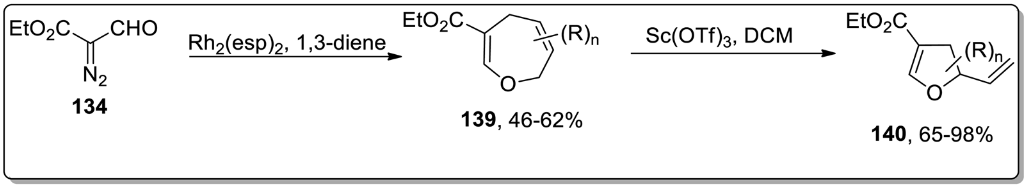
In 2018, Piotrowski and Kerr reported the rhodium-mediated cyclopropanation of 1,3-dienes **135** with ethyl 2-formyldiazoacetate **134**, which was proceeded further *via* Cloke–Wilson rearrangement to give dihydrofurans **137** or dihydrooxepines **138**. The Rh-catalyzed cascade cyclopropanation and Cloke–Wilson rearrangement of aryl-substituted butadienes **135** with ethyl 2-formyldiazoacetate **134** gave dihydrofurans **137** in moderate yields, while the dihydrooxepine **139** scaffolds were obtained when the simple 1,3-butadiene was used instead. Furthermore, dihydrofurans **137** were converted to dihydropyrroles **138** through Pd-catalyzed oxygen to nitrogen transposition (Scheme 42).[78]



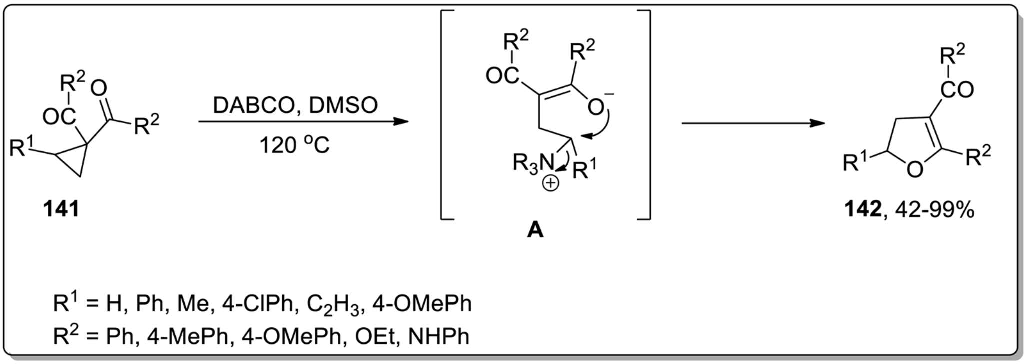
Scheme 41 Synthesis of substituted dihydrofurans **133** *via* Cloke–Wilson rearrangement.



Scheme 42 Synthesis of dihydropyrroles **138** *via* Cloke–Wilson rearrangement.



Scheme 43 Synthesis of dihydrofurans **140** *via* Cloke–Wilson rearrangement.



Scheme 44 Synthesis of 2,3-dihydrofurans **142** *via* Cloke–Wilson rearrangement.

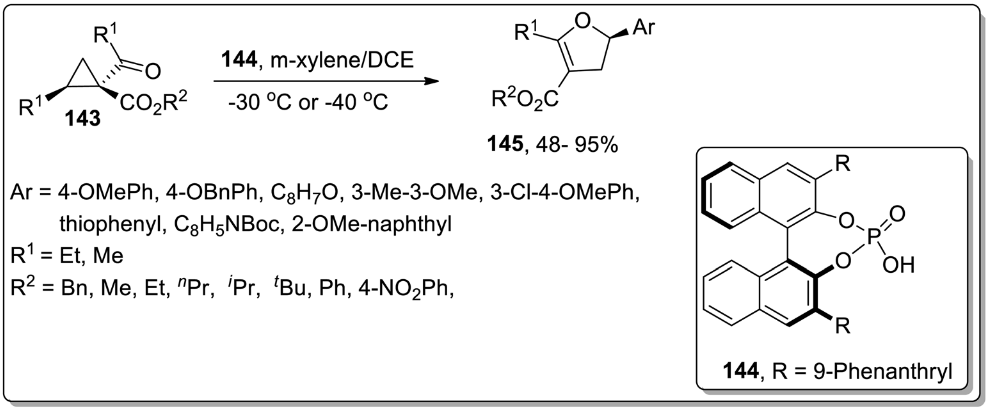
Dihydrooxepines **139** were subjected to Lewis-acid, *i.e.*, $Sc(OTf)_3$-induced rearrangement involving 1,3-oxygen migration to attain dihydrofurans **140** in moderate to excellent yields (Scheme 43).[41a]

6.7. Organo-catalytic/mediated rearrangement

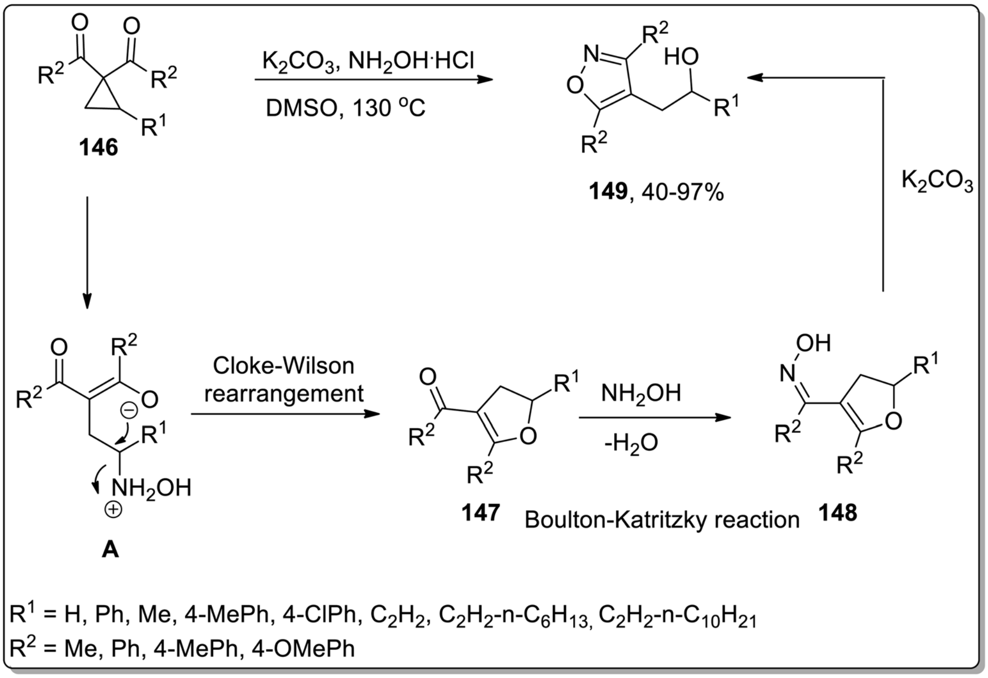
In 2017, Xu and co-workers designed the development of 2,3-dihydrofurans **142** by an organo-catalyzed DABCO-promoted Cloke–Wilson ring enlargement of cyclopropyl ketones **141**. In this transformation, the nucleophilic attack of DABCO on cyclopropane led to the formation of an enolate intermediate **A**, which further underwent cyclization to produce the desired products **142** and released the catalyst. These established conditions for the rearrangement reaction (such as DABCO in DMSO at 120 °C) are compatible for a wide array of substrates, thereby giving the desired products in fair to excellent yields with complete regioselectivity (Scheme 44).[44a]

In 2018, Vicario and co-workers discussed the chiral phosphoric acid-catalyzed enantioselective Cloke–Wilson rearrangement of substituted cyclopropanes **143** to achieve the synthesis of dihydrofuran scaffolds **145**. During this transformation, the D–A cyclopropanes **143** were activated by chiral phosphoric acid-catalyst **144** that promoted the cleavage of the ring to result in carbocationic intermediate, which upon further cyclization gave dihydrofuran derivatives **145** in fair to excellent yields. The established conditions are suitable to get the corresponding dihydrofurans in high yields with remarkable enantioselectivity. The size of the R^3-substituent significantly affected the product yield, such that in the presence of sterically hindering *tert*-butyl ester, the reaction did not take place (Scheme 45).[44b]

In 2018, Xu and co-workers reported the hydroxylamine-mediated one-pot cascade Cloke–Wilson rearrangement/Boulton–Katritzky reaction of cyclopropylketones **146** to afford the



Scheme 45 Synthesis of dihydrofurans derivatives **145** *via* Cloke–Wilson rearrangement.



Scheme 46 Synthesis of substituted isoxazoles **149** *via* Cloke–Wilson rearrangement.

