Bis- and Trisindolylmethanes (BIMs and TIMs)†

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1. Introduction and Importance of Bis- and Trisindolylmethanes (BIMs and TIMs)

The indole ring system is present in many natural products, pharmaceuticals, agrochemicals, and other compounds of importance.[1–8] The indole unit forms the basis for general BIM and TIM structures (Figure 1).

The main purpose of this review is to provide a comprehensive summary of the various synthetic strategies to synthesize BIMs and TIMs. A number of BIM and TIM applications will be briefly pointed out, although this is not the main aim of this review.

Many of the most important BIMs and TIMs were widely isolated from various terrestrial and marine natural sources. These natural products have novel structures and exhibit a range of important biological activities.[9–19] Cancer chemotherapy with bis(3-indolyl)methane was recently reviewed and numerous activities are reported.[20] 3,3′-Diindolylmethane and derivatives also are used as dietary supplements for humans.[21–24] BIMs inhibit bladder cancer growth,[25] inhibit renal cell carcinoma growth,[26] have growth inhibitory activity on lung cancer cells,[27] are active against colon cancer,[28,29] inhibit mammary tumor growth,[30,31] induce apoptosis in prostate cancer,[32–34] inhibit the proliferation process in breast tumor cells,[35–50] have growth inhibitory activity on prostate cancer cell lines,[51,52] have antitumorigenic activity,[53] serve as topoisomerase II_α catalytic inhibitors,[54] serve as inhibitors of the platelet-derived growth factor receptor kinase,[55] exhibit antimicrobial and antifungal activities,[56,57] exhibit antibiotic activity[58] and antibacterial activity,[59] have inhibitory effects on phenobarbital-induced hepatic CYP mRNA expression,[60] serve as cytodifferentiating agents,[61] are antiangiogenic and cytotoxic agents,[62] have antimetastatic activity,[63] have radical scavenging activity,[64] growth promoting activity,[65] and analgesic and anti-inflammatory activities,[66] and are also utilized as tranquilizers[67] and glass-forming high-triplet-energy materials.[68] The oxidized form of BIMs and TIMs are utilized as dyes,[69–74] as well as colorimetric sensors.[75–78]

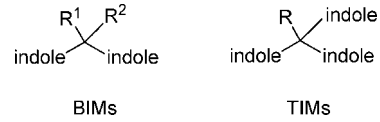

Figure 1. The structure of BIMs and TIMs.

A patent[79,80] disclosed the synthetic method of chromogenic 3,3′-bisindolyl-4-azaphthalides **1** and their uses as color formers in pressure- and heat-sensitive recording materials (Figure 2).[81] A recent patent describes the synthesis of BIMs forming complexes **2** with radioactive metal ions (Gd^{3+}), which are useful contrast agents for radio-imaging and visualization of various tissues and organs (Figure 2).[82]

Recently Maciejewska et al.[83] used DNA-based electrochemical biosensors to demonstrate that bis(5-methoxyindol-3-yl) methane, **3**,[84] considerably reduces the growth of cancer cell lines such as HOP-92 (lung), A498 (renal), and MDA-MB-231/1TCC (breast) (Figure 3). Their results also indicate that BIMs could potentially be applied as chemotherapeutic agents against tumors.[83,85]

Recently Lee and co-workers have found that 1,1,3-tri(3-indolyl)cyclohexane, **4**, inhibits cancer cell growth in lung cancer cells of xenograft models (Figure 4).[86]

Ghaedi et al.[87,88] have used BIMs coated on an alumina−sodium dodecyl sulfate (SDS) surface for preconcentration and determination of Cu(II), Zn(II), Pb(II), and Fe(III) ions by flame atomic absorption spectrometry. Also BIMs and TIMs have been used as ligands for the synthesis of more complex molecules, and different properties of these complexed molecules have been investigated.[89–94]

† This paper is dedicated to Prof. Dr. Junes Ipaktschi on occasion of his 70th birthday.

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Morteza Shiri was born in 1978 at Hamedan (Iran). He obtained his B.Sc. in Applied Chemistry from Bu-Ali Sina University and a M.Sc in Organic Chemistry from Shiraz University with Prof. Habib Firouzabadi in 2004. He received his Ph.D under the supervision of Prof. Mohammad Ali Zolfigol in 2007. He has been selected as a distinguished Ph.D student in 2007. He joined the Alzahra University in 2008. His field of research involves the synthesis of heterocyclic compounds such as indoles and quinolines.

Mohammad Ali Zolfigol was born in 1966 in Salehabad (Ashtian) and obtained his B.Sc. from Arak University, his M.Sc. from Isfahan University of Technology with Prof. Shadpour Mallakpour as supervisor, and his Ph.D from Shiraz University with Prof. Nasser Iranpoor. He has been a faculty member of Bu-Ali Sina University since 1997 and was promoted to Professor in 2005. The Ministry of Science, Research and Technology of Iran selected him as a distinguished researcher in 2001. He won 21st International Khwarizmi Festival and also COMSTEC awards in 2008. Zolfigol became General Secretary of Chemical Society of Iran in 2007 and has been the president of Bu-Ali Sina University since 2008. Zolfigol's research involves the discovery and development of new synthetic methods through the synthesis and application of new solid-supported reagents, especially silica-based resins.

Gert (H. G.) Kruger graduated from Potchefstroom University, South Africa, in 1996 under the supervison of Frans (F. J. C.) Martins and Attie (A. M.) Viljoen. His Ph.D. lineage is traced back to Rudolf Criegee (Wutzburg) via Johan Dekker (Karlsruhe). The Dekkers introduced cage chemistry to South Africa, which Kruger actively pursues at the University of Kwazulu-Natal (see www.ukzn.ac.za/ggkm/ggkm.htm).

Zahra Tanbakouchian obtained her B.Sc. in Applied Chemistry from Islamic Azad University (Tehran Center Unit) and a M.Sc in Organic Chemistry from Bu-Ali Sina University, Hamedan, in 2006 with Prof. Ardeshir Khazaei as supervisor. Her research area is new methodology in organic functional transformations.

It was recently discovered that TIMs isolated from bacteria[95] serve as bacterial metabolic[96] and cytotoxic agents.[97] TIMs show an affinity for hydride ions[98] and dye materials[99,100] and can potentially be utilized as acceptors for these substances. They are also effective frameworks for the construction of very bulky π-acidic phosphine ligands.[101]

It is therefore clear that there are various attractive reasons why researchers want to synthesize various variations of BIMs and TIMs. Due to the versatile application possibilities of BIMs and TIMs, there is a continuous quest for more efficient methods for indole derivative synthesis. Thus far, only a few books have appeared on this topic since 1970.[1,8,102] Although some individual reports for the synthesis of the title compounds have appeared in recent years,[103,104] a single comprehensive review report on the synthetic approaches for the synthesis of BIMs and TIMs would obviously be a welcome resource for researchers in the field.

The rest of this review will focus on the variations found in literature to synthesize this family of useful aromatic heterocycles. The discussion will cover the various systematic approaches in a logical fashion. First we introduce different synthetic routes to 3,3′-BIMs from usual to more exotic methods. Then preparation of 2,2′- and 2,3′-BIMs and yuehchukenes as a special kind of 2,3′-BIMs, followed by other BIMs, are presented. Finally, the formation of TIMs is summarized.

2. BIMs

BIMs are molecules containing two indolyl moieties connected to the same carbon atom.

2.1. 3,3′-BIMs

The indole ring is more reactive at the 3-carbon atom. The majority of BIM's found in literature are therefore 3,3′-BIMs.

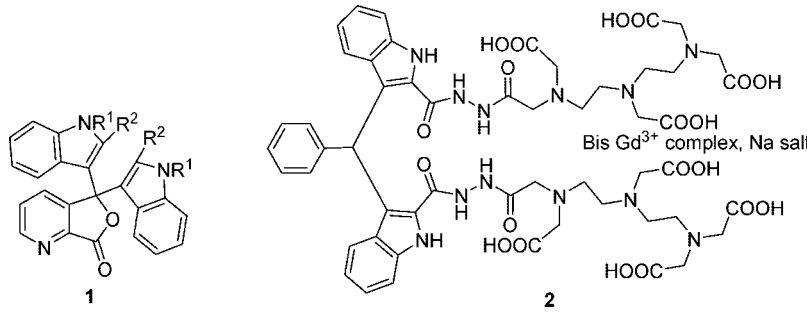


Figure 2. The structure of 3,3′-bisindolyl-4-azaphthalides, **1**, and BIM complex **2**.

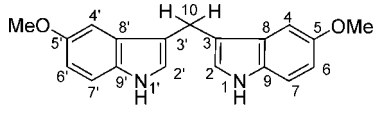


Figure 3. Bis(5-methoxyindol-3-yl) methane.

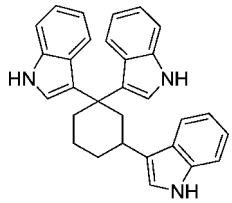


Figure 4. 1,1,3-Tris(3-indolyl)cyclohexane.

2.1.1. 3,3′-BIMs from Aldehydes or Ketones and Indoles

3,3′-BIMs were prepared by Fischer in 1886 for the first time.[105,106] The standard method for the synthesis of 3,3′-BIMs is the Friedel−Crafts reaction between indoles and carbonyl compounds in the presence of acid or base.

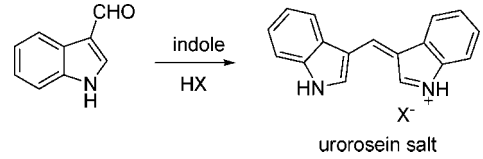
For the benefit of the reader, a general mechanism for the formation of BIMs is provided in Scheme 1. The acid-catalyzed reaction of electron-rich heterocyclic compounds such as indoles and pyrroles with *p*-dimethylaminobenzaldehyde is known as the Ehrlich test.[107] Generally, 3,3′-BIMs are synthesized by an analogous reaction to the Ehrlich test, where indoles react with aliphatic or aromatic aldehydes or ketones in the presence of an acid catalyst to produce azafulven **5**.[108,109] The enamine **5** can undergo further addition with a second indole molecule to produce BIMs.[110]

The following example follows the same mechanism. 3-Formylindole in the presence of HCl[99,111] or $HClO_4$[112] reacts with indole to produce the urorosein salt that was isolated and identified (Scheme 2).

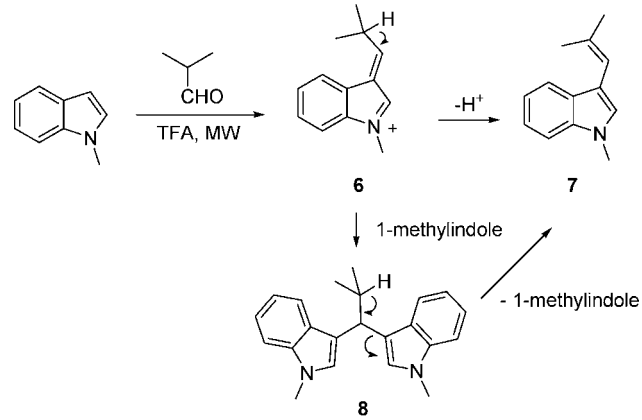
Very recently, it was reported that when 1-methylindole was reacted with isobutyraldehyde and TFA in toluene at 140 °C for 5, 10, 20, 60, and 120 min, 3-vinylindole **7** and bisindolylalkane **8** were formed in ratios of 7:3, 8:2, 9:1, 96:4, and 100:0, respectively (Scheme 3).[113] This kinetically formed product (**8**) appears to form due to nucleophilic attack of a second 1-methylindole onto the unsaturated iminium intermediate **6** to provide BIM **8**. BIM **8** may alternatively eliminate 1-methylindole to give 3-vinylindole **7**, which could also be generated directly from the intermediate **6**.

Also Mallik et al. found that indole in the reaction with α,β-unsaturated ketones yields BIMs **10** in 52−63% yield (Scheme 4).[114] The proposed mechanism via azafulven **9** is presented in Scheme 4. The same observation has been reported by Bergman.[115]

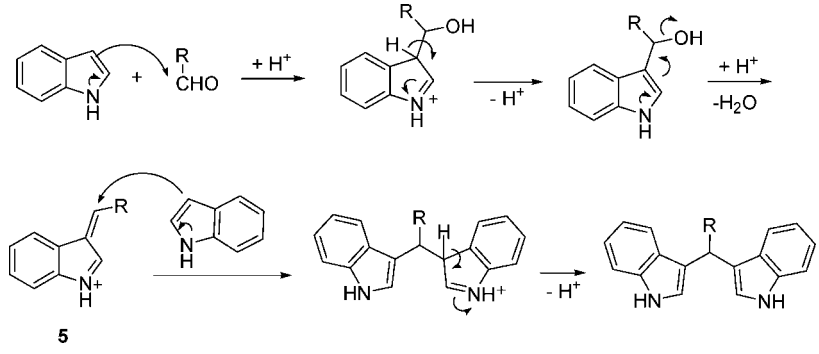
Scheme 2. Urorosein Salt Formation



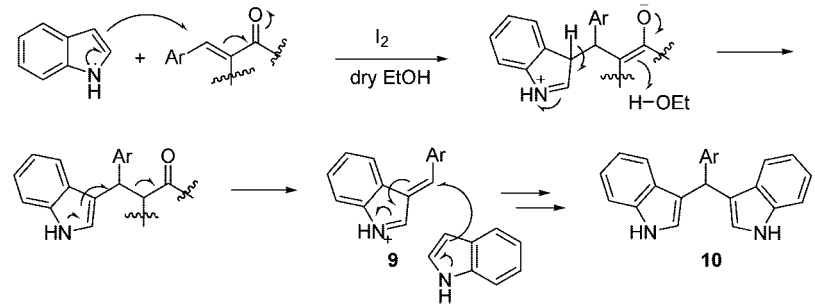
Scheme 3. Reaction of 1-Methylindole with Isobutyraldehyde



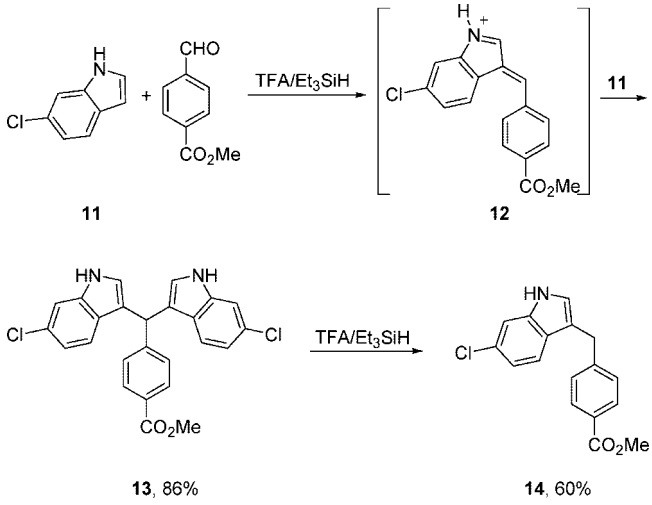
Scheme 1. The Mechanism of BIM Formation via Azafulven 5



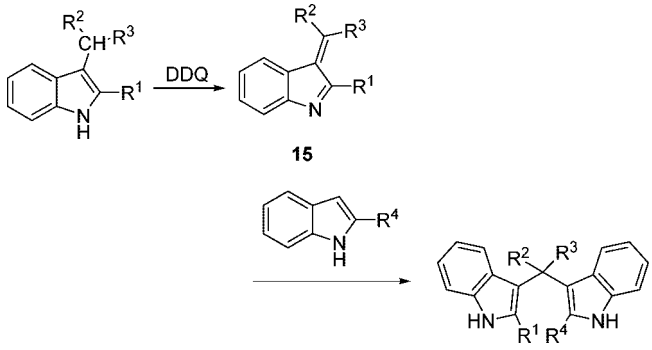
Scheme 4. BIMs from α,β-Enones and Indoles



Scheme 5. One-Pot Synthesis of Alkylindole 14



Scheme 6. DDQ Yielding Azafulven 15

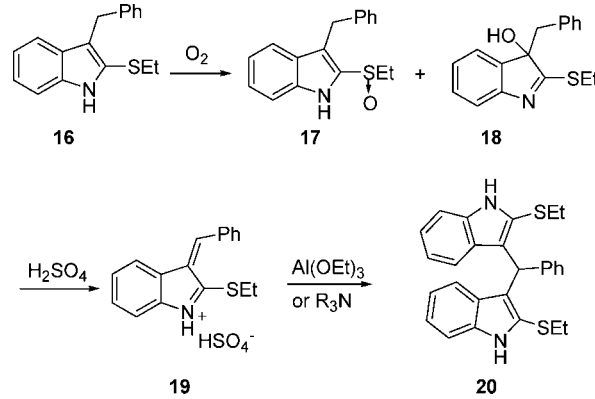


It is noteworthy to mention that isolated BIM **13** from 6-chloroindole **11** with the corresponding aldehyde in the presence of TFA/Et_3SiH is reduced to product **14** in 60% yield (Scheme 5).[116] Under the same reaction conditions (with TFA/Et_3SiH),[117] indolyl derivative **14** is directly formed via a one-pot Friedel−Crafts reaction of aldehydes and indoles.[116] This observation suggests the formation of the intermediate **12** (Scheme 5). Rizzo et al. have also used a variation of this method for the alkylation of indoles by changing TFA to trichloroacetic acid (TCA).[118]

DDQ dehydration of indoles to **15** followed by treatment with different indoles gives asymmetric 3,3′-BIMs. This serves as further evidence for the suggested azafulven formation (Scheme 6).[119]

Indole **16** due to autoxidation with oxygen yields sulfoxide **17** and hydroxyindolenin **18**. Dehydration of **18** to **19** is accomplished with concentrated sulfuric acid at room temperature. Treatment of **19** with aluminum ethoxide or tertiary amines gives **20** (Scheme 7).[120] The salt **19** was isolated and

Scheme 7. Oxidative Azafulven 19 Formation and Conversion to BIM 20



also indirectly identified via reduction of **19** with $NaBH_4$ to yield the parent indole **16**.

In 1900, Walther and Clemen used formaldehyde and different indoles for the synthesis of simple BIMs.[121] Through the reaction of indoles and acetaldehyde corresponding BIMs have been produced in 60% yield in an ethanol−water solution.[122] Kamal and Qureshi carried out an extensive synthesis of 3,3′-BIMs with various aliphatic, aromatic, substituted aromatic, and heterocyclic groups in aqueous medium and at various pH conditions.[123] Many advances in the strategy of BIM synthesis were published as result of the variation of the catalyst. Other factors that prompted new research include the price of catalysts, finding milder reaction conditions, reusability of catalysts, yield of products, reaction rates, simplicity of the workup, green chemistry, etc. Typical protic acids[124–126] used to catalyze the reaction include silica sulfuric acid (SSA),[127] oxalic acid,[128,129] zeolites HY[130,131] and ZnY,[132] amberlyst,[133–135] *p*-(ω-sulfonic-perfluoroalkylated)polystyrene (FPS) resins,[136] H_2SO_4,[101,137,138] HBr,[139,140] HCl,[68,141–146] HCOOH,[147] CH_3COOH,[148–150] *p*-TsOH,[151] NH_2SO_3H,[152–155] HBF_4-SiO_2,[156] $NaHSO_4-SiO_2$,[133] $KHSO_4$,[157] $NaHSO_3$,[66] $2KHSO_5\cdot KHSO_4\cdot K_2SO_4$ (oxone),[158] $H_4SiMo_{12}O_{40}$,[159] $H_3PMo_{12}O_{40}$,[160] $H_3PW_{12}O_{40}$,[56,161] $H_{3+n}PMo_{12-n}V_nO_{40}$,[162] $H_3PW_{12}O_{40}-ZrO_2$,[163] $H_3PW_{12}O_{40}-SiO_2$, $-TiO_2$, or $-Al_2O_3$,[164] $H_6P_2W_{18}O_{62}$,[165] $H_{14}[NaP_5W_{30}O_{110}]$)/$SiO_2$/sonoirradiation,[166] $(NH_4)_2HPO_4$,[167] $H_3PO_4-SiO_2$,[168] PEG-supported sulfonic acid[169] and AcOH−MW,[170] Lewis acids, such as lanthanide resins,[171] zeolite (ZnY),[172] bentonitic clay/IR,[173] montmorillonite clay K-10,[174,175] cerium ammonium nitrate (CAN),[176] nanoceria (CeO_2) supported on vinyl pyridine polymer,[177] $CeCl_3\cdot 7H_2O$/glycerin,[178] $M(HSO_4)_x$,[179,180] $KAl(SO_4)_2\cdot 12H_2O$,[181,182] $AlPW_{12}O_{40}$,[183a] $AlMe_3$,[183b] $ZrOCl_2$,[184] $ZrOCl_2\cdot 8H_2O-SiO_2$,[185] Cp_2ZrCl_2,[186] $ZrCl_4$,[187] InF_3,[188] $In(OTf)_3$−MW,[189] $InCl_3$, $In(OTf)_3$,[190] $SnCl_2\cdot 2H_2O$,[191] $MoO_2(acac)_2$,[192] $LiClO_4$,[193,194] $MgSO_4$,[195] $BiOClO_4\cdot xH_2O$, $Bi(OTf)_3$,[196] $Bi(NO_3)_3\cdot 5H_2O$,[197–199] $NbCl_5$,[200] $SbCl_3$,[201,202]

Table 1. Effect of Different Lewis Acids on the Reaction of Indole with Benzaldehyde

catalyst (10 mol %)	time (h)	isolated yield (%)	catalyst (10 mol %)	time (h)	isolated yield (%)
none	10	0	$Ga(ClO_4)_3$	8	90
$BiCl_3$	5	87	$Pr(ClO_4)_3$	8	92
$Bi(NO_3)_5 \cdot 5H_2O$	4	86	$LaCl_3$	15	8
$CuCl_2$	2	93	LiBr	24	18
$InCl_3$	6	91	LiCl	24	16
$InBr_3$	2	92	$SrCl_2 \cdot 6H_2O$	15	0
$In(OTf)_3$	0.8	78	$Ti(SO_4)_2$	4	92
$CoCl_2 \cdot 6H2O$	24	37	$AlCl_3$	15	89
$ZnCl_2$	24	11	$ZrO(NO_3)_2 \cdot 2H_2O$	20	73
$ZnBr_2$	24	20	$ZrSO_4 \cdot 4H_2O$	8	84
$FeCl_3$	24	73	$ZrOCl_2 \cdot 8H_2O$	20	62
$Cu(OTf)_2$	5	90	$Zr(NO_3)_5 \cdot 5H_2O$	5	88
$NiCl_2 \cdot 6H_2O$	24	*a*	$ZrCl_4$	0.5	96
$Mg(ClO_4)_2$	24	46			

[a] Trace.

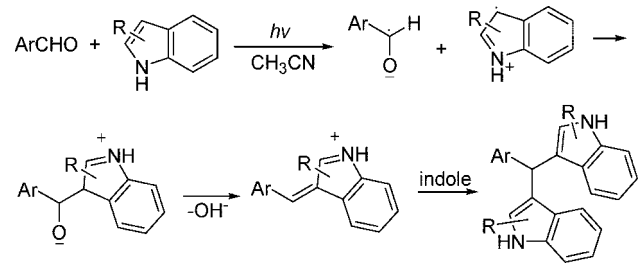
$Sb_2(SO_4)_3$,[203a] SmI_2,[203b] $CuSO_4$,[204] $Cu(NO_3)_3 \cdot 3H_2O$,[205] $CuCl_2 \cdot 2Py$,[206] $CuBr_2$,[207–210] [Cu(3,4-tmtppa)]$(MeSO_4)_4$,[211] $Cu_{1.5}PMo_{12}O_{40}$,[212] Fe(III)(salen)Cl,[213] ZnO,[214] $ZnCl_2$,[215] clay K-10/$ZnCl_2$,[216] TiO_2,[217] $TiCl_4$,[218] VCl_3,[219] Pd^{2+},[220] Ru^{3+},[221] $Eu(NTf_2)_3$,[222] $La(NO_3)_3 \cdot 6H_2O$,[223] $Dy(OTf)_3$,[224] $Al(OTf)_3$,[57] $Yb(OTf)_3 \cdot 3H_2O$,[225] and Ti(O-*i*-Pr)$_4$/(*S*)-BINOL[226] have been reported. Other promoters, such as PO_4^{3-}/ZrO_2,[227] SO_4^{2-}/ZrO_2,[228] $S_2O_8^{2-}/ZrO_2$,[229] SO_4^{2-}/TiO_2,[230] polyindolyl $HFeCl_4$,[231–233] Meldrum's acid/H_2O/sonoirradiation,[234] SBA-15-supported poly(4-styrenesulfonyl(perfluorobutylsulfonyl)-imide),[235] carbohydrate-based tolylsulfonyl hydrazines,[236] triphenyl phosphonium perchlorate (TPP),[237] tetrakis[3,5-bis(trifluoromethyl)phenyl]borate,[238] hexamethylenetetraamine-bromine (HMTAB),[239,240] tetrabutylammonium tribromide (TBATB),[241] silica chloride,[242,243] NH_4Cl,[244] I_2,[245,246] $P_2O_5-SiO_2$,[247] PCl_5,[248] $NaBF_4$,[249] Ph_3CCl,[250] and *N*-bromosuccinimide (NBS),[251] have also been reported. As seen from these reports, numerous catalysts can efficiently promote the reaction of aldehydes or ketones and indoles to form 3,3′-BIMs in good to high yield and in reasonable times.

In addition, Wang and his group have studied the efficacy of various Lewis acids for the conversion of benzaldehyde and indole to bis(indol-3-yl)phenylmethane. Among these catalysts, zirconium tetrachloride was found to be superior in terms of yield and reaction rate. Their results are tabulated in Table 1.[252]

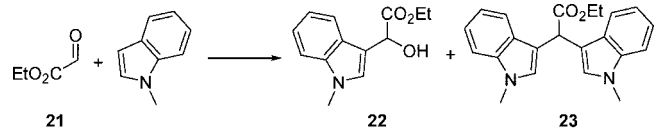
Green and ecofriendly conditions as the main drive have also lead to reasonable development of this field of chemistry. Ionic liquids,[65,253–261] as green solvents with low vapor pressure, have been largely used in the synthesis of BIMs. In some cases, the reactions were promoted by $In(OTf)_3$,[262] $FeCl_3 \cdot 6H_2O$,[263,264] or $LaCl_3 \cdot 7H_2O$.[265] However, Yadav et al. reported that the use of ionic liquids such as 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) or 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) for BIM synthesis allows for the efficient recovery and reuse of the ionic liquid.[266]

Recently, a new type of water-usable catalyst, namely, "Lewis acid−surfactant-combined catalyst (LASC)", has shown high efficiencies in various organic transformations.[267] It was reported that LASCs, such as metal dodecyl sulfates,[268] can be efficiently employed in the synthesis of 3,3′-BIMs.[269–272] Dodecylbenzenesulfonic acid (DBSA)[273] and dodecylsulfonic acid (DSA)[274,275] also promote BIM formation from aldehydes and indoles in water.

Scheme 8. Photoirradiation in BIM Synthesis



Scheme 9. The Effect of pH on Product Distributions



21 22 23

conditions	pH	Yield (%)	Yield (%)
NaH_2PO_4–Na_2HPO_4	7.5	87	0
NaH_2PO_4–Na_2HPO_4	7.1	82	2
NaH_2PO_4–Na_2HPO_4	6.4	63	16
NaH_2PO_4–Na_2HPO_4	6	34	54
1M $NaHSO_4$	5.5	0	74

Wang et al. prepared some new rare earth perfluorooctanoates and successfully utilized them as catalysts in the formation of BIMs from indoles and carbonyl compounds in ethanol with reported yields between 60% and 96%.[276] Lanthanide triflates (trifluoromethanesulfonate)[277] and sulfonic acid functionalized crystal-like mesoporous benzene−silica[278] as water-usable catalysts are also effective for this transformation.

It is worth mentioning that catalyst-free formation of BIMs in glycerol at 90 °C has been reported.[279]

In addition to microwave (MW)[280a] and sonochemistry,[166,234] the photochemical reaction of arylaldehydes and indoles was also investigated as shown in Scheme 8.[281] Matsuura and others have also widely reported the reaction of indoles and carbonyl compounds under solid-state photochemical and thermal conditions that generally produced BIMs.[282–287]

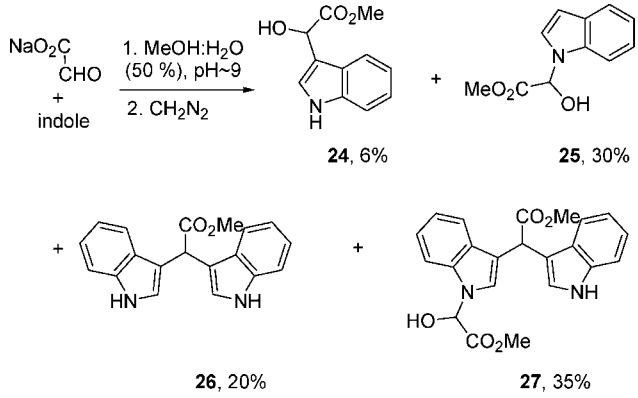
The pH-dependent Friedel−Crafts reaction of ethyl glyoxylate **21** and 1-methylindole in aqueous conditions was shown to produce products **22** and **23** in different yields (Scheme 9).[288] An increase in acidity led to optimum yield of **23**. These results reveal that by increase of the concentration of H^+, the OH group of **22** is protonated, leading to facile production of H_2O upon attack of the second indole.

