Heterocycles

DOI: 10.1002/anie.201309973

Rapid Synthesis of Fused N-Heterocycles by Transition-Metal-Free Electrophilic Amination of Arene C–H Bonds**

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Abstract: *We disclose an efficient and operationally simple protocol for the preparation of fused N-heterocycles starting from readily available 2-nitrobiaryls and PhMgBr under mild conditions. More than two dozen N-heterocycles, including two bioactive natural products, have been synthesized using this method. A stepwise electrophilic aromatic cyclization mechanism was proposed by DFT calculations.*

The carbazole ring system appears as a motif in a large number of biologically active natural products, active pharmaceutical ingredients (APIs), and novel functional organic materials (Figure 1).[1]

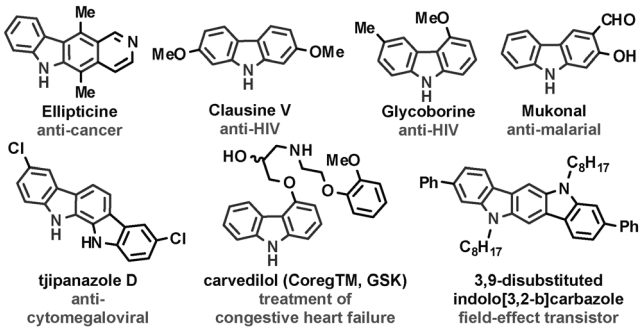

Figure 1. The carbazole structural motif in biologically active natural products, pharmaceuticals, and functional materials.

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[**] Financial support from the UT Southwestern Endowed Scholars in Biomedical Research Program (W.W. Caruth, Jr., Endowed Scholarship in Biomedical Research), the Robert A. Welch Foundation (grant I-1764), the ACS-PRF (grant 51707-DNI1), and the American Cancer Society & Simmons Cancer Center Institutional Research Grant (ACS-IRG 02-196) is greatly appreciated. D.H.E. thanks BYU and the Fulton Supercomputing Lab. We also express our gratitude to Professors E. J. Corey (Harvard University), Arthur J. Catino (Scranton University), Paul Knochel (LMU Munich), and Fabio Ragaini (University of Milan) for insightful discussions.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201309973.

Given the tremendous importance of functionalized carbazoles and their derivatives across many fields, it is not surprising that during the past 50 years dozens of synthetic methods have been developed to access this valuable heterocyclic framework with a variety of substitution patterns (see Figure 2 for representative methods):[2–8] 1) the Fischer–Borsche synthesis[2a] that relies on the [3,3]-rearrangement of arylhydrazones derived from cyclic ketones followed by

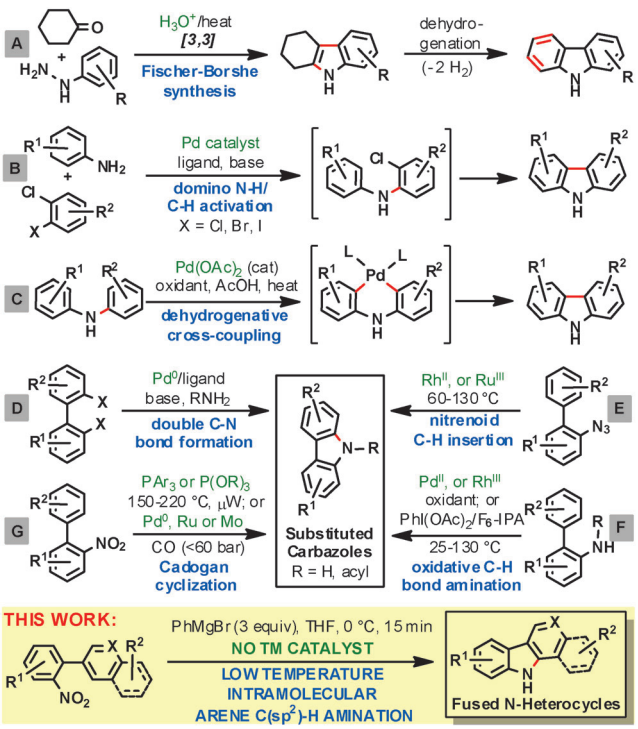
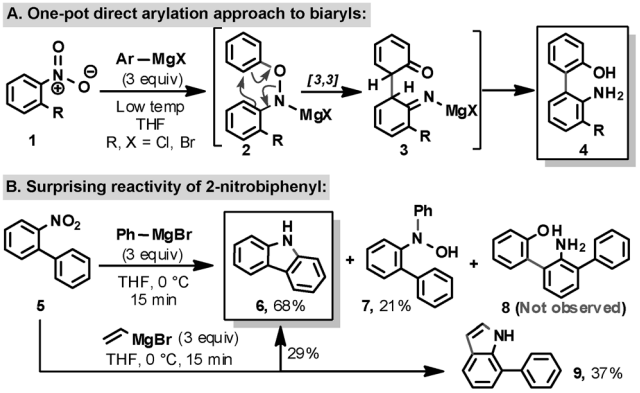


