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Graphical Abstract

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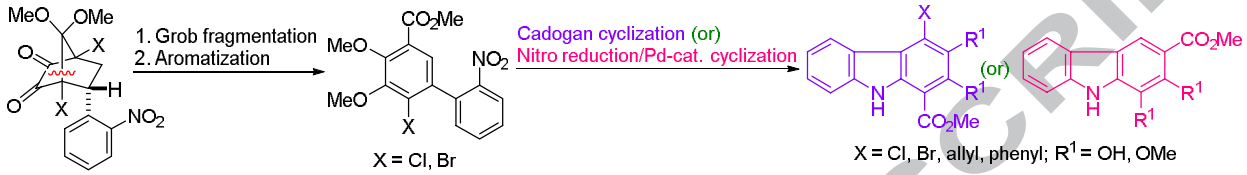
*Kadavergu Sravanthi[a], Sumit Kumar Agrawal[b], Chintada Nageswara Rao[b] and Faiz Ahmed Khan[a]**



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Synthesis of Carbazole Analogs via Grob Fragmentation of Norbornyl α-Diketones

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ABSTRACT

A regioselective synthesis of carbazole analogs belonging to both the categories of natural origin, *viz*, microorganisms and higher plant source is reported. The synthesis of carbazole derivatives possessing a methylester group at C-1 position has been achieved by Cadogan cyclization of nitro bi-phenyl derivatives. Whereas, the carbazole analog possessing a methylester group at C-3 position was synthesized by Buchwald-Hartwig Pd-catalyzed cyclization of amino bi-phenyl derivatives. Suitably substituted bi-phenyl precursors were accessed from norbornyl α-diketones via Grob fragmentation, *O*-methylation and DBU aromatization reaction sequence. The reported carbazole derivatives posses structural features that are common with many carbazole natural products: Mukonine, Clausine-L, Murrayafoline-A and their sibling natural products.

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Keywords: Diketones; Fragmentation; Aromatization; Bi-phenyls; Cadogan cyclization; Pd-catalyzed cyclization; Carbazoles

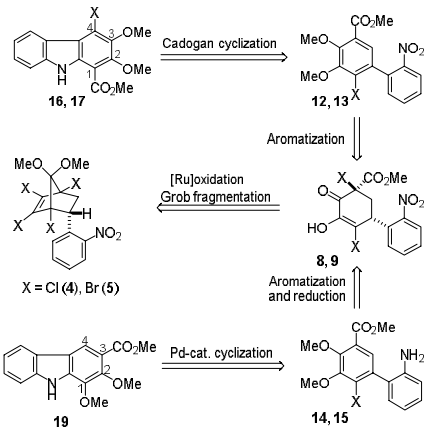
1. Introduction

After the first isolation of carbazole from coal tar in 1872 by Graebe and Glazer,[1] subsequent isolation and antibiotic activity of *Murrayanine*, a carbazole alkaloid from *Murraya koenigii spreng* was disclosed by Chakraborty *et al.* in 1965.[2] This heterocyclic carbazole alkaloid is present in leaves of curry-tree, a native of India and Sri Lanka often used as an ingredient in making curry, commonly known as curry patta.[3]There has been continuous efforts in exploring the carbazoles due to their interesting biological and material applications.[4,5]

Based on the natural prevalence, the carbazole natural alkaloids were divided in to two categories. The first category of carbazoles isolated from the natural microorganisms, usually possess a methyl or methyl oxidized functional group at C-1 position.[6] Whereas, the other category of carbazole natural alkaloids isolated from higher plant source constituting a basic methyl or methyl oxidized functional groups at C-3 position.[7]

For the synthesis of *N*-heterocyclic carbazoles and their derivatives, a number of methods and protocols have been developed.[8-14] However, most of these synthetic routes demonstrate the synthesis of carbazole alkaloids possessing a methyl or methyl equivalent functional group at C-1 position. Herein we report a fruitful utilization of previously reported Grob fragmentation protocol[15] to further devise a strategy for the synthesis of both the classes of carbazole alkaloid analogs from easily accessible norbornyl α-diketones.