The reaction of sodium glyoxylate with indole under basic aqueous conditions followed by treatment with diazomethane leads to the formation of 3-indolylglycolate **24**, the 1-substituted derivative **25**, and 3,3′-BIMs **26** and **27** in 6−35% yields (Scheme 10).[289]

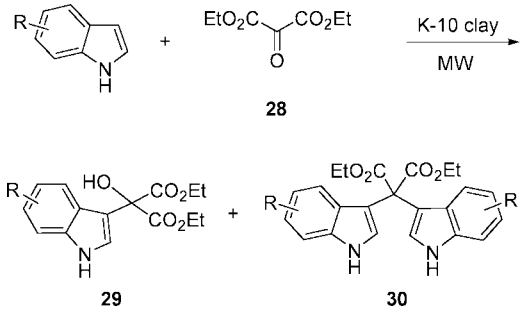
Although the formation of BIMs from indoles and ketones is not as easy as with that with aldehydes, the use of microwave irradiation[280b] was reported for indoles and diethyl ketomalonate **28** in the presence of montmorillonite K-10 clay to give the corresponding indol-3′-ylcarbinols (**29**; 20−45%) and the respective BIMs[290] (**30**; 5−35%) (Scheme 11).

Srihari et al. demonstrated that phosphomolybdic acid (PMA) together with silica (SiO_2) works efficiently for the one-pot three-component coupling reaction of aldehydes, excess *N*-methylaniline, and indole to yield 3-substituted indole derivatives **31** (Scheme 12).[291] However, when *n*-octanal and *n*-butyraldehyde were used, the corresponding bisindolyl alkanes have been obtained in 60% yield.[291]

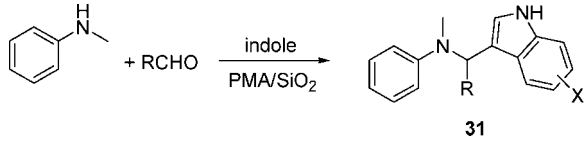
Scheme 10. Reaction of Sodium Glyoxylate with Indole



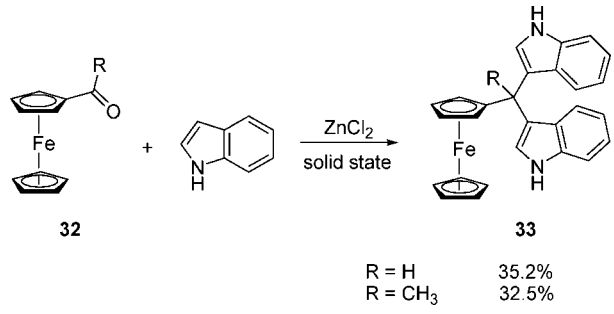
Scheme 11. MW Irradiation in BIM Formation



Scheme 12. One-Pot Manich-Type Reaction



Scheme 13. Ferrocene BIMs 33

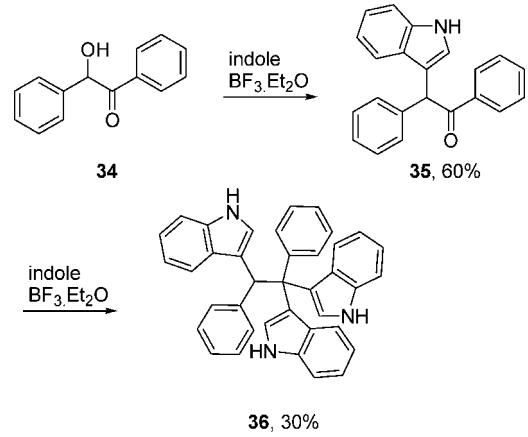


The synthesis of special BIMs is a challenging target for chemists in this field. In the presence of $ZnCl_2$, the indole moiety undergoes a solid state condensation reaction with ferrocene ketones and aldehydes **32**.[292] For instance, when R = H, **33** was obtained in 35.2% yield and for R = CH_3 in 33.5% yield (Scheme 13). The report demonstrates that the solid-state reaction exhibits higher selectivities and yields than the corresponding reaction in solution.[293]

Although the synthesis of BIM **36** had been reported by Russian chemists many years ago, it was also isolated in 30% yield from **35** and indole in the presence of boron trifluoride etherate (Scheme 14).[294] The intermediate **35** has been obtained in a Friedel−Crafts reaction of benzoin **34** and indole.[294]

Indole-3-carboxaldehydes undergo indium-mediated ternary reactions with allyl bromide and indoles, as well as other stabilized C-nucleophiles (e.g., electron-rich heteroarenes, electron-rich aromatics, and stabilized enols) and N-nucleophiles (e.g., azoles) to generate a library of variously functionalized indolylbutenes in good to excellent yields. Some BIMs are formed in this process (Figure 5).[295,296]

Scheme 14. Synthesis of 1,1,1,2,2-Pentaarylethane 36



Sato et al. performed an interesting study on the C-glycosylation of indoles. For example under optimized reaction conditions, glucose reacts with indole to produce **37** in 70% yield in the presence of 10 mol % $Sc(OTf)_3$. The latter is a well-known water-usable catalyst, and the reaction takes about 11 h at 80 °C (Scheme 15).[297,298] Yadav et al.[299] have also shown that montmorillonite KSF clay is a suitable catalyst for the synthesis of BIM sugar derivatives.[300]

Furanose and allose 3,3′-BIM derivatives **38** and **39** were produced from the reaction of indole and the corresponding aldehydes in the presence of $HClO_4$−SiO_2 in good yield (Figure 6).[301]

Combination of the Friedel−Crafts and Michael addition reactions gave a new model of BIMs. 1,1,3-Tri(1*H*-indol-3-yl) alkanes were isolated from the reaction of indoles and α,β-enals or enones (Table 2). The suitability of some catalysts, such as $AuCl_3$,[302,303] $Zr(OTf)_4$,[304] I_2, cerium ammonium nitrate (CAN)[305] and $SbCl_3$,[202] was investigated for this reaction. It was discovered that the well-established Lewis acid $AlCl_3$ is more effective than most of the other modern Lewis acids. For example, the reaction of crotonaldehyde **40** and indole in CH_3CN with $AlCl_3$ is completed in 8 min to produce **41** in 96% yield. Although the reaction proceeds in similar yields with some of the other catalysts, the required reaction times are considerably longer. In some cases, the catalysts were not effective at all. The results are tabulated in Table 2 for comparison.[306]

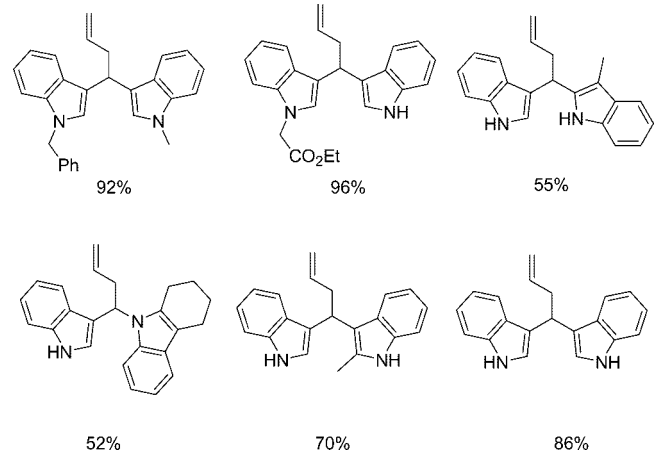
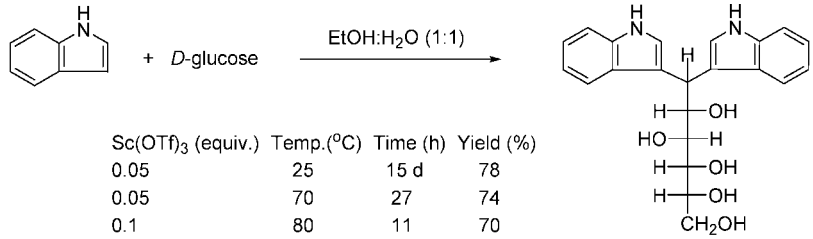


Figure 5. Allylic indolyl compounds.

Scheme 15. $Sc(OTf)_3$-Promoted Sugar-Containing BIMs



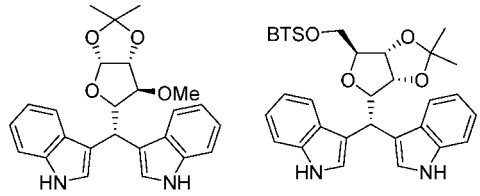
$Sc(OTf)_3$ (equiv.)	Temp.(°C)	Time (h)	Yield (%)
0.05	25	15 d	78
0.05	70	27	74
0.1	80	11	70

37

In the course of indolyl hydroquinone synthesis from the addition of indoles to quinone derivatives, it was found that *N*-methylindole can add two times to Lawsone methyl ether **42** in the presence of *para*-toluene sulfonic acid (PTSA) to give BIM **43** in 21% yield. However, *gem*-diindolyl **43** under azeotropic reflux conditions in toluene in the presence of PTSA was transformed to derivative **44** in 86% yield (Scheme 16).[307] Synthesis of similar BIMs **43** has also been reported via condensation of 2-hydroxynaphthoquinone and 1-methylindole in protic media.[308]

Gong and Kato[309,310] investigated the reaction of arenes and trifluoroacetaldehyde hemiaminals **45** catalyzed by BF_3 and ZnI_2 and found, for instance, that in the presence of BF_3, indole and **45** (when R = Me) gave compounds **46**, **47**, and **48**[311] in 63.0%, 4.4%, and 32.6% yield, respectively (Scheme 17).

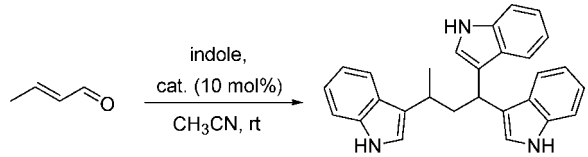
Another example of BIMs bearing a fluorine tag has been reported from the treatment of hexafluoroacetone with indole.[312] Also when 2-(4′-fluorophenyl)indole or 5-fluoro-2-(4′-fluorophenyl)indole **49** are treated with different aromatic aldehydes via reflux in acetic acid, substituted BIMs



38, 82% **39**, 85%

Figure 6. Sugar-containing BIMs.

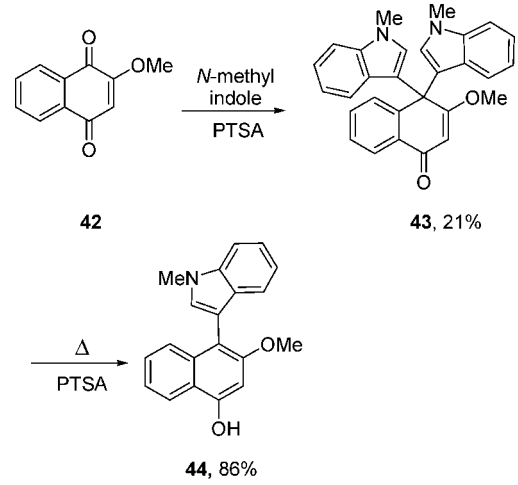
Table 2. Condensation of Indole and Crotonaldehyde 40 in the Presence of Various Catalysts



40 **41**

catalyst	time	isolated yields (%)	catalyst	time	isolated yields (%)
$AlCl_3$	**8 min**	**96**	SSA	12.5 h	97
$AuCl_3$[302]	12 h	70	$Al(HSO_4)_3$	4.5 h	89
I_2	24 h	95	$NaHSO_4 \cdot H_2O$	24 h	88
CAN	3.5 h	90	$Zr(HSO_4)_4$	7 h	70
$FeCl_3 \cdot 6H_2O$	24 h	94	$ZrOCl_2 \cdot 8H_2O$	1.5 h	97
$Fe(NO_3)_3 \cdot 9H_2O$	4 h	98	$ZrCl_4$	4.5 h	94
$Cr(NO_3)_3$	4 h	98	$Zr(NO_3)_4$	6.5 h	89
$Bi(NO_3)_3$	24 h	0	LiOTf	24 h	0
$Ni(NO_3)_3$	24 h	0	$ZnCl_2$	24 h	0
$Cd(NO_3)_3$	24 h	0	$CoCl_2 \cdot 6H_2O$	24 h	0

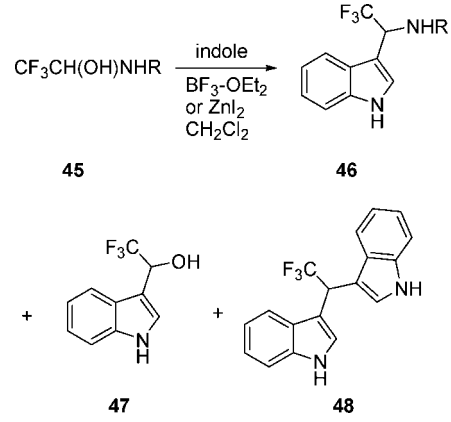
Scheme 16. Arylindole 44 via BIM 43



42 **43**, 21%

44, 86%

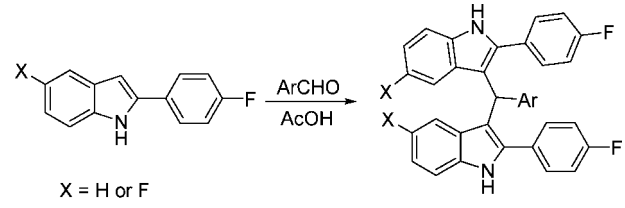
Scheme 17. Indoles with a Fluorine Tag



45 **46**

47 **48**

Scheme 18. Synthesis of Fluoro-Containing BIMs 50

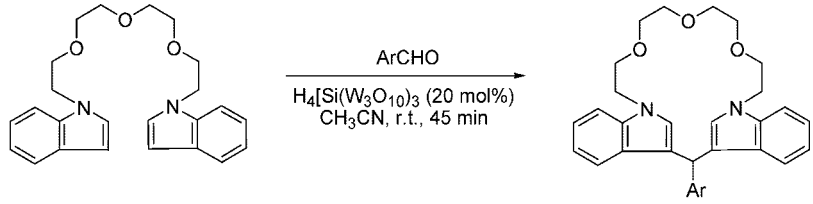


49 **50**

50 are obtained in reasonable yield (Scheme 18).[313] Other reactions such as the formylation or acetylation of **49** have been used for similar conversions. The produced fluoro derivatives are potential psychopharmacological agents.

BIMs served as a profitable subject for the synthesis of polycyclic compounds. In this regard, $H_4[Si(W_3O_{10})_3]$ efficiently catalyzed the condensation of indole **51** and anis-

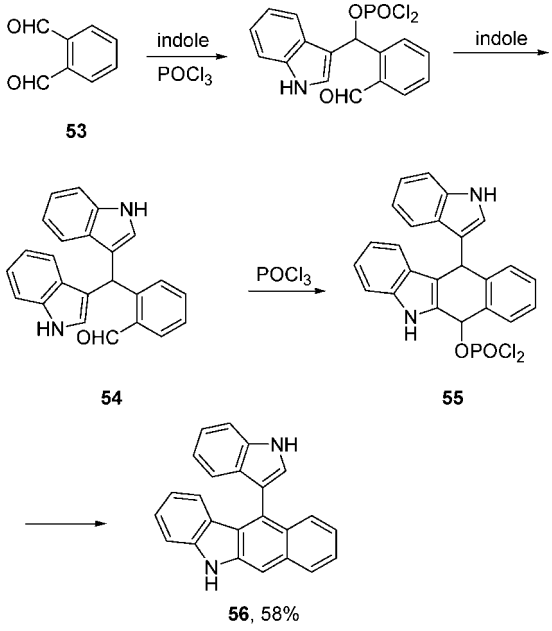
Scheme 19. Formation of Aza-crown Ethers 52



51 52

Ar: *p*-$OMeC_6H_4$, 43%
Ar: *p*-$NMe_2C_6H_4$, 52%

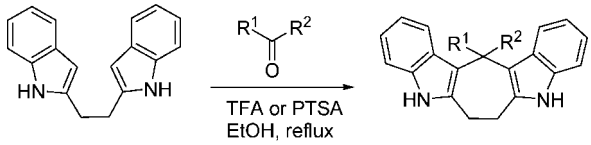
Scheme 20. Indole and *o*-Phthaldialdehyde in the Presence of $POCl_3$



53 54 55

56, 58%

Scheme 21. Condensation of 57 with Aldehydes and Ketones



57 58

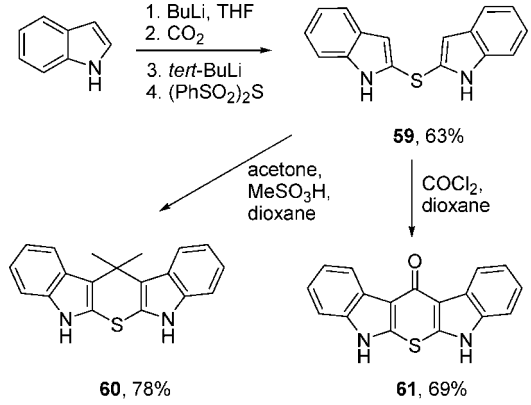
aldehyde or substituted benzaldehydes to form the indolyl aza-crown ethers **52** in moderate yields (Scheme 19).[314]

In a noncyclic synthetic attempt, indole was reacted with *o*-phthaldialdehyde **53** (in a 2:1 ratio) in anhydrous chloroform and in the presence of phosphoryl chloride (Scheme 20). The reaction was completed after 1 h and afforded the 11-(3-indolyl)benzo[*b*]carbazole **56** in 58% yield. The suggested mechanism involves formation of a 3,3′-BIM **54**, which undergoes cyclization to **55** and aromatization to give the benzocarbazole **56**.[315] Also the reactions of phthalaldehydic acid with indoles have been disclosed.[316,317]

Bergman and his group synthesized pentacyclic compounds **58** from 1,2-bis(1*H*-indol-2-yl)ethane **57** and *p*-nitrobenzaldehyde, 3,4-methylenedioxybenzaldehyde, or acetone under acidic conditions (TFA or *p*-TsOH) in good yields (65−86%, Scheme 21).[318] When triethyl orthoformate was used instead of aldehydes or ketones, the subsequent reduction of the intermediate with $NaBH_4$ leads to the formation of **58** (when $R^1 = R^2 = H$) in 88% yield.[318]

They also prepared bisindolyl sulfide **59** through lithiation of indole followed by treatment with bis(phenylsulfonyl)

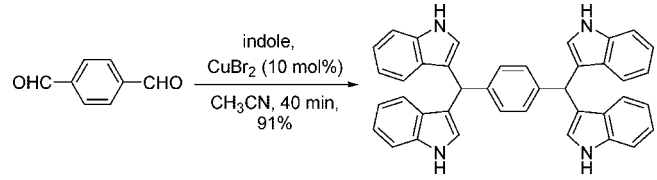
Scheme 22. Bisindolyl Sulfide 59 with Carbonyl Compounds



59, 63%

60, 78% 61, 69%

Scheme 23. Dialdehyde 62 in BIM Formation



62 63

sulfide. The sulfide **59** gives the alternative BIM **60** upon treatment with acetone under acidic conditions, whereas the reaction of **59** with phosgene affords the keto derivative **61** in reasonable yields (Scheme 22).[319]

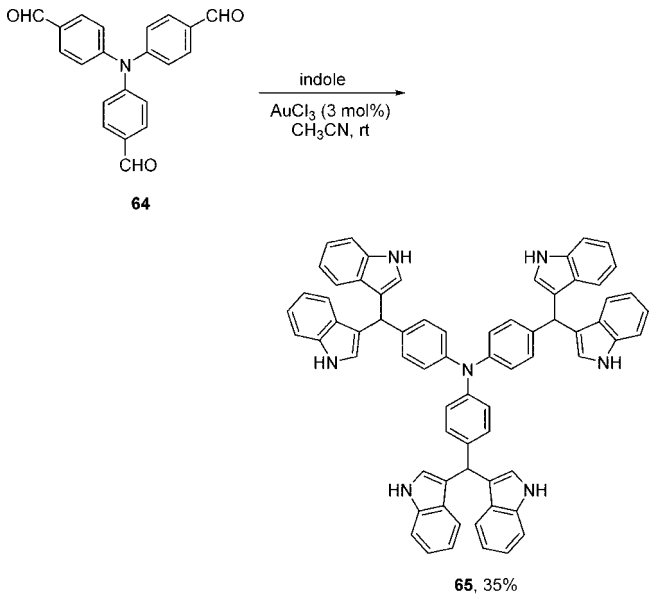
A method from the literature for the preparation of a supramolecular complex containing BIMs, namely, 3,3′,3″,3‴-tetraindolyl(terephthalyl)dimethane, **63**, was reported. The reaction of terephthalaldehyde **62** and indole in the presence of $CuBr_2$ gave **63** in 91% yield (Scheme 23).[320]

Nair and his group reported the synthesis of trimeric BIMs **65** from the reaction of tris[(4-formyl)phenyl]amine, **64**, and indole, catalyzed by $AuCl_3$, in 35% yield (Scheme 24).[321] This method is also sufficient for the condensation of other aldehydes and activated arenes such as 1,3,5-trimethoxybenzene, substituted indoles, 2-methyl thiophene, and 2-methyl furane.[321]

Other indolyl compounds, such as **66**,[322] **67**, **68**, and **69**,[323] have been reported from indole and their corresponding aldehydes (Figure 7).

In this area Kim and co-workers have prepared the bis(indolyl)calix[4]crown-6 **70** (Figure 8). Successful application of **70** in dual colorimetric sensing for both alkaline earth cations and F^- in CH_3CN has also been examined. Cations form a complex with the crown ether, while anions interact with the indole moieties. It is interesting to note that complexation of Ca^{2+} is enhanced in the presence of F^-. Compound **70** can also operate as three independent combinational NOR logic gates toward metal cations and

Scheme 24. Trialdehyde 64 in BIM Formation



anions.[324] Jimenes et al. have also synthesized thiophene derivatives **71** and investigated their optical and electronic properties (Figure 8).[325]

Ovsyannikova et al. reported the synthesis of a new polymer containing BIMs, **73**, from the reaction of 5,5′-bis(2-ethyl carboxylatoindolyl) ether **72** and benzaldehyde promoted by a Brönsted acid (Scheme 25).[326] This polymer is suggested to exhibit potential interesting biological activity.

Other forms of polymers bearing BIMs, **77**, were synthesized by Xu et al. via bisindolylation of 4-(*N*,*N*-diphenylamino) benzaldehyde **74**. This reaction leads to **75**, which is then converted to 4-[bis(1-carbodithioic acid benzyl ester-indol-3-yl)methyl]phenyl]diphenylamine **76** as shown in Scheme 26. Compound **76** is used as a reversible addition−fragmentation chain transfer (RAFT) agent to mediate the polymerization of styrene to yield the polymer **77** (Scheme 26).[327]

The synthesis of numerous naturally occurring BIMs has also been developed. Streptindole **80** was isolated from natural products[328] and displays various interesting pharmacological activities.[329–331] It has been synthesized in three steps as outlined in Scheme 27. In the first step, indole reacts with ethyl glyoxylate catalyzed by $CeCl_3 \cdot 7H_2O-NaI-SiO_2$ to give ethyl bis-1*H*-indol-3-yl-acetate **78**. The latter was reduced to the corresponding alcohol **79** by means of lithium aluminum hydride. Finally, the alcohol **79** was O-acetylated in the presence of $Mg(ClO_4)_2$ to afford streptindole **80** (Scheme 27).[332]

It is known that 2-methyl-3-formylpyridine **81** reacts with 2-ethylindole and yields BIM **82**, which under thermolytic and low-pressure conditions decomposes to form 2-ethylindole and olivacine **83** as proposed in Scheme 28.[333]

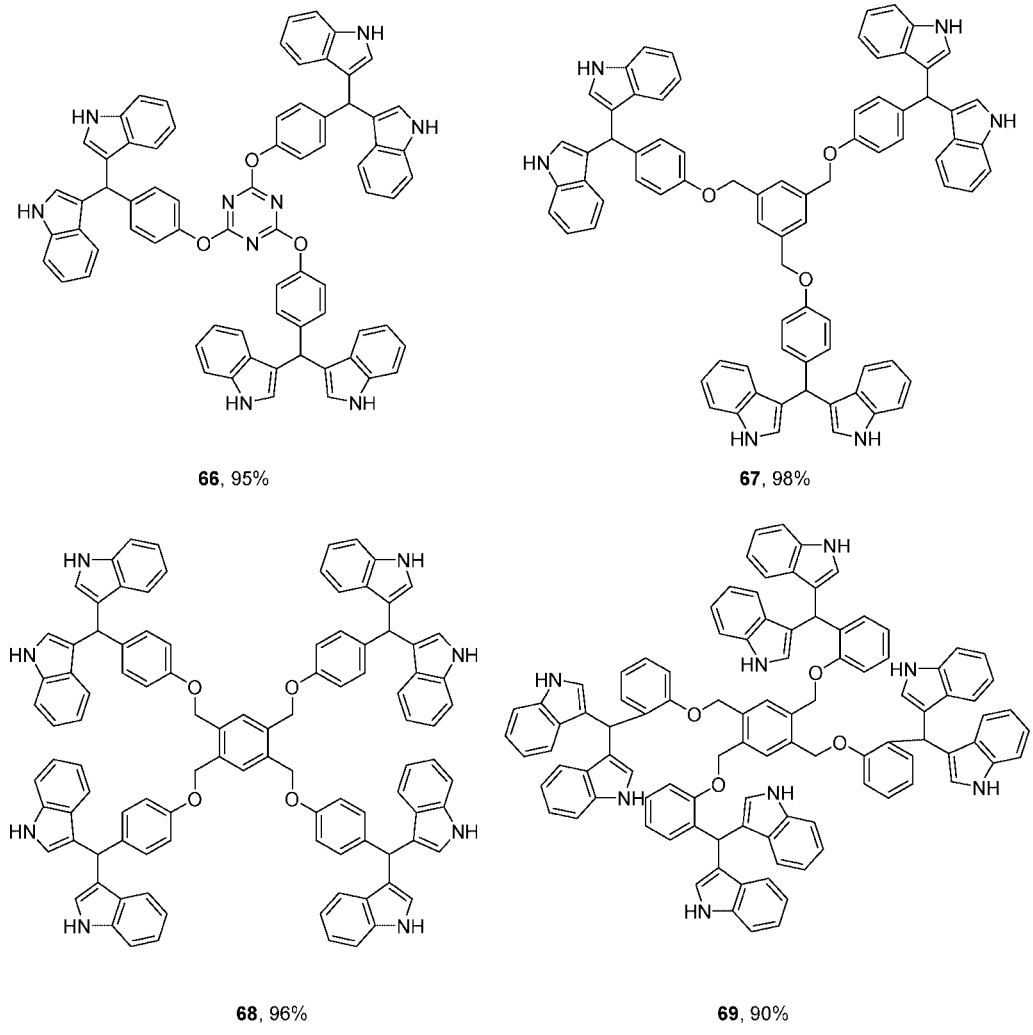
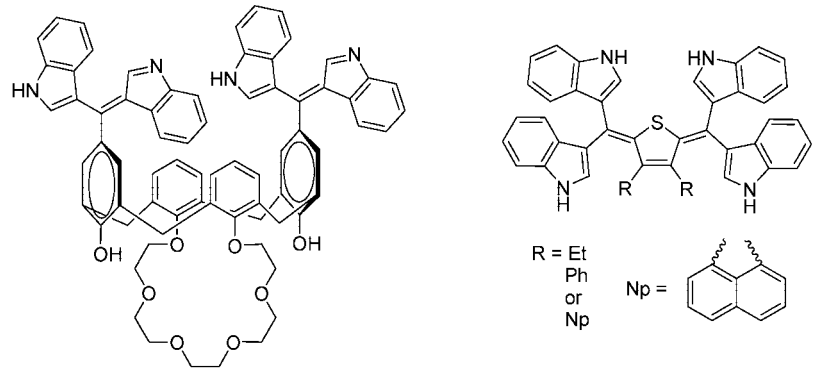


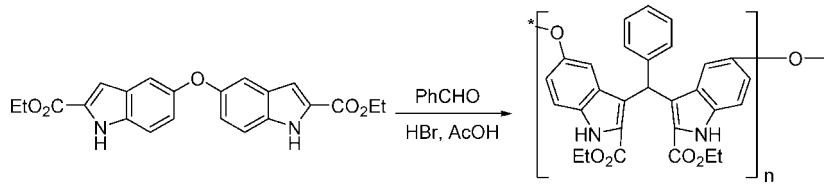
Figure 7. Polyindolyl compounds.