Figure 2. Selected methods for the synthesis of structurally diverse carbazoles, including our low-temperature, transition-metal (TM)-free intramolecular amination of aromatic C(sp^2)–H bonds.

dehydrogenation (Figure 2A); 2) one-pot, Pd-catalyzed domino N–H/C–H bond activation[2b,g,h] using substituted anilines and halogenated arenes (Figure 2B); 3) oxidative cyclization (i.e., dehydrogenative cross-coupling) of substituted *N,N*-diarylamines[3] to form an aryl–aryl bond (Figure 2C); 4) Pd-catalyzed double amination[4] of 2,2′-dihalo-1,1′-biaryls (Figure 2D); 5) insertion of transition metal (TM)-nitrenoids[5] into aromatic C(sp^2)–H bonds at elevated temperatures (Figure 2E); 6) oxidative aromatic C(sp^2)–H bond amination of 2-aminobiaryls[6] (Figure 2F); 7) Cadogan cyclization[7] of 2-nitrobiaryls at very high temperatures (150–220 °C) using either excess arylphosphines (e.g., PPh_3,

DPPE), excess trialkylphosphites [e.g., $P(OMe)_3$], or catalytic amounts of transition metal complexes[7b] (e.g., Pd, Ru, and Mo) in the presence of pressurized (5–60 bars) carbon monoxide (Figure 2G); 8) reaction of arynes with nitrosoarenes,[2i] and 9) iron-mediated synthesis of carbazoles.[8]

Recently we have developed a regioselective, TM-free, scalable direct aryl–aryl bond-forming process for the synthesis of halogenated 2-amino-2′-hydroxy-1,1′-biaryls (Scheme 1A).[9] This transformation requires the presence



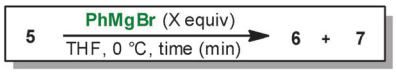
Scheme 1. Remarkable difference in reactivity of 2-substituted nitroarenes.

of a halogen substituent in the *ortho* position of the nitroarene substrate (**1**) and likely involves the formation of a *N,O*-biarylhydroxylamine intermediate (**2**) that then undergoes [3,3]-sigmatropic rearrangement to afford the corresponding biaryl product (**4**) upon re-aromatization of intermediate **3**. During these studies, we tested a number of different substituents (alkyl, alkoxy, azido, etc.) in the 2-position of nitroarenes under our optimized reaction conditions [PhMgBr (3 equiv), THF, 0 °C] and found dramatically different reactivities. For example, 2-nitrobiphenyl (**5**) did not afford the expected functionalized biaryl (**8**), but furnished 68% isolated yield of NH-carbazole (**6**) and 21% yield of hydroxylamine **7** (Scheme 1B). Even more interesting was the observation that exposing **5** to vinylmagnesium bromide (3 equiv) at 0 °C (i.e., Bartoli indole synthesis) led to an approximately 1:1 mixture of **6** and 7-phenyl indole (**9**) in a combined 66% yield.

These findings were surprising since an intramolecular amination of an aromatic $C(sp^2)$–H bond has taken place in a preparatively useful manner and under very mild conditions in order to form **6**. In general, aromatic $C(sp^2)$–H bonds are much harder to functionalize than alkenyl $C(sp^2)$–H bonds;[7b] indeed, a literature search after this discovery revealed a single report describing the reductive cyclization of 2-alkenyl nitroarenes to the corresponding indoles at low temperature (−40 °C).[10] The analogous low-temperature transformation of *ortho*-arylated nitroarenes to carbazoles has never been studied systematically. This transformation (**5**→**6**) is also surprising because the amination reaction proceeds by a formal electrophilic nitrene insertion under highly reducing conditions. Here we present the development of this transition-metal-free intramolecular amination reaction for *ortho*-arylated nitroarene substrates. We find that the reactions have a wide substrate scope and the cyclization is highly regioselective. We also present density functional calculations that probe possible cyclization mechanisms under reducing conditions.

