Rhodium-Catalyzed Crossed [2+2+2] Cycloaddition with Ynamides: Key-Strategy for the Concise Total Synthesis of 3-Oxygenated Carbazole Alkaloids

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RHODIUM-CATALYZED CROSSED [2+2+2] CYCLOADDITION WITH YNAMIDES: KEY-STRATEGY FOR THE CONCISE TOTAL SYNTHESIS OF 3-OXYGENATED CARBAZOLE ALKALOIDS

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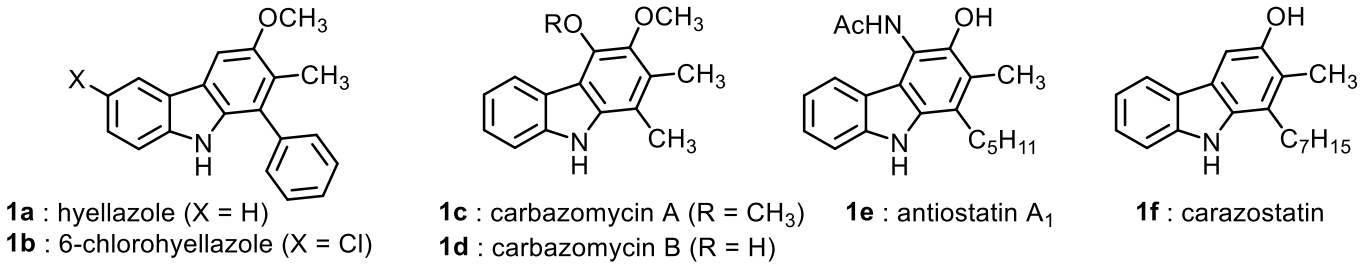
Manuscript dedicated to Prof. Dr. Yasuyuki Kita on the celebration of his 77th birthday

Abstract – Total syntheses of a set of naturally occurring 3-oxygenated carbazole alkaloids - 6-chlorohyellazole, carazostatin, carbazomycins A and B - are described. The key-strategy underlines a highly chemo- and regioselective rhodium-catalyzed [2+2+2] cyclotrimerization between appropriately tailored yne-ynamides and 1-methoxypropyne that is stirred by the interplay of stereoelectronic and steric effects allowing the introduction of four ring substituents of the natural carbazoles within a single step and making the overall syntheses short and efficient.

Carbazole alkaloids are an important class of natural products displaying high diversity in their substitution pattern and revealing a broad range of biological activities.[1] In the case of 3-hydroxycarbazole alkaloids, an alkyl chain is typically displayed at position C-1 but some exceptions are found. For example, hyellazole and 6-chlorohyellazole have the particularity of bearing a phenyl group at this position (Figure 1). Both are of marine origin and have been isolated from the blue-green alga *Hyella caespitosa*.[2] Other 3-hydroxycarbazoles such as antiostatin A_1,[3] carazostatin,[4] and the carbazomycins[5] A and B were isolated from micro-organisms, *Streptomyces cyaneus* 2007-SV_1, *Streptomyces chromofuscus*, and *Streptoverticillium ehimense* H1051-MY 10, respectively.

Very recently, the carbazomycin B producing strain *Streptomyces luteoverticillatus* SZJ61 was isolated from marine sediment in China.[6] Carbazomycins A and B are the first carbazole-related antibiotics possessing weak antibacterial and antiyeast activity and inhibit the growth of some phytopathogenic fungi.[5a,6] Carbazomycin A displays weak cytotoxicity against cancerous (MCF-7, KB, NCI-H187) and non-cancerous (Vero) cells.[7] Carbazomycin B shows antimalarial activity against *Plasmodium falaparum* (IC_{50}