70 71

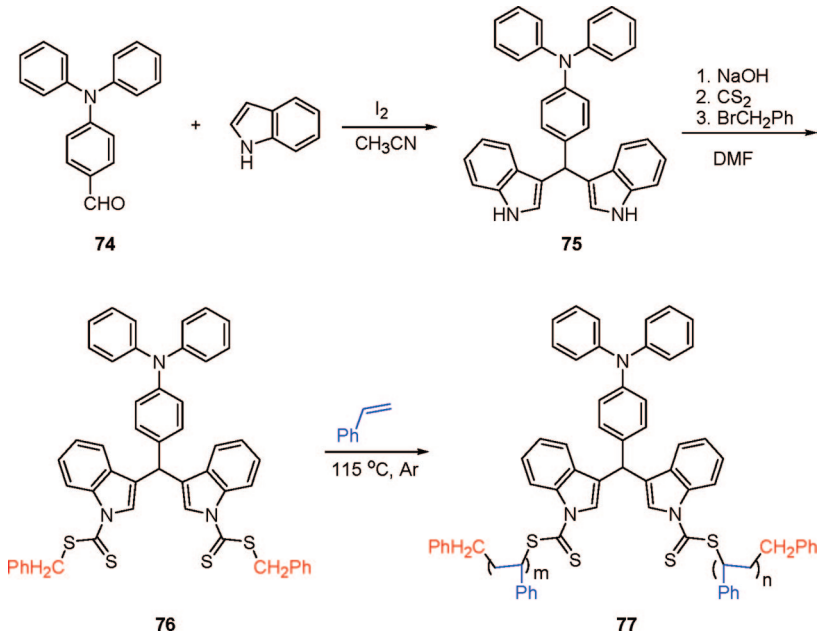
Figure 8. Structure of bis(indolyl)calix[4]crown-6 **70** and thiophene derivatives **71**.

Scheme 25. Polymer-Based BIMs 73



72 73

Scheme 26. Polymer-Containing BIM 77

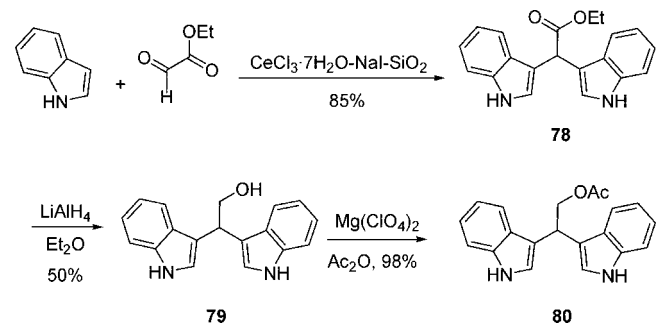


74 75 76 77

Ellipticine **86** is formed via this method in good yields.[334] Woodward et al. reported a procedure in which **86** was isolated in only ca. 2% overall yield as outlined in Scheme 29. Indole is condensed with 3-acetylpyridine in acetic acid in the presence of zinc chloride to yield BIM **84**. The latter is reduced by zinc and acetic anhydride under reflux conditions to form BIM **85**. Pyrolysis of **85** at 200 °C *in vacuo* gives a distillate from which ellipticine **86** was separated (Scheme 29).[335]

BIM **89**, which was isolated from natural sources, was obtained from the condensation of isatin **87** and 2 equiv of indole in the presence of 10 mol % **88** in 72% yield (Scheme 30).[336] The synthesis of **89** was first reported by Seidel in 1950.[337] This reaction is also efficiently promoted by other

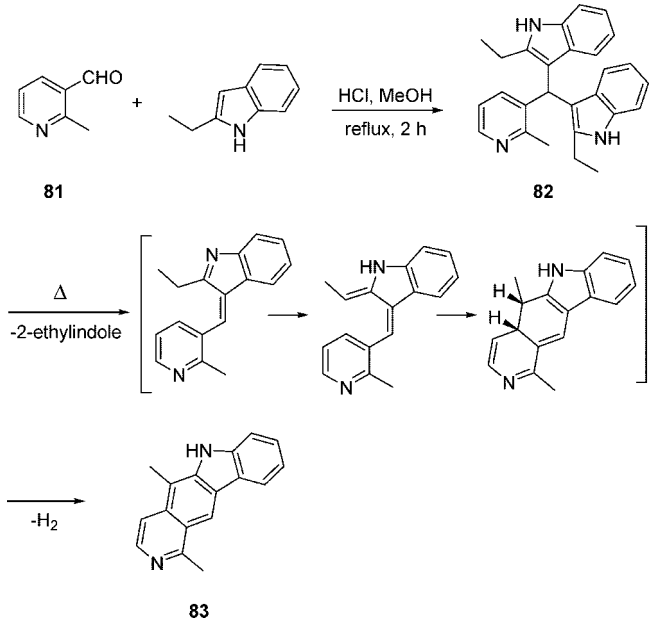
Scheme 27. Streptindole 80 Synthesis



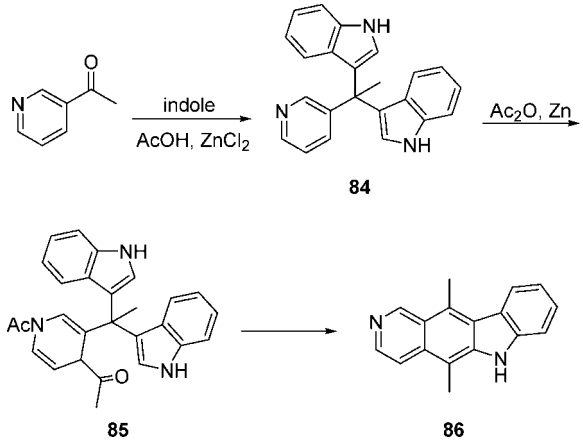
78 79 80

catalysts such as $Bi(OTf)_3$,[338] I_2,[339] SSA,[340] CAN,[341] $KAl(SO_4)_2 \cdot 12H_2O$,[342] and montmorillonite K-10 clay.[343] Very

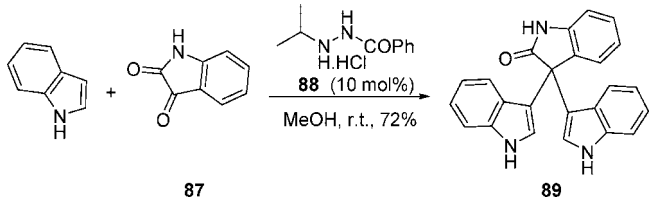
Scheme 28. Olivacine 83 via BIM 82



Scheme 29. Synthesis of Ellipticine 86



Scheme 30. Synthesis of Natural Product 89

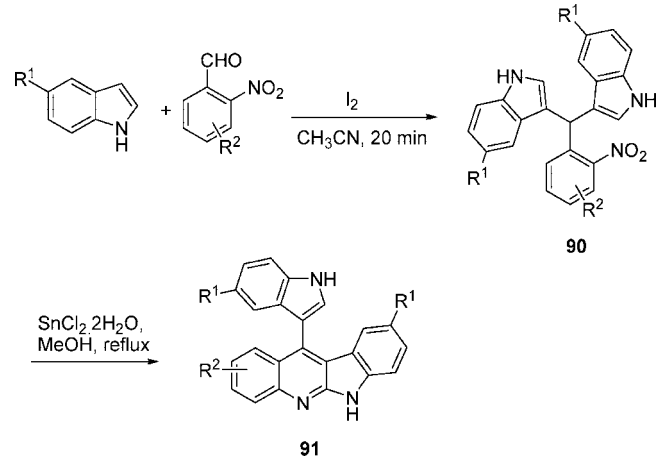


recently, a variation of this reaction was reported where **89** is isolated under reflux conditions in EtOH/H_2O and in the absence of catalyst.[344]

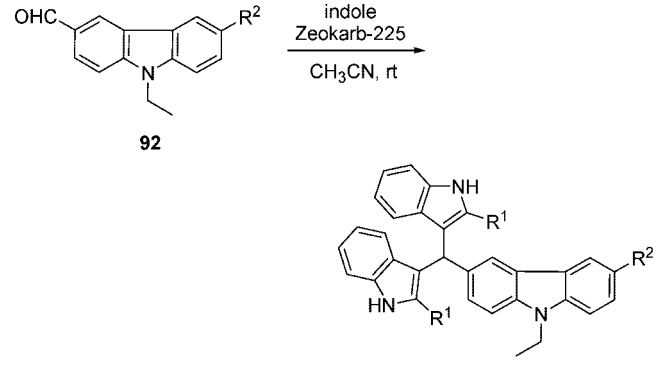
In an attempt to reduce the nitro group of **90** and combine that with the Pictet−Spengler reaction, it was found that alkaloid cryptotackieine derivatives **91** were generated from the intramolecular cyclization of 2-substituted nitroarenes **90** via C−N bond formation using $SnCl_2 \cdot 2H_2O$ (Scheme 31).[345]

The variance in biological activities of different heterocyclic compounds is well-known. Naturally occurring molecules bearing two or more different heterocyclic moieties have shown promising bioactivity, and this encouraged synthetic chemists to combine a heterocyclic system with indole rings. This approach would allow the development of a new class of biologically active molecules and useful synthetic building blocks in organic and medicinal chemistry.

Scheme 31. Cryptotackieine Derivatives from BIMs



Scheme 32. The Reaction of Indoles and Formylcarbazoles 92



$R^1 = R^2 = H$ 60% yield after 6 h
$R^1 = H$, $R^2 = CH_3$ 73% yield after 7.5 h
$R^1 = CH_3$, $R^2 = H$ 82% yield after 8 h

With this idea in mind, chemists started to select various conditions for the proposed combination of other heterocycles with indoles. An example is the formation of bisindolylcarbazolylmethanes **93** in high yields from the appropriate indoles and carbazoles **92** (Scheme 32). This reaction is efficiently catalyzed by Zeokarb-225, a cation exchange resin.[346]

Preparation of di(bisindolylmethyl)carbazoles **94** and di(bisindolylmethyl)pyrroles **95** is a novel example where heterocyclic materials were obtained in good yield. Substituted indoles react with the corresponding carbazole and pyrroledicarboxaldehydes in the presence of $PPh_3 \cdot CF_3SO_3H$ as catalyst (Figure 9). The colorimetric and fluorometric detection of DNA utilizing **94** has been explored.[347]

The efficient synthesis of pyrazolyl derivatives **97** was developed using an Amberlyst 15 catalyzed condensation of

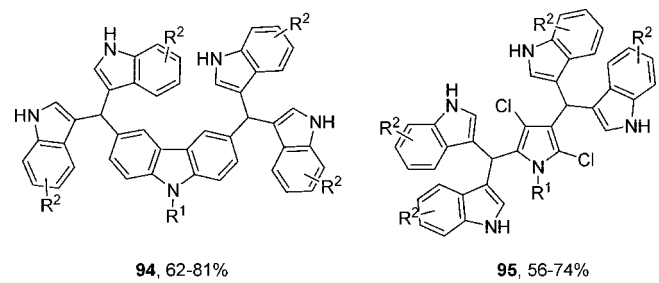
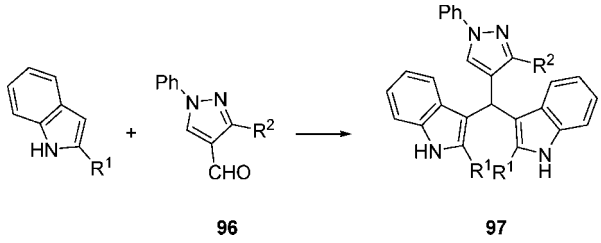
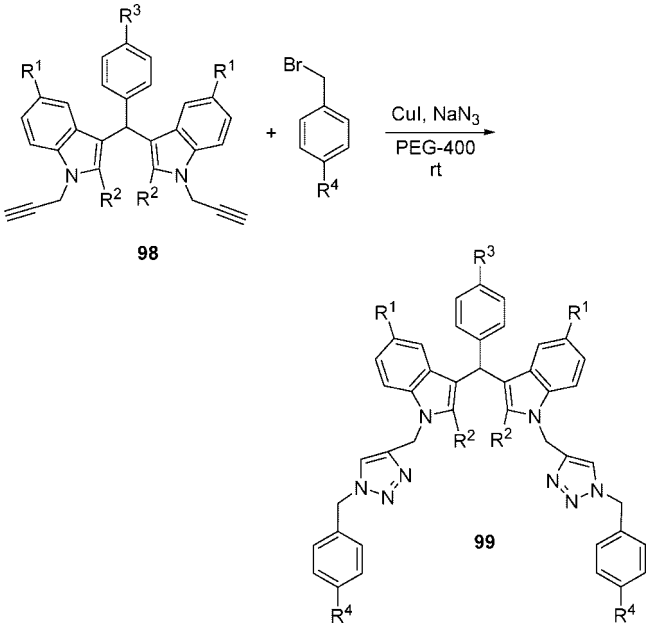


Figure 9. Structure of carbazol and pyrrolyl BIMs.

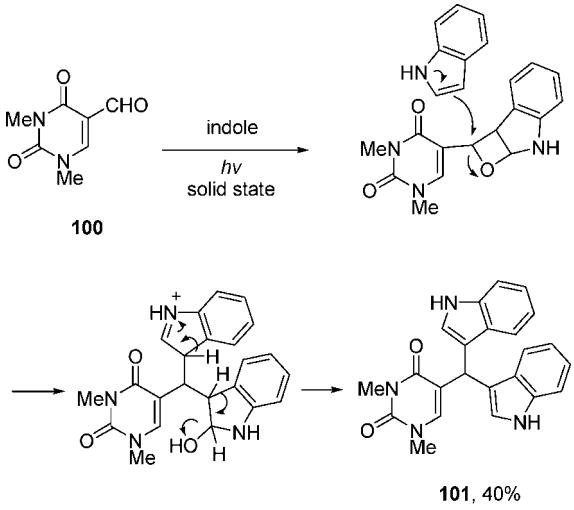
Scheme 33. BIMs 97 Bearing a Pyrazole Unit



Scheme 34. Triazole BIM Derivatives



Scheme 35. *hv*-Promoted BIM Bearing Uracil, 101, Preparation



1,3-diaryl-4-formyl pyrazoles **96** with indoles in 77−96% yields (Scheme 33).[348] H_2PtCl_6 is used as a catalyst in this reaction.[349]

Perumal and his group have prepared 1,4-disubstituted 1,2,3-bis-triazole BIMs **99**. Products **99** were obtained from a variety of *N*-propargyl BIMs **98** and benzyl bromides with sodium azide using CuI as the catalyst in the presence of PEG-400. These BIMs have also been screened for their biological activity (Scheme 34).[350]

Meng et al. recorded a multistep photoirradiation of 5-formyl-1,3-dimethyluracil **100** and indole with a 300 W high-pressure mercury lamp for 4 h at room temperature in the solid state to produce BIM **101** according to the following proposed mechanistic pathway (Scheme 35).[351] When the reaction is performed in a solution of acetonitrile without UV irradiation for 15 h, it results in complete deformylation of **100**.

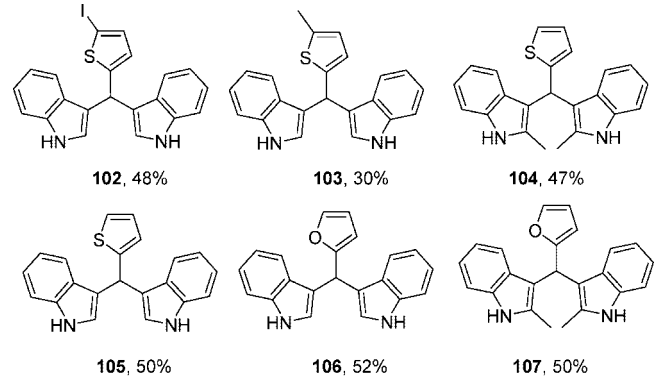


Figure 10. Thienyl and furyl BIM derivatives.

D'Auria used a photochemical technique in solution phase to prepare thienyl and furyl derivatives **102**−**107** from the corresponding thienyl and furyl aldehydes and indoles in moderate yields (Figure 10).[281] It is noteworthy to mention that he used a 500 W high-pressure mercury lamp and large excess of indoles in the reaction.

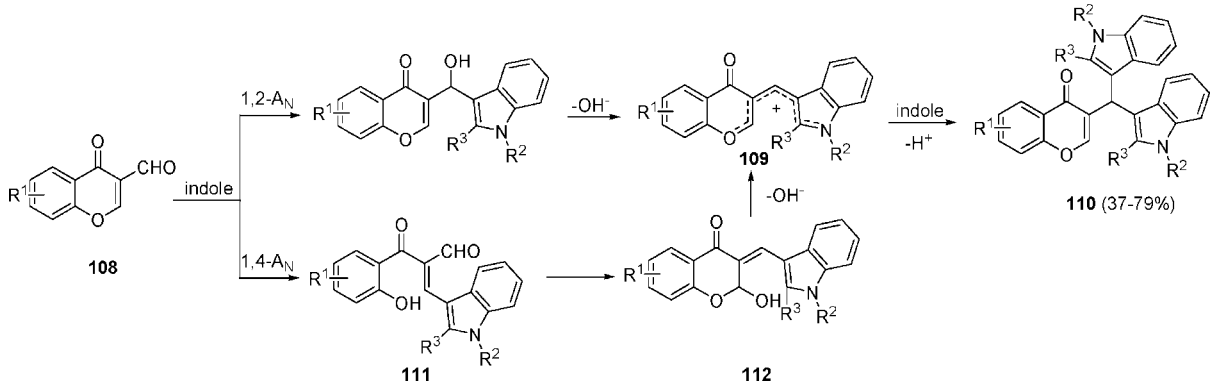
Chromones are more widely distributed in Nature and exhibit low toxicity along with a wide spectrum of useful properties. The reaction of 3-formylchromones **108** and indoles under thermal conditions without solvent and catalyst produced a new class of biologically interesting (chromon-3-yl)bis(indol-3-yl)methanes **110** and *E*-2-hydroxy-3-(indol-3-ylmethylene)chroman-4-ones **112** (Scheme 36).[352,353] The reaction turned out to be very sensitive depending on the nature of the substituent at C-6 of **108**. The proposed mechanism involves two possible phathways, namely, 1,4-A_N and 1,2-A_N, as outlined in Scheme 36. The first is the general pathway, 1,2-A_N, with addition of indole to the formyl group of **108** followed by elimination of hydroxyl and formation of the highly delocalized cation intermediate **109**. In the second pathway, indole initially attacks C-2 of the chromone ring with concomitant opening of the pyrone ring and subsequent intramolecular cyclization of the intermediate **111** at the CHO group to form the chromanone **112**. This intermediate loses a hydroxyl group to form the same cation **109**. In both pathways, the addition of indole to the intermediate **109** leads to **110**. The presence of an electron-withdrawing substituent on the benzene ring of the chromones inhibits the bis-addition due to destabilization of intermediate carbocation **109**, which stops the reaction after the first step (compounds **112**).[352]

Freter found that in the cycloalkenylation of indoles with cycloketones in acidic media, 1,2,3-unsubstituted indoles with *N*-methyl-4-piperidone **113** gave **114** and **115** in comparable yields (Scheme 37).[354] However with other indoles the major product is an alkenyl indole.

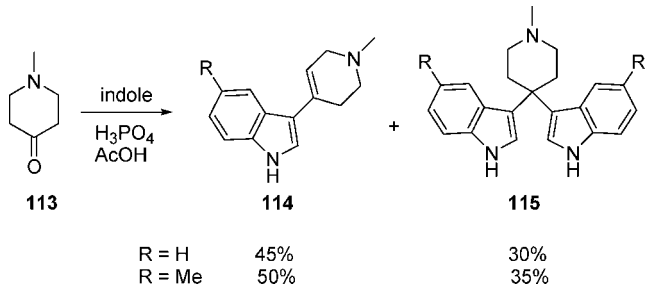
2.1.2. 3,3′-BIMs from Alcohols, Amines, or Related Derivatives and Indoles

Usually nucleophilic substitution of the alcohols, amines, or related compounds with indoles leads to alkylation of indoles. Using this strategy, Bergman synthesized the BIM **118** from biindole **116** and *N*-methylindole-3-carbinol **117**

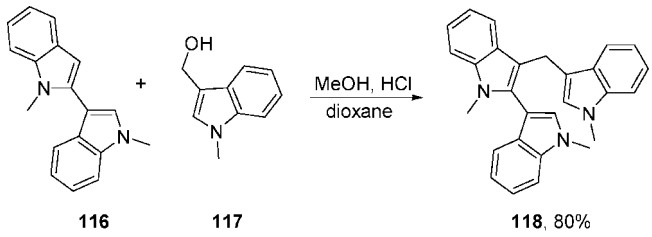
Scheme 36. Chromone Derivatives of BIM



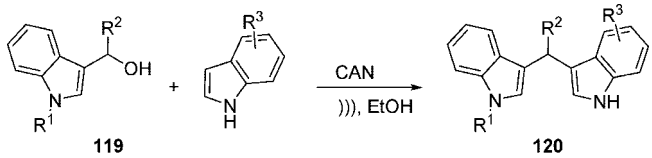
Scheme 37. Cycloalkenylation of Indoles



Scheme 38. Treatment of Biindole 116 with *N*-Methylindole-3-carbinol 117



Scheme 39. CAN-Catalyzed Unsymmetrical BIMs 120



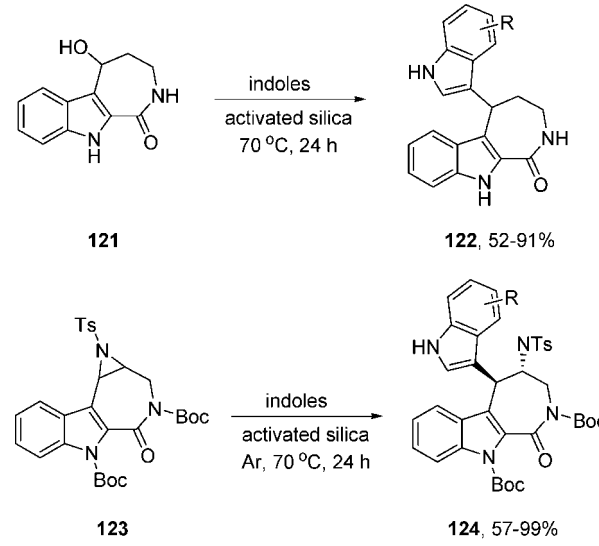
R^1, R^2, R^3 = H, aryl, alkyl, alkoxy

in a solution of methanolic hydrochloric acid in 80% yield (Scheme 38).[355]

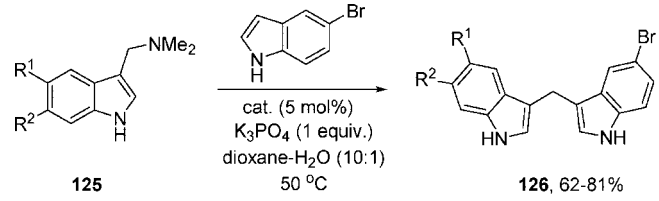
Ji and his group prepared indolyl **120** from the reaction of indoles and (1*H*-indol-3-yl)(alkyl) methanol **119** catalyzed by CAN under ultrasonic treatment in good to excellent yields (Scheme 39).[356] The advantage of this method is the synthesis of unsymmetrical BIMs.

Tse and co-workers have synthesized alcohol **121** and aziridine precursors **123** and used them as key intermediates for the preparation of potentially pharmacologically active bisindoles **122** and **124** by a solvent-free C−C bond-formation reaction with indoles on activated silica in good to excellent yields (Scheme 40).[357,358] Optimization of the reaction conditions revealed that a large excess of indole (10 equiv) at 70 °C overnight (12−20 h) is required for the desired conversion. Further transformations of the indole aziridines **123** with H-, N-, and O-nucleophiles also demonstrated the power of this versatile precursor in diverse oriented synthesis.

Scheme 40. Treatment of Indoles with Alcohol 121 and Aziridine Precursor 123



Scheme 41. Gramines 125 in the Preparation of Nonsymmetrical BIMs 126

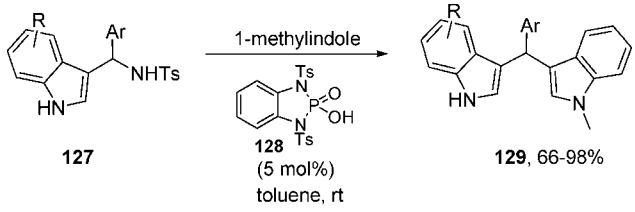


Starting with gramines **125** and 5-bromoindole in the presence of Ir(I) or Rh(I) as catalyst generated a new family of nonsymmetrical BIMs **126** (Scheme 41).[359] Modification of this method to exclude 5-bromoindole and elimination of trimethylamine gave symmetrical BIMs. Since gramines are readily prepared by the Mannich reaction and since the other materials are readily available, this reaction is attractive to synthetic chemists. The reaction is also popular since it can be performed in aqueous media, which stimulates the design of efficient manufacturing processes.

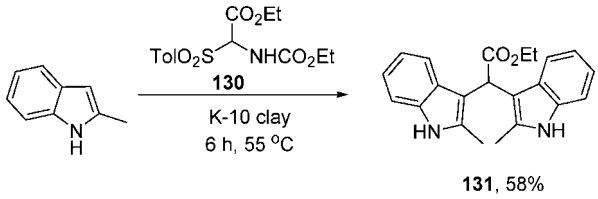
The acid-catalyzed Friedel−Crafts reaction of *N*-methylindole with amine **127** was examined in the presence of the Brønsted acid **128**. Unsymmetrical BIMs **129** are isolated in good to excellent yields in the presence of 5 mol % catalyst in toluene as solvent at room temperature (Scheme 42).[360]

The alkylation of indoles with α-amido sulfone **130** was attempted by Ballini et al. Unexpectedly the BIM **131** was

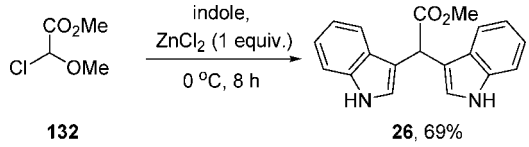
Scheme 42. Brønsted Acid Catalyzed Synthesis of BIMs 129



Scheme 43. Reaction of 2-Methylindole with α-Amido Sulfone 130



Scheme 44. Reaction of Indole with 132



isolated in 58% yield from 2-methylindole and **130** catalyzed by montmorillonite K-10 at 55 °C under solvent-free conditions (Scheme 43).[361]

Similarly the reaction of methyl chloromethoxyacetate **132** and indole in the presence of stoichiometric amounts of $ZnCl_2$ gave **26** in 69% yield (Scheme 44).[362]

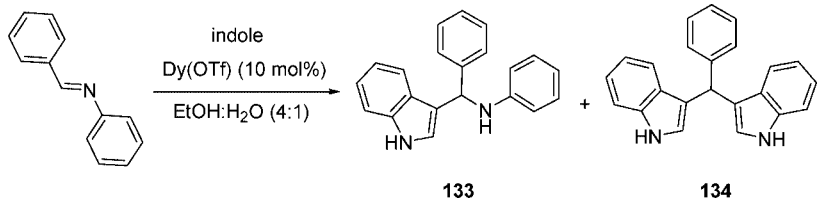
Electrochemical oxidation of alcohols utilizing cyclodextrins followed by reaction with indoles leading to the formation of BIMs is another interesting example of these systems.[363]

2.1.3. 3,3′-BIMs from $R^1R^2C{=}NR^3$ and Indoles

Although imines are less reactive to nucleophiles in relation to aldehydes or ketones, examples are found in the literature where imines react with indoles to generate 3,3′-BIMs. The reaction of a Schiff base with indole is efficiently catalyzed by dysprosium triflate, $Dy(OTf)_3$, in a solution of ethanol and water (4:1) to afford predominately secondary indolyl amines **133**, as well as BIMs **134** as byproduct (Scheme 45).[364] But when an ionic liquid was used as solvent for this transformation, the yield of **133** to **134** is comparable.[365]

In related studies, it was found that imines react with indoles[366,367] to yield BIMs in good yields under different conditions such as MW/Lewis acids,[368] $InCl_3$,[369] montmorillonite clay K-10 and KSF,[370] ion exchange resins,[371] and

Scheme 45. Imines and Indoles in the Presence of $Dy(OTf)_3$



Time (h)	Temp. °C	Yield (%)	Yield (%)
24	rt	57	12
96	0	83	10

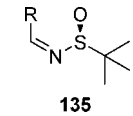
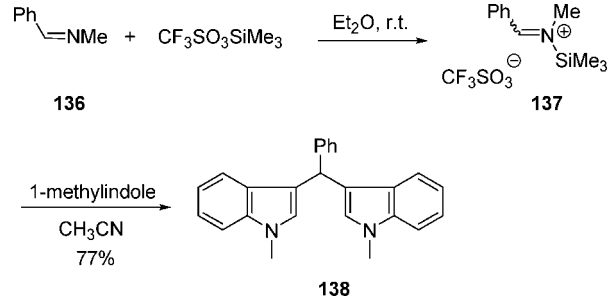


Figure 11. *N-tert*-Butanesulfinyl aldimine **135**.

