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Synthesis of the carbazole scaffold directly from 2-amino-biphenyl by means of a concurrent C–H activation and C–N bond formation

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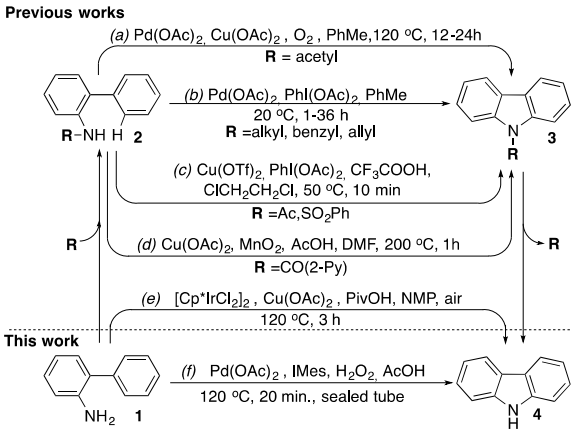
Abstract. An efficient synthetic method for the synthesis of the carbazole scaffold was designed and investigated. The method was developed to produce substituted carbazoles by an intramolecular combination of a free amine group and an arene. The steps of the method involves a concurrent Pd catalysed C−H activation and intramolecular C-N bond formation. The method shows good functional group tolerance, where the substituent(s) might be installed on either of the two rings or on both of the two rings of the 2-amino biphenyl substrate. After the ring closure, the reduced Pd catalyst is oxidized to Pd(II) by means of hydrogenperoxide. The novel method was demonstrated to operate excellently with the corresponding 2-N-acetylamino biphenyls as well.

Keywords: C-H activation; C-N bond formation; carbazole; palladium; hydrogen peroxide

Introduction

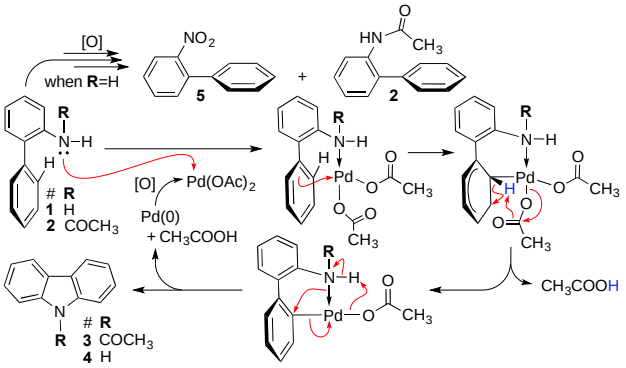
The carbazole framework constitutes an essential kernel of numerous indispensable applications in the society and the industry. Therefore, a considerable effort has been devoted to the development of efficient methods exploitable for the synthesis of such molecular motifs.[1] A decade ago, Buchwald and collaborators[2] disclosed a seminal work that describes an attractive strategy and methodology that permit the synthesis of the carbazole framework through a concurrent C–H activation and C–N bond formation, Scheme 1 path *(a)*. This strategy involves 2-*N*-acetylamino biphenyl **2** as the substrate, which was exposed for C–H activation at the 2'-position assisted by a Pd(II) moiety coordinated to the 2-*N*-acetylamino group. The subsequent step results in C–N bond formation that affords the carbazole scaffold concomitant with release of Pd(0). Pd(0) was oxidized to Pd(II) by O_2, which allowed a recycling of Pd as a catalyst, Scheme 2. The major drawbacks of this method[2] comprises; a rather long reaction time and the need of a protective or auxiliary group attached to the 2-amino group, which is provoked by the fact that the oxidative conditions can also support the parasite oxidation reaction, **1**→**5**.

During the last decade, a few more methods based on concurrent C–H activation and C–N bond formation have been revealed.



Scheme 1. Intramolecular C-H activation and C-N bond formation that results in the carbazole framework.

Gaunt and collaborators[3] disclosed a process that also involves $Pd(OAc)_2$ as the catalyst, but with the hypervalent iodine compound phenyliodosyl diacetate in DMF as the re-oxidant for the palladium catalyst, Scheme 1 path *(b)*. An important improvement offered by this method is the low reaction temperature (20 °C), although the method is still saddled with drawbacks, namely the need of a protective or auxilliary group and the production of stoichiometric quantities of the reduced oxidant as a by-product.

