Prins Spirocyclization

Recent Advances in Prins Spirocyclization

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Abstract: The classical Prins cyclization has been one of the most intensively studied reactions during the last two decades, and it has found many applications in key steps of natural product syntheses, especially for products containing tetrahydro-pyran motifs and related structures in their core skeletons. The application of this reaction to the synthesis of spirocyclic networks has made substantial progress recently. Spiro motifs are found in many natural products with promising biorelevance and are increasingly being incorporated in drug candidates. Further, various spirocyclic chiral ligands have shown promising efficiency in asymmetric synthesis. Here a compilation of recent spiroannulation reactions by Prins cyclization is presented, focusing on the scope and versatility of this method.

1. Introduction

The design and synthesis of various spirocyclic structures has received considerable interest and attention from the scientific community, due to the diverse molecular architectures and biological activities of compounds of this class. They appear in natural products[1] and in potent biologically active molecules.[2] The inherent rigidity of spirocycles is also ideal for the construction of chiral ligands containing such spiro structures (examples being spirobisoxazoline, spirox, sprix, spirospiral derived phosphoric acid etc.) which plays crucial role in its catalytic activity.[3] Owing to their complex structures and well-defined three-dimensional spatial arrangements, they exhibit specific action with biological receptors and enzymes.[4] These properties make them attractive synthetic targets, and substantial research is in progress into various methods and reactions through which spirocycles of importance in various contexts can be prepared.[5]

Prins cyclization has been of great interest in recent times for the stereoselective construction of oxygen-containing heterocycles. It has become established as an efficient method for the stereoselective synthesis of tetrahydropyran moieties, often found as core structures in many natural products.[6] Many research groups such as Yadav and co-workers, Dobbs and co-workers, Overman and co-workers, Saikia and co-workers, Rychnovsky and co-workers, Willis and co-workers, Loh and co-workers, Padron and co-workers, etc. have made outstanding contributions to the development of the chemistry of the Prins cyclization.[7] In particular, the intramolecular Prins cyclization has in recent times become a method of interest for synthesizing various complex heterocycles including fused and bridged representatives.[8] The application of these reactions in domino-type processes to synthesize spirobicycles seems to be the least explored topic in the context of this reaction.

A homoallylic alcohol incorporating a suitable nucleophile offers an interesting synthetic route to spirobicycles of synthetic or pharmacological importance through Prins cyclization. A side chain bearing a nucleophile is attached to the inner carbon atom of the olefinic moiety of the homoallylic part, thus leaving a terminal alkene. The choice of side chain is important, because the chain length will decide the size of the ring in the product. A general method is outlined in Scheme 1.

Scheme 1.

Presumably, the pathway of the mechanism involves an oxocarbenium ion of type 3, formed in situ from the alkenol 1 and an aldehyde 2, likely after activation with a Lewis acid. Attack of the olefinic moiety on 3 followed by trapping of carbocation 4 with the nucleophile on the side chain would give the desired spirocycle 5.[7o]

Domino Prins reactions largely employ nucleophiles of two types. In the first category, the nucleophile is an aromatic carbon atom that is attached to the homoallylic part through the side chain. In the other category a hydroxy group is em-
employed in order to access a five- or six-membered oxygenated heterocycle.

2. Domino Prins Reaction: Bicyclization

2.1. Carbon as Nucleophile

Reddy and co-workers reported a Prins cascade reaction through which hexahydro-1H-spiro[isoquinoline-4,4′-pyran] derivatives 8 were accessed synthetically.\(^9\) This class of compounds falls into the category spiroisoquinolines, which are known to exhibit a broad spectrum of biological activities such as anti-arrhythmic, antidepressant, stimulant effects on respiration, analgesic and cardiotoxic behaviour.\(^10\) The method employed a reaction between various aldehydes and 3-[(benzylamino)methyl]but-3-en-1-ol (6) in the presence of BF\(_3\)·OEt\(_2\) (Scheme 2). The reaction proceeds better with the reaction of enol 6 and benzaldehyde, with an excellent yield of 95%. The scope of the reaction was well illustrated with a variety of aldehydes of various electronic natures. Representatives with different electron-withdrawing or -donating substituents on the aromatic ring showed excellent potential. This method was successfully investigated with various aliphatic aldehydes, acid-sensitive cinnamaldehyde and phenylacetaldehyde, and sterically hindered 2-naphthaldehyde, as well as with the heterocyclic thiophene-2-carbaldehyde.

