Pyrrole Synthesis | Hot Paper

DOI: 10.1002/anie.201407221

Insertion of Nitriles into Zirconocene 1-aza-1,3-diene Complexes: Chemoselective Synthesis of N–H and N-Substituted Pyrroles**

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Dedicated to Professor Tamotsu Takahashi on the occasion of his 60th birthday

Abstract: *The direct insertion of nitriles into zirconocene-1-aza-1,3-diene complexes provides an efficient, chemoselective, and controllable synthesis of N-H and N-substituted pyrroles upon acidic aqueous work-up. The outcome of the reaction (that is, the formation of N-H or N-substituted pyrroles) results from the different cyclization patterns, which depend on the relative stability and reactivity of the enamine–imine tautomers formed by hydrolysis of the diazazirconacycles.*

Zirconocene π-complexes and/or zirconacycles are among the most important organometallic reagents in promoting C−C bond formation reactions in organic synthesis, because of their unique structural features and their high reactivities toward a wide range of electrophiles.[1] In this regard, zirconocene complexes of 1-aza-1,3-dienes,[2,3] first reported by Whitby et al. in 1991,[2a] are attractive synthetic precursors for selective transformations. Based on X-ray crystal analysis, these complexes are described as σ^2,π-azazirconacyclopentenes (**A**) with a folded five-membered-ring moiety rather than η^4-azadiene complexes (**B**).[2b,i] In some cases, a rapid ring-flipping process between the two conformers has been verified by variable-temperature NMR experiments and DFT calculations (Figure 1).[2a,i] Because of the existence of highly polarized Zr−C and Zr−N bonds, they can be viewed as N,C dianion or homoenolate equivalents,[4] which engage in a series of addition reactions. In spite of the potential synthetic utility of these zirconacycles in the development of novel methodologies, it is somewhat surprising that unlike the zirconocene–butadiene complexes,[5] so far only the reactions with *tert*-butylisocyanide,[2a] ketones,[2b,d,i] special imine,[6] and $PhBCl_2$[2h] have been achieved. During our ongoing research on the chemistry of early-transition-metal complexes of conjugated organic substrates,[7] we found that the cross-coupling reactions of 1-azabuta-1,3-dienes with nitriles could be efficiently promoted by low-valent zirconocene species. Herein, we report the direct insertion of nitriles[8] into zirconocene-1-aza-1,3-diene complexes, which provided an efficient, chemoselective, and controllable synthesis of N-H and N-substituted pyrroles in a one-pot procedure. Interestingly, the chemoselectivity of these reactions depended on the substitution patterns of the azadiene substrates (Scheme 1).

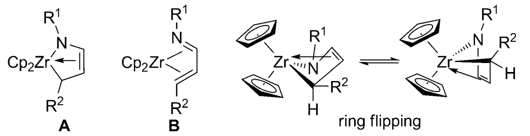
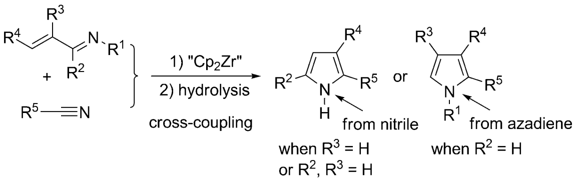


Figure 1. Structural description of zirconocene-1-aza-1,3-diene complexes.



Scheme 1. Zirconium-mediated synthesis of N-H or N-substituted pyrroles.

Zirconocene-1-aza-1,3-diene complexes **2** can be conveniently prepared by a ligand-exchange reaction of azadienes **1** with zirconocene–butene complexes[2a,i] generated from the Negishi reagent.[9] Thus, treatment of 1,4-diphenyl-substituted azadiene (**1a**) with the Negishi reagent [Cp_2ZrBu_2] led to azazirconacyclopentene **2a** ($R^1 = Ph$), which was rapidly and cleanly coupled with three equivalents of PhCN at room temperature to give 2,3-diphenyl-1*H*-pyrrole (**3a**) in 72% yield after hydrolysis with 3 M HCl (Table 1, entry 1). The results indicated that only one equivalent of nitrile was incorporated into the pyrrole product. When the amount of PhCN was decreased to two equivalents, the yield of **3a** also decreased to 61%. When the reaction was quenched by a saturated aqueous solution of $NaHCO_3$, the desired product was not obtained; according to TLC analysis, a complicated mixture resulted instead. We thus concluded that pyrrole was formed under acidic conditions. To determine the electronic effect of the N substituents of azadienes on the reaction course, we next synthesized substrates **1b**–**1j** bearing various R^1 groups. A series of aryl groups as R^1 were compatible with