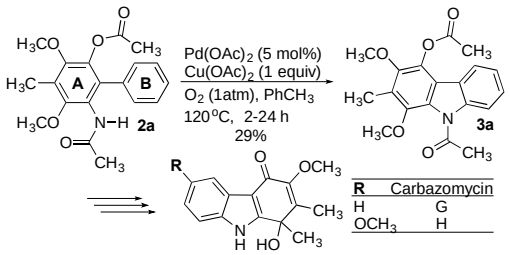


Scheme 2. Reaction mechanism proposal for the concurrent Pd – catalysed C–H activation and C–N bond formation resulting in the carbazole scaffold using 2-amino biphenyl as the substrate.

Satho, Miura and collaborators[4] communicated lately a method that encompassing an Ir(III) / Cu based catalytic system with air as the terminal oxidant, Scheme 1 path *(e)*. This method is until now the only intramolecular amination method allowing the preparation of the carbazole scaffold from unprotected 2-amino biphenyl, but this protocol requires an expensive Ir based catalyst along with several other additives to operate the ring closing reaction. Two various methods involving copper as catalyst were disclosed by Chang and collaborators[5a] and Hirano, Miura and collaborators[5b] shown in paths *(c)* and *(d)*, respectively. Both of these methods also request supporting / auxiliary groups installed on the amino group and stoichiometric quantities of oxidants, $PhI(OAc)_2$ and MnO_2, respectively.

Results and Discussion

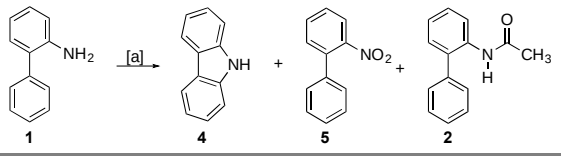
For a project in progress in our group dedicated to a novel total synthesis of the natural products carbazomycin G and H,[6] several new methods were needed: preparation of the functionalized benzene moieties[7] needed for the 2-amino biphenyl precursor, Suzuki cross-coupling methods suitable for the preparation of the 2-nitro biphenyls,[8] and an efficient method for nitro-group reduction.[9] Moreover, we aimed to utilize the C–H activation and intra-molecular C–N formation strategy disclosed by Buchwald and collaborators.[2] Thus, we initiated to use the Buchwald protocol in attempts to accomplish the intramolecular amidation with the biphenyl **2a**, Scheme 3.



Scheme 3. Intramolecular C–H activation and C–N formation leading to the carbazole precursor 3a (29%) for carbazomycin G (R=H) and H (R=OCH_3).

However, probably due to the highly congested substitution pattern of the A-ring combined with the acetyl group attached to the 2-amino group, the ring closing reaction afforded a yield of only 29% of target carbazole **3a**. This somewhat disappointing result spurred us to undertake further investigations of the ring closing protocol. Even thought the amino group can be oxidized to the nitro group under various conditions,[10] we wanted to investigate the ring closure using the non-protected 2-amino biphenyl framework. 2-Nitro biphenyl **5** might be a parasite reaction product under the oxidative conditions used in a Pd catalysed intramolecular amination. Indeed, we observed this oxidation product as soon as unprotected 2-amino biphenyl **1** was tried as the substrate, Table 1.

Table 1. Screening experiments for the ring closing of 2-amino biphenyl to achieve the carbazole scaffold[a]



#	Catalyst/Ligand	t [min]	Measured response[b]			
			Conv.	y_4	y_5	y_2
1	$Pd(OAc)_2$	90	93	39	26	20
2	$Pd(OAc)_2$	60	86	48	30	nd
3	$Pd(OAc)_2$	20	67	30	10	24
4	$Pd(OAc)_2$ /IMes·HCl	20	84	45	18	15
5	$Pd(TFA)_2$	20	77	49	9	16
6	$Pd(TFA)_2$ /IMes·HCl	20	83	43	15	21
7 [c]	$Pd(OAc)_2$ /IMes·HCl	10	97	67	2	28