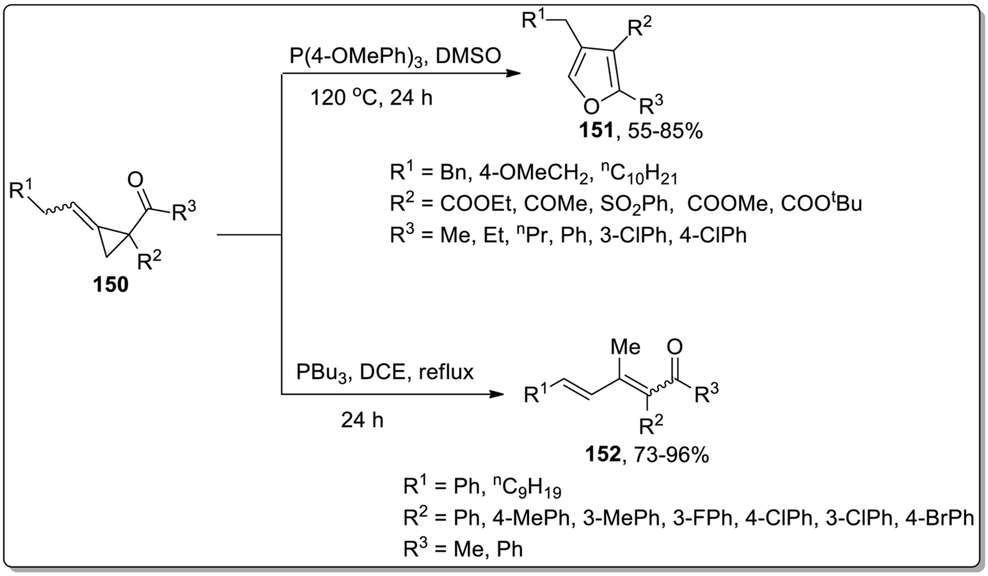
synthesis of fully substituted isoxazoles **149** utilizing hydroxylamine as a catalyst for Cloke–Wilson rearrangement. However, in the Boulton–Katritzky reaction, it was employed as the reactant. Substituted isoxazoles **149** were obtained in fair to excellent yields. This strategy was also applied to synthesize pyrazoles (biologically active scaffolds[79]) and tricyclic heterocycles; both were accomplished in efficient yields (Scheme 46).[44c]

In 2019, Xu and co-workers performed the phosphine-catalyzed synthesis of 2,3,4-trisubstituted furans **151**, fully substituted furans, and 1,2,4-trisubstituted dienones **152** from electron-deficient alkylidenecyclopropanes **150**. In this transformation, the initial nucleophilic attack of phosphine cleaved the alkylidenecyclopropane ring **150**, followed by the subsequent release of phosphine *via* intramolecular S_N2 reaction to generate 2,3,4-trisubstituted furans **151** (when R^2 was employed as the electron withdrawing group). However, using aryl groups as R^2 substitution, the intramolecular 1,4-proton transfer reaction was processed, followed by the 1,4-elimination of the phosphonium to achieve heat-resistant 1,2,4-trisubstituted dienones **152** (Scheme 47).[44d]

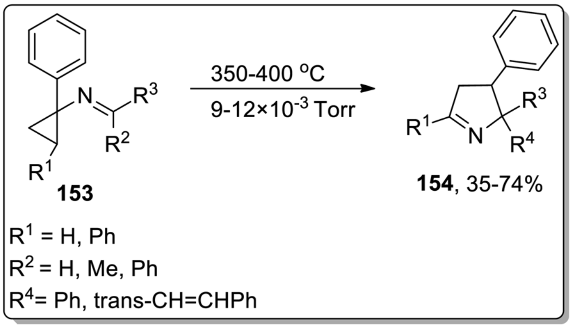
7. Synthesis of N-heterocycles

7.1. Thermal rearrangement

In 2002, Campos and co-workers proposed the thermal Cloke–Wilson rearrangement of *N*-cyclopropylimines **153** to generate 1-pyrroline derivatives **154.** The reaction proceeded successfully within the temperature range of 350–400 °C regiospecifically in the presence of various substituents, *i.e.*, alkyl, alkenyl, and aryl.



Scheme 47 Synthesis of 2,3,4-trisubstituted furans **151** *via* Cloke–Wilson rearrangement.



Scheme 48 Synthesis of 1-pyrroline derivatives **154** *via* Cloke–Wilson rearrangement.

Furan derivative **155** and nornicotine precursor **156** were also synthesized in 32% and 26% yields, respectively, at 350 °C under 20 torr pressure (Scheme 48 and Fig. 2).[8c]

In 2003, Kuduk and coworkers designed the synthesis of 2,3-diaminodihydropyrroles **160** by thermal cyclopropyl thioimidate **157** rearrangement. 2,3-Diaminodihydropyrroles **160** formation was achieved by carrying out three steps, which involved the preparation of imidate **158**, rearrangement, and displacement of amine. The Cloke–Wilson rearrangement of thiomethylimidate cyclopropane **157** was the key step in the developed protocol, leading to the formation of pyrrolothiomethylimidate intermediate **160.** Diverse range of amines such as ammonia, primary amines, and weakly nucleophilic amine reacted efficiently with pyrroloimidate **159** (Scheme 49).[80]

In 2005, Shi and Yang reported the Cloke–Wilson rearrangement of cyclopropyl amides **161** to generate *N*-substituted pyrrolidin-2-ones **164** in good to excellent yields *via* the ring expansion of *in situ* generated imidoyl halides intermediate **162.** Intermediate **162,** consisting of two electron withdrawing groups, facilitated the ring expansion *via* thermal Cloke–Wilson-type rearrangement to generate the next intermediate **163,** which upon the elimination of bromine by hydroxyl group yielded *N*-substituted pyrrolidin-2-ones **164** (Scheme 50).[81]

In 2009, Doye and coworkers designed the one-pot generation of *N*-substituted 2-(arylmethyl)pyrrolidines **169** in good yields by treating aryl-substituted cyclopropylalkynes **165** and primary amines **166** *via* Cloke–Wilson rearrangement. The reaction was initiated with the generation of cyclopropylimine **167** *via* the regioselective hydroamination of the aryl-substituted cyclopropyl moiety using [Ind$_2$TiMe$_2$] as the catalyst. Later on, intermediate **167** underwent heat-induced Cloke–Wilson rearrangement to produce 2-pyrrolines **168** by employing ammonium chloride catalyst. 2-Pyrrolines **168** were further reduced with NaBH$_3$CN/ZnCl$_2$ to give the target functionalized pyrrolidines **169** with up to 90% yields (Scheme 51).[82]

Another example of thermally-induced Cloke–Wilson rearrangement was reported by Tomilov and colleagues to attain the synthesis of condensed azoles **172** and **173** in moderate to good yields from cyclopropylazoles **170** by exploiting the neat conditions. Benzopyrroloimidazoles **174** and benzopyrrolothiazolium salts **175** were afforded in comparatively good yields utilizing this synthetic approach (Scheme 52 and Fig. 3).[22b]

In 2012, Werz and coworkers demonstrated the synthesis of bispyrroles **178** and oligopyrroles **179.** For this purpose, diketones-substituted cyclopropanes with furan core **181** were obtained from furan **8** by treating it with substituted imines