![Scheme 2](image)

Structural variations with the side chain provided access to spirooxindoles, an important class of compounds considered privileged scaffolds due to their broad range of biological activities including anticancer, antimalarial, and antituberculosis activity, and as growth hormone secretagogue and progesterone receptor agonists.\(^11,12\) Aldehydes 10 underwent smooth coupling with 4-hydroxy-N-methyl-2-methylene-N-phenylbutanamide derivatives 9 in the presence of BF\(_3\)·OEt\(_2\) to produce spirooxindole derivatives 11 and 12 (Scheme 3).\(^13\) Aromatic, heteroaromatic, and aliphatic aldehydes underwent cyclization smoothly under standard conditions. Although, in general, the...
Prins cyclization proceeds with electron-rich olefins, in this study the reaction was equally successful with electron-deficient alkenes. Like in previous reports, the nature of the substituents on the aromatic aldehydes had little effect, whereas, unlike in previous reports, both aromatic and aliphatic aldehydes reacted excellently under the standard protocol.

Scheme 3.

Reddy and co-workers reported a spirocyclization of 3-[[3-(2-aminophenyl)prop-2-ynylamino]methyl]but-3-en-1-ol derivatives 13 to access octahydrospiro[pyran-4,4′-pyrido[3,4-b]-indole] derivatives 15. A Ph3PAuCl/AgSbF6/In(OTf)3 catalyst system was utilized to synthesize compounds 15 by this strategy (Scheme 4). This was the first successful attempt to synthesize spiro-f-carbolines through a multicatalytic cascade process. The coupling of compounds 13 with benzaldehyde occurred in the presence of a Ph3PAuCl/AgSbF6 mixture, and In(OTf)3 catalyzed the reaction and yielded the desired products. This procedure was also extended to different aldehydes and ketones with consistent success. Aromatic, heteroaromatic, and aliphatic aldehydes, ketones such as cyclohexanone, acid-sensitive substrates such as phenylacetaldehyde and α,β-unsaturated aldehydes, and the sterically hindered substrate naphthaldehyde successfully underwent reaction.

Scheme 4.

Reddy and co-workers developed a Prins/pinacol method utilizing the cyclobutanol derivative 1-(4-hydroxybut-1-en-2-yl)cyclobutanol (16) by which 7-substituted 8-oxaspiro[4.5]decan-1-ones such as 18 were synthesized on treatment with various aldehydes such as 17. Investigation of the scope of the reaction began with 4-bromobenzaldehyde in the presence of either BF3·OEt2 or TMSOTf, which afforded the corresponding oxaspirocycle 18 as a single diastereomer in 85% yield (Scheme 5).

Scheme 5.

Other aromatic aldehydes such as 4-chlorobenzaldehyde, 4-cyanobenzaldehyde, 2,4-dichlorobenzaldehyde, 4-nitrobenzaldehyde, 4-tolualdehyde, 2,4,5-trifluorobenzaldehyde, 4-isopropylbenzaldehyde, aliphatic aldehydes such as 3-methylbutanal and pivalaldehyde, heteroaromatic aldehydes such as 4-bromothiophene-3-carbaldehyde, and acid-sensitive cinnamaldehyde were used to demonstrate the generality of the method with excellent results. A variant of the cyclobutanol – 1-(4-hydroxy-6-phenylhex-1-en-2-yl)cyclobutanol (19) – was successfully tested in a determination of the versatility of the proposed protocol. Treatment of 19 with 2,4,5-trifluorobenzaldehyde (20) afforded 7-phenethyl-9-(2,4,5-trifluorophenyl)-8-oxaspiro[4.5]decan-1-one (21) in 78% yield (Scheme 6).

