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HIGHLIGHT

Efficient synthesis strategies by application of transition metal-catalyzed carbene/nitrene insertions into C–H bonds

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Transition metal-catalyzed insertion of carbenes and nitrenes into C–H bonds has become a powerful tool for the construction of C–C and C–N bonds in the synthesis of complex natural products. In this *Highlight*, a selection of syntheses are detailed involving the implementation of C–H insertion reactions leading to strategies marked by improved efficiency.

1 Introduction

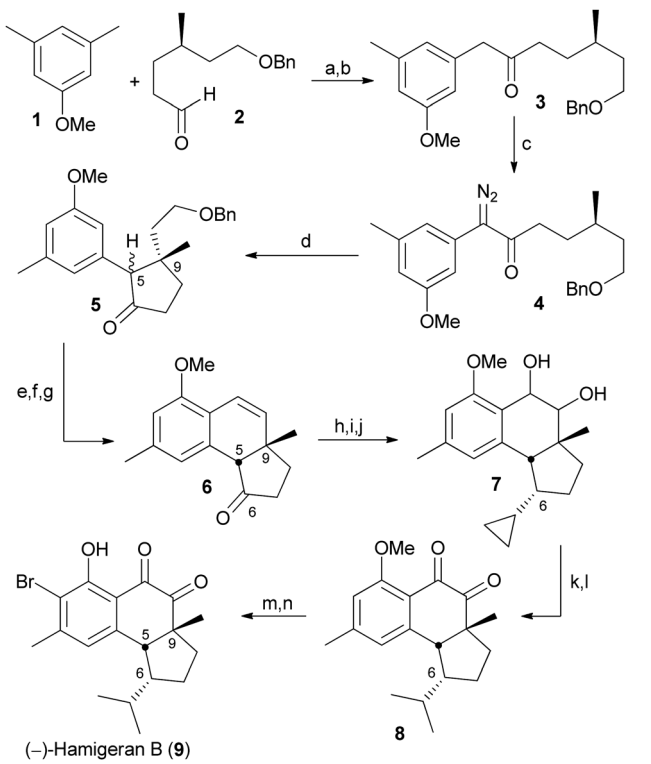
Carbenes and nitrenes are neutral, low-valent carbon and nitrogen species possessing only six valence electrons. Because of their electron deficiency they constitute highly reactive intermediates and exhibit a wide range of reactivity manifested in cycloadditions, C–H insertions and ylide formation. Metal-bound carbenes or nitrenes display an attenuated reactivity which can be fine-tuned by the variation of the metal, ligand and substitution pattern around the carbene/nitrene. Their ease of generation and high reactivity has made them attractive entities for the synthesis of complex natural products, used for the construction of retrosynthetically critical C–C and C–N bonds, enabling efficient and concise approaches to challenging target structures. We discuss some of the recent syntheses in which C–H functionalization is pivotal to the strategy.[1]

2 C–H insertions of carbenes

Taber's synthesis of (−)-Hamigeran B

In 2008, Taber employed a Rh-mediated intramolecular C–H insertion reaction of an α-aryl-α-diazoketone in the synthesis of (−)-Hamigeran B (Scheme 1).[2] As a consequence of its challenging architecture and notable biological activity, the molecule had been the subject of three synthetic approaches prior to Taber's work.[3,4] Taber's synthesis provides quick access to an α-aryl ketone **3** which was efficiently transformed into the α-aryl-α-diazoketone **4** through the use of 2,4,6-triisopropylbenzenesulfonyl azide and DBU at 0 °C for the diazotransfer.

Under carefully chosen reaction conditions using Rh_2(*R*-pttl)$_4$ as a catalyst, the key insertion reaction into the tertiary C–H bond occurred in 83% yield, thereby setting the quaternary stereocenter at C9 in a stereospecific manner with a retention of configuration. The reaction product **5** was not unexpectedly isolated as a mixture of diastereomers at C5. As



Scheme 1 Taber's synthesis of (−)-Hamigeran B. *Reagents and conditions*: a) *t*-BuOK/*n*-BuLi, THF, −78 °C, 76%; b) H_5IO_6, PCC, MeCN, 0 °C, 71%; c) DBU, 2,4,6-triisopropylbenzene-sulfonyl azide, PhMe, 0 °C, 90%; d) Rh_2(*R*-pttl)$_4$, PhMe, rt, 83%; e) Pd/C, H_2, THF–water (500 : 1), 98%; f) Dess–Martin periodinane, CH_2Cl_2, rt, 95%; g) $BF_3{\cdot}OEt_2$, Et_2O, rt, 37%; h) (*c*-$C_3H_5)_2TiCp_2$, $NaHCO_3$, PhMe, 60 °C, 60%; i) Ir black, H_2 (1100 psi), EtOH, rt, 80%; j) $K_2OsO_4{\cdot}2H_2O$, NMO, CCl_4–water–acetone–*t*-BuOH (4 : 1 : 8 : 4), rt, 60%; k) PtO_2, H_2, AcOH, 50 °C, 67%; l) TBAP, NMO, CH_2Cl_2, rt, 54%; m) LiCl, DMF, reflux, 88%; n) NBS, i-Pr_2NH, CH_2Cl_2, rt, 81%.