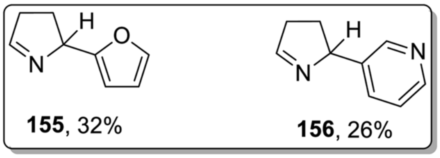
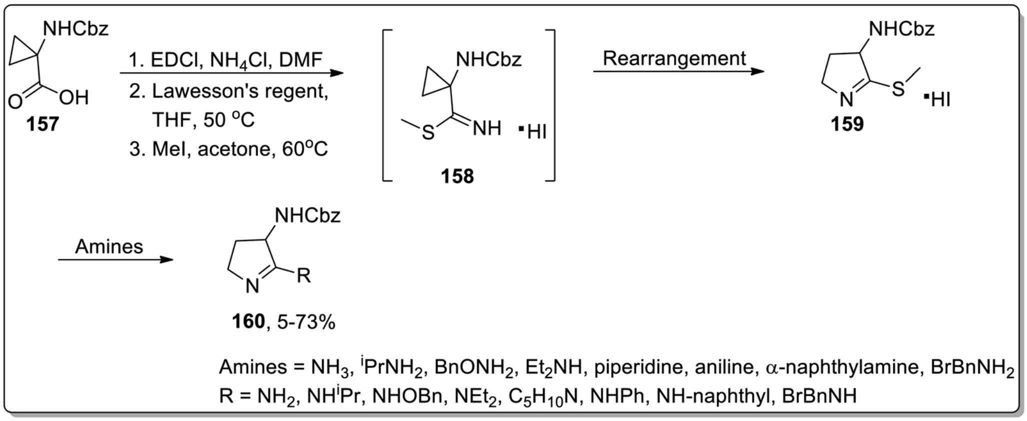
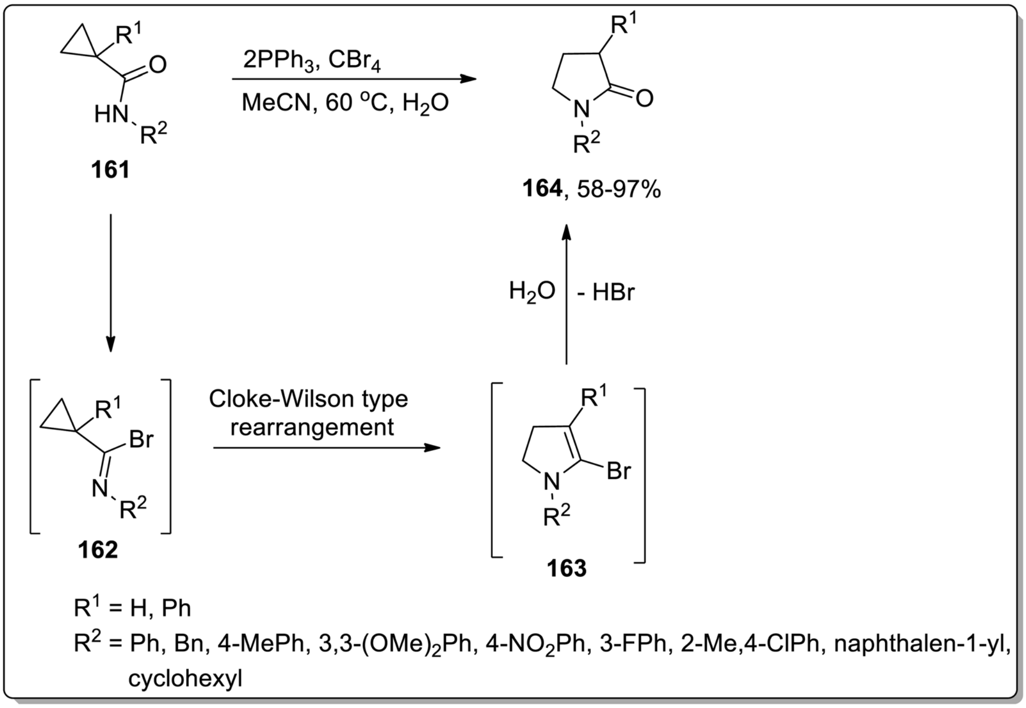


Fig. 2 Structures of furan derivative **155** and nornicotine precursor **156**.



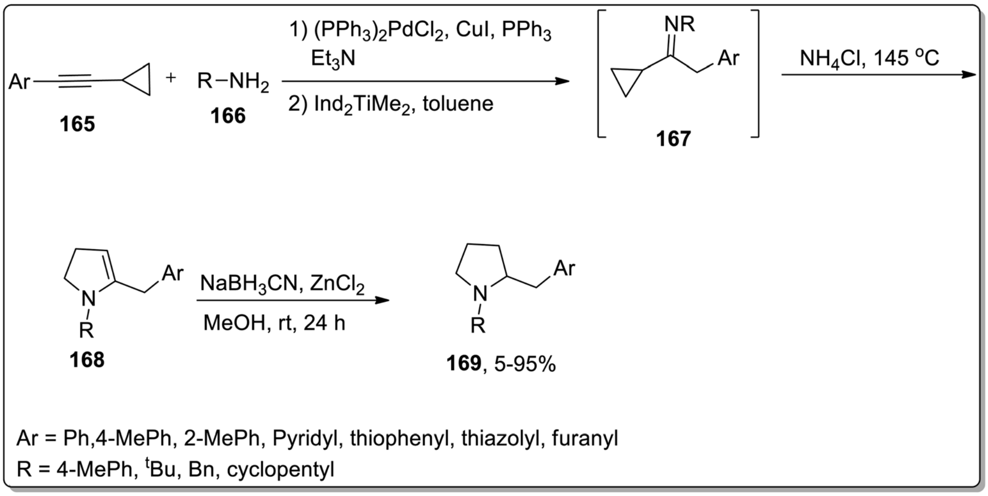
Scheme 49 Synthesis of 2,3-diaminodihydropyrroles **160** *via* Cloke–Wilson rearrangement.



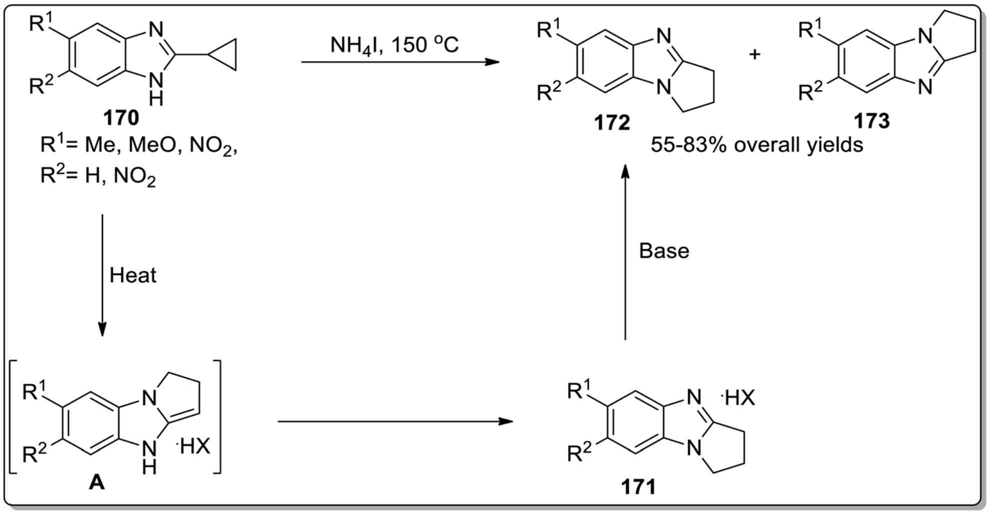
Scheme 50 Synthesis of *N*-substituted pyrrolidin-2-ones **164** *via* Cloke–Wilson rearrangement.

176, followed by reaction with Weinreb amides to yield tricyclic diketones **177**. Diketones **177** were then treated with substituted amines and *p*-TsOH in benzene to afford bispyrroles **178** and **179** with up to 90% yields *via* Cloke–Wilson rearrangement. When extended oligoacetalic diketones **180** were used as starting materials, oligopyrroles **181** were accessed in a single step in moderate yields. With the increasing number of pyrrole units, the synthetic yield of target molecules went downhill due to the intrinsic instability of these oligopyrroles (Schemes 53 and 54).[83]

In 2013, Tomilov and coworkers performed the synthesis of substituted pyrrolidine-based benzimidazoles **183** *via* thermal Cloke–Wilson cyclopropyliminium rearrangement. The 2-cyclopropylbenzimidazoles **182** bearing substituent at the C1 of the cyclopropane ring resulted in C3-substituted 2,3-dihydropyrrolo[1,2-*a*]benzimidazoles **183**, while the substituent at position 2 of cyclopropane **184** led to the formation of a mixture of isomers **184** and **185** because the cyclopropane ring-opening proceeded *via* the cleavage of less or more substituted bonds. The ratio of both the isomers yield was observed to be dependent upon the polarity of the solvent. The polar solvent promoted the ring cleavage of the more substituted bond while weakly polar solvents cleaved the less substituted bond. In contrast, 2-spiropentylbenzimidazole **186** rearrangement furnished product **188**, placing the spiro-cyclopropane fragment at the C2 of pyrrolo-benzimidazoles **188** regioselectively (Schemes 55 and 56).[84]



Scheme 51 Synthesis of functionalized pyrrolidines **169** *via* Cloke–Wilson rearrangement.



Scheme 52 Synthesis of condensed azoles **172** and **173** *via* Cloke–Wilson rearrangement.

In 2013, Tomilov and colleagues designed the synthesis of fused heterocycles, *i.e.*, pyrrolo-thiazolium bromides **193** and pyrrolo-thiazolium iodides **194** by subjecting 2-cyclopropylthiazole **191**/**192** with hydrobromides/iodides, respectively, followed by heat-induced Cloke–Wilson cyclopropyliminium rearrangement reaction at 150 °C (Scheme 57).[85]

Another thermal Cloke–Wilson rearrangement was reported by Tomilov and colleagues to synthesize a mixture of two possible products, *i.e.*, a six-membered tetrahydropyridazines **196** and tryptamines **197** by reacting cyclopropylketone arylhydrazones **195.** The protonation at nitrogen atom facilitated the ring-opening of cyclopropane to generate halides **A** that either followed ring-closure, thereby giving tetrahydropyridazines **196,** or followed Cloke rearrangement to generate pyrroline intermediate **B.** The intermediate **B** upon subsequent domino Steve–Grandberg rearrangement furnished tryptamines **197** in 25–80% yields. The ratio of the product decided the type of the precursor hydrazones (Scheme 58).[86]

In 2014, Tomilov and co-workers depicted the regioselective synthesis of two isomers of dihydro-pyrrolo-benzimidazoles **199** and **200** by the thermally-promoted Cloke–Wilson reaarangement of benzimidazole-substituted cyclopropyl scaffolds **198.** These isomers were obtained by dominating one isomer over

