Leibniz-Institut für Katalyse e.V. an der Universität Rostock

Development of a focused chemical library: synthesis of novel bioactive hymenialdisine derivatives

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So eine Arbeit wird eigentlich nie fertig,
man muß sie für fertig erklären,
wenn man nach Zeit und Umständen
das Möglichste getan hat.

(J. W. Goethe, Italienische Reise, 16. März 1787)

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Table of Contents

Abbreviations

cat.	catalytic
°C	degree Celsius
Ac	acetyl
Ar	aryl
ATP	adenosine triphosphate
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BTA	1-hydroxy-benzotriazole
Bu	butyl
d	days
DBU	1,8-diazabicycloundec-7-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane,
DMF	*N*,*N*-dimethylformamide
EDCl	1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride
EOM	ethoxymethyl
Et	ethyl
h	hours
IC	inhibitory concentration
KHMDS	potassium bis(trimethylsilyl)amide
LiHMDS	lithium bis(trimethylsilyl)amide
Me	methyl
min	minutes
Ms	methylsulfonyl
MS	molecular sieve
N	normality
NBS	*N*-bromosuccinimide
nM	nanomolar
Ph	phenyl
PMB	*para*-methoxybenzyl
PPA	polyphosphoric acid
rt	room temperature
SEM	2-(trimethylsilyl)ethoxymethyl
TFA	trifluoroacetic acid
THF	tetrahydrofurane
μM	micromolar

1. Introduction

The search for new pharmaceuticals requires intensive collaboration in different research areas including pharmacology, clinical sciences, chemistry, bioinformatics, molecular biology and in particular genomic sciences.[1] In billion-years of evolution, living organisms have advanced their internal signaling, communication and defense by utilizing small molecules. These pre-validated small-molecule natural products provide the fruitful resources for the pharmaceutical industry. However, in the development of novel drug candidates, the isolation, identification and synthesis of natural products remain an ongoing big challenge for organic chemists.[2] Consequently a number of drugs are natural products, such as erythromycin,[3] taxol[4] and lovastatin,[5] or their derivatives, like aspirin.

In many cases interesting pharmacological properties guided the synthesis of novel natural product hybrid structures as lead compounds.[6,7] The pharmacological activity of compounds from nature and their derivatives are especially promising, since those structures or substructures thereof have been selected by evolution and are therefore privileged structures.[8] Interestingly statistical studies indicated that structural complexity and diversity of drug molecules is much closer to natural products, than to compounds obtained by random combinatorial library synthesis.[9] Therefore complexity and diversity are key-factors for success in navigating the vast chemical space to identify regions containing relevant bioactive compounds.[10] Although marketed drugs have addressed only a limited number of biological targets, which are usually proteins like enzymes, ion channels or receptors, researchers from genomics are identifying more and more previously unknown targets simultaneously.[11] Today the time consuming hit and lead finding efforts progress with modern high-throughput techniques, which are able to screen

thousands of small molecules within days. Medicinal chemists thus face the challenge of the tremendous demand for more new compounds to address novel targets.

In order to increase the efficiency for identification of novel drug candidates, different synthetic strategies have been developed to compose small molecule libraries.[12] On the one hand target-oriented synthesis can be used to synthesize natural product derivatives with common structural features for pre-selected protein targets. Organic chemists usually perform a retro-synthetic analysis as a problem-solving method to discover key structural elements in the initial stage.[13] Thereby fragment-coupling reactions are identified as crucial steps to connect building blocks to the structural complex molecule. Derived from this synthetic analysis, these chemical transformations might lead to a synthetic diversification strategy to gain structurally related target molecules for focused libraries. Depending on their specific efficiency, standard solution phase protocols, solid phase synthesis and their combinations have been applied to create small molecule libraries based on natural product scaffolds, e.g. vancomycin[14] and sarcodictyin.[15]

On the other hand diversity-oriented synthesis does not aim on a certain target. This concept emphasizes on the generation of structural diversity and complexity for a compound library aiming on a successful genetic-like screening against various targets.[16] Solid phase synthesis combined with a split-and-pool synthesis strategy and the spatial segregation of polymer beads is very often employed. In practice diversity-oriented synthesis for drug discovery is embedded in a three step process: combinatorial generation of diverse small molecules, followed by various biological screenings, and finally structural characterization of the small molecules, which gave positive hits in the corresponding assays. Typically only very small quantities of complex molecules are synthesized. For the difficult backwards analysis of the active structure, encoded one-bead-one-stock systems with high capacities per bead have been developed. The encoding

information supports the independent chemical synthesis of the active compound and its derivatives.[17]

In the last decade crossovers of methods and tools described above have been implemented. Recently Shair and co-workers demonstrated the application of diversity-oriented synthesis as a strategy to produce a diverse natural-product based library to identify molecules with totally new biological functions.[18] In their one-bead-one-stock approach, the split-and-pool synthesis was designed analogous to a natural product synthesis. Subsequent phenotype screening led to the identification of novel biological functions of natural product derivatives. Merging the concept of target-oriented synthesis and privileged structures, Nicolaou et al. applied a two step approach: first statistical identification of the privileged structural motif (e.g. benzopyrane), followed by a combination of this structural feature with six different natural product scaffolds to obtain focused natural-product like compound libraries for their screenings against certain targets.[19]

In general the design and diversity of the compound library is intrinsically more important than the library size to find relevant biological activity.[20] In recent years small collections of smart library molecules appear more valuable than a large mindlessly assembled one. It increases the hit rate during the search for improved or novel bioactivities.[21] The success of drug development from natural product origins has been proofed by the large number of pharmaceuticals in the last 25 years.[22] Structural and statistical analysis guided the design, synthesis and selection of compounds for the setup of focused chemical libraries. This development was supported by experimental and computational approaches towards the helpful concepts of drug-like properties[23] and privileged structures of potential drug candidates.[24]

The natural product hymenialdisine and its analogues exhibit a variety of interesting biological activities. A detailed analysis of reported syntheses of hymenialdisine and related natural products as well as their non-natural derivatives guided the way to the development of a focused library of novel bioactive compounds.

1.1. Synthesis of natural products from the hymenialdisine family

In the last decades a broad variety of pyrrole alkaloids has been isolated, synthesized and studied in detail as potential pharmaceuticals.[25,26] Among them natural products containing a pyrrolo[2,3-*c*]azepinone motif like hymenialdisine (**1**),[27,28,29] hymenin (**2**),[30] stevensine (**3**),[31,32] latonduine A (**4**) and B,[33] (*E*)-anxinohydantoin (**5**)[34,35] (the corresponding (*Z*)-isomers of the anxinohydantoins are also named as spongiacidins C and D),[36] aldisine[37] and other derivatives of the related oroidin family[38] have been isolated and characterized (Figure 1).[39] Due to their interesting pharmacological properties, significant efforts have been made to achieve independent synthesis of these natural products. All compounds related to the hymenialdisine family share the structural element of the fused bicyclic pyrrolo[2,3-*c*]azepinone. Additionally, the majority of these complex molecules possess a third heterocycle connected to the pyrrolylic carbon.

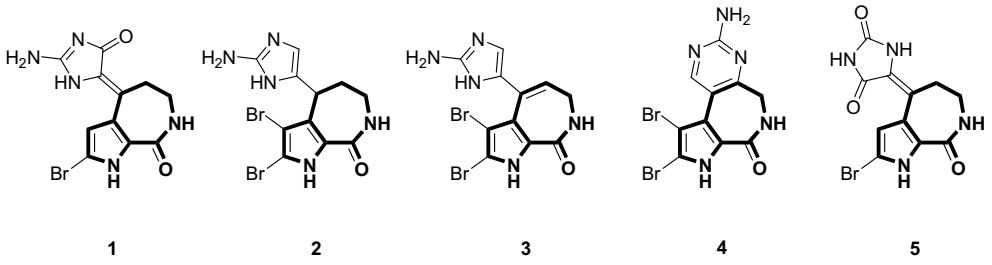


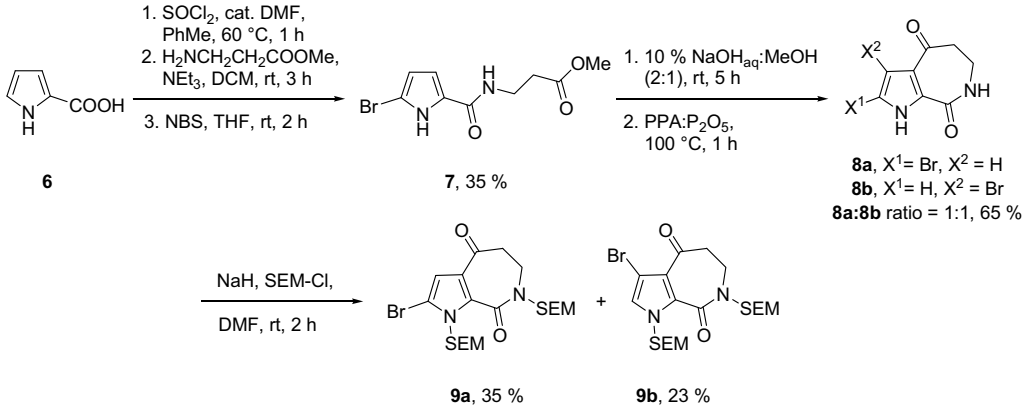
Figure 1. Natural products with a pyrrolo[2,3-*c*]azepinon core structure: (*Z*)-hymenialdisine (**1**), hymenin (**2**), stevensine (**3**), lantonduine A (**4**) and (*E*)-axinohydantoin (**5**).

Among natural products with a pyrrolo[2,3-*c*]azepinone core structure, hymenialdisine (**1**) was studied extensively. In the early 1980s (*Z*)-hymenialdisine (**1**),[27,28] (*Z*)-2-debromo-hymenialdisine[40] and 3-bromohymenialdisine[41] were isolated from different marine sponges like *Acanthella aurantiaca*,[27] *Hymeniacidon aldis*,[28] *Axinella verrucosa* (syn. *Stylissa*)[34] and *Pseudoaxinyssa cantharella*.[42] The molecular structure of (*Z*)-hymenial-disine (**1**) was confirmed by X-ray crystallographic analysis. Later (*E*)-hymenialdisine was also found in nature by extraction of *Stylotella aurantium* from Palau.[29] The (*Z*)-isomer (**1**) appeared to be more thermodynamically stable than the corresponding (*E*)-hymenial-disine.[43] (*Z*)-Debromohymenialdisine was first isolated in 1980 out of the sponge *Phakellia flabellata* from the Great Barrier Reef[44] and was structurally confirmed during the discovery of hymenialdisine (**1**) two years later.[27] Analogous to its brominated derivative **1**, the (*E*)-isomer of debromohymenialdisine has been also isolated and characterized.[29] In 1990 the isolation and characterization of hymenialdisine (**1**) by Pettit et al. was driven by the discovery of antiproliferative properties of a hymenialdisine-containing natural product extract on cultured lymphocytic leukemia cells.[34] Later hymenialdisine (**1**) was identified to inhibit various protein kinases such as cyclin-dependent kinases CDK1, CDK2 and CDK5, glycogen synthase kinase GSK3β, casein kinase CK1,[45] mitogen-activated protein kinases MEK1 and MAPK1,[46] checkpoint kinases Chk1 and Chk2,[47,48] p90 ribosomal S6 kinase p90RSK, kinase domain-containing receptor KDR, tyrosine kinases Fes and c-KIT, p21-activated kinase PAK2, pyruvate dehydrogenase kinase PDK1, protein kinase PKCθ, protein kinase PKD2, ribosomal kinase Rsk1, and serum- and glucocorticoid-inducible kinase SGK.[49] The kinase inhibiting properties are of great potential for the development of novel pharmaceuticals e.g. in the area of cancer,[50] Alzheimer's disease,[49] arthritis,[51] etc. Further hymenialdisine (**1**) inhibits the interleukin-1-induced proteoglycan degradation,[52] the production of cytokine[53] and was identified to be active against NFκB-mediated gene

transcription and the IL-8 production in U937 cells resulting in anti-inflammatory effects.[54,55,56]

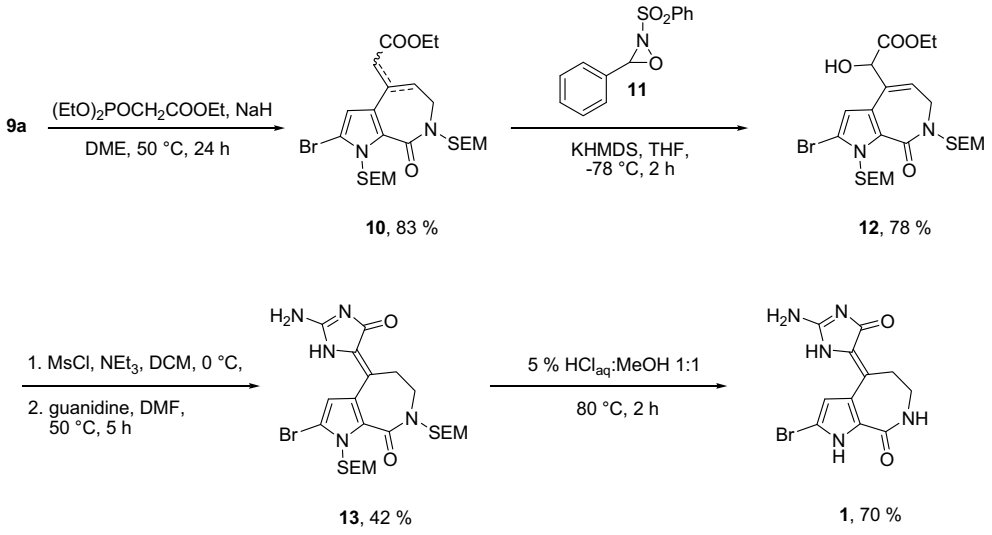
The close related derivative hymenin (**2**) was isolated by Kobayashi and coworkers in 1986 from the marine sponge *Hymeniacidon* and found to be an α-adrenoceptor blocking agent.[30,57] Meanwhile stevensine (**3**) was isolated from an unidentified Micronesian sponge[31] and a *Pseudaxinyssa Cantharella* sponge simultaniously.[42] Recently, the novel marine alkaloids latonduine A and B have been isolated from the sponge *Stylissa cateri* and were subsequently synthesized since an extract of this sponge showed significant in vitro cytotoxicity against human cancer cell lines.[33] Additionally, in 1990 the natural product (*E*)-axinohydantoin (**5**) was obtained from the marine sponge *Axinella* and its structure was determined by X-ray crystallography.[34] In 1997 two other isomers, (*Z*)-axinohydantoin and (*Z*)-debromoaxinohydantoin have been isolated from the sponge *Stylotella aurantium* and were found to inhibit protein kinase C (PKC) in micro molar concentrations with IC_{50} values of 9.0 and 22 μM respectively.[35] Subsequent to the isolation of four new natural products from the sponge *Hymeinacidon* Kobayashi and coworkers renamed the corresponding (*Z*)-axinohydantoin and (*Z*)-debromoaxinohydantoin in their series as spongiacidins C and D.[36]

The first total synthesis of hymenialdisine (**1**) was established by Annoura *et al.*[58] In their synthesis the fused pyrrolo[2,3-*c*]azepinone motif was introduced via a 2-bromoaldisine[42] synthon **8a**, which was synthesized starting from commercially available pyrrole-2-carboxylic acid (**6**). Via the transformation to an acid chloride, **6** was reacted with β-alanine methyl ester to obtain intermediate **7** in 35 % yield after bromination. Saponification and acidic cyclization yielded 2-bromoaldisine (**8a**) in a 1:1 mixture with 3-bromoaldisine (**8b**) (combined yield: 65 %). Separation of both isomers succeeded via column chromatography after the introduction of 2-(trimethylsilyl)ethoxymethyl (SEM) protecting groups (yields: **9a**: 35 %, **9b**: 23 %) (Scheme 1).



Scheme 1. Synthesis of SEM-protected 2-bromoaldisine (**9a**).

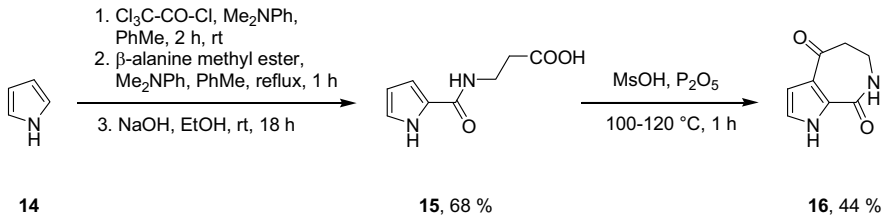
Aldisine derivative **9a** was subsequently converted into (*Z*)-hymenialdisine (**1**) in six additional steps to install the third heterocycle and remove the SEM-protecting groups (Scheme 2). First **9a** was reacted in a Horner-Emmons reaction yielding intermediate **10**, followed by deprotonation and treatment with 2-benzenesulfonyl-3-phenyloxaziridine (**11**) to give pyrrole[2,3-*c*]azepinone **12**. Introduction of a leaving group and reaction with guanidine led to cyclization of hydantoin derivative **13** in 42 % yield. Finally, deprotection of the SEM groups with hydrochloric acid in methanol yielded the natural product (*Z*)-hymenialdisine (**1**).



Scheme 2. First total synthesis of (*Z*)-hymenialdisine (**1**).

The same procedure was employed to prepare the natural product (*Z*)-debromohymenialdisine. Thereby the SEM-protected aldisine derivative was synthesized in very similar overall yield.

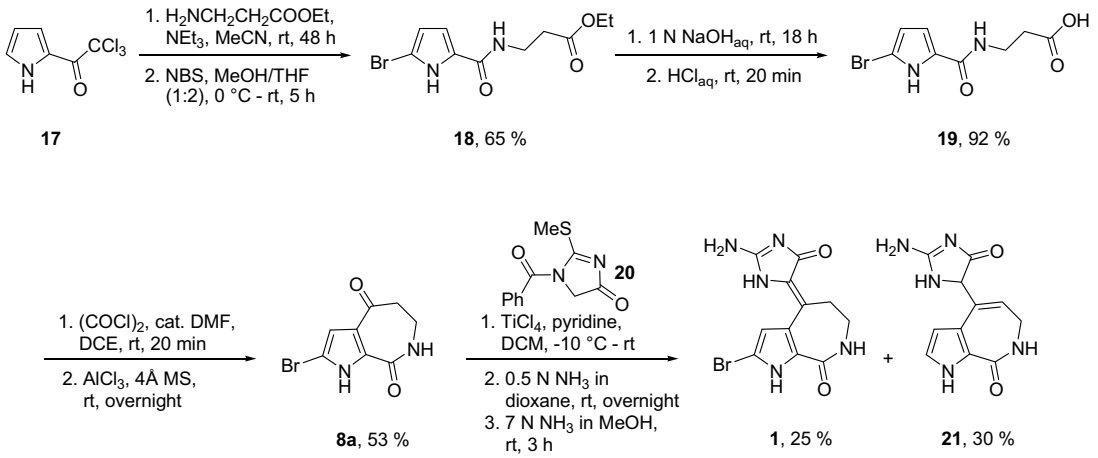
One year later new cyclization conditions implemented for the indolo-derivatives using polyphosphoric acid in the absence of phosphorus pentoxide resulted in 77 % yield of an annulated aldisine derivative.[59] In the same year Cho et al. reported the application of a 9:1 mixture of methanesulfonic acid and phosphorus pentoxide as a more efficient (up to 90 % yield) and easy to handle method.[60] A novel synthesis of the pyrrole-2-carboxylic acid derivatives starting from pyrrole (**14**) and phosgene analogues in the presence of a base was developed to obtain the substrate **15** in a cheap and large scale manner. In subsequent cyclization with P_2O_5/MsOH the natural product aldisine (**16**) was obtained (Scheme 3).[61] Similar synthetic strategies have often applied in the total synthesis of aldisine derivatives later on.



Scheme 3. Cyclization to aldisine (**16**) with P_2O_5 and MsOH.

Recently, the total synthesis of (*Z*)-hymenialdisine (**1**) was completed by Papeo *et al.* employing a new glycociamidine ring precoursor (Scheme 4).[62] During their studies a Friedel-Crafts type cyclization to access 2-bromoaldisine (**8a**) motif was introduced. The reaction conditions reported for the synthetically challenging 2-bromoaldisine (**8a**) are advantageous due to the low reaction temperature, but this route required one more step to obtain the acid chloride intermediate from **19**. Followed by a three-step one-pot

methodology involving a titanium-mediated Aldol-reaction, (*Z*)-hymenialdisine (**1**) was obtained in 25 % yield. Surprisingly, the main product in the final step of the hymenialdisine formation was *endo*-debromohymenialdisine (**21**) (30 % yield).

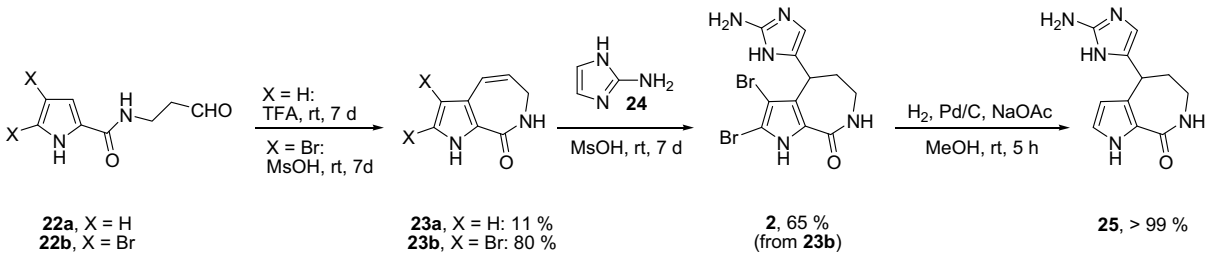


Scheme 4. Papeo´s total synthesis of (*Z*)-hymenialdisine (**1**).

In the past twenty years Horne and coworkers accomplished the total synthesis of a series of the pyrrolo[2,3-*c*]azepinone based natural products such as hymenialdisine (**1**), hymenin (**2**),[63] stevensine (**3**) and debromohymenialdisine.[64,65] A novel synthesis to access the core structure of hymenin (**2**) was developed. Starting from **2**, other previously isolated marine alkaloids have been synthesized for the first time.

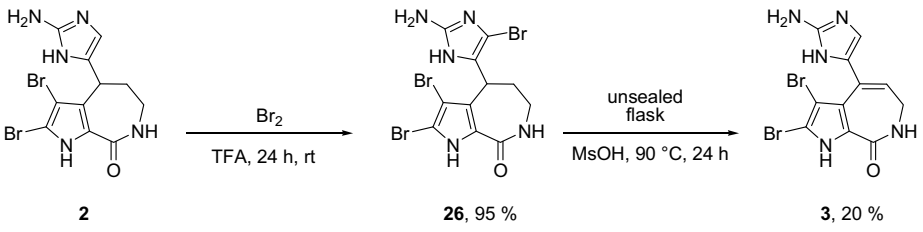
As a starting point for the synthesis of hymenin (**2**), a novel cyclization from aldehyde derivatives **22a** and **22b** was established. Acidic cyclization to the olefins **23a** and **23b** was employed instead of previously described ring closure of acid intermediates to aldisin (**16**) or derivatives **9a** and **9b**. Thereby the introduction of two bromine substituents into the pyrrole moiety was crucial to avoid dimerization of olefin **23a** (59 % isolated yield for dimerized product). Subsequent treatment of intermediate **23b** with 2-aminoimidazole (**24**) under acidic conditions yielded hymenin (**2**) in 65 % yield (Scheme 5). Reductive

debromination of hymenin (**2**) with hydrogen in the presence of palladium on charcoal and NaOAc led to debromohymenin (**25**) in quantitative yield.