[a]Reaction conditions: A solution of 2-aminobiphenyl **1** (84.5 mg, 0. 5 mmol) in glacial acetic acid (5 mL), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol or $Pd(TFA)_2$ (8.3 mg, 0.025 mmol)]) (5 mol-%), IMes·HCl (8.5 mg, 0.025 mmol) when specified, and H_2O_2 (35%, 0.128 mL, 1.45 mmol) were placed in a reactor tube and immersed into the cavity of the microwave oven for *t* min. at *T*=90 °C. [b]The reaction was monitored by means of GC-MS; Conv. = conversion of **1**. Yields (*y*) of compound **4** and **5** were corrected using the response factors; 2-aminobiphenyl **1**, rf_1=1.00; carbazole, rf_4=1.00, and 2-nitrobiphenyl, rf_5=1.29. The selectivity and yield of compound **2** and **5** are uncorrected with response factor. [c]20 mol-% (22.4 mg, 0.100 mmol) of $Pd(OAc)_2$ was used.

Although, alterations of the reaction time, reaction temperature, and the compositions of the catalytic system were revealed to affect not only the yield of the target carbazole **4**, but also the distribution of the side-products **2** and **5**. Evidently, the NHC ligand IMes with $Pd(OAc)_2$ operated reasonable well as a catalyst for the ring closing. Moreover, the reaction time appeared also to be of paramount importance, Table 1. The reaction trial of entry 7 was used as a basis in an attempt to discover a higher yielding protocol. A series of experiments with various Pd loading (5-20 mol%) was conducted and monitored over a period of 20 min. The alterations of the Pd loading revealed a great effect on the outcome of the reaction, Figure 1a. Moreover, after a reaction time of 10-15 min. the target molecule started to depredate concomitantly as two parasite products **2** and **5** were produced.

Further optimisation of the method was conducted by means of a systematic variation (in a grid pattern) of the reaction temperature and time, Figure 1b.

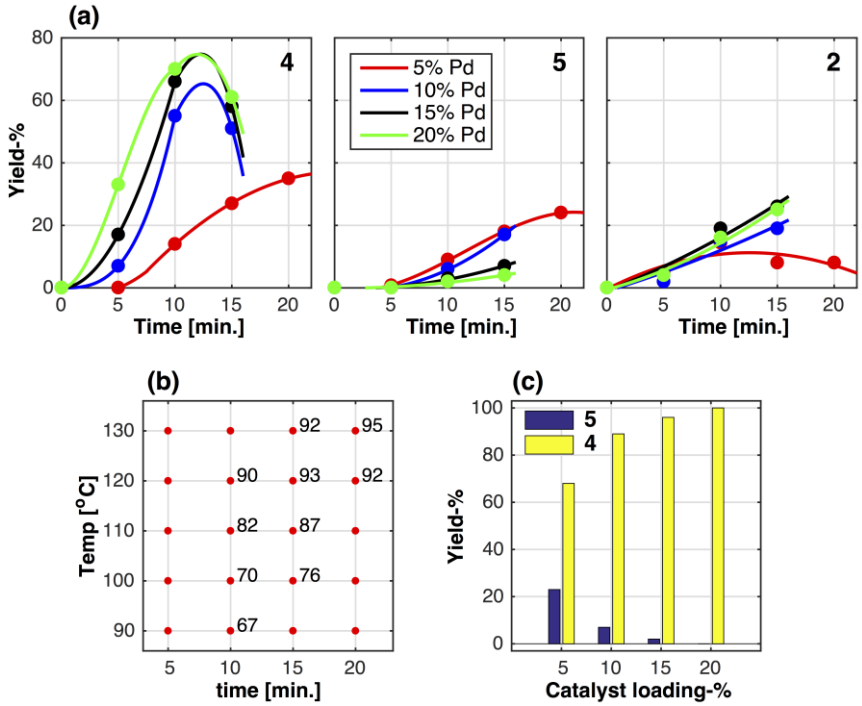


Figure 1. (a) Reaction profile showing the outcome of **4**, **5**, and **2** at various Pd loading. To a solution of 2-aminobiphenyl (84.5 mg, 0.5 mmol) in glacial acetic acid (5 mL), $Pd(OAc)_2$ (5-20 mol%), IMes • HCl (8.5 mg, 0.025 mmol) and H_2O_2 (35%, 0.128 mL, 1.45 mmol) were added to perform the above reactions under microwave irradiation (μW) for 15-20 min. at 90 °C. **(b)** Screening of the reaction time (5-20 min.) versus reaction temperature (90-130 °C) reveals optimized conditions at the higher temperature and longer reaction time. **(c)** Variation (5-20%) of the catalyst loading (using 20 min. and 120°C) afforded a high conversion (≥97%) of the 2-amino-biphenyl **1** with **4** and **5** as reaction products.

