Gram-Scale Total Synthesis of Carbazomycins A–D

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Abstract. Gram-scale total synthesis of carbazomycins A–D is described. The total synthesis of carbazomycin A was achieved in 44% overall yield over six steps from symmetrical 5-chloro-1,2,3-trimethoxybenzene. The key aryne-mediated carbazole-formation and methylation steps provided the multiply substituted carbazole. The regioselective demethylation of the trimethoxycarbazole was performed using boron trichloride. Thereafter, the phenolic hydroxy group was converted into the methyl group to provide carbazomycin A. Subsequent installation of the methoxy group realized the total synthesis of carbazomycin D. Regioselective demethylation was performed using 1-dodecanethiol, effecting the conversions of carbazomycins A and D into carbazomycins B and C, respectively.

Introduction

Carbazomycins A–D were isolated from the culture broth of *Streptoverticillium ehimense* by Nakamura and co-workers in the 1980s and represent the first class of antibiotics containing a carbazole framework to be discovered (Figure 1).[1] They have highly unsymmetrical structures in which one of the benzene rings carries four electron-donating groups to form a fully substituted aromatic ring. Carbazomycins A (**1**) and B (**2**) show antifungal, antibacterial, and anti-yeast activities,[2a] and while both exhibit antioxidant activity, that of carbazomycin B (**2**) is stronger, owing to it bearing a phenolic hydroxy moiety instead of the methyl ether of carbazomycin A (**1**).[2b,c] In addition, carbazomycins B (**2**) and C (**3**) exhibit 5-lipoxygenase inhibitory activity;[3] however, their structure–activity relationships have not been investigated.

The biological activities and unique structural features of carbazomycins have aroused the interest of synthetic chemists. Accordingly, 13 total syntheses of carbazomycins A–D have been reported over the recent decades.[4] In 1989, Moody and co-workers accomplished the total synthesis of carbazomycins A (**1**) and B (**2**) (Scheme 1a).[4c] They synthesized the multiply substituted carbazole through a regioselective Diels–Alder reaction of the pyrone-fused indole and trimethylsilylacetylene derivative. Installation of the functional groups onto the benzene moiety allowed for the synthesis of carbazomycin B (**2**). Subsequent methylation of the phenolic hydroxy group gave carbazomycin A (**1**). Similar cyclization strategies have been employed by Argade,[4i] Nishida,[4j] Witulski,[4l] and Parsons[4n] to form the fully substituted benzene as a general method for the total syntheses of carbazomycins A (**1**) and B (**2**). An alternative strategy involving iron-carbonyl-complex-mediated electrophilic aromatic substitution of aniline was developed by Knölker and co-workers to synthesize carbazomycins A–D, achieving the only reported total synthesis of carbazomycin C (**3**) (Scheme 1b).[4a,b,e] They efficiently constructed the carbazole skeleton using tricarbonyl(diene)iron complexes to synthesize densely functionalized anilines, the oxidative cyclization of which afforded the carbazoles. In 2008 and 2010, Catellani and co-workers reported the synthesis of carbazomycins A (**1**) and D (**4**) through one-pot C–C and C–N bond formation via Catellani reactions of multiply substituted aryl iodides and 2-bromoacetanilides (Scheme 1c).[4f,g] However, these synthetic approaches by Knölker and Catellani necessitate pre-modification of the benzene moiety to synthesize carbazomycins.