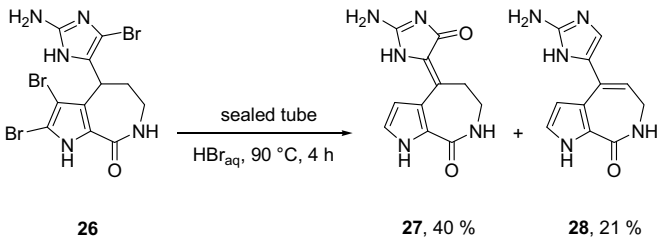
Scheme 5. Horne´s synthesis of hymenin (**2**) and debromohymenin (**25**).

Further chemical transformation of the previously synthesized hymenin (**2**) allowed the total synthesis of stevensine (**3**) in two additional steps (scheme 6).[32] Bromination of the imidazole heterocycle in substrate **2** yielded 4´-bromohymenin (**26**) followed by a proto-debromination/trans-bromination event to yield stevensine (**3**) in 20 % yield. In the final step hymenin (**2**) was re-obtained in 40 % isolated yield.



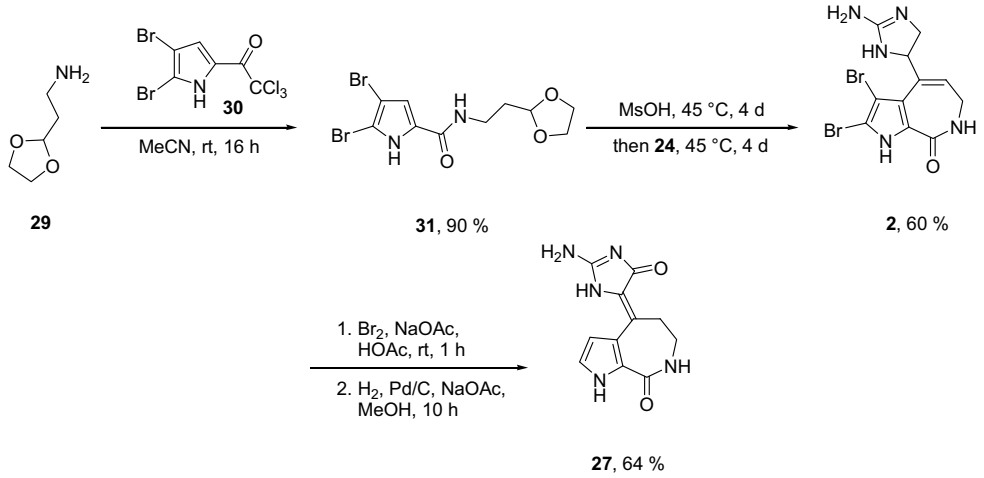
Scheme 6. Total synthesis of stevensine (**3**) starting from hymenin (**2**).

A debromination procedure applied to intermediate **26** employing aqueous hydrobromic acid led to (*Z*)-debromohymenialdisine (**27**) (40 % yield) and debromostevensine (**28**) (21 % yield) in one step (Scheme 7).



Scheme 7. Synthesis of (*Z*)-debromohymenialdisine (**27**) and debromostevensine (**28**).

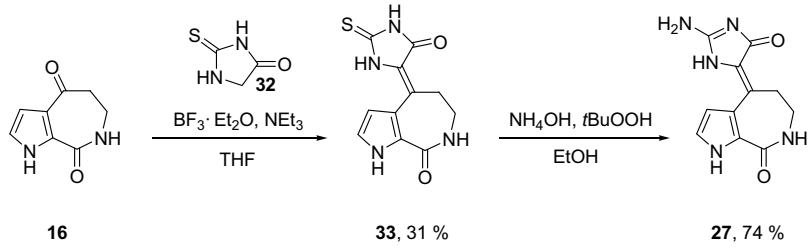
In the last decade more practical protocols for the synthesis of hymenin (**2**) and (*Z*)-debromohymenialdisine (**27**) have been developed. Combining short and high yielding reactions, the acidic cyclization to the core structure and the attachment of the 2-aminoimidazole heterocycle (**24**) onto the pyrrole[2,3-*c*]azepinone structure within a one-pot-two-steps reaction as key transformation yielded hymenin (**2**) in excellent yields (overall 54 %) (Scheme 8).[64] A two-fold oxidation of hymenin (**2**) and subsequent treatment with hydrogen in the presence of palladium on charcoal yielded the target compound **27** in 34 % allover yield.



Scheme 8. Practical synthesis of hymenin (**2**) and (*Z*)-debromohymenialdisine (**27**).

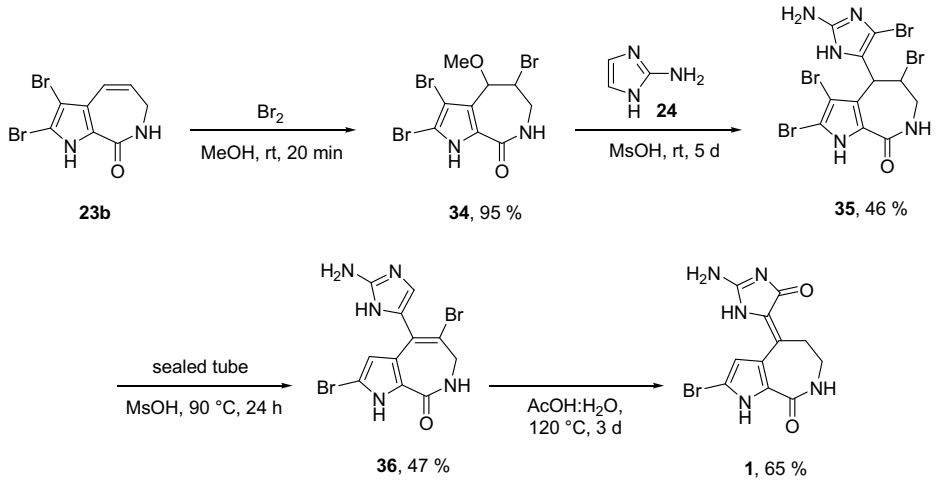
In their multigram preparation of (*Z*)-debromohymenialdisine (**27**), Portevin et al. employed the synthetic strategy of Cho and coworkers (see above, Scheme 3) to obtain

aldisine (**16**) in four steps starting from pyrrole.[66] Further transformation of **16** (Scheme 9) with 2-thiohydantoin (**32**) in the presence of $BF_3 \cdot Et_2O$ to intermediate **33**, followed by treatment of aqueous ammonia in the presence of *tert*-butyl peroxide yielded the natural product (*Z*)-debromohymenialsine (**27**) in six steps and overall 6.6 % yield starting from pyrrole.



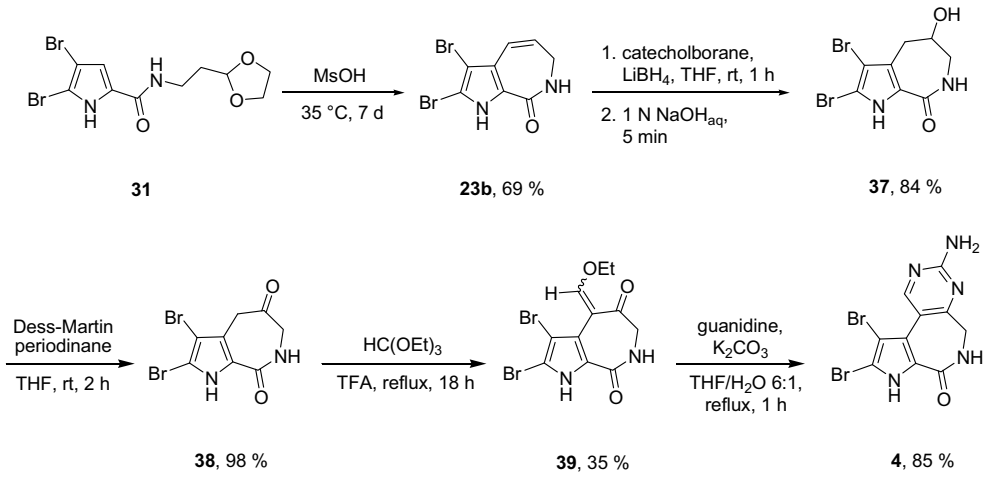
Scheme 9. Preparation of (*Z*)-debromohymenialdisine (**27**) from aldisine (**16**).

Synthetic efforts to synthesize hymenialdisine (**1**) were also successful starting from the olefinic intermediate **23b** using cascades of bromine-chemistry (Scheme 10).[65] Reaction of olefin **23b** with bromine in methanol at room temperature led to the functionalized lactam **34** in 95 % yield. Intermediate **34** reacted with 2-aminoimidazole (**24**) under acidic conditions to give the carbon-carbon coupling product **35** in 46 % yield. The subsequent formation of olefin **36** involved an elimination of hydrobromic acid, followed by a protodebromination of the β-pyrrolic position. Simultaneous production of bromine resulted in a reaction to 5-bromo-3-debromostevensine (**36**). Finally, olefin **36** was treated with aqueous acetic acid under reflux conditions to give hymenialdisine (**1**) in 65 % as the major product.



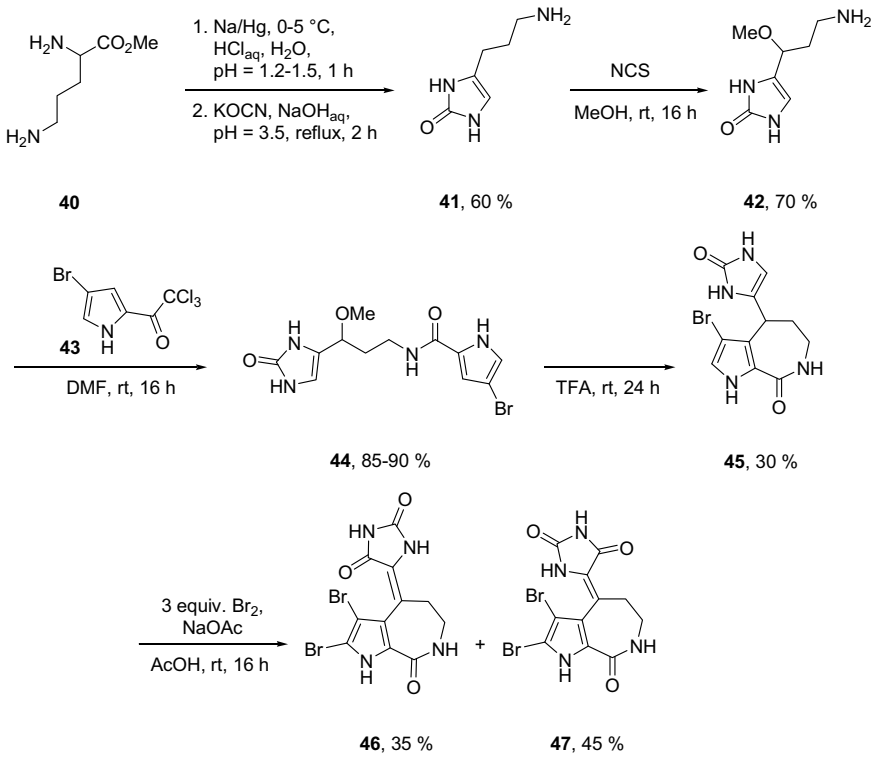
Scheme 10. Synthesis of hymenialdisine (**1**) from olefin **23b**.

Inspired by the strategy of cyclization to olefin **23b**, Linington et al. developed a synthesis of lantonduine A (**4**) and B.[33] First protected aldehyde **31** was cyclized to olefin **23b**. The attachment of the fused pyrimidine heterocycle to the seven membered ring system was achieved via hydroboration of olefin **23b** in the presence of catecholborane and lithium borohydride and subsequent hydrolysis with base to yield alcohol **37** in 84 % over two steps. This intermediate **37** was further oxidized with Dess-Martin periodinane to give the cyclic ketone **38** in almost quantitative yield (Scheme 11). Treatment with ethyl orthoformate resulted in functionalization in α-position to the pyrrole ring system and further reaction of **39** with guanidine led to lantonduine A (**4**) in 17 % overall yield.



Scheme 11. Synthesis of lantonduine A (**4**).

Another class of natural products containing the pyrollo[2,3-*c*]azepinone core structure is the group of anxinohydantoins. In 2002 Horne and coworkers completed the synthesis of debromo- and bromoaxinohydantoin in both (*E*)- and (*Z*)-forms.[67] Starting from α-functionalized imidazolones **42**, the route might reflect a possible biosynthetic pathway analogous to a cyclization of the natural product oroidin. The synthesis follows the concept of amide bond formation previous to the acidic cyclization as already described above. But in contrast to earlier protocols the third heterocycle of the natural product was already connected in the synthon **44** before cyclization to intermediate **45** occurs (Scheme 12). Bromination with three equivalents bromine gave the (*E*)- and (*Z*)-isomers **46** and **47** of bromoaxinohydantoin in 35 % and 45 % isolated yield, respectively.



Scheme 12. Synthesis of (*E*)-bromoaxinohydantoin (**46**), (*Z*)-bromoaxinohydantoin (**47**).

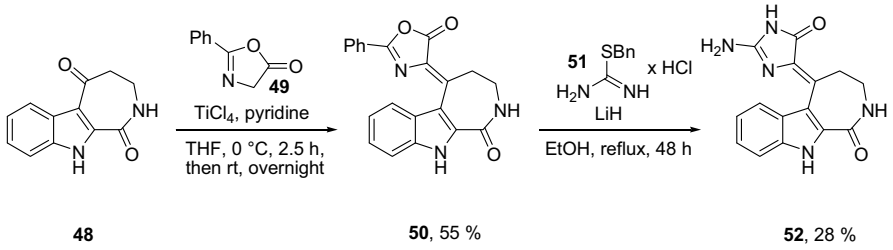
Both isomers **46** and **47** were separately debrominated in a hydrogenation reaction with hydrogen gas in the presence of palladium on charcoal at room temperature in methanol to give (*E*)-debromoaxinohydantoin and its (*Z*)-isomer 40 % and 80 % respectively.

In summary different syntheses of pyrrolo[2,3-*c*]azepinone derived natural products from the hymenialdisine family have been analyzed in detail. A significant number of preparation protocols are based on the preformation of the pyrrolo[2,3-*c*]azepinone core structure in form of an aldisine derivative or an olefinic intermediate. Usually the third heterocycle is connected or created subsequently. These methods commonly provide robust reactions with respect to stable yields and isolatable intermediates for further synthetic procedures. Additionally, a number of biological studies with natural products from the hymenialdisine family have been reported. In combination of the chemistry and biology, hymenialdisine (**1**) and analogues are attractive synthetic targets for further derivatisation. A compound library derived from these structures is a valuable tool for the improvement of existing biological properties and discovery of novel pharmacological activities.

1.2. Preparation and biological activities of hymenialdisine derivatives

Attracted by the biological properties of the hymenialdisine family, different research groups revisited the synthesis for the development of novel hymenialdisine-derived indolo[2,3-*c*]azepines aiming on investigation of novel biological functions of these small molecules. The synthesis of direct indolo-analogues of hymenialdisine (**1**) has been reported.

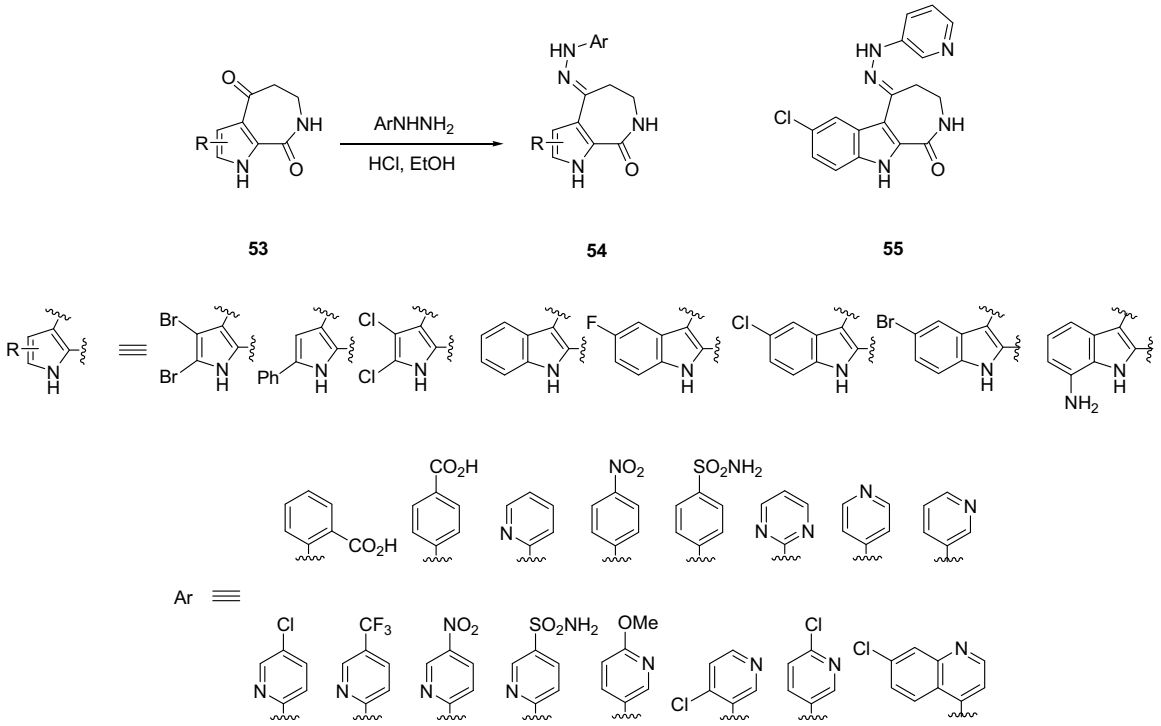
Starting from indole-2-carboxylic acid, Tepe and coworkers synthesized an annulated aldisine derivative **48** via amide bond formation with β-alanine ethyl ester, subsequent saponification and acidic cyclization based on known procedures in the total synthesis of hymenialdisine (**1**). A titanium-mediated Aldol-condensation with 5-phenyloxazolone (**49**) as a precursor resulted in intermediate **50** in 55 % yield (Scheme 13). Treatment of the oxazolone derivative **50** with *S*-benzylthiourea (**51**) and lithium hydride led to the direct annulated hymenialdisine analog **52** in 12 % overall yield.[53]



Scheme 13. Synthesis of annulated hymenialdisine derivative **52**.

In biological screenings the non-natural product **52** inhibited interleukin-2 (IC_{50} = 3.5 μM) and the tumor necrosis factor α (IC_{50} = 8.2 μM). Additionally, it was identified as a potent inhibitor of the cell cycle checkpoint kinase Chk2 in nanomolar concentrations (IC_{50} = 8 nM).[48] Interestingly annulated compound **52** led to significantly increased selectivities towards the inhibition of kinases Chk1 and Chk2 compared to hymenialdisine (**1**) or debromohymenialdisine (**27**).

In another study, the synthesis and novel target identification of direct hymenialdisine analogs and annulated derivatives were accomplished.[49] Beside the intense efforts to synthesize close related derivatives with pyrrolo- and indolo[2,3-*c*]azepinone core structures, a novel library of hydrazones **54** (Scheme 14) was generated starting from various aldisine derivatives **53** in order to modify the heterocycle at α-position to the pyrrole moiety.

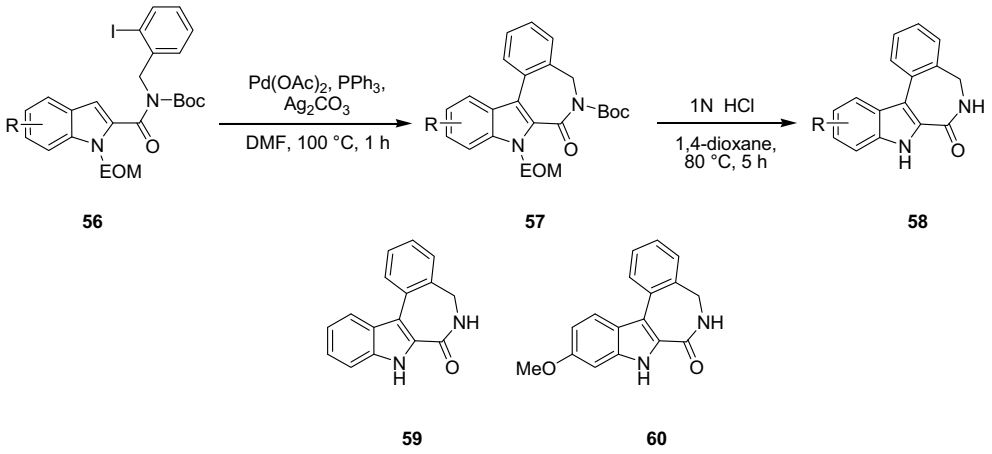


Scheme 14. Derivatisation of pyrrolo[2,3-*c*]azepinones **53** via hydrazone formation to **54**.

Screening of the focused library against a panel of 60 recombinant enzymes resulted in the discovery of eleven new targets including the kinases p90RSK, KDR, c-Kit, Fes, MAPK1, PAK2, PDK1, PKCθ, PKD2, Rsk1 and SGK. The novel natural product analogs **54** turned out to possess dramatically increased or changed selectivities compared to hymenialdisine (**1**) itself; e.g. the annulated hydrazone derivative **55** exhibits 30-fold higher anti-proliferative activities than hymenialdisine (**1**).

Inspired by these studies, the modification of substituents on the azepinone-ring system turned out to be another attractive goal for synthetic chemists. Recently two further research groups published their synthetic progress in the preparation of latonduine derivatives carrying a fused benzene moiety instead of a pyrimidine ring system in the natural product **4**. In 2005 Joseph and coworkers developed a synthesis of indolo[2,3-*c*]-azepinones as a part of their novel strategy to obtain the natural product derivatives **58** (Scheme 15).[68] Condensation of protected indole-2-carboxylic acid derivatives to

2-iodobenzamine and subsequent intramolecular palladium-catalyzed Heck-reactions yielded the corresponding indolo[2,3-*c*]benzazepinones **57**. Recently the synthetic protocol was extended by a variation with removable protecting groups. After deprotection of the *tert*-butyloxycarbonyl (boc) and ethoxymethyl (EOM) groups the desired target compounds **58** were obtained.[69]

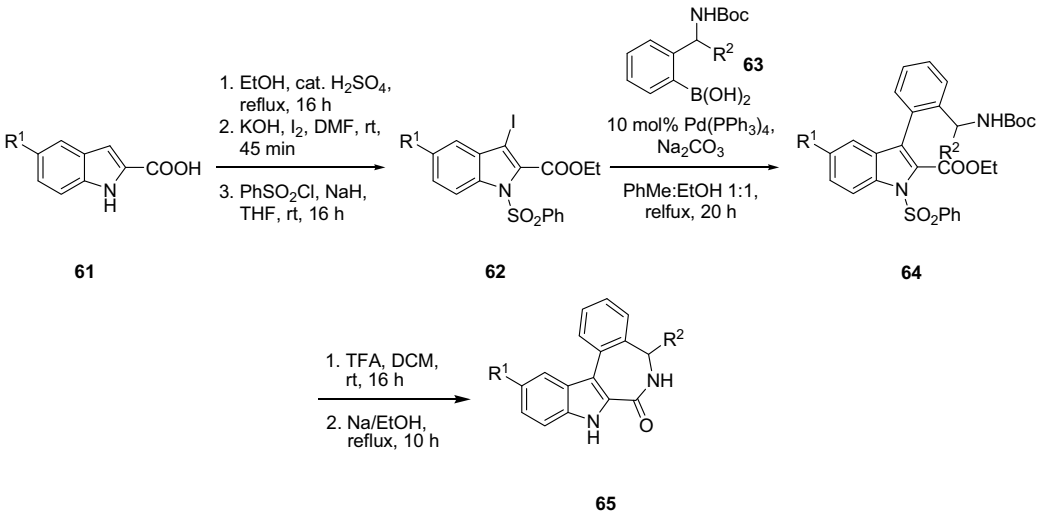


Scheme 15. Synthesis of latonduine derivatives **58** via intramolecular Heck-reaction.