Scheme 1: Retrosynthetic analysis of carbazole alkaloid analogs



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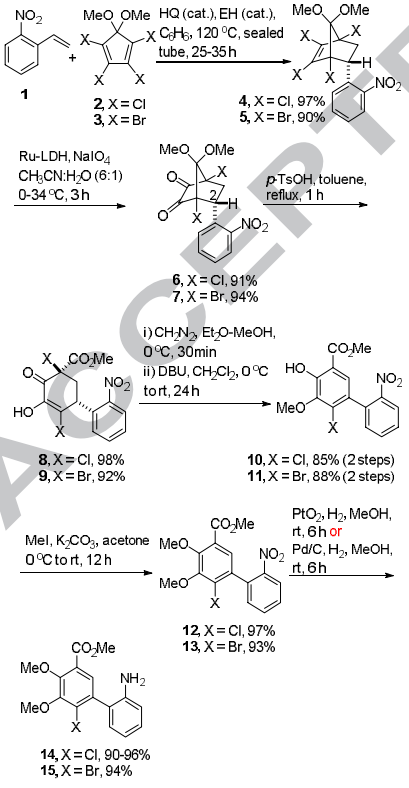
As depicted in retrosynthetic Scheme 1, carbazole analogs **16**, **17** could be accessed from nitro bi-phenyl derivatives **12** and **13** by Cadogan reductive cyclization respectively. On the other hand, carbazole analog **19** could be synthesized from amino bi-phenyl derivatives **14** or **15** via Pd-catalyzed cyclization. These suitably substituted bi-phenyl compounds **12-15** could be synthesized from the α-ketoenols **8**, **9** via *O*-methylation, DBU mediated aromatization and nitro to amine reduction in case of **14**, **15**.

The α-ketoenols **8** and **9** could be easily prepared from the corresponding tetrahalo norbornyl derivatives **4** and **5** via the ruthenium catalyzed oxidation followed by acid catalyzed Grob fragmentation reaction.

Result and discussion

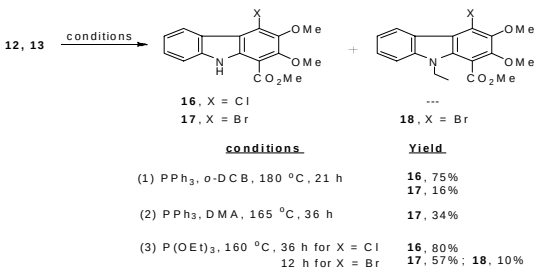
The dienophile 1-nitro-2-vinylbenzene **1** was prepared by the Wittig olefination of *o*-nitro benzaldehyde in THF at 0 ^{o}C by using KHMDS as a base. Dienophile**1** was treated with the corresponding 1,2,3,4-tetrahalo-5,5'-dimethoxy cyclopenta-1,3-diene **2** or **3** in benzene solution at 120-130 ^{o}C in the presence of catalytic amount of epichlorohydrin and hydroquinone in a sealed tube over 25-34 h to furnish the cycloaddition products **4**, **5** in excellent yield (Scheme 2). The Diels-Alder adducts **4**, **5** were subjected to Ru-LDH in the presence of co-oxidant $NaIO_4$ in acetonitrile-water (6:1), a method developed earlier in our laboratory,[16] to provide the α-diketones**6** and **7** in excellent yield 91-94%.

Scheme 2: *Synthesis of carbazole precursors* ***12-15*** *from norbornyl α-diketones*



The α-diketone **6** or **7** was refluxed with two equivalent of *p*-toluenesulfonicacid monohydrate (*p*-TsOH.H_2O) in dry toluene to furnish the Grob fragmentation products **8** and **9** in excellent yield 92-98% (Scheme 2). Observation of a single regioisomer **8** or **9** is due to the cleavage of front bond followed by the formation of half-chair intermediate, wherein the ester group occupies sterically less hindered pseudoequatorial position.[15] The ketoenols **8**, **9** were smoothly converted to the corresponding *O*-methylated bi-phenyl derivatives **10** and **11** in two steps. First step involved in the treatment of freshly prepared diazomethane in methanol-ether solution at -10 to 0 ^{o}C to afford the *O*-methylated products. Subsequently, the crude products were subjected to DBU in DCM to furnish the corresponding bi-phenyl compounds **10** and **11** in high yield 85-88%. The obtained bi-phenyl derivatives **10**, **11** were treated with K_2CO_3 and MeI in anhydrous acetone to provide the corresponding *O*-methylated derivatives **12** and **13** in excellent yield 93-97%. These highly substituted nitro-bi-phenyl derivatives **12**, **13** are suitable for the Cadogan reductive cyclization reaction.

