Highlight Review

Synthesis of Biologically Active Carbazole Alkaloids Using Selective Transition-metal-catalyzed Coupling Reactions†

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Abstract

Highly convergent syntheses of substituted carbazoles are most conveniently achieved using organometallic chemistry. Construction of the carbazole framework via the iron-mediated route proceeds by a sequence of C–C and C–N bond formation. In the highly efficient palladium-catalyzed route the C–N bond is formed first followed by generation of the C–C bond. This article highlights some recent developments and applications to the total synthesis of biologically active carbazole alkaloids.

♦ Introduction

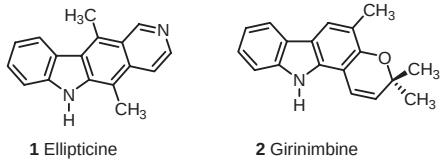
The chemistry and biology of carbazole alkaloids has attracted an increasing interest over the last 50 years. Important milestones for the tremendous development of this class of natural products were the isolation of ellipticine (**1**), the first pyrido[4,3-*b*]carbazole alkaloid, by Goodwin et al. in 1959 from the leaves of *Ochrosia elliptica* Labill,[1] and of girinimbine (**2**), the first pyrano[3,2-*a*]carbazole alkaloid, by Chakraborty et al. in 1964 from the stem bark of *Murraya koenigii* Spreng (Figure 1).[2]

Since then a broad range of structurally interesting carbazole alkaloids with useful biological activities has been isolated from diverse natural sources.[3,4] The pharmacological potential of these natural products initiated the development of novel synthetic methods for efficient routes to carbazoles.[4] We have established an iron-mediated and a palladium-catalyzed route, which are based on transition metal-induced coupling reactions of arylamines.[5] The present article briefly summarizes these achievements and shows recent applications to total synthesis.

♦ Iron-mediated Synthesis of Carbazoles

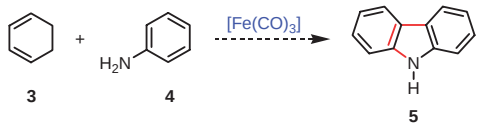
One of the typical features of tricarbonyl(η^4-cyclohexa-1,3-diene)iron complexes is their useful reactivity, which is significantly different from the noncoordinated diene and which has been exploited for organic synthesis in many ways.[6] Most characteristic is the activation of the allylic C–H bonds in the coordinated cyclohexadiene moiety. This increased reactivity of the allylic C–H bonds can be utilized for oxidative bond formations, either via hydride abstraction or by direct oxidative addition.[6] Based on an iron-mediated oxidative coupling of a cyclohexa-1,3-diene (**3**) and arylamine **4**, we have developed a highly efficient approach to carbazoles **5** (Scheme 1).[7]

This synthesis exploits the unique reactivity of iron–diene



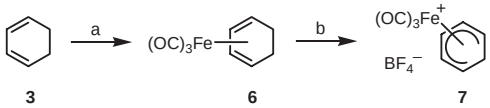
1 Ellipticine **2** Girinimbine

Figure 1. Carbazole alkaloids: ellipticine (**1**) and girinimbine (**2**).



3 **4** **5**

Scheme 1. Iron-mediated oxidative coupling of cyclohexa-1,3-dienes (**3**) and arylamines **4** to carbazoles **5**.



3 **6** **7**

Scheme 2. Synthesis of the iron-coordinated cyclohexadienylium salt **7**. Reagents and conditions: a) $Fe(CO)_5$, cat. 1-(4-methoxyphenyl)-4-phenyl-1-azabutadiene, dioxane, 101 °C, 45 h, 99%; b) Ph_3CBF_4, CH_2Cl_2, rt, 40 min, 98%.

complexes for a consecutive C–C and C–N bond formation of the tricarbonyliron-coordinated cyclohexadiene and an arylamine furnishing the carbazole framework. Coordination of cyclohexadienes to the tricarbonyliron fragment is most efficiently achieved by the 1-azadiene-catalyzed complexation developed in our laboratories.[8–10] Thus, catalytic complexation of cyclohexa-1,3-diene (**3**) with pentacarbonyliron quantitatively provides tricarbonyl(η^4-cyclohexa-1,3-diene)iron (**6**). It is important to note that this process can be applied as well to substituted cyclohexadienes leading to the corresponding substituted iron–diene complexes.[10,11] Subsequent hydride abstraction affords the tricarbonyliron-coordinated cyclohexadienylium salt **7** (Scheme 2).[8,12]