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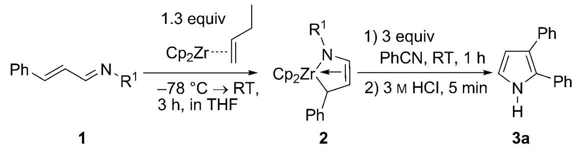
[**] We thank the National Natural Science Foundation of China (Grant Nos. 21125210 and 21121062), the Chinese Academy of Science, and the Major State Basic Research Development Program (Grant No. 2011CB808700) for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201407221.

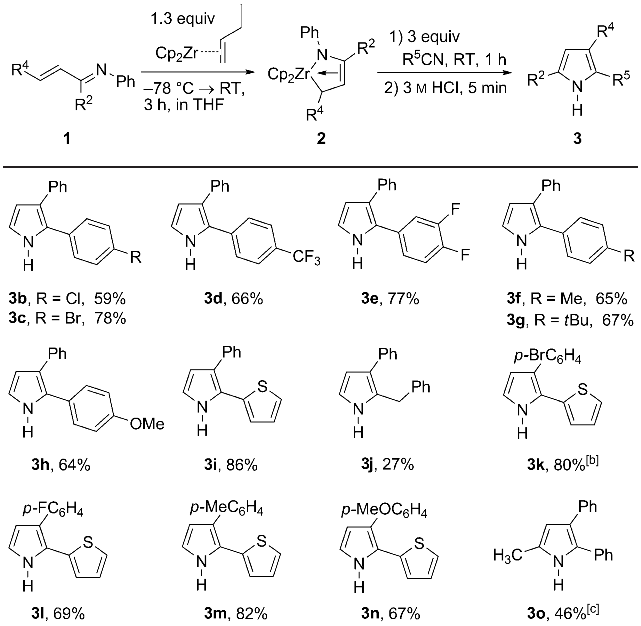
Table 1: Effect of N substituents of azadienes on zirconium-mediated cross-coupling reactions with nitriles.



Entry	R^1	Yield [%][a]	Entry	R^1	Yield [%][a]
1	Ph (**1a**)	72	6[b]	1-naphthyl (**1f**)	74[c]
2	p-ClC_6H_4 (**1b**)	68	7[b,d]	*n*Bu (**1g**)	40
3	p-$CF_3C_6H_4$ (**1c**)	28	8[b,d]	cyclopropyl (**1h**)	33
4	o-FC_6H_4 (**1d**)	54	9[b,d]	*t*Bu (**1i**)	49
5	p-$MeOC_6H_4$ (**1e**)	63	10[e]	NMe_2 (**1j**)	34

[a] Yields of isolated products. [b] The coupling reactions with nitriles were carried out at 50 °C for 2–3 h. [c] Naphthalen-1-amine was also isolated in 66 % yield. [d] Azazirconacycles **2** were prepared at 50 °C for 3 h. [e] The coupling reaction with nitrile was carried out at 80 °C for 6 h.

Table 2: Synthesis of N-H pyrroles.[a]



[a] Yields of isolated products. [b] The coupling reaction with nitrile was carried out at 50 °C for 1 h. [c] The coupling reaction with nitrile was carried out at room temperature for 1 h, and 50 °C overnight.