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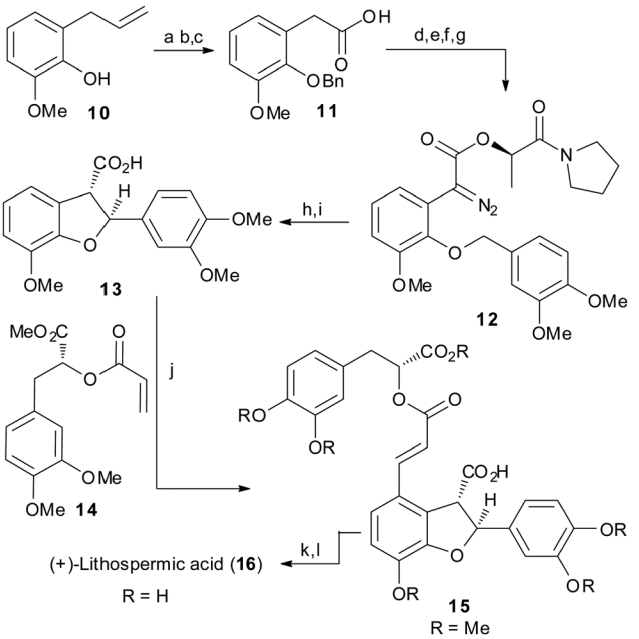
the two diastereomers interconvert upon storage, the material was taken forward as a diastereomeric mixture and afforded, after a Friedel–Crafts reaction and condensation of the *cis*-isomer, the intermediate tricyclic alcohol **6**. In another five steps the isopropyl group, which resides on the more hindered, concave face of the molecule, was installed and the alkene was oxidized to the vicinal diketone to arrive at the known intermediate **8**. This was then transformed into (−)-Hamigeran B (**9**), according to known literature procedures.

Yu's synthesis of (+)-Lithospermic Acid

The synthesis of (+)-Lithospermic acid reported by Yu in 2011 relies on two key C–H functionalization steps, allowing efficient access to the natural product (Scheme 2).[5] A late-stage Pd-catalyzed C–H olefination reaction (**13** + **14** → **15**) enables a highly convergent synthetic strategy, with the chiral dihydrobenzofuran **13** efficiently constructed by an intramolecular Rh-catalyzed asymmetric C–H insertion (**12** → **13**). The synthesis commenced with *o*-eugenol **10**, which was transformed to carboxylic acid **11** in 3 steps. An installation of the (*S*)-lactamide chiral auxiliary, developed by Fukuyama,[6] under Mitsunobu conditions was followed by an exchange of the benzyl protection group for the 3,4-dimethoxy arene, present in the natural product. After diazotransfer, the stage was set for the Rh_2(*S*-DOSP)$_4$ catalyzed diastereoselective carbene insertion into the benzylic C–H bond to obtain **13** as the desired *trans* product (dr = 8 : 1). Hydrolysis of the chiral auxiliary and Pd-catalyzed C–H olefination of **13** with acrylate **14** (available in 3 steps from rosmarinic acid) gave **15** in an impressive yield of 93%. Global demethylation following a known literature 2 step sequence[7] afforded (+)-Lithospermic acid (**16**) in 12 steps and 11% overall yield.[8]



Scheme 2 Yu's synthesis of (+)-Lithospermic acid. *Reagents and conditions*: a) BnBr, K_2CO_3, acetone, 50 °C, 99%; b) $RuCl_3$, Bu_4NI, $NaIO_4$, EtOAc–water, rt; c) NaH_2PO_4, H_2O_2, $NaClO_2$, MeCN–water, rt, 86% over 2 steps; d) pyrrolidinyl (*S*)-lactamide, PPh_3, DEAD, PhMe, 0 °C to rt; e) Pd/C, H_2, MeOH, rt; f) 3,4-dimethoxybenzyl bromide, K_2CO_3, THF, 80 °C, 71% over 3 steps; g) *p*-ABSA, DBU, MeCN, 0 °C to rt, 82%; h) Rh_2(*S*-DOSP)$_4$, CH_2Cl_2, rt, 85%, dr = 8 : 1; i) $Ba(OH)_2 \cdot 8H_2O$, THF–MeOH (1 : 1), 0 °C to rt, 86%; j) $Pd(OAc)_2$, Ac-Ile-OH, O_2, $KHCO_3$, *t*-amyl-OH, 85 °C, 93%; k) Me_3SnOH, ClH_2CCH_2Cl, 80 °C, 91%; l) TMSI-quinoline, neat, 130 °C, 31%.