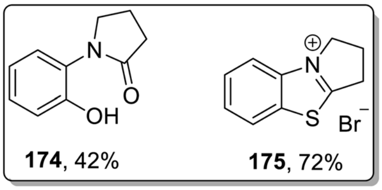
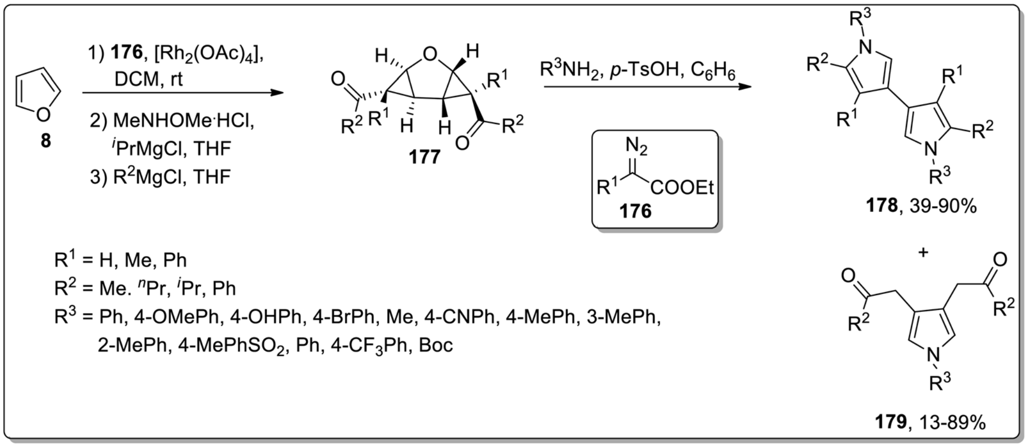
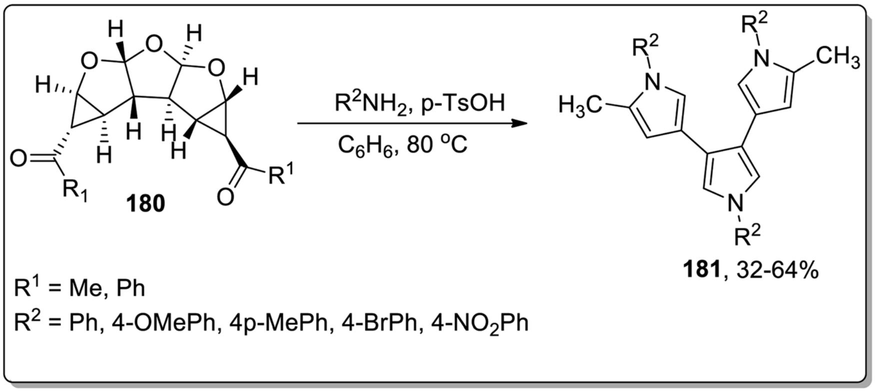


Fig. 3 Structures of benzopyrroloimidazoles **174** and benzopyrrolothiazolium salts **175**.

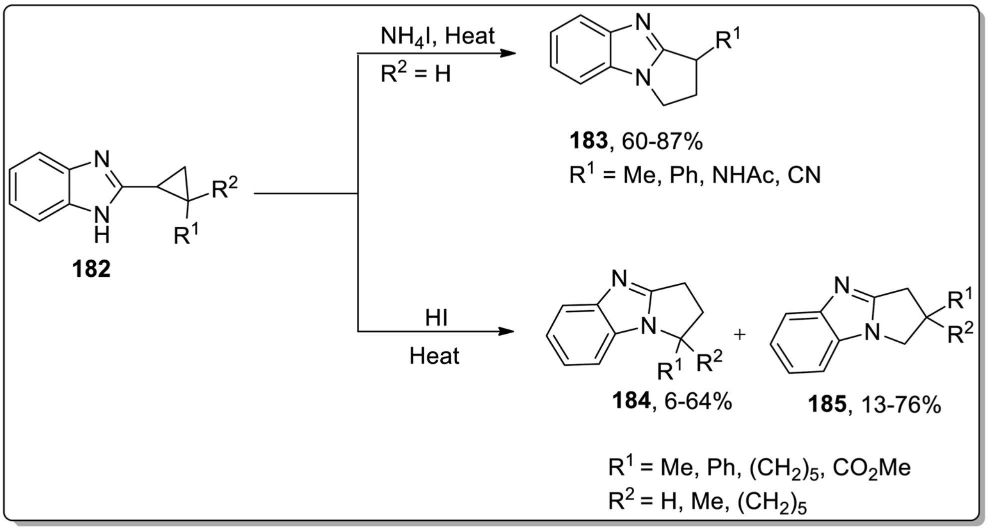


Scheme 53 Synthesis of bispyrroles **178** and oligopyrroles **179** *via* Cloke–Wilson rearrangement.

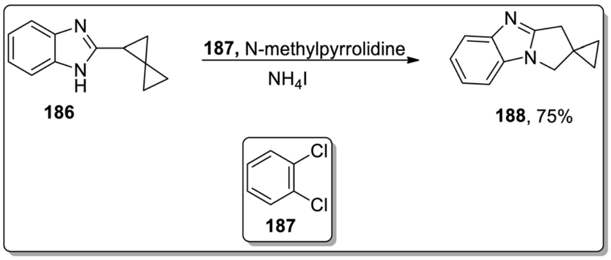


Scheme 54 Synthesis of oligopyrroles **181** *via* Cloke–Wilson rearrangement.

the other. Initially, cyclopropyl ring opening gave intermediate **A,** which was immediately transformed to intermediate **C** and **B** by proton migration. Later, both were cyclized to give **200** and **199,** respectively. Intermediate **B** was stabilized as a result of H-bonding interaction with the nitro group, which ensured its higher concentration in the reaction than another isomer. On the other hand, the –ve inductive effect of the nitro group is responsible for the lower nucleophilicity of nearby nitrogen and



Scheme 55 Synthesis of benzimidazoles **183**, mixture of isomers **184** and **185** *via* Cloke–Wilson rearrangement.



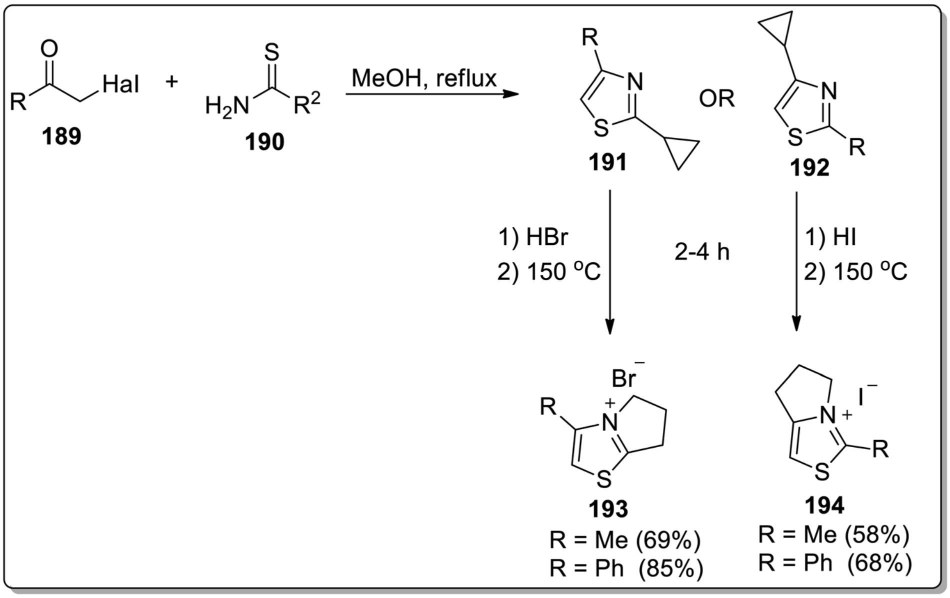
Scheme 56 Synthesis of pyrrolo-benzimidazoles **188** *via* Cloke–Wilson rearrangement.

thus decreased the rate of cyclization of intermediate **C**. This transformation was found to be highly regioselective due to the thermodynamic, electronic, and steric effects (Scheme 59).[8d]