Scheme 6.

Reddy and co-workers reported a Prins/pinacol reaction route for the synthesis of 2,3,5,6-tetrahydro-1′H-spiro[pyran-4,4′-quinoline]-2′,3′-dione derivatives 24 (Scheme 7). Eneediols 22 were successfully employed in the reaction with various aldehydes 23 in the presence of BF3·OEt2 to afford the corresponding dione derivatives. A wide array of aromatic aldehydes with varying electronic and substitution patterns were investigated with excellent results. Aliphatic aldehydes such as pivaldehyde and propanaldehyde and ketones such as cyclohexanone also provided excellent results. The efficiency of substituted enediols was investigated with 5-methoxy and 5-chloro derivatives, and those results were also excellent.

Spiropyrrolidine and spiropiperidine scaffolds were synthesized by tandem Prins spirocyclization through treatment of
aldehydes 26 with 3-[(3-methylbut-2-enylamino)methyl]but-3-en-1-ol (25; Scheme 8) and 3-[(4-methylpent-3-enylamino)methyl]but-3-en-1-ol (29; Scheme 9), respectively, in the presence of TMSOTf.\[17\]

With 25 (Scheme 8) the protocol resulted in a mixture of diastereomers 27 and 28. Aromatic, aliphatic, and heteroaromatic aldehydes 26 with varying electronic natures and substitution patterns smoothly underwent cyclization. With ketones the case was similar, with ketones such as acetone and cyclohexanone also giving the corresponding products in good yields. Acid-sensitive aldehydes such as cinnamaldehyde and phenylacetaldehyde afforded the products in relatively lower yields. Sterically hindered substrates such as 1-naphthaldehyde and 2-chloro- and 2-methylbenzaldehydes also reacted quite effectively under this protocol. Reactions involving aldehydes bearing electron-deficient groups were generally faster than those involving aldehydes with electron-rich substitution. The variation with compound 29 (Scheme 9) and aldehydes successfully gave the corresponding spiropiperidines 31 and 32.

2.2. Oxygen as Nucleophile

Spiro oxacycles such as spirochromans are often core moieties of various natural products of biorelevance and of their synthetic analogues as essential pharmacophores.\[18\] Another class of compounds, spirobenzodioxane scaffolds, can be found in vesicular acetylcholine transporters, α1 receptor ligands, non-peptidic inhibitors of caspase-3 and the positive allosteric modulators.\[19,20\] In addition, compounds containing more than one heteroatom with one of them being oxygen, such as spironorpholinic derivatives, often exhibit biological activities such as anti-HIV activity, NK1 receptor antagonism, and antiproliferative activity.\[21\] The general strategy of intramolecular nucleophilic attack on the olefinic bond in the homoallylic alcohol part with a suitably chosen side chain containing a hydroxy group would produce strategic access to compounds of these classes.

Reddy and co-workers reported spirocyclization of N-(4-hydroxy-2-methylenebutyl)-N-(2-hydroxyethyl)-4-methylbenzenesulfonamide (33) with various aldehydes 34, through which spiromorpholinotetrahydropyran (1,9-dioxa-4-azaspiro[5.5]undecane) derivatives 35 were synthesized for the first time through a Prins cascade process.\[22\] In the reaction protocol, diol 33 was treated with p-chlorobenzaldehyde in the presence of BF₃·OEt₂ to yield the corresponding spiromorpholinotetrahydropyran derivative 35 (Scheme 10). A number of aromatic aldehydes with various substitution patterns, such as electron-withdrawing and -donating, participated efficiently in the reaction. Acid-sensitive cinnamaldehyde and phenylacetaldehyde, sterically hindered 2-naphthaldehyde, aliphatic aldehydes, and the heterocyclic aldehyde thiophene-2-carbaldehyde were also investigated in the protocol and gave consistent results under the standard conditions.