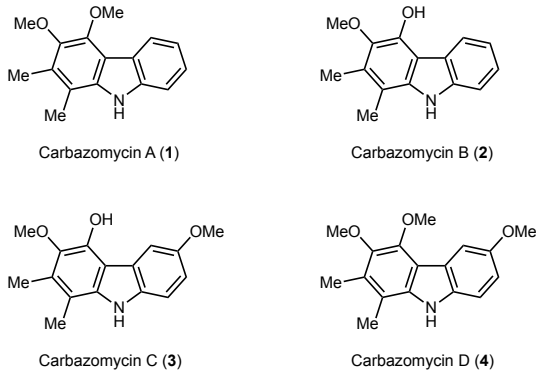
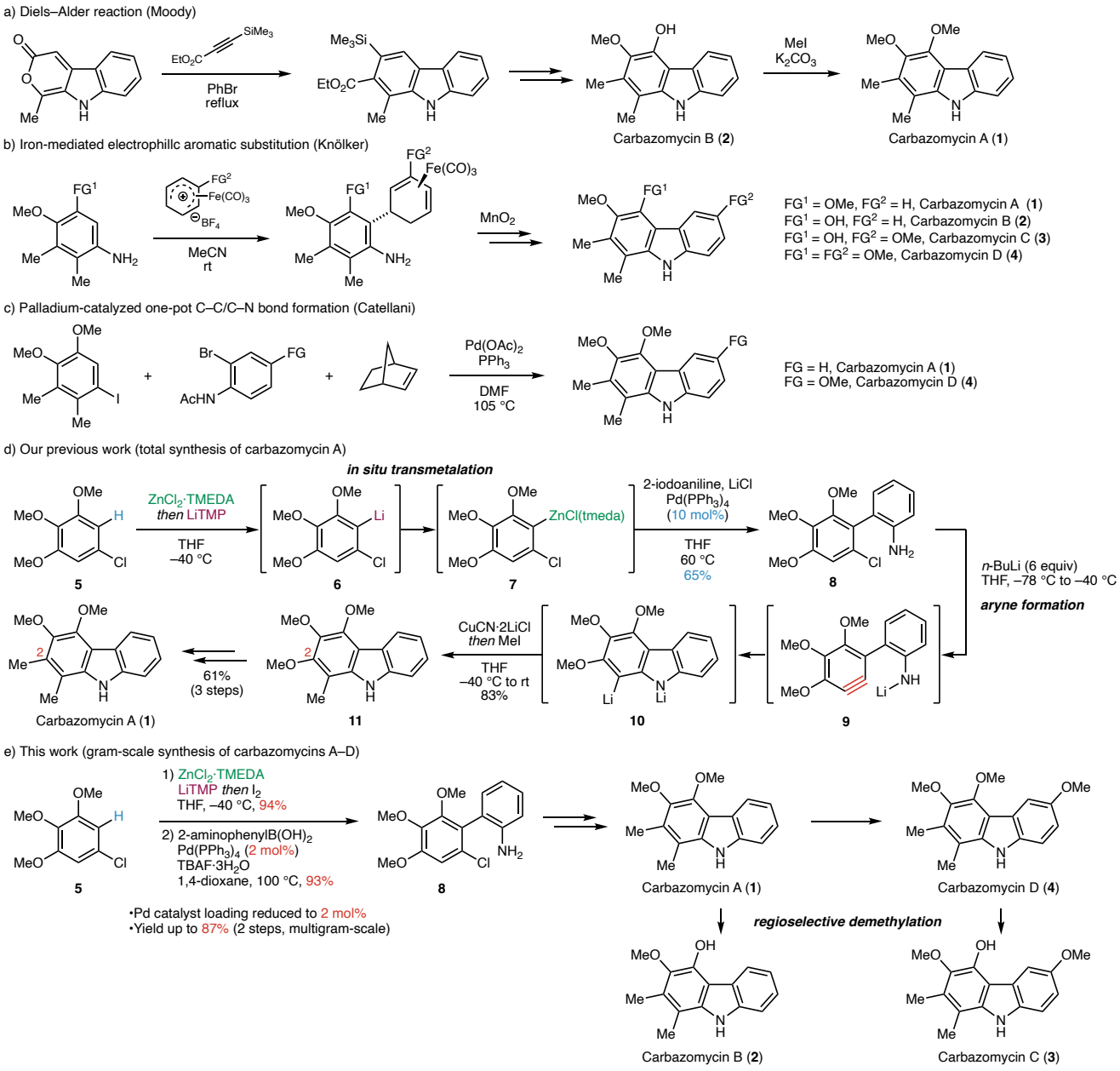


Figure 1. Molecular structures of carbazomycins A–D.

Recently, we reported a novel approach for the gram-scale synthesis of carbazomycin A (**1**) (Scheme 1d).[5] The symmetrical chlorotrimethoxybenzene **5** was deprotonated using lithium tetramethylpiperidide (LiTMP) to generate the transient organolithium

species **6**, which underwent *in situ* transmetalation with a $ZnCl_2$·TMEDA complex[6] to provide the stable organozinc **7** without aryne formation.[7] Subsequent Negishi coupling with 2-iodoaniline afforded 2-aminobiphenyl **8** in 65% yield, albeit with the use of 10 mol% $Pd(PPh_3)_4$ to ensure a moderate yield. Employing six equivalents of *n*-BuLi led to aryne **9**, which bears an amino moiety that underwent intramolecular nucleophilic addition to afford the carbazole dianion **10**. Following treatment with a combination of CuCN·2LiCl[8] and iodomethane, 1-methylcarbazole **11** was obtained in 83% yield. Finally, carbazomycin A was synthesized in 61% yield by transforming the methoxy group at the C-2 position into a methyl group in a regioselective manner over three steps.