Davies' synthesis of (−)-Colombiasin A and (−)-Elisapterosin B

(−)-Colombiasin A (**25**) and (−)-Elisapterosin B (**26**) are two prominent members of a family of diterpenes isolated from gorgonian corals that have attracted considerable attention for their challenging architecture and intriguing biological activity.[9] The groups of Nicolaou[10] and Rychnovsky[11] provided elegant solutions for the construction of **25** and **26** from a diene precursor **24** relying on intramolecular [4 + 2] and [5 + 2] cycloadditions, respectively. Compared to these elegant and highly efficient cyclization reactions in the final stage of the existing syntheses of **25** and **26**, the stereoselective construction of the three distinctive stereocenters (C3, C6, and C7) in the cyclization precursor **24** has proven to be a nontrivial problem.

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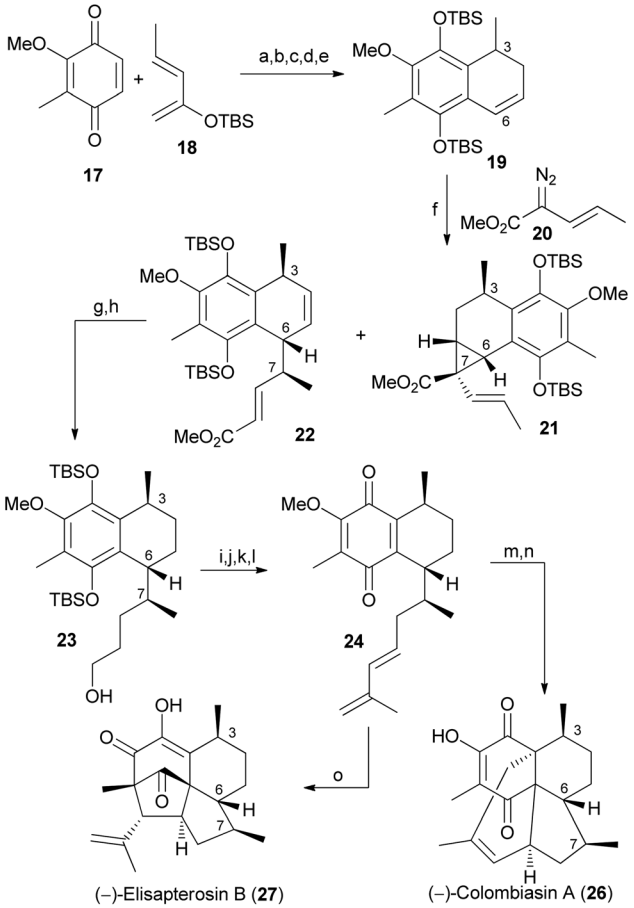
Erick M. Carreira was born in Havana, Cuba, in 1963. He received his BSc from the University of Urbana-Champaign working with Prof. Scott Denmark, before he joined the group of Prof. David A. Evans at Harvard University to undertake his doctoral studies. After postdoctoral research at the California Institute of Technology with Prof. Peter Dervan, he joined the faculty at this institute. Since 1998, he has been a full professor at the ETH Zürich, Switzerland.

The challenge around these stereocenters can be attributed to the fact that they are relatively isolated and no neighbouring functional groups are present that would assist their stereoselective installation.

The Davies group found a fascinating solution for this synthetic problem by utilizing a highly enantioselective, intermolecular allylic C–H insertion, formally combined with a subsequent Cope rearrangement (Scheme 3).[12] Starting from quinone **17** and diene **18**, dihydronaphthalene **19** was obtained *via* a sequence of routine transformations. The treatment of **19** with vinyldiazoacetate **20**, in the presence of Rh_2(*R*-DOSP)$_4$, provided an enantioselective allylic C–H insertion product that directly underwent a Cope rearrangement to yield α,β-unsaturated ester **22**. All three stereocenters were set in this one operational step.[13] Furthermore, it is intriguing that the chiral Rh-prolinate catalyst is capable of differentiating and resolving the two C3-epimers of **19**. In the mismatched case, the dihydronaphthalene is subjected to a cyclopropanation process affording **21**, whereas in the matched case the desired combination of allylic C–H insertion and Cope rearrangement occurred to give **22**. Afterwards, reduced alcohol **23** was isolated in 34% yield (50% is the theoretical maximum yield) as a single diastereomer in >95% *ee*. In another series of steps, **23** was transformed into diene **24**, which in turn was transformed into the natural products (−)-Colombiasin A (**25**) and (−)-Elisapterosin B (**26**), employing the conditions developed by Nicolaou and Rychnovsky.



Scheme 3 Davies' synthesis of (−)-Colombiasin A and (−)-Elisapterosin B. *Reagents and conditions*: a) EtOH, rt; b) TBSCl, imidazole, DMF, rt; c) TFA, CH_2Cl_2, rt, 84% over 3 steps; d) NaHMDS, 2-(NTf_2)-5-Cl-pyridine, THF, −78 °C, 75%; e) $Pd(PPh_3)_4$, LiBr, Et_3SiH, THF, reflux, 96%; f) Rh_2(*R*-DOSP)$_4$, **20** over 1 h *via* syringe pump, 2,2-DMB, rt; g) Pd/C, H_2 (45 psi), EtOH, rt; h) $LiAlH_4$, THF, 0 °C to rt, 34% over 3 steps (50% theoretical maximum yield), 95% *ee*; i) PCC, CH_2Cl_2, 0 °C to rt, 87%; j) isopropenyl-MgBr, Et_2O, −78 °C to 0 °C, 85%; k) 2,6-di-*t*-butylpyridine, Tf_2O, CH_2Cl_2, −78 °C, 75%; l) *n*-Bu_4NF, air, THF, rt, 89%; m) PhMe, 180 °C, 88%; n) $AlCl_3$, $PhNMe_2$, CH_2Cl_2, 0 °C to rt, 70%; o) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 51%.

