STATE-OF-THE-ART APPROACHES TO THE SYNTHESIS OF 2*H*-PYRROLES

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Abstract. *1H-Pyrrole is one of the most abundant five-membered heterocycles to occur as part of a wide range of natural compounds. This abundance reflects the high aromaticity and thermodynamic stability of 1H-pyrroles. By contrast, 2H-pyrroles are thermodynamically less stable, although a number of naturally occurring compounds contain a 2H-pyrrole skeleton. This raises the question of how 2H-pyrroles can best be prepared. Hence, the present review summarizes the basic procedures available for the preparation of 2H-pyrroles. These procedures are divided into two types, namely (i) transition metal-catalyzed reactions and (ii) transition metal-free reactions. In addition, a brief overview of recently discovered procedures for the preparation of 3H-pyrroles is also provided for the purpose of comparison.*

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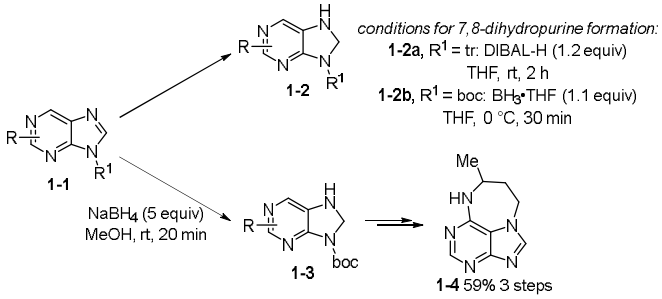
1. Introduction

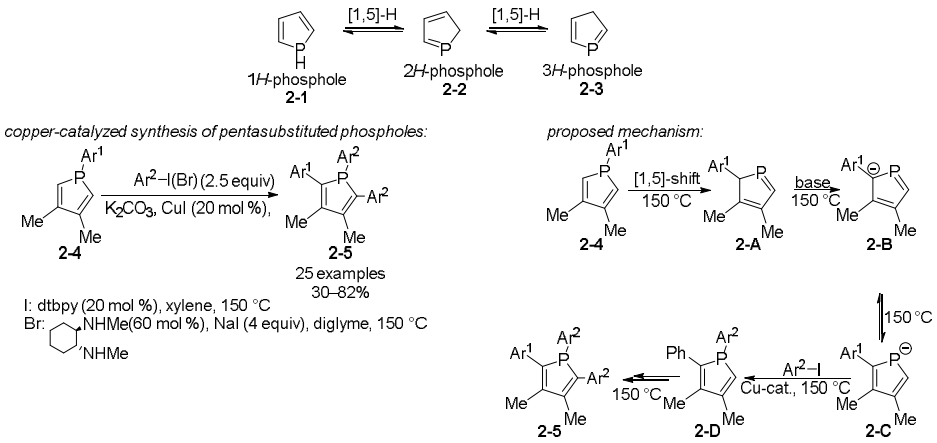
Heterocyclic compounds are cyclic substances that contain a heteroatom or several heteroatoms within their structures. Pyridine, piperidine, and 1,2,3-triazoles are all well-known heterocyclic compounds. A number of naturally occurring or artificially prepared compounds feature a heterocyclic moiety as an important component. Such substances have a wide range of applications, including bioactive agents or agrochemicals.[1] A large number of heterocyclic compounds exhibit significant aromaticity, which can be determined using different approaches.[2] From a synthetic perspective, heterocyclic hydrocarbons can be prepared by means of cyclization processes or *via* the modification of easily available heterocycles.[3] An important type of heterocycle modification involves the partial or full dearomatization of the parent heterocycle. An example of the partial dearomatization of the parent heterocycle is shown in Scheme 1. The starting N^9-substituted purine **1-1** can be reduced to 7,8-dihydropurines **1-2** by means of DIBAL-H,[4] the BH_3•THF complex,[5] or $NaBH_4$.[6] The 7,8-dihydropurines **1-2a** and **1-2b** are air-stable compounds that can be used for the preparation of N^7-alkylated halogenpurines,[4,5] adenines, guanines, and 6-mercaptopurines,[7] or for the total synthesis of heteromines I and J.[8] Alternatively, the synthesis of tetrahydro[1,4]diazepino[1,2,3-*gh*]purine **1-4** can be accomplished using the 7,8-dihydropurines **1-3**.[6]

A substantially different situation is found in the case of 1*H*-phosphole and 1*H*-pyrrole as examples of five-membered heterocycles. The structure of phosphole can be expressed by three tautomers, namely 1*H*-phosphole **2-1**, 2*H*-phosphole **2-2**, and 3*H*-phosphole **2-3** (Scheme 2). Quantum chemical calculations have revealed that 2*H*-phospole **2-2** has the lowest energy of the three.[9] More specifically, 3*H*-phosphole **2-3** has approximately 3.72 kcal·mol^{-1} higher energy and 1*H*-phospole **2-1** approximately 6.53 kcal·mol^{-1} higher energy than 2*H*-phosphole **2-2**. However, experimental efforts to investigate the properties and reactivity of phosphole derivatives have led to the preparation of an enormous number of substituted 1*H*-phospholes, while only a limited number of substituted 2*H*-phospholes are currently known. In addition, the activation energy required for the isomerization of phosphole **2-1** into **2-2** is 16.0 kcal·mol^{-1}, which is consistent with the observation that *P*-unsubstituted phospholes undergo smooth dimerization through the initial conversion

of 1*H*-phospholes into 2*H*-phospholes.[10] Recently, the reactivity of 2*H*-phospholes has been exploited for the preparation of the pentasubstituted phosphole **2-5** (Scheme 2).[11] The reported transformation makes use of copper-catalyzed arylation and the alkenylation of the trisubstituted phosphole **2-4**. The proposed mechanism relies on the formation of the 2*H*-phospholes **2-A** and **2-B** as key intermediates. Then phospholide **2-C** is transformed into tetrasubstituted phosphole **2-D** by copper-catalyzed *P*-arylation. The repetition of these steps ends the synthesis of phospholes **2-5**.



Scheme 1. The synthesis of stable 7,8-dihydropurines from *N*[9]-substituted purines.



Scheme 2. The use of unstable 2*H*-phospholes for the synthesis of the pentasubstituted phosphole **2-5**.

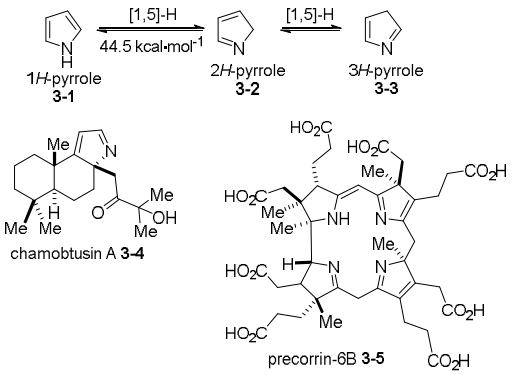
Yet, 1*H*-pyrrole **3-1** is strongly aromatic when compared with 1*H*-phosphole **2-1** (Scheme 3). The consequence of the high aromaticity of 1*H*-pyrrole **3-1** is the high activation energy of 44.5 kcal·mol^{-1} in relation to the isomerization of 1*H*-pyrrole **3-1** into 2*H*-pyrrole **3-2**.[9] In addition, the high aromaticity of 1*H*-pyrrole **3-1** is also responsible for the increased energy of the non-aromatic pyrrole derivatives **3-2** and **3-3** (13.02 kcal·mol^{-1} and 15.19 kcal·mol^{-1}, respectively). Nevertheless, some naturally occurring substances contain 2*H*- and 3*H*-pyrroles within their structures. Selected examples of such compounds include chamobtusin A **3-4** and precorrin-6B **3-5**. The superior thermodynamic stability of 1*H*-pyrrole and the different structures of 2*H*- and 3*H*-pyrrole prompted us to compare the procedures used for the preparation of 2*H*- and 3*H*-pyrroles in the present review.