The tricarbonyliron-coordinated cations are useful electrophiles for regioselective electrophilic aromatic substitution of arylamines. This reactivity is exploited to construct the central C–C bond of the carbazole framework. Our strategy is demonstrated by an application to the total synthesis of marine carbazole alkaloids (Scheme 3).[13]

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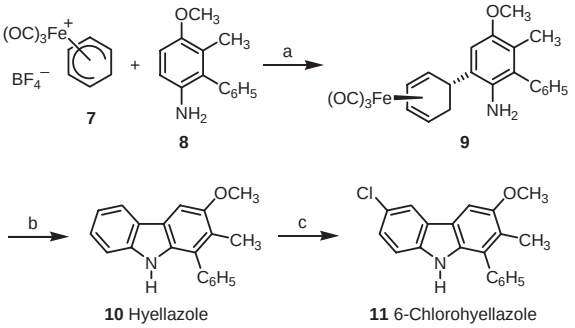
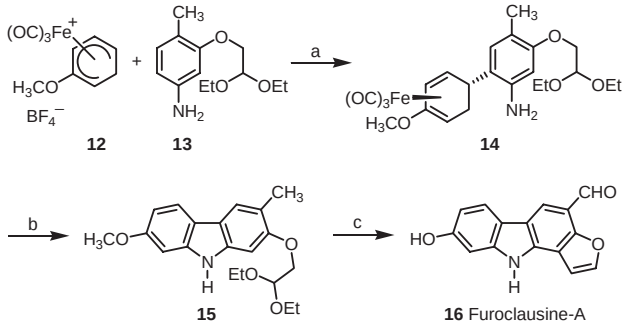
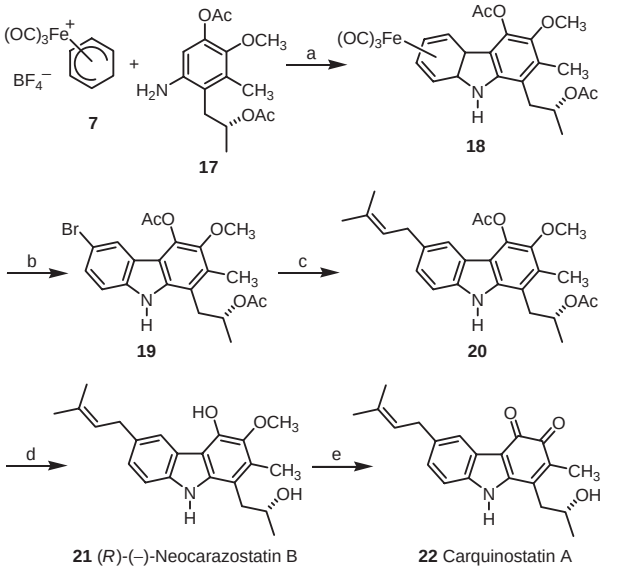


Scheme 3. Synthesis of hyellazole (**10**) and 6-chlorohyellazole (**11**). Reagents and conditions: a) MeCN, 82 °C, 2.5 h, 98%; b) 1. Cp_2FePF_6, CH_2Cl_2, Na_2CO_3, rt, 22 h; 2. Me_3NO, Me_2CO, rt, 4 h; 3. MeI, K_2CO_3, Me_2CO, 56 °C, 6 h, 84%; c) 1. NBS, cat. HBr, MeCN, rt; 2. CuCl, DMF, 153 °C, 6 h, 88%.



Scheme 4. Synthesis of furoclausine-A (**16**). Reagents and conditions: a) MeCN, 25 °C, 23 h, 87%; b) I_2, pyridine, air, 90 °C, 6 h, 71%; c) 1. amberlyst 15, C_6H_5Cl, 120 °C, 20 h; 2. DDQ, $MeOH/H_2O$, 25 °C, 55 min; 3. BBr_3, CH_2Cl_2, −78 to −20 °C, 3 d, 14%.



