Transition Metals in Organic Synthesis, Part 100:[1] Highly Efficient Palladium(II)-Catalyzed Oxidative Cyclization to the 1,7,8-Trioxygenated Carbazole Alkaloid Murrayastine

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Abstract: Consecutive palladium-catalyzed C–N and C–C bond formation provides an efficient route to the 1,7,8-trioxygenated carbazole alkaloid murrayastine.

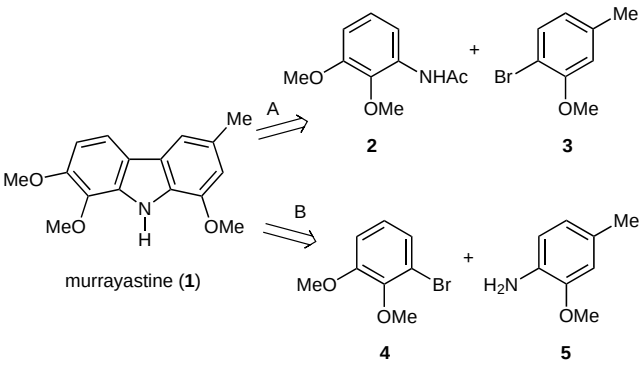
Key words: alkaloids, catalysis, cyclization, palladium

Carbazole alkaloids have attracted a lot of interest due to their broad range of useful biological activities.[2–5] The biogenesis of carbazole alkaloids in terrestrial plants proceeds via 3-methylcarbazole as parent compound.[2,3] Subsequent biogenetic transformations are oxygenation at different positions, oxidation of the methyl group, prenylation and annulation of additional rings. Thus, the large structural variety of naturally occurring carbazoles from plants is generated from a key biogenetic precursor. Based on the oxygenation pattern of the tricyclic carbazole alkaloids, we have introduced a classification system for these natural products.[3]

We have developed efficient synthetic routes to highly oxygenated carbazole alkaloids which are electron-rich and thus, sensitive towards oxidation. Our iron-mediated approach to carbazoles takes advantage of the activation of the allylic C–H bonds in tricarbonyl(η^4-cyclohexa-1,3-diene)iron complexes.[6] This route has been applied to the synthesis of a broad range of carbazoles oxygenated at different positions.[7]

In our palladium-catalyzed approach to carbazoles the central biaryl C–C bond of the framework is generated in a palladium(II)-catalyzed oxidative cyclization of an *N*,*N*-diarylamine precursor.[8] This process is based on the palladium(II)-mediated oxidative cyclization of *N*,*N*-diarylamines originally reported by Åkermark in 1975.[9] Although this process required stoichiometric amounts of palladium(II) acetate, it has found several applications in synthesis.[10] In 1994, we have reported for the first time that this cyclization becomes catalytic in palladium by reoxidation of palladium(0) to palladium(II) using a copper(II) salt.[11] Subsequently, the palladium(II)-catalyzed cyclization was exploited for the synthesis of carbazole-1,4-quinones.[12] We also applied the palladium(II)-catalyzed double C–H bond activation to the synthesis of 7-oxygenated,[13] 6-oxygenated,[14] 2-oxygenated,[15] 2,7-dioxygenated,[15b] 1,6-dioxygenated,[16] 2,6-dioxygenated,[17] and 1,7-dioxygenated carbazole alkaloids.[18] Herein, we describe a highly efficient palladium(II)-catalyzed oxidative cyclization leading to the 1,7,8-trioxygenated carbazole alkaloid murrayastine (**1**; Scheme 1).

In 1986, Furukawa et al. isolated murrayastine (**1**) from the stem bark of *Murraya euchrestifolia* Hayata collected in Taiwan.[19] The structural assignment for the natural product was supported by synthesis (Scheme 1, approach A). Goldberg–Ullmann coupling of the acetanilide **2** with the bromoarene **3** was followed by hydrolysis of the amide and palladium(II)-mediated cyclization to **1** (no yields were given). We envisaged a synthesis via route B starting from 3-bromoveratrole (**4**) and 2-methoxy-4-methylaniline (**5**). This approach using our palladium(II)-catalyzed oxidative cyclization of the intermediate *N*,*N*-diarylamine as key step appeared to be much more promising.