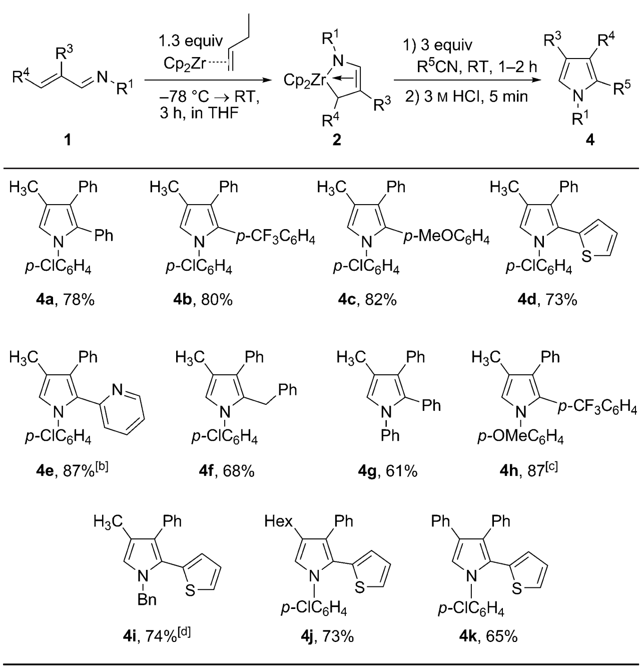
this reaction, furnishing the same product **3a** in yields of 54–74 % under mild conditions (Table 1, entries 2 and 4–6). However, when N-(p-$CF_3C_6H_4$)-substituted azadiene **1c** was employed, only 28 % of the desired product **3a** was obtained (Table 1, entry 3). N-Alkyl-substituted azadienes could also be used in this reaction, but the product was obtained in lower yields ranging from 33 % to 49 % (Table 1, entries 7–9). Hydrazone **1j** was identified as a suitable substrate for the formation of azazirconacycle **2j**,[2a] but a higher reaction temperature of 80 °C was required when it was coupled with benzonitrile (Table 1, entry 10). The above results also indicated that one amine molecule, derived from the N-R^1 moiety of azadiene **1**, was eliminated during the process, as evidenced by the isolation of naphthalen-1-amine in the case of **1f** (Table 1, entry 6).

The scope of this zirconium-mediated cross-coupling reaction toward N-H pyrroles was then investigated with a variety of azadiene substrates bearing an N-phenyl group. As shown in Table 2, a wide range of nitrile components were examined. Both electron-withdrawing (Cl, Br, CF_3, 3,4-difluoro) and electron-donating (Me, *t*Bu, OMe) groups on the aryl ring of nitriles were well tolerated, producing the corresponding 2,3-disubstituted N-H pyrroles **3b**–**3h** in 59–78 % yields. The coupling reaction of (2-thienyl)nitrile with azadiene **1a** furnished pyrrole **3i** in a high yield of 86 %. The use of 2-phenylacetonitrile afforded **3j** in a low yield of 27 %, possibly as a result of the instability of the pyrrole product. The effect of the R^4 group at the alkene terminus of the azadienes was also tested, and aryl groups bearing halide, methyl, and methoxy substituents were all compatible with the process, leading to **3k**–**3n** in good yields of 67–82 %. An azadiene bearing one more substituent (R^2 group) at the imino carbon atom on the azadiene was also coupled smoothly with benzonitrile to give the corresponding 2,3,5-trisubstituted pyrrole **3o** in 46 % yield.