2. Synthesis of 2*H*-pyrroles by means of transition metal-catalyzed reactions

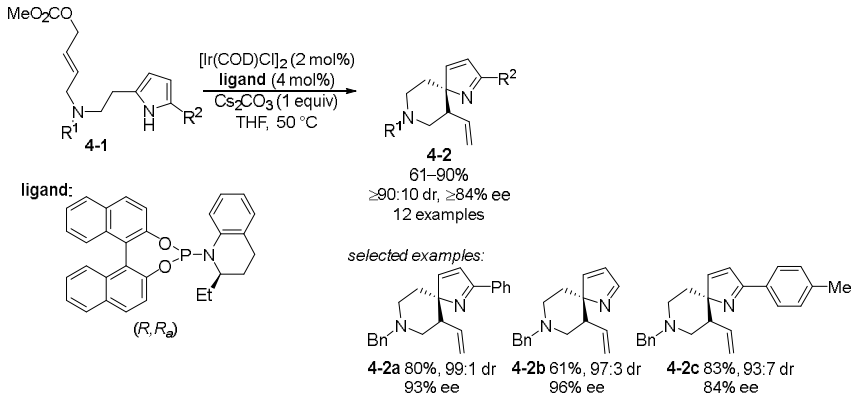
2.1. Iridium-, rhodium-, and silver-catalyzed synthesis of 2*H*-pyrroles

The You's group reported the Ir-catalyzed intramolecular asymmetric dearomatization of pyrrole **4-1** to produce the six-membered spiro-*2H*-pyrrole **4-2** with high diastereo- and enantioselectivity (Scheme 4).[12] The reaction was catalyzed by $[Ir(cod)Cl]_2$ in the presence of the nonracemic BINOL-derived ligand. Under

optimized conditions, a series of variously functionalized spiro-*2H*-pyrroles **4-2** was efficiently generated from the starting 2-pyrrolyl allylic carbonate **4-2** in good isolated yields and with high dr and ee, as shown by selected examples **4-2a**–**4-2c**.



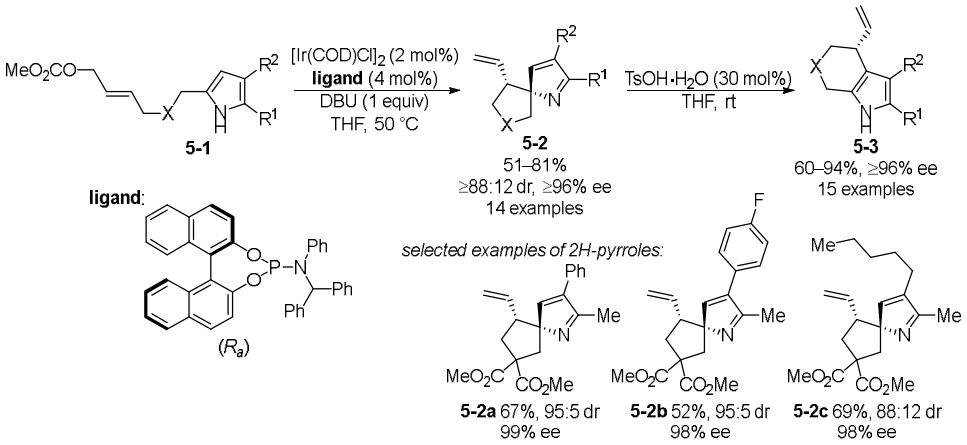
Scheme 3. Structures of 1*H*-, 2*H*-, and 3*H*-pyrrole and naturally occurring examples of such compounds.



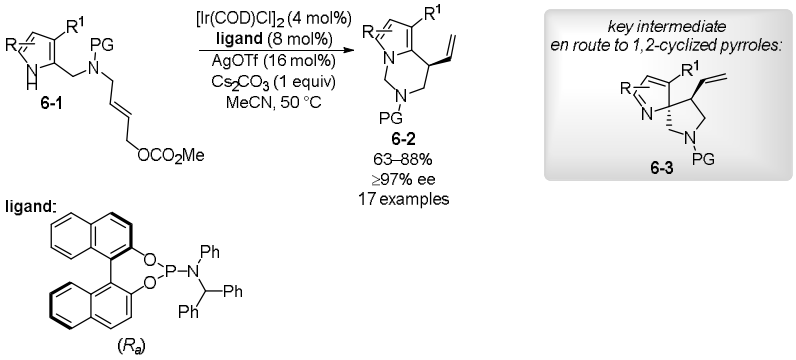
Scheme 4. Enantioselective Ir-catalyzed dearomative spirocyclization of 2,5-disubstituted pyrroles.

The same group has shown that the spirocyclization-dearomatization strategy can be used for the synthesis of five-membered spiro-*2H*-pyrrole derivatives **5-2** from pyrroles bearing an all-carbon tethered allylic carbonate **5-1** (Scheme 5).[13] Again, the $[Ir(cod)Cl]_2$ catalyst was employed to catalyze the transformation, furnishing the spiro-products **5-2** in satisfactory yields (51-81%) and with uniformly excellent diastereo- and enantioselectivities as highlighted by the synthesis of 2*H*-pyrroles **5-2a**–**5-2c**. When the 2*H*-pyrroles were treated with catalytic amounts of $TsOH{\cdot}H_2O$, the five-membered spiro-*2H*-pyrroles **5-2** smoothly underwent C2-to-C3 ring-expansive allylic migration to produce the corresponding six-membered bicyclic pyrroles **5-3** with preserved stereochemistry in high yields.

Further expanding the use of the dearomatization/migration reaction sequence, the You's group reported the enantioselective synthesis of tetrahydropyrrolo[1,2-c]pyrimidine derivatives **6-2** from carbonates **6-1** (62-88% yield, up to >99% *ee*) from *in situ*-generated C3-substituted spiro-*2H*-pyrroles **6-3** (Scheme 6).[14] In contrast to their previous study,[13] the C2-to-C3 migration was deliberately blocked in this system, which instead favored ring expansion *via* C2-to-N1 alkyl migration. The Ir-based catalytic setup ($[Ir(cod)Cl]_2$, chiral phosphoramidite ligand, AgOTf) was crucial to efficiently promoting this transformation.

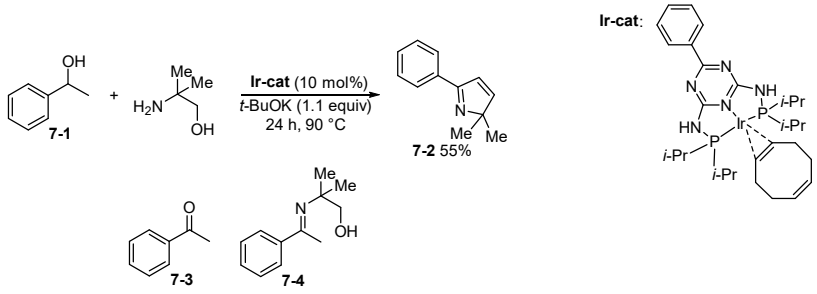


Scheme 5. Ir-catalyzed synthesis of 2*H*-pyrroles en route to tetrasubstituted 1*H*-pyrroles.



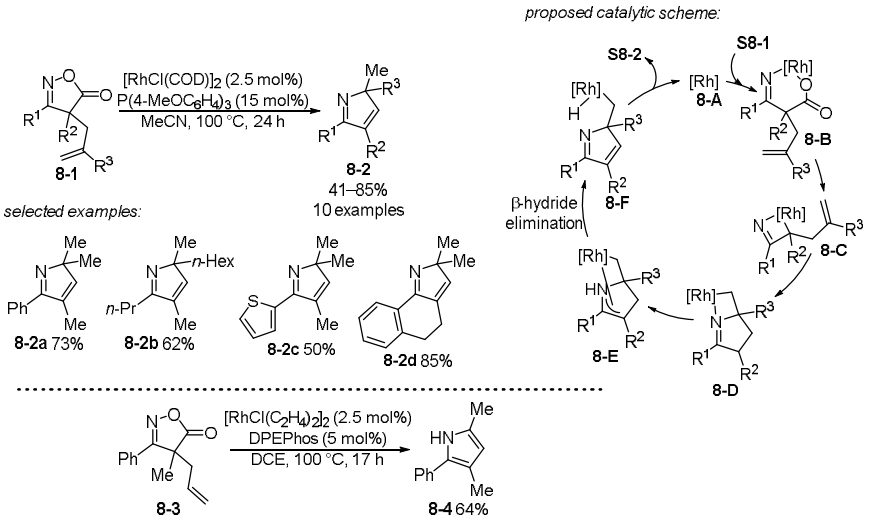
Scheme 6. 2*H*-Pyrroles as intermediates in Ir-catalyzed C–2 to N–1 cyclization.