In an additional diversification the indole moiety was exchanged to pyrrole and benzothiofurane to obtain modified structures and gain novel non-natural derivatives. But in contrast to the indole derivatives **58**, these structures remained all mono-methylated on the lactam nitrogen atom, which might be unfavorable in biological screenings. Nevertheless, the compounds have been tested in vitro on MCF-7 breast adenocarcinoma cell lines. The best antiproliferative activity was found as expected for close derivatives **59** (IC_{50} = 1.2 μM) and **60** (IC_{50} = 0.6 μM), which do not carry any *N*-protecting group.

Very recently an inverted synthetic sequence was applied in a study about inhibitors of tubulin polymerization resulting in antitumor and cytotoxic activities (Scheme 16).[70] The synthetic strategy started with Suzuki-couplings of arylboronic acids **63** to a 3-iodoindole derivative **62**, followed by the deprotection of the boc-protecting group. Subsequent

removal of the sulfonyl-protecting group and formation of a ring-closing amide-bond was achieved in one-step to obtain the alkylated latonduine derivatives **65**.



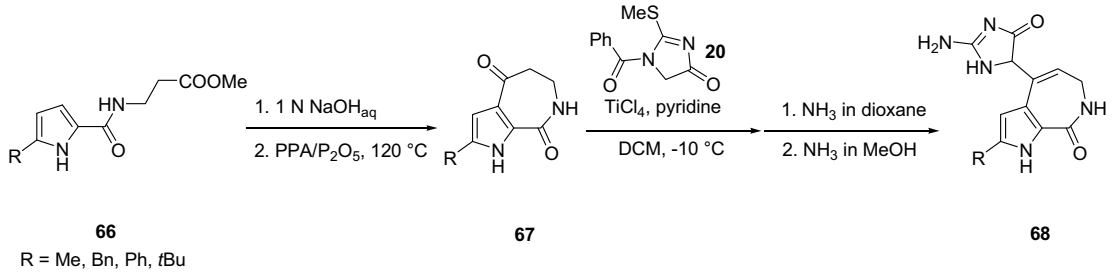
R^1 = H, OMe, F; R^2 = H, Me, (*R*)-Me, (*S*)-Me, (*R*)-Et, (*S*)-Et, *n*Pr, *n*Bu, *i*Pr.

Scheme 16. Synthesis of a small library of alkylated latonduine analogues **65**.

This novel synthetic concept led to a small compound library of structures with the general core structure **65**, which were identified as potent antiproliferative agents in a variety of cancer cell lines.

Since the X-ray structure of the CDK2-hymenialdisine complex indicates that some lipophilic effects of the bromine atom in hymenialdisine (**1**) might play a crucial role for its protein kinase inhibition potency,[45] the synthesis of novel 2-substituted hymenialdisine derivatives has been developed.[71] According to the preparation of different the corresponding pyrrole-5-carboxylic acid derivatives, amide bond formation with β-alanine esters was carried out followed by a sequence of saponification and acidic cyclization to give 2-substituted aldisine derivatives **67**. Adoption of the synthetic strategy from Papeo et al.[62] led to four different hymenialdisine derivatives **68**; surprisingly the compounds were

obtained in the non-natural *endo*-form (Scheme 17). Isomerisation of *endo*-analogues **68** into the corresponding *exo*-compounds by irradiation was unsuccessful.



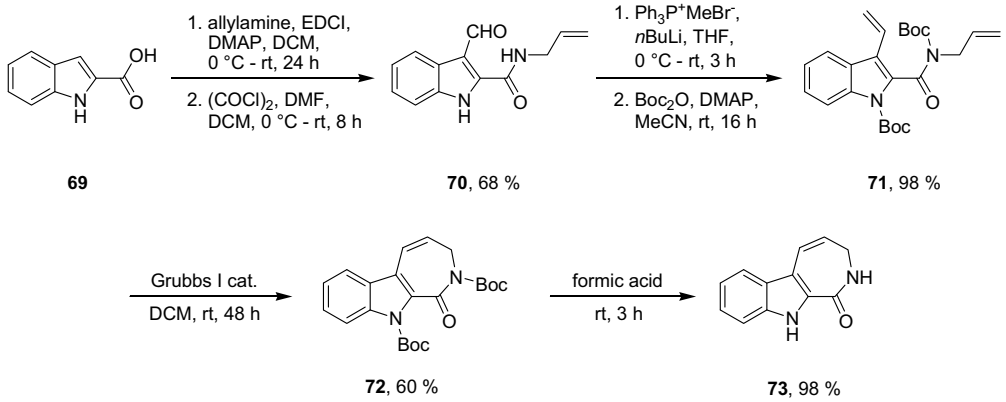
66
R = Me, Bn, Ph, *t*Bu

67

68

Scheme 17. Synthesis of 2-substituted *endo*-hymenialdisine derivatives **68**.

Moreover, a couple of research groups applied modern catalytic methods in the synthesis and modification of pyrrolo[2,3-*c*]azepinones. Mérour and coworkers were interested to find new catalytic pathways to fused bicyclic indolo-lactam derivatives as innovative scaffolds in drug development. Thereby olefin metathesis was introduced for the first time to prepare the pyrrolo[2,3-*c*]azepinone motif (Scheme 18).[72] Suitable substrates like vinyl-indole **71** were obtained starting from indole-2-carboxylic acid **69**, coupling to allylamine, followed by the installation a vinyl group at 3-position of the indole. Protection of the NH-functionalities with boc-groups gave intermediates **71**. Subsequent ring-closing alkene methathesis with a Grubbs I catalyst yielded the seven-membered olefin **72** in 60 % yield. The non-protected olefin **73** was obtained by acidic deprotection in high yields at room temperature.



69

70, 68 %

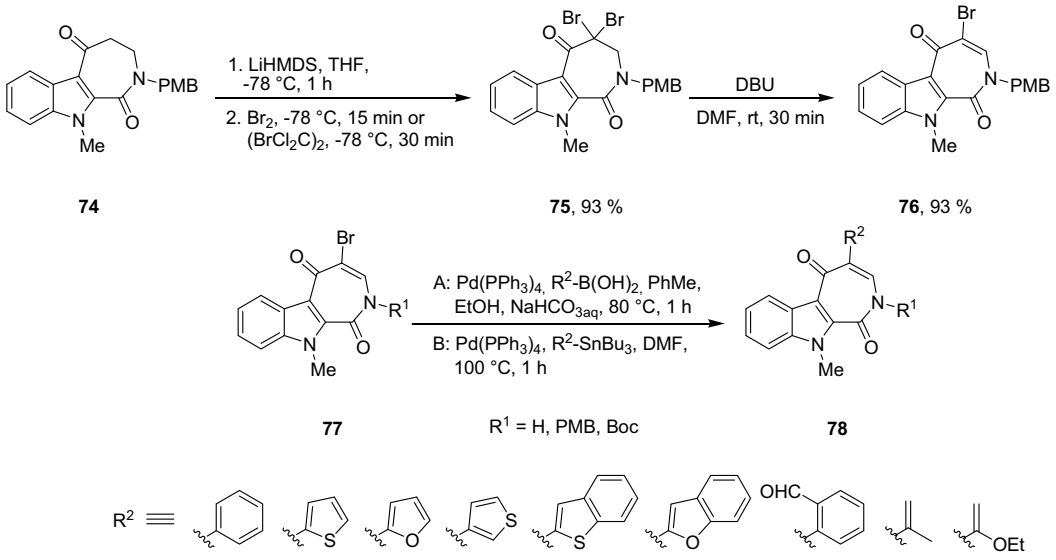
71, 98 %

72, 60 %

73, 98 %

Scheme 18. Synthesis of olefin **73** via ring-closing metathesis.

Another catalytic diversification approach has been reported for the synthesis of derivatives **78** (Scheme 19). Palladium-catalyzed cross-coupling reactions have been employed to link various arylboronic acids or arylstannates with the brominated synthon **76**.[73] In the fist step protected aldisine-derivatives **74** were synthesized and subsequently double-brominated to give intermediate **75** in 93 % yield. Subsequent formal elimination of hydrobromic acid under basic reaction conditions yielded the vinyl bromide derivative **76** in high yields (93 %). Cross-coupling reactions with either arylboronic acids or aryl stannates were used to create a focused chemical library of natural-product derived structures **78**.

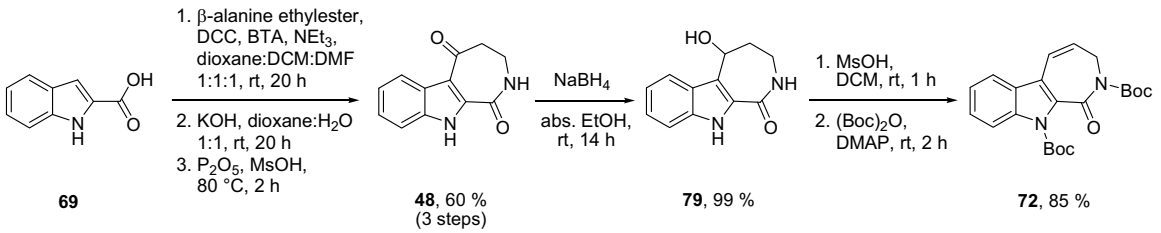


Scheme 19. Synthesis of natural product derivatives **78**.

The careful analysis of the chemistry and biology of natural products derived from the hymenialdisine family showed the great potential of these privileged structures as a starting point for navigating chemical space for improved or novel biological activities. Beside the synthesis of the fused-bicyclic lactam the attachment of the third heterocycle to the pyrrolo[2,3-*c*]azepinone moiety was identified as the crucial fragment-coupling key step.

Additionally, in the majority of the described syntheses and diversifications of the bicyclic pyrrolo[2,3-*c*]azepinones, the syntheses were preformed with aldisine-derived or olefinic intermediates. These two building blocks are beneficial with respect to the short synthesis, good yields, high product stability and short reaction time. On this basis a novel concept employing oxidation chemistry has been investigated in the diversification of indolo[2,3-*c*]azepinones.[74] A linear synthesis of aziridines, epoxides and hydroxyl precursors containing the natural product derived core structure has been developed to obtain building blocks for rapid diversification with various reagents. These key intermediates were then attacked by a variety of different nucleophiles, mostly indoles, to prepare a focused library of novel functionalized annulated hymenialdisine derivatives.

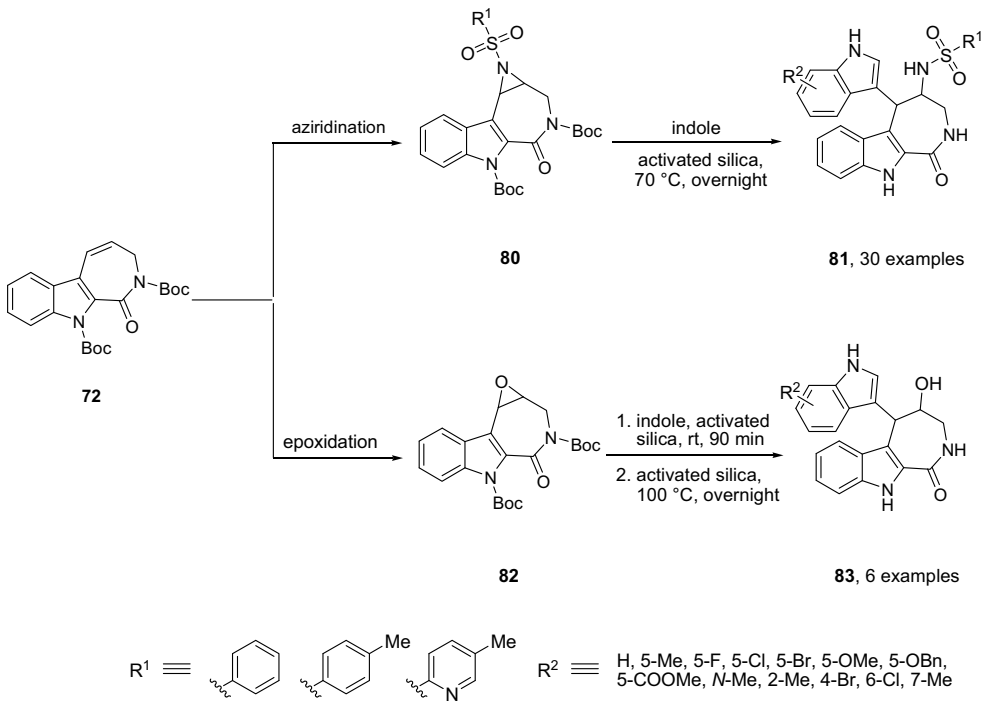
The linear synthesis to the key building blocks benefited from the advantages of high yielding and robust reactions such as the amide bond formation, saponification and acidic cyclization to annulated aldisine **48** and could be performed on multigram scale. Reduction of aldisine derivative **48** with sodium borohydride to the racemic alcohol **79** and a one-pot elimination-protection sequence yielded olefin **72** in 50 % yield over five steps (Scheme 20). The introduction of boc-protecting groups was necessary to obtain a more stable and storable alkene from the acidic elimination reaction.



Scheme 20. Linear synthesis of protected olefin **72** for further derivatisation.

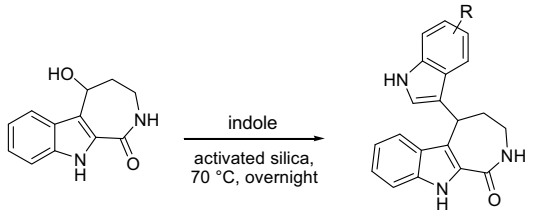
Subsequent oxidation of the protected olefin **72** led to the desired aziridines **80** and epoxides **82** as building blocks for diversification.[75,76] The key intermediates **80** and **82** were exposed to various indoles in solvent-free ring-opening reactions on solid support

(Scheme 21). In situ deprotection reactions in case of aziridines **80** and a separated second deprotection step for epoxides **82** led to a focused library containing novel bisindole-type hymenialdisine derivatives **81** and **83**.



Scheme 21. Preparation of a focused library of bisindoles **81** and **83**.

Further transformations of aziridines with H-, N-, and O-nucleophiles demonstrated their versatility as useful intermediates in library synthesis. For direct comparison in biological studies the corresponding bisindoles without a side chain at the seven-membered ring were also desired synthetic targets. Surprisingly, alcohol intermediate **79** reacted regioselectively with indoles at 3-position of the nucleophile under the same reaction conditions (Scheme 22). The desired hymenialdisine-type bisindoles **84** were obtained in only five steps.



79 **84**, 11 examples

R = H, 5-Me, 5-F, 5-Cl, 5-Br, 5-OMe, 5-OBn, *N*-Me, 2-Me, 4-Br, 6-Cl, 7-Me

Scheme 22. Synthesis of bisindole-type hymenialdisine derivatives **84** from alcohol **79**.

As described above much attention has been paid to several biological activities of natural products from the hymenialdisine family and its non-natural derivatives. Among them the relatively general protein kinase inhibiting properties have been widely recognized and make the core structure of hymenialdisine a suitable starting point in chemical space for the search of novel biological targets or for improved properties on known targets.

During the last two decades, protein kinases were found to be involved in essential regulatory cellular functions such as gene expression, cellular proliferation, differentiation, membrane transport, and apoptosis.[77] Since a number of small molecule kinase inhibitors entered clinical trials,[78] there is an ongoing academic and industrial interest for the development of new kinase inhibitors and the identification of novel targets.[79] The most protein kinases phosphorylate serine, threonine, tryosine, arginine or histidine side chains of proteins and are of great interest in current drug research.[80] Meijer and coworkers were able to show on molecular level by X-ray crystallography of a hymenialdisine (**1**) complex in the ATP (adenosine triphosphate) binding pocket of the protein kinase CDK2 (Figure 2). Hymenialdisine blocks this pocket in a competitive manner[45] and the binding structural elements of the molecule were identified.

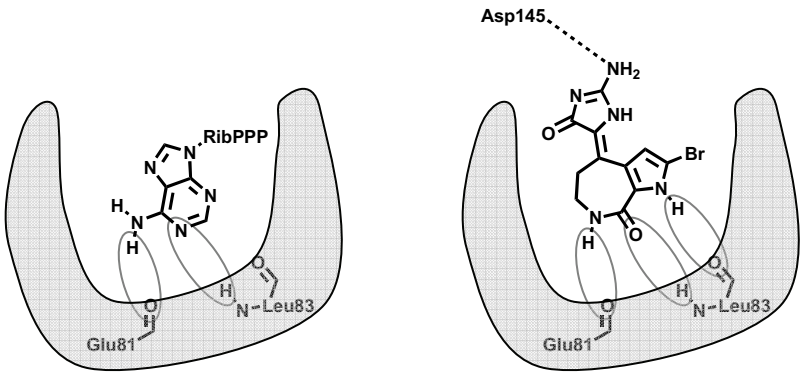
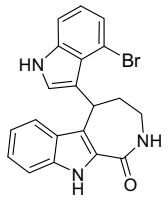


Figure 2. Schematic representation of the ATP binding pocket of CDK2 in complexes with ATP (left) and hymenialdisine (**1**) (right).[81]

On the one hand the NH-CO-C-NH sequence on the lower part of the molecule (Figure 2) is crucial for the binding affinity to the protein. On the other hand the heterocycle connected at α-position is also required for coordination on the upper part. This complex binding mode might be the reason for the relatively general kinase inhibiting action of hymenialdisine as a privileged structure. At the same time its molecular complexity could be the key factor for positive results in other unrelated screenings since the molecule might allow a number of different binding modes.

A screening of our focused chemical library of around 80 hymenialdisine-derivatives of **81**, **83** and **84** and of their synthetic intermediates and fragments was performed to identify novel inhibitors for the protein kinases DYRK1A, CDK1, CDK5, CK1 and GSK3.[82] Thereby the annulated bisindole-type hymenialdisine analogue **85** (Figure 3) exhibited significant activities in the inhibition of DYRK1A (IC_{50} = 1.8 μM) and GSK3 (IC_{50} = 44 μM) in low micromolar concentrations.



85

Figure 3. Novel kinase inhibitor **85** for the kinases DYRK1A and GSK3.

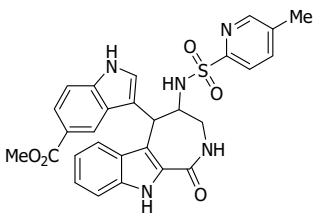
Due to the 4-bromine substitution pattern on the attached indole moiety other 4-substituted and various halogenated indole derivatives are currently being synthesized in our laboratories. In this iterative screening program, we are aiming on getting more information about the structural-activity relationship on molecular level to improve activity and selectivity of the novel kinase inhibiting structure.

In contrast to the most synthetic programs for target-oriented synthesis, we employed our focused library also for diverse screenings of biological targets. With the help of the high-throughput devices at the Center for Life Science Automation at the University of Rostock, a very similar compound library of our hymenialdisine derivatives was screened in various assays. Among them the compounds were tested in a cell-based assay in the area of genome (de)activation by zinc finger proteins.

Zinc finger proteins are the most studied DNA-binding proteins.[83] Around one third of all zinc finger DNA-binding proteins possess a so called Krüppel-associated box (KRAB) domain.[84] These KRAB zinc finger proteins are further assumed to build the largest family of transcription factors within the human genome.[85] When such a zinc finger protein binds to DNA, the KRAB domain acts as a potent transcriptional repressor for a certain gene function.[86] In 1995 Thiesen and coworkers have successfully linked a KRAB repressor domain of the human Kox1 zinc finger protein to a tetracycline-depending repressor protein (TetR) and incorporated them into HeLA A12 cells.[87] Transfection of the same

cells with a luciferase reporter gene bearing seven tetracycline operator (tetO) sequences yielded stable cells for further studies. Inside the transfected cell system, the TetR protein of the TetR-KRAB protein binds to the tetO sequences of the reporter gene. Thereby the KRAB domain represses the function of a certain part of the reporter gene (luciferase). In the presence of tetracycline the TetR domain competitively coordinates to tetracycline molecule and the connection to the tetO sequences of the reporter gene gets lost. Since the KRAB domain is not linked to the reporter gene furthermore, its repression function is deactivated. This consequence leads to an activation of the artificial reporter gene and results in luminescence. For future application, the binding selectivity of zinc finger proteins and the mechanisms of repression and activation of a certain gene function need to be identified. Small molecules which bind to the KRAB domain of zinc finger proteins undoubtedly alter the function of signaling. This concept is of great potential for the direct activation and/or repression of discrete DNA functions. So far no molecule has been identified to bind to the KRAB domain. This fundamental concept of controlling signaling domains might be applied for the search of novel drugs in the future.

During the establishment of an automated cell-based assay with those transfected HeLa cells from the Thiesen research laboratories, the novel hymenialdisine-type bisindole **86** (Figure 4) was identified to show around 90 % activity compared to the tetracycline positive control in low micromolar concentrations.[88]



86

Figure 4. Hymenialdisine-type bisindole **86**.

In this study compound **86** was already proven to possess the ability to enter the cell nucleus and act under given physiological conditions without significant influence on the vitality and metabolism of the cells.[89] Beside the function of the molecule, this implies the ability of our novel-designed class of compounds to pass cell membranes without affecting the cell-life cycle significantly. Subsequently the small molecule **86** was exposed to two different discrimination assays to clarify action of the activating molecule **86**. Further biological measurements and chemical synthesis are under investigation to gain more information about the mode of action, which might take part on the KRAB or tetO domaine, and structural influences of the natural product-derived bisindole **86** to activity.

In summary the necessity to navigate chemical space in order to find novel pharmacologically active compounds was shown. Especially natural products as privileged structures from nature are excellent starting points to prepare focused chemical libraries for subsequent biological activity screenings. In the past limited number of chemical libraries with hymenialdisine-derived structures were synthesized with respect to their promising biological functions. These investigations led to a number of novel synthetic methods for the preparation of promising drug candidates. Subsequently the development of novel diversification strategies was established during the attachment of the third heterocyclic moiety.

Following the general concept of target-oriented synthesis, we started to navigate the chemical space starting from the hymenialdisine core structure. The lower part of the pyrrolo[2,3-*c*]azepinone structure and one further coordination part on the upper heterocycle connected to the lactam moiety were identified as crucial structural elements for bioactive new molecules. Further oxidation chemistry and subsequent diversification resulted in a focused library of novel hymenialdisine derivatives. In contrast to common target-oriented studies, we performed biological testings for already established targets and

extended our search to unrelated biological activities. Our collection of smart molecules was accessible to biologists for a diversity-oriented screening approach including test systems in the area of kinase inhibition and novel cell-based assays e.g. with zinc finger proteins. So far our efforts resulted in to two significant hits in the biological screenings, which actively guide our compound synthesis in further diversifiactions. More basic understanding of the mode of action for bisindole-type hymenialdisine derivatives **85** and **86** is currently awaited.

1.3. References

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2. Objectives of this work

Natural products and their derivatives have been candidates for the development of novel drugs for a long time due to their important structural complexity and diversity. In the preparation of focused chemical libraries, target-oriented synthesis usually aims on direct natural product analogues for preselected biological targets. Also diversity-oriented synthesis has been applied to generate a large number of novel molecules, which occupy a lot of regions in the chemical space for the evaluation in a variety of biological activities.