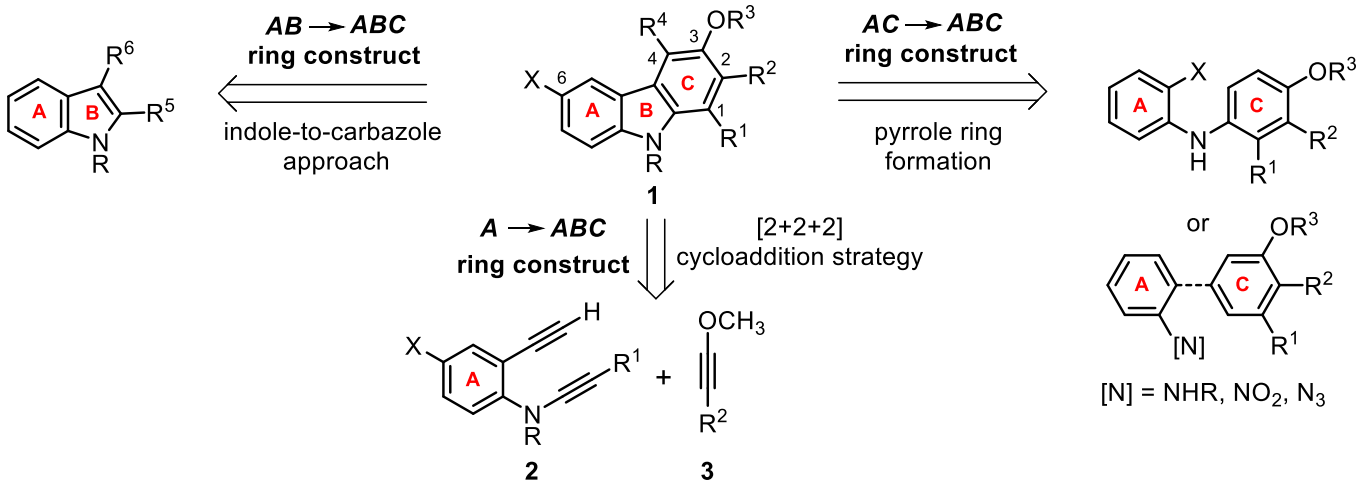
= 2.37 μg/mL).[7] Moreover, it is an inhibitor of 5-lipoxygenase[8] (IC_{50} = 1.5 μM) and exhibits inhibitory activity against lipid peroxidation induced by free radicals.[9] The 3-hydroxycarbazoles antiostatin A_1 and carazostatin are potent natural antioxidants.[3,10] Carazostatin was shown to exhibit much stronger *in vitro* inhibitory activity against lipid peroxidation of rat brain homogenate (IC_{50} = 0.17 μg/mL) than the well-known antioxidants, α-tocopherol, the biological and chemically most active form of vitamin E (IC_{50} > 100 μg/mL), and the food additive BHT (3,5-*tert*-butyl-4-hydroxytoluene, IC_{50} = 4.89 μg/mL).[9,11] Moreover, a strong *ex vivo* free radical scavenging activity of carazostatin in mouse blood plasma upon oral administration was demonstrated.[9] In view of potential applications of antioxidants as therapeutic agents against free radical induced oxidative damage affecting DNA, lipids and proteins,[12] radical scavengers such as antiostatin A_1, carazostatin and carbazomycin B are interesting targets for total synthesis.



1a : hyellazole (X = H)
1b : 6-chlorohyellazole (X = Cl)
1c : carbazomycin A (R = CH_3)
1d : carbazomycin B (R = H)
1e : antiostatin A_1
1f : carazostatin

Figure 1. Selected naturally occurring 3-oxygenated carbazoles

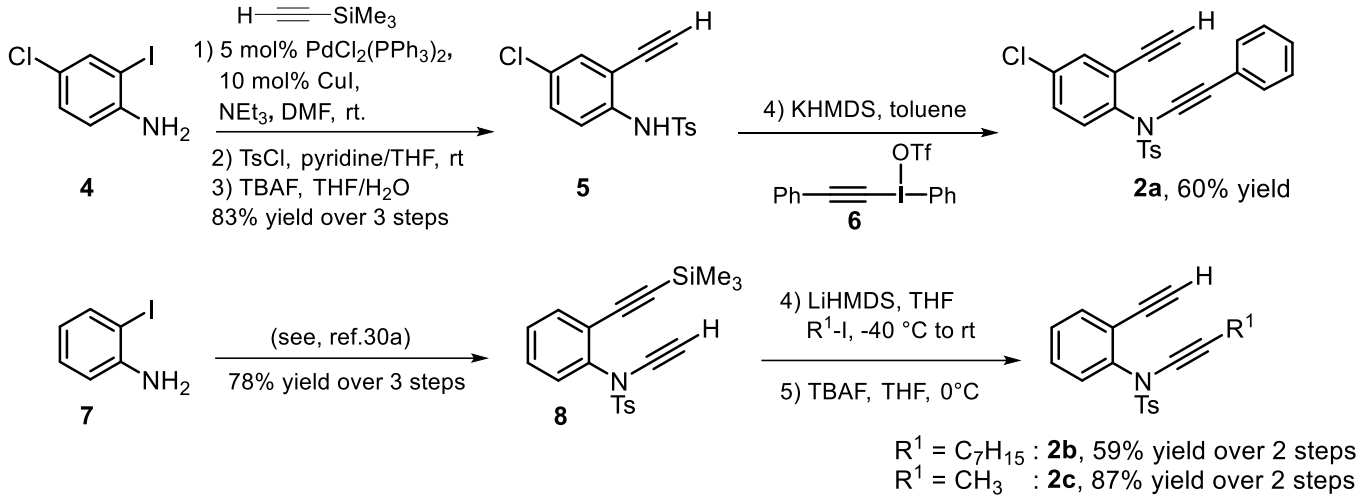
A literature survey on total syntheses of 3-oxygenated carbazole based natural products shows that the assembly of their scaffold relies on two main strategies (Scheme 1). The first one is the indole-to-carbazole approach (*AB→ABC* ring construct).[13] It comprises a variety of reactions such as 6π-electrocyclization,[14] Diels-Alder reaction,[15] Cadogan reaction,[16] intramolecular Friedel-Crafts reaction,[17] aldol condensation,[18] or ring-closing metathesis.[19] The second strategy (*AC→ABC* ring construct) involves the formation of the pyrrole unit from the A and C ring components that were assembled step-wise or *in situ* prior to ring closure. Transition metal-catalysis or metal free conditions were used to perform this ring closure from biphenylamines via *C-N* bond[20] or from *N,N*-diphenylanilines via *C-C* bond[21] forming reactions respectively (Scheme 1). Linking two aryl compounds and subsequent ring closure can be performed within a "one-pot procedure" using palladium catalysis[22] or *via* an iron-mediated coupling between anilines and iron complex salts.[23] Most of the reported routes towards carbazole alkaloids thus require multistep sequences to gain access to the required functionalized indole, biphenylamine or aryl halide precursors. A one-pot protocol (*A→ABC* ring construct), however, should facilitate step and atom economical approaches towards biologically relevant functionalized and/or substituted carbazole alkaloids.[24,25]