In 2013, a general procedure for the preparation of substituted 1*H*-pyrroles was published (Scheme 7).[15] The developed procedure can be used for the preparation of 2*H*-pyrroles, as demonstrated by the preparation of the 2*H*-pyrrole **7-2** in a 55% isolated yield. Based on the proposed mechanism for the synthesis of 1*H*-pyrroles, it can be deduced that the Ir-catalyst dehydrogenates the starting alcohol **7-1** into the ketone **7-3**. Then, the condensation of the formed acetophenone **7-3** with the amino alcohol affords the imine **7-4**. Finally, the synthesis of the 2*H*-pyrrole **7-2** is accomplished by the Ir-catalyzed dehydrogenative alkylation of the imine **7-4**.



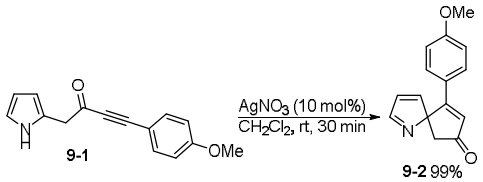
Scheme 7. Ir-catalyzed synthesis of 2*H*-pyrroles.

A different approach for the transition metal-catalyzed synthesis of 2*H*-pyrroles was described by Okamoto and Ohe (Scheme 8).[16] The authors discovered that isoxazolone **8-1** can be transformed into 2*H*-pyrroles **8-2** using a Rh-catalyst. Optimal reaction conditions were obtained by means of extensive optimization, which included the heating of the reagent, the Rh-catalyst, and the P(4-MeOC$_6$H$_4$)$_3$ ligand in acetonitrile. This methodology allows for the preparation of 2*H*-indoles with aliphatic, aromatic, and heteroaromatic substituents. The preparation of fused 2*H*-pyrroles is also feasible, as illustrated by the selected examples **8-2a–8-2d**. For the preparation of 2*H*-pyrroles, the R^3 must be a carbonaceous substituent. For the isoxazolone **8-3** with an allyl group, the formation of the *1H*-pyrrole **8-4** was observed in a 64% isolated yield under slightly modified reaction conditions. The proposed mechanism involves the reaction of Rh-catalyst **8-A** with the starting isoxazolone **8-1** to form the complex **8-B**, which readily decarboxylates. The resulting complex **8-C** undergoes intramolecular cycloaddition, while the subsequent isomerization of the complex **8-D** provides the η^3-allylrhodium intermediate **8-E**. Finally, 2*H*-pyrroles are formed by means of β-hydride elimination followed by reductive elimination from the complex **8-F**.



Scheme 8. Rh-catalyzed isoxazolone isomerization into 2*H*-pyrrole.

Similar to the Pd-catalyzed spirocyclization of ynones for the preparation of 3*H*-pyrroles (Scheme 25), the Ag-catalyzed spirocyclization of the ynone **9-1** can be used for the preparation of the 2*H*-pyrrole **9-2** (Scheme 9).[17] The reaction conditions were mainly optimized for the preparation of 3*H*-indoles, although the monosubstituted pyrrole **9-1** isomerized into the 2*H*-pyrrole **9-2** in a quantitative yield under modified reaction conditions.

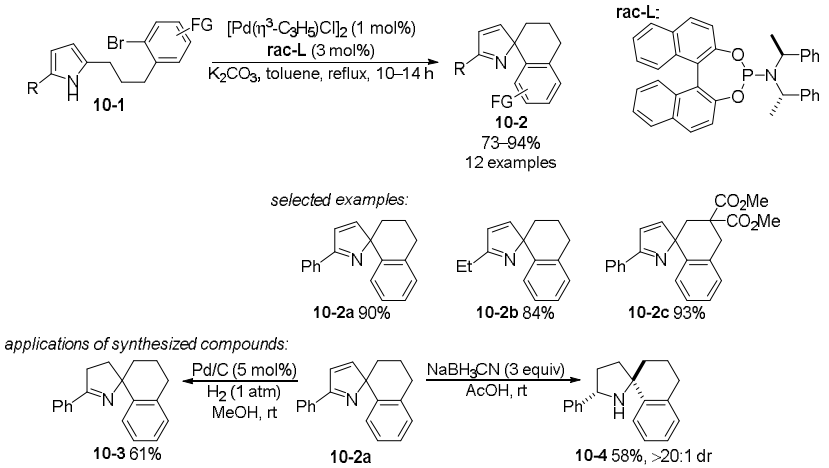


Scheme 9. Ag-catalyzed spirocyclization of monosubstituted 1*H*-pyrrole **9-1**.

2.2. Palladium-catalyzed synthesis of 2*H*-pyrroles

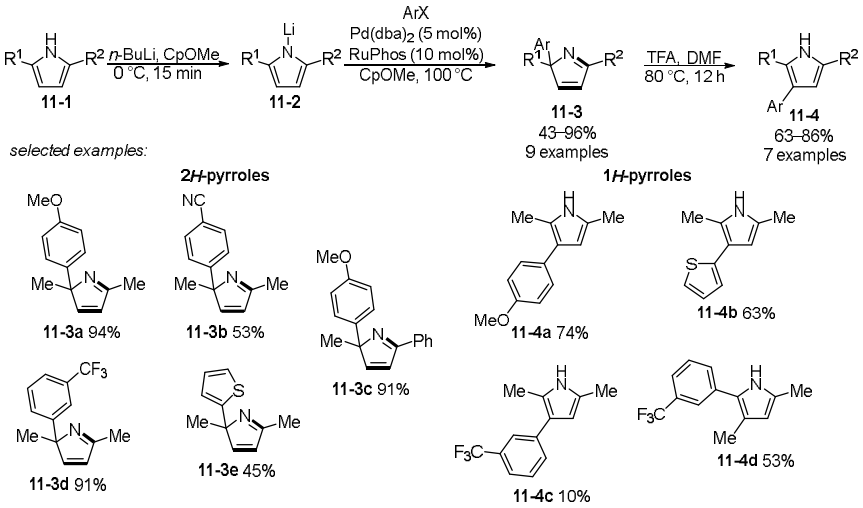
The Pd-catalyzed intramolecular arylation of 1*H*-pyrroles was published in 2013 (Scheme 10).[18] In this case, the starting 2,5-disubstituted 1*H*-pyrrole **10-1** was converted into the spirocompound **10-2** with a

2*H*-pyrrole moiety using a Pd-catalyst and **rac-L** ligand in refluxing toluene and potassium carbonate as a base. This procedure succeeded in the synthesis of 12 examples of 2*H*-pyrroles in high yields including three selected examples **10-2a**–**10-2c**. Then, based on the selected example of 2*H*-pyrrole **10-2a**, chemoselective hydrogenation using a Pd/C catalyst under mild conditions was performed to give the cyclic imine **10-3** in an 61% yield. By contrast, reduction using sodium cyanoborohydride ($NaBH_3CN$) provided pyrrolidine **10-4** with high diastereoselectivity.



Scheme 10. Pd-catalyzed dearomative coupling of 2,5-disubstituted pyrroles **10-1**.