As a starting point for our development of new bioactive chemical libraries, a collection of unsymmetrical bisindoles based on the natural product hymenialdisine was prepared. As a part of this project, we investigated a solvent-free, efficient and easy to handle diversification strategy for annulated hymenialdisine-type bisindoles. A C-C bond-formation reaction on activated silica under mild reaction conditions starting from aziridines or hydroxyl compounds is the crucial technology. The arylation reactions proceeded in a highly regio- and stereoselective manner at the benzylic position of the indolo[2,3-*c*]azepinone moiety and at the 3-position of the attached indole. In addition, boc-protecting groups can be removed in situ smoothly. The versatility of various aziridines as key building blocks was demonstrated with H-, O-, and N-nucleophiles in a diversity oriented synthesis to build up a small compound library. X-ray analysis confirmed the molecular structures of six important key intermediates and library compounds. This gives direct evidence for the *trans*-ring-opening reaction (see 3.1., *Org. Lett.* **2006** and 3.2., *J. Org. Chem.* **2007**). In our ongoing synthetic efforts, we also implemented the application of epoxidation chemistry for the synthesis of the key building block. Due to the higher reactivity of the epoxide, the diversification to the corresponding

bisindoles was achieved in a two-step ring-opening and deprotection sequence on solid support under mild reaction conditions. This method can also be extended to synthesize enantiomerically pure bisindole-type hymenialdisine analogues (see 3.3., *Tetrahedron* **2008**). Subsequent biological screenings led to the identification of two bisindoles with inhibiting effects on protein kinases and zinc finger proteins (see 1.2., *unpublished results*).

Parallel to our efforts in the preparation of a focused chemical library of hymenialdisine derivatives, we were interested in the development of novel synthetic methodologies for the introduction and transformation of important functional groups for the synthesis of potential biological active molecules.

Following our general library concept starting from indole-2-carboxylic acids, we identified 7-substituted indoles as rare substrates in organic synthesis. In order to reach these difficult accessible substrates for our compound library, we applied iridium-catalyzed borylation to 2-substituted indoles. Hence, 7-borylated indoles were obtained in excellent regioselectiviy. In the presence of an excess of the borylation reagent 2,4,7-trisubstituted indoles were obtained preferentially (see 3.4., *Tetrahedron Lett.* **2007**). Further investigations were guided by the idea to introduce potentially biologically relevant functional groups into the prefunctionalized borylated compounds. In this context a novel palladium-mediated fluorination of arylboronic acids was developed. The functional group tolerance, broad substrate scope, and regiospecificity of this reaction provide a general method for fluorination of structurally complex arenes, especially in the late stage (see 3.5., *Angew. Chem.,* **2008**, accepted). Moreover we developed a general copper-catalyzed method for the sulfonylation of arylboronic acids with sulfinate salts. A variety of alkyl-aryl, diaryl, and alkyl-heteroaryl sulfones were synthesized in good yield (see 3.6., *Org. Lett.* **2007**). On the other hand, a self-catalyzed selective oxidation of sulfides to sulfoxides has been developed to access sulfur-containing functional groups in lower oxidation state.

Compared with previous protocols, this system has the advantage that no organic solvents or any additional catalyst is necessary (see 3.7., *Adv. Synth. Catal.* **2007**).

Attracted by our previous development of CH-functionalization via borylation and subsequent functional group transformation in fluorination and sulfonylation reactions, we sought a synthetic method for the direct functionalization of arenes without "pre-activation" in form of arylhalides, arylboronic acids or other reagents. A novel general gold-catalyzed oxidative homocoupling of arenes was developed. Theoretically this double CH-functionalization is the most efficient process for the synthesis of biaryls, which constitute an important structural component in natural products, pharmaceuticals, agrochemicals and materials (see 4.8., *Chem. Commun.* **2007**). Additionally, hetero-coupling was achieved for the first time (see 4.9., *J. Organomet. Chem.* **2008**, submitted).

3. Publications

3.1. New synthetic protocols for the preparation of unsymmetrical bisindoles

Organic Letters **2006**, *8*, 5761-5764.

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H.M.K. planned, performed and analyzed experiments for the development of unsymmetrical bisindoles. H.M.K. wrote the manuscript and compiled the supporting information, and was involved in discussions. The work of H.M.K. to this publication accounts to approximately 80 %.

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New Synthetic Protocols for the Preparation of Unsymmetrical Bisindoles

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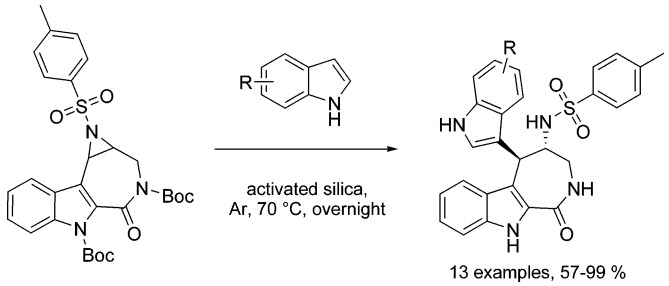
ABSTRACT



Novel unsymmetrical bisindoles were synthesized by a solvent-free C−C bond-formation reaction under mild conditions. Starting from aziridines or hydroxyl precursors, indoles have been used as C-nucleophiles to form new pharmacologically interesting bisindoles via an electrophilic aromatic substitution pathway in good to excellent yields.

During the last two decades, protein kinases were found to be involved in essential regulatory cellular functions such as gene expression, cellular proliferation, differentiation, membrane transport, and apoptosis.[1] Staurosporine (**1**), a bisindole, has been found as one of the first kinase inhibitors in nanomolar concentrations.[2] In addition, various small molecular kinase inhibitors are known.[3] Among them, Hymenialdisine (HMD) (**2**)[4] and annulated derivatives **3**[5] (Figure 1) have been found to inhibit a number of different kinases very selectively. Additionally, compounds **2** and **3** prevent the production of cytokines.[6]

We have been interested in the application of catalytic reactions for the synthesis of potential pharmaceuticals for some time.[7] As a starting point for the development of new bioactive kinase inhibitors, we decided to prepare a small

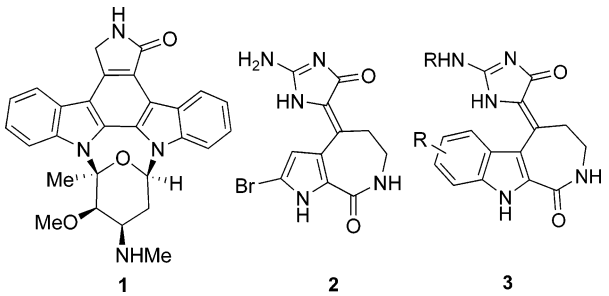


Figure 1. Structures of Staurosporine (**1**), Hymenialdisine (HMD) (**2**), and HMD analogues **3**.

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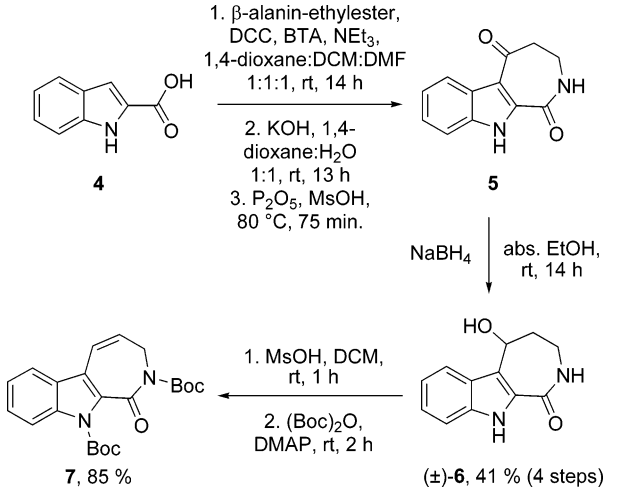
compound library of unsymmetrical bisindoles. As a part of this project, we developed a solvent-free, efficient, and easy to handle diversification strategy for annulated HMD-type bisindoles via a C−C bond-formation reaction on activated silica under mild reaction conditions starting from aziridines or hydroxyl compounds.

In the past, different synthetic strategies have been developed for the synthesis of the pyrrolo[2,3-*c*]azepine motif of HMD. The first total synthesis of HMD (**2**) was published by Annoura;[8] later, Horne introduced another synthetic strategy.[9] Recently, a new total synthesis was introduced by Papeo.[10] Annulated HMD derivatives usually were prepared via the azepino[3,4-*b*]indole-1,5-dione (**5**) intermediate or the corresponding alcohol (±)-**6** and subsequent attachment of the imidazole heterocycle.[5] Azepino-indole **5** is usually synthesized via intramolecular cyclization reactions with $MsOH/P_2O_5$.[11] Also, protocols employing ring-closing metathesis[12] and polyphosphoric acid[13] were introduced so far.

It has been shown that the kinase inhibiting activities of annulated HMDs **3** vary very much when other heterocycles instead of imidazole are introduced.[5] Hence, we aimed to develop a general and easy manageable preparation of unsymmetrical HMD-type bisindoles. On the basis of our experience on oxidation methods,[14] we planned to use different oxidation reactions as a toolbox for diversity-oriented synthesis.[15] Until now, relatively little use has been made applying oxidation methodologies for this purpose. The starting material **7** was synthesized in a one-pot elimination−protection procedure from (±)-**6** (Scheme 1).[5] Boc-protecting

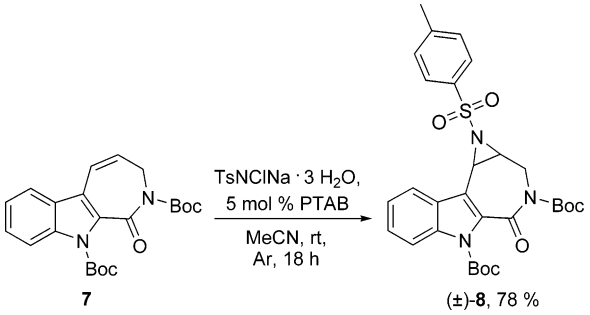
Scheme 1. Synthesis of Intermediates (±)-**6** and **7**



groups were introduced to obtain a more stable and storable alkene, which smoothly reacts in the subsequent aziridination reaction.

Although initial exploratory experiments employing standard epoxidation methods such as *m*-CPBA or MTO[16] were not successful, we turned our interest to the aziridination of olefin **7**.[17] It is well documented that *N*-arylsulfonylaziridines react with C, O, S, N, halogen, or hydrogen nucleophiles[18] in the presence of a base, an acid, or a Lewis acid. In general, it should be possible to perform these reactions highly regio- and stereoselectively.[19] For aziridination of olefins, a number of different metal-catalyzed nitrene transfer methods with copper, rhodium, ruthenium, iron, cobalt, manganese, silver, and gold catalysts were described.[20] With respect to synthetic application, we decided to perform the bromine-catalyzed aziridination developed by Sharpless and co-workers because this protocol does not require an excess of olefin (Scheme 2).[21]

Scheme 2. Bromine-Catalyzed Aziridination of **7**



To our delight, the aziridination of **7** proceeded smoothly to give (±)-**8** in good yield (78%). In contrast to the reported literature conditions, the reaction is favorably carried out

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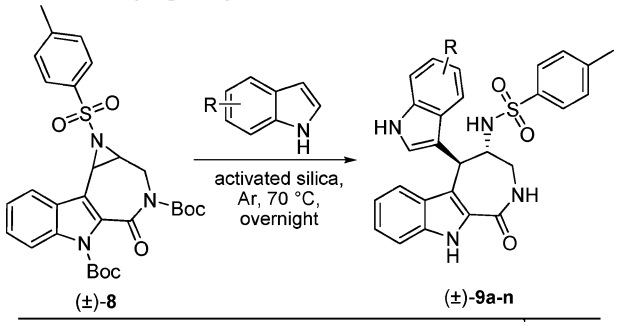
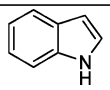
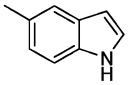
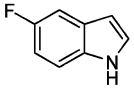
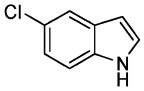
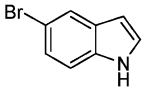
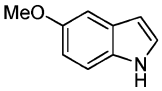
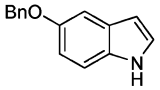
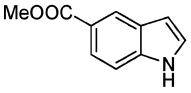
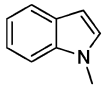
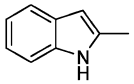
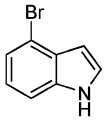
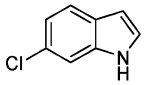
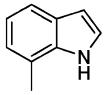
Table 1. Ring-Opening Reactions of (±)-**8**[a]



(±)-**8** (±)-**9a-n**

entry	substrate	product	yield[b] [%]
1		(±)-**9a**	93
2		(±)-**9b**	81
3		(±)-**9c**	99
4		(±)-**9d**	57
5		(±)-**9e**	84
6		(±)-**9f**	93
7		(±)-**9g**	72
8		(±)-**9h**	67
9		(±)-**9i**	86
10		(±)-**9k**	96
11		(±)-**9l**	70
12		(±)-**9m**	85
13		(±)-**9n**	76

[a] Reaction conditions: aziridine (±)-**8** (113 mg, 0.20 mmol), indole derivative (2.00 mmol), activated silica (0.040−0.063 mm, 429 mg), 70 °C, Ar, overnight. [b] Isolated yield.

employing an understoichiometric amount of chloramine-T trihydrate (1 equiv) in the presence of only 5 mol % of phenyltrimethylammonium tribromide (PTAB) and 2 equiv of **7** to reduce side products such as the brominated olefin and the ring-opening product of the formed aziridine with the amide salt.[22] Next, we attempted the direct arylation of various indoles using (±)-**8** as the key building block in the presence of acidic heterogeneous catalysts such as clay[23] or silica.[24] The arylations took place highly regioselectively at the benzylic position of (±)-**8** applying Hudlicky's protocol of solvent-free conditions on silica (Table 1).[24a] All reactions ran overnight at 70 °C and yielded the ring-opening product in good to excellent yields.

The crystal structure of product (±)-**9f** clearly showed that the reaction yielded a trans ring-opening product (Figure 2).[25]

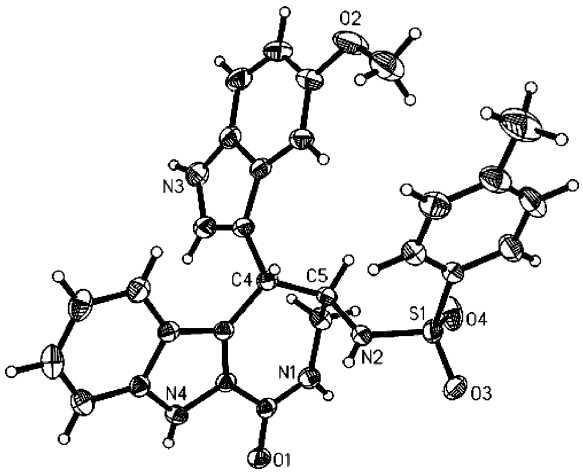


Figure 2. Molecular structure of (±)-**9f**. The thermal ellipsoids correspond to 30% probability.[25]

Functional groups such as alkyl, halide, alkoxy, and ester groups were tolerated by the mild reaction conditions. However, nitro- and cyano-substituted indoles did not react well in this protocol. In the case of 5,6-dimethylindole, we obtained an unseparable 70:30 mixture of two different

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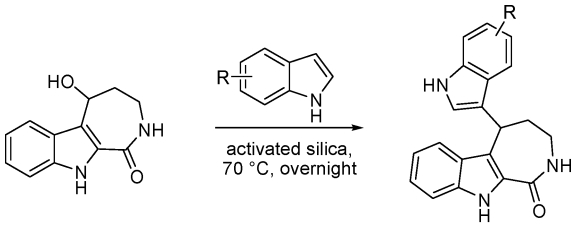
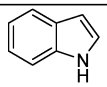
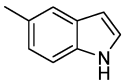
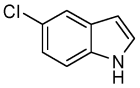
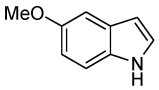
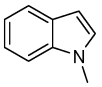
(25) X-ray crystallographic study of **9f**: data were collected with a STOE-IPDS diffractometer using graphite-monochromated Mo Kα radiation. The structure was solved by direct methods [SIR2004: Burla, M. C.; Caliandro, R.; Camalli, M.; Carrozzini, B.; Cascarano, G. L.; De Caro, L.; Giacovazzo, C.; Polidori, G.; Spagna, R. *J. Appl. Cryst.* **2005**, *38*, 381−389] and refined by full-matrix least-squares techniques against F^2 [Sheldrick, G. M. *SHELXL-97*; University of Göttingen: Germany, 1997.] XP (BRUKER AXS) was used for a structural representation. Space group $P2_1/c$, monoclinic, $a = 13.641(3)$, $b = 16.424(3)$, $c = 12.005(2)$ Å, $b = 94.29(3)°$, $V = 2682.1(9)$ Å^3, $Z = 4$, $r_{calcd} = 1.354$ g/cm^{-3}, 28 216 reflections measured, 4732 were independent of symmetry, of which 2669 were observed ($I > 2s(I)$), R1 = 0.042, wR^2 (all data) = 0.090, 367 parameters.

Table 2. Formation of Bisindoles (±)-**10a**−**e** from (±)-**6**[a]



(±)-**6** (±)-**10a-e**

entry	substrate	product	yield[b] [%]
1		(±)-**10a**	91
2		(±)-**10b**	52
3		(±)-**10c**	64
4		(±)-**10d**	53
5		(±)-**10e**	56

[a] Reaction conditions: alcohol (±)-**6** (100 mg, 0.462 mmol), indole derivative (4.62 mmol), activated silica (0.040−0.063 mm, 800 mg), 70 °C, overnight. [b] Isolated yield.

regioisomers likely caused by the electron-rich aromatic system of the substrate.

In all cases, the functionalization took place in the 3-position of the employed indoles, which is in agreement with an electrophilic aromatic substitution mechanism. Interestingly, both nitrogen atoms were deprotected in situ giving products (±)-**9a**−**n** directly. This desired parallel reaction avoids any other further deprotection steps.

For direct comparison in biological screenings, we also prepared the analogues (±)-**10a**−**e** without the tosylamide side chain. Under similar reaction conditions, the hydroxyl compound (±)-**6** yielded the corresponding bisindoles (±)-**10a**−**e** in moderate to good yields (Table 2). Presumably, a carbocation is formed in situ at the benzylic position, which reacted afterwards in an electrophilic aromatic substitution pathway with the various indoles. Also a reaction following Horne's azafulvenium ion pathway seems possible.[9a] To the best of our knowledge, this is the first direct benzylation of indoles at the 3-position with a hydroxyl precursor under solvent-free reaction conditions.[26]

In summary, we have developed new synthetic protocols for the preparation of unsymmetrical bisindoles. The ring-opening arylation of the aziridine or the direct arylation of the hydroxyl precursor proceeds highly regio- and stereoselectively with various indoles solvent free on solid support. This reaction enables an easily manageable and fast diversification pathway for a number of unsymmetrical bisindoles and pharmaceutically interesting HMD derivatives.

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Supporting Information Available: Experimental procedures, characterization of all compounds, and crystallographic data of (±)-**9f**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062338P

(26) For a similar reaction employing α-amino sulfones, see: Ballini, R.; Palmieri, A.; Petrini, M.; Torregiani, E. *Org. Lett.* **2006**, *8*, 4093−4096.

3.2. Preparation of novel unsymmetrical bisindoles under solvent-free conditions: synthesis, crystal structures, and mechanistic aspects

Journal of Organic Chemistry **2007**, *72*, 8847-8858.

Hanns Martin Kaiser, Ivo Zenz, Wei Fun Lo, Anke Spannenberg, Kristin Schröder, Haijun Jiao, Dirk Gördes, Matthias Beller, and Man Kin Tse*

H.M.K. planned, executed and analyzed experiments for the development of unsymmetrical bisindoles and derivatives. H.M.K. prepared all crystals for subsequent X-ray analysis and performed experimental mechanistic studies. H.M.K. wrote the manuscript and compiled the supporting information, and was involved in discussions. The work of H.M.K. to this publication accounts to approximately 80 %.

JOC Article

Preparation of Novel Unsymmetrical Bisindoles under Solvent-Free Conditions: Synthesis, Crystal Structures, and Mechanistic Aspects

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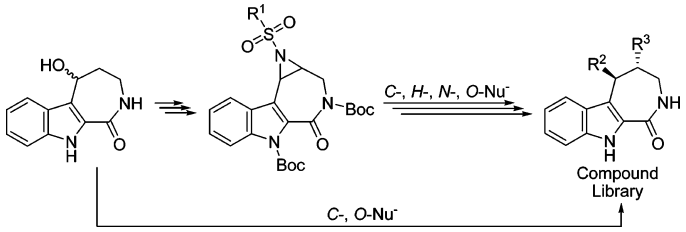

Indole aziridines and their hydroxyl derivatives have been used for the preparation of a small library of novel functionalized bisindoles. Diversification of these building blocks by solvent-free C−C-bond formation on solid support yielded annulated Hymenialdisine analogues under mild reaction conditions. Indoles as *C*-nucleophiles form potentially pharmacologically active bisindoles through an electrophilic aromatic substitution pathway in good to excellent yields. Further transformations of the indole aziridines with *H*-, *N*-, and *O*-nucleophiles demonstrate their versatility as key intermediates in diversity oriented synthesis. The hydroxyl precursor leads also to unsymmetrical bisindoles under similar reaction conditions. Important intermediates and final library compounds were confirmed by X-ray analysis. Theoretical studies on these systems show the possible cationic intermediate in the substitution pathway.

Introduction

Aziridines are versatile and highly valuable intermediates in organic synthesis.[1] In addition, natural products containing an aziridine moiety are known; some of them like Mitomycin A and B exhibit interesting biological activity.[2] Probably most importantly, aziridines serve as building blocks in drug research, such as in the development of neuramidase inhibitors[3] and calcium sensing receptor ligands,[4] and allow a straightforward preparation of diversified compound libraries. Thus, during the last decades significant attention has been paid to the racemic and stereoselective preparation of these nitrogen-containing three-membered-ring systems.[5] *N*-Arylsulfonylaziridines are especially important since they react smoothly with *C*-,[6] *O*-,[7] *S*-,[8] *N*-,[9] halogen-,[10] and hydrogen-nucleophiles[11] in the presence of Brønstedt bases, Brønstedt acids, or Lewis acids.[12]

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(1) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A., Ed.; Wiley-VCH: Weinheim, Germany, 2006.

(2) For an overview, see: Lowden, P. A. S. Aziridine Natural Products—Discovery, Biological Acitvity and Biosynthesis. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A., Ed.; Wiley-VCH: Weinheim, Germany, 2006; pp 399−442.

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In general, aziridines are prepared either via traditional cyclization reactions of 1,2-aminoalcohols, 1,2-aminohalides, or 1,2-azidoalcohols or via catalytic carbene- or nitrene-transfer methods to double bonds (C═N or C═C). Unfortunately, most catalytic aziridinations of olefins require a large excess of olefin, and need metal catalysts based on copper, rhodium, ruthenium, iron, cobalt, manganese, silver, or gold.[13] Also, electrochemical nitrene transfer methods were introduced.[14] Notably, these protocols were transferred to easily manageable protocols with phenyliodo(III) diacetate as an oxidant later on.[15] In addition, Sharpless and co-workers introduced the bromine-catalyzed aziridination procedure that does not necessarily require an excess of alkene.[16]

Kinase inhibitors are involved in fundamental regulatory cellular functions such as gene expression, cellular proliferation, differentiation, membrane transport, and apoptosis.[17] As one of the first kinase inhibitors, the bisindole Staurosporine (**1**) was found to be active in nanomolar concentration in the 1980s.[18] Besides, some other small molecules also act as kinase inhibitors as well.[19] Among them natural products like Hymenialdisine (HMD) (**2**) and its annulated derivatives **3** showed very promising kinase inhibiting properties[20] and prevent the production of cytokines (Figure 1).[21]

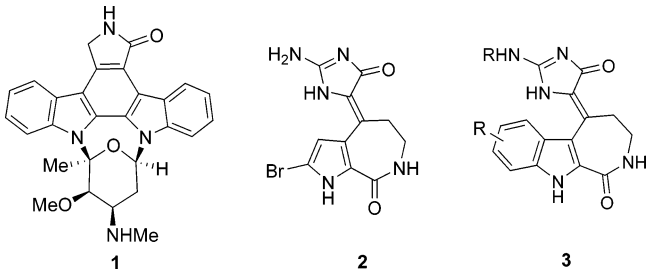

FIGURE 1. Structures of Staurosporine (**1**), Hymenialdisine (HMD) (**2**), and HMD analogues **3**.