Since we obtained **6** in a synthetically useful yield (68%), we decided to examine the transformation of **5**→**6** more closely and determine if it can be extended to other 2-nitrobiaryl systems. Among the different solvents we tried (THF, DME, Et_2O and toluene), THF gave the best results between −40 and 0 °C, both in terms of the highest yield (33–68%) of **6** and the lowest yield (21–31%) of the hydroxylamine side product (**7**). Thus we chose THF as the preferred solvent as we began our studies by conducting a thorough screen of reaction conditions such as the optimum temperature and the number of equivalents of phenylmagnesium bromide (Table 1). It was clear from these experiments that in order to consume all the starting material (**5**), three equivalents of PhMgBr had to be used at 0 °C (Table 1, entry 7). At lower temperatures (Table 1, entries 1–5), either substantial amounts of **5** was recovered or the ratio of **6** to **7** was too low to be useful.

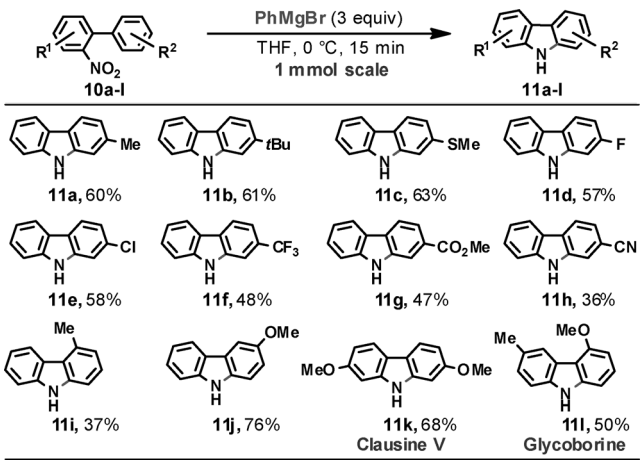
Table 1: Optimization of the reaction conditions for the conversion of **5** to **6**.[a]



Entry	X [equiv]	*T* [°C]	*t* [min]	Recov. of **5** [%]	Yield[b] of **6** [%]	Yield[b] of **7** [%]
1	3	−40	30	42	28	12
2	3	−20	20	15	37	19
3	2.5	−20	20	18	38	21
4	3	−10	20	0	57	26
5	3	−10	15	0	46	31
6	2.5	0	15	6	63	22
7	**3**	**0**	**15**	**0**	**68**	**21**
8	3	0	20	0	58	21
9	3	20	15	0	57	23

[a] Reactions were performed on 1 mmol scale (0.1 M solution) under Ar atmosphere for the indicated amount of time. [b] Yield of isolated product after column chromatography.