Scheme 3: *Reductive cyclization of nitro bi-phenyl derivatives* ***12, 13*** *leading to the carbazole derivatives* ***16***, ***17*** *and* ***18***



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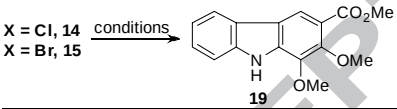
Initially, the reductive cyclization reaction of nitro bi-phenyl derivatives **12**, **13** was carried out using triphenylphosphene (PPh_3) in 1,2-dichlorobenzene (1,2-DCB) at 180 ^oC. Under these conditions, methyl 6-chloro-4,5-dimethoxy-2'-nitrobiphenyl-3-carboxylate **12** furnished the cyclized product **16** in good yield (75%). However, the methyl 6-bromo-4,5-dimethoxy-2'-nitrobiphenyl-3-carboxylate **13** sluggishly reacted to give **17** in 22% yield. Replacing the solvent 1,2-DCB with *N*,*N*-dimethylacetamide (DMA) or lowering the reaction temperature could not improve the yield of bromo product **17** (Scheme 3). Interestingly, when we employed triethoxyphosphate $P(OEt)_3$ in place of PPh_3, the yield of **17** was increased to 57% along with 10% *N*-ethylcarbazole derivative **18**, as mentioned in Scheme 3.

In order to operate the other regioselective C-N bond formation via intramolecular Buchwald-Hartwig coupling reaction,[17] the nitro bi-phenyl derivatives **12** and **13** were first reduced to the corresponding amino group under PtO_2-H_2 or Pd-C/H_2 hydrogenation conditions in methanol to furnish the bi-phenyl derivatives **14**, **15** in excellent yield (Scheme 2). The bi-phenyl derivative **14** was then subjected to Pd-catalyzed C-N bond formation as described in optimization Table 1. $Pd(PPh_3)_4$ and Na_2CO_3 in toluene at reflux temperature, furnished the cyclization product **19** in low yield (entry 1).

While $Pd(OAc)_2$ in presence of 1,3-bis(cyclohexylphosphino)propane or 10 mole% $Ni(acac)_2$ in presence of the 2,2`-bipyridyl ligand gave **19** in 23% yield (Table 1, entries 2, 3). However, when **14** was reacted with 2-5 mole% $Pd(OAc)_2$ and 10 mole% of *rac*-BINAP in presence of CS_2CO_3 as a base (Table 1, entry 4, 5), the carbazole derivative **19** was obtained in 65-75% yield. Interestingly, under similar reaction conditions the bromo bi-phenyl derivative **15** furnished **19** in high yield 85% (Table 1, entry 6).

Table 1: *Pd-catalyzed regioselective cyclization of **14**, **15** leading to the carbazole derivative **19***

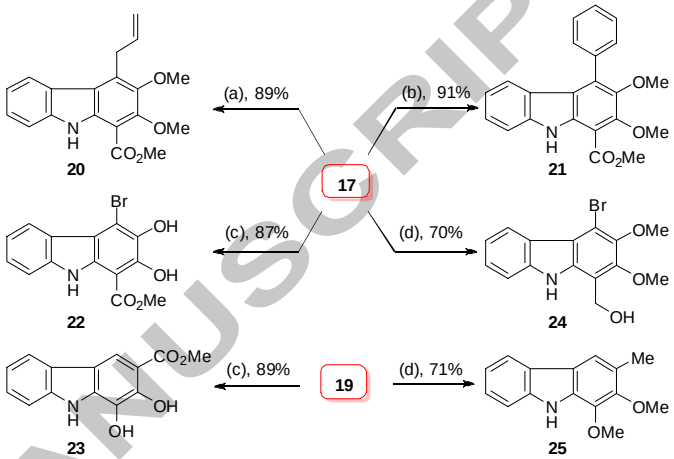


19

S. no.	Substrate	Conditions	**19** (% yield)
1	**14**	$Pd(PPh_3)_4$ (0.5 equiv.), Na_2CO_3, (2 equiv.), toluene, 120 ^oC, 5 d	11%
2	**14**	$Pd(OAc)_2$ (10 mole%), 1,3-bis(cyclohexylphosphino)propane (20 mole%), *t*-BuOK (3 equiv.), toluene, 120 ^oC, 20 h	23 %
3	**14**	$Ni(acac)_2$ (10 mole%), 2, 2`Bipyridyl (20 mole%), *t*-BuOK (1.4 equiv.), dioxane, 100 ^oC, 24 h	23 %
4	**14**	$Pd(OAc)_2$ (2 mole%), *rac* -BINAP (10 mole%), CS_2CO_3, DMF, 120 ^oC, 3d	65 %
5	**14**	$Pd(OAc)_2$ (5 mole%), *rac*-BINAP (10 mole%), CS_2CO_3(2 equiv), DMF, 100 ^oC, 30 h	75 %
6	**15**	$Pd(OAc)_2$(5 mole%), *rac*-BINAP (10 mole%), CS_2CO_3(2 equiv), DMF, 100 ^oC, 12 h	85 %