On the basis of our experience with the application of catalytic reactions for the synthesis of new pharmacologically interesting compounds[22] and our background in catalytic oxidation methods,[23] we have been interested in the synthesis of potentially bioactive bisindoles as kinase inhibitors employing catalytic aziridination and epoxidation for diversity oriented synthesis[24] on complex organic natural product analogues. The prior work of Gray and co-workers[20c] showed that the kinase inhibiting activities of annulated HMDs (**3**) vary a great deal, if other heterocycles instead of imidazole are introduced. Therefore we focused on the introduction of different indoles onto the structure of annulated HMDs (**3**) to form new unsymmetrical bisindoles. Here, we report the detailed studies of a solvent-free, efficient, and easy to handle diversification strategy for annulated HMD-type bisindoles via C−C bond formation reaction on activated silica under mild reaction conditions, in which aziridines and hydroxyl compounds were used as the starting materials.

Results and Discussion

Several strategies for the synthesis of the pyrrolo[2,3-*c*]-azepine motif of HMD and the annulated derivatives have been published. The first total synthesis of HMD (**2**) was developed by Annoura.[25] Later Horne introduced another synthetic pathway[26] and Papeo developed a new total synthesis recently.[27]

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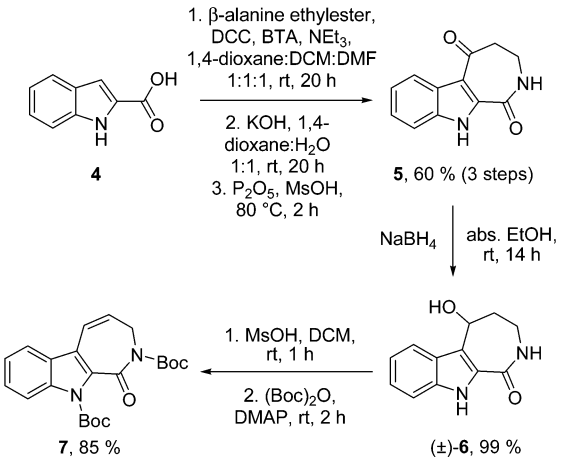
SCHEME 1. Synthesis of Alcohol (±)-6 and Olefin 7

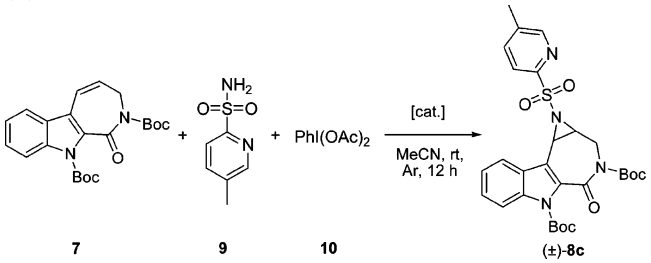


Annulated HMD derivatives (**3**) were usually prepared via the ketone **5** intermediate or the corresponding alcohol (±)-**6** and subsequent attachment of the imidazole heterocycle.[20c] Azepinoindole **5** is usually synthesized via intramolecular cyclization reactions with $MsOH/P_2O_5$.[28] In addition, protocols employing ring-closure metathesis[29] and polyphosphoric acid[30] were introduced.

Starting from indole-2-carboxylic acid (**4**) amide-bound formation with *β*-alanin ethyl ester in the presence of dicyclohexylcarbodiimine (DCC), triethylamine, and 4-hydroxybenzotriazole (BTA), subsequent ester cleavage and cyclization with phosphorus(V) oxide in methansulfonic acid yielded azepinoindole **5** (60%). Subsequent reduction of the keto-group with sodium borohydride in ethanol gave (±)-**6** in excellent yield (99%). The ease of isolation of (±)-**6** is strongly dependent on the purity of the azepino-indole **5**. Compound **5** has very low solubility in common organic solvents and can be purified by treatment with activated charcoal in hot acetone and subsequent recrystallization from a concentrated acetone solution. Olefin **7** was obtained by a one-pot elimination−protection procedure from (±)-**6** (Scheme 1).[20c] Introduction of two boc-protecting groups was crucial to provide a more stable and storable alkene from these acidic reaction conditions.

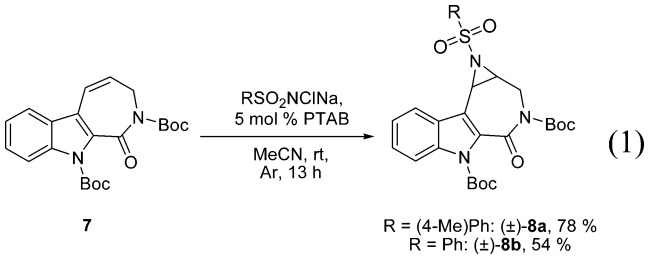
Next, we focused on the oxidation of olefin **7** to aziridines (±)-**8a**−**c**. As stated above, most catalytic aziridination methodologies generally require an excess of olefin. As a key building block for subsequent chemical diversification, it was crucial to introduce applicable and high-yielding aziridination methods. In this respect, we utilized the bromine-catalyzed aziridination protocol developed by Sharpless and co-workers,[16] because this method, in principle, does not require an excess of olefin. In contrast to conditions reported in the literature, we obtained our best results ((±)-**8a**: 78%) with an understoichiometric amount of the nitrogen source (chloramine-T) in the presence of only 5 mol % of phenyltrimethylammonium tribromide (PTAB) and 2 equiv of alkene **7** (eq 1).

TABLE 1. Copper-Catalyzed Aziridination of 7 to Aziridine (±)-8c[a]



entry	molar ratio of **7**:**9**:**10**	catalyst	conv [%]	yield[b] [%]
1	1:0.8:0.8	5 mol % of $Cu(OTf)_2$	45	27
2	1:0.8:0.8	5 mol % of $Fe(acac)_3$	23	0
3	1:0.8:0.8	5 mol % of $Cu(tfac)_2$	55	70
4	1:1.5:1.5	5 mol % of $Cu(tfac)_2$	50	62
5	1:0.8:0.8	10 mol % of $Cu(tfac)_2$	51	69

[a] Reaction conditions: olefin **7** (100 mg, 0.25 mmol), appropriate amounts of **9**, **10**, catalyst, 4 Å MS (500 mg), anhydrous CH_3CN (2 mL), Ar, 13 h. [b] Isolated yield based on recycled precursor **7**.



(1)

Employing these reaction conditions, we were able to reduce the degree of reaction side products such as the brominated olefin and the ring-opening product of the product aziridine with the amide salt.[31] Applying the same procedure to compound **7** with chloramine-B, aziridine (±)-**8b** was obtained in a reasonable (54%) yield.

Next, we planned to introduce a heterocyclic sulfonyl group to the aziridine motif. Once again the major drawback of most of the synthetic methods was the large excess of olefin required.[32] Optimization of the reaction conditions of the copper-catalyzed aziridination method introduced by Chang and coworkers[33] showed that a large excess of olefin **7** was not necessary to obtain the desired product (±)-**8c** in high yield (70%) (Table 1). The best result with respect to conversion and yield was obtained employing 5−10 mol % of copper(II) trifluoroacetylacetonate [$Cu(tfac)_2$] with a slight excess of olefin **7** (Table 1, entries 3 and 5). Unfortunately further attempts to introduce the 2-nitrobenezenesulfonyl group onto the aziridine via a gold-catalyzed procedure gave only a trace amount of the product.[13b]

We were delighted to be able to apply all of these methods for the preparation of aziridines (±)-**8a**−**c** in multigram-scale. With three different aziridines in hand, we looked for suitable conditions to affect the nucleophilic ring-opening reaction of

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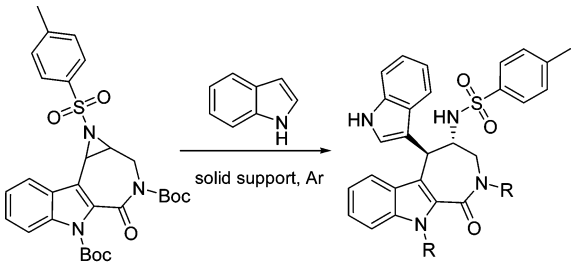
TABLE 2. Variation of Solid Support, Temperature, and Amount of *C*-Nucleophile in the Ring-Opening Reaction of Aziridine (±)-8a with Indole[a]



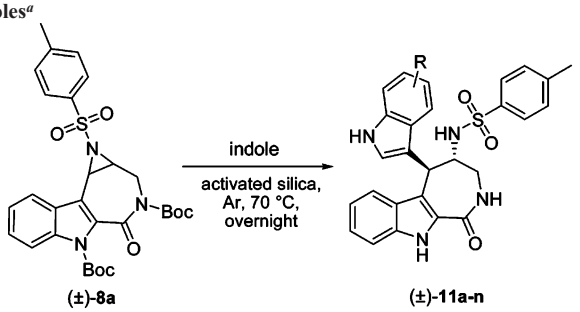
entry	solid support	temp [°C]	ratio of indole:(±)-**8a**	yield[b] [%]
1	activated silica	rt	10:1	0 (34)[c]
2	activated silica	40	10:1	75
3	activated silica	70	10:1	93
4	activated silica	70	3:1	81
5	activated silica	70	1:1	40
6	montmorillonite K-10	70	10:1	70
7	alumina (neutral)	70	10:1	21

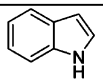
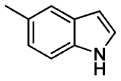
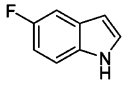
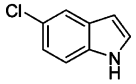
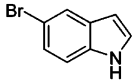
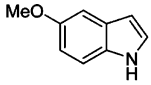
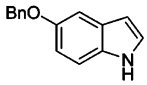
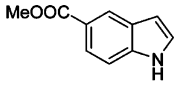
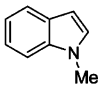
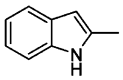
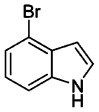
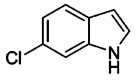
[a] Reaction conditions: aziridine (±)-**8a** (113 mg, 0.2 mmol), indole (234 mg, 2.00 mmol), 429 mg of solid support, Ar, 16 h. [b] Isolated yield of product (±)-**11a**. [c] Isolated yield of product (±)-**12**.

these aziridines. Therefore, key intermediate (±)-**8a** was allowed to react with indole as *C*-nucleophile in the presence of different acidic solid supports such as silica,[34,6d] alumina, and clay (Montmorillonite K-10).[35] Moreover, the reaction temperature and the ratio of indole to (±)-**8a** were varied (Table 2).

The results demonstrate that a high molar ratio of indole at a moderate temperature of 70 °C (Table 2, entry 3) gave the desired bisindole (±)-**11a** in excellent yield (93%). In principle, only a slight excess of indole is consumed and it can be recycled. Since indole sublimes during the reaction, 10 equiv of indole is used to ensure efficient conversion of the aziridine to our product. All arylations proceeded with excellent regioselectivity at the benzylic position of (±)-**8a** and at the 3-position of the attached indole. The best conditions were then tested with other solid supports such as clay (Montmorillonite K-10) (Table 2, entry 6) and alumina (Table 2, entry 7). These solid supports exhibit significant disadvantages such as side product formation or lower yields. For example, employing clay as the solid support we observed both possible ring-opening products of the aziridine by ^{1}H NMR. In the case of neutral alumina the desired product (±)-**11a** was formed in lower yield. The ^{1}H NMR spectrum of the reaction mixture indicated also that deprotection of both boc-groups under the employed reaction conditions on clay or alumina was not complete. In contrast, the protecting boc-groups could be easily removed under the reaction conditions on activated silica. The isolation of the *N,N*-di-boc-protected ring-opening product (±)-**12** in low yields at room temperature (Table 2, entry 1) provides direct evidence that the ring-opening reaction proceeds significantly faster than the deprotection of the boc-protecting groups under mild conditions. Moreover, the deprotection of the nitrogen atoms does not seem to be required for the activation of the indole for the ring-opening reaction. In a few attempts (Table 2, entries 1, 2, and 7), the ring-opening products with only one protecting group were also observed (^{1}H NMR) on the lactam moiety.

TABLE 3. Ring-Opening Reactions of (±)-8a with Various Indoles[a]



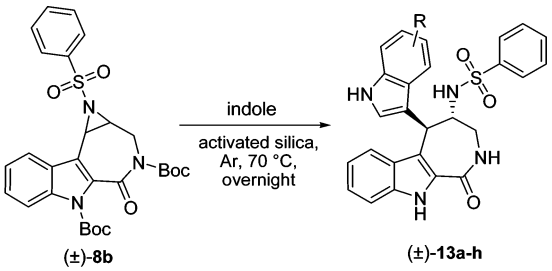
entry	substrate	product	yield[b] [%]
1		(±)-**11a**	93
2		(±)-**11b**	81
3		(±)-**11c**	99
4		(±)-**11d**	57
5		(±)-**11e**	84
6		(±)-**11f**	93
7		(±)-**11g**	72
8		(±)-**11h**	67
9		(±)-**11i**	86
10		(±)-**11k**	96
11		(±)-**11l**	70
12		(±)-**11m**	85
13		(±)-**11n**	76

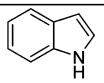
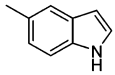
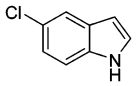
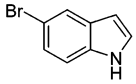
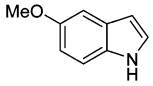
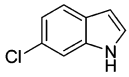
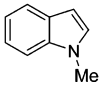
[a] Reaction conditions: aziridine (±)-**8a** (113 mg, 0.20 mmol), indole derivative (2.00 mmol), activated silica (0.040−0.063 mm, 429 mg), 70 °C, Ar, overnight. [b] Isolated yield.

(34) Hudlicky, T.; Rinner, U.; Finn, K. J.; Ghiviriga, I. *J. Org. Chem.* **2005**, *70*, 3490−3499.

(35) Nadir, U. K.; Singh, A. *Tetrahedron Lett.* **2005**, *46*, 2083−2086.

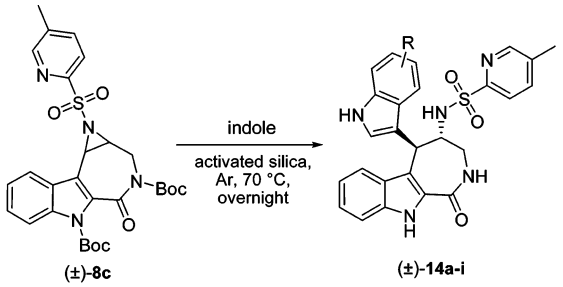
TABLE 4. Ring-Opening Reactions of (±)-8b with Various Indoles[a]

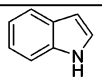
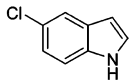
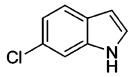
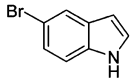
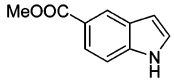
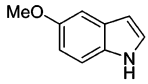
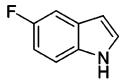
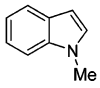


entry	substrate	product	yield[b] [%]
1		(±)-**13a**	66
2		(±)-**13b**	58
3		(±)-**13c**	41
4		(±)-**13d**	83
5		(±)-**13e**	59
6		(±)-**13f**	61
7		(±)-**13g**	39
8		(±)-**13h**	36

[a] Reaction conditions: aziridine (±)-**8b** (111 mg, 0.20 mmol), indole derivative (2.00 mmol), activated silica (0.040−0.063 mm, 429 mg), 70 °C, Ar, overnight. [b] Isolated yield.

TABLE 5. Ring-Opening Reactions of (±)-8c with Various Indoles[a]



entry	substrate	product	yield[b] [%]
1		(±)-**14a**	92
2		(±)-**14b**	72
3		(±)-**14c**	89
4		(±)-**14d**	60
5		(±)-**14e**	66
6		(±)-**14f**	47
7		(±)-**14g**	68
8		(±)-**14h**	62
9		(±)-**14i**	82

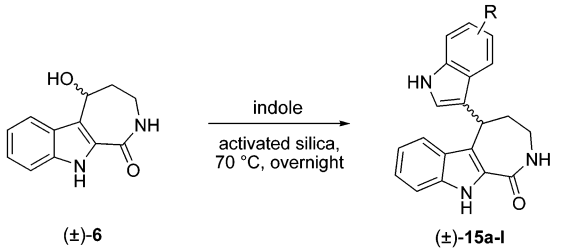
[a] Reaction conditions: aziridine (±)-**8b** (114 mg, 0.20 mmol), indole derivative (2.00 mmol), activated silica (0.040−0.063 mm, 429 mg), 70 °C, Ar, overnight. [b] Isolated yield.

Next, we adopted the optimized protocol to the preparation of unsymmetrical bisindoles starting from aziridines (±)-**8a**−**c**. All reactions ran overnight at 70 °C and yielded the trans-ring-opening product (see the crystal structure of (±)-**11f**) in good to excellent yields (Table 3).

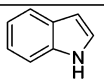
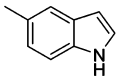
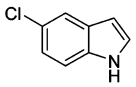
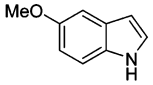
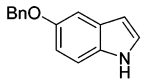
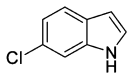
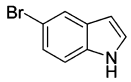
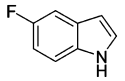
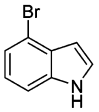
Functional groups on the indole ring such as halides and alkoxy and ester groups were tolerated under these mild reaction conditions. However, under similar conditions the ring-opening product with 5-nitro-indole was only obtained in poor (<20%) yields. Using 5,6-dimethylindole we obtained an inseparable 70:30 mixture of two different regioisomers likely caused by the electron-rich aromatic system of the substrate. The reaction of (±)-**8a** with indole (Table 3, entry 1) also can be performed on gram-scale and provided the desired product in excellent yield (95%). Employing the precursors (±)-**8b** and (±)-**8c** under the same reaction conditions, compounds (±)-**13a**−**h** (36−83%) and (±)-**14a**−**i** (47−92%) were obtained in moderate to good yield.

To determine the structural influence of the aryl-sulfonamide side chain in biological screenings, we also decided to prepare the analogues (±)-**15a**−***l***. For this purpose we tested the hydroxyl-precursor (±)-**6** under similar reaction conditions. Fortunately the desired bisindoles (±)-**15a**−***l*** were obtained in moderate to good yields (Table 6). Direct benzylations with alcoholic precursors were of significant interest for the preparation of diarylmethanes.[36] Usually Lewis acid catalyst in homogeneous solution is required for this reaction.[37] To the best of our knowledge this is the first direct benzylation of indoles

TABLE 6. Formation of Bisindoles (±)-15a−l from Alcohol (±)-6[a]



(±)-6 (±)-15a-l

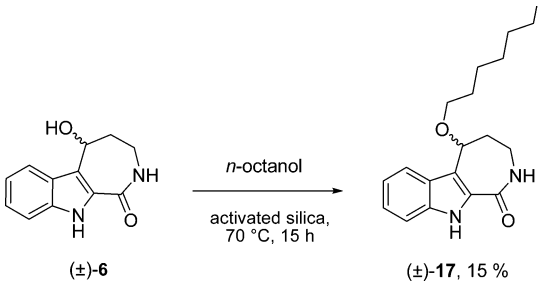
entry	substrate	product	yield[b] [%]
1		(±)-**15a**	91
2		(±)-**15b**	52
3		(±)-**15c**	64
4		(±)-**15d**	53
5		(±)-**15e**	56
6		(±)-**15f**	38
7		(±)-**15g**	58
8		(±)-**15h**	44
9		(±)-**15i**	62
10		(±)-**15k**	56
11		(±)-**15l**	51

[a] Reaction conditions: alcohol (±)-**6** (100 mg, 0.462 mmol), indole derivative (4.62 mmol), activated silica (0.040−0.063 mm, 800 mg), 70 °C, overnight. [b] Isolated yield.

with an alcohol precursor on solid support.[22a] The reaction of alcohol (±)-**6** with *C*-nucleophiles on silica enables a convenient access to this class of compounds. Compared with the method employing olefin **7a** and other heterocyclic *C*-nucleophiles under strong acidic conditions (MsOH as solvent), our method is more managable.[20c]

To demonstrate the versatility of the aziridines for further diversification reactions, we examined aziridine (±)-**8a** in ring-opening reactions with *H*-, *O*-, and *N*-nucleophiles. First (±)-**16a** was prepared by reductive ring-opening reaction with ammonium formate in the presence of palladium on charcoal.[38] After deprotection with TFA, (±)-**16b** was obtained in excellent yield (73%, over two steps). This product can give direct comparison information for the structural influence of the indole group in products (±)-**11a**−**n**. Direct deprotection of crude (±)-**16a** with TFA in CH_2Cl_2 gave (±)-**16b** in similar yield (68%) (Scheme 2).[39] It should be noted that this two-step aziridination−hydrogenation sequence offers a straightforward approach to novel sulfonylated tryptamine derivatives, which may be of interest in various pharmaceutical applications.

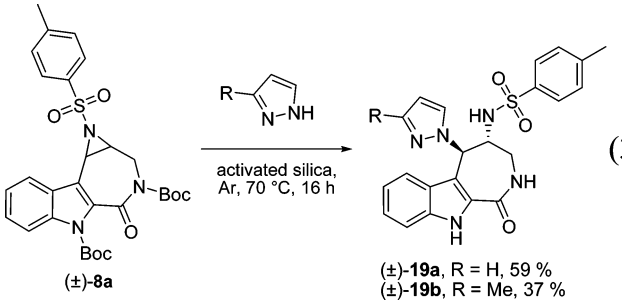
Next, we turned our interests to other nucleophiles such as alcohols or amines. Initial experiments designed to react aziridine (±)-**8a** with *n*-octanol similar to the indole-ring-opening reactions on silica led only to the decomposition of the starting material. However, the reaction of alcohol (±)-**6** with *n*-octanol proceeded overnight with low conversion of (±)-**6** on silica. After 15 h the desired substitution product (±)-**17** was isolated in 15% yield (eq 2). Further we tried to convert alcohol (±)-**6** on silica with tosylamide and various amines. Unfortunately these reactions failed to produce any conversion.



(±)-6 (±)-17, 15 % (2)

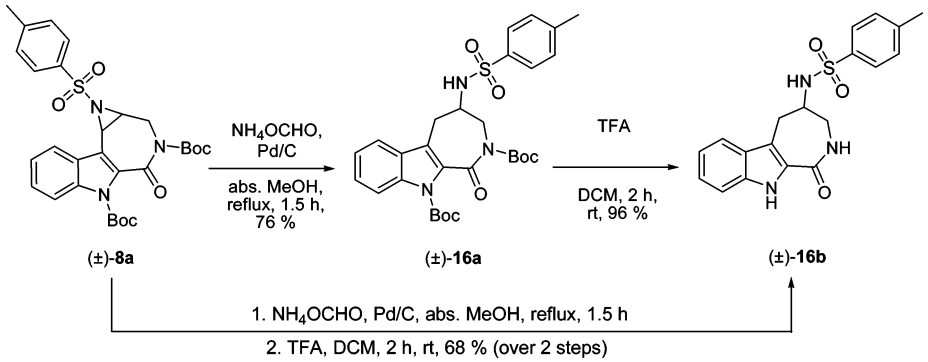
Next, aziridine (±)-**8a** was successfully converted with MeOH as an *O*-nucleophile by reaction with ceric ammonium nitrate (CAN) (Scheme 3).[40] Hence, (±)-**18a** was synthesized from (±)-**8a** in MeOH with 10 mol % of CAN at room temperature for 9 h in excellent yield (99%) based on recycled aziridine (±)-**8a** (52%). Further, the catalyst loading up to 40 mol % gave full conversion of (±)-**8a** (TLC) and the subsequent deprotection of (±)-**18a** on silica at 70 °C yielded (±)-**18b** in good yield (74%).