Scheme 5. Synthesis of (*R*)-(−)-neocarazostatin B (**21**) and carquinostatin A (**22**). Reagents and conditions: a) MeCN, air, 25 °C, 7 d, 68%; b) 1. NBS, Na_2CO_3, MeCN, 25 °C; 2. NBS, cat. HBr, MeCN, 25 °C, 88%; c) 1. prenyl bromide, $Ni(CO)_4$, C_6H_6, 60 °C; 2. **19**, DMF, 65 °C, 16 h, 66%; d) $LiAlH_4$, Et_2O, 25 °C, 45 min, 92%; e) CAN, $MeCN/H_2O$, 0 °C, 2 h, 92%.

Arylamine **8** is readily prepared in five steps and 76% overall yield from 2,6-dimethoxytoluene.[13] Reaction of **8** with the complex salt **7** affords complex **9** almost quantitatively. The electrophilic substitution of arylamine **8** by **7** proceeds via initial *N*-alkylation followed by rearrangement to the thermodynamically more stable C-substituted arylamine **9**. Since the mechanism of this substitution has been subject of previous investigations,[14] it will not be discussed here any further. Oxidative cyclization of complex **9** with ferricenium hexafluorophosphate in the presence of sodium carbonate using optimized conditions provides the marine alkaloid hyellazole (**10**) in 84% yield.[15] The mechanism of this iron-mediated arylamine cyclization has been studied previously.[16] Taking into account the route to the arylamine **8**, the iron-mediated synthesis affords hyellazole (**10**) in eight steps and 63% overall yield based on commercially available 2,6-dimethoxytoluene. Comparison with alternative syntheses reported in the literature shows the efficiency of the iron-mediated route.[4c] Hyellazole (**10**) and 6-chlorohyellazole (**11**) have been isolated by Moore from the blue-green alga *Hyella caespitosa*.[17] In an attempt to convert hyellazole (**10**) directly into 6-chlorohyellazole (**11**) by electrophilic chlorination, we obtained 4-chlorohyellazole in 90% yield.[13] However, for steric reasons bromination of **10** takes place at C-6 and subsequent ipso-substitution by treatment with cuprous chloride led to 6-chlorohyellazole (**11**).

Using the 2-methoxy-substituted cyclohexadienylium salt **12** for coupling with arylamines affords carbazoles substituted in both benzo rings (Scheme 4). The arylamine **13**, prepared in two steps and 80% overall yield, served previously as precursor in our total synthesis of furostifoline.[18,19] The reaction of the complex salt **12** with arylamine **13** provided complex **14** which on oxidative cyclization led to carbazole **15**. Annelation of the furan ring, oxidation of the methyl group and cleavage of the ether provided furoclausine-A (**16**), which was obtained in five steps and 9% overall yield.[20] Wu et al. isolated furoclausine-A (**16**) from the root bark of Chinese medicinal plant *Clausena excavata*.[21] The furocarbazole alkaloids have attracted a lot of interest due to their pharmacological potential.[22]

Most intriguing for the iron-mediated approach to carbazoles, formation of the C–C and the C–N bond can be performed in a one-pot reaction by carrying out the electrophilic substitution in air (Scheme 5).[23] Starting from guaiacol, the enantiopure arylamine **17** was prepared in eight steps and 65% overall yield by using (*R*)-propene oxide as chiral building block. Thus, stirring a solution of complex salt **7** and the arylamine **17** in air at room temperature afforded the tricarbonyliron-coordinated 4a,9a-dihydro-9*H*-carbazole **18** as stable compound. Treatment with NBS under basic reaction conditions led to aromatization and demetalation. Subsequently, under acidic conditions electrophilic bromination took place at C-6 to afford the 6-bromocarbazole **19**. Prenylation by reaction with a dimeric π-prenylnickel bromide complex, prepared in situ, afforded di(*O*-acetyl)neocarazostatin B (**20**). Removal of the acetyl groups by treatment with lithium aluminum hydride provided (*R*)-(−)-neocarazostatin B (**21**) (five steps and 36% overall yield based on **7**).[23] Kato et al. isolated neocarazostatin B from *Streptomyces* sp. strain GP 38.[24] However, the absolute configuration was not assigned. We have been able to determine the absolute configuration of the natural product by comparison of the value observed for