High yielding conditions were located at a reaction time of 15-20 min. with a temperature of 120-130 °C. The so far optimized protocol (Figure 1a,b) was then repeated, although under various Pd loadings (5-20%), Figure 1c. A high conversion (≥97%) of the 2-amino-biphenyl **1** substrate was achieved for all of these experiments. When a Pd loading of <20% was used, an oxidation of the amino group into the nitro group occurred. In fact, as much as 23% of 2-nitro biphenyl **5** was formed using 5% Pd and only ≈2% of **5** was formed with a Pd loading of 15%. With a Pd loading of 20%, the carbazole scaffold was obtained in 97% yield.

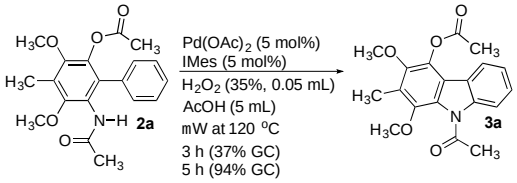
A scope and limitation study of our new method was then undertaken by means of a series of substituted 2-amino biphenyls, Table 2. Overall, the method tolerates both electron-withdrawing and -donating groups to afford moderate to excellent yields of target carbazole scaffold. However, some few exceptions were observed; 2'-methoxy and 3'-methoxy-2-amino biphenyls afforded yields of ≈10% only (entries 6 and 7) and 4'-methoxy-2-amino biphenyl provided a moderate yield (entry 8). These observations might be due to the inductive effect of the methoxy substituent that would disrupt the intermediate, but the oxidative condition present for the catalytic cycle might as well give rise to oxidation of the aromatic kernel into a de-methoxylated quinoid framework[11] followed by additional degradation reactions. Moreover, as expected, the method did not operate with substrates that contained a free hydroxy group; nevertheless by means of standard protection (*t*-butyldimethylsilyl chloride) of the hydroxyl group, a high yield of target carbazole was obtained (entry 15, Table 2).

The method was also explored with 2-*N*-acetyl-amino biphenyls as substrates, Table 3. In this context, minor alterations of the experimental conditions were found to be beneficial, namely a lowered Pd loading (5 mol%) and an extended reaction time (3 h). Using these conditions with 3'-methoxy- and 4'-methoxy-2-*N*-acetyl-amino biphenyls, the corresponding carbazoles were achieved in high yields (entries 7 and 8 of Table 3). Although the 2´-methoxy- substituted substrate provided a low yield (25%) only. The 3'-methoxy- substituted substrate (entry 7) provided two regioisomers, viz. 1-(3-methoxy-9*H*-carbazol-9-yl) ethan-1-one **3g** (major) and 1-(2-methoxy-9*H*-carbazol-9-yl)ethan-1-one (minor). The methylated substrates (entries 3 and 4) provided low to moderate yields, this applied also for a substrate with a strong electron-withdrawing group (entry 2). The observed results were consistent with previous observations.[2]

Electrophilic substitution on carbazole scaffold favours normally the position 3 and 6. However, our new method allows functionalization in the positions 2 and 4, which might be valuable for the synthesis of natural products that contain the carbazole scaffold.

As an ultimate test of the new protocol we attempted to perform the transformation **2a** → **3a** previously performed with the Buckwald method,[2] Scheme 2. Only a minor alteration of the conditions of our new method was needed; while 3h afforded 37% yield, a

reaction time of 5h provided an excellent yield of 94%. The conditions and results are summarized in Scheme 4.