Carreira's synthesis of epoxyisoprostanes PECPC/PEIPC

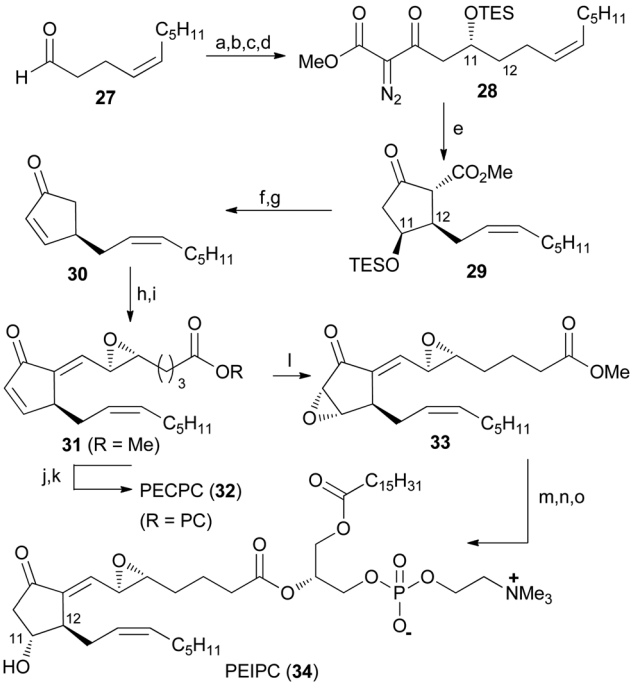
The epoxyisoprostane phospholipids PECPC (**32**) and PEIPC (**34**) are transient and elusive natural products occurring in humans and other higher organisms. Although a number of biological effects were expected to be associated with these molecules, a detailed investigation of their biological activity has been hampered by the lack of a pure reference material. Two independent synthetic routes for PECPC (**32**) and PEIPC (**34**) have been published by the groups of Kobayashi[14] and Jung,[15] which both rely on traditional strategies. A general and efficient synthetic route for both epoxyisoprostane phospholipids has been devised by Carreira (Scheme 4).[16]

The approach implements a highly diastereoselective intramolecular C–H insertion of a Rh-carbenoid exclusively into the less activated homoallylic C–H bond. Commencing from aldehyde **27**, a cyclization precursor **28** was obtained in 4 steps. The stereocenter C11 in **28** was established by an enantioselective cycloaddition of **27** with *in situ* generated ketene. In the next step of the sequence (**28** → **29**), this stereocenter C11 assisted the correct installation of the stereocenter at C12. Treatment of **28** with [Rh_2(*S*-PTAD)$_4$] mediated the formation of the desired cyclopentanone **29** with the lower of the two side chains fully installed. The cyclization occurred with high diastereoselectivity (dr = 9 : 1), and no allylic C–H insertion product or olefin cyclopropanation was observed. Decarboxylation and elimination of TES-silanol transformed **29** into cyclopentenone **30**. The upper side chain was then installed in a 2 step process, namely an aldol addition followed by an elimination to obtain dienone methyl ester **31**. Enzymatic ester hydrolysis and coupling to 1-palmitoyl-phosphatidylcholine (PC) furnished PECPC (**32**). Diastereo- and regioselective epoxidation of **31** afforded epoxide **33** that was, after coupling to 1-palmitoyl-phosphatidylcholine, reductively opened in a regioselective manner to obtain PEIPC (**34**). With the synthesized material in hand, unprecedented anti-inflammatory effects of these epoxyisoprostane phospholipids were observed.