Scheme 46. Catalyst-Free BIM Formation



p-(ω-sulfonic-perfluoroalkylated)polystyrene (FPS) resins.[136] For example, *N-tert*-butanesulfinyl aldimine **135** (Figure 11) reacts with indoles to give BIMs in good yields.[372]

Iminium salt **137** is a highly reactive intermediate (easily accessible by reacting trimethylsilyl triflate with the imine **136**) that is condensed with *N*-methylindole without any catalyst to afford the bis-indole **138** in 77% yield (Scheme 46).[373] Condensation of indole derivatives with Mannich-type bases has also been reported in the literature.[374–379]

Nitrones as another form of imine have been subjected to the reaction with indoles.[380] Vallee et al. investigated the condensation of nitrone **139** (derived from various aliphatic aldehydes) with indoles in different conditions and found that the distribution of products **140** and **141** varied in different media. In the presence of Me_3SiCl as neutral catalyst, **141** was generated as sole product (Scheme 47).[381]

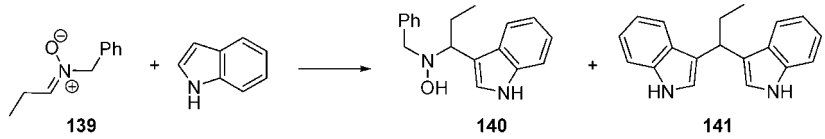
Vallee in a subsequent attempt applied the same methodology described in Scheme 48 for the synthesis of naturally occurring 3,3′-BIMs such as 2,2-bis(6′-bromo-3′-indolyl)-ethylamine **142**.[382] The latter was isolated in 1991 from tunicate *Didemnum candidum*[11] and is also present in *Orina* sp. sponges (Scheme 48).[19]

Benzoylhydrazone **143**, a more stable imine, easily reacts with indole in the presence of the ionic liquid 1-butylpyridinium tetrafluoroborate [bupy][BF_4] and $Dy(OTf)_3$ as catalyst to produce **134** as the sole product after 24 h. In the proposed mechanism, the indole−imine adduct **144** undergoes elimination to generate a benzylidene−indole intermediate **145**, which then reacts with a second indole to yield **134** (Scheme 49).[365]

2.1.4. 3,3′-BIMs from Indoles and Alkynes or Alkenes

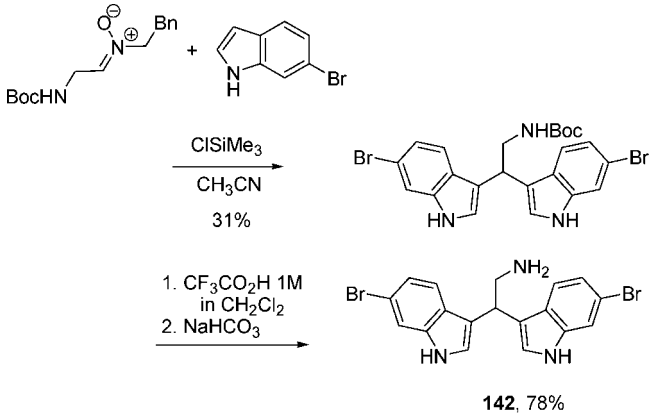
The reaction of indoles with π-bonds, opened a new route for the synthesis of a large variety of indolyl compounds.

Scheme 47. Nitrone 139 and Indoles in Different Conditions

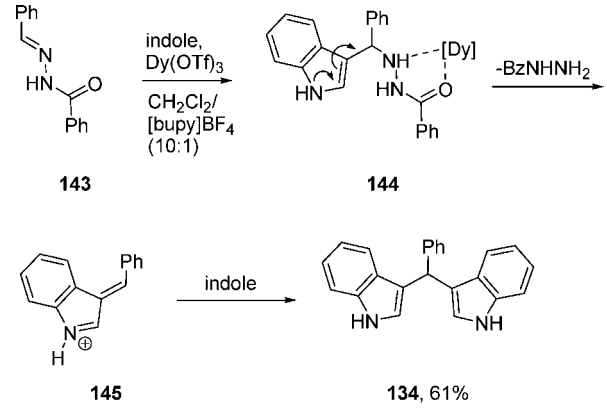


Conditions	Yield (%)	
HCl (2 eq.), MeOH, 0 °C, 2 h	82	0
CF_3CO_2H (3 eq.), MeOH, 0 °C, 1 h	70	0
Pyridinium *para*-toluenesulfonate (1.5 eq.), r.t., 20 h	41	5
Me_3SiCl (1 eq.), Pyridine, Toluene, r.t., 48 h	55	0
Me_3SiCl (1 eq.), CH_2Cl_2, r.t., 2 h, Indole/Nitrone = 2/1	0	85

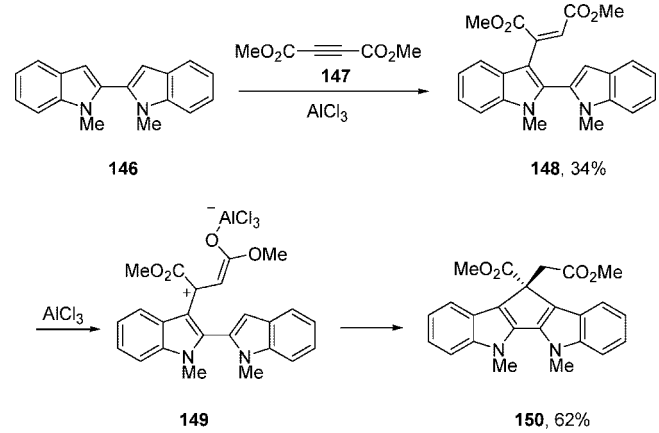
Scheme 48. Utilization of Nitrone and Indole for the Synthesis of the Natural Product 142



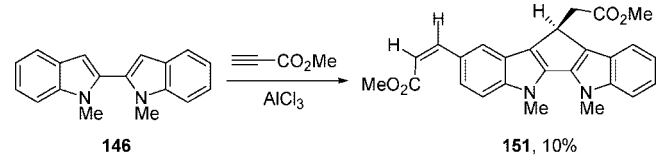
Scheme 49. Hydrazone and Indole in BIM Formation



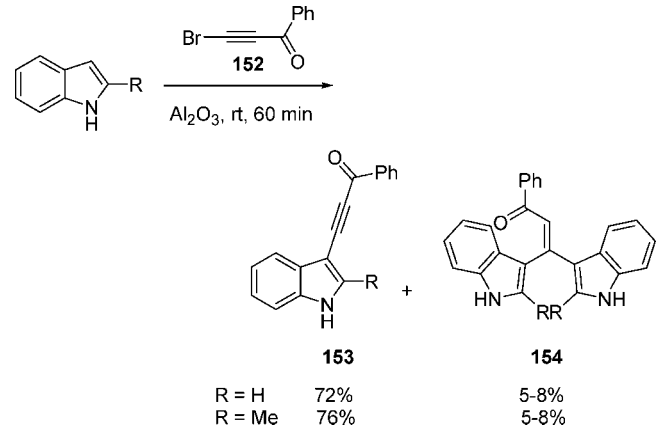
Scheme 50. Acetylene 147 in Reaction with Biindole 146



Scheme 51. $AlCl_3$-Promoted Preparation of 151



Scheme 52. Alkynylation of Indoles



R = H	72%	5-8%
R = Me	76%	5-8%

The reaction of biindolyl **146** with dimethyl acetylenedicarboxylate **147** is catalyzed by $AlCl_3$ to afford the biindolyl **148** in 34% yield. The latter was cyclized with $AlCl_3$ to form compound **150** in 62% yield (Scheme 50).[383] As can be seen from the proposed mechanism, aluminum(III) chloride serves to activate **148**, since the resulting complex **149** is much more prone to cylization (Scheme 50).

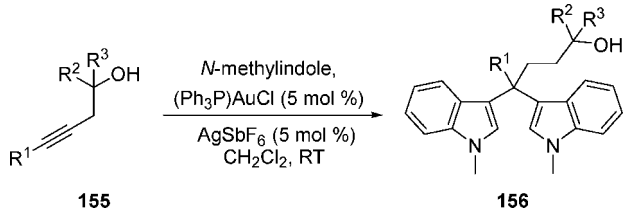
In an analogous way, biindole **146** reacts with methyl propynoate in the presence of $AlCl_3$ to form the cyclopentadiindole **151** in only 10% yield (Scheme 51).[384]

Petrova et al.[385] in a study of the alkynylation of indole and 2-methylindole with 1-benzoyl-2-bromoacetylene **152**, isolated BIMs **154** as byproducts in 5−8% yield; however 3-(2-benzoylethynyl)indoles **153** were isolated as the major products in 72% and 76% yields, respectively, when R = H and Me (Scheme 52).[386]

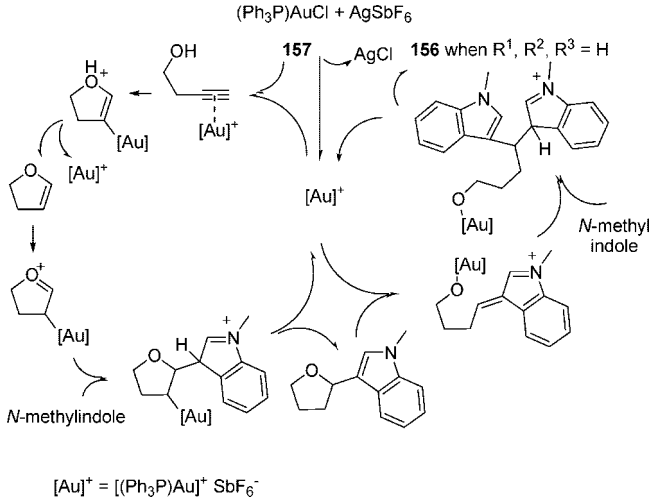
Barluenga and his group explored the reaction of 3-butyn-1-ol derivatives **155** with *N*-methylindole via a catalytic amount of an *in situ* formed cationic gold complex that led to the formation of **156**. When terminal alkynes are used, the double addition of the indole occurs at the terminal carbon of the triple bond. When internal alkynes are used, the double addition occurs at the carbon distal to the free hydroxyl group (Scheme 53).[387]

A catalytic mechanism that explains the formation of products **156** (when R^1, R^2, R^3 = H) from 3-butyn-1-ol **157** and *N*-methylindole is presented in Scheme 54.[387] As shown in Scheme 54, 3-butyn-1-ol is activated by [Au] to form

Scheme 53. Gold-Catalyzed BIM 156 Synthesis



Scheme 54. Mechanism of Gold-Catalyzed Synthesis of BIMs 156



dihydrofuran, but double activation of the starting material leads to the effective attraction of two indole units to yield the final BIMs **156** as products. Other catalysts such as Au(III),[388] Au(I),[389] $GaBr_3$, and $GaCl_3$[390] also facilitate the formation of BIMs from alkynes and indoles.

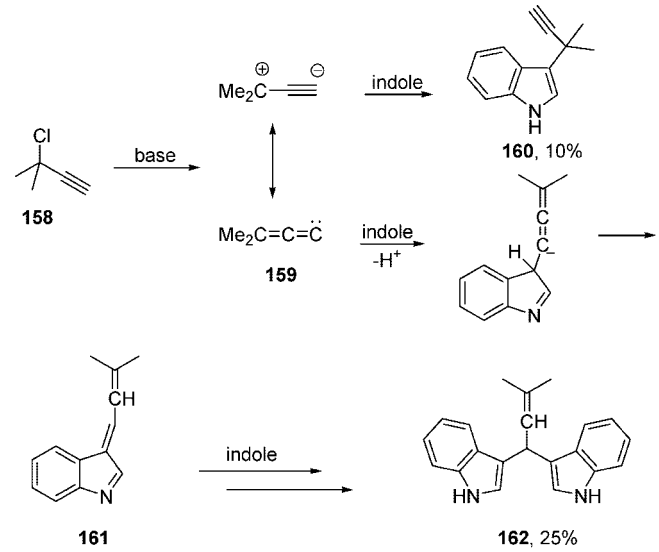
The prenylation of indoles by exposure of indole to an excess of the reactive chloride **158** and potassium *tert*-butoxide in a hexane solution afforded a simpler mixture of reaction products, namely, indoles **160** and **162** in 10% and 26% yields, respectively. The formation of indole **162** implies that the desired β-dehydroprenylation of indole had taken place, but the product had not been stable in the form of prenylindole; the corresponding tautomer **161** had undergone a Michael condensation with indole (Scheme 55).[391] For a similar example, see also Scheme 118.

In a special example, 1,2-allenic ketones **163** are twice attacked with indoles in the same position while the reaction is catalyzed by $Sc(OTf)_3$. If two different indoles were added to **163** in two steps, an unsymmetrical β,β-bisindolyl ketones **165** resulted in 50−78% yield. If 2.5 equiv of indoles are added in one step under the same conditions, symmetrical BIMs are prepared (Scheme 56).[392] Interestingly, the first step of this method is an efficient method for the synthesis of α,β-unsaturated enones **164**.

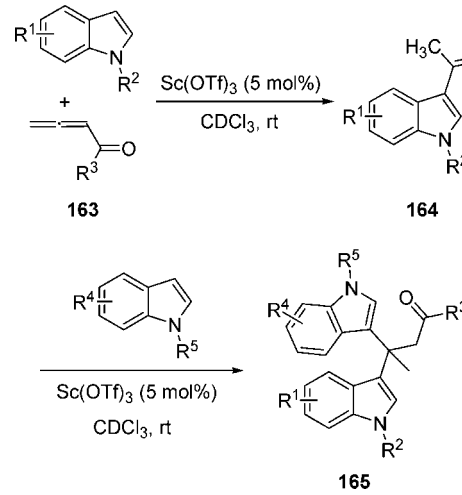
Yadav et al. reported that indole and 5-substituted indoles such as 5-bromo and 5-methoxy derivatives with 3,4-dihydro-2*H*-pyran (DHP) or 2,3-dihydrofuran in the presence of $InCl_3$ afford the corresponding BIMs **166** in 70−80% yields (Scheme 57).[393] A similar reaction was reported for the THP reaction, which is promoted by $PtCl_2$.[394]

Bis(indolyl)nitroethanes **168** are utilized as suitable precursors for the synthesis of some naturally occurring analogues. These bis(indolyl)nitroethanes are obtained via the Michael addition of indoles to 3-(2-nitrovinyl)indole **167** on silica gel under microwave irradiation in high yields

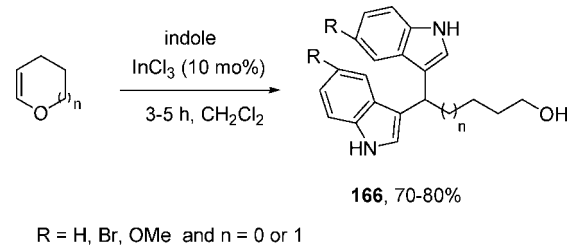
Scheme 55. The Proposed Mechanism for the Synthesis of BIM 162



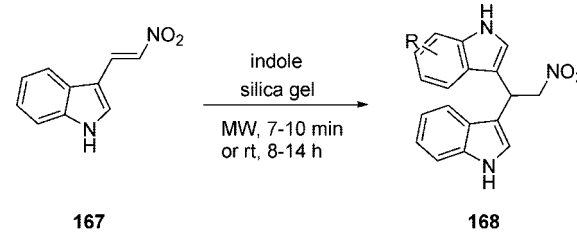
Scheme 56. Allene Employed in the Formation BIMs



Scheme 57. Hydroxyl BIMs 166

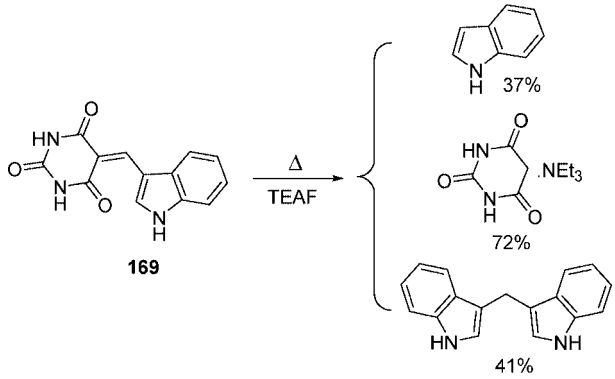


Scheme 58. Nonsymmetrical Bis(indolyl)nitroethanes 168

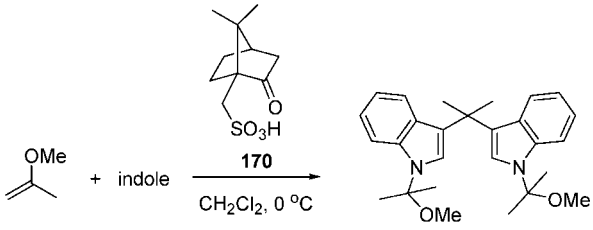


(70−86%).[395] The same products were also obtained in 69−84% yields without microwave irradiation, but the reactions requires 8−14 h for completion (Scheme 58).[395]

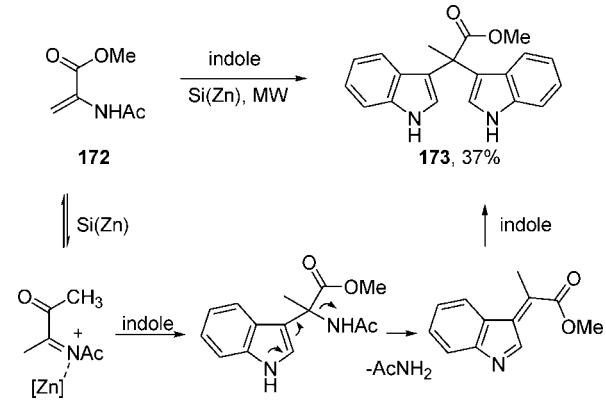
Scheme 59. Reduction of Barbituric Acid Derivatives



Scheme 60. *N,N′*-Bis(1-Methoxy-1-methylethyl) BIM 171



Scheme 61. Mechanism for the Synthesis of 173



If, in this method, 3-substituted indoles were used, 2,3′-BIMs would be obtained.[396]

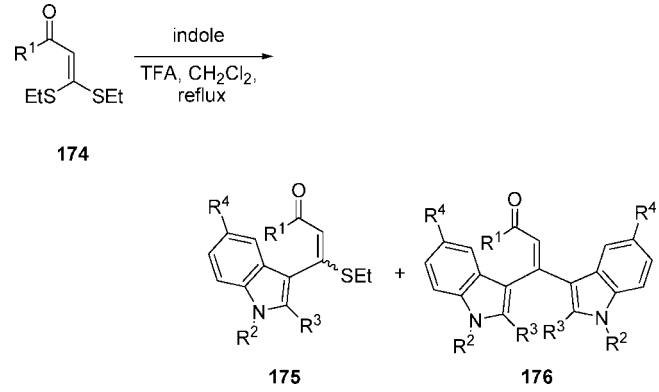
Sekiya et al. examined the reduction ability of formic acid on barbituric acid derivatives. They heated the mixture of 5-(3-indolylmethylene) barbituric acid **169** and TEAF ($5HCO_2H \cdot 2NEt_3$) to afford 37% indole, 72% barbituric acid−triethyl amine, and 41% 3,3′-bisindolyl methane (Scheme 59).[397]

Kobayashi and co-workers found that the use of excess 2-methoxypropene with indole catalyzed by (±)-camphor-10-sulfonic acid **170** affords 2,2-bis[1-(1-methoxy-1-methylethyl)indol-3-yl]propanes **171** (Scheme 60).[398]

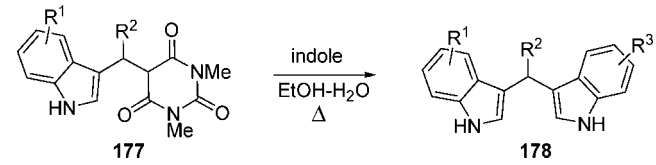
Methyl α-acetamidoacrylate **172** in the reaction with indole under microwave irradiation and with $ZnCl_2-SiO_2$ as catalyst affords BIM **173** in 37% yield via the mechanism outlined in Scheme 61.[399] Tautomerization of the enamine to an imine takes place, followed by attack with indole. An active azafulven is formed, which leads to the synthesis of BIM **173** via amide elimination and excess addition of indole (Scheme 61).

Yu and Yu reported a metal-free direct alkenylation of indoles by using acid-mediated substitution reactions of α-oxo ketene dithioacetals **174** with indoles. This reaction

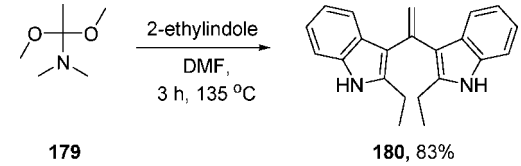
Scheme 62. α-Oxo Ketene Dithioacetals 174 and Indoles



Scheme 63. Catalyst-Free Synthesis of BIMs 178 from 177 and Indoles



Scheme 64. 2-Ethylindole and 179 Afforded 180



selectively affords *β*-indolyl mono- and disubstitituted α,*β*-unsaturated carbonyl compounds. When one equimolar amount of indole relative to **174** is reacted in the presence of TFA, the indolyl **175** is isolated. When two equimolar amounts of indole relative to **174** are used, then the bisindolyl **176** is produced as the major product (Scheme 62).[400]

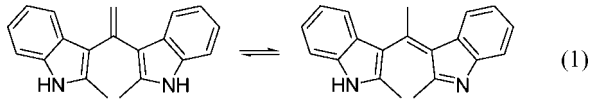
2.1.5. 3,3′-BIMs from Indoles Reacting with Other Functional Groups

More examples of other functional groups that were used in the reaction with indoles for the synthesis of BIMs have been reported. Very recently, it has been reported that unsymmetrical 3,3′-BIMs **178** can be obtained from a three-component reaction of indole, aldehyde, and *N,N′*-dimethylbarbituric acid. The intermediate **177** undergoes an elimination−addition reaction with another indole molecule in the absence of a catalyst (Scheme 63).[401]

Treatment of indole with hexamethylenetetramine (HMTA) in the presence of a catalytic amount (10 mol %) of $InCl_3$ results in the formation of 3,3′-BIM in excellent yields.[402]

Bergman found that 2-ethylindole reacts with *N,N*-dimethylacetamide dimethylacetal **179** to yield BIM **180** in the absence of a catalyst (Scheme 64).[355]

Also 2-methylindole with ethyl acetate and sodium ethoxide,[403] when refluxed in acetyl chloride[404,405] or in acetyl cyanide and ethanolic potassium hydroxide[406,407] gives the BIM **181** (eq 1). The same structure was also reported from the reaction of indole and acetic anhydride in acetic acid.[408]

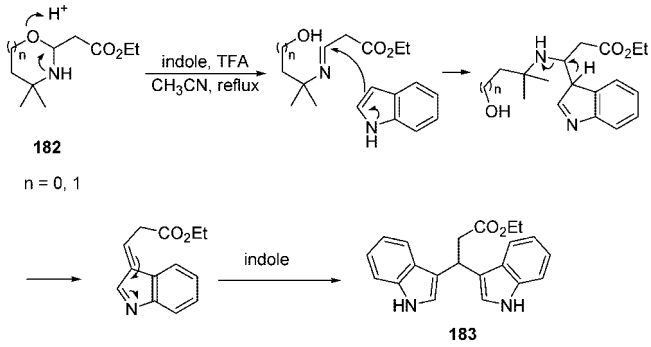


181

Singh and co-workers have utilized oxazolidines and oxazines **182** for the synthesis of the BIM **183** as shown in Scheme 65.[409,410] In this reaction, C2 of **182** is transferred first to one indole via the acid-catalyzed formation of imine from **182**. The intermediate is then attacked by a second indole to yield the BIM **183** in two steps.

A similar carbon transfer from 2-alkyl-4,5-dihydrooxazole **184** allows for the synthesis of yet another class of BIMs. In the proposed mechanism for this transformation, oxazol **184** is activated with acetic anhydride to facilitate the addition of indole followed by ring-opening and formation of the azafulven **185**. Addition of indole to **185** followed by elimination of the alcohol group and subsequent hydrogen transfer yield the intermediate **186**. Acylation of the latter produces the final product **187** (Scheme 66).[411]

Scheme 65. Employment of Oxazolidines and Oxazines 182 in BIM Synthesis

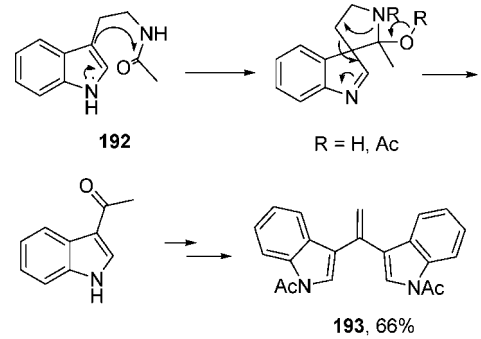


182

n = 0, 1

183

Scheme 68. Synthesis of 193 from Tryptamine and Acetic Anhydride



192

R = H, Ac

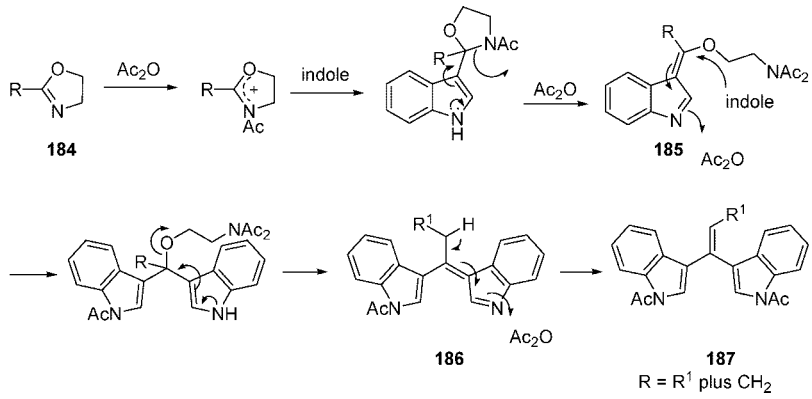
193, 66%

In a different route, a product from indole and S-stabilized carbocation **188** was isolated with either structure **189** or **190** (Scheme 67).[412] The authors were not able to distinguish between the two possible structures. In a subsequent paper, structure **190** was preferred, however without sufficient evidence.[413] Structure **190** was eventually established by hydrolysis of the product to the carbonyl compound **191** (Scheme 67).[355]

Treatment of tryptamine with hot acetic anhydride, acetic acid, and pyridine produces bisindolylethylene **193** as the sole product (Scheme 68).[414] This may be the result of intramolecular cyclization experienced by *N*-acetyltryptamine **192** and expulsion of the ethylamine side chain as shown in Scheme 68.

In an interesting report, indoles with ethers gave a variety of BIMs via iron-catalyzed C−H bond oxidation and C−O bond cleavage.[415] A plausible mechanism of reaction was

Scheme 66. Mechanism for the Synthesis of 187 from Indole and 2-alkyl-4,5-dihyrooxazole 184



184

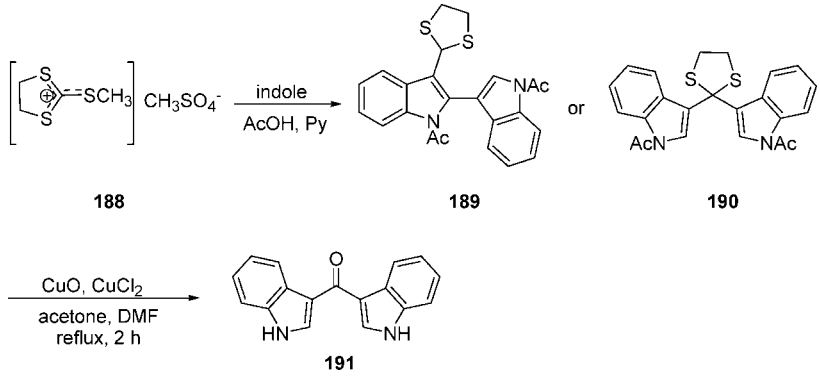
185

186

187

R = R¹ plus CH₂

Scheme 67. Reaction of Indole and Carbocation 188



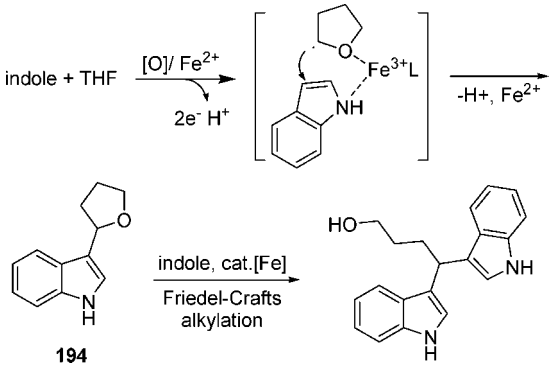
188

189

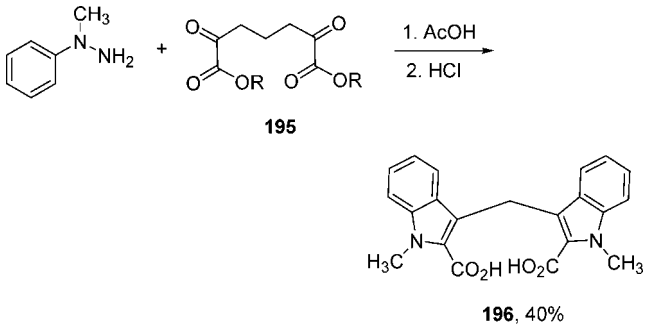
190

191

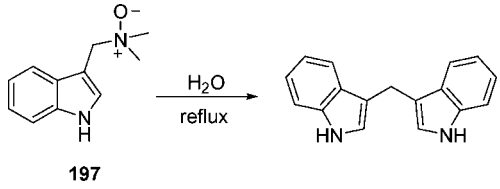
Scheme 69. BIMs from Indoles and Ethers



Scheme 70. Fischer Indole Method Led to the Synthesis of 3,3′-BIMs 196



Scheme 71. Decomposition of 197



proposed and is presented in Scheme 69. H-abstraction from THF gives a radical intermediate that forms a complex with indole and iron(II). Product **194** is isolated upon oxidative coupling of the two organic ligands. The double indolation through a Friedel−Crafts alkylation reaction forms the corresponding BIMs (Scheme 69). It is noteworthy that addition of diferrent indoles to the product **194** leads to the generation of unsymmetrical BIMs.