Scheme 1 Retrosynthetic analysis of murrayastine (**1**)

Regioselective *ortho*-bromination of guaiacol (**6**) using the procedure of Pearson afforded 2-bromo-6-methoxyphenol (**7**; Scheme 2).[20] Subsequent O-methylation led to 1-bromo-2,3-dimethoxybenzene (**4**). A preparation of 2-methoxy-4-methylaniline (**5**) has been reported earlier.[7h] The Buchwald–Hartwig coupling offers an easy access to *N*,*N*-diarylamines.[21] A brief study showed that using SPhos or XPhos as ligand for the palladium(0)-catalyzed coupling of **4** and **5** provided the best yields for the *N*,*N*-diarylamine **8** (Table 1).[22]

Oxidative cyclization of compound **8** with stoichiometric amounts of palladium(II) acetate in acetic acid as solvent

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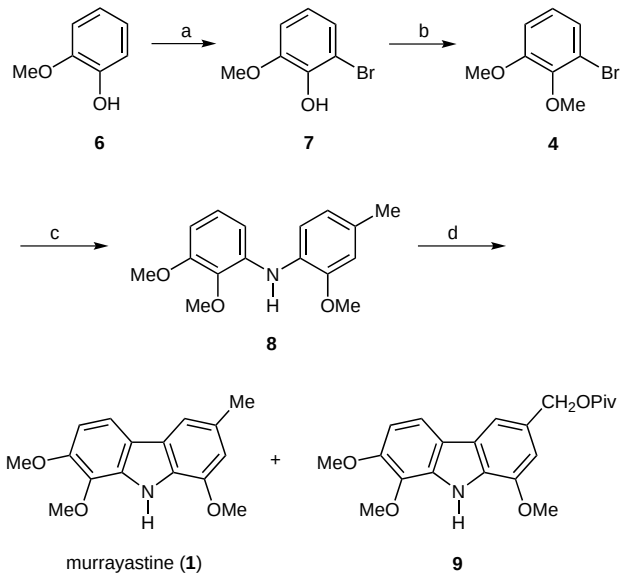


Scheme2 Palladium-catalyzed synthesis of murrayastine (**1**). *Reagents and conditions*: (a) Br_2 (1 equiv), *tert*-$BuNH_2$ (2 equiv), CH_2Cl_2–toluene, –30 °C to r.t., 6 h (86%); (b) MeI (2 equiv), K_2CO_3 (3 equiv), acetone, 56 °C, 1.5 d (85%); (c) **5** (1.2 equiv), $Pd(OAc)_2$ (7 mol%), XPhos (18 mol%), Cs_2CO_3 (1.4 equiv), toluene, 111 °C, 3 d (95%); (d) $Pd(OAc)_2$ (3 mol%), K_2CO_3 (5 mol%), HOPiv, 120 °C, air, 20 h (81% **1**, 3% **9**).

Table 1 Optimization of the Buchwald–Hartwig Coupling of Bromoarene **4** with Arylamine **5** to the Diarylamine **8**[a]

Ligand[b]	Amount (mol%)	**8**, Yield (%)	**4** (%)[c]
BINAP	8	79	11
SPhos	10	92	0
XPhos	18	95	3

[a] All reactions were carried out using $Pd(OAc)_2$ (7 mol%) and Cs_2CO_3 (1.4 equiv) in toluene at reflux for 3 d.
[b] BINAP = 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl, SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.
[c] Reisolated starting material (**4**).

gave murrayastine (**1**) in only 36% yield and led largely to decomposition (Table 2, entry 1). Using 10 mol% of palladium(II) acetate and 2.5 equivalents of copper(II) acetate either in acetic acid, or with a few drops of DMF and microwave heating,[23] led to similar yields of the natural product and left some unchanged starting material (entries 2 and 3). Performing the palladium(II)-catalyzed (10 mol%) cyclization in dioxane at reflux afforded murrayastine (**1**) in up to 51% yield (entry 4). In pivalic acid as solvent at 120 °C and with air as reoxidant for the palladium,[15b,24] the turnover of the oxidative cyclization was much better (entries 5–10). Using 3 mol% of palladium(II) acetate gave the best result (81% of **1**, turnover number: 28).[25] With just 0.5 mol% of the palladium catalyst, the yield of murrayastine (**1**) was still 72% corresponding to a turnover number of 154 (entry 8). Lower amounts of the catalyst resulted in even higher turnover numbers. However, increasing amounts of starting material were recovered and the yield of **1** decreased significantly (entries 9 and 10).