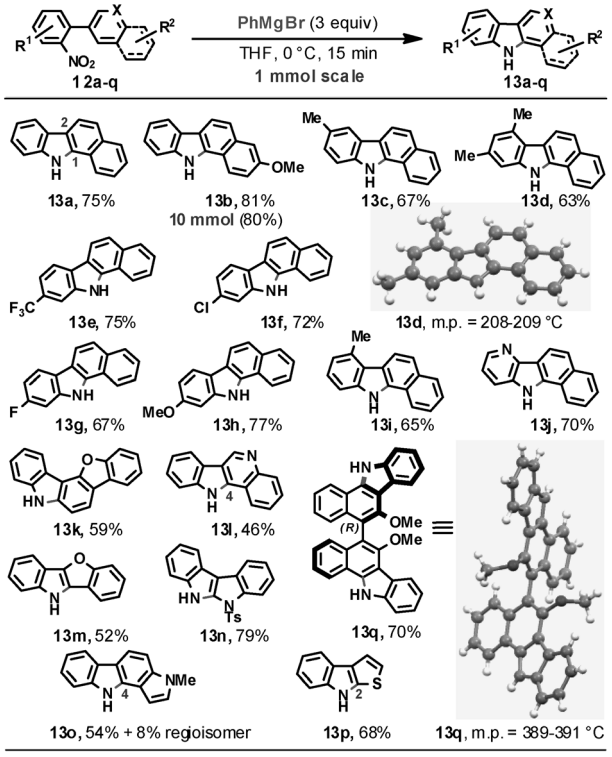
With these optimized reaction conditions in hand, we initiated an extensive study to determine the scope of substrates. First, both electron-rich and electron-poor 2-substituted carbazoles were prepared (**11a–f**, Scheme 2) and there was little difference in yields, except when the substituent was CF_3 (**11f**). To our surprise, despite the presence of excess PhMgBr, the CO_2Me group was well-tolerated; presumably the reduction of the nitro group is significantly faster than addition to the ester functionality (**11g**). The substrate containing a nitrile group (CN), however, furnished the product (**11h**) only in fair yield. We found that the C–N bond formation was regiospecific when **10j** was subjected to the reaction conditions: only 3-methoxycarbazole (**11j**) was formed and not even traces of the regioisomeric 1-methoxy carbazole product were detected. Using this



Scheme 2. Preparation of mono- and disubstituted carbazoles including the bioactive alkaloids **11k** and **11l**. Reactions were performed on a 1 mmol scale (0.1 M solution) under Ar atmosphere. Structures, compound numbers, and yields of isolated products are given.

method, two bioactive carbazole alkaloids, clausine V[11] (**11k**) and glycoborine (**11l**), were also obtained in preparatively useful quantities.

Next, we conducted an in-depth investigation (Table 3 was reformatted as Scheme 3) to determine the regioselectivity of the method; *ortho*-nitrobiaryls featuring fused aromatic rings such as 2-naphthyl (**12a–j**), 1-dibenzofuranyl (**12k**), 3-quinolinyl (**12l**), 2-benzofuranyl (**12m**), 3- and 5-indolyl (**12n**,**o**), 3-



Scheme 3. Highly regioselective preparation of substituted fused carbazoles. Reactions were performed on a 1 mmol scale (0.1 M solution) under Ar atmosphere. Structures, compound numbers, and yields of isolated products are given.

thiophenyl (**12p**), and 3,3′-disubstituted (*R*)-BINOL (**12q**) were subjected to our low-temperature intramolecular C-(sp^2)–H amination protocol. *ortho*-(2-Naphthyl)nitroarenes (**12a–j**) underwent regiospecific cyclization to the corresponding 11*H*-benzo[*a*]carbazoles[12] (**13a–j**); not even trace amounts of the possible regioisomeric 5*H*-benzo[*b*]carbazoles were detected. Clearly the more hindered C(sp^2)–H bond (i.e., the 1-position of naphthalene) is specifically and invariably aminated in all 10 cases (**13a–j**). This regiochemical outcome is complementary to that of fused carbazoles obtained using other methods[13,6d] in which invariably the less hindered C(sp^2)–H bonds undergo amination. C(sp^2)–H bonds that are part of fused heteroaromatic systems also underwent amination readily, yielding complex fused N-heterocycles such as the benzofuro-carbazole[14] (**13k**), indolo-quinoline (**13l**), benzofuro-indole (**13m**), dihydroindolo-indole (**13n**), dihydropyrrolo-carbazole[15] (**13o**), thienoindole (**13p**, and dimeric benzo[*a*]carbazole[16] (**13q**). The only substrate that led to a 7:1 mixture of regioisomers was 5-(2-nitrophenyl)-*N*-methylindole **12o**; *o*-nitrobiaryls **12l** and **12p** gave rise to **13l** and **13p**, respectively, as single regioisomers.