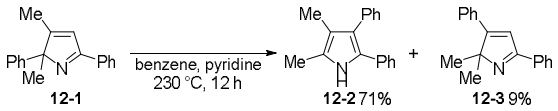
The intermolecular dearomative arylation of the 2,5-disubstituted pyrrole **11-1** was reported in 2017 (Scheme 11).[19] The starting pyrrole **11-1** was *N*-lithiated with *n*-butyllithium to form *N*-lithiated pyrroles **11-2**, and the Pd-catalyzed arylation gave 2*H*-pyrroles **11-3** in satisfactory isolated yields. The selected examples **11-3a–11-3e** illustrate that lower yields of 2*H*-pyrroles were achieved for the substrates with a nitrile group in *para* position **11-3b** as well as for the 2-thienyl substituent **11-3e**.



Scheme 11. Pd-catalyzed intermolecular arylation of 1*H*-pyrroles.

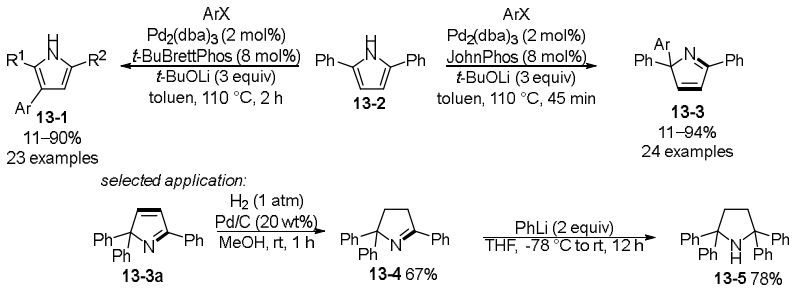
The starting pyrrole with phenyl and methyl groups gave **11-3c** as the product of regioselective arylation. Then, the prepared 2*H*-pyrroles were regioselectively transformed into 1,2,5-trisubstituted 1*H*-pyrroles **11-4** by means of trifluoroacetic acid in DMF at 80 °C as illustrated by the selected examples of 1*H*-pyrroles **11-4a** and **11-4b**. The exception in this case was a 2*H*-pyrrole with a 3-(trifluoro)phenyl group **11-3d**, which gave a mixture of the regioisomers **11-4c** and **11-4d** (Scheme 11).

The facile conversion of the 2*H*-pyrroles **11-3** into the 1*H*-pyrroles **11-4** under acid catalysis is in good agreement with the calculated thermodynamic stability of 1*H*-pyrroles when compared with 2*H*- and 3*H*-pyrroles. The same was also demonstrated by the thermal isomerization of the 2*H*-pyrrole **12-1**, which was successfully isomerized into the 2*H*-pyrrole **12-3** and 1*H*-pyrrole **12-2** in 71% yield by heating to 230 °C for 12 h (Scheme 12).[20]



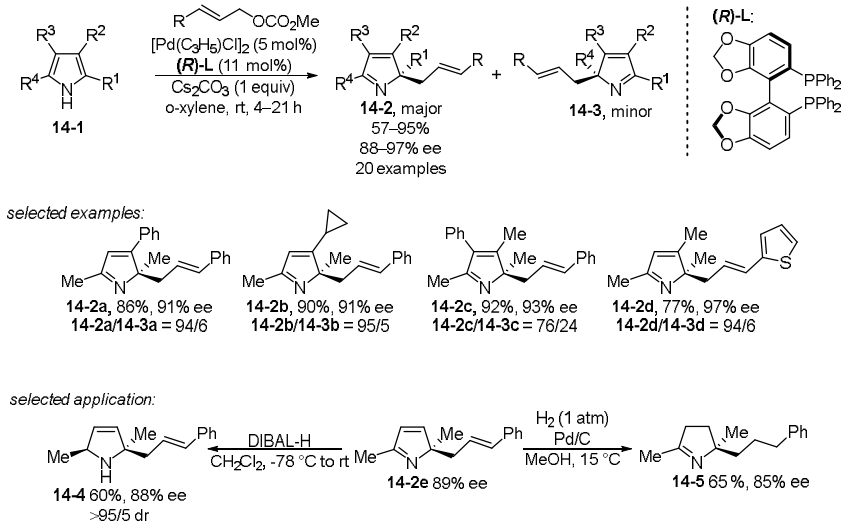
Scheme 12. Thermal isomerization of 2*H*-pyrrole **12-1**.

The regioselective C2- and C3-arylation of 2,5-disubstituted pyrroles has also been described (Scheme 13).[21] The regioselective course of the arylation was achieved using a JohnPhos ligand that favored the C2-arylation product **13-3**, while *t*-BuBrettPhos favored the formation of the C3-arylation product **13-1**. This procedure was mainly optimized for the 2,5-diphenyl-1*H*-pyrrole **13-2**, although other substituents were also used to a limited extent. An application of the synthesized 2*H*-pyrroles involved the preparation of the 2,2,5,5-tetraphenylpyrrolidine **13-5** by means of the regioselective hydrogenation of the 2*H*-pyrrole **13-3a** to 2,2,5-triphenyl-3,4-dihydro-2*H*-pyrrole **13-4** followed by phenyllithium addition to the imino group.



Scheme 13. Pd-catalyzed dearomative C2- and C3-arylation of 1*H*-pyrrole **13-2**.

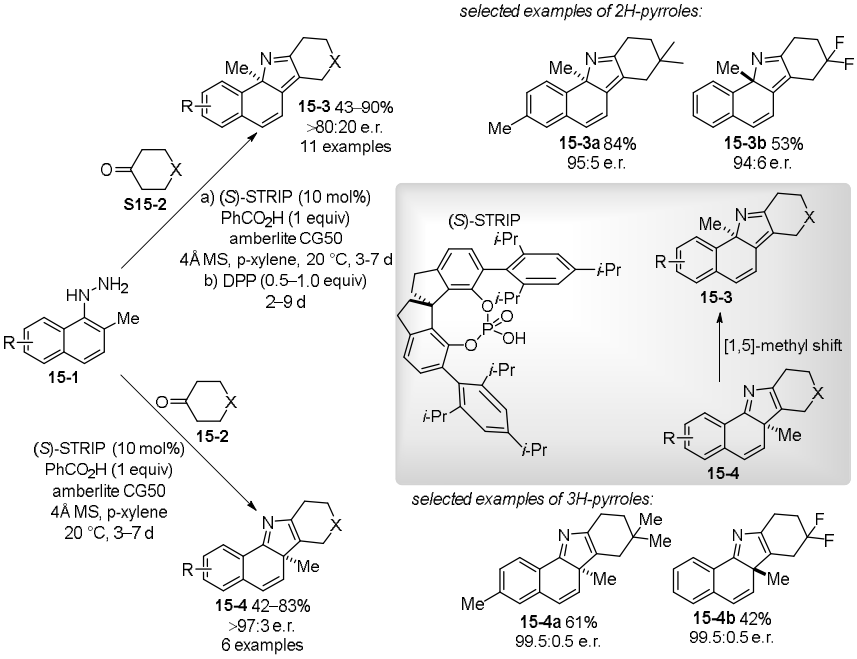
The enantioselective preparation of the 2*H*-pyrroles **14-2** *via* Pd-catalyzed allylation was reported by You in 2014 (Scheme 14).[22] In contrast to dearomative arylations, the published dearomative allylation process of 1*H*-pyrroles **14-1** proceeds under mild reaction conditions in *o*-xylene at room temperature. The high enantioselectivity of the overall process is achieved through the use of the bidentate ligand **(*R*)-L**. This reaction also relies on a high regioselectivity to predominantly form the regioisomer **14-2**, while the formation of the opposite regioisomer **14-3** is suppressed. Selected examples of 2*H*-pyrroles **14-2a**–**14-2d** illustrate the overall isolated yields and regioselectivity of 2*H*-pyrrole formation. As with other Pd-catalyzed arylations, the use of 1,2-disubstituted pyrroles is necessary, although the reaction also works in the case of 1,2,3,4-tetrasubstituted pyrroles, as shown by the synthesis of the fully substituted 2*H*-pyrrole **14-2c**. You emphasized the practical application of this protocol through the chemoselective reduction of the imino group of 2*H*-pyrrole **14-2e** leading to the 2,5-dihydro-1*H*-pyrrole **14-4** or through the enantioselective preparation of the 3,4-dihydro-2*H*-pyrrole **14-5** by means of the chemoselective reduction of both C=C bonds. Density-functional theory (DFT) calculations were used to explain the mechanism behind these observations.[23]



Scheme 14. Enantioselective Pd-catalyzed dearomative arylation of substituted pyrroles to give 2*H*-pyrroles.