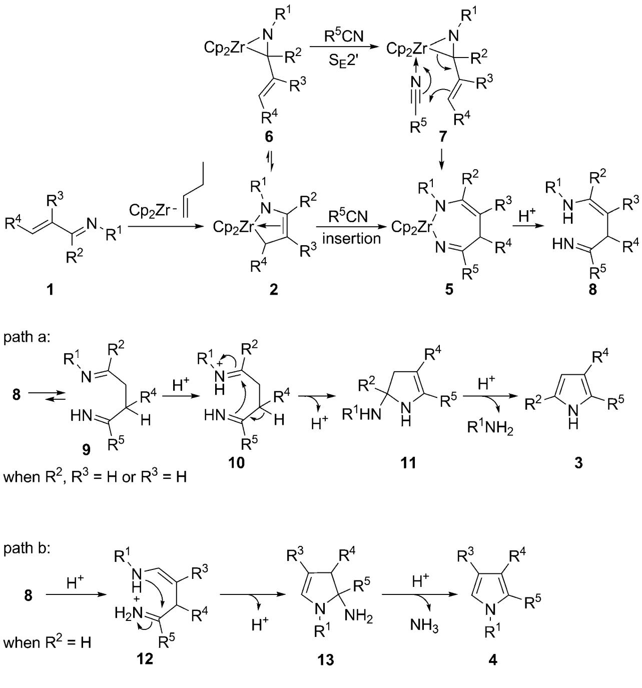
Interestingly, when 1,3,4-trisubstituted azadienes were used as the substrates, N-substituted pyrroles **4** were formed selectively under similar reaction conditions. Unlike in the above reactions, the N-R^1 group of the azadienes was incorporated into the pyrrole products in these cases. As shown in Table 3, this one-pot process offers a highly flexible synthesis of pyrroles with various substituents. For example, the reaction worked well for various aryl nitriles, providing **4a**–**4c** in 78–82 % yields. Heteroaryl nitriles, including (2-thienyl)nitrile and even (2-pyridyl)nitrile, were coupled efficiently with a 1,3,4-trisubstituted azadiene to afford the corresponding pyrroles **4d** and **4e** in 73 % and 87 % yields, respectively. In the case of (2-pyridyl)nitrile, the reaction was quenched by a saturated aqueous solution of $NaHCO_3$, and the desired pyrrole **4e** was formed during the purification process. 2-Phenylacetonitrile was well accommodated to give product **4f** in good yield of 68 %. Regarding the N substituents on the azadienes, N-aryl- or N-benzyl-substituted azadienes were compatible with this reaction, and substrates with an *n*-hexyl or a phenyl group as R^3 were also smoothly converted to the pyrrole derivatives **4j** and **4k** in 73 % and 65 % yields, respectively. The structures of N-substituted pyrroles were unambiguously confirmed by X-ray crystallographic analysis of compounds **3k** and **4e**.[10] Polysubstituted pyrroles are of significant interest, as they can find a lot of applications in synthetic,[11] pharmaceutical,[12] and material science.[13] Our method provides a mild and efficient route to these compounds.[14]

A proposed reaction mechanism for the formation of N-H and N-substituted pyrroles is shown in Scheme 2. Insertion of the C≡N bond of the nitrile into the Zr−C(sp^3) bond of azazirconacyclopentene **2** affords diazazirconacycle **5**. However, the nitrile attacking from this side may encounter large steric hindrance. Alternatively, azazirconacycle **2** might be in equilibrium with alkenylazazirconacyclopropane **6**, although the equilibrium lies far toward azazirconacycle **2**. The

Table 3: Synthesis of N-substituted pyrroles.[a]



[a] Yields of isolated products. [b] The reaction was quenched by a saturated aqueous solution of $NaHCO_3$. [c] Azazirconacycle was prepared at 50 °C for 3 h, and the coupling reaction with nitrile was carried out at 50 °C for 1 h. [d] The coupling reaction with nitrile was carried out at room temperature for 1 h, and 50 °C overnight.



Scheme 2. Possible reaction mechanism.

addition of a CN group to the allyl zirconium moiety through a syn-S_E2'[7d] process leads to **5**, which upon hydrolysis gives the enamine–imine intermediate **8**. Intermediate **8** equilibrates with its tautomers, such as **9**,[2d] through enamine–imine tautomerization,[15] and the equilibrium ratio depends very much on the substitution patterns. In the cases of 1,4- and 1,2,4-substituted azadienes (path a), fast tautomerization to the more stable tautomer **9** with an imine moiety derived from azadienes occurs, which undergoes ring closure via the enamine intermediate to afford the corresponding cyclized intermediate **11**. This process is followed by the elimination of the amine to give the di- or trisubstituted N-H pyrrole **3**. In the case of 1,3,4-trisubstituted azadienes (path b), the enamine moiety in **8**, derived from azadienes, may be stable enough because of the presence of the R^3 group on the C=C bond to undergo the subsequent intramolecular nucleophilic addition/elimination to deliver the N-substituted pyrrole **4**.