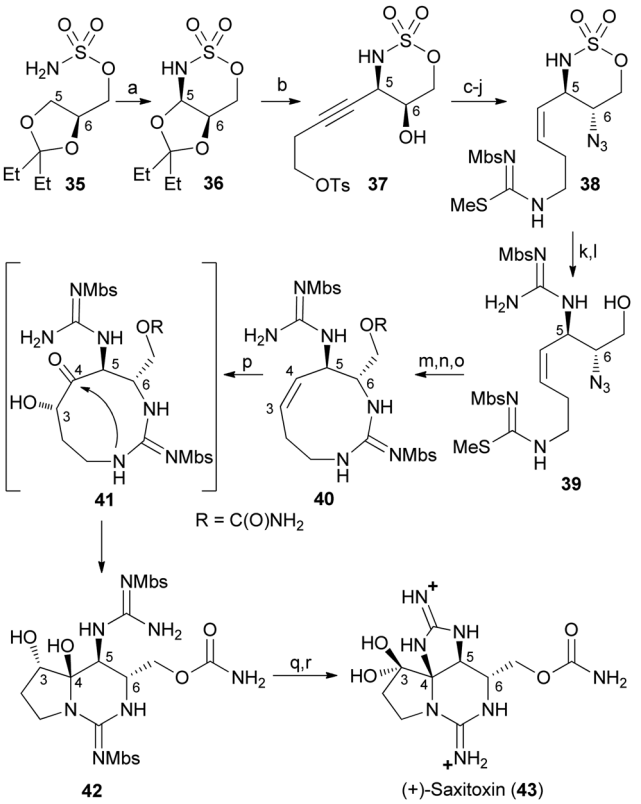
3 C–H insertions of nitrenes

Du Bois' synthesis of (+)-Saxitoxin

The potent neurotoxin (+)-Saxitoxin (**43**) has proven to be a prominent synthetic challenge for synthetic organic chemists. Efforts within the synthetic community resulted in two racemic total syntheses of this tricyclic, heteroatom rich natural product



Scheme 4 Carreira's synthesis of PECPC and PEIPC. *Reagents and conditions*: a) $LiClO_4$, TMS-quinidine, i-Pr_2NEt, AcCl over 4 h *via* syringe pump, Et_2O/CH_2Cl_2, −78 °C, 62%, 92% ee; b) i-Pr_2NLi, methyl acetate, THF, −78 °C, 77%; c) *p*-ABSA, Et_3N, MeCN, 0 °C to rt, 97%; d) TESCl, imidazole, DMF, 0 °C to rt, 98%; e) $Rh_2(S\text{-PTAD})_4$, CH_2Cl_2, reflux, 71%, dr = 9 : 1; f) NaCl, DMSO, 140 °C, 65%; g) DBU, CH_2Cl_2, 0 °C, 93%; h) $LiN(SiMe_3)_2$, methyl 4-((2*R*,3*S*)-3-formyloxiran-2-yl) butanoate, THF, −78 °C; i) $MeSO_2Cl$, Et_3N, CH_2Cl_2, −78 °C, then Al_2O_3, CH_2Cl_2, rt, 64% over 2 steps; j) *Novozyme*, buffer pH 7/THF, 70%; k) 2,4,6-$Cl_3C_6H_2COCl$, DMAP, lyso-PC, $CHCl_3$, 69%; l) *t*-BuOOH, DBU, THF, 0 °C, 74%; m) Novozyme, buffer pH 7/THF, 74%; n) 2,4,6-$Cl_3C_6H_2COCl$, DMAP, lyso-PC, $CHCl_3$, 69%; o) SmI_2, THF–MeOH, −90 °C, 43%.



Scheme 5 Du Bois' synthesis of (+)-Saxitoxin. *Reagents and conditions*: a) $Rh_2(tpa)_4$, $PhI(OAc)_2$, MgO, CH_2Cl_2, rt, 92%; b) (4-(tosyloxy) but-1-yn-1-yl)zinc(II) chloride, $BF_3{\cdot}OEt_2$, THF, 40 °C, 70%, dr = 20 : 1; c) H_2, $Pd/CaCO_3/Pb$, THF; d) NaN_3, *n*-Bu_4NI, DMF, 90% over 2 steps; e) *p*-$MeOC_6H_4CH_2Cl$, *n*-Bu_4NI, K_2CO_3, MeCN, 85%; f) Me_3P, THF–water; g) MeS(Cl)C=NMbs, i-Pr_2NEt, MeCN, 72% over 2 steps; h) Tf_2O, C_5H_5N, DMAP, CH_2Cl_2; i) NaN_3, DMF, −15 °C, 70% over 2 steps; j) $(NH_4)_2Ce(NO_3)_6$, *t*-BuOH–CH_2Cl_2, 74%; k) KO*t*-Bu, Cl_2C=NMbs, then $(Me_3Si)_2NH$, 70%; l) aq. MeCN, 70 °C, 95%; m) Me_3P, THF–water; n) $AgNO_3$, Et_3N, MeCN, 65% over 2 steps; o) $Cl_3CC(O)NCO$, THF–MeCN, −78 °C, then K_2CO_3, MeOH, 82%; p) $OsCl_3$, oxone, Na_2CO_3, EtOAc–MeCN–water, 57%; q) $B(O_2CCF_3)_3$, CF_3CO_2H, 82%; r) DCC, $C_5H_5N{\cdot}CF_3CO_2H$, DMSO, 70%.