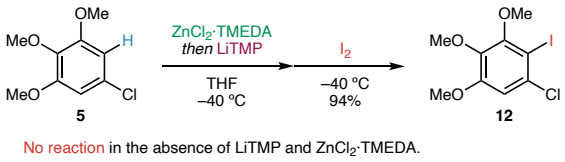
Herein, we describe a divergent strategy for the total synthesis of carbazomycins A–D involving a modified synthesis of 2-aminobiphenyl **8**. Synthesis of carbazomycin D (**4**) was achieved by regioselective installation of the methoxy group onto carbazomycin A (**1**). During our thorough investigation of the regioselective demethylation of trimethoxycarbazole **11**, we identified reaction conditions to obtain all possible isomers. These findings realized one-step, gram-scale transformations of carbazomycins A (**1**) and D (**4**) into carbazomycins B (**2**) and C (**3**), respectively, demonstrating the synthetic utility of the presented method.



Scheme 1. Selected synthetic strategies and our approaches for the total synthesis of carbazomycins A–D.

Results and Discussion

Initially, we modified the synthesis of aminobiphenyl **8** discussed above to address its rather high catalytic loading (10 mol%) of $Pd(PPh_3)_4$ and moderate yield (65%). Although an additional step is required, we planned to perform iodination of chlorotrimethoxybenzene **5** and use the resulting iodoarene **12** as an aryl halide, introducing the 2-aminophenyl moiety by a cross-coupling reaction (Scheme 2). Previously, we developed a protocol to generate 2-halophenyllithium species in the presence of zinc halide diamine complexes through deprotonative lithiation using LiTMP as a base. The products can be converted into the corresponding organozinc reagents *in situ* without aryne formation.[5] A THF solution of **5** and $ZnCl_2$·TMEDA complex was treated with LiTMP at −40 °C. The generated organozinc reagent reacted with iodine to afford the desired iodoarene **12** in 94% yield on a multigram scale. Control experiments indicate that both LiTMP and the $ZnCl_2$·TMEDA complex are necessary for this iodination; no reaction proceeded in the absence of LiTMP, and a complex mixture was obtained in the absence of $ZnCl_2$·TMEDA due to aryne formation from the resulting 2-chlorophenyllithium species. These results indicate that the reaction proceeds through deprotonative lithiation, *in situ* transmetalation of the transient 2-chlorophenyllithium with $ZnCl_2$·TMEDA, and iodination of the corresponding organozinc species.

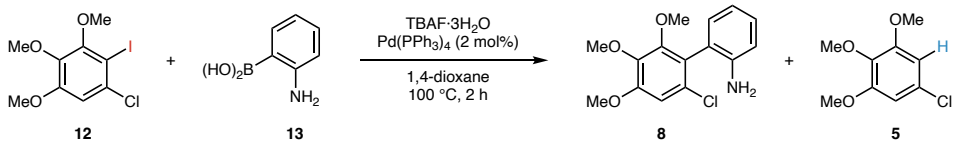


Scheme 2. Preparation of the iodoarene through deprotonative lithiation followed by *in situ* transmetalation.

With iodoarene **12** in hand, we then turned our attention to the synthesis of aminobiphenyl **8** through Suzuki–Miyaura cross-coupling reaction[9] with the commercially available 2-aminophenylboronic acid (**13**) (Table 1). A mixture of iodoarene **12** and 1.5 equivalents of 2-aminophenylboronic acid (**13**) in 1,4-dioxane was heated at 100 °C for 2 h with 2 mol% $Pd(PPh_3)_4$ and three equivalents of tetrabutylammonium fluoride trihydrate ($TBAF·3H_2O$), providing the desired aminobiphenyl **8** in 93% isolated yield along with 5% of the reduced starting material, chlorotrimethoxybenzene **5** (entry 1).[10] When the reaction temperature was increased to 125 °C, the yield of aminobiphenyl **8** was slightly decreased to 84% (entry 2). The use of $TBAF·3H_2O$ proved effective for a high-yielding process. Using potassium fluoride and cesium fluoride instead of $TBAF·3H_2O$ significantly decreased the yields of aminobiphenyl **8** to 11% and 51%, with the recovery of the starting iodoarene **12** in 83% and 38% yields, respectively (entries 3 and 4). These lower conversions are likely due to the poor solubility of the fluoride source. Accordingly, we then performed the reaction using 1,4-dioxane and H_2O to dissolve the cesium fluoride; however, the yield of aminobiphenyl **8** remained practically unaltered despite the improved conversion (89%) of the starting iodoarene **12** (entry 5). Regrettably, the yield of the undesired chlorotrimethoxybenzene **5** was significantly increased to 31%.