To support the mechanism, zirconium-containing intermediate **5e**, derived from the coupling reaction of the azadiene (**1p**) and 2-pyridinecarbonitrile, was successfully isolated (74 % yield) and characterized by X-ray single-crystal diffraction (Figure 2). The analysis of **5e** showed a seven-membered azazirconacycle. The results indicated that pyrroles were formed after hydrolysis of the zirconacycles. The Zr1–N1 distance of 2.024(2) Å indicates a σ bond between Zr and the sp^2-hybridized imino N atom.[8h] The Zr1–N2 distance of 2.199(2) Å is in the range of a single bond, and the N2 atom is only slightly pyramidalized (summation of bonding angles at N2 356.35°). The N1–C6 distance (1.251(3) Å) corresponds to an imine moiety.[8h] The large distances of Zr1–C9 and Zr1–C8 (exceeds 3.0 Å) do not indicate a π interaction between Zr and the C=C bond.

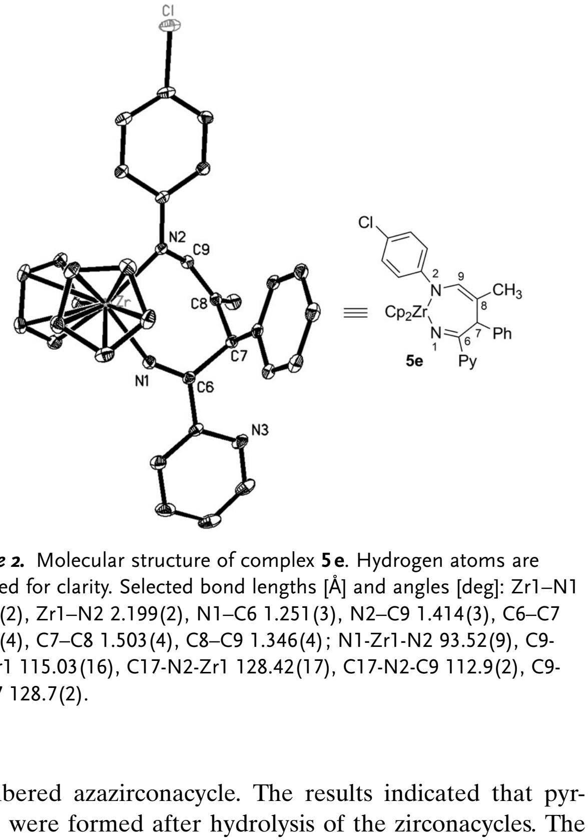


Figure 2. Molecular structure of complex **5e**. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [deg]: Zr1–N1 2.024(2), Zr1–N2 2.199(2), N1–C6 1.251(3), N2–C9 1.414(3), C6–C7 1.545(4), C7–C8 1.503(4), C8–C9 1.346(4); N1-Zr1-N2 93.52(9), C9-N2-Zr1 115.03(16), C17-N2-Zr1 128.42(17), C17-N2-C9 112.9(2), C9-C8-C7 128.7(2).

In summary, we have disclosed a new reactivity of zirconocene-1-aza-1,3-diene complexes in insertion reactions with nitriles, providing an efficient and chemoselective route to N-H and N-substituted pyrroles upon acidic aqueous work-up. These two types of pyrroles are obtained selectively by choosing azadiene substrates with different substituents. The outcome of the reaction results from the different cyclization patterns, which depend on the relative stability and reactivity of the corresponding enamine–imine tautomers formed by hydrolysis of the diazazirconacycles. Further investigations to explore the synthetic utility of zirconocene-1-aza-1,3-diene complexes are currently underway in our group.

Received: July 15, 2014

Keywords: azazirconacycles · cyclization · insertion · nitriles · pyrroles

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