Scheme 1. Major strategies towards 3-oxygenated carbazole alkaloids

Some years ago we established the first reliable synthesis of functionalized ynamides applying alkynyl iodonium salts as *N*-ethynylation reagents.[26] The use of ynamides as novel building blocks and synthons in combination with transition metal catalyzed reactions opened new pathways towards *N*-heterocycles as being demonstrated by us[27] and others.[28] However so far, the potential use of ynamides in total synthesis has been scarcely explored.[29] Using ynamide chemistry we were able to achieve one of the shortest total syntheses of hyellazole[25] (6 steps, 39% overall yield) starting from commercially available 2-iodoaniline. Furthermore, the first total synthesis of antiostatin A_1 was realized by us in 16% overall yield and within 10 steps.[30] Our respective strategy follows an *A→ABC* ring construct approach and is based on the transition metal catalyzed [2+2+2] cycloaddition[31] between suitably functionalized diynes **2** and 1-methoxypropyne **3**, which allows the assembly of the carbazole core through the formation of three *C-C* bonds in a single step. In this report we wish to underline the usefulness of our developed methodology by further describing concise syntheses of naturally occurring 3-oxygenated carbazole alkaloids – 6-chlorohyellazole,[32] carazostatin,[33] and the 3,4-dioxygenated carbazole natural products carbazomycins A and B. [34]

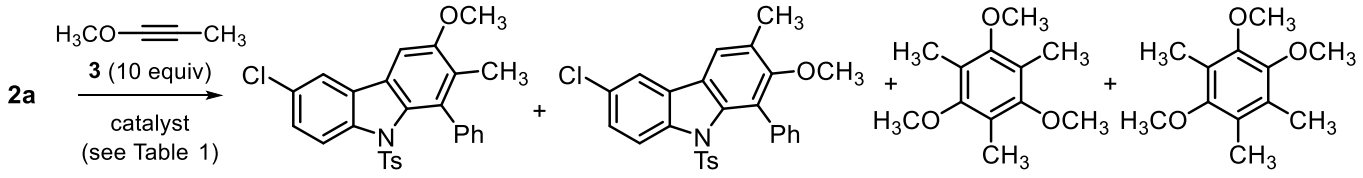
The diyne-ynamides **2a-c** were prepared from the readily available precursors **5** and **8**, which were synthesized from the commercially available 2-iodoanilines **4** and **7** respectively (Scheme 2). The *N*-ethynylation of anilide **5** with alkynyl iodonium salt **6** delivered **2a** (X = Cl, R^1 = Ph) in 60% isolated yield. The diynes **2b** ($R^1 = C_7H_{15}$) and **2c** (R^1 = Me) were prepared by deprotonation of ynamide **8** with LiHMDS and alkylation with 1-iodoheptane and iodomethane respectively, followed by desilylation with TBAF. Compounds **2b** and **2c** were isolated in yields of 59% and 87% (over 2 steps) respectively.