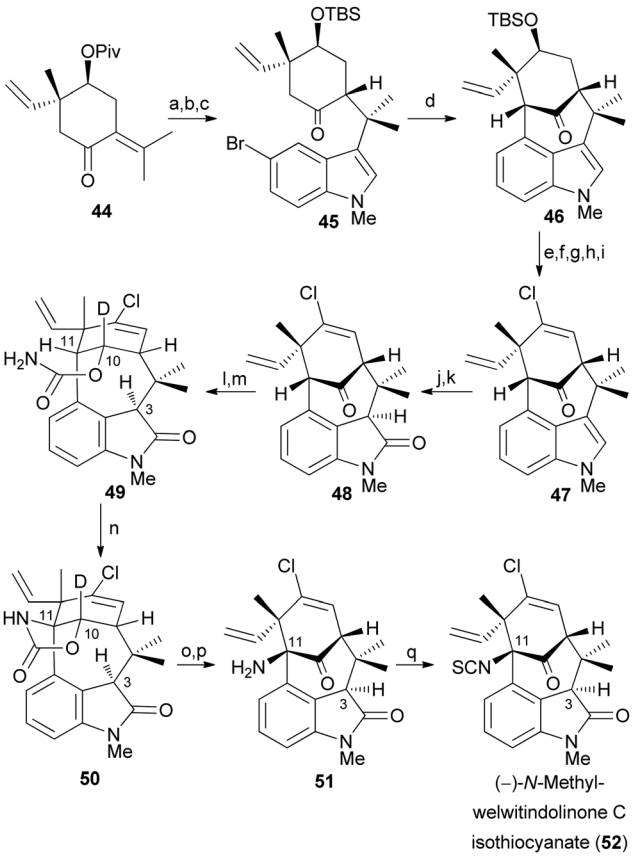
by the groups of Kishi[17] and Jacobi.[18] In 2006, Du Bois reported an impressive 19 step asymmetric synthesis that provided the target compound in 1.6% overall yield (Scheme 5).[19] The retrosynthetic analysis focussed on the disconnection of the C4 spiroaminal and opening of the resulting nine-membered guanidine ring. The resulting acyclic retron exhibits two adjacent stereocenters C5 and C6, of which C5 is nitrogen substituted. Stereocenter C6 is provided by the chiral starting material, namely sulfamoylated (*R*)-glycerol acetonide (**35**), whereas stereocenter C5 was efficiently installed by a Rh-catalyzed nitrene C–H insertion to obtain chiral *N*,*O*-acetal **36**.[20] The obtained *N*,*O*-acetal represents a latent iminium ion equivalent that served upon activation with $BF_3{\cdot}OEt_2$ as an excellent electrophile for the diastereoselective addition of a Zn-acetylene (**36** → **37**).[21] The C5- and C6-stereodefined compound **37** was further transformed into azide **38** that gave the guanidine cyclization precursor **39** upon sulfamate hydrolysis and installation. After the reduction of the azide functionality in **39**, the primary amine obtained was intramolecularly condensed with pseudothiourea to afford **40**. Under carefully optimized reaction conditions the olefin in **40** was oxidized in a regioselective manner to furnish intermediate hydroxyl ketone **41** that directly formed the bicyclic hemiaminal **42**. Guanidine deprotection and formation of the spiroaminal through treatment with $B(O_2CCF_3)_3$, followed by an oxidation state adjustment at C3 finally gave (+)-Saxitoxin (**43**).

Garg's synthesis of (−)-*N*-Methylwelwitindolinone C isothiocyanate

The welwitindolinones are a class of densely functionalized, compact structures that have proven to be challenging synthetic targets. While Welwitindolinone A isonitrile, possessing a C3 spirooxindole core, has been synthesized independently by the groups of Baran[22] and Wood,[23] it was not until 2011 that one of the other welwitindolinone members, possessing a [4.3.1]-bicyclic core system, was completed. In an impressive synthetic effort, Rawal achieved the first total synthesis of (±)-*N*-Methylwelwitindolinone D isonitrile.[24] In the same year, Garg was able to synthesize another member of the group with a

[4.3.1]-bicyclic core structure, and therefore provided the first total synthesis of (−)-*N*-Methylwelwitindolinone C isothiocyanate (**52**) (Scheme 6). Due to the generality of his synthetic approach, he was also able to synthesize other related welwitindolinones and determine their stereoconfiguration at C3.[25]