On the basis of literature precedents,[11,12] employing deuterium oxide (D_2O) instead of H_2O as a solvent led to a remarkable improvement in the yield of the desired aminobiphenyl **8** (85%) (entry 6). This enhanced yield with D_2O can be attributed to its kinetic isotope effect, which accelerates the transmetalation step in the Suzuki–Miyaura coupling as it results in poorer solvation of the boronic acid compared with that by H_2O.[12a] Poorer solvation hampers stabilization of 2-aminophenylboronic acid (**13**) and increases the rate of the transmetalation step in Suzuki–Miyaura coupling, thus suppressing the deiodination.

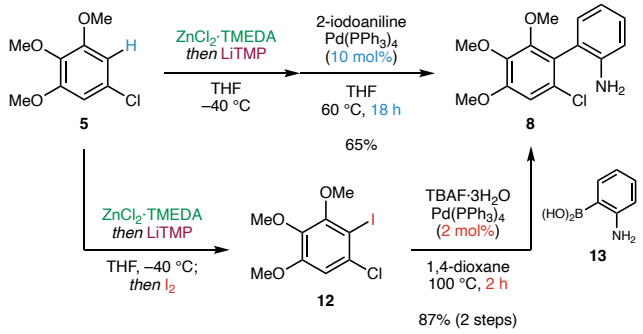
Table 1. Optimization of Suzuki–Miyaura coupling to synthesize the aminobiphenyl[a]



entry	deviations	**8** (%)[b]	**5** (%)[b]	**12** (%)[b]
1	none	91 (93[c,d])	5	–[e]
2	125 °C	84	7	–[e]
3[f]	**entry 2** *then* KF (3.0 equiv.) instead of $TBAF·3H_2O$	11	4	83
4	**entry 2** *then* CsF (3.0 equiv.) instead of $TBAF·3H_2O$	51	2	38
5	**entry 4** *then* 1,4-dioxane/H_2O = 4:1 (1.5 mL)	50	31	11
6	**entry 4** *then* 1,4-dioxane/D_2O = 4:1 (1.5 mL)	85	7	–[e]

[a] Optimized reaction conditions: iodoarene **12** (0.15 mmol, 1.0 equiv.), 2-aminophenylboronic acid (**13**) (0.23 mmol, 1.5 equiv.), $Pd(PPh_3)_4$ (0.003 mmol, 2 mol%), $TBAF·3H_2O$ (0.45 mmol, 3.0 equiv.), and 1,4-dioxane (1.5 mL). [b] Yield determined from the ^1H NMR spectrum of the crude product using 1,1,2,2-tetrachloroethane as an internal standard. [c] Isolated yield. [d] Iodoarene **12** (12.9 mmol) was used. [e] Not observed. [f] Reaction performed for 14 h.

The modified two-step synthesis provided aminobiphenyl **8** with an increased yield of 87% compared with our previous report (65%), and with a lower palladium catalyst loading of 2 mol% (from 10 mol%; Scheme 3). In addition, the reaction time required for the cross-coupling step was shortened to 2 h.

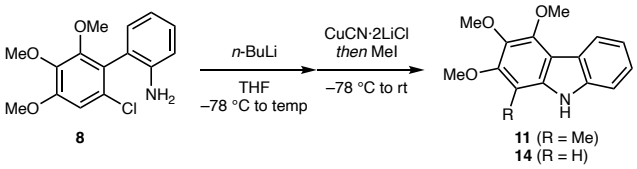


Scheme 3. Comparison of the present modified aminobiphenyl synthesis with that from our previous work.