Scheme 2. Synthesis of diynes **2a-c**

A set of metal complexes classically used as catalysts in [2+2+2] alkyne cycloadditions[31] was tested to compare their reactivity with that of Wilkinson's catalyst [$RhCl(PPh_3)_3$]. The latter was used by us already in the synthesis of hyellazole[25] and antiostatin A_1,[30a] as well as in the first total syntheses of alcyopterosins – distinctive phthalides of marine origin.[35] The reaction between diyne **2a** and 1-methoxypropyne (**3**) was selected as the model reaction. When the crossed [2+2+2] cycloaddition between diyne **2a** and alkyne **3** (10 equiv.) was carried out in toluene at room temperature in the presence of 5 mol% of [$RhCl(PPh_3)_3$] the expected carbazole **9a** was chemo- and regioselectively obtained (93% yield, ratio of regioisomers **9a**/**9b** = 19:1), (Table 1, entry 1). Extending the reaction time from 1 to 2 days gave a slightly higher yield (96%) without affecting the isomer ratio (entry 2). In comparison, the catalytic activity of [$CoBr(PPh_3)_3$] was significantly lower and was lacking any regioselectivity. A 1:1 mixture of the regioisomers **9a** and **9b** was isolated in 15% yield after 8 days at room temperature with a catalyst load of 10 mol% of [$CoBr(PPh_3)_3$] (entry 3). No significant change was observed when the reaction was performed at 60 °C (entry 4 *versus* 3). Iridium catalysis was tested using the catalyst system [$IrCl(cod)_2$] (4 mol%) and *bis*(diphenylphosphino)ethane (DPPE, 8 mol%). After 6 days at 60 °C carbazole **9a** was formed as the major regioisomer (**9a**/**9b** = 6:1) and isolated in 53% yield (entry 5). Moreover, the homotrimerisation products **10a** and **10b** of 1-methoxypropyne **3** were now isolated as side products in 39% yield (ratio of isomers **10a**/**10b** = 3:2). The use of [$Ni(cod)_2$] (20 mol%) and triphenylphosphine (20 mol%) as catalyst consumed the substrate **2a** within 2 days at room temperature. However, only traces of the desired products **9a** and **9b** with a ratio of isomers of **9a**/**9b** = 1:1 were isolated (entry 6). Main products were now **10a** and **10b,** which were isolated in 30% yield (ratio of isomers **10a**/**10b** = 2:3). The formal [2+2+2] cycloaddition with the Grubbs' catalyst (10 mol%) – whose mechanism certainly differs from those of the other catalysts tested in this series and that most likely

Table 1. Catalyst screening for the [2+2+2] cycloaddition of diyne **2a** with 1-methoxypropyne **3**

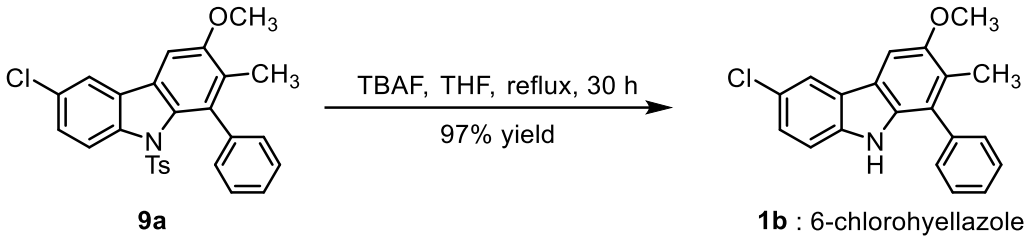


Entry	Catalyst (mol%)	Additive (mol%)	T (°C)	t (d)	**9a/9b** (%)[a]	Ratio[b] **9a**:**9b**	**10a/10b** (%)[a]	Ratio[b] **10a**:**10b**
1	$RhCl(PPh_3)_3$ (5)	--	20	1	93	19:1	-[c]	-
2	$RhCl(PPh_3)_3$ (5)	--	20	2	96	19:1	-[c]	-
3	$CoBr(PPh_3)_3$ (10)	--	20	8	15	1:1	-[c]	-
4	$CoBr(PPh_3)_3$ (10)	--	60	8	22	1:1	-[c]	-
5	$IrCl(cod)_2$ (4)	DPPE (8)	60	6	53	6:1	39	3:2
6	$Ni(cod)_2$ (20)	PPh_3 (80)	20	2	--[c]	1:1	30	2:3
7	Grubbs II (10)[d]	--	60	5	13	1:1	5	3:2