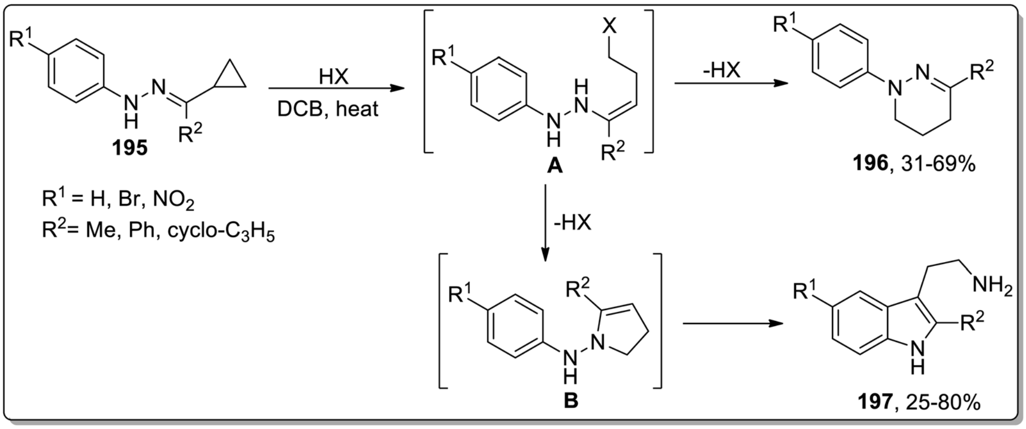
In 2016, Samet and co-workers demonstrated another solvent-free, thermally-promoted Cloke–Wilson rearrangement, leading to the synthesis of fused 2-aryliminothiazolines **204** and cyclopropyl-substituted aminothiazole **205**. The hydromides **202** were obtained in a single step by the Hantzch reaction of aryl-substituted thiourea and cyclopropyl ketone **201**. They were then treated in two ways. In route 1, they were subjected to Cloke–Wilson rearrangement using heat, which melted to produce pyrrolo-thiazolium bromides **203** in excellent yields, which upon treatment with sodium hydroxide resulted in the elimination of hydrogen bromide, thereby giving iminothiazoline derivatives **204** in good yields. In route 2, hydrobromides **202** were subjected to treatment with sodium hydroxide directly to afford thiazole derivatives **205** (Scheme 60).[87]

7.2. Photo-chemical rearrangement

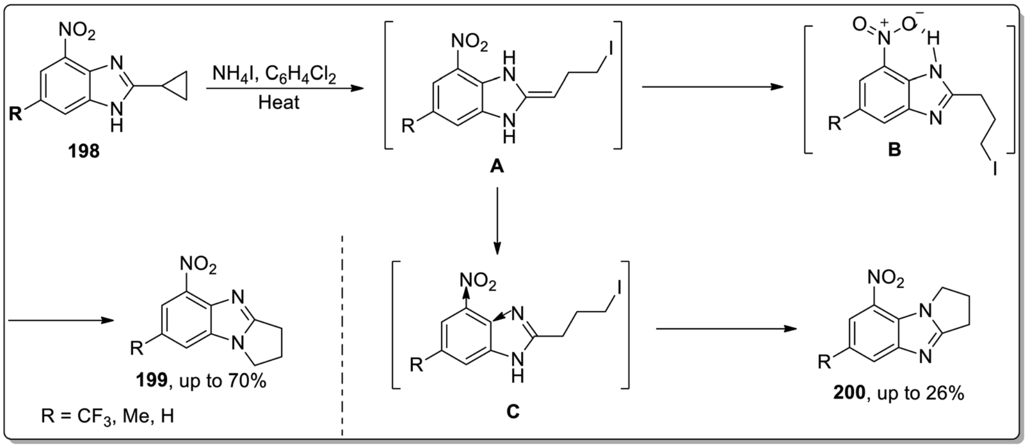
In 2001, Campos and coworkers proposed the synthesis of 1-pyrrolines **207** by photochemical the Cloke–Wilson rearrangement of *N*-cyclopropylimines **206** in hexane. *N*-Cyclopropylimines



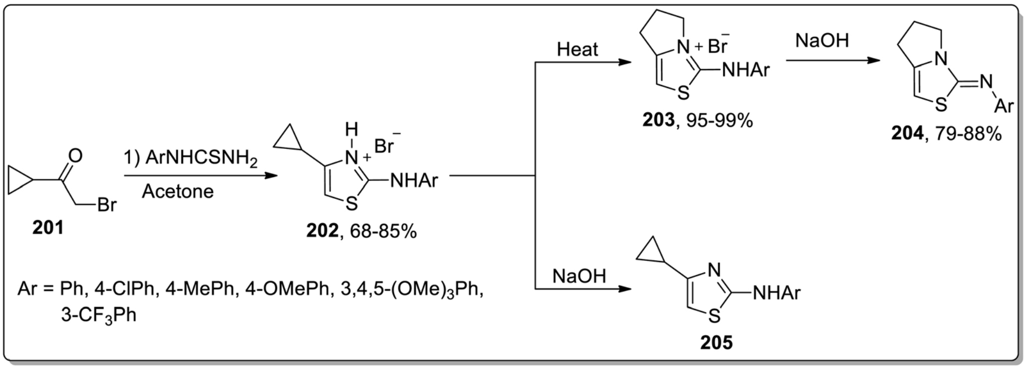
Scheme 57 Synthesis of pyrrolo-thiazolium bromides **193** and pyrrolo-thiazolium iodides **194** *via* Cloke–Wilson rearrangement.



Scheme 58 Synthesis of tetrahydropyridazines **196** and tryptamines **197** *via* Cloke–Wilson rearrangement.



Scheme 59 Synthesis of dihydro-pyrrolo-benzimidazoles **199** and **200** *via* Cloke–Wilson rearrangement.

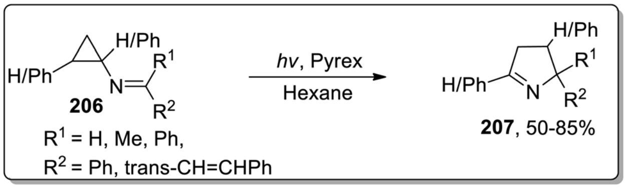


Scheme 60 Synthesis of iminothiazoline derivatives **204** *via* Cloke–Wilson rearrangement.

206 were irradiated *via* pyrex glass whose absorption was noted to be 290 nm. The product distribution was not generally affected by varying the substituents (Scheme 61).[8b]

7.3. Brønsted acid-catalyzed/mediated synthesis

In 2006, Meijere and co-workers designed the one-pot synthesis of pyrrole derivatives **211** by the treatment of 2-lithiated *N*,*N*-dibenzylcyclopropylamines **210** (obtained by reacting substituted alkenes **208** with aldehydes **209**) with nitriles *via* the formation of *N*,*N*-dibenzylaminocyclopropyl ketimines intermediate **A.** The ketimines intermediate **A** in the presence of AcOH underwent protonation to give intermediate **B,** which was then readily cyclized to an amino-2,3-dihydropyrrole **C,** followed by the removal of dibenzylamine to generate the substituted pyrroles **215** in moderate to good yields (Scheme 62).[88]

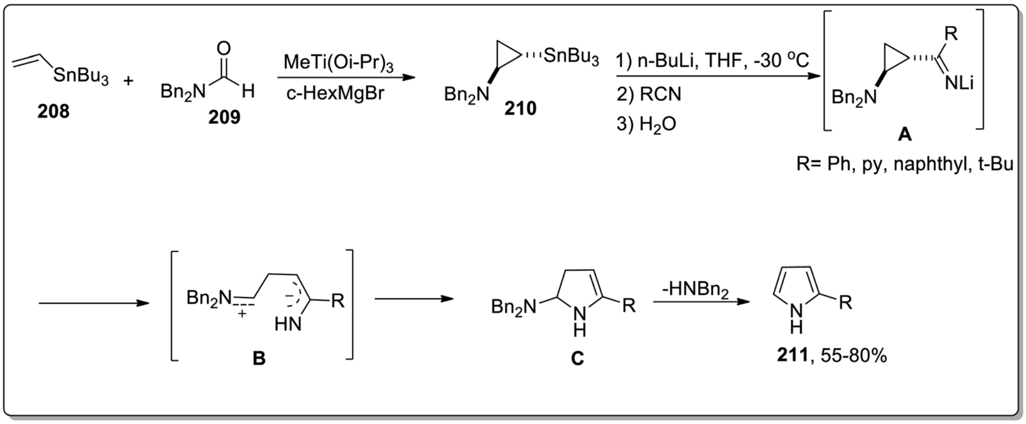


Scheme 61 Synthesis of 1-pyrrolines **207** *via* Cloke–Wilson rearrangement.