Having established an efficient methodology to access aminobiphenyl **8**, we next investigated the aryne-mediated carbazole formation/methylation sequence without protecting the primary amino group. It is noteworthy that, despite extensive investigation over the last three decades into aryne-mediated synthesis of substituted benzene-fused nitrogen heterocycles from aromatic compounds bearing a secondary amine tether, methods allowing one-pot cyclization/functionalization for substrates containing a primary amino group remain limited.[13]

Our investigation first addressed the effects of temperature in the deprotonation step (Table 2). A THF solution of aminobiphenyl **8** was treated with six equivalents of *n*-butyllithium (*n*-BuLi) at –78 °C. The reaction mixture was then allowed to warm to –40 °C and stirred at the same temperature. After cooling to –78 °C, the reaction mixture was treated with CuCN·2LiCl followed by iodomethane. The resulting mixture was then warmed to room temperature with stirring to give 1-methylcabazole **11** in 83% yield (entry 1). When the deprotonation was performed at –78 °C, less than 1% of the desired carbazole **11** was observed, and carbazole **14** was obtained in 12% yield with 87% recovery of aminobiphenyl **8** (entry 2). These results indicate that this very low reaction temperature decreases the rates of deprotonation for both the amino group and the benzene ring, despite a small amount of the carbazole anion being generated. This anion is quickly protonated by the amino group of aminobiphenyl **8**. Similarly, undesired carbazole **14** was obtained in 19% yield with 30% recovery of **8** at –60 °C, while methylcarbazole **11** was generated in 22% yield (entry 3). The yields of **11** were slightly lower at –20 °C, 0 °C, and room temperature, likely due to decomposition of the generated organolithium species at higher reaction temperatures (entries 4–6). The optimized reaction conditions were sufficiently robust to provide methylcarbazole **11** in 83% yield on a gram scale (entry 7).

Table 2. Effects of reaction temperature on the one-pot aryne-mediated carbazole formation and methylation[a]

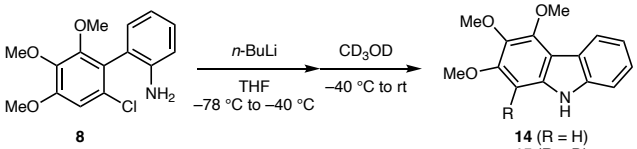


entry	temp (°C)	**11** (%)[b]	**14** (%)[b]	**8** (%)[b]
1	–40	83	4	_[c]
2	–78	<1	12	87
3	–60	22	19	30
4	–20	63	4	_[c]
5	0	71	4	_[c]
6	rt	75	5	_[c]
7[d,e]	–40	83[f]	_[g]	_[g]

[a] Reaction conditions: aminobiphenyl **8** (0.30 mmol, 1 equiv.), *n*-BuLi (1.8 mmol, 6 equiv.), THF (3.0 mL), then CuCN·2LiCl (0.30 mmol, 1 equiv.), then iodomethane (1.5 mmol, 5 equiv.). [b] Yield determined from the ^{1}H NMR spectrum of the crude product using 1,1,2,2-tetrachloroethane as an internal standard. [c] Not observed. [d] Aminobiphenyl **8** (4.52 mmol) was used. [e] CuCN·2LiCl and iodomethane were added at –40 °C. [f] Isolated yield. [g] Not determined.

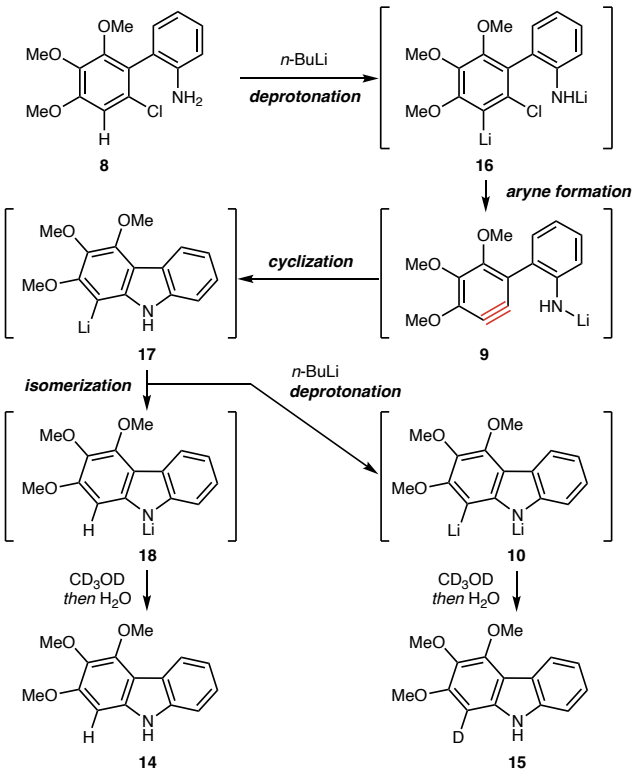
We also evaluated the effects of the amount of *n*-BuLi on the reaction (Table 3). After the formation of the carbazole anion under the established reaction conditions, the reaction mixture was treated with CD_3OD at –40 °C and then warmed to room temperature. When three equivalents of *n*-BuLi were used, an inseparable mixture of **14** and deuterated carbazole **15** was obtained in 82% combined yield in a ratio of 16:84 (entry 1). The use of six equivalents of *n*-BuLi improved the ratio of **14** and **15** to 5:95 in 92% combined yield (entry 2).