In order to functionalize the bromocarbazole derivative, we treated **17** with allytributyltin reaction and AIBN in benzene reflux for 1 h. The allyl carbazole derivative **20** was obtained in high yield 89% (Scheme 4). Similar C-C bond coupling was achieved via Pd-catalyzed Suzuki reaction of **17** with phenylboronic acid in the presence of K_2CO_3 and dioxane to furnish the phenyl carbazole derivative **21** in excellent yield 91% as mentioned in Scheme 4.

Scheme 4: *Derivatization of carbazoles **17**, **19** leading to the carbazoles **20**, **21**, **22**, **23**, **24** and **25***



(a) ATBT, C_6H_6, reflux, 1 h; (b) Phenylboronic acid, $Pd(PPh_3)_4$ (10 mole%), K_2CO_3 (3 mole%),dioxane, 1 h; (c) BBr_3, CH_2Cl_2, -78 to 0 ^oC, 1-2 h; (d) $LiAlH_4$, rt, 5 h, Et_2O:CH_2Cl_2 (1:1).

Among the active pharmacophores, a free hydroxyl group at C-1 or C-2 position is a common featuring functional group in many carbazole alkaloids (Figure 1). Therefore, the carbazole derivatives **17** and **19** were subjected to Lewis acid, borontribromide (BBr_3), generally employed for *O*-demethylation of aromatic methyl ether.[18] As expected, the dihydroxycarbazole derivatives **22** and **23** were obtained in high yield 87-89% (Scheme 4). Since the carbinol moiety served as an important functional group in many carbazole natural products,[19] we checked the reduction feasibility of methylester group in **17** and **19** with $LiAlH_4$ in CH_2Cl_2-Et_2O (1:1) at room temperature. Interestingly, bromocarbazole **17** provided 1-hydroxymethylcarbazole **24** in good yield. Whereas, carbazole derivative **19** furnished an unexpected 3-methylcarbazole **25** under the above mentioned reduction conditions (Scheme 4).

In summary, we have reported a regioselective synthesis of carbazole analogs from a suitably substituted norbornyl α-diketones via Grob fragmentation, *O*-methylation and aromatization reaction sequence. The synthesis of carbazole derivatives possessing a methylester group at C-1 position was achieved by Cadogan reductive cyclization of nitro bi-phenyl derivatives. Whereas, carbazole analog possessing a methylester group at C-3 position was synthesized by Buchwald-Hartwig Pd-catalyzed intramolecular cyclization of amino bi-phenyl derivatives. The bromocarbazole derivative was utilized efficiently in radical mediated allylation, Pd-catalyzed Suzuki coupling transformation, borontribromide mediated *O*-demethylation and $LiAlH_4$ mediated reduction reactions. Many of the carbazole analogs presented in this paper share common structural features with natural carbazoles such as mukonine, clausine-L, murrayafoline-A and their sibling natural products.

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References

(1) Graebe, C.; Glazer, C. Ber. *Dtsch. Chem. Ges.* **1872**, 5, 12.(2) a) Chakraborty, D. P.; Barman, B. K.; Bose, P. K. *Sci. Cult.* **1964**, *30*, 445; b) Chakraborty, D. P.; Barman, B. K.; Bose, P. K. *Tetrahedron* **1965**, *21*, 681.

(3) a) Das, K. C.; Chakraborty, D. P.; Bose, P. K. *Experientia***1965**, *21*, 340; b) Chakraborty, D. P. In Progress in the Chemistry of Organic Natural Products; Herz, W., Griesebach, H., Kirby, G. W., Eds.; Springer: Wien, Austria **1977**, *34*, 299.