The procedure was also efficient with other aldehydes bearing functional groups such as cyano, olefinyl, nitro, methoxy,
and halo. Aromatic aldehydes with halo or alkyl groups as substituents provided the products with better yields than other substrates. Acid-sensitive substrates such as cinnamaldehyde, sterically hindered substrates such as 1-naphthaldehyde, and the heterocyclic aldehyde 4-bromothiophene-2-carbaldehyde participated with no differentiation in the reaction outcome. Although the reaction worked well with aromatic aldehydes and other variants, it was less successful with their aliphatic counterparts, with those products being obtained as inseparable diastereomeric mixtures.

Reddy and co-workers reported a Prins spirocyclization process through which the synthesis of tetrahydro-3H-spiro[benzo[b][1,4]dioxine-2,40-pyran] derivatives \(41\) (Scheme 12) and hexahydropyran-benzob[b][1,4]oxazine-2,4\'-pyran derivatives \(44\) and \(45\) (Scheme 13) was achieved by treatment of aldehydes with 2-(4-hydroxy-2-methylenebutoxy)phenol (39) and \(N\)-(4-hydroxy-2-methylenebutyl)-\(N\)-(2-hydroxyphenyl)-4-methylbenzenesulfonamide (42), respectively.[24] Treatment of 39 with \(p\)-bromobenzaldehyde in the presence of InCl\(_3\) afforded 41 (\(R = 4\)-bromophenyl).

\[
\begin{align*}
\text{R} &= 4\text{-bromophenyl}, 4\text{-nitrophenyl}, \\
\text{isopropyl, 2-naphthyl, etc.}
\end{align*}
\]

Scheme 12.

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\begin{align*}
\text{R} &= 4\text{-bromophenyl, 4-nitrophenyl,} \\
\text{isopropyl, 2-naphthyl, etc.}
\end{align*}
\]

Scheme 12.

Barbero and co-workers employed organosilanes in a Sakurai–Prins cyclization reaction sequence based on a similar strategy. They developed a multicomponent Prins cyclization in which an alkenyl monoalcohol underwent a tandem allylation/Prins spirocyclization process. This reaction mainly proceeds through the internal trapping of a tetrahydropyranyl cation, which leads to the formation of dioxaspirodecanes.[26] Prins cyclization between allylsilyl alcohol \(49\) and benzaldehyde in the presence of TMSOTf (Scheme 15) proceeded in high yield and with very high stereocontrol (>95:5). This reaction required an excess of benzaldehyde in order to supply the expected product, because use of an equimolar amount of benzaldehyde resulted in dioxaspirodecane \(51\) along with a minor amount of side product \(52\). A variety of alkyl, aryl, and \(\alpha\),\(\beta\)-unsaturated aldehydes gave the products efficiently. The product outcome varied with changes in the nature of the aldehyde and in the electronic character of its attached substituents. Electron-rich aromatic aldehydes found better success in terms of both yield and diastereoselectivity. An otherwise competitive reaction under standard conditions, TMSOTf-catalyzed Hosomi–Sakurai coupling between allylsilanes and aldehydes, is not favored here, whereas the target spirocyclization is readily promoted in

\[
\begin{align*}
\text{R} &= 4\text{-nitrophenyl, 4-chlorophenyl, 2-chlorophenyl,} \\
\text{\(n\)-pentyl, 2-naphthyl, etc.}
\end{align*}
\]

Scheme 14.
the presence of a silyl ether used as a coreactant.\[^{[27]}\] The success of the Sakurai reaction may be attributed to the catalytic amount of triflic acid present in TMSOTf solution.\[^{[28]}\]

Scheme 15.

In line with the previous report, Barbero and co-workers extended the protocol to the synthesis of dioxaspiroundecanes 55 through a tandem Sakurai–Prins cyclization of allylsilyl alcohol 53 in the presence of TMSOTf (Scheme 16).\[^{[29]}\] The reaction is general both for aryllic and vinylic aldehydes, with good yields over two steps. The process was almost instantaneous, with reaction times ranging from 5 to 15 min. The reaction is highly chemoselective, leading to the corresponding dioxaspiroundecanes. Moreover, the reaction was very stereoselective, providing the expected dioxaspiroundecanes as single diastereoisomers, except in the case of the reaction with 4-methoxybenzaldehyde, in which a minor amount of byproduct 56 (R = 4-methoxyphenyl) was isolated along with the major product.