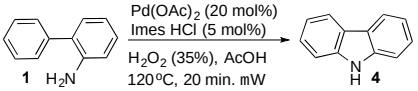


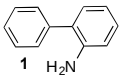
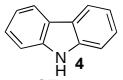
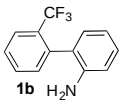
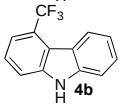
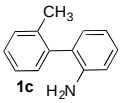
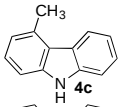
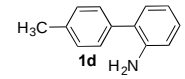
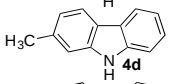
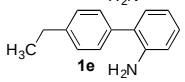
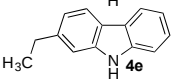
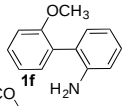
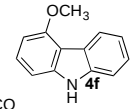
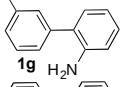
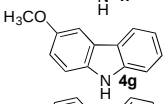
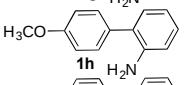
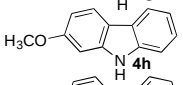
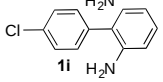
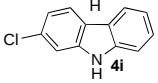
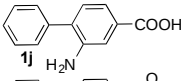
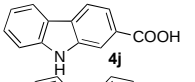
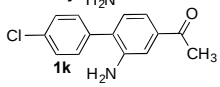
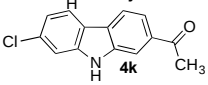
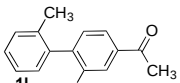
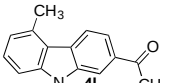
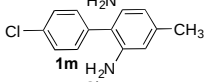
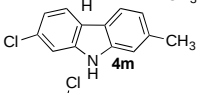
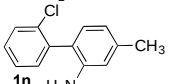
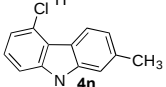
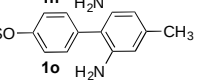
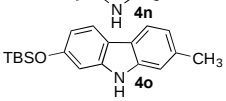
Scheme 4. Intramolecular C–H activation and C–N formation leading to the carbazole 3a (94%) as a precursor for carbazomycin G.

Conclusion

In summary, we have developed a new highly efficient and high rate method for the synthesis of the carbazole framework by means of a Pd catalysed concurrent C–H activation and intramolecular C–N bond formation using the 2-amino biphenyl scaffold as the substrate. In general, the method tolerates both electron withdrawing and donating groups on one or both of the two aromatic rings of the substrate. Even substrates labile for oxidation such as aromatics that contain the hydroxyl and/or the methoxy groups can be converted into their corresponding carbazoles. However, if the 2-amino biphenyl scaffold is substituted with the methoxy group, an acetyl group should be introduced on the 2-amino group as an auxiliary group. Free hydroxyl groups should be protected.

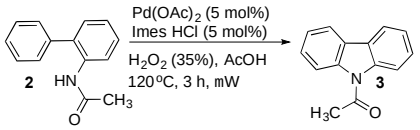
Table 2. Scope of reaction using 2-amino biphenyls 1 as substrate.



#	2-Amino- biphenyls	Carbazole	Responses[a] y[%]	yi[%]
1			92	84
2			na	60
3			>99	82
4			na	71
5			>99	70
6[b]			na	9
7			na	10
8			na	41
9			90	70
			na	75
11			94	73
12			98	85
13			91	77
14			>99	81
15[c]			82	61

a) y = conversion yield based on GC, yi =isolated yield after column chromatography (silica gel), na=not analyzed on GC.
b) An additional experiment using 20 mol% IMes was also conducted. The outcome was similar to the experiment where 5 mol% IMes was used.
c) An experiment without the TBS protective group installed did not afford the target carbazole.

Table 3. Scope of reaction using using 2-N-acetylamino biphenyl 2 as substrate.



#	2-Amino- biphenyls	Carbazole	Responses[a] y[%]	yi[%]
1	**2**	**3**	91	85
2	**2b**	**3b**	20	ni
3	**2c**	**3c**	17	ni
4	**2d**	**3d**	51	46
5	**2e**	**3e**	100	81
6	**2f**	**3f**	25	ni
7[b]	**2g**	**3g**	75	61
8	**2h**	**3h**	82	70

a) y = conversion yield based on GC, yi =isolated yield after column chromatography (silica gel), ni=not isolated.
b) In addition to the major product **3g**, a minor quantity (12%) of the 5'-methoxy derivative was obtained.