(4) a) Ito, C.; Katsuno, S.; Itoigawa, M.; Ruangrungsi, N.; Mukainaka, T.; Okuda, M.; Kitagawa, Y.; Tokuda, H.; Nishino, H.; Furukawa, H. *J. Nat. Prod.* **2000**, *63*, 125; b) Shi, X. -J.; Ye, G.; Tang, W. -J.; Zhao, W. -M. *Helv.Chim.Acta***2010**, *93*, 985; c) Wang, Y. -S.; He, H. -P.; Shen, Y.-M.; Hong, X.; Hao, X. -J. *J. Nat. Prod.* **2003**, *66*, 416; d) Ito, C.; Itoigawa, M.; Aizawa, K.; Yoshida, K.; Ruangrungsi, N.; Furukawa, H. *J. Nat. Prod.* **2009**, *72*, 1202; e) Ruangrungsi, N.; Ariyaprayoon, J. *J. Nat. Prod.* **1990**, *53*, 946; f) Jana, A. K.; Mal, D. *Chem. Commun.* **2010**, *46*, 4411.

(5) a) Wakim, S.; Bouchard, J.; Blouin, N.; Michaud, A.; Leclerc, M. *Org. Lett.***2004**, *6*, 3413; b) Arulselvan, P.; Subramanian, S. P. *Chem. Biol. Interact.***2007**, *165*, 155.

(6) a) Chowdhury, B. K.; Jha, S.; Bhattacharyya, P.; Mukherjee, M. *Indian J. Chem.* **2001**, *40B*, 490; b) Wu, T. -S.; Huang, S. -C.; Wu, P. -L.; Kuoh, C. -S. *Phytochemistry***1999**, *52*, 523; c) Sakano, K. -I.; Ishimaru, K.; Nakamura, S. J. *Antibiot.* **1980**, *33*, 683; d) Sakano, K. -I.; Nakamura, S. J. *Antibiot.* **1980**, *33*, 961; e) Kondo, S.; Katayama, M.; Marumo, S. J. *Antibiot.* **1986**, *39*, 727; f) Naid, T.; Kitahara, T.; Kaneda, M.; Nakamura, S. J. *Antibiot.* **1987**, *40*, 157; g) Knölker, H. -J.; Bauermeister, M. *Helv. Chim. Acta* **1993**, *76*, 2500; h) Dračínský, M.; Sejbal, J.; Rygerová, B.; Stiborová, M. *TetrahedronLett.* **2007**, *48*, 6893.

(7) a) Schmidt, A. W.; Reddy, K. R.; Knölker; H. -J. *Chem. Rev.* **2012**, *112*, 3193; b) Knölker, H. -J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303; c) Yauub, G.; Hussain, E.; Rehman, M.A.; Mateen, B. *Asian J. Chem.* **2009**, *21*, 2485; d) Song, J. J.; Reeves, J T.; Fandrick, D. R.; Tan, Z.; Yee, N. K.; Senanayake, C. H. *ARKIVOC* **2010**, 390; e) Kataeva, O.; Krahl, M. P.; Knölker, H. -J. *Org. Biomol. Chem.* **2005**, *3*, 3099; f) Knölker, H. -J.; Reddy, K. R. In The Alkaloids; Cordell, G. A., Ed.; Academic Press: Amsterdam **2008**, *65*, 1; g) Chakraborty, D. P. *Planta Med.***1980**, *39*, 97; h) Xin, Z. -Q.; Lu, J. -J.; Ke, C. -Q.; Hu, C. -X.; Lin, L. -P.; Ye, Y. *Chem. Pharm. Bull.***2008**, *56*, 827; i) Naffziger, M. R.; Ashburn, B. O.; Perkins, J. R.; Carter, R. G. *J. Org. Chem.* **2007**, *72*, 9857.

(8) a) Cadogan, J. I. G. *J. Quart Rev.* **1962**, *208;* b) Cadogan, J. I. G.; Mackie, G. *Org. Syn. Coll.* **1973**, *5*, 1941; c) Bunyan, P. J.; Cadogan, J. I. G. *J. Chem. Soc.* **1963**, 42; d) Cadogan, J. I. G.; Cameron-Wood, M.; Mackie, R. K.; Searle, R. J. G. *J. Chem. Soc.* **1965**, 4831; e) Blouin, N.; Leclerc, M. *Acc. Chem. Res.* **2008**, *41*, 1110; f) Roy, J.; Jana, A. K.; Mal, D. *Tetrahedron***2012**, *68*, 6099.Therein references.