3. Transition metal-free synthesis of 2*H*-pyrroles

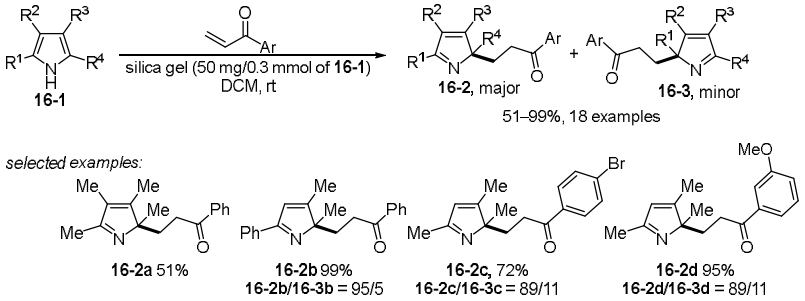
A modification of the Fischer indole synthesis can be used for the preparation of 2*H*- and 3*H*-pyrroles (Scheme 15).[24] In this paper, the starting naphthyl hydrazine **15-1** was mixed with the cyclohexanone **15-2** in the presence of a catalytic amount of (*S*)-STRIP. Then, the 3*H*-pyrroles **15-4** were obtained as the main product with excellent enantiomeric excess.



Scheme 15. Organocatalytic synthesis of 2*H*- and 3*H*-pyrroles **15-3** and **15-4**.

Moreover, it was experimentally verified that the addition of diphenyl phosphate (DPP) to 3*H*-indoles induces a [1,5]-methyl shift to form the 2*H*-pyrroles **15-3**. During this isomerization, limited erosion of the absolute configuration at the stereogenic center occurs, as shown on selected pairs of synthesized 2*H*- and 3*H*-pyrroles **15-3a** and **15-3b**, **15-4a** and **15-4b**, respectively (Scheme 15).

The dearomative alkylation of substituted pyrroles (Scheme 16) was reported in 2015.[25] The conversion of the starting 1*H*-pyrrole **16-1** into 2*H*-pyrroles **16-2** was achieved by means of the reaction with α,β-unsaturated ketones in the presence of silica gel. During the optimization experiments, it was shown that the supplier and size of the silica gel had minimal effects on the course of the reaction. The reaction is characterized by high regioselectivity as indicated by the ratio of the 2*H*-pyrroles **16-2** and **16-3**. Selected examples of the 2*H*-pyrroles **16-2a**–**16-2d** show that the scope of the reaction is limited to 1*H*-pyrroles with simple alkyl and aryl substituents, while the tolerance of the functional groups at the ketone is also limited to the methoxy group and halogens.



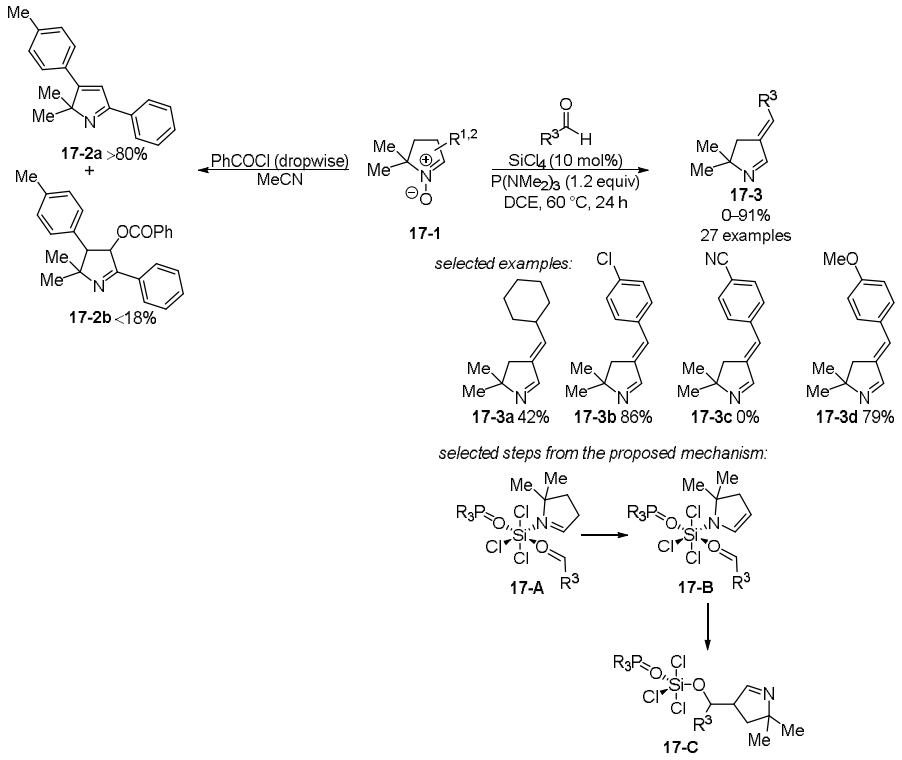
Scheme 16. Silica gel promoted dearomative Michael addition for the synthesis of 2*H*-pyrroles.

2*H*-Pyrroles can also be prepared from nitrones represented by the general structure **17-1** (Scheme 17). However, the course of the reaction depends on both the structure of the starting nitrone **17-1** and the reaction conditions. If a nitrone is treated with benzoyl chloride, the 2*H*-pyrrole **17-2a** is formed as the main product alongside by-product **17-2b**. The formation of the main reaction product **17-2a** proceeds *via* hetero-Cope rearrangement. However, the scope of the reaction is limited to a few examples.[26a] Yet, the reaction of nitrones with aldehydes in the presence of a catalytic amount of silicon chloride and a base gives α,β-unsaturated imines **17-3**.[26b] This reaction works well with benzaldehydes bearing electron-donating **17-3d** or halogen **17-3b** substituent and aliphatic aldehydes **17-3a**. This reaction works well with benzaldehydes bearing electron-donating **17-3d** or halogen **17-3b** substituent and aliphatic aldehydes **17-3a**. If the starting compound with a nitrile group **17-3c** is used, the reaction does not work. The authors hypothesize that the formation of the α,β-unsaturated imines **17-3** involves the formation of the silylated imine **17-A** that isomerizes into the enamine **17-B**. The next step involves an aldol reaction that affords the intermediate **17-C**, and the target product is formed by means of elimination.

Enones can also undergo a spirocyclization reaction to form 2*H*-pyrroles. An example of this cyclisation is shown in Scheme 18.[27] The starting substances are transformed into the 2*H*-pyrroles **18-2** under optimized reaction conditions. The scope of the reaction is limited to the preparation of only eight 2*H*-pyrroles, while halogens are well tolerated, as can be seen from the selected examples **18-2a** and **18-2b**. This reaction is interesting from a mechanistic perspective because, unlike previous work, the authors explained the formation of the final products **18-2** *via* aerobic oxidation of the benzyl group. Thus, the starting αβ-unsaturated ketone **18-1** undergoes cyclization to form the intermediate **18-A**. Subsequent protonation produces the exocyclic alkene **18-B**, which is isomerized to the 2*H*-pyrrole **18-C**. The hydroperoxide **18-D**, which is formed by oxidation of a benzyl CH_2 group with oxygen, isomerizes to the reaction product **18-2**.

An extension of the above-mentioned work[27] involves the cyclization of the β-enaminones **19-1** in the presence of cesium carbonate as base in acetonitrile to give the 2*H*-pyrroles **19-2** including five examples of the synthesized 2*H*-pyrroles **19-2a**–**19-2e** (Scheme 19).[28] The proposed mechanism is similar to that

described in previous work,[27] and **19-A**–**19-C** have been proposed as intermediates leading to 2*H*-pyrroles **19-2**. The absence of a benzyl CH_2 group does not allow for the oxidation of the CH_2 group into a carbonyl group. The scope of the reaction is wide and the isolated yields are high. However, the tolerance of the functional groups is limited to the nitro and methoxy groups and halogens.