Experimental Section

All reagents and solvents were purchased from commercial sources and used as received. Melting points were determined in open capillaries. Reagent grade chemicals were purchased from commercial sources and used without further purification. All reaction mixtures and column eluents were monitored by TLC (TLC plates Merck Kieselgel 60 F254). The TLC plates were observed under UV light at λ = 254 nm and λ = 365 nm. IR spectra were recorded as KBr discs with a Shimadzu FTIR-8300 spectrophotometer, and ^{1}H and ^{13}C NMR spectra were recorded with Bruker AV 400 MHz and 500 MHz instruments. High- resolution mass spectra (HRMS) were performed with a Q-TOF Micro YA263 instrument.

General methods. GC analyses were performed with a capillary gas chromatograph equipped with a fused silica column (l25 m, 0.20 mm i.d., 0.33 mm film thickness) at a helium pressure of 200 kPa, split less/split injector and flame ionization detector. Mass spectra were obtained with a GC–MS instrument, with a gas chromatograph equipped with a fused silica column (l30 m, 0.25 mm i.d., 0.25 mm film thickness) and helium as the carrier gas. DARTmass spectra were obtained by using PEG as an internal standard in positive ionization mode with a TOF mass analyzer. 1H and ^{13}CNMR spectra were recorded at ambient temperature at a frequency of 400, 500 MHz and 100, 125 MHz respectively. The chemical shifts are reported in ppm relative to residual $CDCl_3$ for proton (δ = 7.26 ppm) and $CDCl_3$ for carbon (δ = 77.0 ppm) and DMSO-d_6 for proton (δ = 2.50 ppm) and carbon (δ = 39 ppm) with tetramethylsilane as an external reference. Flash chromatography was performed by using the indicated solvent system and silica gel (230–400 mesh). All reagents used were commercially available from Aldrich Chemical Co. For new compounds HRMS data were also recorded.

The microwave-assisted experiments were performed by means of a Biotage Initiator Sixty EXP Microwave System, that operates at 0–400 W at 2.45 GHz, in the temperature range of 40–250 °C, a pressure range of 0–20 bar (2 MPa, 290 psi), and with reactor vial volumes of 0.2–20 mL.

General procedure for 2-aminobiphenyl derivatives (1-1o). 2-Nitrobiphenyl (1 mmol, 0.2 g) was dissolved in EtOH (4 mL) and transferred to a tube reactor. Then, a mixture of NH_4Cl (2 mmol, 0.107 g) in H_2O (1.2 mL) and indium powder (3 mmol, 0.344 g, 99.99% 100 mesh, use preferably a freshly opened bottle or stored under Ar) were added whereupon a magnetic stirrer bar was transferred to the tube. The tube was then sealed and the reaction mixture was stirred and heated at 120 °C for 3 h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (30 mL). The resulting mixture was filtered through a pad of celite to remove the catalyst. Another portion (20 mL) of ethyl acetate was used to wash through the filter pad. The resulting transparent organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure using a rotary evaporator to obtain the 2- aminobiphenyl compound.

2'-methyl-[1, 1'-biphenyl]-2-amine (1c). 2'-methyl-2-nitro-1, 1'-biphenyl (0.324 g, 1.52 mmol), NH_4Cl (0.161 g, 3.04 mmol) and indium powder (0.523 g, 4.56 mmol). The title compound was obtained as a yellow liquid (0.259 g, 93%): R_f = 0.66 [(Hx:EtOAc, 80:20)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 7.17-7.22 (m, 3H), 7.12-7.14(m, 1H), 7.08-7.11 (td, *J*= 1.5 Hz, 7.5 Hz, 1H), 6.93-6.95 (dd, *J*= 1 Hz, 7 Hz, 1H), 6.72-6.75 (td, *J*= 1 Hz, 7 Hz, 1H), 6.68-6.70 (dd, *J*= 1 Hz, 8 Hz, 1H), 2.10 (s, 3H),; ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 143.6, 138.6, 137.0, 130.3, 130.1, 130.0, 128.4, 127.7, 127.5, 126.2, 118.3, 115.1, 19.7; HR-MS (DART): $(M+H)^+$; Calcd for $C_{13}H_{13}N$ 184.1126; Found 184.1127); IR (cm^{-1}): 3465, 3375, 3018, 2921, 1612, 1480, 1447, 1296.