In addition, we also explored the ring-opening reaction of aziridine (±)-**8a** in the presence of pyrazoles on activated silica. To our delight, reactions employing our standard reaction conditions (Table 2) yielded compounds (±)-**19a** and (±)-**19b** in moderate yields (37% and 59%, eq 3).

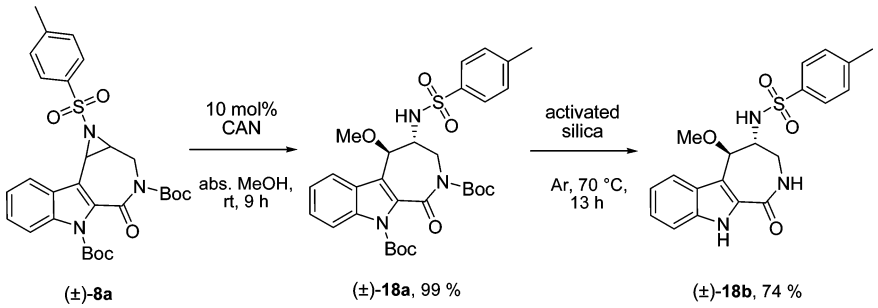


(±)-8a (±)-19a, R = H, 59 %
(±)-19b, R = Me, 37 % (3)

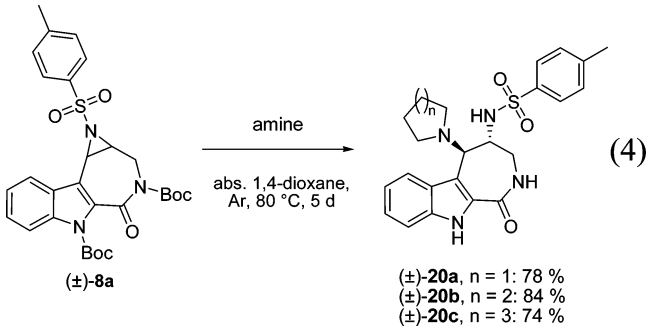
SCHEME 2. Formation of Protected Sulfonamides (±)-16a from (±)-8a and Subsequent Deprotection to (±)-16b



SCHEME 3. Synthesis of (±)-18a and Subsequent Deprotection to (±)-18b



Aziridine (±)-**8a** could be opened smoothly with more volatile secondary amines.[41] To our surprise, (±)-**8a** underwent the direct amination reaction smoothly at 80 °C in homogeneous solution without any catalyst or further activating reagent (e.g., organic base, etc.) to give also the in situ deprotected compounds (±)-**20a**−**c** (eq 4). Depending on the solubility of the products during the recrystallization step, we obtained good to very good yields (74−84).



(4)

X-ray Crystallographic Studies. Single crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of methanol, ethyl acetate, diethyl ether, or dichlormethane solutions. The molecular structures of **7**, (±)-**8a**, (±)-**8b**, (±)-**8c**, (±)-**11f**, and (±)-**15d** confirmed our assignments (see the Supporting Information). Among them, the crystal structure of bisindole (±)-**11f** has been reported by us previously.[22a] The C═C double bond in olefin **7** exhibits a length of 1.323(2) Å. Possibly with respect to the nonplanarity of the seven-membered ring, the olefinic C═C bond puckered from the plane of the indole moiety [torsion angle: 156.0(2)°]. The molecular structures of aziridines (±)-**8a**−**c** showed that the angles between the three-atom-ring plane of the aziridines and the indole plane are almost in the same range for all aziridines [(±)-**8a**: 57.7-(2)°; (±)-**8b**: 60.3(1)°; (±)-**8c**: 61.4(1)°]. Also, the bond lengths of the aziridine moieties of (±)-**8a**−**c** showed the structural similarities of these compounds: (a) C−C: (±)-**8a** 1.471(4) Å, (±)-**8b** 1.473(2) Å, (±)-**8c** 1.472(2) Å; (b) N−C: (±)-**8a** 1.502(4) Å, (±)-**8b** 1.501(2) Å, (±)-**8c** 1.512(2) Å; (b) C−N: (±)-**8a** 1.490(4) Å, (±)-**8b** 1.488(2) Å, (±)-**8c** 1.493(2) Å. The X-ray analysis of bisindole (±)-**11f** gives direct evidence for the trans configuration of the ring-opening product. The comparison of bisindole (±)-**11f** and its analogue (±)-**15d** without the tosyl-amide side chain showed significant differences in the angle between the two planes of the indole ring systems [(±)-**11f**: 83.37(6)°; (±)-**15d**: 73.87(5)°] in the crystal structures. However, in both cases the planes of the indole systems are clearly out of the same plane from each other.

Mechanistic Aspects. Inspired by the previous reports about the concept of an aza-fulvenium ion as the intermediate in the reaction mechanism,[26a] we became interested in the process of the charge-stabilization of the cationic intermediate during the bisindole formation from alcohol (±)-**6** and aziridines (±)-**8a**−**c**. It is well-known that the elimination of benzylic OH-groups proceeds smoothly to afford olefins in the presence of acids. Thus a carbocationic intermediate is formed in situ and subsequent elimination of proton yields the corresponding olefin.

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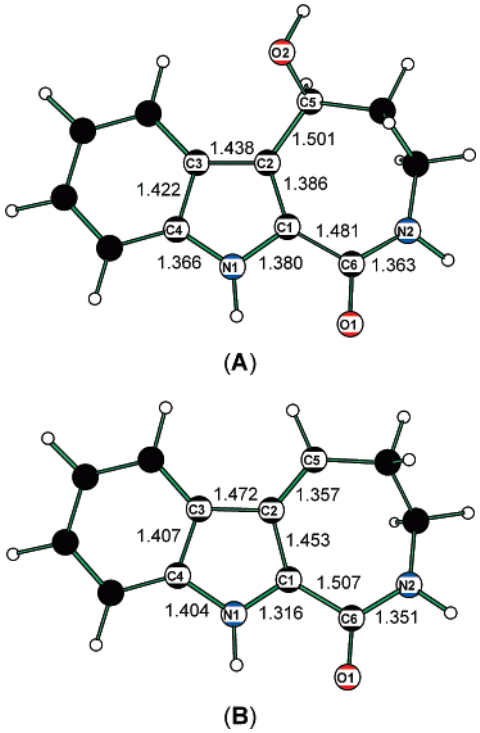
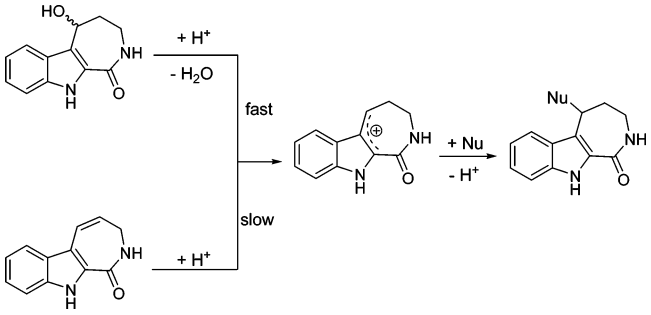


FIGURE 2. Calculated molecular structures of alcohol (±)-**6** (**A**) and the cationic intermediate (**B**).

During initial ^{1}H NMR experiments of alcohol (±)-**6** with MsOH in CD_2Cl_2, only olefin **7a** was observed immediately after addition of a catalytic amount of MsOH to alcohol (±)-**6**. Further, the boc-protected olefin **7** did not react with indole on silica to form the desired product (±)-**15a**. Here, only olefin **7a** was observed on TLC. In fact, olefin **7** can be deprotected on activated silica at 70 °C overnight to yield the *N*,*N*-deprotected olefin **7a** in 98% yield. Attempts to produce bisindole from **7a** on silica or in MsOH with indole were performed. However, no reaction was observed on silica and no well-defined product could be isolated from the MsOH-reaction system. This indicates that the generation of the active cationic intermediate from **7a** is significantly slower than that from the hydroxyl precursor (±)-**6**.

To understand the structure of the cationic intermediate (**B**), we have carried out B3LYP/6-311G(d) density functional theory calculations along with the alcohol (**A**) by using the Spartan 04 program package.[42] As shown in Figure 2, the five-membered ring in **A** has a pyrrole moiety and the exocyclic C2−C5 bond length is 1.501 Å. In the cationic intermediate (**B**), however, the C2−C5 and C1−N1 bond lengths become shorter (1.357 and 1.316 Å, respectively) and the C1−C2 bond length becomes longer (1.453 Å). This change is due to the delocalization effect with the formation of the butadiene moiety of N1−C1−C2−C5. In addition to the changes of the bond lengths, it is also interesting to compare the Mulliken charges between **A** and **B**. Therefore it seems to be clear that the positive charge from a theoretical perspective point of view has to be delocalized over C1, C2, and C5 (the computed Mulliken charges—for **A**: N1 = −0.701; C1 = 0.156; C2 = −0.021; C5 = −0.030; for **B**: N1 = −0.632; C1 = 0.242; C2 = −0.018; C5 = −0.094). This

SCHEME 4. Proposed Mechanism for the Synthesis of Unsymmetrical Bisindoles from Alcohol (±)-6



stands in contrast to the known literature and established azafulvenium ion.[26a]

On the basis of the DFT calculations and our observations of the reactions of alcohol (±)-**6** with indoles on silica, we believe the reaction proceeds through the attack of the indole to the LUMO of the cationic diene species, which is stabilized by delocalization of the positive charge on the N1−C1−C2−C5 moiety (Scheme 4). It is also possible for the same charge stabilization mechanism to proceed during the ring-opening and subsequent aromatic substitution reactions of aziridines (±)-**8a**−**c** with indoles.

Conclusion

In summary, a practical and easy to handle protocol for the synthesis of unsymmetrical bisindoles was developed. The arylation reactions proceed in a highly regio- and stereoselctive manner at the benzylic position of the azepino[3,4-*b*]indol-1(10*H*)-one moiety and at the 3-position of the attached indole on a solid support. The solvent-free synthetic protocol is easily manageable and yields the desired bisindoles from the aziridines or alcohols. In addition, boc-protecting groups can be removed in situ smoothly. The versatility of these aziridines was demonstrated with *H*-, *O*-, and *N*-nucleophiles in a diversity oriented synthesis to build up a small compound library. X-ray analysis confirmed the molecular structures of important key intermediates and library compounds. Specifically, the molecular structure of (±)-**11f** gives direct evidence for the trans-ring-opening reaction. In addition, DFT calculations indicate that the mechanism might proceed via a charge stabilized azabutadiene motif, which reacts further exclusively at the benzylic position to rebuild the aromatic ring system.

Experimental Section

5-Hydroxy-2,3,4,5-tetrahydroazepino[3,4-*b*]indol-1(10*H*)-one ((±)-6). Ketone **5** (3.31 g, 15.5 mmol) was suspended in degassed absolute ethanol (250 mL) under argon.[43] Then freshly ground $NaBH_4$ (2.92 g, 77.3 mmol) was added and the reaction mixture was stirred at ambient temperature overnight (~14 h). The mixture was filtered over celite and washed with acetone. After removal of the solvent under reduced pressure, purification by column chromatography (silica gel 70−230 mesh, CH_2Cl_2 to CH_2Cl_2:MeOH 100:7 as a gradient eluent) yielded an off-white solid (3.30 g, 99%). R_f 0.40 (CH_2Cl_2:MeOH:NEt_3 100:10:1). Mp 167−169 °C (ethyl acetate). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 11.29 (1H, br s), 8.15 (1H, dd, J = 6.0, 3.2 Hz), 7.78 (1H, d, J = 7.9 Hz), 7.41 (1H, d, J = 8.1 Hz), 7.19 (1H, ddd, J = 8.1, 7.0, 1.1

(42) *SPARTAN'04*: Copyright 1991−2005 by Wavefunction Inc.; www.wavefun.com.

(43) For the synthesis of the precursors, please see the Supporting Information.

Hz), 7.04 (1H, ddd, J = 8.1, 7.0, 1.0 Hz), 5.23 (1H, d, J = 6.6 Hz), 5.18−5.10 (1H, m), 3.59−3.45 (1H, m), 3.22−3.08 (1H, m), 2.22−2.10 (1H, m), 2.07−1.93 (1H, m). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 163.7, 135.8, 127.7, 126.8, 123.9, 121.5, 119.5, 119.1, 112.1, 63.5, 36.5, 35.5. IR (KBr) ν (cm^{-1}) 3520 m, 3281 s, 3211 sh, 3051 m, 2952 m, 2917 m, 2861 sh, 1647 s, 1550 s, 1478 s, 1456 m, 1412 m, 1362 m, 1334 s, 1297 m, 1239 w, 1185 w, 1160 w, 1144 w, 1063 w, 1047 m, 1003 m, 958 m, 924 w, 881 m, 792 m, 740 s, 680 m, 606 w, 539 w, 465 w, 435 w. MS (EI) *m*/*z* (rel. intensity) 217 (13), 216 (72), 200 (13), 199 (36), 198 (100), 197 (50), 189 (13), 186 (11), 172 (10), 171 (25), 170 (37), 169 (50), 168 (13), 159 (35), 158 (17), 155 (14), 154 (15), 149 (14), 145 (16), 144 (30), 143 (29), 142 (12), 141 (11), 140 (15), 130 (12), 129 (12), 128 (10), 117 (13), 116 (17), 114 (11), 89 (17), 83 (11), 78 (13), 77 (18), 71 (14), 69 (12), 63 (19), 57 (22), 55 (16), 44 (46), 43 (14), 41 (17). HRMS (ESI) calcd for $C_{12}H_{12}N_2O_2Na$ (M + Na$^+$) 239.0791, found 239.0803. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.59; H, 5.33; N, 12.90.

(*Z*)-Di-*tert*-butyl 1-Oxoazepino[3,4-*b*]indole-2,10(1*H*,3*H*)-dicarboxylate (7). To a solution of alcohol (±)-**6** (3.30 g, 15.3 mmol) in CH_2Cl_2 (500 mL) was added methanesulfonic acid (0.730 g, 7.63 mmol) dropwise. The solution was stirred at room temperature for ∼40 min. After the full conversion of (±)-**6** as indicated by TLC analysis, 4-dimethylaminopyridine (4.47 g, 36.6 mmol) and di-*tert*-butyl dicarbonate (6.97 g, 30.5 mmol) were added. The reaction was monitored by TLC (CH_2Cl_2:MeOH:NEt_3 100:10:1) and portions of di-*tert*-butyl dicarbonate (3 × 2.30 g, 3 × 10.2 mmol) were added further to complete the reaction. The solvent was removed in vacuo and the residual brown reaction mixture was purified via column chromatography (silica gel 70−230 mesh, *n*-hexane:ethyl acetate 6:1, packed with 1% NEt_3) to yield a white solid (5.19 g, 85%). Crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of a solution of diethyl ether at room temperature. R_f 0.23 (*n*-hexane:ethyl acetate 6:1). Mp 127−128 °C (Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.11 (1H, d, J = 8.5 Hz), 7.67 (1H, d, J = 7.9 Hz), 7.48 (1H, ddd, J = 8.4, 7.2, 1.3 Hz), 7.31 (1H, ddd, J = 8.1, 7.2, 0.9 Hz), 7.19 (1H, d, J = 9.6 Hz), 6.57 (1H, dt, J = 9.7, 6.5 Hz), 4.29 (2H, br s), 1.64 (9H, s), 1.55 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.3, 151.4, 149.5, 138.3, 132.1, 131.2, 128.0, 125.9, 125.5, 123.8, 123.4, 120.4, 114.8, 84.8, 83.5, 43.6, 28.2, 27.9. IR (KBr) ν (cm^{-1}) 3438 w, 3053 w, 2983 m, 2940 w, 1764 s, 1730 s, 1691 sh, 1670 w, 1532 w, 1448 m, 1418 m, 1373 s, 1339 s, 1326 s, 1278 m, 1264 m, 1229 s, 1141 s, 1118 s, 1027 m, 1016 m, 1011 m, 976 m, 951 w, 895 w, 862 m, 834 m, 805 m, 780 m, 767 m, 747 s, 695 w, 674 w, 607 w, 588 w, 511 w, 470 w, 442 w. MS (EI) *m*/*z* (rel. intensity) 398 (2), 242 (7), 199 (11), 198 (100), 197 (33), 170 (6), 169 (20), 157 (6), 56 (7), 44 (21), 41 (13). HRMS (ESI+) calcd for $C_{22}H_{26}N_2O_5Na$ (M + Na$^+$) 421.1734, found 421.1735.

(*Z*)-2,3-Dihydroazepino[3,4-*b*]indol-1(10*H*)-one (7a). Olefin **7** (600 mg, 1.51 mmol) was dissolved in CH_2Cl_2 and activated silica (1.0 g, 0.040−0.063 mm) was added. After removal of the solvent the mixture was heated at 70 °C for 16 h. Purification by column chromatography (silica gel 70−230 mesh, *n*-hexane:ethyl acetate 1:1 to ethyl acetate as the gradient eluent) yielded a white solid (293 mg, yield: 98%). R_f 0.44 (ethyl acetate). Mp 198 °C (*n*-hexane: ethyl acetate). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 11.86 (1H, br s), 7.91 (1H, unresolved dd), 7.76 (1H, d, J = 8.1 Hz), 7.45 (1H, unresolved ddd), 7.28 (1H, ddd, J = 8.1, 7.0, 1.1 Hz), 7.15 (1H, d, J = 10.0 Hz), 7.12 (1H, ddd, J = 7.9, 7.0, 0.9 Hz), 6.04 (1H, dt, J = 9.9, 6.5 Hz), 3.53 (2H, unresolved dd). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 163.9, 136.1, 130.6, 125.3, 125.2, 124.5, 124.0, 120.0, 119.9, 116.0, 112.3, 38.4. IR (KBr) ν (cm^{-1}) 3209 s, 3060 sh, 2984 sh, 2924 sh, 1911 w, 1627 s, 1574 sh, 1525 s, 1500 m, 1478 s, 1438 m, 1419 m, 1394 m, 1333 s, 1301 m, 1271 m, 1246 w, 1233 w, 1156 m, 1114 w, 1071 w, 1021 w, 1007 w, 932 w, 904 m, 854 w, 810 m, 775 m, 758 s, 675 m, 620 w, 596 m, 586 w, 564 w, 515 m, 436 m, 423 m. MS (EI) *m*/*z* (rel. intensity) 199 (20), 198 (100), 170 (20), 169 (77), 168 (12), 155 (16), 154 (16), 140 (11), 115 (24), 86 (30), 84 (50), 83 (13), 71(12), 70 (11), 69 (14), 63 (11), 57 (21), 55 (18), 51 (18), 49 (62), 43 (19), 41 (18). HRMS (EI) calcd for $C_{12}H_{10}N_2O$ (M$^+$) 198.0788, found 198.0782.

Aziridiniation of (*Z*)-Di-*tert*-butyl 1-Oxoazepino[3,4-*b*]indole-2,10(1*H*,3*H*)-dicarboxylate (7) with Chloramine-T, Synthesis of (±)-8a. Olefin **7** (3.10 g, 7.78 mmol) was dissolved under argon in anhydrous acetonitrile (200 mL), then $PhNMe_3Br_3$ (146 mg, 0.390 mmol) and chloramine-T × $3H_2O$ (1.10 g, 3.89 mmol) were added. The mixture was stirred for 13 h and was quenched with saturated Na_2SO_3(aq) (200 mL). After extraction with ethyl acetate (3 × 200 mL), the combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude orange solid product was purified by column chromatography (silica gel 70−230 mesh, *n*-hexane to *n*-hexane:ethyl acetate 5:1 as the gradient eluent) to yield a white solid product (1.74 g, 78%) and a pure fraction of starting material **7** (1.19 g, 38%). The product was recrystallized from ethyl acetate:*n*-heptane (1:4) at 4 °C. Crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of a solution of ethyl acetate at room temperature. Mp 169−170 °C (ethyl acetate). R_f 0.24 (*n*-hexane: ethyl acetate 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.03 (1H, d, J = 8.5 Hz), 7.89 (2H, d, J = 8.3 Hz), 7.44−7.34 (3H, m), 7.17−6.95 (2H, m), 4.60 (1H, br s), 3.92 (1H, d, J = 6.9 Hz), 3.81−3.72 (1H, m), 3.60 (1H, br s), 2.49 (3H, s), 1.59 (9H, s), 1.56 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.9, 151.8, 148.9, 145.4, 137.9, 134.6, 130.3, 130.1, 128.5, 127.8, 126.9, 123.7, 120.2, 117.1, 114.8, 85.3, 84.5, 35.6, 28.2, 27.7, 21.9. ^{1}H NMR (300 MHz, 323 K, $CDCl_3$) δ (ppm) 8.04 (1H, ddd, J = 8.6, 1.0, 0.7 Hz), 7.89 (2H, unresolved ddd), 7.37 (1H, ddd, J = 8.5, 6.7, 1.8 Hz), 7.21−7.12 (2H, m), 4.60−4.47 (1H, m), 3.95 (1H, d, J = 6.8 Hz), 3.76 (1H, ddd, J = 9.0, 7.0, 4.5 Hz), 3.72−3.58 (1H, m), 2.48 (3H, s), 1.59 (9H, s), 1.57 (9H, s). ^{13}C NMR (75 MHz, 323 K, $CDCl_3$) δ (ppm) 159.8, 152.1, 149.0, 145.3, 138.1, 135.2, 130.5, 130.1, 128.5, 127.8, 127.1, 123.7, 120.4, 117.2, 114.8, 85.3, 84.5, 45.7 (br s), 41.9 (br s), 35.8, 28.3, 27.8, 21.8. IR (KBr) ν (cm^{-1}) 3428 w, 2977 w, 2934 w, 1745 s, 1723 s, 1701 s, 1596 w, 1556 w, 1477 w, 1447 m, 1396 m, 1369 s, 1323 s, 1289 s, 1260 m, 1225 m, 1207 m, 1160 s, 1124 m, 1111 m, 1091 m, 1018 w, 999 w, 974 w, 951 w, 876 w, 864 w, 829 w, 811 w, 768 w, 741 m, 706 w, 679 m, 659 w, 590 w, 567 m, 548 m, 509 w. MS (EI) *m*/*z* (rel. intensity) 567 (3), 511 (2), 367 (4), 356 (7), 300 (21), 256 (24), 212 (53), 181 (26), 155 (11), 131 (31), 91 (18), 59 (56), 57 (47), 56 (100), 55 (36), 53 (12), 51 (13), 49 (13). HRMS (ESI) calcd for $C_{29}H_{33}N_3O_7SNa$ (M + Na$^+$) 590.1931, found 590.1937. HPLC (column: Reprosil 100 Chiral-NR 8 μm, solvent: *n*-hexane:ethanol 97:7, flow = 0.8 mL/min) t_R = 63.37, 70.22 min. Anal. Calcd for $C_{29}H_{33}N_3O_7S$: C, 61.36; H, 5.86; N, 7.40; S, 5.65. Found: C, 61.16; H, 5.57; N, 7.16; S, 5.68.