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specific rotation of our synthetic product with that reported for the natural product. This assignment was supported by an X-ray crystal structure analysis of the 6-bromocarbazole **19**. Finally, (*R*)-(−)-neocarazostatin B (**21**) was converted to carquinostatin A (**22**) by oxidation with cerium(IV) ammonium nitrate.[23] The final transformation confirmed the absolute configuration of carquinostatin A (**22**) and represents a novel route to this carbazole-3,4-quinone alkaloid,[25] which has been isolated by Seto from *Streptomyces exfoliatus* 2419-SVT2.[26]

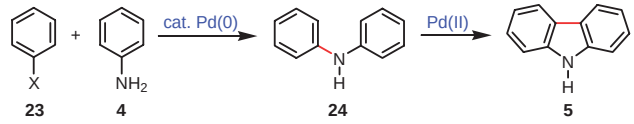
The examples described above as well as further recent applications,[27] emphasize the efficiency of the iron-mediated approach for the synthesis of biologically active carbazoles.

♦ *Pd-catalyzed Synthesis of Carbazoles*

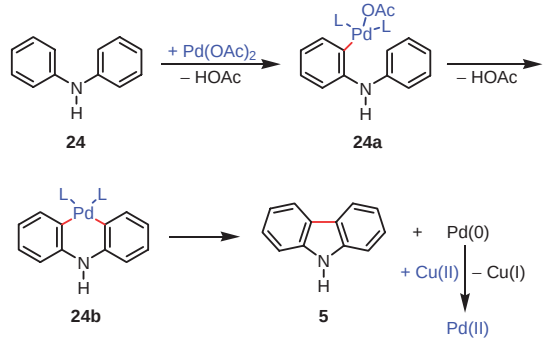
Starting from arylamine **4**, an alternative approach to carbazoles has been realized by coupling with an arene **23** to an intermediate *N*,*N*-diarylamine **24** and subsequent oxidative cyclization to carbazoles **5** (Scheme 6).

The preparation of the *N*,*N*-diarylamine **24** is easily achieved by the Buchwald–Hartwig amination of aryl halides or triflates **23** with arylamine **4**.[28] Åkermark et al. reported first the cyclization of the *N*,*N*-diarylamine **24** to carbazole **5** by using palladium(II) acetate as oxidizing agent.[29] The palladium(II)-mediated oxidative cyclization found several applications to organic synthesis.[30] However, the drawback of this intramolecular oxidative coupling by double C–H bond activation was the use of stoichiometric amounts of palladium(II). This is rationalized by the mechanism which has been proposed for the palladium(II)-catalyzed oxidative cyclization (Scheme 7).

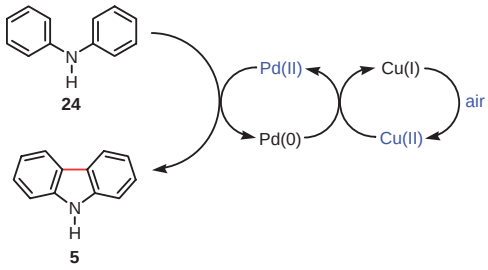
Electrophilic attack of palladium(II) acetate at **24** affords the palladium(II) complex **24a**. A second, intramolecular C–H bond activation leads to the palladacycle **24b**, which on reductive elimination with concomitant formation of the central C–C bond generates the carbazole framework. We have thought that a catalytic process might be feasible by reoxidation of palladium(0) to palladium(II). For the Wacker process, a palladium(II)-catalyzed C–O bond formation, the catalytic cycle involves reoxidation of palladium(0) using a copper(II) salt.[31] In fact, we have been able to demonstrate first that a palladium(II)-catalyzed double C–H bond activation to form the central C–C bond of the carbazole skeleton can be achieved using copper(II) as reoxidant.[32–34] Thus, optimization of this process led us to a sequence of catalytic cycles, where finally air represents the oxidizing agent for the cyclization of *N*,*N*-diarylamines **24** to the carbazoles **5** (Scheme 8).



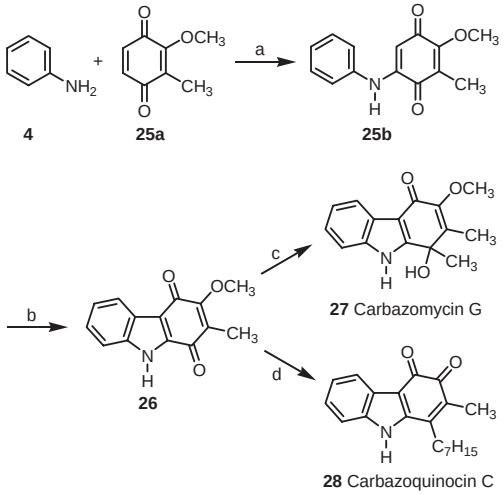
Scheme 6. Synthesis of carbazoles **5** by palladium(II)-mediated oxidative cyclization of *N*,*N*-diarylamines **24**; X = Cl, Br, I, and OTf.