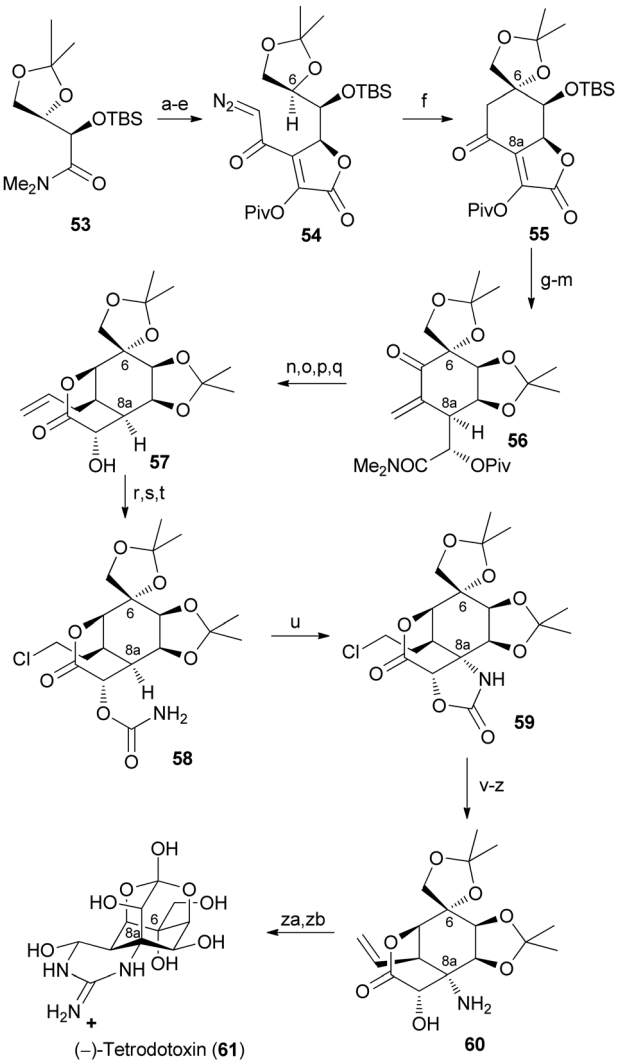
The [4.3.1]-ring system in Garg's synthesis was built by implementing the indolyne chemistry (**45** → **46**) he has developed. For the functionalization of the highly congested bridgehead carbon (C11), he chose to apply a late-stage, intramolecular C–H nitrene insertion, relying on conditions developed by He.[26] The synthesis commenced from a known enone **44**, accessed in 5 steps from carvone.[27] Iodine-catalyzed conjugate addition of 5-bromo-1-methylindole and protecting group exchange furnished **45**. The treatment of bromine **45** with $NaNH_2$/*t*-BuOH in THF generated the corresponding indolyne as an intermediate that subsequently formed the [4.3.1]-bicyclic core ring system **46**. In five steps the TBS-protected alcohol **46** was transformed into the corresponding vinyl chloride to afford the intermediate **47** that was converted into oxindole **48** in two additional steps. In their initial synthetic report, the following nitrene C–H insertion (**49** → **50**) suffered from low regioselectivity (concomitant insertion into the C(10)–H bond) and consequently diminished yield (33%). The authors improved the efficiency of this process by taking advantage of the deuterium kinetic isotope effect. Deuteride mediated reduction of the C10-ketone in **48**, followed by carbamoylation, furnished **49** that underwent a Ag-catalyzed nitrene insertion into the desired C–H bond with improved regioselectivity, to obtain the C11-functionalized cyclic carbamate **50** in 60% yield. Alkaline hydrolysis, oxidation and isothiocyanate installation completed the synthesis of (−)-*N*-Methylwelwitindolinone C isothiocyanate (**52**) in 17 steps and 2.2% overall yield starting from the known enone **44**. With the developed route in hand, Garg was furthermore able to access (−)-*N*-Methylwelwitindolinone C isonitrile and other oxidized welwitindolinones.



Scheme 6 Garg's synthesis of (−)-*N*-Methylwelwitindolinone C isothiocyanate. *Reagents and conditions*: a) K_2CO_3, MeOH, 60 °C; b) 5-bromo-1-methylindole, I_2, MeOH, rt, 54% over 2 steps; c) TBSCl, imidazole, *n*-Bu_4NI, DMAP, DMF, 100 °C, 90%; d) $NaNH_2$, *t*-BuOH, THF, 23 °C, 33%; e) *n*-Bu_4NF, THF, 60 °C; f) Dess–Martin periodinane, CH_2Cl_2, rt, 95% over 2 steps; g) KHMDS, 2-(NTf_2)-5-Cl-pyridine, THF, −78 °C; h) $(Me_3Sn)_2$, $Pd(PPh_3)_4$, LiCl, dioxane, 110 °C, 74% over 2 steps; i) $CuCl_2$, dioxane, rt to 80 °C, 75%; j) NBS, CH_2Cl_2, 0 °C; k) HCl, EtOH, 80 °C, 89% over 2 steps; l) $LiEt_3B$-D, THF, −78 °C to −10 °C; m) $Cl_3CC(O)NCO$, CH_2Cl_2, 0 °C to rt, then K_2CO_3, MeOH, quantitative over 2 steps; n) Ag(OTf), $PhI(OAc)_2$, bathophenanthroline, MeCN, 82 °C, 60%; o) $Ba(OH)_2 \cdot 8H_2O$, water–dioxane, 110 °C; p) Dess–Martin periodinane, TFA, CH_2Cl_2, rt, 66% over 2 steps; q) *O*,*O*′-di-2-pyridyl thiocarbonate, DMAP, ClH_2CCH_2Cl, 90 °C, 77%.