Table 3. Effects of the amount of *n*-BuLi on the one-pot aryne-mediated carbazole formation and methylation[a]



entry	*n*-BuLi (equiv)	yield (%)[b]	H/D ratio[c]
1	3	82	16:84
2	6	92	5:95

[a] Reaction conditions: aminobiphenyl **8** (0.30 mmol, 1 equiv.), *n*-BuLi, THF (3.0 mL), then CD_3OD (0.5 mL). [b] Isolated yield. [c] Ratio determined by ^{1}H NMR spectroscopy.

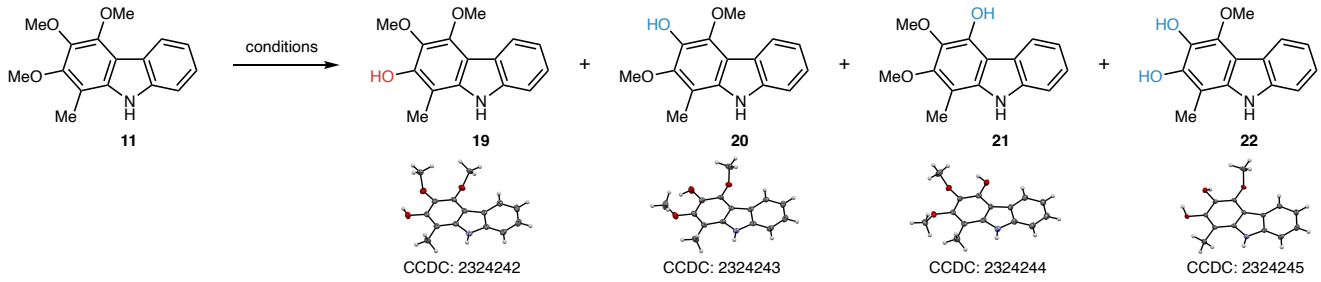


Scheme 4. Plausible rationale for the effect of excess *n*-BuLi in the double functionalization of aryne.

A rationale for the effect of the amount of *n*-BuLi is shown in Scheme 4. First, the dianion **16** is generated by successive deprotonation, then converted into aryne **9** with elimination of lithium chloride. Subsequent nucleophilic addition of the tethered aniline moiety to the aryne leads to the formation of carbazole anion **17**. Considering the significant difference in the acidities of benzene C–H (pK_a 43)[14] and carbazole N–H (pK_a 17),[15] carbazole anion **17** prefers isomerization to the more stable carbazole anion **18**. Treatment with CD_3OD followed by aqueous workup provides the undesired carbazole **14**. Thus, excess *n*-BuLi is necessary to prevent isomerization by deprotonating the N–H proton of **17** upon its generation to form carbazole dianion **10**, which is transformed into deuterated carbazole **15**.

We then explored the regioselective demethylation of 2,3,4-trimethoxycarbazole **11** to generate 2-hydroxy-3,4-dimethoxycarbazole **19** (Table 4). The use of concentrated hydrochloric acid[16] led to the formation of a mixture of the desired hydroxycarbazole **19**, 3-hydroxycarbazole **20**, and 4-hydroxycarbazole **21** with 63% recovery of **11** (entry 1). A combination of trimethylsilyl chloride (TMSCl) and sodium iodide[17] improved the yield of the desired carbazole **19** (23%); however, regioisomers **20** and **21** were also observed in 13% and 9% yields, respectively (entry 2). Replacing TMSCl with triethylsilyl chloride (TESCl) did not produce a favorable result, with only the yield of **20** increased to 23% (entry 3). We then explored nucleophilic demethylation under basic conditions using a combination of odorless 1-dodecanethiol and sodium hydroxide.[18] The thiolate effectively reacted with trimethoxycarbazole **11** under heating to provide the undesired hydroxycarbazole **21**[19] in 40% yield as a major product (entry 4). In addition, another regioisomer **20** was observed in only trace amounts. We next referred to the study of Nishida and co-workers on the regioselective demethylation employing $NbCl_5$[20] as a Lewis acid, which provided the undesired regioisomer **20**[21] in 51% yield (entry 5). Encouraged by the strikingly different regioselectivity achieved with $NbCl_5$, we used boron tribromide (BBr_3)[22] as a Lewis acid, generating catechol **22**[23] in 61% yield (entry 6). Replacing BBr_3 with the less Lewis-acidic boron trichloride (BCl_3)[24] gave the desired 2-hydroxycarbazole **19**[25] in 65% yield (entry 7).