Scheme 7. Mechanism of the palladium(II)-catalyzed oxidative cyclization of *N*,*N*-diarylamines **24** to carbazoles **5**.



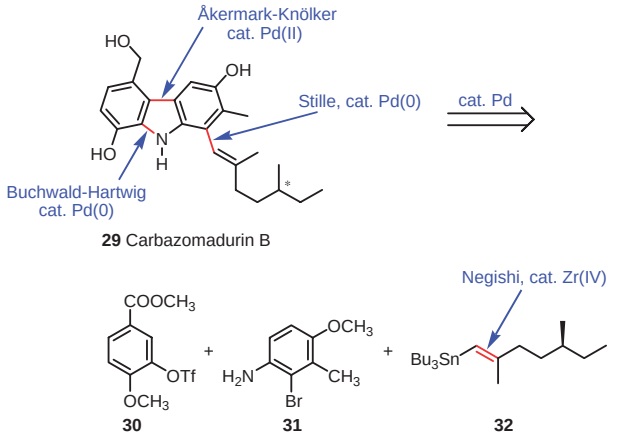
Scheme 8. Catalytic cycles of the palladium(II)- and copper(II)-catalyzed oxidative cyclization of *N*,*N*-diarylamines **24** to carbazoles **5**.



Scheme 9. Synthesis of carbazomycin G (**27**) and carbazoquinocin C (**28**). Reagents and conditions: a) MeOH, rt, 1 h, 84%; b) cat. $Pd(OAc)_2$, $Cu(OAc)_2$, HOAc, 117 °C, 3 d, 91%; c) MeLi, THF, −78 to 25 °C, 71%; d) 1. $C_7H_{15}MgCl$, THF, −78 °C, 3 h; 2. MeOH/HBr, rt, 1 h, 51%.

Further applications of this process have been described subsequently by other groups as well.[35] We have utilized the palladium(II)-catalyzed oxidative cyclization for the synthesis of carbazomycin G and H, and carbazoquinocin C (Scheme 9).[36]

Regioselective addition of aniline (**4**) to quinone **25a** led to arylaminoquinone **25b**, which on palladium(II)-catalyzed cyclization provided the carbazole-1,4-quinone **26**. We could demonstrate that compound **26** represents a versatile precursor for a range of bioactive carbazole alkaloids. Addition of methyllithium afforded the antifungal carbazomycin G (**27**),[36] isolated by Nakamura et al. from *Streptoverticillium ehimense*.[37] Addition of heptylmagnesium chloride followed by ether cleavage and elimination of water gave carbazoquinocin C (**28**).[38] This carbazole-3,4-quinone alkaloid was isolated by Seto from *Strepto-*



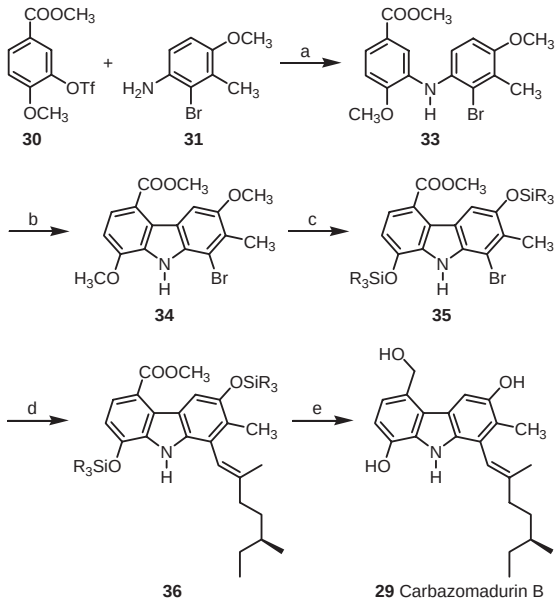
Scheme 10. Retrosynthetic analysis of carbazomadurin B (**29**).