Scheme 17. Synthesis of 2*H*-pyrroles from nitrones.

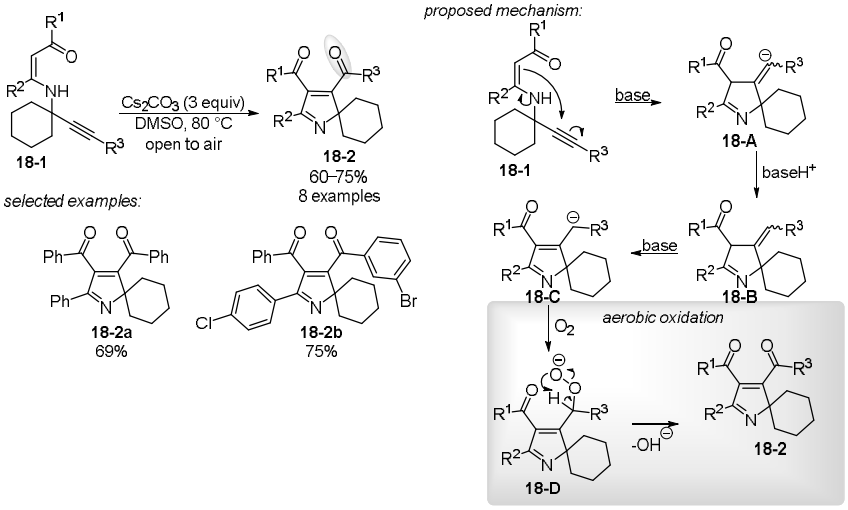
A highly enantio- and diastereoselective multicomponent-oxidation approach to the preparation of 2*H*-pyrroles was described by Wang in 2017 (Scheme 20).[29] Initially, the spirocyclic 2-oxindoles **20-4** are prepared *via* the reaction of 2-oxindole **20-1** with aldehyde **20-2** and ynone **20-3**. Then, the formed 2-oxindoles **20-4** are oxidized into 2*H*-pyrroles **20-5** by means of DDQ. This enantioselective formation of 2-oxindoles using [3+2] cycloaddition is catalyzed by a nonracemic phosphoric acid (**Cat**), and products **20-4** are formed in quantitative yields and with excellent enantioselectivity exceeding 97% ee in most cases. The generated enantioselectivity is preserved during oxidation into the 2*H*-pyrroles **20-5** as illustrated by the selected examples **20-5a**–**20-5d**.

A similar approach involving DDQ oxidation for the synthesis of 2*H*-pyrroles **21-2** was described in 2003 by Vennerstrom (Scheme 21).[30] The starting compound **21-1** is readily available from γ-nitroketones, and the oxidation of the pyrrolidines is carried out in 1,4-dioxane at room temperature. Selected examples of synthesized 2*H*-pyrroles **21-2a**–**21-2g** illustrate that the scope of the reaction is limited to 2*H*-pyrroles with simple aryl and heteroaryl substituents without functional groups.

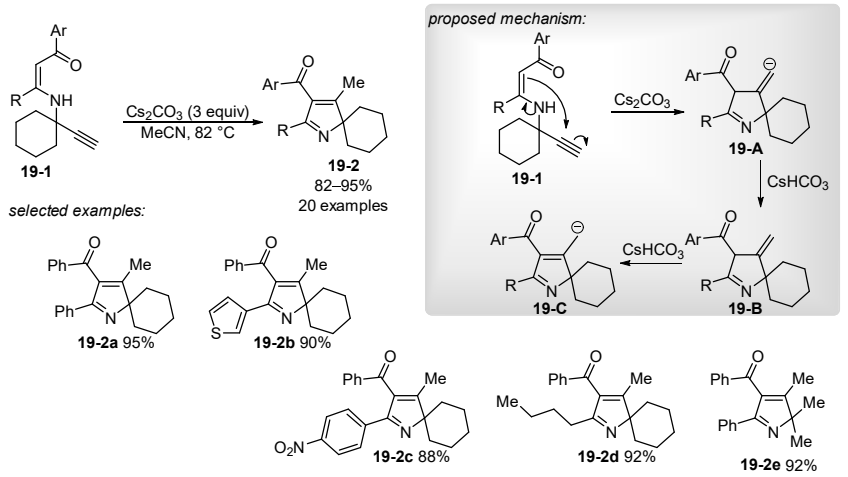
The oxidation of substituted pyrrolidine using DDQ in 1,4-dioxane was also used for the preparation of spirocyclic 2*H*-pyrrole by Wang[31] and Lu.[32]

Recently, a novel approach for the synthesis of 2*H*-pyrroles was described (Scheme 22).[33] The one-pot two-step preparation of the 2*H*-pyrroles **22-3** is based on the [3+2] cycloaddition of alkylimines **22-1** with terminal alkynes **22-2** to form the pyrroline **22-4**. The prepared pyrroline **22-4** is subsequently oxidized into

2*H*-pyrroles **22-3** using chloranil. The optimized reaction conditions can be applied for the synthesis of 2*H*-pyrroles **21**, but the functional group tolerance is limited as illustrated by selected examples **22-3a**–**22-3d**.



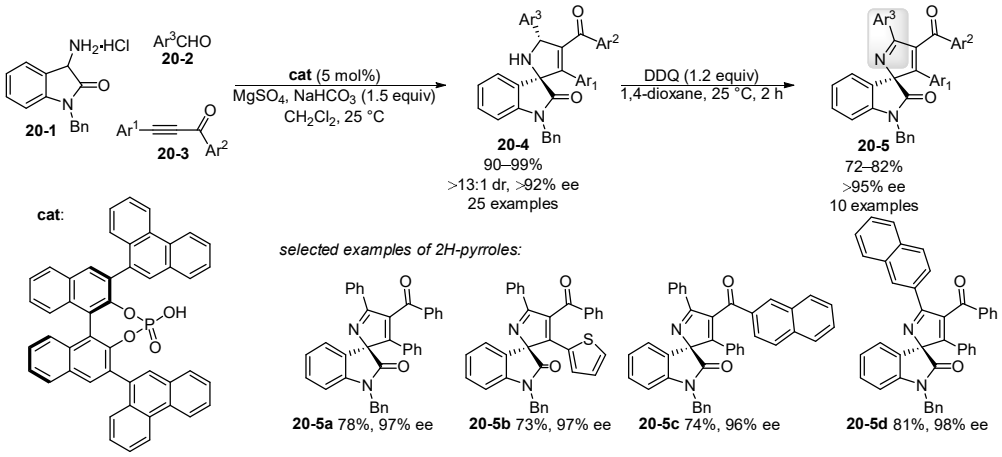
Scheme 18. Spirocyclization of enones leading to 2*H*-pyrroles.



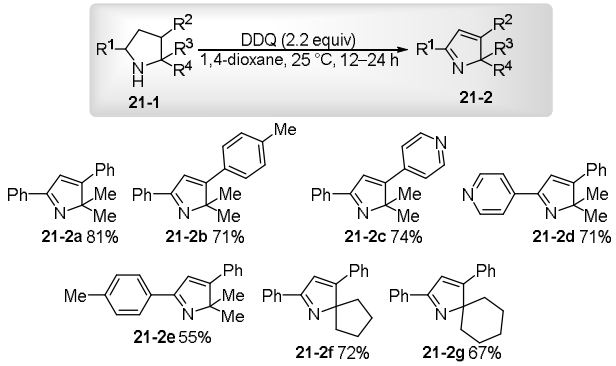
Scheme 19. Synthesis of 1-azaspiro[4.5]deca-1,3-dienes 2,2-disubstituted 2*H*-pyrroles from *N*-propargylic β-enaminones.