Naturally, we were eager to explore the possibility of forming indolines as well as six- or seven-membered N-heterocycles using our method. None of the nitroarenes (**14–20**) shown in Figure 3 undergo cyclization to form the

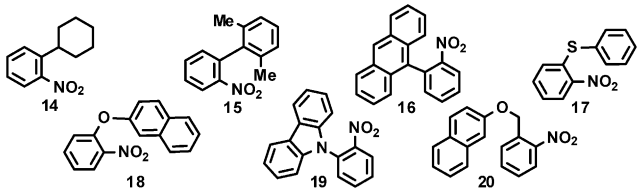
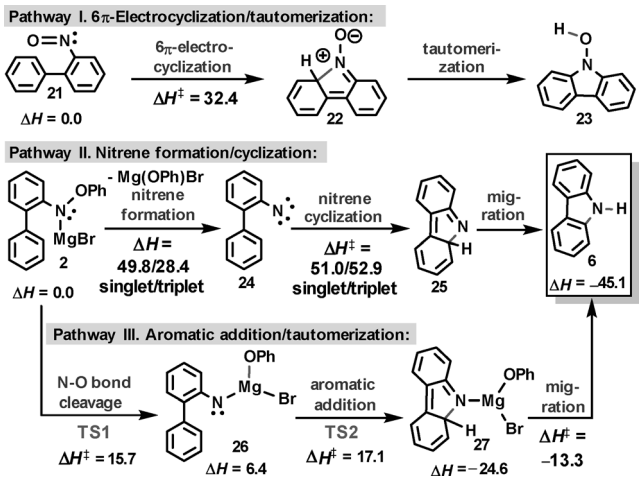


Figure 3. Substrates that failed to undergo cyclization to five-, six-, or seven-membered N-heterocycles.

expected indoline or larger N-containing rings; complex reaction mixtures were obtained that contained varying amounts of *N*,*N*-diaryl hydroxylamine products. These results are in good agreement with the performance of current intramolecular arene-amination methods[2a,c–f,h–i,3a,f] as these furnish only products with five-membered rings.

An initial examination of likely mechanisms for this transformation was carried out using unrestricted M06-2X/6-31 + G(d,p) density functional calculations in Gaussian 09 with the SMD solvent model for THF.[17] Explicit THF solvent was also examined.[18] Open-shell singlet energies were spin-projected.[19] At the outset we examined the possibility that carbazole **6** results from electrocyclization of nitroso intermediate **21** (Scheme 4). Pathway I is reasonable to consider given that a nitroso intermediate has been proposed in the Bartoli indole synthesis and low barriers have been reported for similar cyclizations.[20] However, the computed ΔH^{+} for **21**→**22** is 32.4 kcal mol^{-1}, which is too high to be consistent with the facile formation of carbazole **6** at the experimental temperature of 0 °C. In addition, not even trace amounts of *N*-



Scheme 4. Possible mechanistic pathways (energies in kcal mol^{-1}).

hydroxyindole **23** were detected or isolated. It is also unlikely that **22** or **23** are readily transformed into carbazole **6**.

We next examined whether discrete nitrene intermediates are involved (Pathway II, Scheme 4). Aryl nitrene intermediates have been suggested in the case of the Cadogan cyclization[7a,c–g] and also in the case of Knochel's reductive indole/benzimidazole synthesis.[10] We were skeptical about the involvement of a discrete nitrene species since **14** and **15** failed to give the corresponding C(sp^3)–H aminated products. In addition, no azo compounds resulting from nitrene dimerization or products derived from azirines were observed. Although prior extensive computational work by Tsao et al. showed that the barriers for conversion of *ortho*-biphenylnitrene **24** into carbazole **6** is small,[21] the thermodynamics for formation of singlet **24** from intermediate **2** through loss of Mg(OPh)Br suggests that this pathway is prohibitively high in energy.[22] Explicit THF solvation and loss of Mg(OPh)(THF)Br does not change this thermodynamic penalty.

Alternative to Pathways I and II, there is the possibility that **2**, which presumably arises from O-addition of PhMgBr to **21**, undergoes MgBr-mediated N–O bond cleavage (via **TS1**)[6] to give nitrenoid[23] **26** followed by aromatic addition/pseudo-electro-cyclization[24] to give **27** (via **TS2**) and then hydrogen migration or tautomerization to give carbazole **6** (Pathway III, Scheme 4). Figure 4 shows **TS1** and **TS2**, which have $\Delta H^{\ddagger}$ values of 15.7 and 17.1 kcal mol^{-1}, respectively, relative to **2**. Inclusion of an explicit THF solvent molecule does not significantly alter $\Delta H^{\ddagger}$. The resulting intermediate

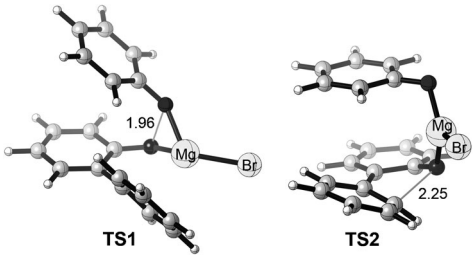


Figure 4. **TS1** and **TS2**. Bond lengths reported in Å.