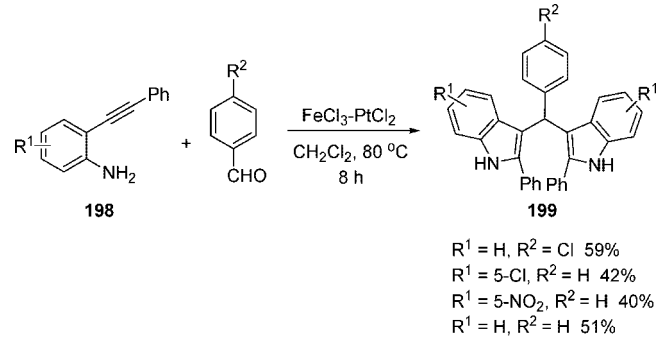
2.1.6. Miscellaneous Methods for the Synthesis of 3,3′-BIMs

There are many other useful methods that were reported for the synthesis of 3,3′-BIMs. Snyder and Eliel employed a Fischer indole synthesis for this purpose, from methylphenyl hydrazine and diketone **195** (Scheme 70).[416]

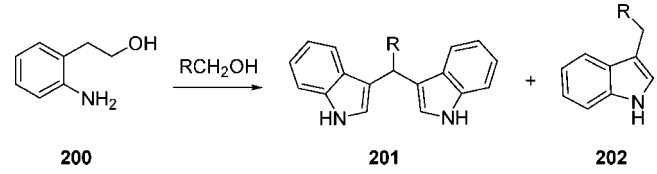
Another modification by Leete involves the use of 3-hydroxymethylindoles, which when heated or refluxed in water produce formaldehyde and the corresponding BIMs without utilizing a catalyst.[417,418] Also when a solution of gramine oxide **197** is heated in water to 100 °C, a polymeric material, bis(1*H*-indol-3-yl) methane, and formaldehyde are produced (Scheme 71).[419] The polymeric material of the reaction was probably formed from 3-hydroxymethylindole, which undergoes self-condensation and elimination of formaldehyde on heating.[420]

Campagne et al. have found that the $FeCl_3-PtCl_2$ couple catalyzes the one-pot formation of **199** through annulation/

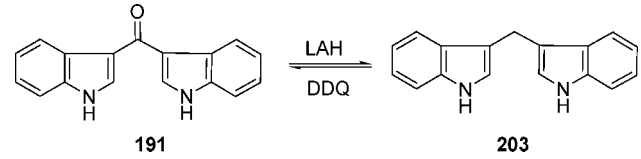
Scheme 72. One-Pot Indolization and BIM Formation



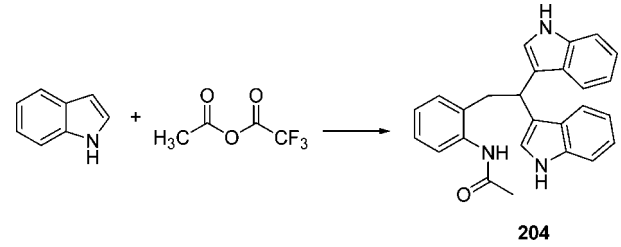
Scheme 73. Conversion of Amino Alcohol 200 to BIM 201 with Ir and Rh Complexes



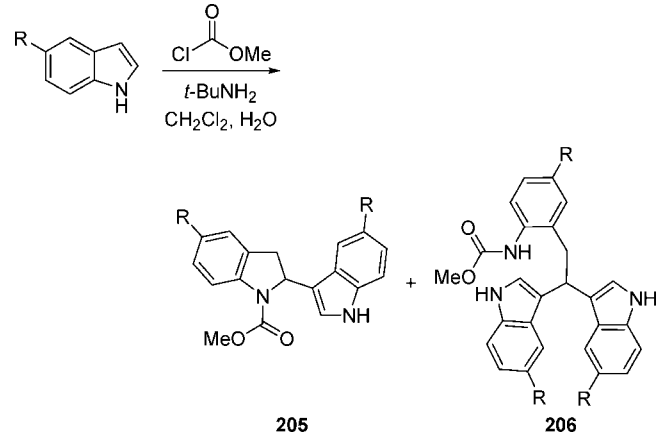
Scheme 74. Conversion of 191 to 203 with LAH and the Reverse Reaction with DDQ



Scheme 75. Formation of 204 from Indole in Acetic-Trifluoroacetic Anhydride



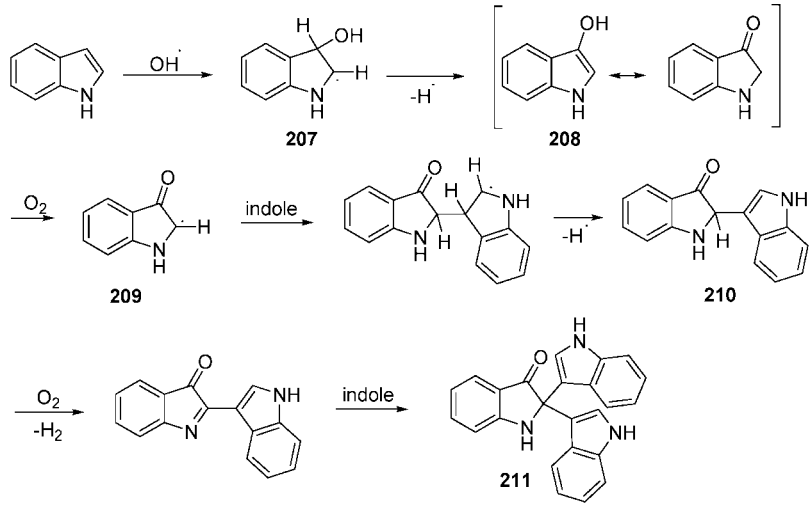
Scheme 76. Reaction of Indoles with MeOCOCl



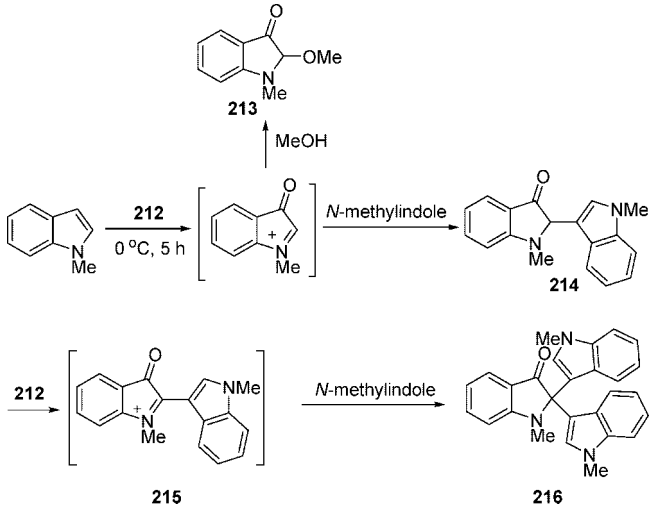
Friedel−Crafts alkylation from the substrate **198** and aldehydes (Scheme 72).[421] The mechanism is not easy to visualize, and it appears that indole formation occurs prior to the Friedel−Crafts step. The same reaction is also catalyzed by AuCl.[422,423]

In 2008 Zanardi et al.[424] reported the one-pot synthesis of **201** from the oxidative cyclization of 2-aminophenyl ethyl

Scheme 77. γ-Irradiation of Indole to form BIM 211



Scheme 78. Treatment of *N*-Methylindole with $MoO_5 \cdot POEt_3 \cdot MeOH$



alcohol **200** to indole followed by the alkylation of the resulting indole by aldehydes that were obtained from the *in situ* oxidation of alcohols. This reaction is catalyzed by both dinuclear complexes of 1,2,4-trimethyltriazolium and iridium[425] and rhodium. Alkylated indole **202** is produced as a byproduct for these reactions (Scheme 73).

Oddo and Toffoli reported the synthesis of 1,1-bis(1*H*-indol-3-yl)ethane from the reaction of 3-indolylmagnesium bromide and acetaldehyde.[426] BIMs are also generated from indolylmagnesium iodide and aldehydes.[427,428] The reaction of indole magnesium bromide and its 2-methyl derivative with trioxane have been reported.[429]

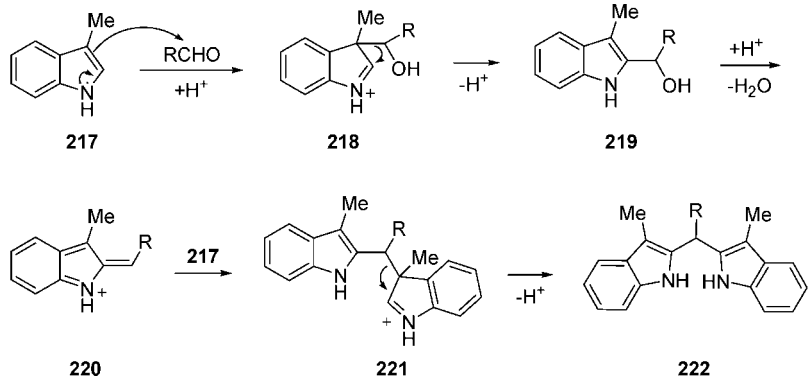
The reduction of the ketone **191** with lithium aluminum hydride (LAH) and the reverse oxidation reaction of BIM **203** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) were described by Bergman et al. (Scheme 74).[430]

Indole in acetic-trifluoroacetic anhydride in ether at 20 °C gave crystals of BIM **204** in modest yield (Scheme 75).[431] The mechanism for this reaction is not straightforward, but it appears that the same type of mechanism for indole addition to a double bond occurs. The C−N bond in the indole that is attacked is destabilized by formation of the amide, while a new double bond is formed upon cleavage of the C−N bond. A second indole then reacts with the new double bond to yield **204**.

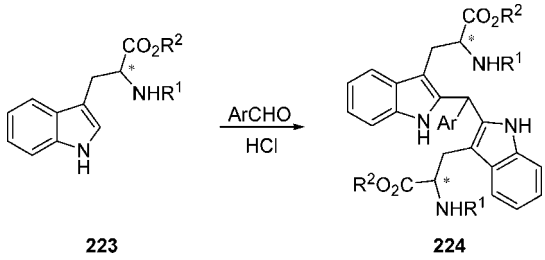
A similar observation was reported for indoles with *t*-$BuNH_2$/MeOCOCl that yield *N*1-carbomethoxylated indolylindolines **205** and BIM **206** (Scheme 76).[432]

By means of γ-irradiation of an aqueous solution of indole under argon atmosphere, in the presence of nitrous oxide and oxygen, 2,2-bis-(3-indolyl)indol-3(2*H*)-one **211** forms as the major product. A plausible mechanism for this reaction is provided in Scheme 77. Hydroxylation of indole in the presence of hydroxyl radicals that were generated *in situ* leads to the formation of the indoxyl **207**, and the latter is converted to indolin-3-one **208** by hydrogen abstraction followed by formation of the indoxyl radicals **209**.[433] Presumably the indoxyl radicals **209** react with more indole to give indoxyl **210** and, finally, 2,2-bis-(3-indolyl)indol-3(2*H*)-one (**211**).[433]

Scheme 79. Rearrangement of Indole Substituents at Position 3 to Position 2

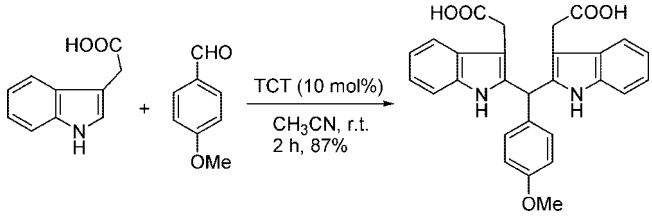


Scheme 80. 2,2′-BIM Derivatives of Tryptophan 223



223 224

Scheme 81. TCT-Promoted Synthesis of 226



225 226

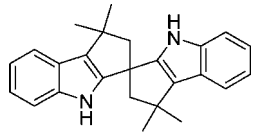
Indoles also react with oxidants or light presumably via the same mechanism to give **211**.[337,434–441] According to another procedure described by Seidel, pulverized indoles when treated with sodium nitrate and concentrated sulfuric acid yield **211**.[440] When *N*-methylindole is oxidized with $MoO_5 \cdot POEt_3 \cdot MeOH$ (**212**), it yields three compounds: **213**, **214**, and **216**. Further oxidation of **214** and the loss of one equivalent of hydride would result in the formation of the intermediate **215**; the latter is converted to product **216** in 46% overall yield (Scheme 78).[442] Later Shen et al. reported the synthesis of **216** utilizing γ radiolysis of *N*-methylindole in the presence of Br_2.[443]

2.2. 2,2′-BIMs

It is well established that indoles substituted in position 3 (such as skatole **217**) and aldehydes usually give 2,2′-BIMs via the mechanism presented in Scheme 79. Formation of **218** and its rearrangement to **219** is followed by elimination of water to yield the cation intermediate **220**. Compound **220** reacts again with skatole and leads to the formation of 2,3′-BIM **221**. A final rearrangement would then give the 2,2′-BIM **222** as shown in Scheme 79.[444] Dittmann and Pindur utilized controlled reaction conditions and isolated some of these intermediates. This enabled them to deduce the full mechanism for this reaction.[445] The promotion of this reaction with HCl[446–449] and montmorillonite K-10 clay are presented in the literature.[450]

Pindur prepared 2,2′-BIM **224** from tryptophan **223** and arylaldehydes. He also investigated the stereoisomers of the prepared compounds **224** (Scheme 80).[451–455]

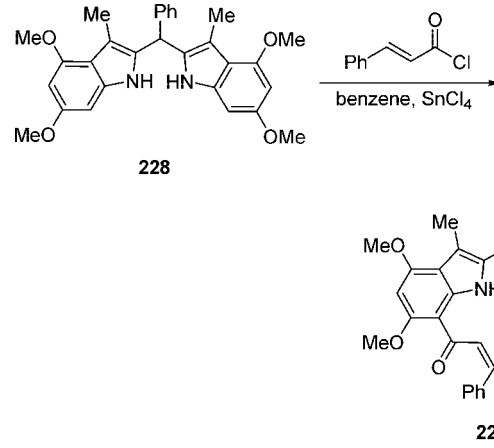
In the presence of catalytic amounts of cyanuric chloride or trichloro-1,3,5-triazine (TCT) indole-3-acetic acid **225** reacts with 4-methoxybenzaldehyde to yield the corresponding BIM **226** (87%, Scheme 81).[456]



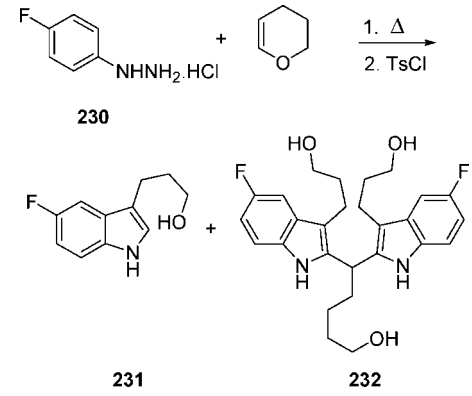
227

Figure 12. Structure of yielded product from indole and acetone.

Scheme 82. Synthesis of Chalcone Derivative 2,2′-BIM 229



Scheme 83. Fischer-type Indole Synthesis



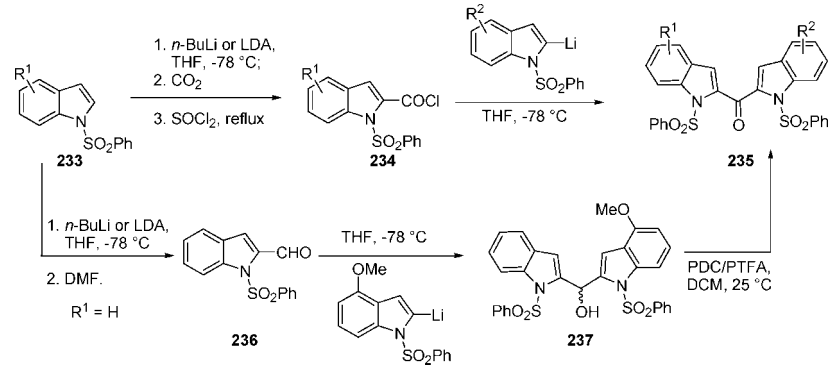
Noland et al. reported that indoles and acetone in acidic media yield the 2,2-BIM **227** (Figure 12).[457] For the more examples, see Scheme 99.

There is one report in the literature about functionalization of 2,2′-BIMs[458] in which **228** is acylated with cinnamoyl chloride and stannic chloride to produce the bis-chalcone **229** in 26% yield (Scheme 82).[459]

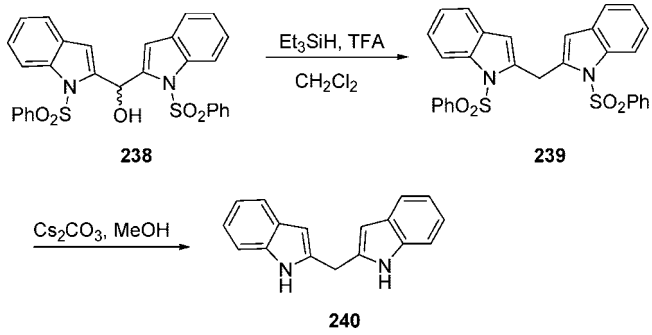
It is worth mentioning that during the large scale synthesis of indole **231** from DHP and the 4-fluorophenylhydrazine salt **230**, the major impurity formed during the indolization step was isolated by preparative chromatography and identified as the triol **232** (Scheme 83).[460]

Direct synthesis of 2,2′-BIMs from indoles that are unsubstituted in position 3 is impossible. However, Mahboodi et al. overcame this obstacle with an innovative method.[55,461,462] Their procedure involves the lithiation of *N*-phenylsulfonated indoles **233** in position 2 followed by treatment with CO_2 and then thionyl chloride. This reaction led to indolyl carboxylic acid chloride **234**. The latter was coupled with another lithiated indolyl to form the bisindolylmethanones **235** (Scheme 84). Furthermore the desired compound **235** can be prepared by coupling of the respective aldehydes **236** and 2-lithiated indoles, followed by oxidation of the resulting carbinols **237** with pyridinium dichromate (PDC). Deprotection of the *N*-phenylsulfonated ketones **236** by tetra-*n*-butylammonium fluoride or sodium hydroxide is possible. The carbonyl group of **235** in the presence of hydrazine and alcoholic KOH solution (Wolf−Kishner reduction) is efficiently converted to CH_2. It was also discovered that bis(1*H*-indol-2-yl)methanones **235** exhibit potent inhibition of FLT3 and platelet-derived growth factor receptor tyrosine kinase.[55,462]

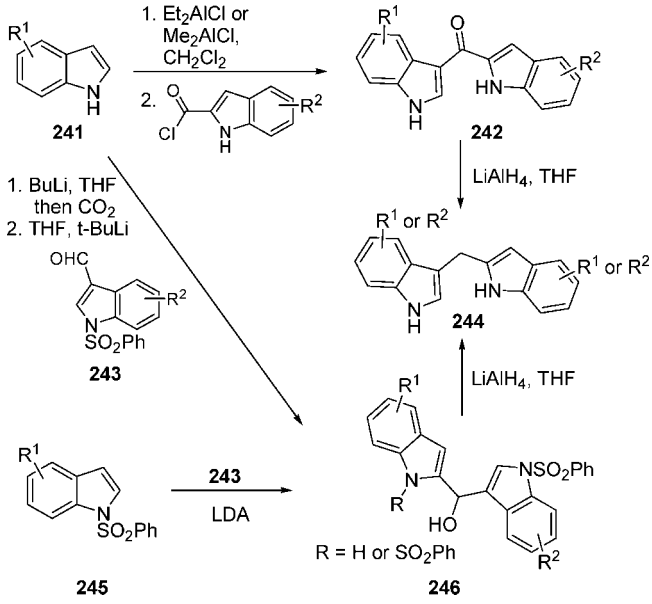
Scheme 84. Synthesis of 2,2′-BIM from 2- and 3-Unsubstituted Indoles



Scheme 85. Synthesis of 2,2′-BIM 240



Scheme 86. Three Different Routes for the Synthesis of 2,3′-BIMs 244

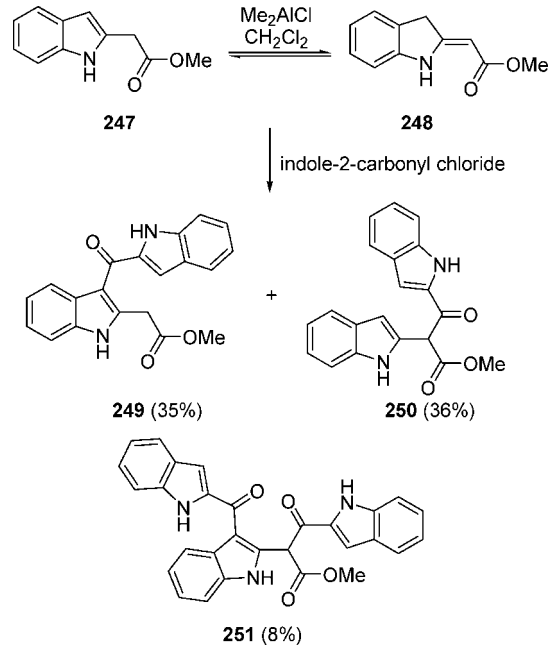


Noguchi-Yachide et al. used this method to prepare the carbinol **238** and then converted it to BIM **239** in the presence of acidic media and Et_3SiH (Scheme 85). The latter was deprotected with Cs_2CO_3, and 2,2′-bisindolylmethane **240** was isolated.[463]

2.3. 2,3′-BIMs

Usually the synthesis of 2,3′-BIMs is quite difficult. The reason for this is the higher reactivity of the indole ring at position 3, and controlling this is not possible. To overcome the lack of nucleophilic reactivity at position 2 of the indole ring a completely different mechanism is required.

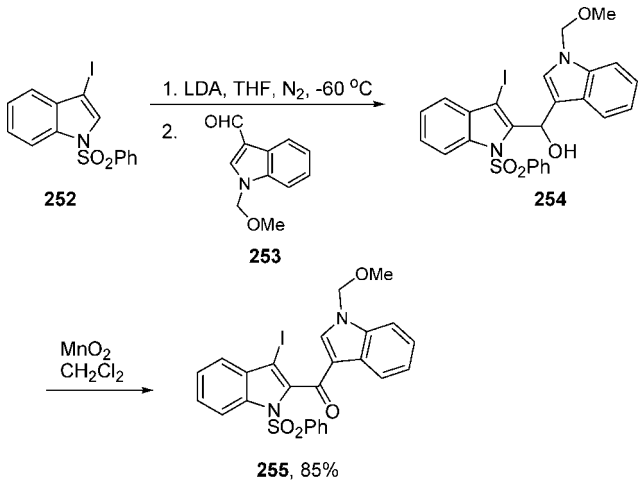
Scheme 87. Employing Indole-2-carbonyl Chloride for the Synthesis of 2,3′-BIMs



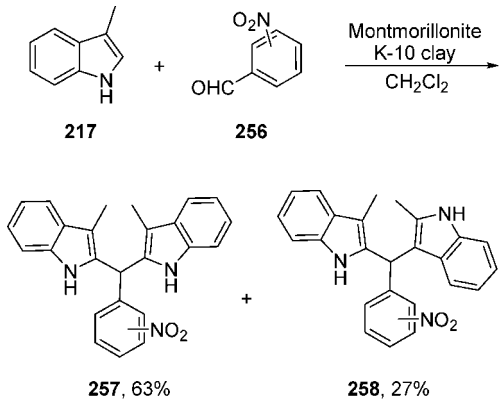
Recently Bergman and his group have provided three different routes for the synthesis of 2,3′-BIMs.[464] In the first route, Lewis acid-assisted acylation of the substituted indoles **241** is used to produce the corresponding ketones **242**, followed by reduction with lithium aluminum hydride to yield **244**. This reaction proceeds according to the same mechanism as before. In the second approach, position 2 of N-protected indole **241** is lithiated, followed by reaction with 1-benzenesulfonylindole-3-carboxaldehydes **243** to give the alcohol **246**; the latter in turn was reduced to **244** (Scheme 86). The change in reactivity of the indole ring is most possibly initiated by the protection of the nitrogen atom with the strong electron-withdrawing sulfonate group. In the third route, the indole derivative **245** was treated with lithium diisopropyl amide (LDA) in tetrahydrofuran followed by 1-benzenesulfonylindole-3-carboxaldehydes **243** to produce the alcohol **246**, which was then reduced with lithium aluminum hydride yielding **244** (Scheme 86).[465]

The same group also synthesized **249**−**251** using the first route as outlined in Scheme 87.[466] Indole-2-carbonyl chloride reacts with both **247** and **248** and yields **249** (35%) and **250** (36%), respectively. Compound **251** is generated by the reaction of indole-2-carbonyl chloride with the two active positions on **247**. This reaction produced compounds

Scheme 88. Synthesis of 255 as a Model of 2,3′-BIMs



Scheme 89. K-10 Clay Catalyzed Synthesis of 2,2′- and 2,3′-BIMs



249−**251**, which were efficiently used as intermediates for the preparation of natural products.

In a modification of this method, (1-benzenesulfonyl-3-iodo-1*H*-indol-2-yl)(1-methoxymethyl-1*H*-indol-3-yl)methanone **255** is obtained through oxidation of the corresponding alcohol **254** with active manganese dioxide. The alcohol **254** is prepared by the reaction of the lithium derivative of **252** with 1-methoxymethyl-1*H*-indole-3-carbaldehyde **253** (Scheme 88).[467]

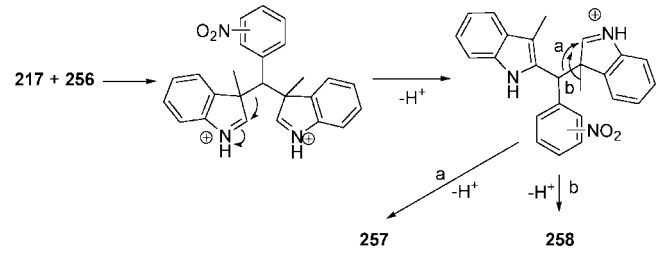
Montmorillonite K-10 clay was successfully used for the synthesis of new types of BIMs. For example, 3-methylindole reacts with *ortho*- or *meta*-nitrobenzaldehyde to yield 2,2′- and also 2,3′-bisindolyl methanes **257** and **258** in 63% and 27% yields (Scheme 89).[468]

A mechanism was proposed based on the Plancher rearrangement.[469,470] The first rearrangement involves the usual migration of an arylalkyl group and leads to the formation of 2,2′-BIMs **257**. The second rearrangement involves the hitherto unreported migration of a methyl group, in preference to an arylalkyl group, and leads to the 2,3′-BIMs **258** (Scheme 90).[468]

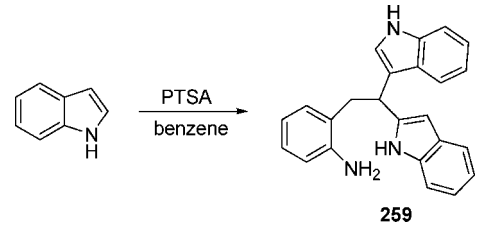
Treatment of indole with PTSA in benzene provides the unusual 2,3′-indole trimer **259** (Scheme 91).[471] A similar migration also appears to occur from position 3 to 2. However, the same indole reaction in the presence of HCl or other protic acids gives the 3,3′-BIM isomer of **259**.[472,473]

Giannini and his group found that indole and 5-hydroxypentanal in methanolic hydrochloric acid afford the 2,3′-BIM **260** in 45% yield (Scheme 92).[474] It is worth mentioning that when $Dy(OTf)_3$ was used as catalyst, 3,3′-BIMs became

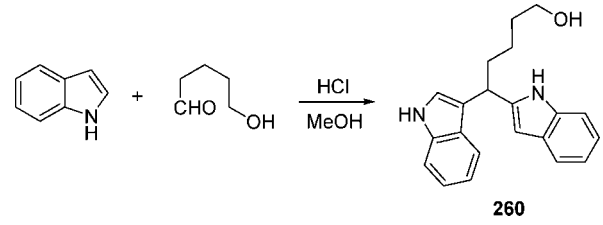
Scheme 90. Plancher Rearrangement in the Synthesis of 257 and 258



Scheme 91. 2,3′-BIM 259 from Indole



Scheme 92. Synthesis of 260 from Indole and 5-Hydroxypentanal in HCl



the predominant product. It appears that protic catalysts favor the formation of 2,3′-BIMs.