Aziridiniation of (*Z*)-Di-*tert*-butyl 1-Oxoazepino[3,4-*b*]indole-2,10(1*H*,3*H*)-dicarboxylate (7) with Chloramine-B, Synthesis of (±)-8b. Olefin **7** (1.51 g, 3.78 mmol) was dissolved under argon in anhydrous acetonitrile (200 mL), then $PhNMe_3Br_3$ (71 mg, 0.189 mmol) and chloramine-B × 3 H_2O (405 mg, 1.89 mmol) were added. The mixture was stirred for 13 h and was quenched with saturated Na_2SO_3(aq) (200 mL). After extraction with ethyl acetate (3 × 200 mL), the combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude orange product was purified by column chromatography (silica gel 70−230 mesh, *n*-hexane to *n*-hexane:ethyl acetate (8:1) as the gradient eluent) to yield a white solid product and the starting material (0.81 g). The product was recrystallized from CH_2Cl_2:*n*-hexane to yield a white solid product (0.57 g, 54%). Crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of a solution of ethyl acetate at room temperature. R_f 0.24 (*n*-hexane:ethyl acetate 6:1). Mp 203 °C (CH_2Cl_2:ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.05−7.99 (3H, m), 7.71 (1H, unresolved dd), 7.59 (2H, unresolved dd), 7.40 (1H, unresolved ddd), 7.13 (1H, unresolved dd), 7.06 (1H, s), 4.60 (1H, s), 3.96

(1H, d, J = 6.6 Hz), 3.85−3.74 (1H, m), 3.61 (1H, s), 1.59 (9H, s), 1.56 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.8, 151.8, 148.9, 137.9, 137.7, 134.2, 130.3, 129.5, 128.4, 127.8, 126.9, 123.8, 120.1, 116.9, 114.8, 85.3, 84.5, 35.8, 28.2, 27.8. ^{1}H NMR (400 MHz, 323 K, $CDCl_3$) δ (ppm) 8.03 (3H, m), 7.69 (1H, unresolved dddd), 7.57 (1H, unresolved dddd), 7.40 (1H, ddd, J = 8.4, 6.7, 1.7 Hz), 7.21−7.12 (2H, m), 4.54 (1H, d, J = 12.5 Hz), 3.90 (1H, d, J = 6.8 Hz), 3.83−3.76 (1H, m), 3.74−3.57 (1H, m), 1.59 (9H, s), 1.57 (9H, s). ^{13}C NMR (100 MHz, 323 K, $CDCl_3$) δ (ppm) 159.8, 152.1, 149.0, 138.3, 138.1, 134.1, 130.5, 129.5, 128.4, 127.8, 127.1, 123.8, 120.3, 117.0, 114.9, 85.3, 84.5, 45.6, 42.0, 36.0, 28.3, 27.8. IR (KBr) ν (cm^{-1}) 3423 w, 3119 w, 3070 w, 2981 m, 2932 w, 1751 s, 1720 s, 1696 s, 1607 w, 1556 w, 1474 sh, 1448 m, 1428 sh, 1395 m, 1369 s, 1338 s, 1322 s, 1290 s, 1261 s, 1222 s, 1208 s, 1170 s, 1150 s, 1125 m, 1091 s, 1020 m, 1002 m, 976 m, 954 m, 895 w, 879 m, 857 m, 811 m, 773 m, 754 m, 744 s, 726 m, 692 w, 670 w, 639 w, 594 m, 555 m, 504 w, 486 w, 442 w. MS (EI) m/z (rel. intensity) 553 (1), 353 (18), 356 (36), 213 (81), 212 (100), 199 (10), 198 (75), 197 (25), 185 (63), 184 (60), 183 (60), 169 (31), 168 (13), 167 (17), 157 (16), 156 (26), 155 (43), 142 (11), 130 (13), 129 (22), 128 (25), 127 (15), 126 (10), 101 (14), 78 (42), 77 (63), 64 (11), 57 (68), 56 (87), 55 (43), 53 (11), 51 (29), 50 (18), 44 (69), 41 (85), 40 (16), 39 (76). HRMS (EI) calcd for $C_{28}H_{31}N_3O_7S$ (M^+) 553.1877, found 553.1877. Anal. Calcd for $C_{28}H_{31}N_3O_7S$: C, 60.74; H, 5.64; N, 7.59; S, 5.79. Found: C, 60.53; H, 5.93; N, 7.56; S, 6.02.

Copper-Catalyzed Aziridiniation of (*Z*)-Di-*tert*-butyl 1-Oxoazepino[3,4-*b*]indole-2,10(1*H*,3*H*)-dicarboxylate, Synthesis of (±)-8c.[33] Olefin **7** (4.00 g, 10.0 mmol), $PhI(OAc)_2$ (2.58 g, 8 mmol), 5-methylpyridine-2-sulfonamide (1.38 g, 8.00 mmol), copper(II) trifluoroacetylacetonate [$Cu(tfac)_2$] (148 mg, 0.40 mmol), and activated 4 Å molecular sieve (20 g) were suspended under argon in anhydrous acetonitrile (80 mL). The mixture was stirred for 13 h. It was then diluted with ethyl acetate (400 mL) and washed with water (400 mL). The aqueous layer was further extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude solid product was purified by column chromatography (silica gel 70−230 mesh, *n*-hexane to *n*-hexane:ethyl acetate 4:1 as the gradient eluent) to yield a white solid product (2.44 g, 76%) and a pure fraction of starting material **7** (1.74 g, 43%). The product was recrystallized from diethyl ether:*n*-hexane. Crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of a solution of CH_2Cl_2 at ambient temperature. R_f 0.06 (*n*-hexane:ethyl acetate 4:1). Mp 149−150 °C (Et_2O:*n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.57 (1H, s), 8.01 (1H, d, J = 8.5 Hz), 7.99 (1H, d, J = 8.0 Hz), 7.71 (1H, dd, J = 8.0, 1.7 Hz), 7.67 (1H, d, J = 8.0 Hz), 7.39−7.44 (1H, m), 7.22−7.27 (1H, m), 4.60 (1H, br s), 4.21 (1H, d, J = 7.0 Hz), 3.93 (1H, ddd, J = 8.9, 7.0, 4.7 Hz), 3.63 (1H, br s), 2.44 (3H, s), 1.57 (9H, s), 1.53 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$, 323 K) δ (ppm) 159.7, 153.4, 151.8, 150.8, 148.8, 138.5, 138.2, 138.0, 130.4, 127.7, 127.0, 123.6, 122.8, 120.7 117.2, 114.6, 85.1, 84.2, 45.4, 42.2, 35.8, 28.1, 27.7, 18.5. IR (KBr) ν (cm^{-1}) 3443 s, 2981 s, 2934 m, 1770 sh, 1749 s, 1721 s, 1635 w, 1558 w, 1447 s, 1394 m, 1370 s, 1315 s, 1292 sh, 1259 s, 1227 s, 1156 s, 1104 s, 1083 s, 1024 m, 1000 m, 975 m, 952 m, 850 m, 832 m, 810 w, 767 m, 751 m, 744 m, 693 m, 679 w, 659 w, 638 w, 589 w, 569 m, 562 m, 549 m, 524 w, 495 w, 469 w, 425 w. HRMS (ESI) calcd for $C_{28}H_{33}N_4O_7S^+$ ($M + H^+$) m/z 569.2064, found 569.2072 and calcd for $C_{28}H_{32}N_4O_7SNa$ ($M+Na^+$) m/z 591.1884, found 591.1897. Anal. Calcd for $C_{28}H_{32}N_4O_7S$: C, 59.14; H, 5.67; N, 9.85; S, 5.64. Found: C, 58.93; H, 5.46; N, 9.54; S, 5.80.

General Procedure for the Ring-Opening Reaction of Aziridines with Indoles (General Procedure A). Aziridine (±)-**8a**−**c** (0.2 mmol) and an indole derivative (2 mmol) were dissolved in an appropriate solvent (e.g., CH_2Cl_2, acetone or ethyl acetate) and activated silica (429 mg, 0.040−0.063 mm) was added. The solvent was removed under reduced pressure and the solid mixture was heated under argon at 70 °C overnight (∼12−16 h). Purification by column chromatography (silica gel 70−230 mesh, CH_2Cl_2 to CH_2Cl_2:MeOH 10:1 as the gradient eluent) yielded the crude product. It was then washed or recrystallized as described below and in the Supporting Information.

***N*-(5-(1*H*-Indol-3-yl)-1-oxo-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]indol-4-yl)tosylamide ((±)-11a).** A crude product was obtained following general procedure A. It was dissolved in CH_2Cl_2; *n*-hexane was added dropwise until some precipitate was formed. Then the solution was cooled to 4 °C and finally filtered to yield a white solid product (90 mg, 93%). R_f 0.12 (CH_2Cl_2:MeOH 20:1). Mp 145−146 °C (CH_2Cl_2:*n*-hexane, dec). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 11.34 (1H, br s), 10.73 (1H, br s), 8.06−7.96 (2H, m), 7.61 (2H, d, J = 8.1 Hz), 7.38 (1H, d, J = 8.1 Hz), 7.27−7.20 (3H, m), 7.08 (1H, unresolved ddd), 7.04−6.96 (1H, m), 6.92 (1H, d, J = 8.1 Hz), 6.80−6.71 (3H, m), 4.69 (1H, d, J = 4.3 Hz), 3.64−3.56 (1H, m), 3.51−3.47 (1H, m), 3.19−3.06 (1H, m), 2.37 (3H, s). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 164.0, 142.4, 137.6, 136.3, 136.2, 129.4, 127.5, 126.6, 125.1, 124.7, 123.7, 120.9, 120.6, 118.7, 118.4, 117.5, 117.4, 116.8, 115.4, 112.1, 111.7, 54.6, 41.6, 25.0, 21.1. IR (KBr) ν (cm^{-1}) 3361 s, 3057 m, 2923 m, 2863 m, 1926 w, 1644 s, 1547 m, 1481 s, 1455 s, 1338 s, 1291 m, 1244 w, 1222 w, 1185 w, 1158 s, 1088 s, 1006 w, 989 w, 943 w, 883 w, 814 m, 744 s, 661 m, 578 m, 552 m, 531 m, 428 w. MS (CI) m/z (rel. intensity) 485 (12), 484 (39), 329 (35), 314 (19), 313 (100), 312 (21), 301 (15), 300 (82), 272 (19), 271 (29), 270 (11), 243 (24), 242 (15), 216 (12), 212 (20), 185 (20), 145 (86), 91 (15). HRMS (ESI) calcd for $C_{27}H_{25}N_4O_3S$ ($M + H^+$) 485.1642, found 485.1639.

***N*-(5-(1*H*-Indol-3-yl)-1-oxo-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]indol-4-yl)benzenesulfonamide ((±)-13a).** A crude product was obtained following general procedure A. It was recrystallized from CH_2Cl_2 to yield a white solid product (61 mg, 66%). R_f 0.37 (CH_2Cl_2:MeOH 10:1) mp 189 °C (CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 11.33 (1H, br s), 10.73 (1H, d, J = 2.2 Hz), 8.10 (1H, d, J = 5.9 Hz), 7.98 (1H, dd, J = 6.3, 3.2 Hz), 7.80−7.74 (2H, m), 7.60 (1H, unresolved dddd), 7.52−7.42 (2H, m), 7.39 (1H, d, J = 8.3 Hz), 7.25 (1H, d, J = 8.1 Hz), 7.09 (1H, unresolved ddd), 7.04−6.97 (1H, m), 6.91 (1H, d, J = 8.1 Hz), 6.83−6.78 (2H, m), 6.75 (1H, unresolved ddd), 6.62 (1H, d, J = 2.2 Hz), 4.71 (1H, d, J = 4.2 Hz), 3.65 (1H, dd, J = 10.8, 6.1 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 164.0, 140.7, 136.3, 126.2, 132.3, 129.0, 127.6, 127.5, 126.5, 125.1, 124.7, 123.7, 121.0, 120.6, 118.7, 118.5, 117.4, 117.0, 115.3, 112.1, 111.7, 54.9, 54.4, 41.3. IR (KBr) ν (cm^{-1}) 3411 s, 3313 s, 3063 m, 2874 m, 1640 s, 1550 m, 1480 s, 1454 m, 1419 m, 1338 s, 1294 sh, 1265 sh, 1245 m, 1220 m, 1161 s, 1088 s, 1011 w, 989 w, 950 m, 879 w, 812 w, 739 s, 688 s, 585 s, 528 m, 488 m, 451 m, 426 m. MS (EI) m/z (rel. intensity) 470 (22), 329 (23), 314 (11), 313 (49), 312 (13), 301 (11), 300 (51), 272 (14), 271 (24), 270 (11), 243 (28), 242 (17), 216 (18), 212 (17), 207 (13), 185 (19), 145 (91), 77 (22), 69 (12), 45 (11), 44 (100), 43 (21), 41 (10). HRMS (EI) calcd for $C_{26}H_{22}N_4O_3S$ (M^+) 470.1407, found 470.1407.

***N*-(5-(1*H*-Indol-3-yl)-1-oxo-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]indol-4-yl)-5-methylpyridine-2-sulfonamide ((±)-14a).** A crude product was obtained following general procedure A. It was washed with diethyl ether and finally filtered to yield a white solid product (89 mg, 92%). R_f 0.17 (CH_2Cl_2:MeOH 100:5). mp >300 °C (Et_2O). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 11.28 (1H, s), 10.67 (1H, d, J = 2.0 Hz), 8.25 (1H, br s), 8.02−8.06 (2H, m), 7.61 (2H, m), 7.34 (1H, d, J = 8.2 Hz), 7.22 (1H, d, J = 8.1 Hz), 7.17 (1H, d, J = 7.9 Hz), 6.96−7.08 (3H, m), 6.81−6.85 (1H, m), 6.71−6.76 (2H, m), 4.82 (1H, d, J = 5.3 Hz), 4.03 (1H, dd, J = 12.9, 6.6 Hz), 3.49 (1H, dd, J = 14.0, 3.9 Hz), 3.17−3.26 (1H, m), 2.30 (3H, s). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 164.3, 155.3, 149.9, 138.1, 136.8, 136.5, 136.4, 127.7, 127.5, 125.4, 124.8, 123.8, 121.0, 120.9, 120.8, 118.8, 118.5, 118.1, 116.9, 115.8, 112.2, 111.8, 55.8, 42.9, 40.1, 18.2. IR (KBr) ν (cm^{-1}) 3411 s, 3359 s, 3191 sh, 3083 sh, 2871 m, 1930 w, 1648 s, 1556 m 1485 s, 1456 s, 1340 s,

1307 s, 1247 w, 1223 m, 1202 w, 1163 s, 1131 w, 1109 m, 1094 s, 1051 w, 1028 w, 1003 m, 993 m, 960 m, 881 w, 835 w, 807 w, 747 s, 663 s, 636 m, 612 m, 575 m, 554 s, 530 m, 501 w, 427 w. HRMS (CI) calcd for $C_{26}H_{22}N_5O_3S$ (M^-) 484.1449, found 484.1437.

General Procedure for the Reaction of 5-Hydroxy-2,3,4,5-tetrahydroazepino[3,4-*b*]indol-1(10*H*)-one ((±)-6) with Indoles (General Procedure B). Alcohol (±)-**6** (100 mg, 0.462 mmol) and an indole derivative (4.62 mmol) were dissolved in the heat with an appropriate solvent (acetone or dichloromethane and ethyl acetate) and activated silica (800 mg, 0.040−0.063 mm) was added. The solvent was removed under reduced pressure and the mixture was heated to 70 °C overnight (∼12−16 h). Purification by column chromatography (silica gel 70−230 mesh, CH_2Cl_2 to CH_2Cl_2:MeOH 20:1 as the gradient eluent) yielded the crude product. It was then washed or recrystallized as described below and in the Supporting Information.

5-(1*H*-Indol-3-yl)-2,3,4,5-tetrahydroazepino[3,4-*b*]indol-1(10*H*)-one ((±)-15a). A crude product was obtained following general procedure B. After recrystallization from hot MeOH a white solid (133 mg, yield: 91%) was obtained at 4 °C. R_f 0.23 (CH_2Cl_2:MeOH 20:1). Mp 271 °C (MeOH, dec). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 11.24 (1H, br s), 10.76 (1H, d, J = 1.9 Hz), 8.11 (1H, dd, J = 5.7, 4.0 Hz), 7.52 (1H, d, J = 7.7 Hz), 7.38 (1H, d, J = 8.1 Hz), 7.32 (1H, d, J = 8.1 Hz), 7.12−7.01 (3H, m), 6.94 (1H, unresolved ddd), 6.79−6.70 (2H, m), 4.95 (1H, dd, J = 5.3, 5.1 Hz), 3.36−3.25 (1H, m), 3.22−3.08 (1H, m), 2.34−2.23 (2H, m). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 164.1, 136.4, 136.0, 127.8, 127.4, 125.8, 123.8, 123.6, 121.0, 120.9, 119.3, 119.0, 118.6, 118.3, 118.3, 112.1, 111.6, 37.7, 34.8, 33.4. IR (KBr) ν (cm^{-1}) 3351 s, 3306 s, 3055 m, 2951 m, 2930 m, 2865 m, 1895 w, 1780 w, 1623 s, 1575 m, 1542 s, 1482 s, 1455 m, 1447 m, 1420 m, 1402 m, 1369 m, 1335 s, 1310 m, 1293 m, 1246 m, 1223 m, 1190 w, 1158 m, 1112 w, 1095 m, 1054 m, 1039 w, 1010 m, 991 w, 973 w, 946 w, 913 w, 880 w, 819 w, 776 m, 765 sh, 752 s, 745 s, 713 m, 678 m, 653 m, 631 w, 605 m, 585 m, 528 w, 505 m, 473 w, 446 w, 424 w, 408 w. MS (EI) *m*/*z* (rel. intensity) 316 (21), 315 (100), 298 (39), 297 (12), 286 (22), 285 (30), 272 (15), 271 (20), 269 (13), 258 (23), 257 (35), 256 (15), 243 (12), 198 (45), 128 (10), 44 (13). HRMS (EI) calcd for $C_{20}H_{17}N_3O$ (M^+) 315.1366, found 315.1366.

Di-*tert*-butyl 4-(4-Methylphenylsulfonamido)-1-oxo-4,5-dihydroazepino[3,4-*b*]indole-2,10(1*H*, 3*H*)-dicarboxylate ((±)-16a). Aziridine (±)-**8a** (200 mg, 0.352 mmol) and ammonium formate (33 mg, 0.528 mmol) were dissolved in absolute MeOH (10 mL). After addition of Pd/C (10 mg, 5%(w/w)) the reaction was heated to reflux for 1.5 h. After cooling to room temperature the reaction mixture was filtered and the solvent was removed in vacuo. Purification by column chromatography (silica gel 70−230 mesh, *n*-hexane:ethyl acetate 6:1) yielded an off-white solid (155 mg, 76%). R_f 0.58 (*n*-hexane:ethyl acetate 1:1). mp 71 °C (ethyl acetate: *n*-hexane). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.97 (1H, d, J = 8.6 Hz), 7.84 (1H, d, J = 7.1 Hz), 7.73 (1H, d, J = 8.3 Hz), 7.51 (1H, unresolved ddd), 7.50−7.44 (3H, m), 7.33 (1H, unresolved ddd), 4.00−3.84 (2H, m), 3.54 (1H, dd, J = 14.7, 8.3 Hz), 2.99 (1H, dd, J = 15.7, 3.2 Hz), 2.88 (1H, dd, J = 15.7, 6.6 Hz), 2.44 (3H, s), 1.53 (9H, s), 1.45 (9H, s). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 161.1, 150.6, 148.5, 143.0, 138.4, 137.4, 130.2, 129.8, 127.8, 127.4, 126.5, 123.3, 123.1, 120.8, 114.0, 84.4, 82.6, 52.3, 47.8, 27.5, 27.2, 26.0, 21.0. IR (KBr) ν (cm^{-1}) 3439 m, 3267 sh, 2978 m, 2927 m, 2856 sh, 1742 s, 1599 w, 1553 w, 1450 m, 1415 m, 1395 m, 1370 s, 1326 m, 1236 m, 1158 s, 1122 sh, 1092 m, 1064 m, 1022 w, 992 m, 956 w, 893 w, 852 w, 816 w, 764 m, 750 m, 707 w, 664 m, 590 w, 552 w, 524 w. MS (EI) *m*/*z* (rel. intensity) 569 (1), 383 (9), 369 (7)339 (12), 275 (6), 199 (14), 198 (100), 197 (19), 185 (33), 184 (18), 91 (8), 56 (42), 55 (14). HRMS (ESI) calcd for $C_{29}H_{35}N_3NaO_7S$ ($M + Na^+$) 592.2088, found 592.2091.

4-Methyl-*N*-(1-oxo-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]indol-4-yl)benzenesulfonamide ((±)-16b). Compound (±)-**16a** (90 mg, 0.158 mmol) was dissolved in 7:1 CH_2Cl_2:TFA and the mixture was stirred for 2 h at room temperature. Then saturated $NaHCO_3$-(aq) (30 mL) was added slowly and the mixture was extracted with CH_2Cl_2 (4 × 30 mL). The combined organic layers were dried over $MgSO_4$. After filtration the solvent was removed under reduced pressure to yield a green oil. Purification by column chromatography (silica gel 70−230 mesh, ethyl acetate) yielded a white solid (56 mg, 96%). R_f 0.46 (*n*-hexane:ethyl acetate 1:1). Mp 206 °C (ethyl acetate). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.27 (1H, s), 8.00 (1H, d, J = 6.2 Hz), 7.97 (1H, unresolved dd), 7.76 (2H, d, J = 8.3 Hz), 7.43−7.32 (4H, m), 7.19 (1H, ddd, J = 8.2, 7.0, 1.0 Hz), 7.00 (1H, unresolved ddd), 3.58−3.46 (1H, m), 3.32−3.27 (2H, m), 3.00 (1H, dd, J = 17.1, 5.4 Hz), 2.91 (1H, dd, J = 16.9, 8.7 Hz), 2.38 (3H, s). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 163.9, 142.7, 138.2, 136.0, 129.7, 127.1, 126.9, 126.5, 124.1, 119.5, 119.2, 112.8, 112.1, 51.9, 46.7, 31.4, 21.0. IR (KBr) ν (cm^{-1}) 3297 s, 3247 s, 3061 sh, 2918 m, 1615 s, 1550 m, 1478 s, 1452 s, 1414 m, 1325 s, 1284 s, 1269 m, 1228 w, 1185 w, 1154 s, 1117 w, 1092 m, 1061 w, 1005 w, 957 w, 916 w, 889 m, 943 w, 832 w, 812 m, 787 w, 761 m, 741 m, 662 m, 590 w, 570 w, 550 m, 522 m, 431 w. MS (EI) *m*/*z* (rel. intensity) 369 (11), 199 (29), 198 (100), 185 (31), 169 (17), 167 (13), 158 (11), 157 (12), 155 (10), 130 (19), 129 (19), 128 (13), 91 (19), 44 (11). HRMS (EI) calcd for $C_{19}H_{20}N_3O_3S$ ($M + H^+$) 370.1220, found 370.1228.

5-(Octyloxy)-2,3,4,5-tetrahydroazepino[3,4-*b*]indol-1(10*H*)-one ((±)-17). Alcohol (±)-**6** (100 mg, 0.462 mmol) and *n*-octanol (602 mg, 4.62 mmol) were dissolved in acetone and activated silica (800 mg, 0.040−0.063 mm) was added. The solvent was removed under reduced pressure and the mixture was heated to 70 °C for 15 h. Purification by column chromatography (silica gel 70−230 mesh, ethyl acetate) yielded 23 mg (15%) of a colorless solid. R_f 0.31 (ethyl acetate). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 11.38 (1H, br s), 8.18 (1H, dd, J = 6.2, 3.0 Hz), 7.63 (1H, d, J = 8.1 Hz), 7.42 (1H, d, J = 8.3 Hz), 7.20 (1H, ddd, J = 8.3, 7.0, 1.1 Hz), 7.04 (1H, ddd, J = 7.9, 7.0, 0.9 Hz), 4.88 (1H, unresolved dd), 3.68−3.50 (2H, m), 3.49−3.37 (1H, m), 3.22−3.09 (1H, m), 2.46−2.32 (1H, m), 1.98−1.84 (1H, m), 1.57−1.43 (2H, m), 1.39−1.14 (10H, m), 0.84 (3H, t, J = 6.9 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 163.4, 135.7, 127.7, 127.6, 123.9, 120.8, 119.4, 117.1, 112.2, 71.7, 67.4, 35.5, 31.2, 30.8, 29.8, 28.8, 28.7, 25.9, 22.1, 14.0. HRMS (ESI) calcd for $C_{20}H_{28}N_2NaO_2$ ($M + Na^+$) 351.2043, found 351.2046.