Murrayastine (**1**) has been fully characterized by its spectroscopic data,[26] which were in good agreement with those reported for the natural product (UV, IR, ^{1}H NMR and MS).[19] Although the natural product was described as colorless syrup,[19] we have obtained murrayastine (**1**) as light yellow crystals (mp 101–102 °C, with correct elemental analysis).[26] The structural assignment for murrayastine (**1**) has been additionally confirmed by an X-ray crystal structure determination (Figure 1).[27]

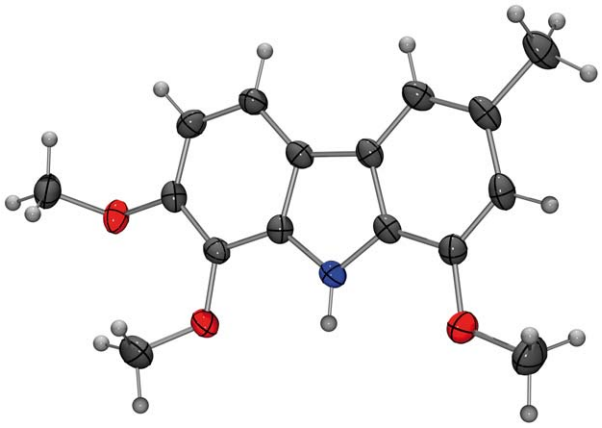


Figure 1 Molecular structure of murrayastine (**1**) in the crystal (ORTEP plot at the 50% probability level)

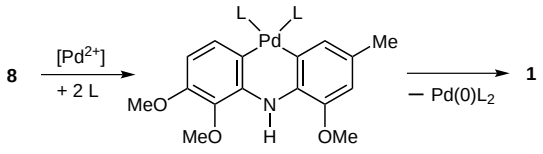
The best results [72–81% yield of murrayastine (**1**), entries 5–8] have been obtained using 0.5–5 mol% of palladium(II) acetate in pivalic acid at 120 °C. These conditions afforded 3-(pivaloyloxymethyl)-1,7,8-trimethoxy-9*H*-carbazole (**9**) as a by-product (3–5% yield).[28] Compound **9** obviously results from a palladium-catalyzed pivaloyloxylation by C–H bond activation at the methyl group and takes place subsequent to the oxidative cyclization by twofold aryl C–H bond activation. To support this hypothesis, murrayastine (**1**) was treated with palladium(II) acetate (3 mol%) and potassium carbonate (7 mol%) in pivalic acid at 120 °C in the presence of air for three days. These strong oxidizing conditions led largely to decomposition (about 70%) but also afforded compound **9** in 8% yield along with 22% of starting material (**1**). If the same experiment was carried out without palladium(II) acetate, murrayastine (**1**) was reisolated in 87% yield. Palladium(II)-catalyzed acetoxylations and pivaloyloxylations have been reported previously.[11,24c,29] However, to the best of our knowledge the present example describes the first palladium(II)-catalyzed pivaloyloxylation at the carbazole C-3 methyl group. We have reported previously that donor-substituted electron-rich carbazoles are readily decomposed by an excess of palladium(II) acetate under the conditions of the oxidative cyclization.[13,14] Therefore, in these cases the yields for the oxidative cyclization achieved with only catalytic

Table 2 Results for the Palladium(II)-Catalyzed Oxidative Cyclization of the Diarylamine **8** to Murrayastine (**1**)