[a] Isolated yield [b] Isomer ratio determined from ^{1}H NMR spectrum. [c] traces
[d] dichloro[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene](benzylidene)(tricyclohexylphosphine)ruthenium(II)

follows a cascade of ring-closing en-yne metathesis steps[36] - only afforded carbazoles **9a** and **9b** in 13% yield. Furthermore, it was lacking any regioselectivity (ratio **9a**/**9b** = 1:1, entry 7). The side products **10a** and **10b** were formed in 5% yield with an isomer ratio of **10a**/**10b** = 3:2. This brief screening concludes that Wilkinson's catalyst displays the highest catalytic activity for the conversion of diyne **2a** into carbazole **9a** in view of significantly shorter reaction times, chemo- and regioselectivity, as well as being an operational simple transformation. Best chemoselectivities were observed with rhodium and cobalt, whereas iridium and nickel catalysts led to the formation of significant amounts of the side products **10a** and **10b** (30-39% yield) through a homotrimerisation reaction of **3**. The preferential formation of the regioisomer **9a** is only observed with the rhodium and iridium catalysts. However, the regioselective outcome of this unique crossed [2+2+2] cycloaddition is much higher with the former (isomer ratio of **9a**/**9b** = 19:1 for Wilkinson's catalyst *versus* 6:1 for the iridium catalyst).

The total synthesis of 6-chlorohyellazole (**1b**) was now completed by *N*-tosyl group deprotection of **9a** with TBAF (tetrabutylammonium fluoride) in refluxing dry THF delivering **1b** in 97% yield (Scheme 4). Thus, the total synthesis of 6-chlorohyellazole (**1b**) was accomplished with 37% overall yield in a very short 6-step sequence starting from commercially available 4-chloro-2-iodoaniline.



9a **1b** : 6-chlorohyellazole

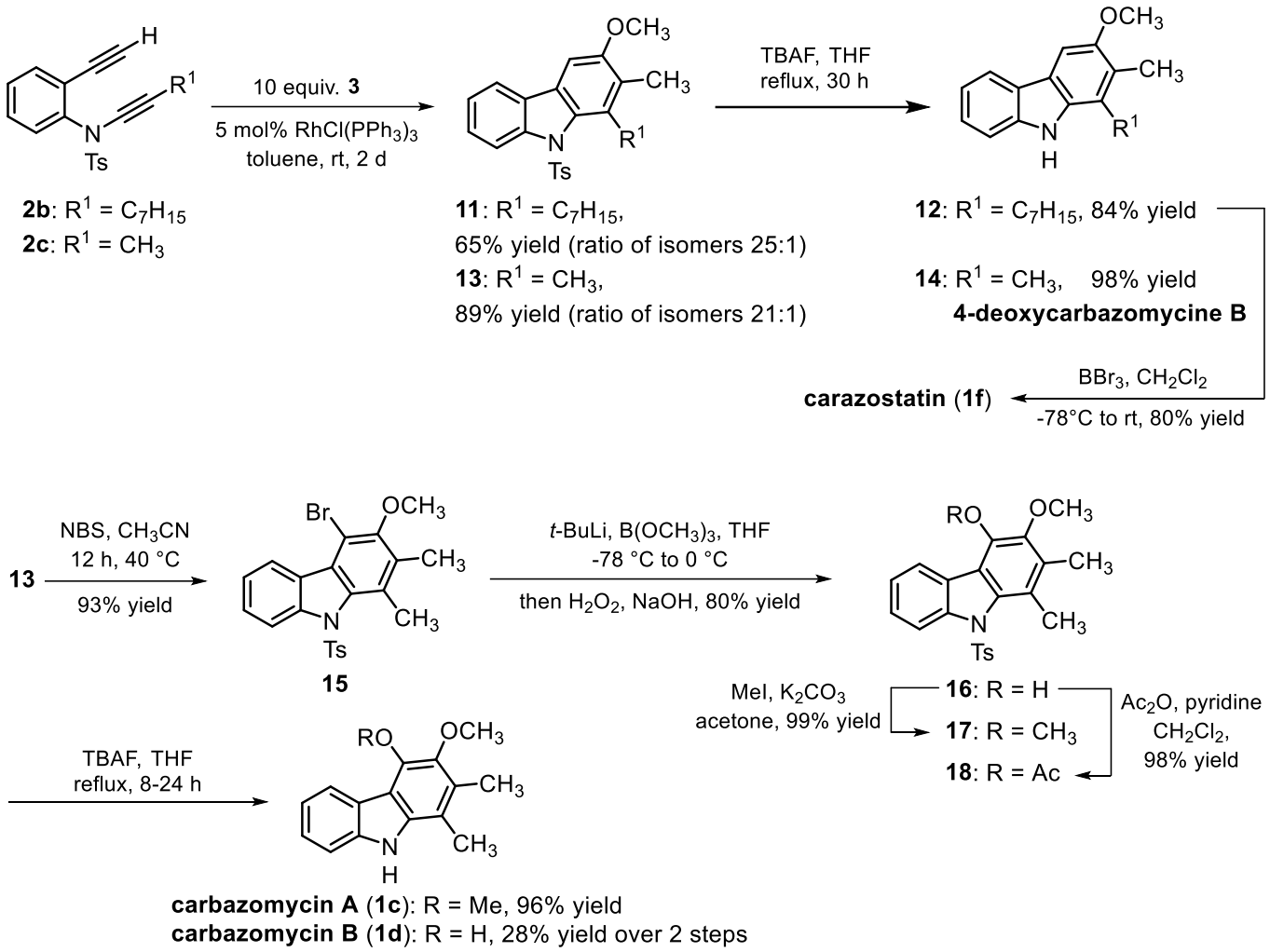
Scheme 3. Synthesis of 6-chlorohyellazole (**1b**)