(9) a) Fischer, E.; Jourdan, F. Ber. *Dtsch. Chem. Ges.* **1883**, *16*, 2241; b) Borsche, W.; Witte, A.; Bothe, W. *Liebigs Ann. Chem.* **1908**, *359*, 49.

(10) Graebe, C.; Ullmann, F. *Liebigs Ann. Chem.* **1896**, *291*, 16.

(11) Stokes, B. J.; Jovanović, B.; Dong, H.; Richert, K. J.; Riell, R. D. ; Driver, T. G. *J. Org. Chem.* **2009**, *74*, 3225.

(12) a) Rasheed, S. k.; Nageswar Rao, D.; Reddy, K. R.; Aravinda, S.; Vishwakarma, R. A.; Das, P. *RSC Adv.* **2014**, *4*, 4960; b) Dhara, K.; Mandal, T.; Das, J.; Dash, J. Angew. Chem. Int. Ed. **2015**, *54*, 15831.

(13) a)Guerra, W. D.; Rossi, R. A.; Pierini, A. B.; Barolo, S. M. *J. Org. Chem.* **2015**, *80*, 928; b) Yuan, Z. -G.; Wang, Q.; Zheng, A.; Zhang, K.; Lu, L. -Q.; Tang, Z.; W. Xiao, -J. *Chem. Commun.***2016**, *52*, 5128; c) Rathore, K. S.; Lad, B. S.; Chennamsetti, H.; Katukojvala, S. *Chem. Commun.***2016**, *52*, 5812.

(14) a) Humne, V. T.; Naykode, M. S.; Ghom, M. H.; Lokhande, P. D. *TetrahedronLett.* **2016**, *57*, 688, b) Naykode, M. S.; Humne, V. T.; Lokhande, P. D. *J. Org. Chem.* **2015**, *80*, 2392; c) Suzuki,C.; Hirano,K.; Satoh,T.; Miura, M. *Org. Lett.***2015**, *17(6)*, 1597; d) Bucinskas, A.; Waghray, D.; Bagdziunas,G.; Thomas, J.; Grazulevicius, J. V.; Dehaen; W. *J. Org. Chem.* **2015**, *80*, 2521; e) Borrero, N. V.; DeRatt, L. G.; Barbosa, L. F.; Abboud, K. A.; Aponick, A. *Org. Lett.***2015**, *17(7)*, 1754; f) Kale, A. P.; Kumar, G. S.; Mangadan, A. R. K.; Kapur, M. *Org. Lett.* **2015**, *17*, 1324; g) Singha, R.; Ahmed, A.; Nuree, Y.; Ghosh, M.; Ray, J. K. RSC Adv., **2015**, *5*, 50174.

(15) Khan, F. A.; Rao, C. N. *J. Org. Chem.* **2011**, *76*, 3320.

(16) a) Khan, F. A.; Sahu, N. *J. Catal.* **2005**, *231*, 438; b) Khan, F. A.; Prabhudas, B.; Dash, J.; Sahu, N. *J. Am. Chem. Soc.* **2000**, *122*, 9558.

(17) a) Wolfe, J.P.; Wagaw, S.; Marcoux, J.F.; Buchwald, S.L. *Acc. Chem. Res.* **1998**, *31*, 805; b) Muci, A. R.; Buchwald, S. L. *Topics in Curr. Chem.* **2002**, *219*, 131; c) Surry, D.S.; Buchwald, S.L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338; d) Hartwig, J. F. *Synlett* **1997**, *4*, 329; e) Hartwig, J. F. *Angew. Chem. Int. Ed.* **1998**, *37*, 2046; f) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852.

(18) a) Julich-Gruner, K. K.; Schmidt, A. W.; Knölker, H. -J. *Synthesis* **2014**, *46*, 2651; b) Gassner, C.; Hesse, R.; Schmidt, A. W.; Knölker, H. -J. *Org. Biomol. Chem.* **2014**, *12*, 6490.

(19) a) Fiebig, M.; Pezzuto, J. M.; Soejarto, D. D.; Kinghorn, A. D. *Phytochemistry***1985**, *24*, 3041; b) Kato, S.; Shindo, K.; Kataoka, Y.; Yamagishi, Y.; Mochizuki, J. *J. Antibiot.***1991**, *44*, 903.

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Highlights

- Regioselective synthesis of carbazole analogs is reported.
- Cadogan or Pd-catalyzed intramolecular cyclization was employed in the final step.
- The reported motifs are present in many carbazole natural products.

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