myces violaceus and represents a potent inhibitor of lipid peroxidation.[39]

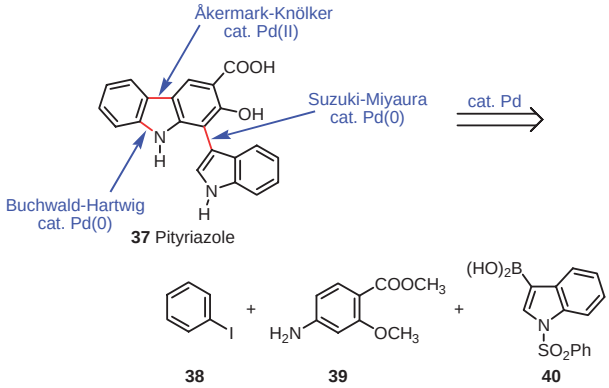
For a range of natural product targets, we have developed highly convergent routes using a sequence of three different Pd-catalyzed coupling reactions to assemble the carbazole. The neuronal cell protecting alkaloid carbazomadurin B (**29**), isolated by Seto et al. in 1997 from *Actinomadura madurae*,[40] has been synthesized by this strategy (Scheme 10). The key steps for the construction of the carbazole framework are a Buchwald–Hartwig amination and subsequent palladium(II)-catalyzed oxidative cyclization using the building blocks **30** and **31**. The alkenyl side chain has been introduced by the Stille coupling.[41] The stereochemistry of the (*E*)-alkenylstannane **32** is built up via Negishi's zirconium-catalyzed carboalumination.[42]

Aryl triflate **30** was prepared in two steps from isovanillic acid (91% yield) and arylamine **31** was prepared from 2-bromo-6-nitrotoluene (five steps, 44% yield).[43] The absolute configuration of the natural product was not assigned previously. However, based on comparison of the value for the specific rotation of carbazomadurin B (**29**) with those given in the literature for compounds containing similar stereogenic centers, we assumed an *S* configuration of **29**. Thus, (*S*)-2-methylbutan-1-ol has been selected as starting material for the alkenylstannane **32**.[43] The Buchwald–Hartwig coupling of **30** and **31** led to diarylamine **33**, which on subsequent oxidative cyclization afforded carbazole **34** (Scheme 11). An exchange of both protecting groups (methyl ether to TBDPS ether) led to compound **35**. Introduction of the alkenyl side chain was achieved by a palladium(0)-catalyzed Stille coupling with alkenylstannane **32** to afford the 1-alkenylcarbazole **36**. Subsequent DIBAL-H reduction and removal of the silyl protecting groups provided enantiopure (*S*)-(+)-carbazomadurin B (**29**).[43] Using our Pd-catalyzed approach, (*S*)-(+)-carbazomadurin B (**29**) is available with more than 99% ee in nine steps and 13% overall yield based on commercial isovanillic acid. The present approach also paved the way for the first total synthesis of epocarbazolin B, which represents the epoxy derivative of carbazomadurin B.[44] The epocarbazolins were isolated from *Streotomyces anulatus* T688-8 in 1993 by a Japanese research group of the company Bristol-Myers and are potent 5-lipoxygenase inhibitors.[45]

Another example in order to demonstrate the efficiency of our strategy is the synthesis of pityriazole (**37**) (Scheme 12). Pityriazole (**37**) represents a structurally unprecedented 1-(in-