The crossed [2+2+2] cycloaddition of diyne **2b** ($R^1 = C_7H_{15}$) with 1-methoxypropyne **3** was performed in toluene at room temperature in the presence of Wilkinson's catalyst [$RhClPPh_3)_3$] and afforded carbazole **11** regioselectively with 65% yield (regioisomer ratio 25:1) (Scheme 4). Isomerically pure **11** was obtained by column chromatography. Thereafter, only minor substituent modifications remained in order to complete the sequence towards carazostatin (**1f**): Removal of the *N*-tosyl group of **11** with TBAF gave the *9H*-carbazole **12** (84% yield) that was then converted into carazostatin (**1f**, 80% yield) by treatment with BBr_3 in CH_2Cl_2. Finally, the total synthesis of carazostatin was accomplished in only 8 steps from commercially available 2-iodoaniline with 20% overall yield.

The crossed [2+2+2] cycloaddition of diyne **2c** (R^1 = Me) with alkyne **3** served in the synthesis of carbazomycins A and B and delivered the corresponding carbazole **13** (R^1 = Me) chemo- and regioselectively in 89% yield with 21:1 ratio of regioisomers (Scheme 4). Isomerically pure **13** was obtained by recrystallization (pentane/CH_2Cl_2). Treatment of **13** with TBAF in refluxing THF gave 4-deoxycarbazomycin B (**14**) in 98% yield. The *9H*-carbazole **14** (4-deoxycarbazomycin B), that is a degradation product of natural carbazomycin B and a synthetic intermediate of the natural bicarbazole sorazolon E,[37] displays inhibitory activity against Gram positive and negative bacteria.[38]

The synthesis of 4-hydroxycarbazole **16** – a common precursor of carbazomycins A and B - was achieved in analogy to a literature procedure from **13**.[34g] The selective bromination of **13** using NBS (*N*-bromosuccinimide) in acetonitrile (93% yield) and subsequent formation of a boronic ester, which thereafter is treated *in situ* by H_2O_2 in basic medium gave the expected 4-hydroxycarbazole **16** (R = H). 4-Hydroxycarbazole **16** was isolated in 80% yield along with carbazole **13** (15% yield). *O*-Methylation of carbazole **16** gave **17** that was followed by removal of the *N*-tosyl group and finally afforded carbazomycin A (**1c**) in 95% yield (2 steps). On the other hand, carbazomycin B (**1d**) was isolated in 14% yield when the TBAF treatment was applied to **16**. However, an overall higher yield of carbazomycin B (**1d**) of 28% over 2 steps was obtained by first protecting the hydroxy function of **16** as *O*-acetate to give **18**, followed by the simultaneous deprotection of the *N*-tosyl and *O*-acetyl group with TBAF to deliver the targeted carbazomycin B (**1d**). Carbazomycins A and B were thus obtained in a quite short 10 step sequence starting from commercially available 2-iodoaniline with an overall yield of 43% and 12%

respectively.