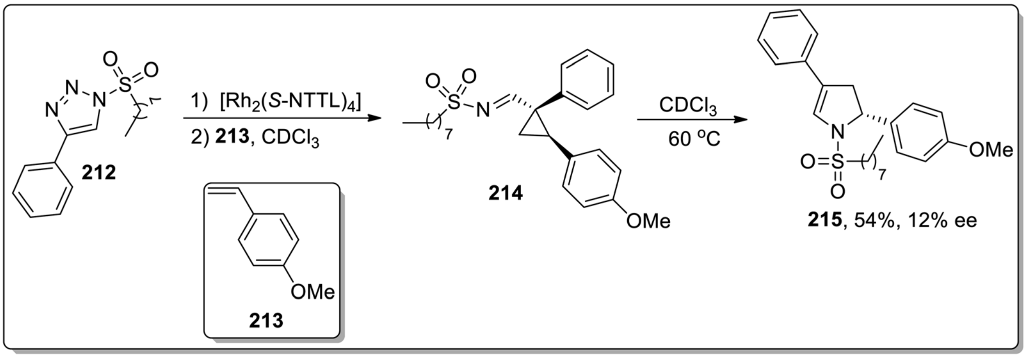
In 2014, Fokin and colleagues designed the one-pot synthesis of enantioenriched 2,3-dihydropyrroles **215** by treating triflated triazoles **212** (which were prepared within the reaction) and olefins **213** involving formation of the triflated cyclopropylaldimine intermediate **214.** In this transformation, the 2,6-di-*tert*-butyl-4-methylpyridinium triflate was exploited as a source of the Brønsted acid, which facilitated the rearrangement of triflated cyclopropylaldimine intermediate **214** to enantioenriched 2,3-dihydropyrroles **215** (Scheme 63).[78] This methodology was further explored to achieve the synthesis of 2,3-dihydropyrrole **217** by chiral phosphoric acid-catalyzed cyclopropylimine rearrangement in toluene. When cyclopropylaldimine was heated by employing rhodium catalyst or under catalyst-free conditions, no product formation was observed. This indicated that heat and Rh catalyst did not play any role in cyclopropylaldimine intermediate **214** to dihydropyrrole conversion; actually, the Brønsted acid facilitated this conversion (Scheme 64).[89a]

8. Synthesis of S-heterocycles

Sulfur-containing heterocycles are of wide medicinal significance and are synthesized by several methods.[89b] In 2011, the synthesis of S-heterocycles, *i.e.*, thieno-pyridine derivatives **219** and **220**, were accomplished by Dong and coworkers *via*



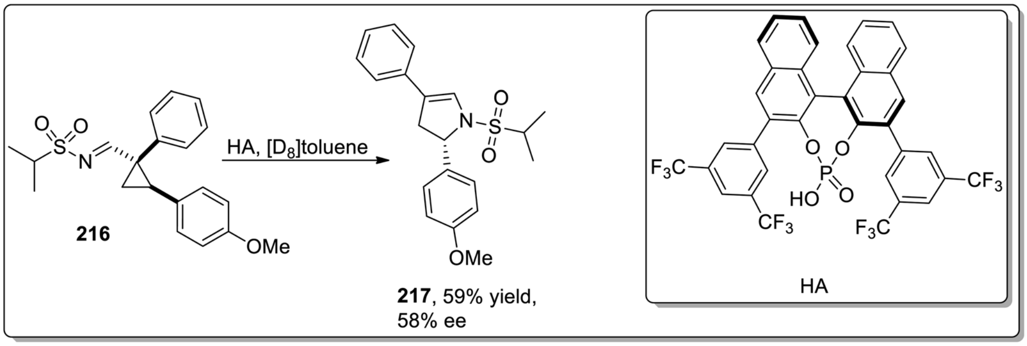
Scheme 62 Synthesis of pyrrole derivatives **211** *via* Cloke–Wilson rearrangement.



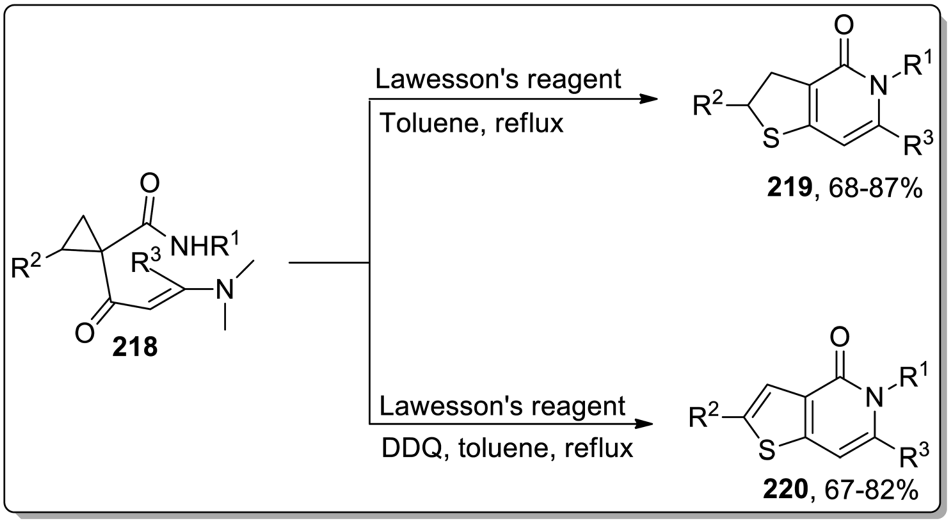
Scheme 63 Synthesis of 2,3-dihydropyrroles **215** *via* Cloke–Wilson rearrangement.

a tandem reaction of dimethylaminopropenoyl cyclopropanes **218** with Lawesson's reagent. This one-pot methodology involved sequential regioselective thionation, thermal Cloke–Wilson rearrangement, and intramolecular aza-cyclization reactions. Dihydrothieno[3,2-*c*]pyridinones **219** were obtained by utilizing Lawesson's reagent in toluene, while the thieno[3,2-*c*]pyridin-4(5*H*)-ones **220** were obtained in moderate to good yields utilizing this protocol in the presence of oxidant, *i.e.*, DDQ (Scheme 65).[9a]

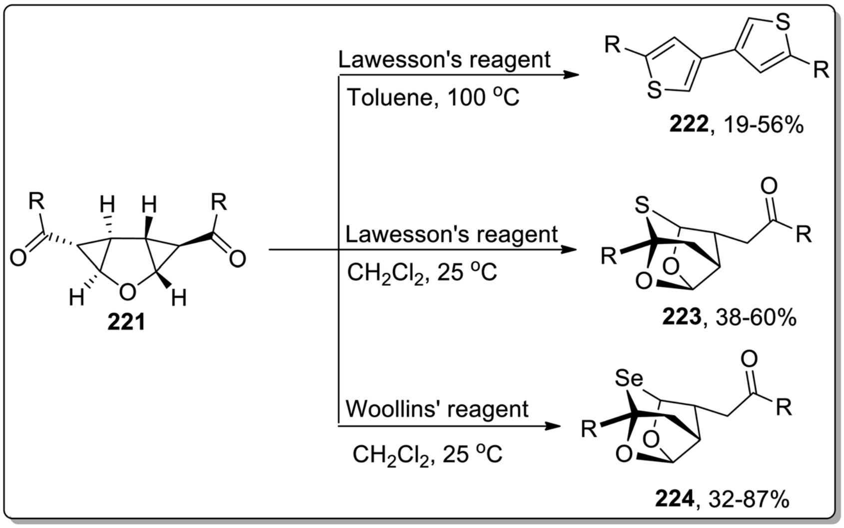
In 2013, Werz and co-workers designed the synthesis of 3,3′-linked bisthiophenes **222**. This reaction commenced by treating diketones-substituted cyclopropanes with the furan core in the presence of Lawesson's reagent that produced thioketones, which further underwent thermal Cloke–Wilson ring enlargement, followed by the loss of water to afford 3,3′-linked bisthiophenes **222** up to 56% yields. Intriguingly, when the reaction was carried out employing electron-withdrawing aromatic substituents or at room temperature in CH_2Cl_2, the "cage-like" structures **223** with a bridging sulfur moiety were obtained in fair yields. Similarly, the high yields of selenium-containing "cage-like" products **224** were managed utilizing Woollins' reagent (Scheme 66).[9b]



Scheme 64 Synthesis of 2,3-dihydropyrrole **217** *via* Cloke–Wilson rearrangement.



Scheme 65 Synthesis of thieno-pyridine derivatives **219** and **220** *via* Cloke–Wilson rearrangement.

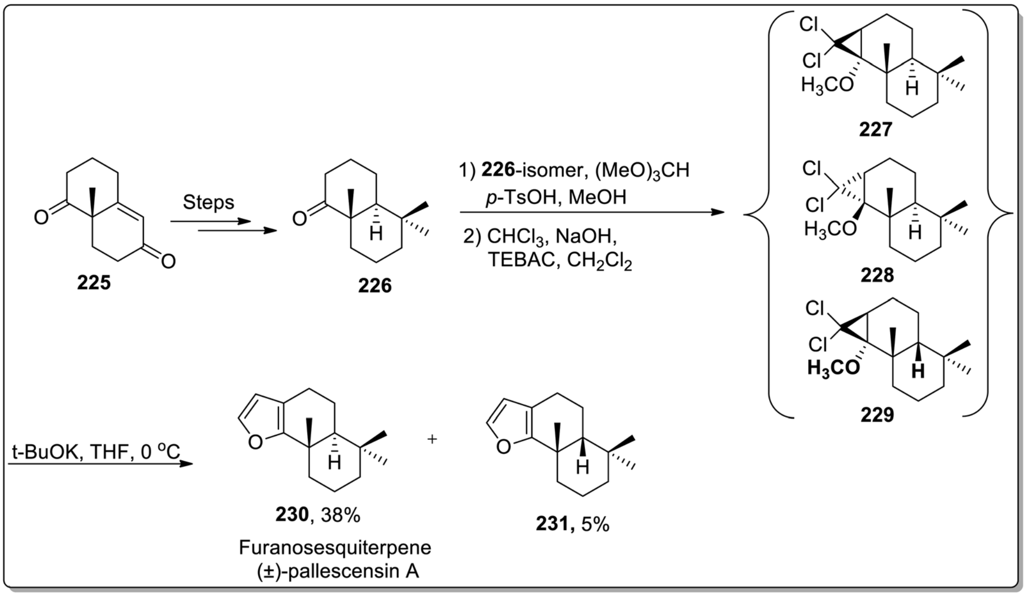


Scheme 66 Synthesis of bisthiophenes **222**, **223**, and **224** *via* Cloke–Wilson rearrangement.