Scheme 16.

3. Spiro Cyclization: Monocyclization

3.1. Five-Membered-Ring Structures

Basavaiah and co-workers synthesized spiro[indene-oxindole] derivatives through Prins cyclization followed by Friedel–Crafts coupling. The reactions between isatin derivatives 57 and 1,1-diphenylethylene derivatives 58 in the presence of TiCl4 provided the desired spiro[3-phenyl-1H-indene-1,3′-indolin-2′-one] derivatives 59 in isolated yields of up to 90 %. The versatility of the method was illustrated with various isatin derivatives and their reactions with compounds 58 under the influence of TiCl4 in moderate to excellent yields (Scheme 17).\[^{[30]}\] This method gave access to spiro-oxindoles, a privileged class of compounds represented in a number of bioactive natural products such as welwitindolinone A, coerulescine, horsfiline, alstonisine, surugatoxin, spirotryprostatin A, elacomine, etc.\[^{[31]}\]

Scheme 17.

To explore the generality of the Prins–Friedel–Crafts sequence, the reaction was repeated with a variety of isatin derivatives and 1,1-diarylethylenes in the presence of TiCl4, and the results were consistent with the previous observations.\[^{[32,33]}\] Substitution of the nitrogen atom of isatin with alkyl groups resulted in increased reaction times and slightly lower yields, whereas alteration at the C-5 position of isatin revealed that a chloro group furnished the best product yields.

Cho and co-workers developed a stereoselective synthesis of 2-oxaspiro[\(m,n\)]alkane derivatives 62 through Prins–pinacol annulation of alkene diols 60 with a wide range of aliphatic or aromatic aldehydes and ketones 61 (Scheme 18).\[^{[34]}\] In the reaction, 60 was tested for Prins–pinacol reaction with p-nitrobenzaldehyde under the catalytic action of TMSOTf. The smooth reaction produced the desired products as single cis isomers.

Scheme 18.

Although these attractive targets had been prepared by multiple methods in the past, synthesis through Prins cyclization to afford substituted 2-oxaspiro[4.5]cyclic derivatives containing a quaternary oxacyclic ring system was very rare.\[^{[35]}\] Other aromatic aldehydes also performed consistently in the reaction, whereas in the case of the electron-rich 4-methoxybenzaldehyde a 1:1 mixture of two diastereomers was formed. Aliphatic aldehydes such as n-hexanal and isobutyraldehyde also proceeded to afford single diastereomers, whereas hexan-2-one gave a 2:1 mixture of two diastereomers. The reaction of acetophenone was diastereoselective, leading only to the cis isomer.

The reactions between 63 and various aromatic and aliphatic aldehydes 64 also proceeded to generate 2-oxaspiro[4.4]-nonanes 65 exclusively (Scheme 19), although the yields of the reactions were slightly decreased in comparison with those of the previous reactions leading to 62. The importance of the method lies in the fact that the 2-oxaspiro[4.5]decane and 2-oxaspiro[4.4]nonane motifs feature in a number of natural products such as wiphaphysalin F, epansolide A, and bakkenoxide A.\[^{[36]}\]
As an extension, the diol 67, prepared from 66 through a sequence of reactions, was treated with various aldehydes to give the oxatricyclic compounds 69 as single isomers with a cis-trans-cis stereochemical relationship between hydrogen (C5a), ketone (C9), hydrogen (C3a), and R (C3) (Scheme 20).

Canesi and co-workers developed an oxidative Prins–pinacol tandem process with phenolic substrates 70 in the presence of iodobenzene diacetate (diacetoxyiodo)benzene, DIB), in a mixture of dichloromethane and hexafluoro-2-propanol (HFIP) (CH2Cl2/HFIP, 3:1). Two quaternary carbon atoms were produced simultaneously, one of them a $\gamma$-betatwo $\beta$-spiro center (Scheme 21).[37] In this protocol, phenols are converted into reactive electrophiles through oxidative activation, and the dienone intermediates are trapped by suitable nucleophiles to yield the expected products. The method gives direct access to spiro[4.5]decanyl systems 71, a motif found in natural products such as anhydro-\betatwo-rotunol[38] and scopadulcic acid A7.[39] (Scheme 21.