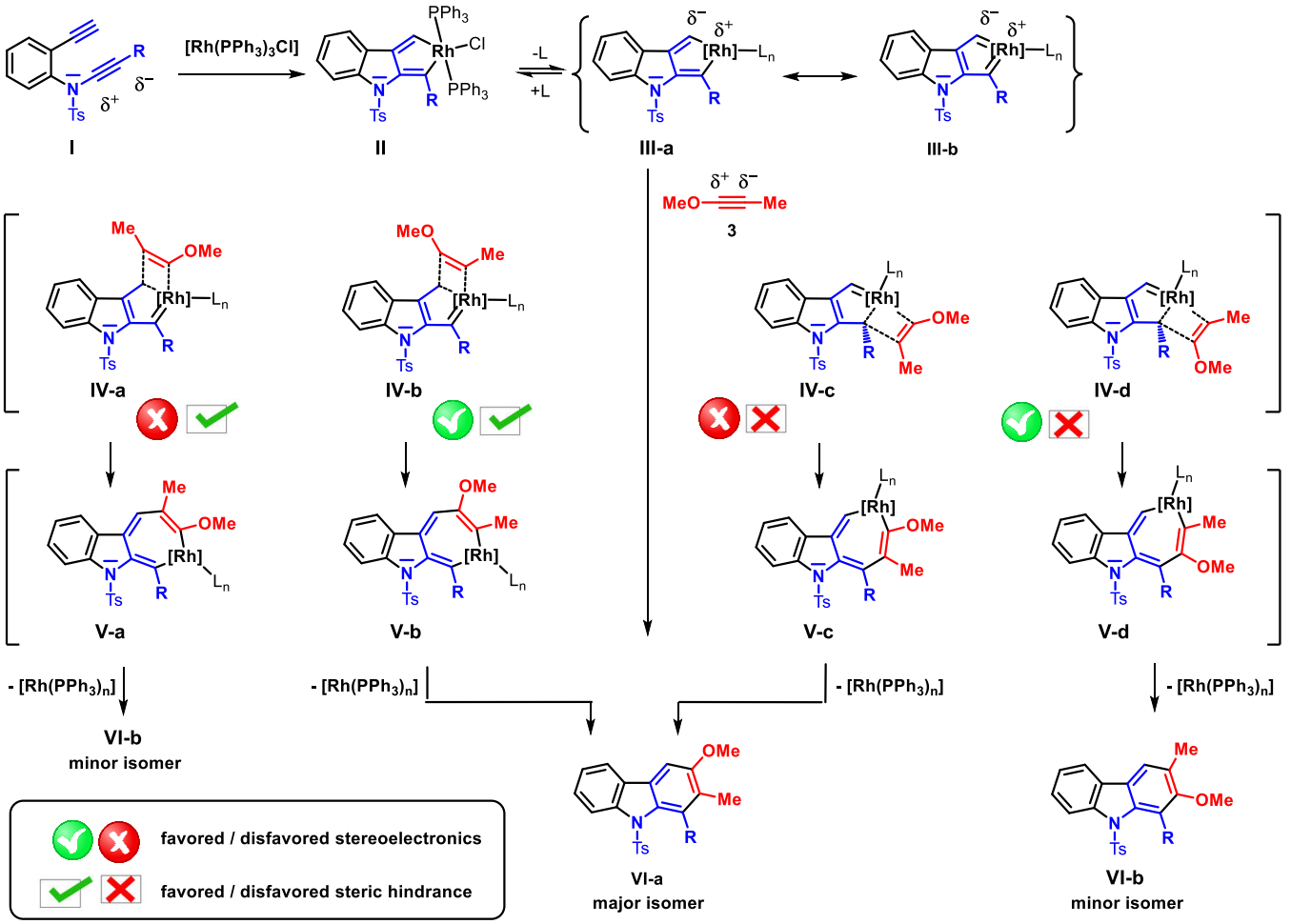


Scheme 4. Synthesis of 4-deoxycarbazomycin B (**14**), carazostatin (**1f**), carbazomycin A (**1c**) and B (**1d**)

Although the synthetic utility of the transition metal catalyzed [2+2+2] alkyne cyclotrimerization has been recognized frequently since the first disclosure of the nickel catalyzed acetylene to benzene reaction by Reppe in the 1940s,[39] mechanistic understanding and details allowing to predict the chemo and regioselective outcome still remain unrevealed. Plausible mechanistic pathways for the reaction of di-ynamides **I** with 1-methoxypropyne **3** adapting a general mechanism proposed for the transition-metal-catalyzed [2+2+2] cycloaddition reaction are outlined in Scheme 5.