General procedure for 2-acetaminobiphenyl derivatives (2-2h). To a solution of 2-aminobiphenyl (0.1 g, 0.59 mmol) and triethylamine (0.09 mL, 0.65 mmol) in 10 mL anhydrous of dichloromethane at 0°C, acetyl chloride (0.04 mL, 0.62 mmol) was added dropwise. The mixture was stirred at room temperature for 1 h. After the reaction time, the solvent was evaporated under reduced pressure. The residue was dissolved in ether (20 ml) washed with water (20 ml). The organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure using a rotary evaporator to obtain the N-acetylated compound.

N-([1, 1'-biphenyl]-2-yl) acetamide. 2'-amino-[1, 1'-biphenyl] **(1a)** (0.10 g, 0.59 mmol), Acetyl chloride (0.04 mL, 0.62 mmol) and Triethylamine (0.09 mL, 0.65 mmol). The title compound was obtained as a pale- white solid (0.115 g, 93%). mp 119.8-120 °C; Rf = 0.24 [(Hx:EtOAc, 80:20)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.26 (d, *J*= 8.5 Hz, 1H), 7.49 (t, *J*= 7 Hz, 2H), 7.38(m, 3H), 7.24 (d, *J*= 7 Hz, 1H), 7.18 (d, *J*= 7.5 Hz, 1H), 2.02 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$); δ = 168.3, 138.2, 134.7, 132.2, 130.1 129.2, 129.1, 128.4, 128.0, 124.4, 121.7, 24.6; HR-MS

(ESI): (M+Na)+: Calcd for $C_{14}H_{13}NNaO$ 234.0895; Found 234.0896); IR (cm-1): 3286, 3027, 1658, 1531, 1433, 1301.

General procedure for carbazole derivatives (4-4o). In a microwave tube, 2-aminobiphenyl (84.5 mg, 0.5 mmol) was dissolved in glacial acetic acid (5mL), $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), IMes.HCl (8.5 mg, 0.025 mmol) and H_2O_2 (35%, 0.128 mL, 1.45 mmol) were added. The vial was sealed whereupon a magnetic stirrer bar was transferred to the tube. The tube was submerged in the microwave cavity for 20 min at 120oC. After the reaction time, the solvent acetic acid was removed under reduced pressure. The crude product was dissolved in EtOAc (25 mL) and washed with water (20 mL). The aqueous phase was extracted with EtOAc (2×20 mL). The combined organic layer was washed with aqueous $NaHCO_3$ (20 mL). The organic layer was filtered off via pad of celite and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using hexanes (mixture of isomers) and ethyl acetate (gradient; 90:10 to 50:50) to obtain the target compound.

9*H*-carbazole (4). 2-amino-1, 1'-biphenyl **(1a)** (0.085 g, 0.50 mmol), $Pd(OAc)_2$ (22.4 mg, 0.1 mmol), IMes.HCl (8.5 mg, 0.05 mmol) and H_2O_2 (35%, 0.128 mL, 1.45 mmol). The title compound was obtained as a pale- brown solid (0.070 g, 84 %). mp 242-243 ^oC ;Rf = 0.49 [(Hx:EtOAc, 80:20)]; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, J= 8 Hz, 2H), 7.42-7.47 (m, 4H), 7.22-7.26 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$); δ = 139.5, 125.8, 123.4, 120.3, 119.4, 110.6; HR-MS (DART): (M+H)+: Calcd for $C_{12}H_{10}N$ 168.0813; Found 168.0814; IR (cm-1): 3415, 3050, 1599, 1449, 1325, 722.