Entry	$Pd(OAc)_2$	Reaction conditions	Yield (%) of **1**	Recovered **8** (%)[a]	Yield (%) of **9**	TON[b]
1	120 mol%	HOAc, reflux, Ar, 2 h	36	–	–	–
2	10 mol%	HOAc, 2.5 equiv $Cu(OAc)_2$, reflux, air, 24 h	27	33	–	2.7
3	10 mol%	MW, 2.5 equiv $Cu(OAc)_2$, DMF,[c] air, 2 h	31	61	–	3.1
4	10 mol%	dioxane, 2.5 equiv $Cu(OAc)_2$, reflux, air, 48 h	51	34	–	5.1
5	5 mol%	HOPiv, 0.1 equiv K_2CO_3, 120 °C, air, 20 h	79	–	5	16.8
6	3 mol%	HOPiv, 0.05 equiv K_2CO_3, 120 °C, air, 20 h	81	traces	3	28
7	1 mol%	HOPiv, 0.03 equiv K_2CO_3, 120 °C, air, 2 d 4 h	75	18	4	79
8	0.5 mol%	HOPiv, 0.02 equiv K_2CO_3, 120 °C, air, 4 d	72	16	5	154
9	0.25 mol%	HOPiv, 0.01 equiv K_2CO_3, 120 °C, air, 3 d 4 h	47	23	traces	188
10	0.10 mol%	HOPiv, 0.01 equiv K_2CO_3, 120 °C, air, 6 d	23	38	traces	230

[a] Recovered starting material **8**.
[b] Turnover number for the catalytically active palladium(II) species based on all products formed by palladium(II)-catalyzed oxidative cyclization (**1** and **9**).
[c] Microwave heating with five drops of DMF.[23]

amounts of palladium(II) are considerably higher than those of the stoichiometric reaction. Thus, low concentrations of palladium(II) prevent decomposition of the carbazole already generated under the conditions of the oxidative cyclization. The present synthesis of a highly electron-rich trioxygenated carbazole represents a strong support for this conclusion. At the same time, donor-substituted *N*,*N*-diarylamines like **8** cyclize very readily in the presence of palladium(II) which is attributed to the high reactivity towards initial electrophilic attack by palladium(II) and subsequent cyclopalladation to the palladacycle **10** followed by reductive elimination leading to murrayastine (**1**; Scheme 3). Such palladacycles have been proposed as intermediates of this process many years ago.[9,30] Recently, we have isolated and characterized for the first time a palladacycle intermediate of this type from a palladium(II)-catalyzed oxidative cyclization of an *N*,*N*-diarylamine.[1]



Scheme 3 Intermediate diaryl palladium(II) complex **10** proposed for the oxidative cyclization to murrayastine (**1**)

Carbazoles are of strong current interest due to their potential as antimicrobial agents.[31] The present synthesis provides murrayastine (**1**) in two steps and 77% yield based on the bromoarene **4**. We have shown that under optimized reaction conditions, the biaryl bond formation via double C–H bond activation is a very efficient palladium(II) catalysis proceeding with high turnover numbers.

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(22) Characteristic spectroscopic data for the diarylamine **8**: pale yellow solid; mp 78 °C. IR (ATR): ν = 3413, 3003, 2968, 2931, 2854, 2836, 1601, 1586, 1498, 1478, 1464, 1447, 1421, 1401, 1336, 1297, 1251, 1220, 1190, 1165, 1134, 1082, 1037, 993, 916, 934, 838, 808, 773, 739 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.33 (s, 3 H), 3.857 (s, 3 H), 3.863 (s, 3 H), 3.88 (s, 3 H), 5.90 (br s, 1 H), 6.46 (m, 1 H), 6.72–6.73 (m, 2 H), 6.92 (d, *J* = 2.4 Hz, 1 H), 6.93 (s, 1 H), 7.28 (d, *J* = 8.3 Hz, 1 H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 21.20 (Me), 55.60 (Me), 55.78 (Me), 60.23 (Me), 103.44 (CH), 107.98 (CH), 111.78 (CH), 117.50 (CH), 120.80 (CH), 123.85 (CH), 129.38 (C), 130.90 (C), 137.46 (C), 138.01 (C), 149.64 (C), 153.00 (C). MS (EI): *m*/*z* (%) = 273 (72) [M^+], 258 (7), 243 (8), 227 (100), 184 (11). Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.33; H, 6.87; N, 5.13.