The reaction was investigated with phenols substituted at any position on the lateral chain or at the ortho positions. The terminal alkene acts as an internal nucleophile to trigger the oxidative Prins process followed by a semipinacol-type rearrangement to produce the spirocyclic system. The presence of bromo substituents in the ortho positions of the phenol leads to higher yields. The anticipated ketones were obtained in good yields with very good diastereoselectivity. The protocol could be extended to the synthesis of targets containing contiguous quaternary carbon centers if the C-1 alkene position in the starting phenolic compound was substituted with two methyl groups (Scheme 22).

This method was also efficiently extended to provide a diastereoselective pathway starting from enantiopure substrate 75, containing a stereogenic allylic alcohol functionality on the acyclic lateral chain (Scheme 23).

Acetylenic substrates 80 were also successfully deployed, albeit the expected enones 81, each containing a tetrasubstituted alkene moiety, were produced only in modest yields (Scheme 24). It is noteworthy that the process is also viable with hindered alkynes, with yields similar to those obtained with unhindered alkynes. Phenols containing a gem-dimethyl benzylic functionality or a phenol propargylic ether in position 6 also underwent smooth transformation under the reaction conditions to afford the desired products.
The developed protocol was successfully extended to the formal total synthesis of (−)-platensimycin \((84)\). Tetrahydrofuran derivative \(82\) reacted with DIB to produce the hydroperoxide \(83\) through the oxidative Prins–pinacol tandem process. Several subsequent synthetic reaction sequences furnished the expected product (Scheme 25).

Scheme 25.

Liu and co-workers reported a cascade C–H activation directed by a transient group in which a reaction between alkynols \(85\) and 7-oxabenzonorbornadiene \(86\) produced spirocyclic dihydrobenzo[\(a\)]fluorenearans \(87\) with the aid of synergistic rhodium and scandium catalysis (Scheme 26). This transformation proceeded through C–H activation directed by a transient hemiketal group, dehydrative naphthylation, and intramolecular Prins-type cyclization. Various alkynols bearing groups such as Me, n-hexyl, \(\mathrm{Bu}, \text{MeO}, \text{BnO}, \text{Tso, Cl, or I at the para position of the aryl ring underwent the reaction efficiently, giving the desired products in good yields. In contrast, alkynols bearing strongly electron-withdrawing groups such as CF\(_3\) or CN did not react, as was also the case with heteroaryl alkynols. Alkynols substituted with phenyl, alkenyl, or ethynyl groups at the para position of the aryl ring were also tolerated, giving the products in good yields. Alkynols substituted with m-Me or m-MeO and o-MeO reacted well. The process tolerated multiple substitution at both the meta and para positions to yield the corresponding products. Alkynols substituted with secondary hydroxy groups gave the appropriate products, but those substituted with tertiary hydroxy groups did not participate in the reaction.

Scheme 26.

Reddy and co-workers employed a Prins/pinacol strategy aided by TMSOTf for the stereoselective synthesis of the spiro\([furan-3,1\prime]-naphthalene\)-2\'(one \(94\); Scheme 27). The model reaction utilized enediel \(92\) and benzaldehyde \((93)\) and the process was extended to various aldehydes of different electronic nature and to ketones such as cyclohexanone and cyclopentanone. Ketones gave lower yields than their aldehyde counterparts.

Scheme 27.

Kim and co-workers described rhodium(III)-catalyzed redox-neutral coupling of \(N\)-acylketimines generated in situ from 3-hydroxyisoinoinolines \(95\) and acrylates or quinones for the synthesis of bioactive spiroindene derivatives. Compounds of this type exhibit various properties such as aldose reductase inhibition or can act as chemical sensors (Scheme 28). Spiroindene \(97\), derived from quinone under the standard protocol, displayed potent anticancer activity, about two to three times stronger than that of the anticancer agent doxorubicin. Attempts to repeat the same methodology with other active olefins such as maleimides, maleates, fumarates, and cinnamates resulted in a different reaction pathway involving [3+2] annulation and yielded spiroindane scaffolds.