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References

[1] a) A. W. Schmidt, K. R. Reddy, H. J. Knölker, *Chem. Rev.* **2012**, *112*, 3193; b) Hartwig, J. F. *Angew. Chem. Int. Ed.* **1998**, *37*, 2046; c) Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 13848; d) L. Ackermann, A. Althammer, *Angew. Chem. Int. Ed.* **2007**, *46*, 1627; e) T. Tsuchimoto, H. Matsubayashi, M. Kaneko, Y. Nagase, T. Miyamura, E. Shirakawa, *J. Am. Chem. Soc.* **2008**, *130*, 15823; f) Z. Shi, S. Ding, Y. Cui, N. Jiao, *Angew. Chem.* **2009**, *121*, 8035; *Angew. Chem. Int. Ed.* **2009**, *48*, 7895; g) A. P. Antonchick, R. Samanta, K. Kulikov, J. Lategahn, *Angew. Chem.* **2011**, *123*, 8764; *Angew. Chem. Int. Ed.* **2011**, *50*, 8605; h) S. V. Ley, A. W. Thomas, *Angew. Chem. Int. Ed.* **2003**, *42*, 5400.

[2] a) W. C. P. Tsang, N. Zheng, S. L. Buchwald. *J. Am Chem. Soc.* **2005**, 127, 14560; b) W. C. P. Tsang, R. H. Munday, G. Brasche, N. Zheng, S. L. Buchwald. *J. Org. Chem.* **2008**, *73*, 7603.

[3] J. A. Jordan-Hore, C. C. C. Johansson, M. Gulias, E. M. Beck, M. J. Gaunt. *J. Am. Chem. Soc.* **2008**, *130*, 16184.

[4] C. Suzuki, K. Hirano, T. Satoh, and M. Miura. *Org. Lett.* **2015**, *17*, 1597.

[5] a) S. H. Cho, J. Yoon, S. Chang, *J. Am. Chem. Soc.* **2011**, *133*, 5996–6005; b) K. Takamatsu, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2014**, *16*, 2892−2895.

[6] a) H.-J. Knölker, W. Fröhner *J. Chem. Soc. Perkin. Trans. 1* **1998**, 173; b) H. Hagiwara, T. Choshi, H. Fujimoto, E. Sugino, S. Hibino*Tetrahedron* **2000**, *56*, 5807; c) H.-J. Knölker, W. Fröhner, K. R. Reddy *Eur. J. Org. Chem.* **2003**, 740.

[7] H.-R. Bjørsvik, G. Occhipinti, C. Gambarotti, L. Cerasino, V. R. Jensen. *J. Org. Chem.* **2005**, *70*, 7290.

[8] a) R. Rodríguez González, L. Liguori, A. Martinez Carrillo, H.-R. Bjørsvik. *J. Org. Chem.* **2005**, *70*, 9591; b) V. Elumalai, H.-R. Bjørsvik. *Eur. J. Org. Chem.* **2016**, 1344.

[9] V. Elumalai, H.-R. Bjørsvik. *Tetrahedron Lett.* **2016**, *57*, 1224.

[10] a) G. A. Russell, E. G. Janzen, *J. Am. Chem. Soc.* **1962**, *84*, 4153. b) P. B. Ayscough, F.P. Sargent, R. Wilson, R. *J. Chem. Soc*. **1963**, 5418; c) H.-R. Bjørsvik, L. Liguori, J. A. Vedia Merinero, *J. Org. Chem.* **2002**, *67*, 7493.

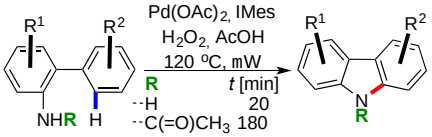
[11] R. R. González, C. Gambarotti, L. Liguori, H.-R. Bjørsvik *J. Org. Chem.* **2006**, *71*, 1703.

COMMUNICATION

Synthesis of the carbazole scaffold directly from 2-amino-biphenyl by means of concurrent C–H activation and C–N bond formation

Hans-René Bjørsvik* and Vijayaragavan Elumalai

An efficient Pd-catalyzed synthetic method for the preparation of the carbazole scaffold was designed and investigated. Non-symmetrical substituted carbazoles can be synthesised by an intramolecular combination of a free amine group and an arene via a concurrent Pd catalysed C−H activation and intramolecular C-N bond formation.



Key Topic: C−H activation