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(25) **Experimental Procedure for the Palladium(II)-Catalyzed Oxidative Cyclization to Murrayastine (1)**: The diarylamine **8** (200 mg, 0.732 mmol), K_2CO_3 (5.4 mg, 0.039 mmol) and pivalic acid (500 mg) were placed in a 10-mL test tube. The mixture was heated at 120 °C under air and recrystallized $Pd(OAc)_2$ (5.0 mg, 0.022 mmol) was added. After 20 h of vigorous stirring at 120 °C in the presence of air, the reaction mixture was cooled to r.t. The residue was dissolved in EtOAc and washed several times with a sat. solution of K_2CO_3 and then with brine. After extraction with EtOAc, the combined organic layers were dried over Na_2SO_4. Removal of the solvent and flash chromatography (pentane–CH_2Cl_2–EtOAc, gradient elution from 40:5:1 to 18:5:1) on silica gel provided murrayastine (**1**; yield: 160 mg, 81%) and 3-(pivaloyloxymethyl)-1,7,8-trimethoxy-9*H*-carbazole (**9**; yield: 9.4 mg, 3%).

(26) Characteristic spectroscopic data for murrayastine (**1**): light yellow crystals; mp 101–102 °C. UV (MeOH): λ_{max} = 223, 245, 253, 297, 321, 334 nm. IR (ATR): ν = 3398, 3343, 3247, 2955, 2921, 2851, 1633, 1583, 1498, 1462, 1440, 1418, 1383, 1344, 1281, 1250, 1221, 1209, 1179, 1134, 1088, 1065, 1031, 1021, 971, 935, 819, 781 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.51 (s, 3 H), 3.97 (s, 3 H), 3.99 (s, 3 H), 4.02 (s, 3 H), 6.69 (s, 1 H), 6.86 (d, *J* = 8.5 Hz, 1 H),

7.38 (s, 1 H), 7.65 (d, J = 8.5 Hz, 1 H), 8.22 (br s, 1 H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 21.90 (Me), 55.46 (Me), 56.77 (Me), 60.85 (Me), 106.10 (CH), 107.12 (CH), 112.21 (CH), 115.50 (CH), 119.57 (C), 124.79 (C), 128.09 (C), 129.58 (C), 133.84 (C), 134.21 (C), 145.24 (C), 149.99 (C). MS (EI): m/z (%) = 271 (100) [M^+], 256 (46), 213 (46), 170 (19). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 71.04; H, 6.51; N, 4.90.

(27) Crystal data for murrayastine (**1**): $C_{16}H_{17}NO_3$, crystal size: 0.25 × 0.24 × 0.23 mm^3, M = 271.31 g mol^{-1}, orthorhombic, space group: Pbca, λ = 0.71073 Å, a = 9.158(1), b = 11.517(1), c = 26.488(3) Å, V = 2793.8(5) Å^3, Z = 8, D_{calcd} = 1.290 g cm^{-3}, μ = 0.089 mm^{-1}, T = 198(2) K, θ range = 3.23–27.00°; reflections collected: 23879, independent: 3044 (R_{int} = 0.0611), 189 parameters. The structure was solved by direct methods and refined by full-matrix least-squares on F^2; final R indices [$I > 2\sigma(I)$]: R_1 = 0.0566, wR_2 = 0.1022; maximal residual electron density: 0.198 e Å^{-3}. CCDC 870640 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.uk/data_request/cif.

(28) Characteristic spectroscopic data for 3-(pivaloyloxymethyl)-1,7,8-trimethoxy-9H-carbazole (**9**): yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.24 (s, 9 H), 3.98 (s, 3 H), 4.01 (s, 3 H), 4.02 (s, 3 H), 5.25 (s, 2 H), 6.85 (s, 1 H), 6.89 (d, J = 8.5 Hz, 1 H), 7.57 (s, 1 H), 7.68 (d, J = 8.5 Hz, 1 H), 8.36 (br s, 1 H). ^{13}C NMR and DEPT (150 MHz, $CDCl_3$): δ = 27.20 (3 × Me), 38.79 (C), 55.55 (Me), 56.77 (Me), 60.89 (Me), 67.18 (CH_2), 105.95 (CH), 106.51 (CH), 112.74 (CH), 115.64 (CH), 119.48 (C), 124.54 (C), 128.32 (C), 129.73 (C), 133.89 (C), 134.22 (C), 145.46 (C), 150.20 (C), 178.50 (C=O). MS (EI): m/z (%) = 371 (55) [M^+], 270 (100).

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