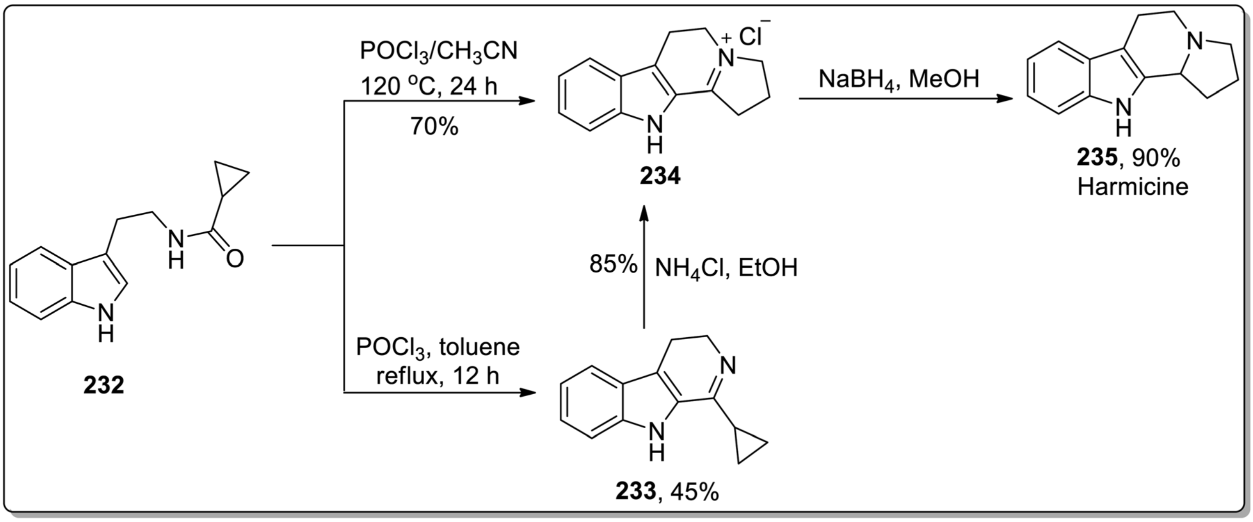
9. Application in total synthesis

The total synthesis of natural products generally involves various named reactions.[90] Cloke–Wilson rearrangement has also found its applications towards the synthesis of various naturally-occurring organic compounds. In 2006, Banwell and co-workers designed the total synthesis of the furanosesquiterpene (±)-pallescensin A **230** by employing Cloke–Wilson rearrangement as the key step. Their synthetic route was initiated by the synthesis of decalone **226**, followed by an array of three steps: the reaction of decalone **226** with $(MeO)_3CH$ in MeOH exploiting *p*-TSOH catalyst gave methyl enol ether along with the precursor ketone. Later on, the reaction mixture was treated with dichlorocarbene, which was generated by Makosza's phase transfer conditions, thereby furnishing precursor ketone in 27% with a mixture of dichlorocyclopropanes **227**–**229**. This mixture of dichlorocyclopropanes was made to undergo Cloke–Wilson rearrangement to afford the chromatographically separable mixture of (±)-pallescensin A **230** in 38% yield with its *cis*-isomer **231** in 5% yield. This synthetic methodology was successfully applied for the conversion of readily available cyclopropanes to annulated furans (Scheme 67).[91]

In 2011, Patro and coworkers performed the synthesis of antileishmania compound, *i.e.*, (±)-harmicine **235** and cytotoxic alkaloid, *i.e.*, (±)-crispine A **239** by sequential tandem cyclization, Bischler Napieralski reaction, and Cloke–Wilson rearrangement (cyclopropylimine rearrangement) reaction, followed by reduction with $NaBH_4$. The reaction of substituted cyclopropanecarboxamide **232** with $POCl_3$ in toluene resulted in the synthesis of compound **233** in 45% yield after 12 h. Compound **233** was then subjected to Cloke–Wilson rearrangement by treating it with NH_4Cl in refluxing ethanol to



Scheme 67 Total synthesis of furanosesquiterpene (±)-pallescensin A **230** *via* Cloke–Wilson rearrangement.

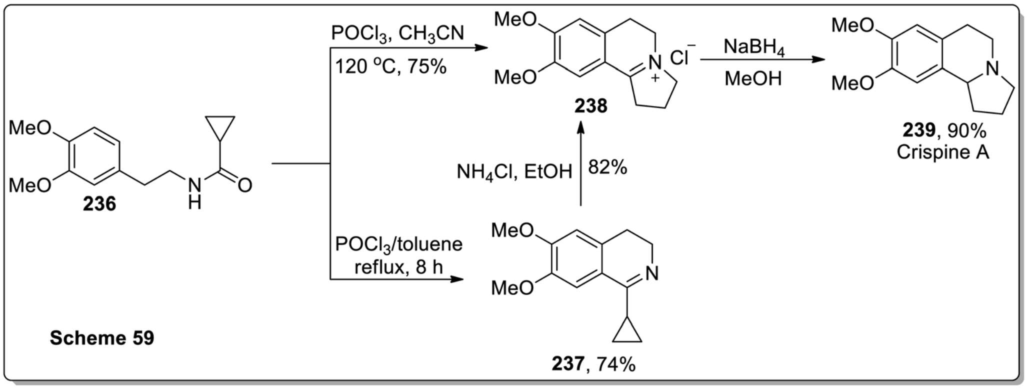


Scheme 68 Total synthesis of harmicine **235** *via* Cloke–Wilson rearrangement.

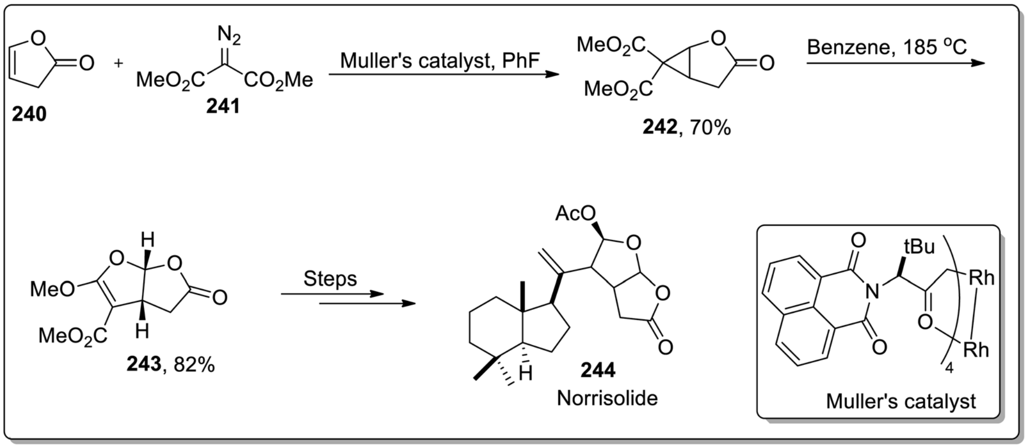
afford compound **234** in 85% yield. The reaction of compound **232** was also carried out with $POCl_3$ in acetonitrile at 120 °C, which gave compound **234** in 70% yield, which upon reduction with $NaBH_4$ in methanol at 0 °C furnished racemic harmicine **235** in 90% yield. Similarly, crispine A **239** was synthesized from *N*-(3,4-dimethoxyphenethyl)cyclopropanecarboxamide **236** in 90% yield (Schemes 68 and 69).[21]

In 2012, Snapper and Granger reported the total synthesis of (+)-norrisolide **244** in which the tetrahydrofurofuranone side chain was synthesized by sequential enantioselective cyclopropanation, which proceeded further by thermal Cloke–Wilson rearrangement, which was a key step in their synthetic methodology. Further, Müller's catalyst promoted the cyclopropanation reaction between lactone **240** and dimethyl-2-diazomalonate **241** to produce D–A cyclopropane **242**, which underwent cyclopropane ring-opening when heated in benzene, accompanied by ring closure to the corresponding bicyclic furan derivative **243**. These furan derivatives **243** were treated in numerous steps to synthesize the target molecule. The total synthesis of (+)-norrisolide **244** consisted of total 14 steps with 1.7% overall yield (Scheme 70).[92]