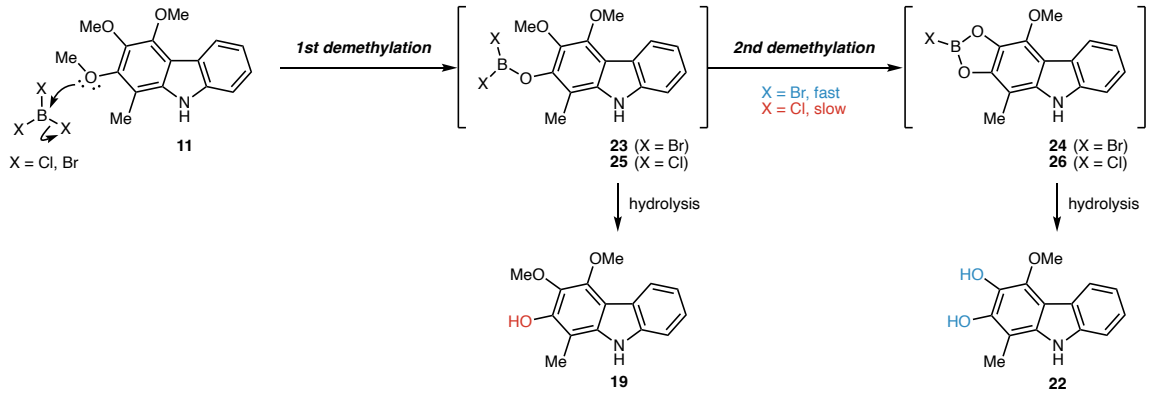
Table 4. Product distributions in the regioselective demethylation of the trimethoxycarbazole



entry	conditions	**19** (%)[a]	**20** (%)[a]	**21** (%)[a]	**22** (%)[a]	**11** (%)[a]
1	*conc.* HCl, 50 °C	8	3	2	–[b]	63
2	TMSCl and NaI, MeCN, rt	23	13	9	–[b]	22
3	TESCl and NaI, MeCN, rt	24	23	12	–[b]	29
4	1-dodecanethiol and NaOH, DMF, 130 °C	23	< 1	45 (40[c])	1	–[b]
5	$NbCl_5$, 1,2-dichloroethane, reflux	28	57 (51[c])	10	5	–[b]
6	BBr_3, CH_2Cl_2, –78 °C to 0 °C	–[b]	–[b]	–[b]	61[c]	–[b]
7	BCl_3, CH_2Cl_2, –78 °C to 0 °C	70 (65[c])	20	–[b]	10	–[b]

[a] Yield determined from the ^{1}H NMR spectrum of the crude product using 1,1,2,2-tetrachloroethane as an internal standard. [b] Not observed. [c] Isolated yield.