The overall exergonic process from di-ynamide **I** to the final carbazoles **VI** covers the formation of three *C-C* σ-bonds and gains aromatic stabilization. Ligand-alkyne substitution in Wilkinson's complex with diyne **I** followed by oxidative coupling results in the 18 electron complex **II**. Related rhodacyclopentadiene (rhodole) derivatives - that are best considered of being resting states in the catalytic cycle - have been isolated and characterized.[40] Subsequent ligand dissociation (**II** to **III-a**/**III-b**) will generate vacant coordination sides for alkyne insertion. Electronically, rhodoles are best described

with mesomeric structures comprising the rhodacyclopentadiene-**III-a** and the bis-carbene structure **III-b**.[41]



Scheme 5. Proposed mechanistic pathways for the evaluation of steric and stereoelectronic effects stirring the rhodium catalyzed crossed [2+2+2] cycloaddition of ynamide **I** with 3-methoxypropyne **3** to give carbazoles **VI-a/b**

Formal [2+2] cycloaddition of alkyne **3** to one of the C_{sp2}-*Rh* carbene bonds (to give **IV**) and subsequent ring-enlargement will give the rhodacycloheptatriene **V** that after reductive elimination and metal complex dissociation liberates carbazole **VI**. However, other scenarios describing the insertion step (i.e. Schore's mechanism, or a [4+2] Diels-Alder-type cycloaddition to give a metallanorbornadiene) are discussed in the literature.[31]

Rhodole formation is considered of being the rate determining step at least for the entirely intermolecular transition metal catalyzed [2+2+2] cyclcoaddition.[42] However, in the here discussed crossed version the formation of **II** and **III-a/b** should be easily accessible due to entropic reasons and the rate determining step therefore should be shifted to the mono-alkyne insertion process. This is in agreement with the exclusively high chemoselectivity observed for this reaction, as only trace amounts of the homotrimerization products of **3**, the benzenes **10a**/**10b**, were found.

The regioselective outcome of the reaction of **I** with 1-methoxypropyne **3** is reasoned as a result of the interplay of steric and electronic effects. Solely steric considerations were discussed in earlier contributions of this reaction, whereas electronic effects stirring the regioselectivity of transition metal catalyzed [2+2+2] cycloadditions involving fully intermolecular or crossed enyne alkyne cycloadditions have been recognized only quite recently.[43] Notably, the ynamide moiety in **I** as well as the 1-methoxypropyne **3** are electron rich alkynes with considerable charge distribution through the *C*(sp)-*C*(sp) triple bond due to heteroatom-*C*(sp) σ-bond inductive effects and n,π-conjugation of the heteroatom lone pair with the *C*(sp)-*C*(sp) triple bond. Such electronic effects will govern the orientation of the alkyne **3** in the insertion process along the formal [2+2] addition to the polarized $C_{carbene}$-*Rh* bond having an electrophilic rhodium center. Eventually, such stereoelectronic effects should favor a reaction pathway along **IV-b** to **V-b** with the methoxy-substituent oriented away from the rhodium center and insertion along the less substituted $C_{carbene}$–*Rh* bond. Whereas the formation of **IV-a** and **IV-c** would contradict such a favorable orbital overlap during alkyne insertion. Furthermore, alkyne insertion along **IV-b** seems to be more favorable than involving **IV-d** due to steric reasons caused by the substituent R. Similar steric reasons would count for the relative energies of rhodacycloheptatrienes **V-a** to **V-d** from which **V-d** and **V-c** certainly show the highest sterically encumbered environment (1,2,3,4-substituted metallacycloheptatriene). Notably, the experimentally observed selectivity is extraordinarily high for this process and does not change significantly with the size of R (R = Me, *n*-heptyl, Ph). This is also an indication for the high preference of the insertion process along the less substituted $C_{carbene}$-*Rh* bond to give **IV-b**. A more detailed mechanistic discussion, however, remains speculative as repulsion of substituents and especially alkyne substituents and phosphine ligands are not easily predictable – neither the number of phosphine ligands nor the complex geometry around the rhodium metal center in the rate determining step are known. However, the high regioselectivity found in the reaction of **2a-c** with the alkyne **3** points to considerable contributions of stereoelectronic and steric effects to explain the outcome of the reaction and the almost exclusive formation of carbazoles **VI-a**. Work evaluating the contribution of stereoelectronic effect in the transition metal catalyzed [2+2+2] cycloaddition with ynamides is in progress.

In summary, the short total synthesis of several naturally occurring 3-oxygenated carbazole alkaloids was described. Common key step is the rhodium-catalyzed crossed alkyne [2+2+2] cycloaddition between yne-ynamides and 1-methoxypropyne, which proceeds with excellent chemo- and regioselectivities and allows the introduction of five benzene ring substituents of the natural carbazoles within a single step. This study highlights the applicability of the chemistry of ynamides - as well as the use of Wilkinson's catalyst with its high tolerance towards functional groups and its high regioselectivity in crossed [2+2+2] alkyne cycloadditions - in the synthesis of natural products and drug related targets.

ACKNOWLEDGEMENTS

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SUPPORTING INFORMATION

Supplementary data (experimental procedures, spectroscopic and analytical data and copies of ^{1}H and ^{13}C NMR spectra) can be found, in the online version at URL: https://wwwheterocycles.jp

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