27 is exothermic by −24.6 kcal mol^{-1}, and therefore the **26**→**27** step is irreversible. Small barriers were found for hydrogen migration as well as tautomerization mediated by MgBr-coordinated phenoxide. Our calculations also rule out the possibility that phenoxide anion or [MgBr]$^+$ dissociates from **2** prior to cyclization or that cyclization occurs prior to N–O bond cleavage. Concerted conversion of **26** to **6** was not considered since Li and others have shown that this type of transition state is significantly higher in energy than a stepwise pathway.[24]

Pathway II also accounts for the lack of reactivity for C(sp^3)–H bonds. For example, **14** lacks an arene π system needed for cyclization. The computed $\Delta H^{\ddagger}$ for the cyclization of **14** via an open-shell singlet TS ($\langle S^2\rangle = 0.7$) is roughly 27 kcal mol^{-1}. For compounds **16**–**20** there is a π system, but cyclization is more difficult since a larger ring would be formed. For example, $\Delta H^{\ddagger}$ for cyclization of **18** is 19.8 kcal mol^{-1}. Lastly, our proposed mechanism can also account for the observed regioselectivity preference in carbazole formation. Calculations show a 3.0 kcal mol^{-1} $\Delta\Delta H^{\ddagger}$ between *para*-**TS2** and *ortho*-**TS2** for cyclization of compound **10j**.

In summary, we have developed a low-temperature, transition-metal-free, rapid, and highly regioselective intramolecular amination of arene C(sp^2)–H bonds, starting from readily available 2-nitrobiaryls. This transformation has a wide scope as demonstrated by the preparation of a total of 30 fused N-heterocycles, including the two bioactive carbazole alkaloids **11k** and **11l**. A preliminary examination of the mechanism using DFT suggests that a stepwise electrophilic aromatic cyclization mechanism may be operative. We anticipate that this transformation may serve as a prototype for related powerful transformations that build molecular complexity rapidly, under mild conditions with exceptional step economy and in an environmentally friendly fashion.

Experimental Section

PhMgBr (0.92 M in THF solution) (33 mL, 30 mmol) was slowly (3 mL min^{-1}) added to the mixture of 2-methoxy-6-(2-nitrophenyl)-naphthalene (**12b**) (2.79 g, 10 mmol) and dry THF (100 mL) at 0 °C in 10 min. During this time the internal temperature was closely monitored and maintained below 3 °C. Then the mixture was stirred at 0 °C for 5 min followed by the slow and careful addition of saturated NH_4Cl aqueous solution (5 mL). The internal temperature was maintained below 5 °C. Then 200 mL water was added and the resulting mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography to give 3-methoxy-11*H*-benzo[*a*]carbazole (**13b**) (1.98 g, 80 %) as a white solid. **13b:** $R_f = 0.35$ (hexanes/ethyl acetate = 5:1); ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 12.08$ (br s, 1H), 8.44 (d, $J = 9.2$ Hz, 1H), 8.15–8.08 (m, 2H), 7.61 (d, $J = 8.0$ Hz, 1H), 7.54 (d, $J = 8.4$ Hz, 1H), 7.47 (d, $J = 2.4$ Hz, 1H), 7.37 (t, $J = 7.2$ Hz, 1H), 7.30 (dd, $J = 8.8$, 2.4 Hz, 1H), 7.19 (t, $J = 7.2$ Hz, 1H), 3.90 ppm (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 157.4$, 139.0, 136.1, 133.9, 124.5, 123.89, 123.85, 120.4, 119.8, 119.5, 118.9, 117.5, 116.6, 116.3, 111.6, 108.3, 55.6 ppm.

Received: November 17, 2013
Published online: January 30, 2014

Keywords: carbazoles · electrophilic amination · N-heterocycles · nitrobiaryls · regioselectivity

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