Scheme 28.

3.2. Six-Membered-Ring Structures

Sabitha and co-workers utilized TMSI (generated in situ) for the synthesis of spiroiodopyran derivatives through Prins-type cyclization. A reagent system consisting of TMSCI and NaI, together with acetone and but-3-en-1-ol \((99)\), provided 2,2-dimethyl-4-iodotetrahydropyran as the product (cf. Scheme 29). To assess its generality, this procedure was extended to cyclic ketones such as cyclopentanone (to afford \(100\)), cyclohexanone, cyclooctanone, and indan-2-one with equally consistent efficiency in terms of product yield.

Scheme 29.
Whereas indan-2-one reacted smoothly under these conditions, 4-tetralone and chromanone did not produce cyclization products. To extend the reaction, investigations were performed with homopropargylic alcohol (102). In the presence of TMSI, cyclohexanone (101, n = 2) reacted with 102 to give a mixture of two compounds (Scheme 30). Spirocyclic 4-iodo-5,6-dihydro-2H-pyran 103 (n = 2) was the major compound, but it was contaminated in a 80:20 ratio with the corresponding iodo-vinyl derivative (tetrahydrofuran) 104 (n = 2). In the case of indan-2-one and cycloheptanone, tetrahydropyran derivatives only separated without detecting any traces of pyran derivatives.

Gais and co-workers synthesized enantiopure spiroethers from α-hydroxydihydropyrans by Prins cyclization.[48] Although spiroethers had been achieved through Prins cyclization already,[49] intramolecular trapping of a dihydropyran cation leading to a spiroether bearing a Cl atom on the carbocyclic ring was a new variant.[50,51] Treatment of 105 with TiCl4 yielded, with high diastereoselectivities, the Cl-substituted spiroethers 106 and 107 in a ratio of 8:1 (Scheme 31). A similar cyclization of the bicyclic α-hydroxy-dihydropyran 108 also occurred to give a mixture of the tricyclic Cl-substituted spiroethers 109 and 110 in the same ratio.

Porco, Jr. and co-workers reported a stereoselective Prins cyclization for the synthesis of spirocyclic oxindole-pyran and -oxepene moieties under the influence of TMSOTf from homallylic and bis(homallylic) alcohols, respectively, and isatin ketal (Scheme 32).[52] The reaction between N-methylisatin dimethylketal[53] (112a) and allylsilane 111a afforded the corresponding spirooxindoles 113 and 114.

The apparent isomerization of the double bond (endocyclic vs. exocyclic olefin) suggested the possibility of a mechanistic pathway different from that of the expected intramolecular silyl-modified Sakurai reaction.[54] Intramolecular Prins-type cyclization[55] of homoallylic silyl ether 111b (R = H) could account for such an outcome. To support this hypothesis, the homoallylic silyl ether was subjected to the standard protocol to afford the corresponding products 113 and 114.

A series of homoallylic alcohols 111c, 111d, and 111e and isatin ketal 111b, 111c, and 111d were screened under these conditions to check the consistency of the method. Isatin ketal containing the NH functionality afforded the expected products. The presence of a bulky group such as a bromo substituent at the 4-position of the isatin ketal had a favorable effect on the diastereoselectivity. Racemization, usually observed during Prins cyclizations due to competing oxonia-Cope rearrangement,[56] was absent during the conversion. This was confirmed by measuring the enantiomeric excesses of the spirocyclic products, which did not deteriorate during the reaction (Figure 1).

Intramolecular Prins cyclization of bis(homallylic) alcohols 119 and isatin ketal 120 also successfully generated spirocyclic oxindole-oxepenes 121 with high diastereo- and regioselectivity (Scheme 33).