4 Du Bois' synthesis of (−)-Tetrodotoxin

(−)-Tetrodotoxin (**61**), an extremely potent neurotoxin produced by bacteria in the japanese pufferfish (*fugu*), is a salient challenge for testing the efficiency and power of synthetic organic chemistry through the assembly of highly complex natural products. Thirty years after the first racemic synthesis of **61** by Kishi (28 steps, 0.49% overall yield),[28] two asymmetric syntheses were reported by the groups of Isobe (39 steps, 0.25% overall yield)[29] and Du Bois (28 steps, 0.96% overall yield) in 2003.[30] The latter represents a masterpiece in streamlining a synthetic approach by using modern and efficient synthetic methods (Scheme 7). The retrosynthetic analysis by Du Bois disconnects the guanidinium and ortho-acid unit from the natural product, resulting in a highly oxygenated cyclohexylamine core that contains two tetrasubstituted stereocenters, C6 and C8a. This central cyclohexane unit was constructed enantioselectively by a Rh-catalyzed carbene C–H insertion, starting from an acyclic precursor. Concomitantly, one of the two tetrasubstituted stereocenters, C6, was established (**54** → **55**). The other one at C8a was installed by a Rh-catalyzed intramolecular C–H insertion of a nitrene. The synthesis started from a readily available amide **53**[31] that was transformed into diazocompound **54** in 5 steps. The treatment of **54** with acetamide catalyst $Rh_2(HNCOCPh_3)_4$, resulted in the clean and exclusive formation of **55** that could be taken further without any purification necessary. Tricycle **55** was then transformed into carbamate **58** that, upon treatment with $Rh_2(HNCOCF_3)_4$, $PhI(OAc)_2$ and MgO in benzene at 65 °C, performed the desired C–H amidation in 77% yield to give **59**. With the C8a center set, a further 6 steps transformed **59** into (−)-Tetrodotoxin (**61**).



Scheme 7 Du Bois' synthesis of (–)-Tetrodotoxin. *Reagents and conditions*: a) i-Bu_2AlH, *n*-BuLi, THF–hexanes; b) NaOAc, $BnO_2CCH_2C(O)CO_2Bn$, THF; c) *t*-BuCOCl, C_5H_5N, THF, 85% over 3 steps; d) H_2, Pd/C, THF, 88%; e) $(COCl)_2$, cat. DMF, THF, then CH_2N_2, CH_2Cl_2, 63–70%; f) $Rh_2(HNCOCPh_3)_4$, CCl_4; g) $NH_3{\cdot}BH_3$, CH_2Cl_2–MeOH, 75% over 2 steps; h) H_2 (1200 psi), Rh/C, CF_3CO_2H–MeOH; i) *p*-TsOH, 2,2-DMP, THF, 77% over 2 steps; j) Me_2NH, THF, 83%; k) TPAP, NMO, 4 Å MS, CH_2Cl_2, 94%; l) Zn, $TiCl_4$, CH_2I_2, cat. $PbCl_2$, THF, 72%; m) Ph_2Se_2, $PhIO_2$, C_5H_5N, C_6H_5Cl, 100 °C, 70%; n) $H_2C{=}CHMgBr$, CuI, THF; o) *t*-$BuNH_2{\cdot}BH_3$, DCE, 77% over 2 steps; p) *t*-$BuCO_2H$, C_6H_5Cl, 200 °C; q) NaOMe, THF–MeOH, 78% over 2 steps; r) $Cl_3CC(O)NCO$, CH_2Cl_2, Zn, MeOH, 93%; s) O_3, then $NaBH_4$, CH_2Cl_2–MeOH, 83%; t) $MeSO_2Cl$, C_5H_5N, ClH_2CCH_2Cl, 86%; u) $Rh_2(HNCOCF_3)_4$, $PhI(OAc)_2$, MgO, C_6H_6, 65 °C, 77%; v) NaSePh, THF–DMF, 77%; w) *m*-CPBA, C_5H_5N, ClH_2CCH_2Cl, 55 °C, 92%; x) Boc_2O, Et_3N, DMAP, THF; y) K_2CO_3, THF–MeOH, 84% over 2 steps; z) water, 110 °C, 95%; za) BocN=C(SMe)NHBoc, $HgCl_2$, Et_3N, MeCN–CH_2Cl_2, 80%; zb) O_3, CH_2Cl_2–MeOH, Me_2S, then aq. CF_3CO_2H, 65%.

5 Conclusions

The examples presented in this review illustrate the power of carbene and nitrene species within the context of natural product synthesis. The reactivity of these species when tempered by metals enables new synthetic analyses allowing for the disconnection of C–C and C–N bonds which would be challenging to construct by other methods. Accordingly, the successful bond construction by means of C–H insertion often results in a diverse and more efficient overall synthetic route. Furthermore, the use of carbenes and nitrenes can lead to impressive degrees of chemo-, regio-, diastereo- and enantioselectivity. Consequently, their application often has enabled the first asymmetric syntheses of many targeted natural products. Moreover, as the loadings of metal-catalysts are generally low, steps relying on this methodology can be used both in late-stage functionalizations as well as in very early large-scale transformations. Overall, the transition-metal catalyzed insertion of carbenes and nitrenes into C–H bonds has been developed into a powerful tool that has allowed improved synthetic routes for complex structures in the context of natural product synthesis.

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