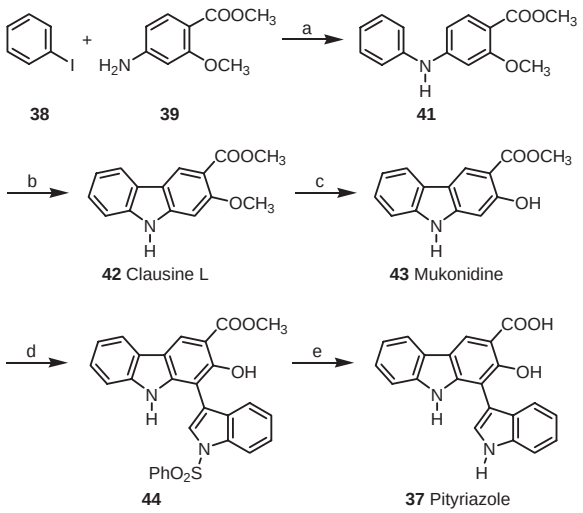


Scheme 11. Synthesis of carbazomadurin B (**29**). Reagents and conditions: a) cat. $Pd(OAc)_2$, cat. BINAP, Cs_2CO_3, toluene, 100 °C, 10 h, 62%; b) $Pd(OAc)_2$, dioxane/HOAc (3:1), 100 °C, 40 h, 43%; c) 1. BBr_3, CH_2Cl_2, −78 °C to rt, 5 d; 2. *t*-$BuPh_2SiCl$ (=R_3SiCl), imidazole, DMF, 70 °C, 19 h, 70%; d) **32**, cat. $Pd(PPh_3)_4$, toluene, 110 °C, 3 d, 90%; e) 1. DIBAL-H, toluene, 0 °C, 2 h; 2. TBAF, THF, rt, 1.5 h, 88%.



Scheme 12. Retrosynthetic analysis of pityriazole (**37**).

dol-3-yl)carbazole alkaloid isolated by Steglich et al. from cultures of the lipophilic yeast *Malassezia furfur*.[46] *Malassezia furfur* is considered to be involved in the generation of pityriasis versicolor, a *Malassezia*-associated skin disease characterized by flaky lesions.[47] We envisaged a construction of the carbazole framework via our established sequence of palladium(0)-catalyzed amination using iodobenzene (**38**) and arylamine **39** as building blocks followed by a palladium(II)-catalyzed oxidative cyclization. Introduction of the indol-3-yl substituent at C-1 of the carbazole skeleton should be feasible via a palladium(0)-catalyzed Suzuki–Miyaura coupling with the indol-3-ylboronic acid **40**.[48] Moreover, we realized the structural relationship of pityriazole (**37**) with the carbazole alkaloids clausine L (**42**) and mukonidine (**43**) (Scheme 13), both previously isolated from plant sources. Thus, we considered them as synthetic intermediates en route to pityriazole (**37**).

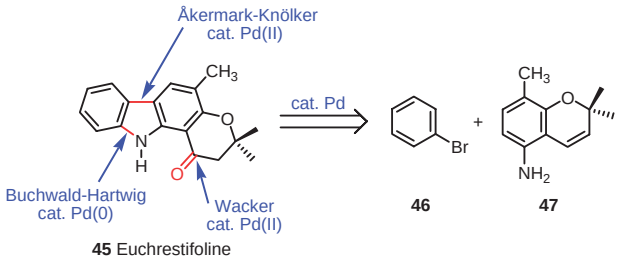


Scheme 13. Synthesis of pityriazole (**37**). Reagents and conditions: a) cat. $Pd(OAc)_2$, cat. BINAP, Cs_2CO_3, toluene, 110 °C, 2 d, 100%; b) cat. $Pd(OAc)_2$, cat. $Mn(OAc)_3 \cdot 2H_2O$, *t*-BuCOOH, air, 100 °C, 3 d, 62%; c) BBr_3, CH_2Cl_2, −78 to −4 °C, 1 h, 95%; d) 1. I_2, $Cu(OAc)_2$, 80 °C (microwave), 2 h; 2. **40**, cat. $Pd(OAc)_2$, cat. S-Phos, K_3PO_4, dioxane, 90 °C (microwave), 3 h, 70%; e) KOH, EtOH, 40 °C, 2 d, 86%.