The Plancher rearrangement is clearly distinguished in the synthesis of indolocarbazols. Although von Dobeneck and Maas investigated the reaction of 3,3′-BIMs and aldehydes under acidic conditions,[475] they assigned the structure of the products to indolo[2,3-*b*]carbazoles **261**. The same products are observed for the reaction of indole with 4-dimethylaminobenzaldehyde.[476] Subsequent studies by a different group proved that the correct structure of the reaction is indolo[3,2-*b*]carbazoles **262** (Figure 13).[477]

Noland and Venkiteswaran suggested structure **263** for the isolated product from the reaction between indole and acetophenone in ethanolic hydrochloric acid (Scheme 93).[478]

1-Substituted indol-2-ylmethanols similarly give indolo[3,2-*b*]carbazoles **262** on treatment with boron trifluoride etherate

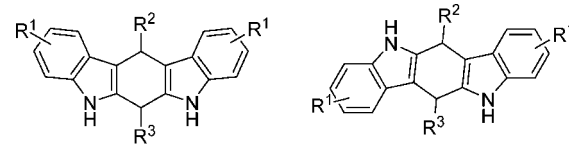
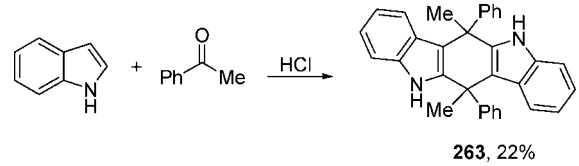
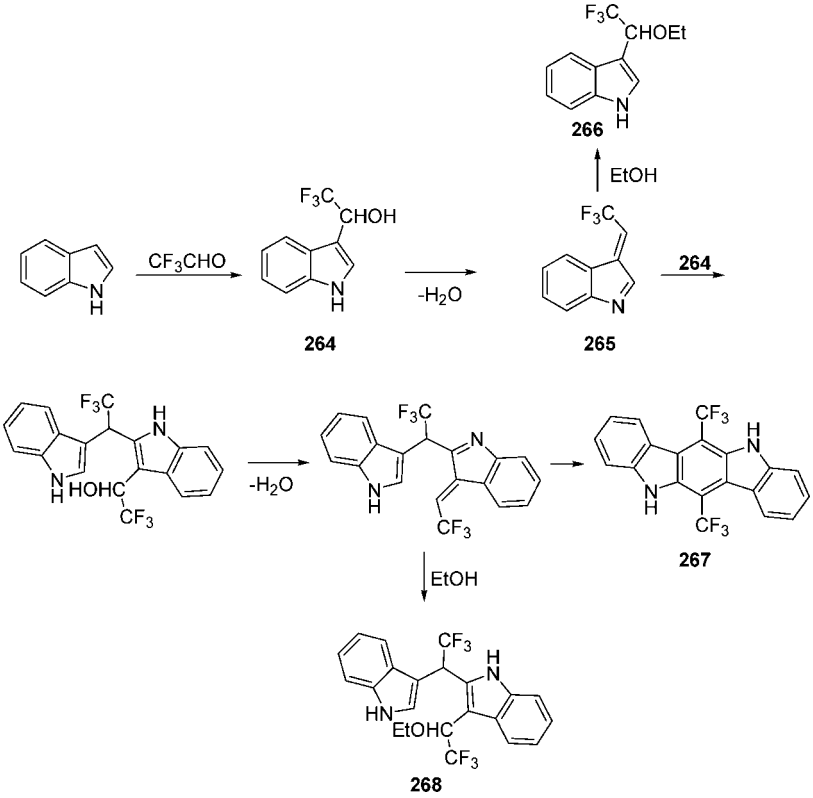


Figure 13. Indolo[2,3-*b*]carbazoles **261** and indolo[3,2-*b*]carbazoles **262**.

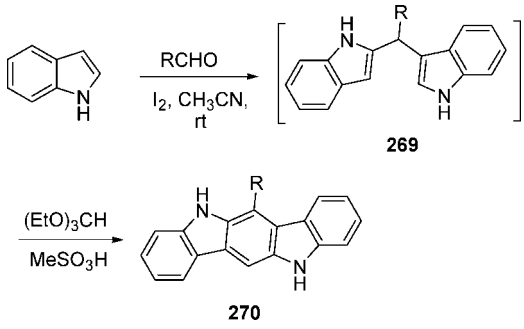
Scheme 93. Reaction of Indole and PhCOMe in HCl Solution



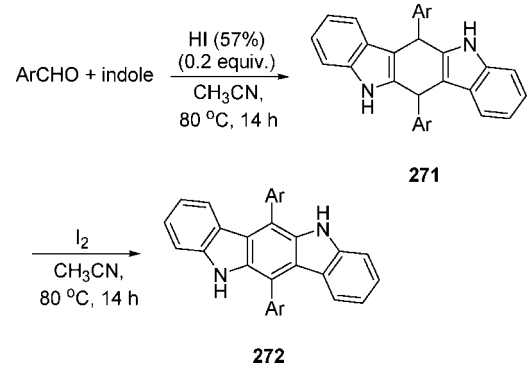
Scheme 94. Reaction of Indole and CF_3CHO in EtOH



Scheme 95. Two-Step Synthesis of Indolocarbazole 270



Scheme 96. Two-Step Synthesis of Indolo[3,2-*b*]carbazoles 272



in benzene Figure 13.[479] Maki and co-workers reported the formation of compounds **266**, **267**, and **268** from the reaction of trifluoroacetaldehyde and indole at 140−150 °C in solvent-free conditions, after workup with ethanol. A plausible mechanism for these conversions via the intermediate **265** is provided in Scheme 94.[480] It appears that this mechanism may be useful to explain the formation of other indolocarbazoles.

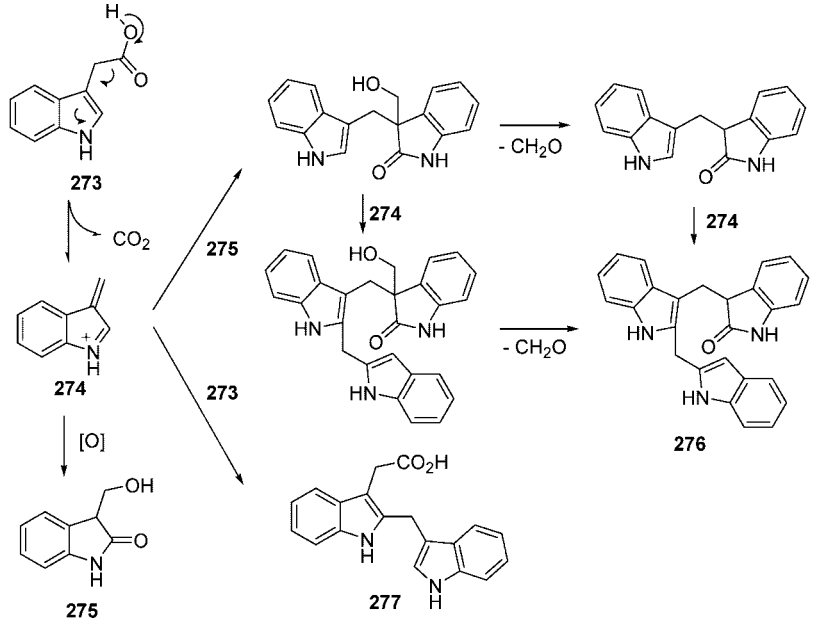
A modified synthesis for the novel 6-monosubstituted 5,11-dihydroindolo[3,2-*b*]carbazoles **270** is accomplished by a three-stage one-pot procedure involving condensation of indole and an aldehyde to afford 3,3′-BIMs, followed by isomerization to 2,3′-BIMs **269**. The latter is converted to the corresponding 6-monosubstituted indolo[3,2-*b*]carbazoles **270** in good overall yield (Scheme 95). The reaction proceeds via an acid-catalyzed intramolecular reaction with triethyl orthoformate.[481] Gu et al. reported the same product **270** but when triethyl orthoester instead of triethyl orthoformate was used.[482]

Recently a facile synthesis of 6,12-diaryl-5,11-dihydroindolo[3,2-*b*]carbazoles **272** from aldehydes and indole catalyzed by HI followed by oxidation of the intermediate **271** with I_2 has been developed (Scheme 96).[483] Similar indolo[3,2-*b*]carbazoles **272** were obtained from the reaction of 4,6-dimethoxyindole and aldehydes in the presence of phosphoryl chloride.[484] The chemistry and applications of indolocarbazoles were recently reviewed, and numerous additional examples of this reaction are reported.[485,486]

New 2,3′-BIMs **276** and **277** are obtained from the oxidation of indolyl-3-acetic acid **273** catalyzed by horseradish peroxidase (denoted as [O] in Scheme 97). The mechanism for the formation of 3-[(2-indol-3-ylmethyl)indol-3-ylmethyl]oxindole (**276**) and 2-(indol-3-ylmethyl)-indolyl-3-acetic acid (**277**) is postulated in Scheme 97.[487] It is proposed that **273** loses CO_2 and is converted to azafulven **274**. The azafulven **274** is converted to **275** under oxidative conditions. The formation of these intermediates assists with understanding the formation of the final products **276** and **277**. The elimination of CH_2O is a typical example of a reversed aldol-type condensation.

Indole-3-carbinol exhibits important biological activity and is a naturally occurring modulator of carcinogenesis. Its

Scheme 97. Effect of Horseradish Peroxidase on 273



activation depends on the reaction media. In a series of investigations, it was found that indole-3-carbinol was converted under mild aqueous conditions to a series of cyclic and acyclic oligomeric products **203** and **278**−**283** in low yields (Figure 14).[488–493]

The trimer **280** was also produced from indole and formaldehyde in the presence of H_2SO_4.[494] Other derivatives of **280** were isolated from the reaction of indole-2- or -3-carbinols and PTSA.[495] The pyrolysis of 3-(diethylaminomethyl)-indolehydrochloride gave a yield of 25% (Figure 14).[496] Recently, Bjeldanes and Staub showed that the reaction of 3-(dimethylaminomethyl)-indole and dimethyl sulfate in the presence of sodium ethoxide affords the trimer **280** in approximately 75% yield.[497] An *N*-methyl derivative of **280** was unexpectedly isolated from the reaction of 2-hydroxymethyl-1-methylindole and α-bromoacetone.[498]

Leete and Marion reported that 3-hydroxymethylindole in hydrochloric acid solution is converted to the polymeric compound **284** as outlined in Scheme 98.[420]

Chatterjee et al. investigated the electrophilic substitution of indoles with acetone.[499–501] They found that indoles react with acetone in the presence of boron trifluoride to yield the

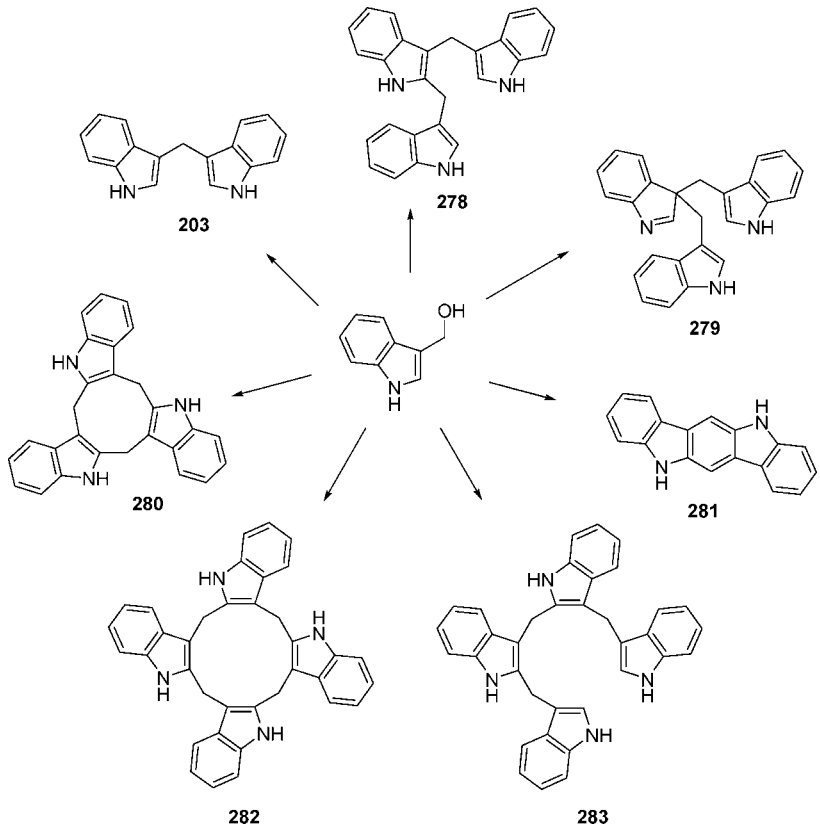
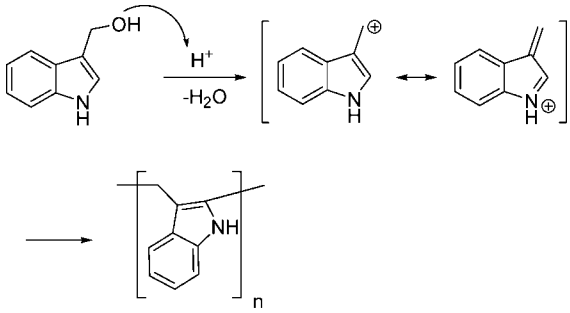


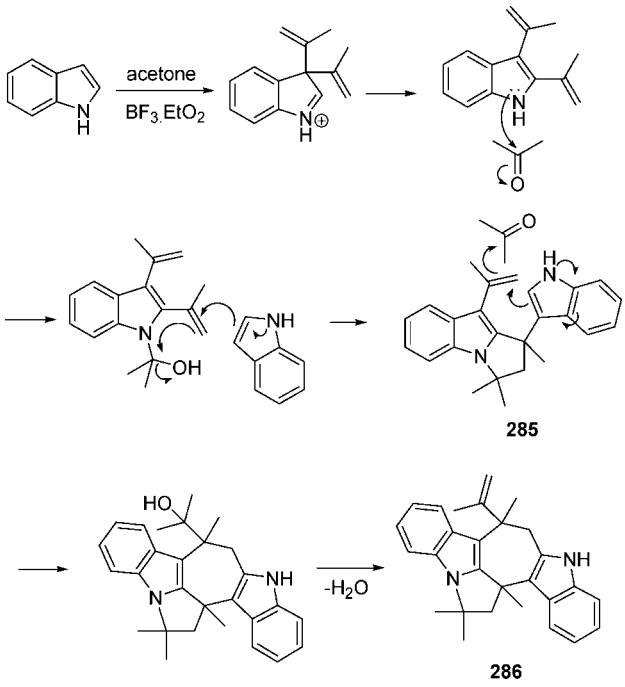
Figure 14. Possible reactions of indole-3-carbinol in acidic media.

Scheme 98. A Mechanism for the Conversion of 3-Hydroxymethylindole to 284



284

Scheme 99. BIM Synthesis from Indole and Acetone in $BF_3 \cdot OEt_2$



285

286

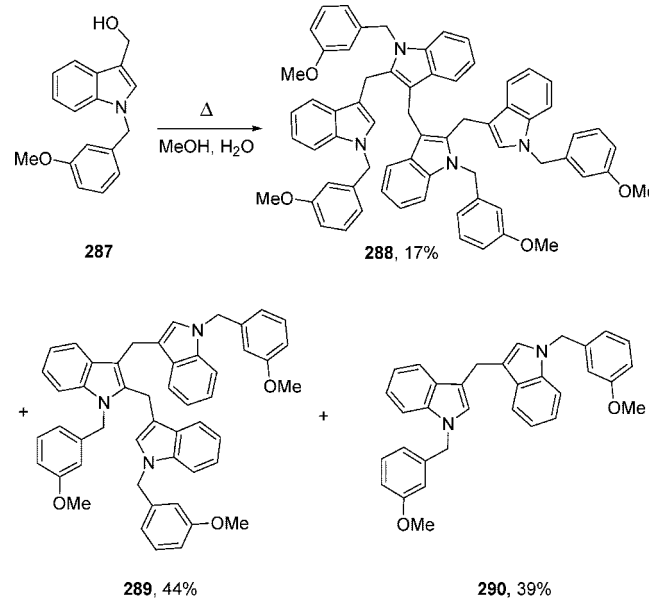
two BIMs **285** and **286** (Scheme 99).[502] In the first step, three acetone units are added to positions 1, 2, and 3 of the indole while an equimolar amount of water is simultaneously eliminated to form alkene substituents. Next, the central alkene is attacked by a molecule of indole from position 3. The resulting intermediate then undergoes intramolecular cyclization to form **285**. The latter again undergoes intramolecular attack of the last added indole at positon 2 with concerted addition of a fourth molecule of acetone. In the last step, H_2O is eliminated to form the polycyclic compound **286** (Scheme 99).

Another example of the formation of trimeric and tetrameric 2,3′-BIMs was reported. The tetramer **288**, the trimer **289**, and also the 3,3′-BIM **290** were isolated when the indolic alcohol **287** was treated under elevated thermal conditions (Scheme 100).[503] It is clear that these transformations are happening through nucleophlic substitution with subsequent elimination of formaldehyde.

Bergman and his group isolated the indolic compound **292** after the Diels−Alder self-cyclization reaction of **291** followed by a hydrogen shift reaction (Scheme 101).[333]

Finally in an alternative method, Jackson et al. prepared 2,3′-bisindolyl methane **296** from indoline-2,3-dione **87** as shown in Scheme 102.[504] The ring-opening of isatin **87**

Scheme 100. Self Condensation of Indolic Alcohol 287 under Thermal Conditions



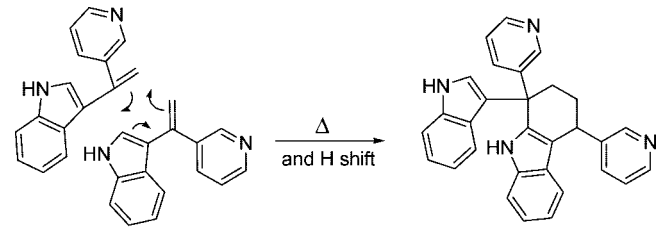
287

288, 17%

289, 44%

290, 39%

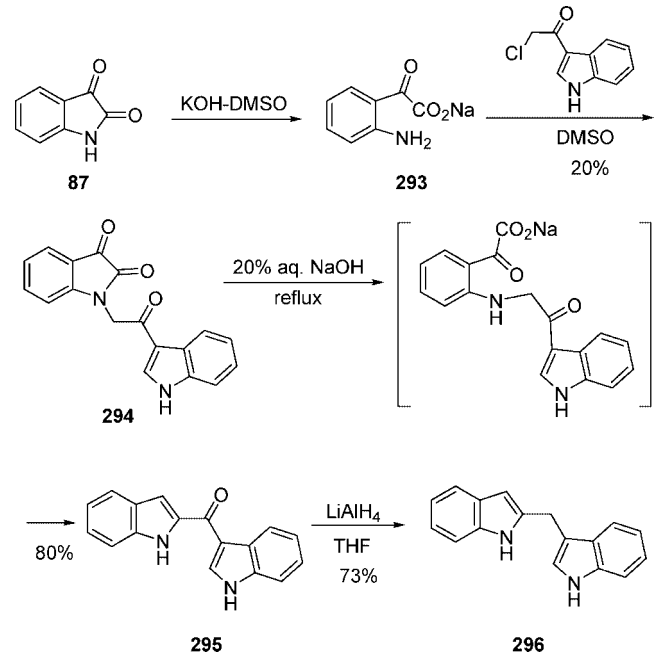
Scheme 101. Self Cyclization of Indole 291



291

292

Scheme 102. Multistep Synthesis of 2,3′-BIM 296



87

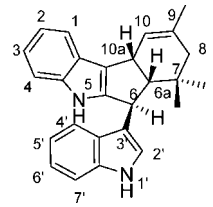
293

294

295

296

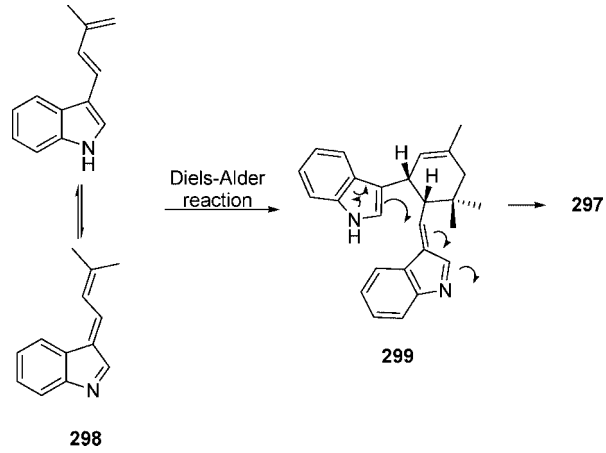
undergoing alkaline hydrolysis in DMSO produced the amine **293**. Reaction of the latter with 2-chloro-1-(1*H*-indol-3-yl)-ethanone followed by ring closure yielded compound **294** in 20% yield. Ring-opening of **294** and consequent formation of the methanone **295** (in 80% yield) occurred under



297

Figure 15. Yuehchukene (YCH).

Scheme 103. Dimerization of 298 To Produce YCH



conditions where aqueous NaOH is heated to reflux. Reduction of **295** with $LiAlH_4$ produced the 2,3′-BIM **296**.

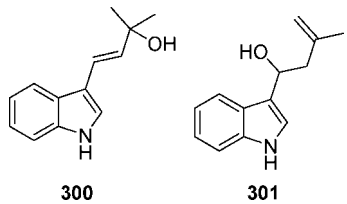
2.4. Yuehchukenes

Since yuehchukene (YCH) **297** is a special kind of 2,3′-BIM, the synthesis and chemistry of this BIM are presented in the separate section. Yuehchukene, a novel type of dimeric indole, is a natural product. The compound was given the Chinese name of the plant (*Murraya paniculata*) from which it was isolated, namely, "yueh-chu". It was isolated in racemic form, in trace quantities (<18 ppm), from the roots of the plant (Figure 15).[505,506]

YCH exhibits anti-implantation activity in rats[506] and mice[507,508] and moderate activity in guinea pigs.[509] YCH is considered to be a potential fertility-regulating agent.

It has usually been synthesized from the dimerization of β-(dehydroprenyl)indole **298** (Scheme 103).[505,510,511] β-(Dehydroprenyl)indole **298** undergoes tautomerization to generate a diene and dienophile required for the Diels−Alder reaction. The adduct **299** experiences intramolecular cylization to give YCH.

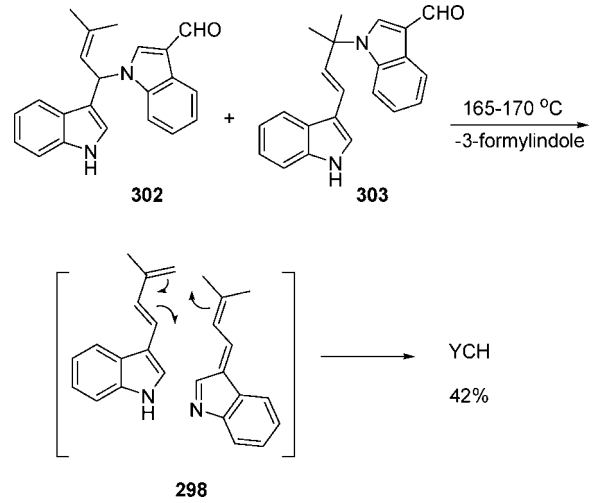
Therefore the synthesis of suitable precursors for **298** has been an attractive target. *E*-β-(3-Hydroxy-3-methylbutenyl)indole **300**[512] and β-(1-hydroxy-3-methylbut-3-enyl)indole **301**[511,513] have been constructed for this purpose. These precursors, under the right conditions, yield YCH in 25% and 26% yields, respectively (Figure 16).



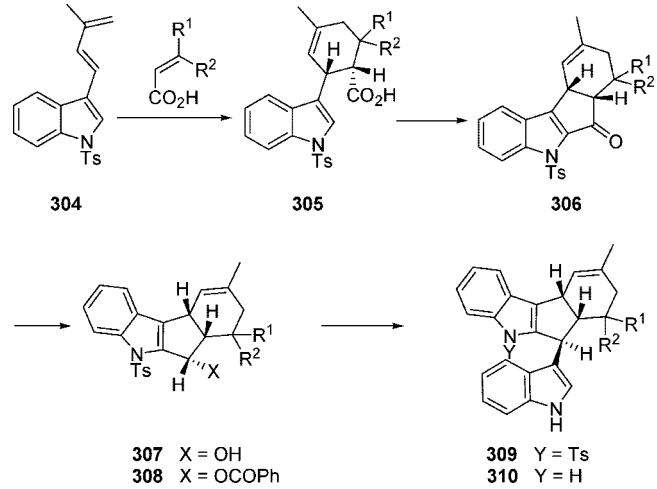
300 301

Figure 16. Precursors for YCH Synthesis.

Scheme 104. Thermal Decomposition of 302 and 303 with Production of YCH



Scheme 105. Diels-Alder Reaction Utilized in YCH Synthesis

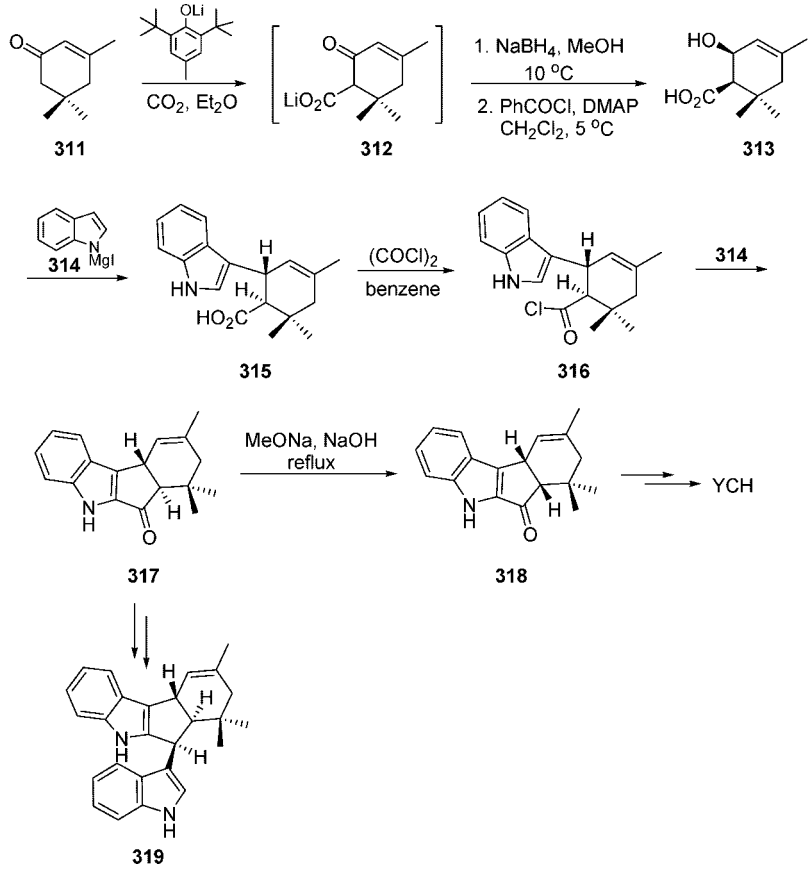


Other suitable precursors are **302** and **303**. When a mixture of these compounds is heated in a neutral solution of ethylene glycol at 165−170 °C, YCH is isolated in 42% yield. This one-step reaction is considered to give β-(dehydroprenyl)indole **298** first, via elimination of 3-formylindole (recovered quantitatively), followed by a subsequent Diels−Alder reaction (Scheme 104).[514]

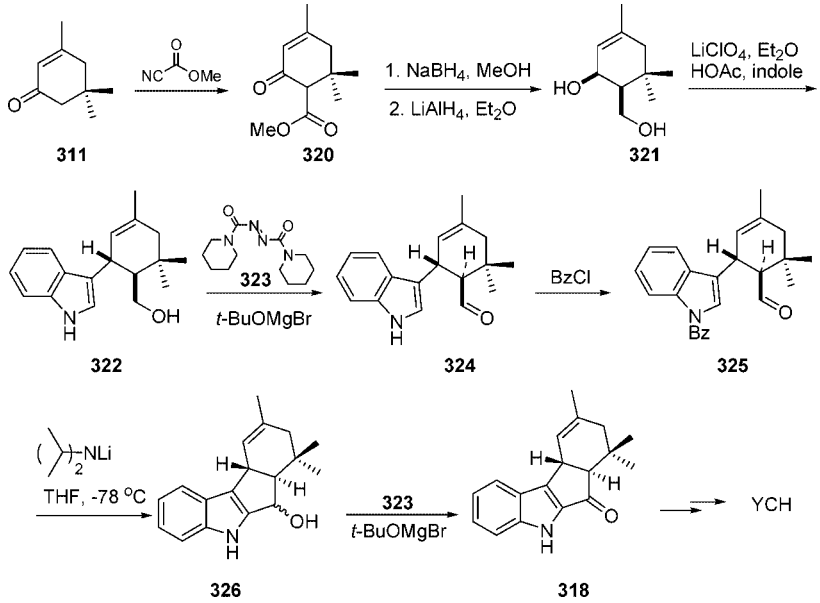
An attractive route (Scheme 105) for the synthesis of YCH involves the conversion of the diene **304** to **305** followed by intramolecular acylation to obtain the key tetracyclic intermediate **306**. Stereoselective transformation of the ketone **306** to the α-benzoate **308** via the alcohol **307** is followed by the S_N2 displacement of the benzoate with the indol-3-yl group and subsequent removal of the N-protection in **309** to give the bis-indole **310**.[515,516]

YCH and its epimer **319** were also prepared according to the method provided by Kutney et al. (Scheme 106).[517,518] In this method, isophorone **311** has been selected as starting material, which is converted to lithium carboxylate **312** followed by reduction of the ketone to the hydroxyl carboxylic acid **313**. Compound **313** is treated with indolyl magnesium iodide **314** to yield **315**. *trans*-Ketone **317** is obtained from the conversion of the carboxylic acid **315** to the acyl chloride **316** followed by treatment with indolyl magnesium iodide **314**. *trans*-Ketone **317** is used as an intermediate for the synthesis of the 6a-epimer of YCH, **319**.