Canesi and co-workers reported an oxidative Prins transformation with phenol derivatives mediated by the hypervalent iodine reagent[58] DIB.[57] Phenols 122, with a terminal alkyne moiety as the nucleophile, in the presence of DIB in HFIP/CH2Cl2 (1:2) medium led to spiro[5.5]undecanyl core 124, found in natural products such as laurencenone B[59] (125) and platenacin[60] (126; Scheme 34).

Structural manipulations on the lateral chain, such as substitution at position 2 (R2), had an influence on the yield. A bromo substituent at the ortho position or, more importantly, a substituent in 1-position (R1), however, clearly increased the yield. The influence of substitution at 1-position was investigated in the
A possible Wagner–Meerwein transposition process was avoided by introducing a methylene group at the 3-position (compound 129) for the synthesis of 130 under the standard conditions. The sp² hybridization at this position should retard the ring-contraction process that would happen in the Wagner–Meerwein reaction in favor of nucleophilic capture (Scheme 36).

Wang and co-workers developed a unique spirocyclization for the development of functionalized spirooxindoles. Treatment of 3-allyl-3-hydroxy-1-methylindolin-2-one derivatives 131 with various aldehydes 132 in the presence of trimethylsilyl acetate (TMSOAc) and acetic acid in dichloromethane afforded tetrahydrospiro[indoline-3,2′-pyran]-2-one derivatives 133 (Scheme 37).

The procedure was assessed with aromatic and aliphatic aldehydes, along with substituted (5-Cl, 5-OMe) allylisatins. Compounds with halo substituents, such as 4-Cl, 4-Br, 4-CF₃, along with electron-donating groups such as 4-Me, 2-OMe on the phenyl ring engaged in cyclization. It was noted that the stereoselectivity and yields of the products were not influenced by the substituents on the aromatic aldehydes. Aromatic aldehydes gave higher yields than aliphatic aldehydes except in the cases of methacrolein and isobutyraldehyde, which gave moderate results. Benzaldehyde dimethylacetal underwent smooth reaction, whereas styrene oxide failed under similar conditions.

The method was further extended to spiro Prins fluorination with a variety of aldehydes 135 and 3-allyl-3-hydroxy-1-meth-
ylindolin-2-ones 134 to generate 4-fluoropyrans 136 (Scheme 38).

\[
\begin{align*}
\text{R}^1 \quad \text{O} \quad \text{O} \quad \text{H} + \text{RCHO} \quad \text{BF}_2\text{OEt}_2 (1.5 \text{ equiv.}) \quad \text{DCM, 0 °C to r.t.} \\
\text{134} \quad \text{135} \quad \text{136} \quad \text{Yield: 71–81%}
\end{align*}
\]

Scheme 38.

Krasavin and co-workers developed a Prins cyclization for the synthesis of spirocyclic amino alcohols 140 through reaction between azacycloalkanone derivatives such as 137 and homobifunctional alcohols such as 138, mediated by aqueous sulfuric acid or methanesulfonic acid (Scheme 39).[62]

\[
\begin{align*}
\text{MeSO}_3\text{H} (5.0 \text{ equiv.)} \quad \text{DCM, r.t.} \\
\text{137} \quad \text{138} \quad \text{139} \quad \text{(a) MeMgBr, THF, r.t.} \\
\text{140} \quad \text{(a or b) LIAHd, THF, reflux} \\
\text{Yield: 44–85%}
\end{align*}
\]

Scheme 39.

4. Conclusion

We have presented the application of tandem Prins cyclization reactions to the construction of spirocyclic frameworks. These spiro compounds can easily be used directly for the synthesis of bioactive spiro structures. The asymmetric catalysis route remains to be developed, although the first successful examples of catalytic asymmetric Prins reactions have appeared recently.[58] These tandem/cascade/domino Prins cyclization reactions provide an excellent platform for the synthesis of complex structures and offer great potential for the synthesis of highly challenging synthetic targets. Therefore, we hope that this review will enlighten researchers and trigger more developments in the utilization of these reactions for the execution of new and original chemistry in the area of organic synthesis.

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