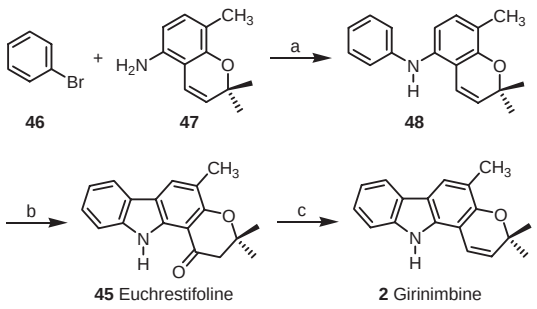
The Buchwald–Hartwig coupling of **38** and **39** followed by palladium(II)-catalyzed oxidative cyclization of **41** afforded clausine L (**42**) (Scheme 13).[49] In an optimization study of this cyclization via double C–H bond activation, we found that catalytic amounts of manganese(III) are as efficient as copper(II) for the reoxidation of palladium(0) to palladium(II). Ether cleavage of clausine L (**42**) led to mukonidine (**43**). Clausine L (**42**) and mukonidine (**43**) have been isolated by Wu et al. in 1993 from the Chinese medicinal plant *Clausena excavata*.[50] One year later, Bhattacharyya et al. obtained mukonidine (**43**) from the stem bark of the Indian medicinal plant *Murraya koenigii*, which is also known as the curry-leaf tree.[51] The present route to mukonidine (**43**) (3 steps, 59% overall yield) represents a considerably improved synthesis (compare ref. 27d). Electrophilic iodination at C-1 and the subsequent Suzuki–Miyaura coupling with **40** afforded the 1-indolylcarbazole **44**. Finally, cleavage of the ester and the phenylsulfonyl group provided pityriazole (**37**) in six steps and 35% overall yield based on **38**.

In 1996, Wu isolated the pyrano[3,2-*a*]carbazole alkaloid euchrestifoline (**45**) from the leaves of the Chinese medicinal plant *Murraya euchrestifolia*.[52] For the total synthesis of this natural product, we have designed a palladium(II)-catalyzed one-pot triple C–H bond activation as key step leading to the Wacker oxidation with concomitant intramolecular oxidative C–C bond formation (Scheme 14). The diarylamine precursor is obtained by a palladium(0)-catalyzed Buchwald–Hartwig coupling of bromobenzene (**46**) and aminochromene **47**.

The aminochromene **47** has been prepared in three steps and 70% overall yield starting from 2-methyl-5-nitrophenol.[53] The Buchwald–Hartwig coupling of bromobenzene (**46**) and the aminochromene **47** afforded diarylamine **48** (Scheme 15). Heating the diarylamine **48** in air in the presence of catalytic amounts of palladium(II) acetate and copper(II) acetate led to a triple C–H bond activation. This palladium(II)-catalyzed process resulted in the Wacker oxidation followed by intramolecular



Scheme 14. Retrosynthetic analysis of euchrestifoline (**45**).



Scheme 15. Synthesis of euchrestifoline (**45**) and girinimbine (**2**). Reagents and conditions: a) cat. $Pd(OAc)_2$, cat. BINAP, Cs_2CO_3, toluene, 110 °C, 36 h, 93%; b) cat. $Pd(OAc)_2$, cat. $Cu(OAc)_2$, $HOAc/H_2O$ (10:1), 90 °C, 48 h, 40%; c) 1. $LiAlH_4$, THF, 0 °C to rt, 17 h; 2. HCl, 60 °C, 1 h, 70%.

C–C bond formation and thus, provided directly euchrestifoline (**45**) in two steps and 37% overall yield based on bromobenzene (**46**). Isolation of the Wacker product after a reaction time of 24 h, and its subsequent conversion into euchrestifoline (**45**) by palladium(II)-catalyzed oxidative cyclization, confirmed that activation of the vinylic C–H bond takes place first.[53]

Euchrestifoline (**45**) could be easily transformed into girinimbine (**2**). Reduction of **45** to the carbinol and subsequent acidic work-up with concomitant heating afforded by elimination directly girinimbine (**2**).[53] The pyrano[3,2-*a*]carbazole girinimbine (**2**) was originally isolated by Chakraborty et al. from the stem bark of *Murraya koenigii*,[2] and later by Joshi et al. from the root bark of *Clausena heptaphylla*.[54]

Further recent examples from our group for applications of the Pd^{II}-catalyzed oxidative cyclization to total synthesis: murrayaquinone A,[55] koeniginequinone A and B,[55] clausine C, M and N,[56] clauszoline-K,[56] the anti-HIV active siamenol,[56] glycomaurrol,[57] the anti-TB active micromeline,[57] the furo[2,3-*c*]carbazole alkaloid eustifoline-D,[57] clausenine,[58] clausenol,[58] the clausines G, I, and Z,[58] glycosinine,[59] and clausine V.[59]

♦ Conclusion

We have developed two highly efficient methodologies for the total synthesis of biologically active carbazole alkaloids. Some of the carbazole derivatives exhibited a potent anti-TB activity.[60,61] Thus, our results emphasize the pharmacological potential of this class of heterocyclic compounds.

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