Scheme 106. Synthesis of YCH and Its Epimer 319 Starting from Isophorone 311



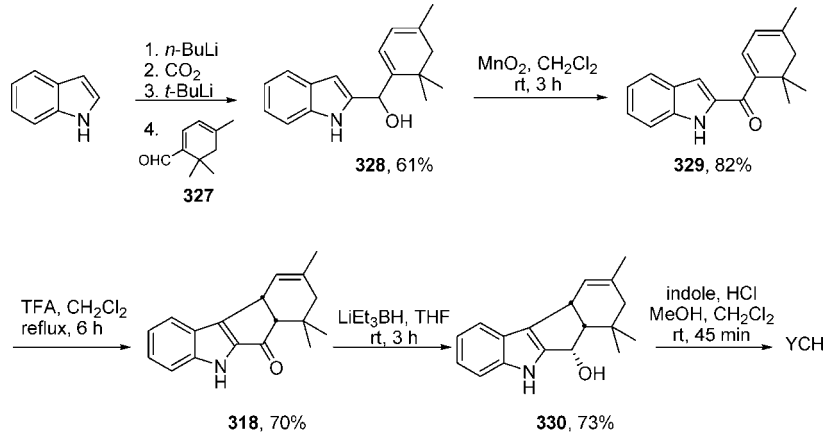
Scheme 107. YCH Synthesis via Formation of the Diol 321



Also **317** in the presence of MeONa is converted to the *cis*-ketone **318**, a known intermediate for the synthesis of YCH.

Methoxycarbonylation of isophorone **311** with methyl cyanoformate, followed by sequential reduction of the 3-keto ester **320** with sodium borohydride in methanol and then lithium aluminum hydride in diethyl ether, yielded the diol **321** (Scheme 107).[519] Treatment of **321** with indole and a $LiClO_4-Et_2O$ solution containing a catalytic amount of acetic acid gave **322** after 1.5 h at ambient temperature in 86% yield. No reaction is observed in the absence of lithium perchlorate. Treatment of **322** with an excess of *tert*-butoxymagnesium bromide in THF followed by the addition of 1,1′-(azodicarbonyl)dipiperidine **323** affords an 81% yield of the aldehyde **324**. Benzoylation of **324** with benzoyl chloride gives **325**, followed by treatment of the latter with lithium diisopropylamide to give a 65% yield of the tetracyclic alcohol **326**. Oxidation of **326** with alkoxymagnesium bromide in the presence of **323** in THF gives rise to the *trans*-fused ketone **318** in 80% yield. Epimerization of **318** to the *cis*-fused ketone followed by reduction and indolization employing the Kutney protocol (see Scheme 106)[517,518] affords YCH in 50% overall yield.

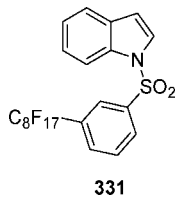
Scheme 108. YCH Synthesis via Activation of C2 in Indole by the Katritzky Method



Bergman and Venemalm introduced yet another route for the synthesis of YCH (Scheme 108).[520–522] In the first step after protection of the indole nitrogen, lithiation of C-2 allows (Katritzky method for activation of C2 in indole)[523] for the reaction of the indole with monoterpenoid aldehyde **327** to yield the alcohol **328** in 61%. The alcohol **328** is oxidized with MnO_2 and converted to the 2-acylindole **329**. Cyclization of **329** to **318** with TFA and reduction of **318** produces the alcohol **330**, which upon treatment with indole yields YCH in 67% (Scheme 108). Note that the nucleophilic attack from **329** to **318** occurs from the C3 atom on the indole ring.

Naka et al. have modified the Bergman method for the synthesis of YCH with a fluorous-tagged indole **331** as starting material (Figure 17). This tag allows for ease of separation of the product in every step.[524]

Ishikura et al. employed a palladium catalyst for the carbonylation and cross-coupling reaction of indolylborates **332** with vinyl triflates **333** to prepare 2-acylindole **334**. Compound **334** is converted to **335** by acid catalysis and then used as precursor for the synthesis of YCHs (Scheme 109).[525–527]



331

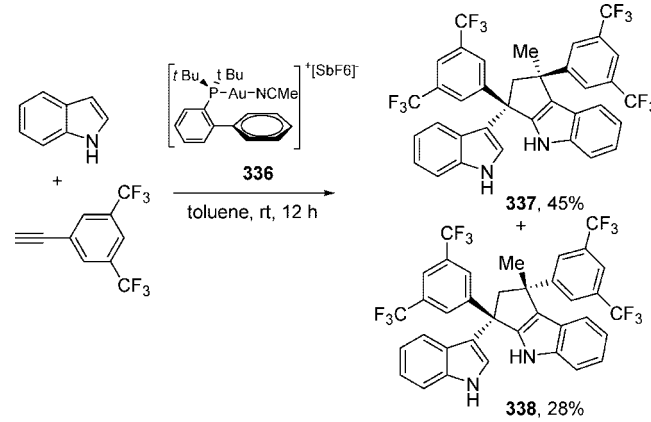
Figure 17. Fluorous-tagged indole **331**.

The gold complex **336** catalyzes the formation of the asymmetric YCH derivatives **337** and **338** in 45% and 28% yields, respectively. The reaction makes use of an indole molecule that adds to the triple bond of 3,5-bis(trifluoromethyl)phenylacetylene (Scheme 110).[389]

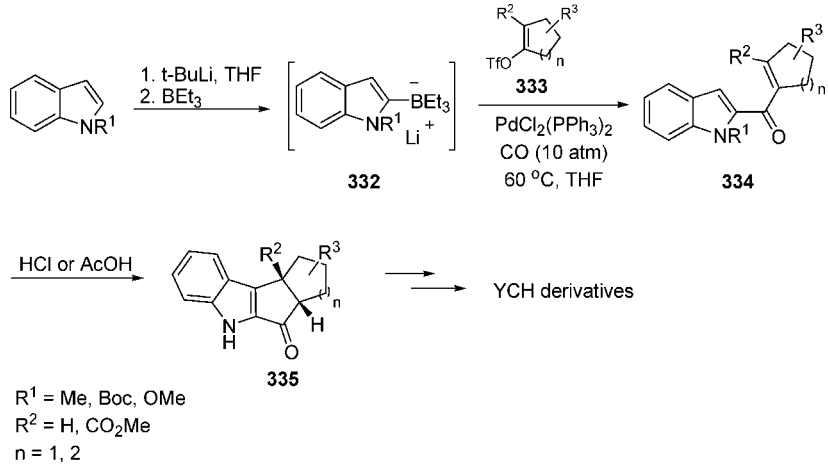
Giannini et al. found that both 3,3′-BIMs **339** and 2,3′-BIMs **340** in the presence of diethylaminosulfur trifluoride (DAST) rearrange to the cyclo forms of BIMs **341** and **342** (Scheme 111).[474,528]

Using the mentioned synthetic methods, the structure−activity relationship (SAR) of YCH was studied for the following analogues of YCH:[529,530] **343**,[531,532] **344**,[533] **345**,[534]

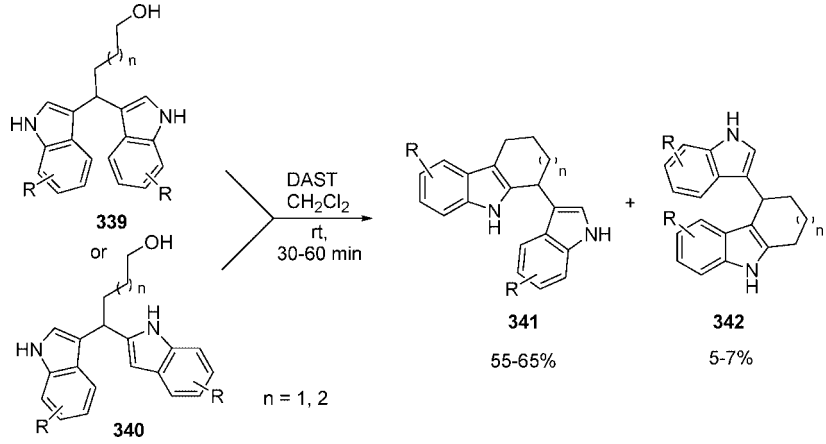
Scheme 110. Gold Complex 336 Promoted Synthesis of Asymmetric YCHs



Scheme 109. Palladium Cross-Coupling in the Synthesis of YCHs



Scheme 111. Rearangments of BIMs with DAST



346,[515a] **347**,[515b] **348**,[535,536] **349**,[537,538] **350**,[539] **351**,[540] precursor **352**,[541] **353**,[542] **354**[543] (Figure 18).

2.5. Other BIMs

In addition to 3,3′-, 2,3′-, and 2,2′-BIMs, numerous interesting types of other BIMs are known and are presented in this section.

For example, asymmetric 1,1′-BIM **356** is isolated from the reaction of the dimer **355**, formed from 3-hydroxy-2,3-dimethylindolenine, and formalin in the presence of an acid. However, under milder reaction conditions (more dilute acid and shorter reaction times), the starting material **355** was converted exclusively to the crystalline *homo* compound **357**. Acid treatment of **357** gives **356** quantitatively (Scheme 112).[544] The reaction to produce **357** is not sensitive to peroxides or oxygen, which are normally excluded for the direct conversion to **356**.

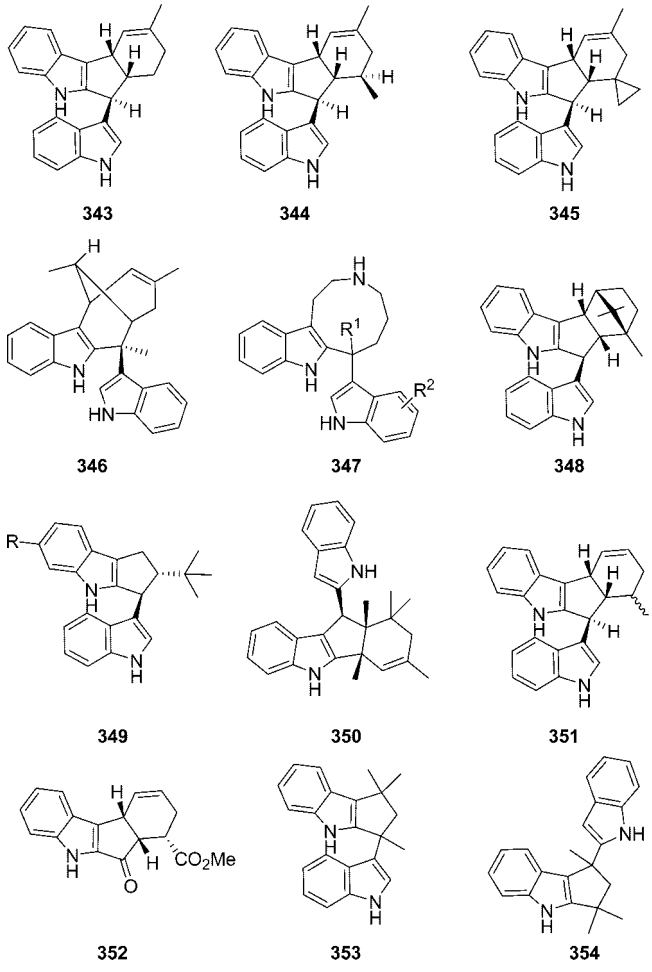
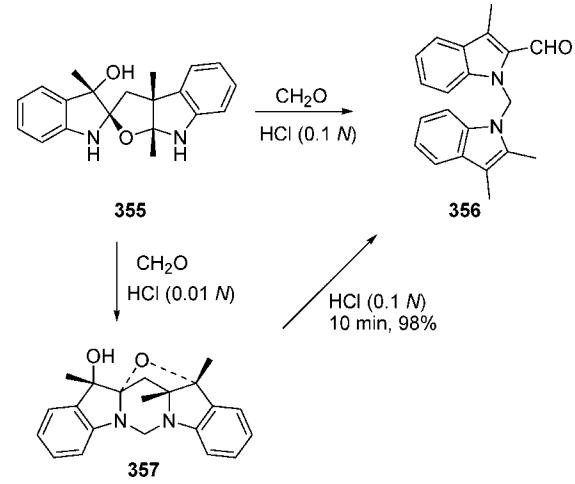
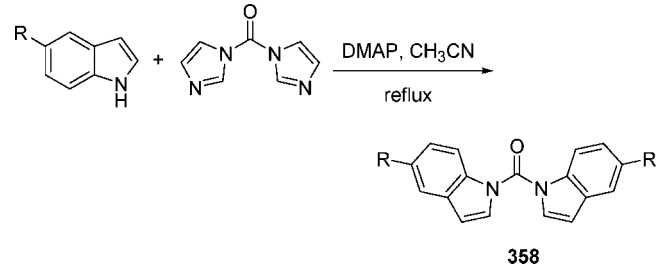


Figure 18. YCH derivatives.

Scheme 112. Dimer 355 and CH_2O at Different pH



Scheme 113. Synthesis of the Carbonylic BIM 358



Also 5-substituted indoles react with carbonyldiimidazole to yield the carbonyl compound **358** under basic conditions (Scheme 113).[545]

The reactions of phosgene[546] and ethyl chloroformate[547] on an indole Grignard reagent have been studied. Bergman et al. investigated the careful cyclization reaction of indole and the indole Grignard reagent with phosgene. They found that in certain solvents and with heating phosgene reacts with indolylmagnesium bromide to give compounds such as **359**−**363** (Figure 19).[430]

Another example of 1,1′-BIM formation follows from treatment of 4,6-dimethoxy-3-arylindoles **364** with triflic anhydride in acetone to produce the pyrroloindole spirodimer **365** and the indolylpyrroloindoles **366** (Scheme 114).[548]

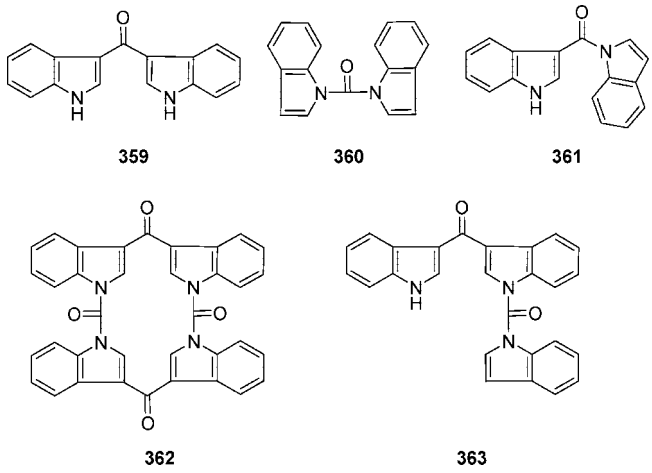


Figure 19. The products from $COCl_2$ and indolylmagnesium bromide.

When methyl ketones react with **364** (R = Me) in methanolic acid for a similar reaction to that in Scheme 114, then the 1,2′-BIM **366** is observed as the major product.[549]

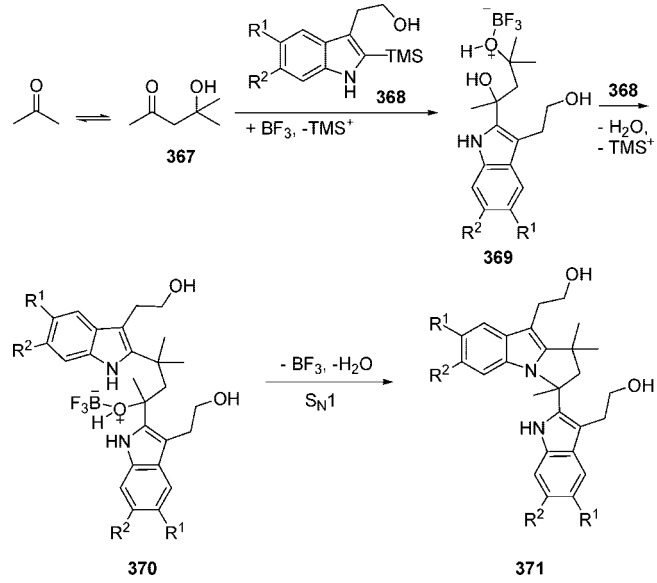
A similar structure to that of **366** is obtained for the reaction between indole derivatives **368** and 4-hydroxy-4-methyl-2-pentanone **367** to produce the dimer **371** (Scheme 115). The BIM dimer is generated with the aid of the BF_3-catalyzed self-condensation of acetone. Condensation of the ketone **367** with **368** gives the intermediate **369**, which acts as the electrophile at the *gem*-dimethyl alcohol site for a Friedel−Crafts-type process at the 2-position of a second equivalent of **368** to form the dimeric species **370**. It is probably due to the steric hindrance of the allylic alcohol site next to the indole core (the other tertiary alcohol) that the intramolecular process occurs only at the less hindered *gem*-dimethyl alcohol position. Finally, an intramolecular cyclization of **370** results in the formation of the dimer **371** (Scheme 115).[550]

By blocking of position 3 in 3-propylindole, the BIM formation reaction with 1-piperidinomethanol **372** is forced to cyclize at position 2 and the calix[3]arene **373** is isolated in acetic acid after a period of 3.5 weeks (Scheme 116).[551] This is a novel 1,2′-BIM calix[3]arene that was not previously reported.

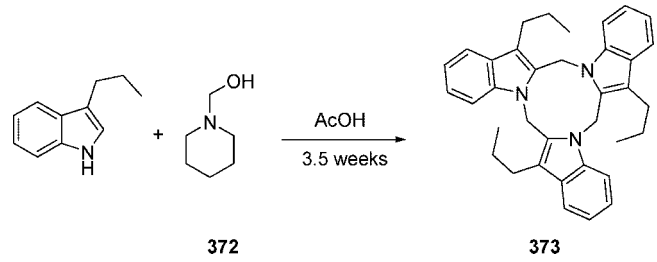
Thesing found that 3-trimethylaminomethylindole **374** in aqueous sodium hydroxide gives 1,3′-BIM **375** also via a S_N2 mechanism (Scheme 117).[552]

Treatment of 3-chloro-3-methylbut-1-yne with aqueous KOH and a catalytic amount of dibenzo-18-crown-6 in the presence of 3-formylindole under reflux conditions in THF gives a mixture that was separated to afford two bis-indoles, 3-[(*E*)-3-methyl-3-(3-formylindol-1-yl)but-1-enyl]indole **303**

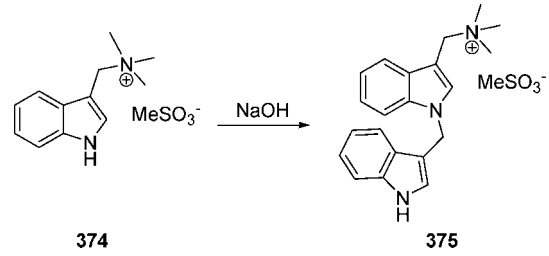
Scheme 115. BF_3-Mediated Reaction of Acetone and 368



Scheme 116. Cyclization of 3-Propylindole and 372 after 25 Days

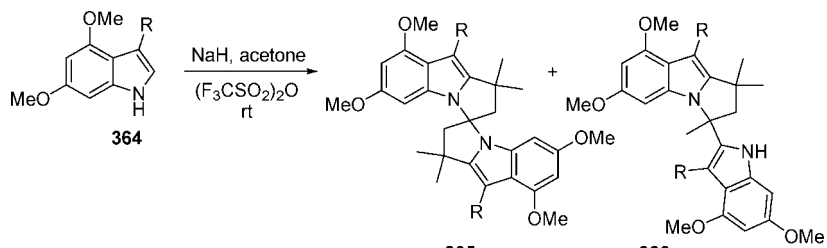


Scheme 117. Behavior of 374 in Basic Solution



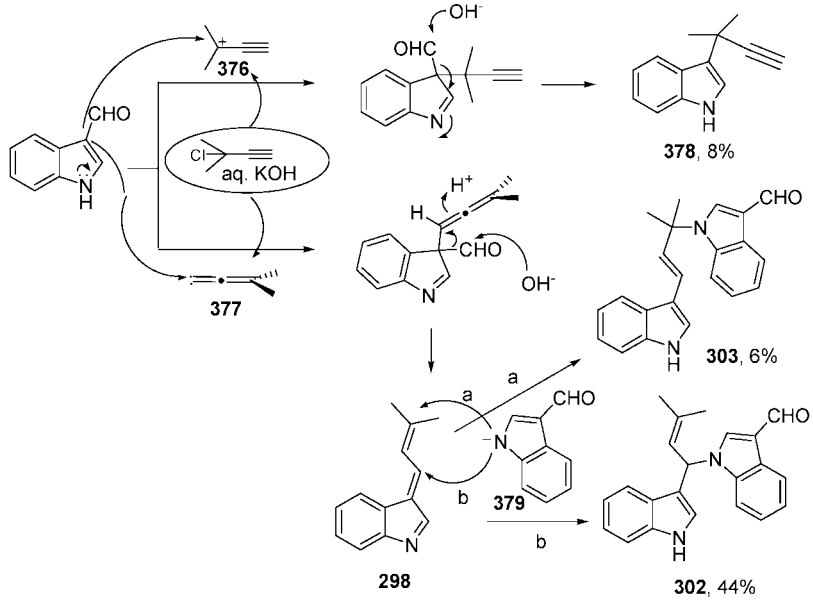
(6%) and 3-[3-methyl-1-(3-formylindol-1-yl)but-2-enyl]indole **302** (44%), as well as 3-(1,1-dimethylprop-2-ynyl)indole **378** (8%) (Scheme 118).[514] The alkyne **378** was considered to be derived from the electrophilic addition of the carbocation **376** at C-3 to the 3-formylindole and subsequent decarbonylation of the intermediate. Electrophilic addition of the carbene **377** at C-1 to the β-carbon of the indolide

Scheme 114. Reaction of 364 and Acetone



R	Yield (%)	Yield (%)
p-MeOC$_6$H$_4$	20	70
Ph	0	70

Scheme 118. Reaction of 3-Formylindole and 3-Chloro-3-methylbut-1-yne in Basic Solution



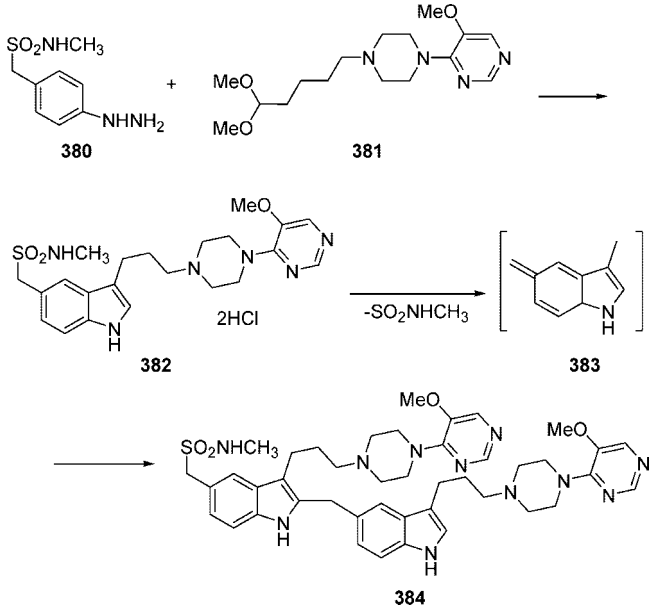
anion **379** and subsequent decarbonylation, on the other hand, would lead to the formation of the indole **298** as the reactive intermediate. Further condensation of the anion **379** at the C-4 and C-2 positions of the side chain of **298** gives the β-prenylindoles **303** and **302**, respectively. The proposed mechanism for this reaction is presented in Scheme 118.[514]

The indole derivative **382** is prepared from the Fischer indole cyclization of hydrazine **380** and acetal **381**. 2,5-BIM **384** is isolated in 20% yield as byproduct via the intermediate **383** (Scheme 119).[553] Compound **384** is a rare model of 2,5′-BIMs.

Photolysis of α-diazo ketone **385** affords the indolylketene **386**, which is only stable below 58 K. Above this temperature, tetrameric indole **387** forms in high yield (Scheme 120).[554–556]

In an interesting study, Pindur and Schiffl prepared 6,6′-BIMs **389** as a novel form of BIMs from the reaction of 2,3-substituted indoles **388** and aldehydes (Scheme 121).[557,558] The obvious reason for this unique reaction is steric hindrance exerted by the bulky substituents of the indole ring.

Scheme 119. Fischer Indolization of 380 and 381

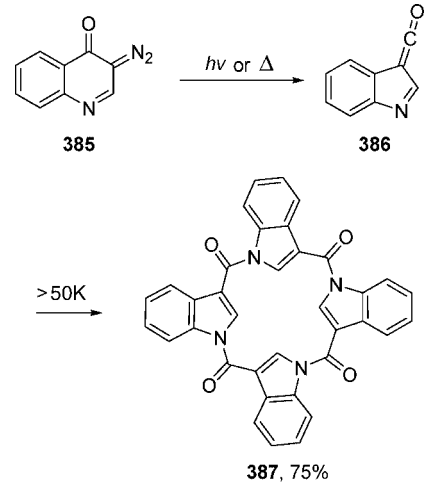


2,7′-BIM **392** was reported from the reaction of 7-hydroxymethyl indole **390** and indole **391** via the S_N2 reaction activated with AcOH by Black et al. (Scheme 122).[559,560] Also, the synthesis of 7,7′-BIMs **394** was effected from the indole **393** and appropriate aldehydes in acidic media in 70−100% yield (Scheme 122).[561]

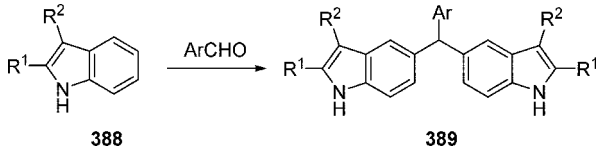
Black et al. in an interesting study have found that the 5,7-dimethoxyindoles **395** selectively alkylated with aldehydes at C4 in acidic media to give 4,4′-BIMs **396** in more than 90% yield (Scheme 123). However, reaction with *o*-phthaldialdehyde results in the formation of a new ring between C3 and C4 and the formation of the trypticene analog **398** in high yield (Scheme 123). It is likely that the initial reaction takes place at C4 (as **397**), followed by cyclization at the less nucleophilic C3 positions. It is worth mentioning that this is the only example of indoles unsubstituted at C3 that are rather attached at C4. This lack of activity at the C3 position may be due to the presence of the methyl carboxylate group that will deactivate the pyrrolic ring. The presence of the two substituted OMe groups on the benzene ring should also activate position C4.[562]

Isomeric BIM **400** was isolated from the reaction of yohimbine **399** and 4-dimethylaminobenzaldehyde in the presence of methanolic hydrogen choloride (Scheme 124).[563]

Scheme 120. Photolysis of α-Diazo Ketone 385



Scheme 121. 6,6′-BIMs 389



Black et al. have focused on the synthesis of calix[*n*]indoles. They reported for the first time that the indole **401** undergoes addition to a range of aryl aldehydes in methanolic hydrochloric acid to give high yields (79−87%) of the 2,2′-BIMs **402**. These BIMs exhibit regioselective addition at C-2 rather than at C-7 (Scheme 125).[458,564,565] In contrast to that, treatment of the indole **401** with the same aryl aldehydes and phosphoryl chloride when heated to reflux in chloroform gives the calix[3]indoles **403** in variable yields 10−81%. The calix[3]indoles **403** are also formed in similar yields from the rearrangement of 2,2′-BIMs **402** on treatment with phosphoryl chloride under reflux conditions in chloroform (Scheme 125).