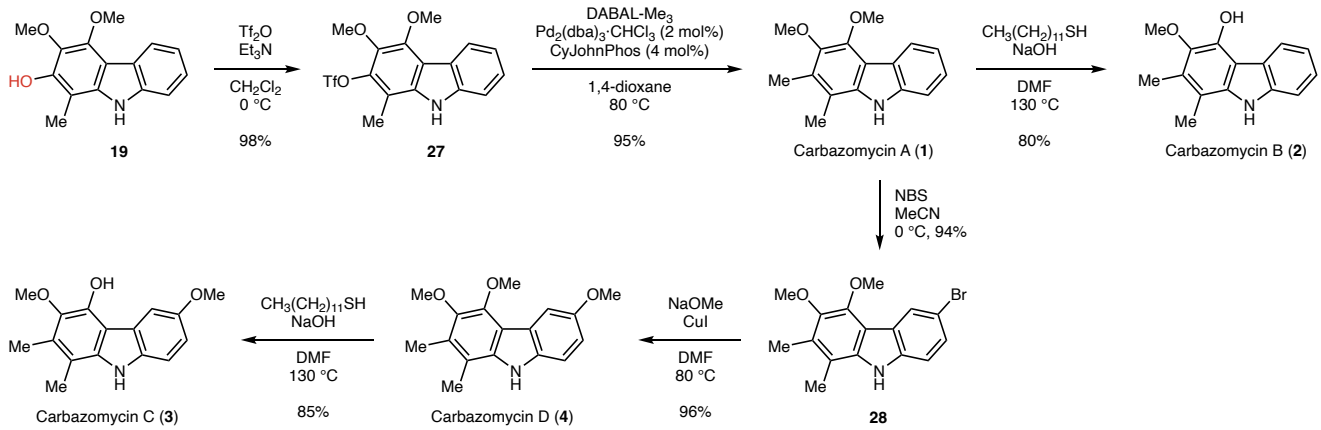
A plausible rationale for the different product distributions observed in the boron trihalide-promoted demethylation is shown in Scheme 5. Considering that 2-hydroxycarbazole **19** was obtained as a major product with BCl_3, the initial coordination of boron trihalide (BX_3) more likely occurs at the oxygen atom attached to the C-2 position, which is the least sterically congested of the methoxy groups. After demethylation with BBr_3, the resulting intermediate **23** undergoes further demethylation of the proximal methoxy group to generate cyclic borate **24**, which is hydrolyzed upon workup to produce catechol **22**. In the case where BCl_3 is used, the boron atom of the intermediate **25** is expected to show weaker Lewis acidity than that of intermediate **23**, based on previous experimental results[26] and theoretical studies[27] showing that BCl_3 is less Lewis acidic than BBr_3. Therefore, the second demethylation step proceeds slowly, providing hydroxycarbazole **19** as a major product with the yield of catechol **22** decreased to 10%.



Scheme 5. A plausible reaction pathway for the regioselective demethylation of the trimethoxycarbazole using boron trihalides.

Total synthesis of carbazomycins A–D was achieved from 2-hydroxycarbazole **19** (Scheme 6). The phenolic hydroxy group reacted with a combination of trifluoromethanesulfonic anhydride (Tf_2O) and triethylamine at 0 °C to afford the corresponding triflate **27** in 98% yield. Carbazomycin A (**1**) was obtained in 95% yield on a gram scale by Negishi coupling[28] using a bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane adduct (DABAL-Me_3),[29] $Pd_2(dba)_3{\cdot}CHCl_3$,[30] and CyJohnPhos.[31]

Next, carbazomycins B–D were synthesized using carbazomycin A (**1**) as a synthetic intermediate. The requisite demethylation at the C-4 methoxy group took place smoothly in a regioselective manner to provide carbazomycin B on a gram scale using a combination of 1-dodecanethiol and sodium hydroxide under heating conditions, as identified during exploration of the regioselective demethylation of trimethoxycarbazole **19** (Table 4, entry 4). Another methoxy group was installed for the synthesis of carbazomycin D (**4**) in a two-step sequence. Regioselective bromination with NBS[4c] exclusively provided bromocarbazole **28** in 94% yield, which underwent Ullman reaction using sodium methoxide and CuI[4m,32] to provide carbazomycin D (**4**) in 96% yield on a gram scale. Finally, the regioselective demethylation of carbazomycin D (**4**) was also performed under the same reaction conditions to give carbazomycin C (**3**) in 85% yield on a gram scale.



Scheme 6. Total synthesis of carbazomycins A–D.

Conclusion

In summary, we have achieved a gram-scale total synthesis of carbazomycins A–D in 34%–44% yields over six to nine steps starting from the symmetrical chlorotrimethoxybenzene. Deprotonative iodination and Suzuki–Miyaura coupling were carried out to efficiently synthesize an aminobiphenyl bearing a chloro group. Treating this aminobiphenyl with *n*-BuLi formed an aryne with an aniline tether for double functionalization of the aromatic ring. Intramolecular nucleophilic addition generated the carbazole dianion, allowing further methylation in one pot to provide the trimethoxycarbazole. The BCl_3-promoted regioselective demethylation of the trimethoxycarbazole was crucial to realize the efficient total synthesis of carbazomycin A. After completing the total synthesis of carbazomycin D by introducing the methoxy group, carbazomycins B and C were synthesized by nucleophilic demethylation using a thiolate. In addition to carbazomycins A–D, hydroxycarbazoles obtained from the trimethoxycarbazole may also be converted into other carbazomycin derivatives through the demethylation protocol we provided, thereby facilitating study of their physiological effects and structure-activity relationships.

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