A simple process for the preparation of 2*H*-pyrroles is shown in Scheme 23.[34] The reaction makes use of the aza-spirocyclization of alkynylimine **23-1**, which is promoted by the presence of tetra-*n*-butylammonium halides. Using TBAB or TBAI, the 2*H*-pyrroles **23-2** and **23-3** with a bromine and an iodine atom in their structures can be prepared including three selected examples **23-2a**–**23-2c**. The authors proposed two alternative mechanisms: electrophilic and radical. The initial step common to both mechanisms involves the two-electron-oxidation (TEO) and one-electron-oxidation (SEO) of the halide ion. The proposed electrophilic mechanism is initiated by the formal electrophilic addition of X^+ to the triple bond to form the intermediate **23-A**, which then reacts with the electron-rich aromate producing the

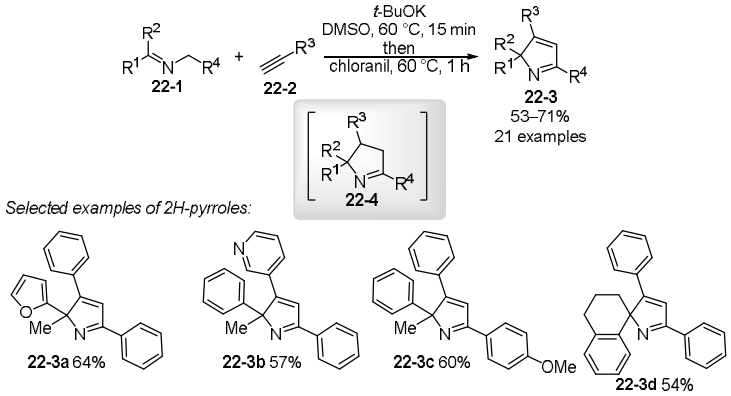
spirocyclic compounds **23-B** and **23-C**. Next, the final products **23-2** and **23-3** are formed by means of the hydrolysis of the methoxy group. The radical mechanism follows similar steps, although the authors have been unable to confirm the mechanism responsible for the formation of the 2*H*-pyrroles.



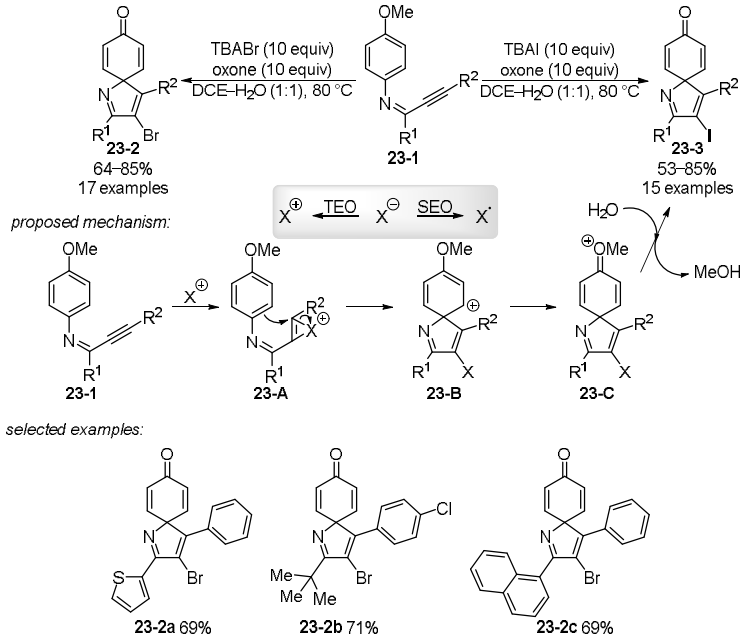
Scheme 20. Synthesis of 2*H*-pyrroles *via* oxidation with DDQ.



Scheme 21. Oxidation of tetrasubstituted pyrrolidines using DDQ to give 2*H*-pyrroles.

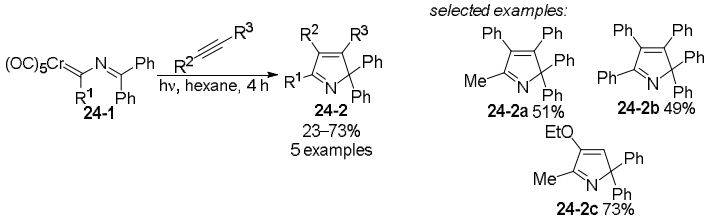


Scheme 22. Synthesis of 2*H*-pyrrole *via* [3+2] cycloaddition followed by pyrrolines oxidation.



Scheme 23. Halogen-promoted spirocyclization for the synthesis of 2*H*-pyrroles.

The rich chemistry of Fischer transition metal carbene complexes[35] can also be used for the preparation of 2*H*-pyrroles, as illustrated in Scheme 24.[36] The starting imine–carbene complex **24-1** can be converted into the 2*H*-pyrroles **24-2** in satisfactory isolated yields *via* a photochemically initiated reaction with alkynes. The scope of the reaction is limited to the preparation of only five compounds including three examples **24-2a**–**24-2c**, although a mechanism for the described reaction has been proposed based on quantum chemical calculations.[36a]



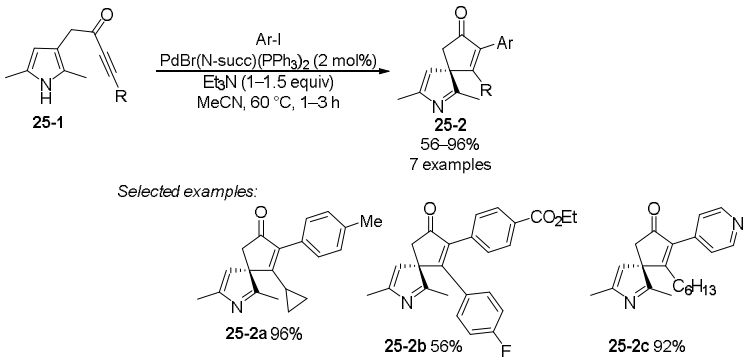
Scheme 24. Reaction of chromium imine–carbene complexes with alkynes leading to substituted 2*H*-pyrroles.

4. Synthesis of 3*H*-pyrroles

Generally, 3*H*-pyrroles can be prepared through the modification of 1*H*-pyrroles or from oximes, nitriles, isonitriles, and carbonyl compounds. These procedures have been examined in recent reviews.[37] Thus, the aim of this section is to provide a basic overview of important recent procedures that can be used for the preparation of 3*H*-pyrroles.

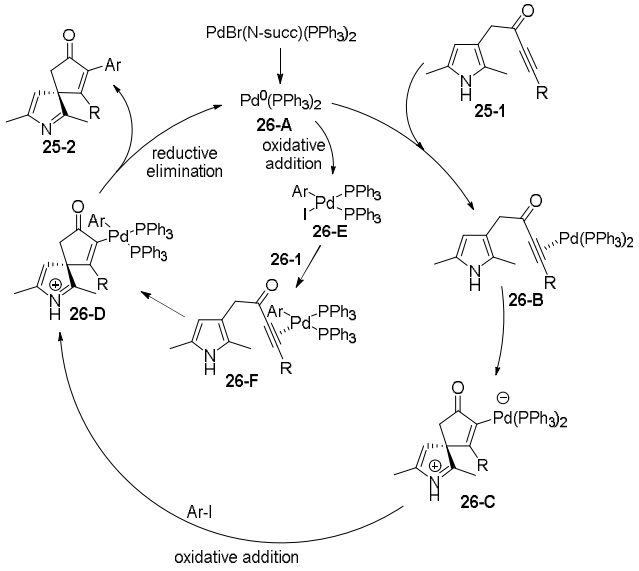
The transition metal-catalyzed preparation of the 3*H*-pyrroles **25-2** was reported in 2019 by Taylor and Unsworth (Scheme 25).[38] The reaction is based on the dearomative spirocyclization of the trisubstituted pyrroles **25-1** to form the 3*H*-pyrroles **25-2** in high yields. The reaction was primarily developed for the

preparation of 3*H*-indoles (40 examples), although it is also suitable for the preparation of 3*H*-pyrroles, as illustrated by the selected examples of synthesized pyrroles **25-2a–25-2c**.