In 2012, Reiser and Harrar reported the enantioselective synthesis of the natural product (−)-paeonilide **251** from the inexpensive starting material furan-3-carboxylic acid **245**. The total synthesis was initiated with the synthesis of furan-substituted ester from acid **245**, which was then subjected to treatment with *t*-butyl diazoacetate **246** *via* stereoselective intermolecular cyclopropanation in the presence of copper(I)

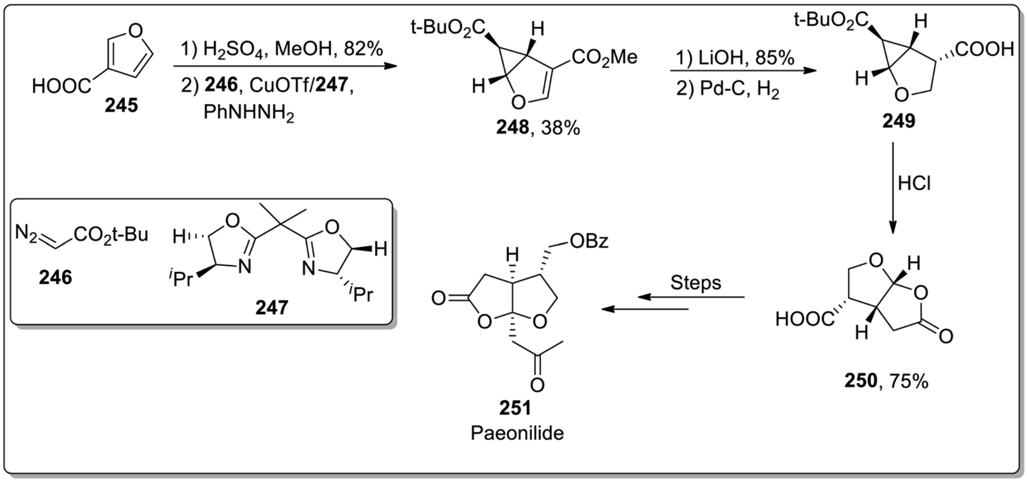


Scheme 69 Total synthesis of crispine A **239** *via* Cloke–Wilson rearrangement.

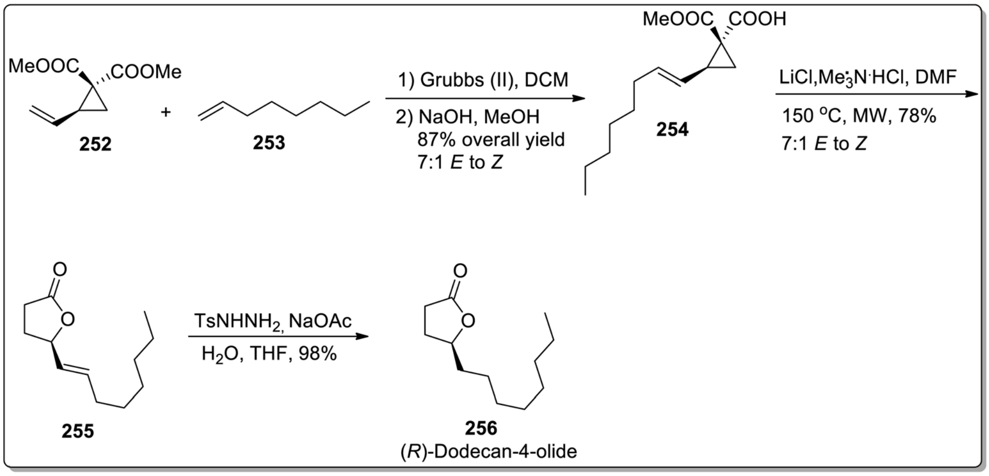


Scheme 70 Total synthesis of (+)-norrisolide **244** *via* Cloke–Wilson rearrangement.

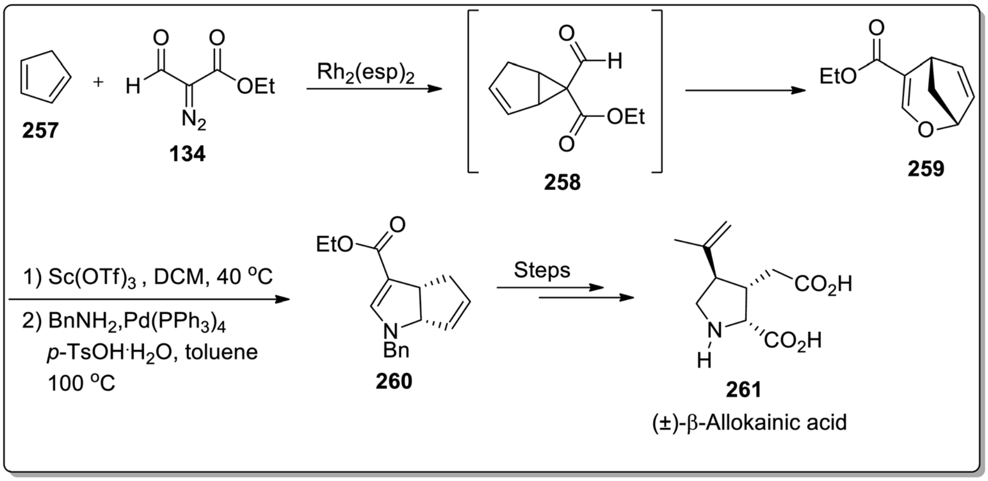
trifluoromethanesulfonate and bis-oxazoline ligand **247**. This led to the generation of cyclopropane **248**, which upon chemoselective hydrolysis and catalytic hydrogenation gave acid **249**. The Brønsted acid-mediated cyclopropane ring cleavage/closure provided lactone **250**, which was proceeded further by the incorporation of the side chain. The total synthesis of (−)-paeonilide **251** consisted of a sequence of 12 steps with 4.4% overall yield (Scheme 71).[93]



Scheme 71 Total synthesis of paeonilide **251** *via* Cloke–Wilson rearrangement.



Scheme 72 Total synthesis of (*R*)-dodecaolide **256** *via* Cloke–Wilson rearrangement.



Scheme 73 Total synthesis of (±)-β-allokainic acid **261** *via* Cloke–Wilson rearrangement.

In 2013, Kerr and co-workers reported the facile approach for the synthesis of substituted butanolides **256** by carrying out cyclopropane hemimalonate **254** cyclization/dealkoxycarbonylation. Cyclopropane hemimalonates **254** (synthesized by subjecting vinyl substituted cyclopropane **252** and octene **253** to the conditions similar to cross-metathesis reaction) were rapidly converted to butanolides **255** with the retention of stereochemistry by exploiting microwave irradiation and inorganic salt, *i.e.*, LiCl. This synthetic route was successfully applied for the synthesis of naturally-occurring (*R*)-dodecaolide **256** with 67% overall yield (Scheme 72).[94]

In 2019, Piotrowski and Kerr reported the total synthesis of kainoid alkaloid, *i.e.*, (±)-β-allokainic acid **261**, which was obtained in 60% yield (3.5% overall yield). During this transformation, the key step involved the Lewis acid-promoted Cloke–Wilson rearrangement of **258** (achieved by the reaction of cyclopentadiene **257** with substituted diazo compound **134**) to the formation of the substituted 2,5-dihydrooxepine ring **259**, followed by the transition metal-induced transformations to produce pyrrolidine core **260**, which was suitable for the generation of a target molecule **261** (Scheme 73).[25]

10. Conclusions

Herein, a detailed summary of recent methodological advances of Cloke–Wilson rearrangement along with its applications in the total synthesis of natural products has been presented, thereby covering the literature reported in the last two decades. Cyclopropanes are three carbon-containing privileged heterocycles, widely employed as building blocks in synthetic organic chemistry utilizing Cloke–Wilson rearrangement. The high angular and torsional strain of cyclopropanes along with the induced polarization of the ring due to the attached donor–acceptor substituents are the main factors, leading to their high reactivity in organic synthesis. Various activated cyclopropanes, *i.e.*, carbonyl and imine-substituted cyclopropyls, have been extensively utilized to synthesize various oxygen and nitrogen-based five-membered heterocycles. Similarly, Cloke–Wilson rearrangement also finds use in the synthesis of sulfur-containing heterocycles. Moreover, the total synthesis of various natural products also utilizes this rearrangement as a key step. The requirement of high temperature was considered to be the limitation of Cloke–Wilson rearrangement. To address this drawback, various novel and efficient methods have been adopted for the activation of cyclopropanes to attain several five-membered heterocycles with broad substrate scope. These novel methods involve transition-metal catalysis, photocatalysis, organo-catalysis, Lewis acid catalysis, Brønsted acid catalysis, and Brønsted base catalysis. This detailed review is expected to motivate synthetic chemists to further advance regarding Cloke–Wilson rearrangement to unveil its synthetic potential in heterocyclic chemistry.

Conflicts of interest

There are no conflicts to declare.

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