Calix[*n*]indoles form when 3-methylindole is replaced by 3-aryl-7-hydroxymethyl-4,6-dimethoxyindoles **404**,[559] 3-aryl-2-hydroxymethyl-4,6-dimethoxyindoles **405**,[559] indolylglyoxylamide **406**, and **407** (Figure 20).[566,567]

It was also found that BIMs **408** undergo formylation in the presence of $POCl_3$ and DMF and when subsequently reduced with $NaBH_4$ under protic acid media form calix[4]indoles **409** (Scheme 126).[568]

By means of a similar method, some alternative BIMs containing a benzofuran moiety such as **410** and **411** were synthesized (Figure 21).[569]

3. TIMs

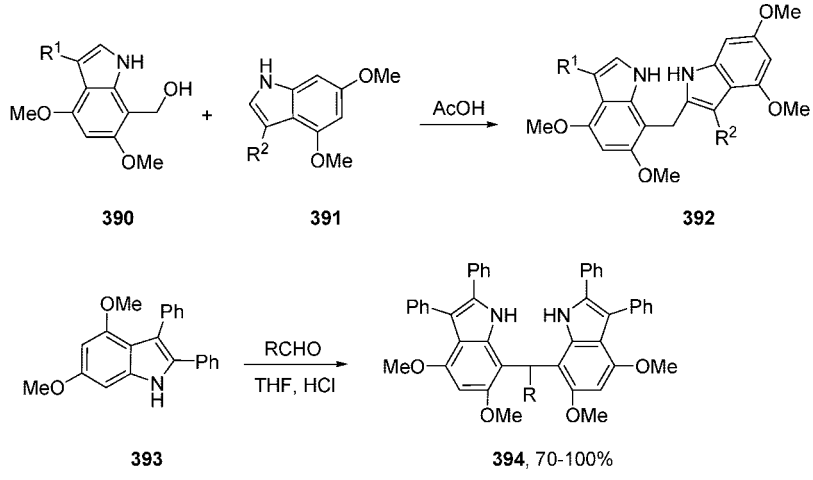
In the preparation of 3,3′,3″-TIMs **412**, the required source of carbon in the center of the indole moieties was intensively studied. The most popular and logic central carbon source for TIM formation should have three leaving groups. As such, orthoformates were widely used with indoles in the presence of a catalyst such as AcOH,[570,571] PTSA,[572] H_2SO_4,[264,476] 5-sulfosalicylic acid,[573] clay K-10,[574] or I_2 (Scheme 127).[575]

TIMs are also obtained from the reaction of indoles and acetic-formic anhydride **413**[431] or diethoxycarbenium salts **414**[355,576] and diethyl carbonate (Figure 22).[577]

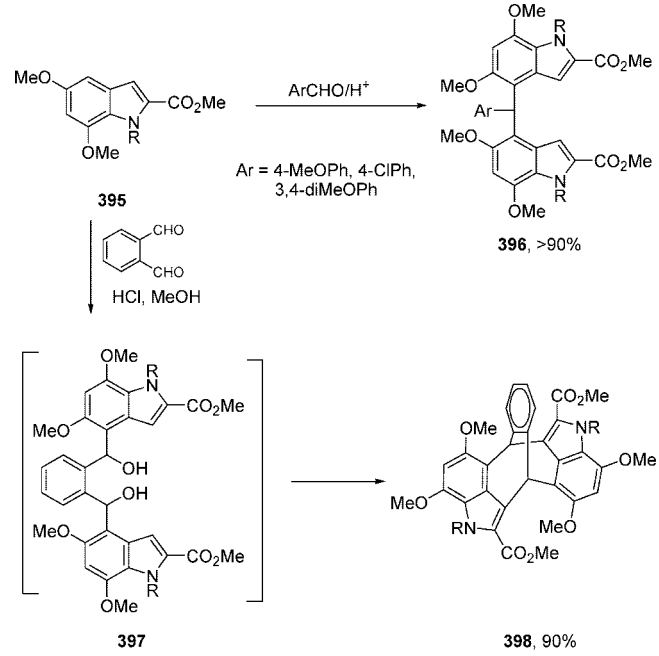
Slice and Stanovnik synthesized tris(2-methyl-1-*H*-indol-3-yl)methane **416** via addition of 2-methylindole to compound **415**. This required the addition of *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) to the 2-methylindole (Scheme 128).[578]

Heating of 4-chloroquinazoline **417** with 2-methylindole leads to the formation of 4-(2-methylindol-3-yl) quinazoline

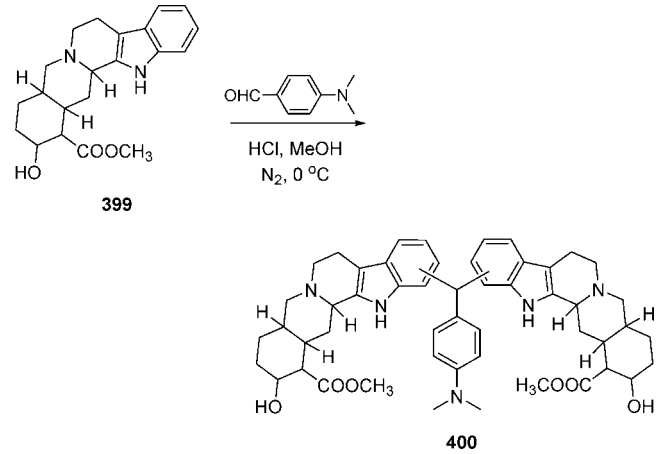
Scheme 122. 2,7′-BIMs 392 and 7,7′-BIMs 394



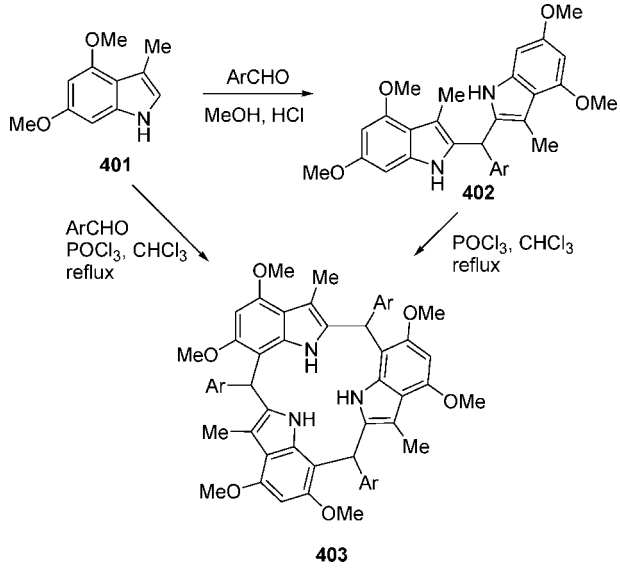
Scheme 123. Regioselective Reactions of 395 with Aldehydes



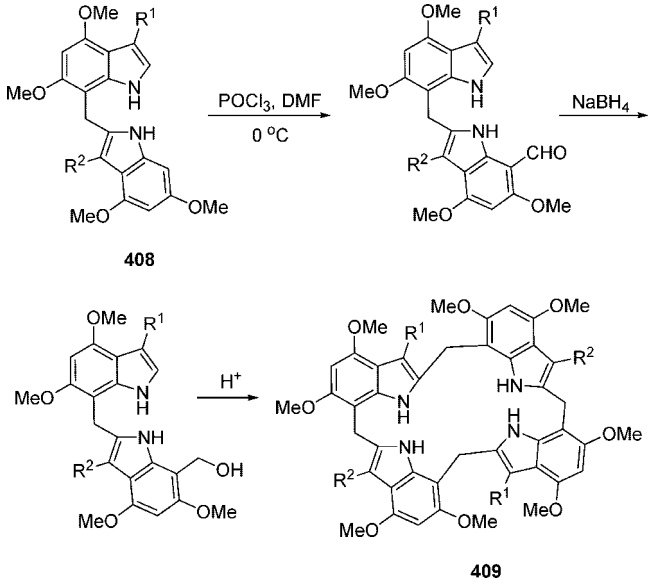
Scheme 124. Bisindolization of Yohimbine 399



Scheme 125. Calix[3]indoles 403 from 401 and Aldehydes



Scheme 126. Calix[4]indoles 409 Starting from 408



418 and tris(2-methylindol-3-yl)methane **416** (Scheme 129).[579] In this reaction, C2 in **417** appears to be transferred to the source of central carbon between the indoles in **416**.

Another useful method for the synthesis of asymmetric 3,3′,3″-TIMs **419** requires the use of 3-formylindoles that react with indoles, mediated by protic acids[97,99,431,580–585] such as Zeokarb-225,[346] $Zr(DS)_4$,[269] NH_4Cl,[586] I_2,[587] Ru^{3+},[588] and zeolites[589] (Scheme 130). Very recently, acidic ionic liquid [hmim]HSO_4 in ethanol has been used for this purpose and a comprehensive library of asymmetrical 3,3′,3″-TIMs have been synthesized.[590]

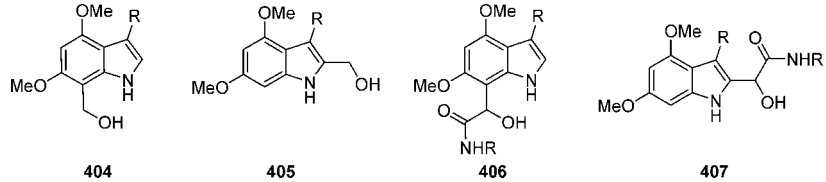


Figure 20. Indoles used for the synthesis of calix[*n*]indoles.

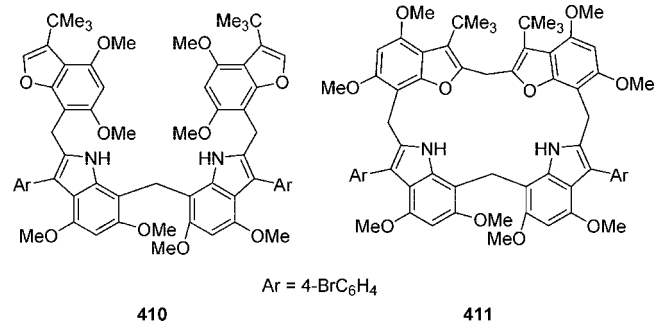
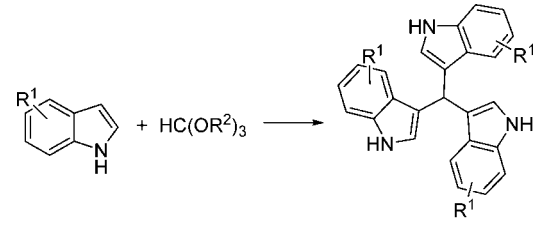


Figure 21. Structure of BIMs **410** and **411**.

Scheme 127. Synthesis of 3,3′,3″-TIMs 412



It was reported that TIMs or N-acetylated TIMs were synthesized with high yields upon treatment of indoles with indole-3-carboxaldehydes in acetic acid and acetic anhydride.[591]

Mahato and his group discovered that when 1-methylindole, dichloroacetyl chloride, and $AlCl_3$ (ratio of 1:0.4:1) are reacted at

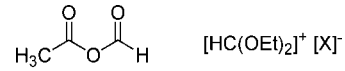
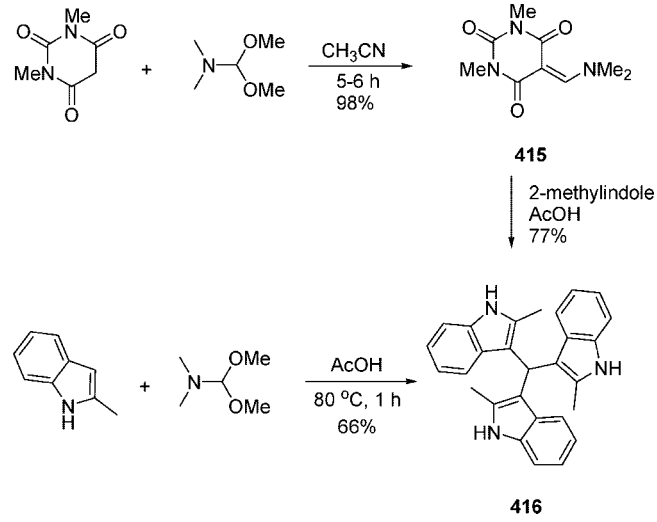
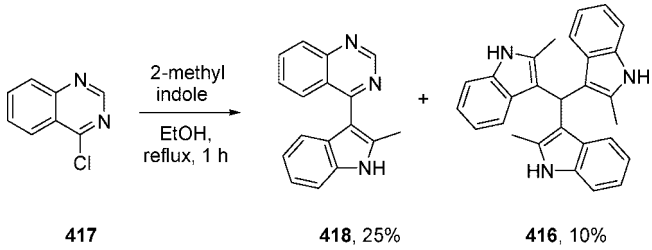


Figure 22. Acetic-formic anhydride **413** and diethoxycarbenium salts **414**.

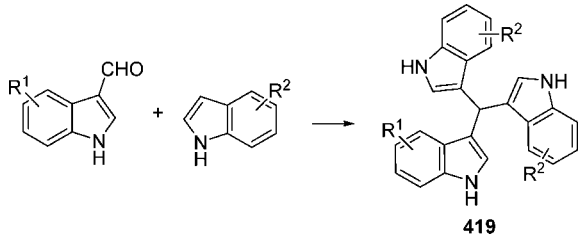
Scheme 128. Synthesis of 3,3′,3″-TIM 416



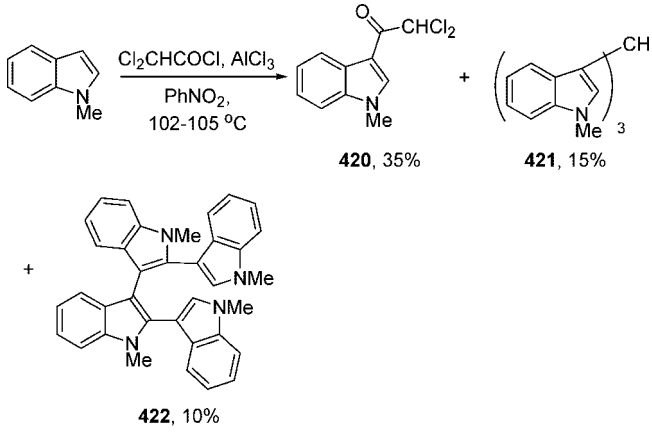
Scheme 129. Reaction of 4-Chloroquinazoline 417 with 2-Methylindole



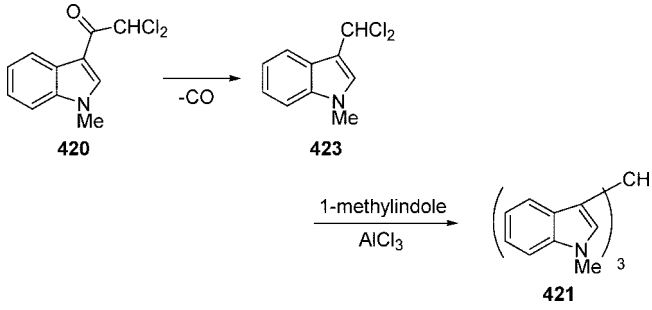
Scheme 130. Synthesis of TIMs from 3-Formylindoles and Indoles



Scheme 131. Reaction of 1-Methylindole and $Cl_2CHCOCl$



Scheme 132. TIM 421 from 420 and 1-Methylindole

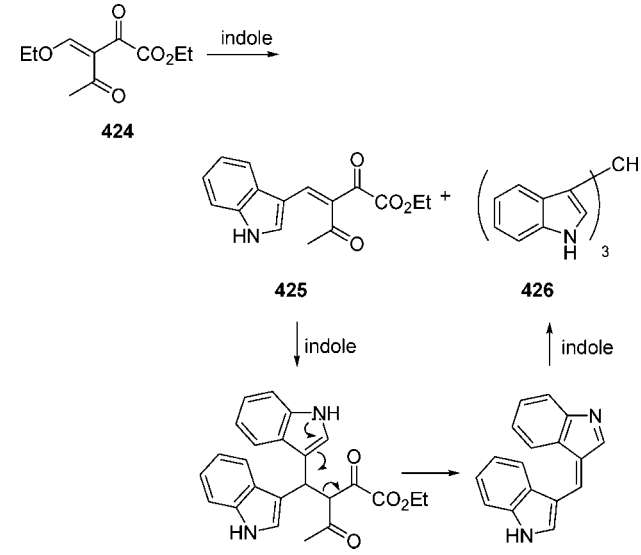


102−105 °C in nitrobenzene, 3-acylated indole **420**, TIM **421**, and the tetramer **422** are isolated (Scheme 131).[592]

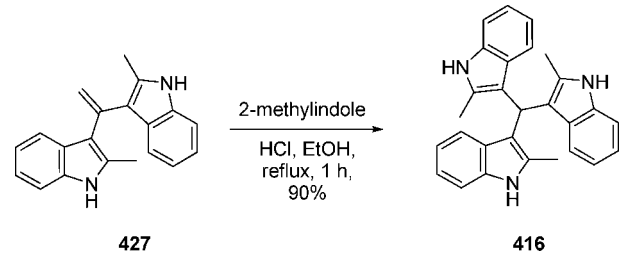
The formation of TIM **421** is rationalized as shown in Scheme 132. The usual Friedel−Crafts acylation of 1-methylindole produces the normal 3-acylated product **420**, which presumably on decarbonylation degrades to form **423** (Scheme 132).[592] Addition of 1-methylindole in the presence of a Lewis acid produces the TIM **421**.

Heating of an equimolar amount of indole with ethyl 3-ethoxymethylene-2,4-dioxovalerate **424** in ethanol gives a mixture of **425** and **426** in 12% and 19% yields, respectively (Scheme 133).[593] The yield of TIM **426** in this

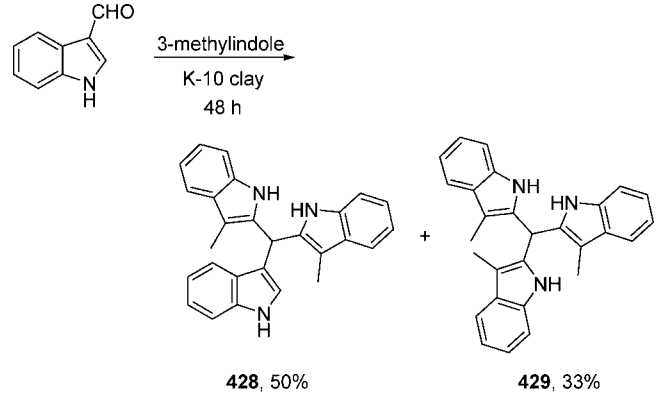
Scheme 133. Reaction of 424 and Indole



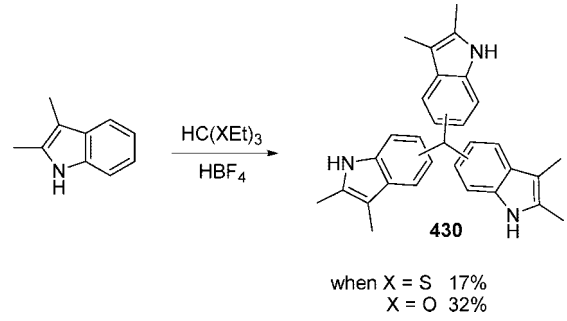
Scheme 134. Reaction of 427 and 2-Methylindole in Protic Media



Scheme 135. Reaction of 3-Formylindole and 3-Methylindole

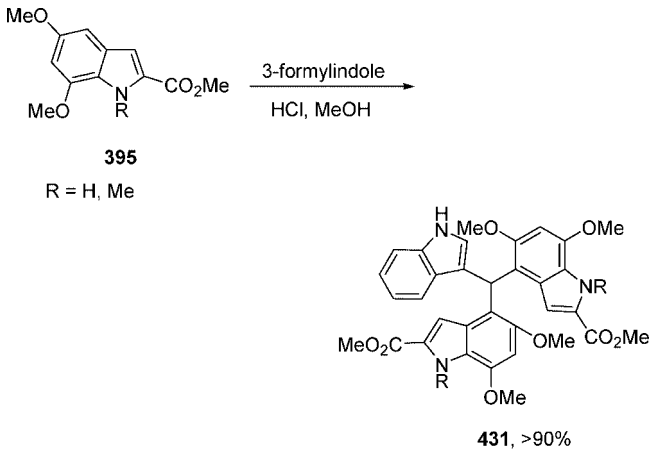


Scheme 136. Synthesis of 5,5′,5″-TIM and 6,6′,6″-TIM 430

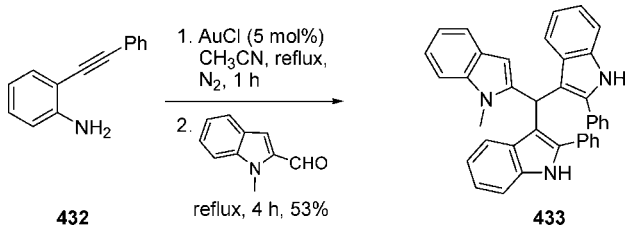


reaction was increased to 42% by using 2 equiv of indole. Also treatment of compound **425** with HCl yields 3-indole

Scheme 137. 3,4′,4″-TIMs 431



Scheme 138. One-Pot Indolization and TIM Synthesis



carboxaldehyde. A plausible mechanism for the formation of the TIM **426** from **425** is shown in Scheme 133.[593]

Bergman demonstrated that 1,1-bis(2-methyl-3-indolyl)-ethane **427** is converted to the TIM **416** (90% yield) when refluxed in the presence of 2-methylindole and ethanolic hydrochloric acid (Scheme 134).[355]

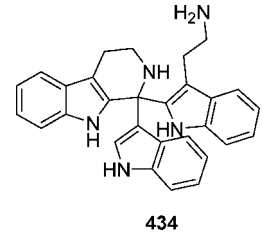
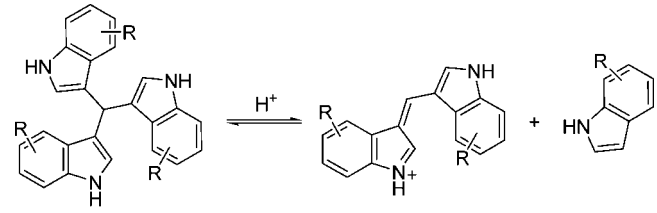


Figure 23. Bengacarboline (**434**).

Scheme 140. Cleavage of 441 to 442

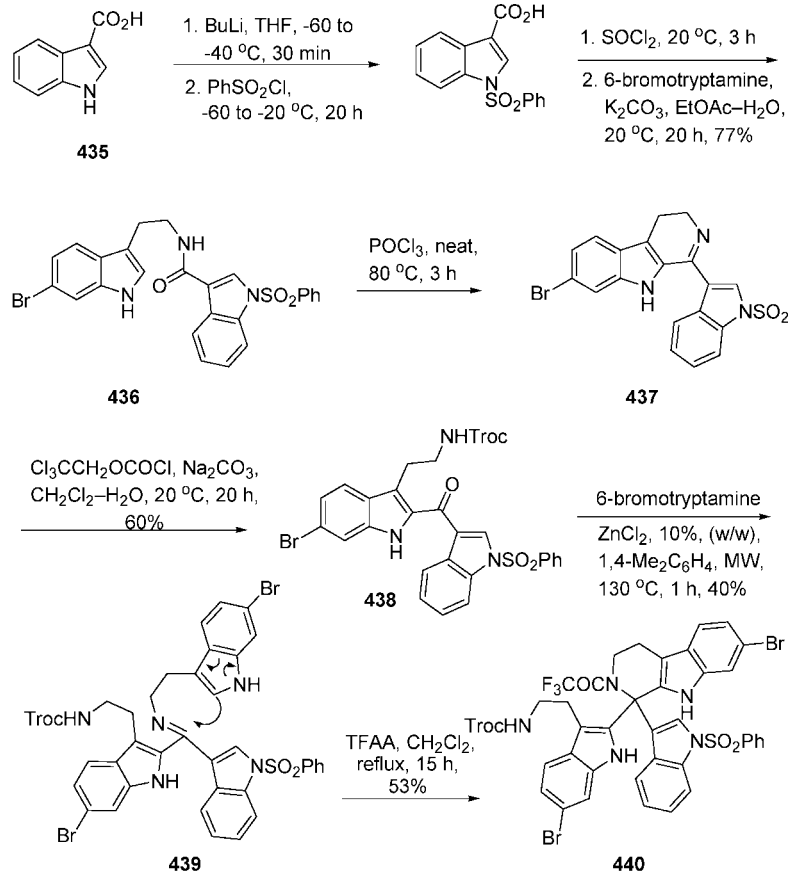


Orthoformates were also used for the synthesis of 2,2′,2″-TIMs in the reaction with 3-substituted indoles catalyzed by HCl.[576,594,595]

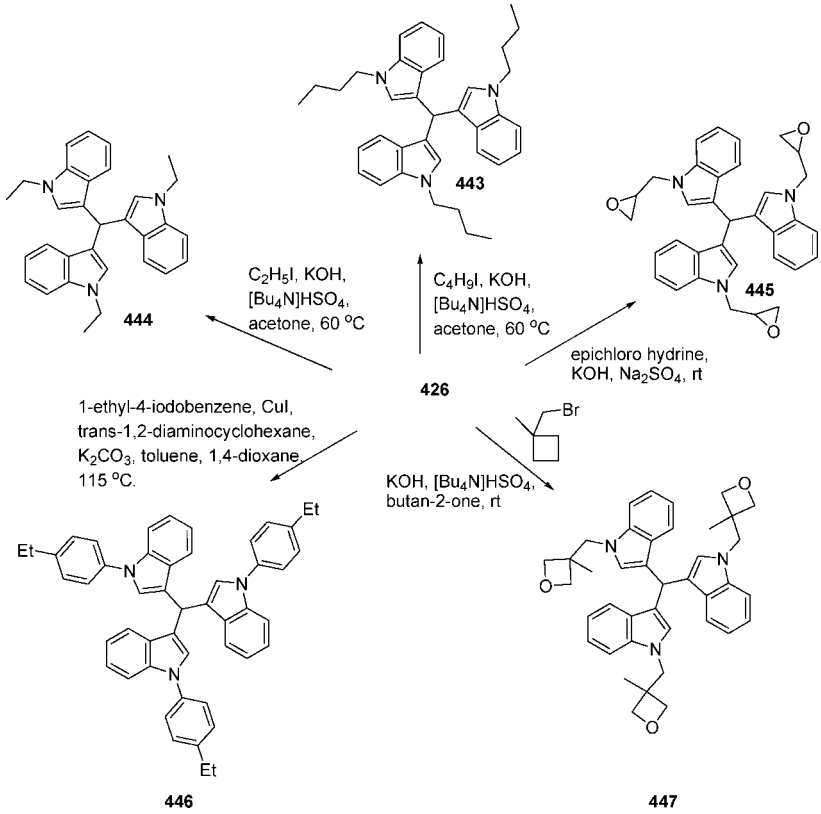
Chakrabarty and Sarkar reported that montmorillonite K-10 clay mediates the reaction of indole-3-carboxaldehyde and 3-methylindole to afford 2,2′,3″-TIM **428** and the unusual 2,2′,2″-TIM **429** in 50% and 33% yields, respectively (Scheme 135). The reaction requires extended reaction times.[596] The same product range was reported for the same reaction mediated by iodine.[597]

2,3-Dimethyl indole in the presence of ethyl orthoformate or ethyl orthothioformate and HBF_4 affords the 5,5′,5″-TIM or 6,6′,6″-TIM **430** (Scheme 136).[598] This is again an

Scheme 139. Bromoderivative of Bengacarboline 440



Scheme 141. Functionalization of TIM 426



example where the benzene ring of the indole is forced to react as result of the introduction of steric hindrance on the normal active sites of the five-membered indole ring (See Scheme 124).[598]

A rare example of 3,4′,4″-TIMs **431** has been reported by the Black group.[562] 3,4′,4″-TIM **431** was obtained in excellent yield from methyl carboxylate **395** and 3-formylindole in acidic methanol (Scheme 137). For more details of the reaction, see also Scheme 123.

2-(Phenylethynyl)aniline **432** utilizes AuCl as a catalyst in acetonitrile under reflux conditions, followed by the addition of *N*-methyl-2-formylindole, to give the TIM **433** in 53% (Scheme 138).[422]

Bengacarboline (**434**) is an inhibitor of topoisomerase II and displays *in vitro* cytotoxicity on a wide range of tumor cell lines. It was isolated from the Fijian ascidian *Didemnum* sp (Figure 23).[599]

Pouilhes et al. have reported the total synthesis of the bromoderivative of bengacarboline **440**. As shown in Scheme 139, the synthesis starts from 3-indole carboxylic acid **435**, followed by protection and treatment with 6-bromotryptamine to yield **436**. Compound **436** cyclizes to form **437**, which upon hydrolysis affords **438**. The intermediate **438** reacts with 6-bromotryptamine for the second time to yield **439**, which is converted to **440** in the presence of TFA (Scheme 139).[600]

The same authors also reported the multistep synthesis of (±)-bengacarboline from indol-3-carboxylic acid and tryptamine.[601]

Trisindolylmethanes **441** are readily cleaved by acids (Scheme 140), presumably as a consequence of the formation of a quaternary ammonium ion. In a study of the interaction of **441** with acid, Konig[602] isolated the indolene-3-indole **442** as the perchlorate salt. Berti and Marchetti also synthesized and investigated the reactivity of compounds **442**. They were able to add Grignard reagents and hydrides to **442** to form the corresponding products.[603]

Kirkus et al. prepared new triindolylmethane-based compounds **443**−**447** including those containing reactive functional groups from indole as shown in Scheme 141. They investigated thermal, optical, photophysical, and photoelectrical properties of compounds **443**−**447**.[604]

4. Conclusions

The synthesis of bis- and trisindolyl methanes (BIMs and TIMs) forms a modest but important field of chemistry. Although the chemistry of BIM and TIM synthesis has been known for slightly more than a century, the bulk of the discoveries have been made since 1990. This review demonstrates the versatility of the condensation of indoles and aldehydes and other functional groups with reasonable yields. This review presents a collection of highly interesting and useful methods for the synthesis of different types of BIMs and TIMs. We dedicate this review to all the researchers that have contributed to this field of chemistry, and we hope that it will inspire current and future chemists to utilize and expand the field of bisindolyl methane and trisindolyl methane synthesis.

5. Abbreviations

BIMs	bisindolyl methanes
bupy	1-butylpyridinium
CAN	cerium ammonium nitrate
CYPs	cytochromes P450
DAST	diethylaminosulfur trifluoride
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMFDMA	dimethyl formamide dimethyl acetal
FPS	*p*-(*ω*-sulfonic-perfluoroalkylated)polystyrene
HMTA	hexamethylenetetramine

HMTAB	hexamethylenetetraamine-bromine
LAH	lithium aluminum hydride
LDA	lithium diisopropyl amide
MW	microwave
PDC	pyridinium dichromate
PEG	poly(ethylene glycol)
PTFA	pyridinium trifluoroacetate
PTSA	*para*-toluenesulfonic acid
SSA	silica sulfuric acid
[Cu(3,4-tmt-ppa)] $(MeSO_4)_4$	tetramethyltetra-3,4-pyridinoporphyrazinato copper(II) methyl sulfate
TCA	trichloro acetic acid
TCT	trichloro-1,3,5-triazine
TEAF	triethylamine formic acid
TFA	trifluoro acetic acid
TIMs	trisindolyl methanes
TPP	triphenyl phosphonium perchlorate
triflate	trifluoromethanesulfonate
YCH	yuehchukene

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