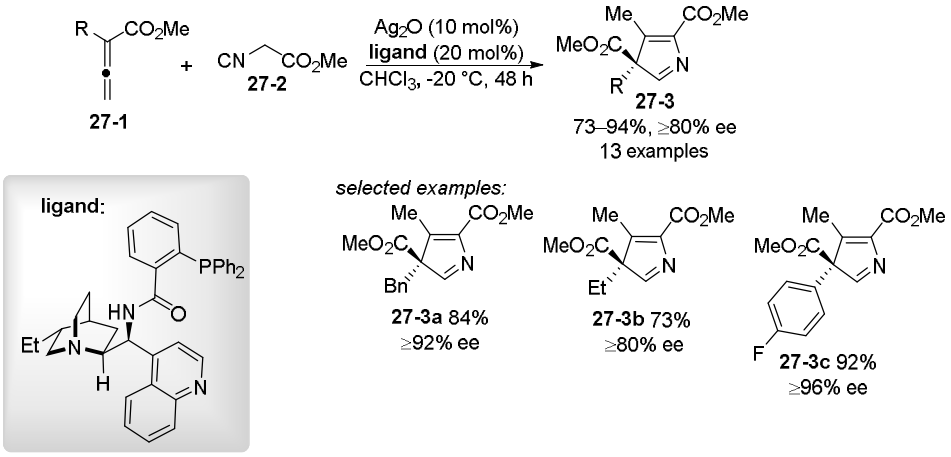
Scheme 25. Pd-catalyzed synthesis of 3*H*-pyrroles *via* dearomative spirocyclization of ynones.

The formation of the 3*H*-pyrrole **25-2** under the optimized reaction conditions can be explained using two catalytic cycles (Scheme 26).[38] The initially formed catalytic particle $Pd(PPh_3)_2$ **26-A** is coordinated by the triple bond of the starting pyrrole **25-1** to form complex **26-B**. The subsequent spirocyclization provides complex **26-C**, which is transformed into the final product **25-2** by means of oxidative addition to give complex **26-D** followed by reductive elimination. An alternative mechanism for the formation of 3*H*-pyrroles involves the oxidative addition of the starting aryl iodide to Pd(0) complex **26-A** to give Pd(II) complex **26-E**. Pd(II) is subsequently coordinated by the triple bond of the starting material **25-1** to yield intermediate **26-F**, which undergoes spirocyclization followed by reductive elimination to provide the final product.



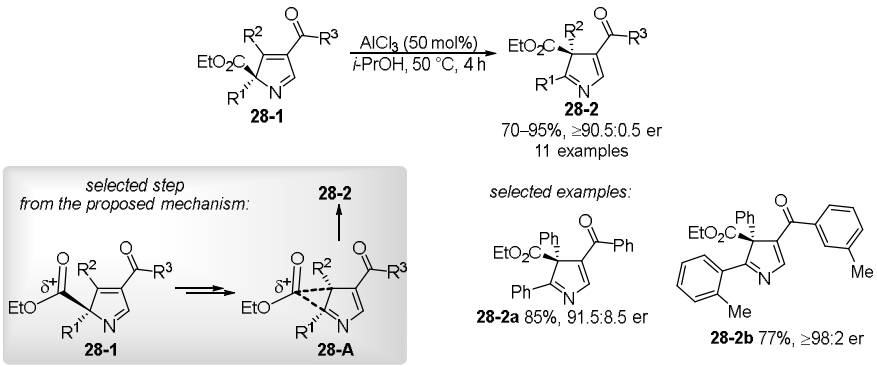
Scheme 26. Proposed mechanism for the formation of 3*H*-pyrroles by means of the Pd-catalyzed dearomative spirocyclization of ynones.

A report concerning the Ag-catalyzed preparation of the 3*H*-pyrroles **27-3** by the reaction of allenoates **27-1** with activated isocyanides **27-2** was published in 2018 (Scheme 27).[39] Optimization of the reaction conditions revealed that the reaction is sensitive to the used ligand. The enantioselective formation of 3*H*-pyrroles **27-3** was observed when the nonracemic **ligand** shown in the Scheme 27 was used. Formation of **27-3a**–**27-3c** demonstrate the good enantioselectivity of this reaction. The use of a triphenylphosphine ligand led to the formation of trisubstituted 1*H*-pyrroles.



Scheme 27. Synthesis of 3*H*-pyrroles by Ag-catalyzed [3+2] cycloaddition of allenoates with isocyanides.

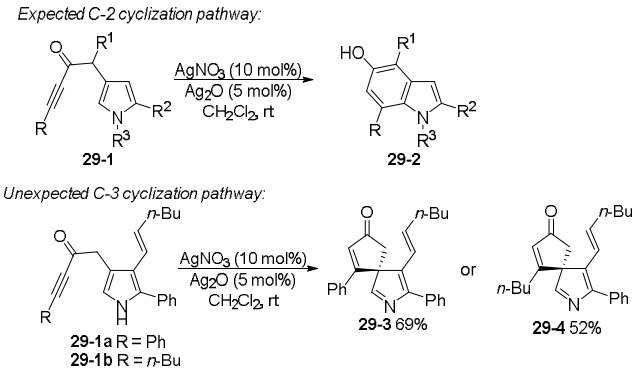
In the introductory section, it was explained that 2*H*- and 3*H*-pyrroles have similar calculated thermodynamic stabilities. Despite this, Wang was able to achieve the Lewis-acid-catalyzed isomerization of the 2*H*-pyrrole **28-1** into the 3*H*-pyrroles **28-2** including two selected examples **28-2a** and **28-2b** (Scheme 28).[40] The initial 2*H*-pyrrole **28-1** was prepared *via* the enantioselective organocatalytic reaction of isonitriles with ynones. The structure of **28-A** indicates that the asymmetric migration of the ethoxycarbonyl group is key to the observed transformation.



Scheme 28. 1,5-Ester shift in the isomerization of 2*H*-pyrroles into 3*H*-pyrroles.

An interesting dichotomy was reported by Unsworth in a paper on the C-2 annulation of the trisubstituted 1*H*-pyrrole **29-1** (Scheme 29).[41] The starting trisubstituted 1*H*-pyrroles underwent conversion into substituted indoles by means of the C-2 annulation reaction. However, the unexpected formation of 3*H*-pyrroles **29-3** and **29-4** was observed in relation to the 1*H*-pyrroles **29-1a** and **29-1b**. Based on DFT calculations, it was shown that 3*H*-pyrroles are the kinetic products of the cyclization reaction, while indole

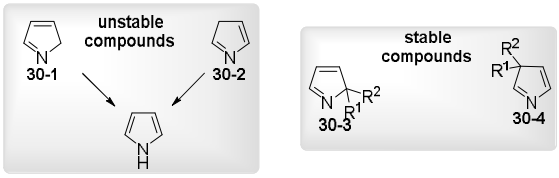
derivative **29-2** is the thermodynamic product. These results suggest that 3*H*-indoles act as intermediates in the conversion of 1*H*-pyrroles into indole **29-2**.



Scheme 29. Formation of 3*H*-pyrroles *via* the unexpected Ag-catalyzed cyclization of ynone **29-1**.

5. Conclusion

The high thermodynamic stability of 1*H*-pyrroles when compared with 2*H*- and 3*H*-pyrroles is consistent with the described preparation of 2*H*- and 3*H*-pyrroles. 2*H*-Pyrroles with two hydrogen atoms at the position two of **30-1** have not yet been prepared by a procedure with general applicability. However, the 2,2-disubstituted 2*H*-pyrrole **30-3** can be efficiently prepared by means of the modification of 1*H*-pyrroles using transition metal-catalyzed reactions, although transition metal-free reactions also play an essential role. A similar situation exists in the case of the preparation of 3*H*-pyrroles **30-2** and **30-4** although the procedures that make use of transition metal-catalyzed reactions for the synthesis of 3,3-disubstituted 3*H*-pyrroles remain rare, which leaves the door open for future research in this regard (Scheme 30).



Scheme 30. General scheme emphasizing the properties of 2*H*-pyrroles.

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