Di-*tert*-butyl 5-Methoxy-4-(4-methylphenylsulfonamido)-1-oxo-4,5-dihydroazepino[3,4-*b*]indole-2,10(1*H*,3*H*)-dicarboxylate ((±)-18a). Aziridine (±)-**8a** (284 mg, 0.50 mmol) was suspended in absolute MeOH (5 mL) and ceric ammonium nitrate (CAN) (27 mg, 0.05 mmol) was added. The reaction was stirred at room temperature for 9 h until no further changes were observed by TLC. The solvent was removed in vacuo. Purification by column chromatography (silica gel 70−230 mesh, *n*-hexane:ethyl acetate 3:1) yielded the starting material (150 mg) and a white solid product (141 mg, 47%, 99% based on recycled starting material). R_f 0.21 (*n*-hexane:ethyl acetate 3:1). Mp 79−80 °C (*n*-hexane:ethyl acetate). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.00 (1H, d, J = 8.6 Hz), 7.82 (1H, d, J = 8.3 Hz), 7.73 (2H, d, J = 8.1 Hz), 7.60 (1H, d, J = 7.8 Hz), 7.55 (1H, ddd, J = 8.4, 7.2, 1.2 Hz), 7.47 (2H, d, J = 7.8 Hz), 7.39 (1H, unresolved ddd), 4.70 (1H, br s), 4.07−3.96 (1H, m), 3.83 (1H, dd, J = 14.9, 5.6 Hz), 3.43 (1H, dd, J = 14.8, 10.4 Hz), 2.99 (3H, s), 2.44 (3H, s), 1.54 (9H, s), 1.38 (9H, s). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 160.4, 150.1, 148.4, 143.2, 138.3, 136.7, 130.7, 130.0, 127.8, 127.7, 126.5, 123.8, 122.4, 120.1, 114.1, 85.0, 82.2, 76.1, 56.5, 55.0, 46.7, 27.5, 27.2, 21.0. IR (KBr) ν (cm^{-1}) 3438 m, 3278 m, 2981 m, 2933 m, 2821 w, 1753 s, 1679 w, 1665 w, 1649 w, 1599, 1548 w, 1477 sh, 1449 s, 1416 m, 1394 sh, 1372 s, 1350 s, 1325 s, 1288 s, 1261 m, 1228 m, 1213 m, 1160 s, 1093 s, 1078 sh, 1043 w, 1025 m, 994 s, 958 w, 892 m, 862 m, 833 m, 815 w, 785 m, 772 m, 753 m, 707 w, 664 m, 596 w, 553 s, 538 sh, 472 w. MS (EI) *m*/*z* (rel. intensity) 599 (1), 499 (4), 399 (13), 339 (11), 338 (15), 288 (33), 274 (17), 244 (29), 228 (11),

215 (15), 214 (13), 213 (26), 212 (100), 198 (12), 187 (14), 186 (28), 185 (92), 184 (31), 183 (19), 169 (12), 156 (17), 155 (20), 130 (24), 129 (16), 128 (14), 92 (13), 91 (36), 60 (15), 57 (12), 56 (51), 55 (14), 44 (72), 41 (79). HRMS (EI) calcd for $C_{30}H_{37}N_3O_8S$ (M^+) 599.2296, found 599.2296.

***N*-(5-Methoxy-1-oxo-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]indol-4-yl)-4-methylbenzenesulfonamide ((±)-18b).** Sulfonamide (±)-**18a** (128 mg, 0.213 mmol) was dissolved in CH_2Cl_2 and activated silica (600 mg, 0.040−0.063 mm) was added. The solvent was removed in vacuo and the residue was heated to 70 °C for 13 h. Purification by column chromatography (silica gel 70−230 mesh, *n*-hexane:ethyl acetate 1:2) yielded a white solid (63 mg, 74%). R_f 0.31 (*n*-hexane:ethyl acetate). Mp 170 °C (*n*-hexane:ethyl acetate). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.54 (1H, br s), 8.01−7.92 (2H, m), 7.77 (2H, unresolved ddd), 7.46−7.37 (4H, m), 7.21 (1H, ddd, J = 8.3, 6.9, 1.0 Hz), 7.04 (1H, ddd, J = 8.3, 6.9, 1.0 Hz), 4.42 (1H, d, J = 3.9 Hz), 3.76−3.69 (1H, m), 3.46−3.38 (1H, m), 3.19−3.10 (1H, m), 3.06 (3H, s), 2.40 (3H, s). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 163.4, 142.7, 138.5, 135.8, 129.6, 128.0, 127.9, 126.6, 124.0, 120.2, 119.7, 112.8, 112.3, 76.5, 55.3, 51.6, 40.9, 21.0. IR (KBr) ν (cm^{-1}) 3349 s, 3284 m, 3199 m, 2927 m, 2823 sh, 1733 w, 1651 s, 1597 w, 1578 w, 1549 m, 1480 s, 1445 m, 1341 s, 1291 m, 1248 w, 1211 w, 1185 sh, 1158 s, 1116 m, 1091 s, 1020 m, 996 m, 960 m, 884 m, 839 w, 815 m, 781 w, 740 m, 663 m, 615 w, 538 m, 430 w. HRMS (EI) calcd for $C_{20}H_{21}N_3NaO_4S$ ($M + Na^+$) 422.1145, found 422.1145.

2,3,4,5-Tetrahydro-5-(1*H*-pyrazol-1-yl)-4-(tosylamino)azepino-[3,4-*b*]indol-1(10*H*)-one ((±)-19a). Aziridine (±)-**8a** (113 mg, 0.2 mmol) and 1*H*-pyrazole (136 mg, 2.0 mmol) were dissolved in an CH_2Cl_2 and activated silica (429 mg, 0.040−0.063 mm) was added. The solvent was removed under reduced pressure and the solid mixture was heated under argon at 70 °C for 16 h. Purification by column chromatography (silica gel 70−230 mesh, CH_2Cl_2 to CH_2Cl_2:MeOH 50:1 as the gradient eluent) yielded the crude product. This was dissolved in CH_2Cl_2 and *n*-hexane was added dropwise. After cooling to 4 °C a white solid (51 mg, 59%) was collected by filtration. R_f 0.34 (CH_2Cl_2:MeOH 10:1). Mp 206 °C (CH_2Cl_2:*n*-hexane). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.67 (1H, s), 8.23 (1H, d, J = 5.1 Hz), 8.20 (1H, d, J = 3.9 Hz), 7.53 (2H, unresolved ddd), 7.46 (1H, d, J = 2.2 Hz), 7.41 (1H, unresolved ddd), 7.31−7.26 (3H, m), 7.18−7.12 (1H, m), 6.89−6.84 (2H, m), 6.05 (1H, unresolved dd), 5.79 (1H, d, J = 6.1 Hz), 3.96 (1H, unresolved ddd), 3.31−3.26 (1H, m), 2.37 (3H, s) ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 163.2, 142.5, 139.0, 138.0, 135.9, 129.7, 129.6, 128.3, 126.9, 126.3, 124.1, 119.8, 119.4, 112.4, 110.4, 105.0, 61.6, 56.4, 42.4, 21.0. IR (KBr) ν (cm^{-1}) 3321 w, 3060 m, 2921 m, 1645 s, 1599 m, 1580 w, 1554 m, 1479 s, 1454 m, 1397 m, 1338 s, 1288 s, 1248 w, 1221 w, 1185 m, 1160 s, 1091 s, 1046 m, 1020 w, 1007 w, 992 w, 944 w, 882 w, 837 w, 814 m, 747 s, 705 m, 662 m, 579 m, 552 m, 534 m, 433 w. MS (EI) *m*/*z* (rel. intensity) 435 (4), 265 (12), 264 (71), 222 (13), 213 (23), 212 (100), 198 (19), 197 (19), 196 (12), 185 (74), 184 (23), 183 (11), 169 (18), 156 (16), 155 (19), 97 (10), 91 (30), 83 (12), 71 (15), 68 (33), 57 (24), 55 (17). HRMS (EI) calcd for $C_{22}H_{21}N_5O_3S$ (M^+) 435.1360, found 435.1360.

General Procedure for Ring-Opening Reactions of Aziridines with Secondary Amines (Procedure C). Aziridine (±)-**8a** (142 mg, 0.25 mmol) was dissolved in absolute 1,4-dioxane (5 mL) under argon in a Schlenk tube with a Teflon screwed stopper. After addition of the appropriate amine (1.25 mmol) the sealed reaction vessel was heated to 80 °C for 5 d. Then it was cooled to room temperature and the solvent was removed in vacuo. Purification by column chromatography (silicagel 70−230 mesh, CH_2Cl_2 to CH_2Cl_2:MeOH 30:1 as a gradient eluent) yielded an oily, pale-yellow product. This was washed or recrystallized from hot diethyl ether as described below and in the Supporting Information.

4-Methyl-*N*-(1-oxo-5-(pyrrolidin-1-yl)-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]indol-4-yl)benzenesulfonamide ((±)-20a). A crude product was obtained following general procedure C. Recrystallization from boiling diethyl ether yielded a white solid (86 mg, 78%). R_f 0.37 (CH_2Cl_2:MeOH 10:1). Mp 185 °C (Et_2O). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 11.49 (1H, br s), 7.89−7.76 (2H, m), 7.72 (2H, d, J = 8.3 Hz), 7.44−7.33 (4H, m), 7.18 (1H, unresolved ddd), 7.01 (1H, unresolved ddd), 3.94 (1H, d, J = 3.4 Hz), 3.81−3.69 (1H, m), 3.52−3.40 (1H, m), 3.11−2.97 (1H, m), 2.40 (3H, s), 2.38−2.26 (2H, m), 2.16−2.01 (2H, m), 1.54−1.35 (4H, br s). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 164.1, 142.5, 138.9, 135.7, 129.5, 128.6, 128.5, 126.6, 123.5, 120.5, 119.1, 113.1, 112.1, 61.0, 54.0, 50.0, 42.8, 22.8, 21.0. IR (KBr) ν (cm^{-1}) 3337 s, 3204 s, 3061 sh, 2964 m, 2873 m, 2803 m, 1918 w, 1739 w, 1645 s, 1577 w, 1547 s, 1484 s, 1444 s, 1337 s, 1305 m, 1289 m, 1246 m, 1214 m, 1186 w, 1156 s, 1092 s, 1042 w, 1007 w, 991 m, 948 m, 877 w, 835 w, 814 m, 776 m, 741 s, 660 s, 579 m, 550 s, 536 s, 436 m. MS (EI) *m*/*z* (rel. intensity) 438 (5), 367 (44), 283 (13), 213 (60), 212 (100), 199 (10), 198 (72), 197 (17), 185 (67), 169 (12), 167 (14), 156 (19), 155 (24), 129 (11), 128 (16), 92 (12), 91 (29), 71 (51), 70 (68). HRMS (EI) calcd for $C_{23}H_{26}N_4O_3S$ (M^+) 438.1720, found 438.1721.

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Supporting Information Available: All experimental procedures, characterization of all other compounds, molecular structures, and crystallographic data of **7**, (±)-**8a**−**c,** (±)-**11f**, and (±)-**15d** and atom coordinates of calculated (±)-**6** (**A**) and cationic intermediate (**B**). This material is available free of charge via the Internet at http://pubs.acs.org.

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3.3. Synthesis of novel hymenialdisine analogues using solvent-free and silica gel-promoted ring opening of epoxides

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Naveenkumar Mangu, Hanns Martin Kaiser, Anirban Kar, Anke Spannenberg, Matthias Beller, and Man Kin Tse*

H.M.K. planned, executed and analyzed experiments for the ring-opening of expoxides. H.M.K. was further involved during the compilation of experimental data, contributed to the writing process of the manuscript and was involved in discussions. The work of H.M.K. to this publication accounts to approximately 40 %.

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Synthesis of novel hymenialdisine analogues using solvent-free and silica gel-promoted ring opening of epoxides

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ABSTRACT

A silica gel-promoted regioselective ring-opening reaction of epoxides with indoles and pyrrole under mild and solvent-free conditions is described. This reaction provides a synthetic pathway for a diverse class of novel hymenialdisine analogues.

1. Introduction

Epoxides are versatile building blocks for novel biologically active compounds since they can be readily opened with different nucleophiles giving a variety of functionalized diverse products.[1] Nucleophilic epoxide opening reactions play a key role especially in the construction of carbon–carbon and carbon–oxygen bonds, essential components of organic compounds.[1,2] These reactions are generally performed with acid or base catalysts. In the absence of such catalysts, the reaction is moderately slow.[3]

More specifically, it has been reported that epoxide ring-opening reactions with indoles and pyrroles can be carried out under acid catalysts[4] or high pressure conditions.[5] In addition, Lewis acid catalysts such as lanthanide triflates,[6] nano-crystalline titanium(IV) oxide,[7] $RuCl_3 \cdot nH_2O$,[8] HBF_4/SiO_2[9] and $InCl_3$/silica[10] have been also reported for such transformations. Some of these known methods require comparably long reaction time, high temperature or pressure conditions, expensive reagents and gave unsatisfactory yields. Thus, the development of clean, efficient and mild conditions for the ring opening of epoxides with indoles and pyrroles is desirable.

Small molecule kinase inhibitors are of significant actual interest, both as potential therapeutics and as experimental tools for understanding the physiological role of these enzymes.[11] Protein kinases act pivotally in signal transduction as well as in cellular proliferation, differentiation and various regulatory mechanisms.[12] Kinase inhibitors have emerged as promising therapeutic molecules for treatment of a number of diseases including cancer and asthma.[12,13] In recent years, intense effort has been devoted towards the development and identification of such small molecule inhibitors associated with diseases; currently 20–30% of pharmaceutical discovery programmes are focused on kinase functions.[11,12] Staurosporine (**1**), a bisindole alkaloid has been found as one of the first kinase inhibitors in nanomolar concentrations (Fig. 1).[14] Several kinase inhibitors have progressed to human clinical trials.[12,15,16] Among them, hymenialdisine (HMD) (**2**), a natural product, exhibited promising results in inhibiting various kinases.[16] We were intrigued by the fascinating structure and highly significant kinase inhibiting activity exhibited by staurosporine (**1**) and hymenialdisine (**2**). As a part of our ongoing efforts to apply catalytic oxidation methodology[18] to synthesize potential bio-active compounds,[19,20] we became interested in preparing a small library of novel bisindoles as hybrid analogues (**3**) of staurosporine and hymenialdisine.[16] It has been reported that the kinase inhibiting activity of HMDs vary much if other heterocycles instead of imidazoles are introduced in its core structure.[17] Therefore, we decided to introduce indoles on annulated HMD scaffold to evaluate their biological activity. Our initial efforts in this field culminated recently in the establishment of a novel strategy for annulated

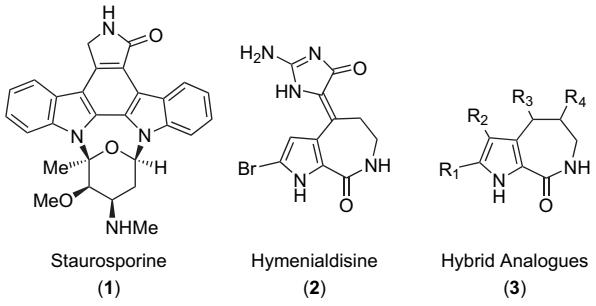

Figure 1. Structures of staurosporine (**1**), hymenialdisine (**2**) and hybrid analogues (**3**).

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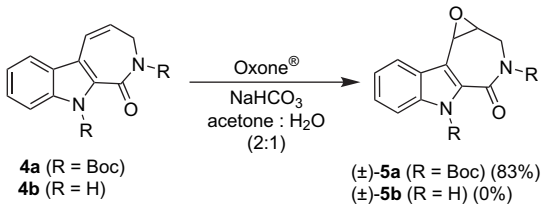
HMD-type bisindoles using aziridines and hydroxyl precursors as starting materials.[20] Here, we disclose another amenable, diversified strategy using silica gel as solid support for ring opening of epoxide (±)-**5a** under mild and solvent-free reaction conditions to give novel bisindole-type hymenialdisine analogues (±)-**8** with a free hydroxyl group.

2. Results and discussion

We initiated a synthetic effort that began with the large scale preparation of the Boc-protected olefin **4a** from commercially available indole-2-carboxylic acid following a previous protocol reported by us.[20] Initial efforts for the epoxidation of **4a** to produce (±)-**5a** utilizing methods such as *m*-CPBA[21] or MTO[22] were unsuccessful. To our delight, we found that the reaction proceeded smoothly to give epoxide (±)-**5a** in 83% yield with in situ generated dimethyloxirane using Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as the terminal oxidant (Scheme 1).[23] The structure of the epoxide (±)-**5a** was confirmed by X-ray crystal structural analysis (Fig. 2). However, when the same reaction conditions were applied to the unprotected olefin **4b**, the formation of the desired epoxide (±)-**5b** was not observed. Transformations of (±)-**5a** into (±)-**5b** have not been performed to avoid unwanted epoxide ring-opening reactions employing the typical Boc-deprotection conditions (HCl/MeOH, TFA/CH_2Cl_2, heat, Na_2CO_3/MeOH, etc.). With the key building block (±)-**5a** in hand, we envisioned to explore silica gel-promoted[21] epoxide ring opening under easily manageable solvent-free conditions to produce hymenialdisine analogues.



Scheme 1. Selective epoxidation of **5a**.

Initial attempts to open epoxide (±)-**5a** with indoles and deprotection of both Boc groups in situ following our previous protocol[20] at 70 °C resulted in the desired ring opened product in moderate to good yields (39–60%). However, the reaction mixture was complicated with concomitant formation of several side products, which in our hands could not be separated and characterized. We hypothesized that the epoxide ring-opening reaction proceeds much faster than the deprotection of the Boc groups. This

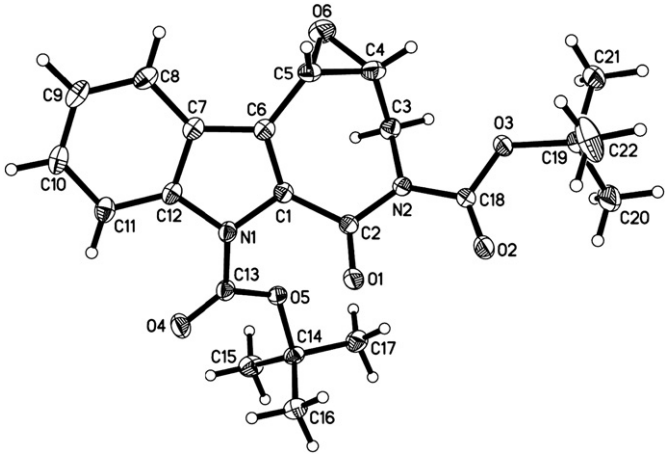
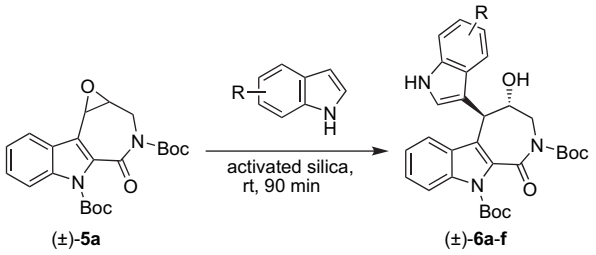
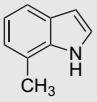
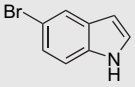
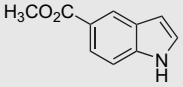
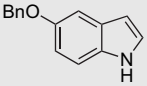
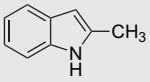


Figure 2. Molecular structure of epoxide (±)-**5a**. The thermal ellipsoids correspond to 30% probability.

Table 1
Ring-opening reactions of (±)-**5a**[a]



Entry	Substrate	Product	Yield[b] (%)
1		(±)-**6a**	74
2		(±)-**6b**	64
3		(±)-**6c**	72
4		(±)-**6d**	55[c]
5		(±)-**6e**	56
6		(±)-**6f**	0

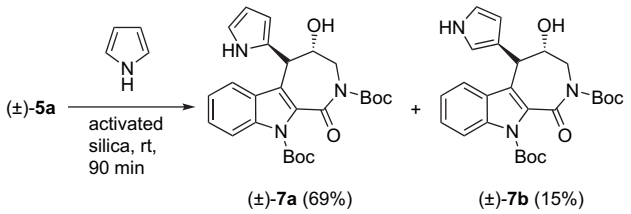
[a] Reaction conditions: epoxide (±)-**5a** (300 mg, 0.72 mmol), indole derivative (7.2 mmol), activated silica (0.040–0.063 mm, 1.56 g), argon, rt, 90 min.
[b] Isolated yield.
[c] Reaction time: 10 h.

enforced us to turn our focus in searching milder conditions to achieve higher selectivity. Fortunately, the reaction proceeded smoothly at room temperature and went to completion with preservation of both Boc groups to give (±)-**6a** in 74% yield.

Next, we applied this protocol to prepare unsymmetrical bisindoles starting from epoxide (±)-**5a** (Table 1). Most of the reactions proceeded at room temperature to give (±)-**6a**–**e** in moderate to good yields (55–74%). Functional groups on the indole ring such as alkyl, halide, alkoxy and ester groups were tolerated under these mild reaction conditions (Table 1, entries 2–5). However, we were unable to isolate the desired product with 2-methyl indole (Table 1, entry 6). The ring-opening reaction of the very reactive epoxide on silica possibly proceeds much faster than the nucleophilic attack of the sterically hindered 2-methyl indole. It is noteworthy to mention that the regioselectivity in all other reactions was excellent. As expected, only one diastereomer is obtained during ring-opening reaction. It takes place at the benzylic position of the (±)-**5a** and at the 3-position of the attached indole, which is in full agreement with an electrophilic substitution mechanism.[10]

Pyrrole opens (±)-**5a** under the same conditions (Scheme 2). The reaction was also regioselective at benzylic position of the substrate affording the corresponding product (±)-**7a** as the major product along with a minor amount of (±)-**7b**.[9]

Standard procedure using TFA to deprotect the Boc groups of (±)-**6a** at room temperature[24] resulted in decomposition of the substrate. As we noticed formation of the desired deprotected compound in the initial screening using our previous protocol,[20] we assumed that the Boc groups can be removed at higher temperature using activated silica as solid support.



Scheme 2. Epoxide opening reaction with pyrrole.

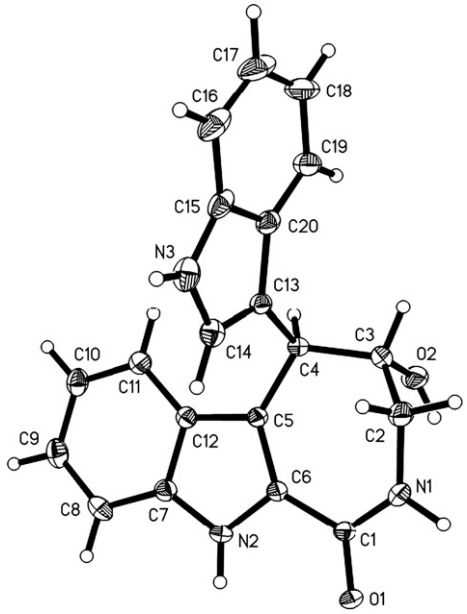
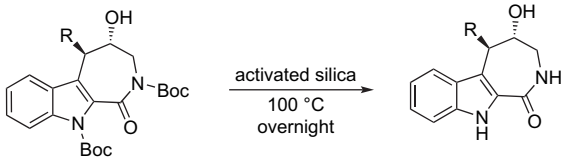


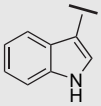
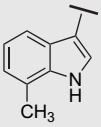
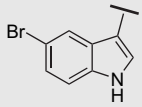
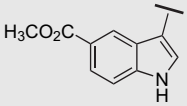
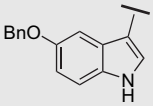
Figure 3. Molecular structure of (±)-**8a**. Only one molecule of the asymmetric unit is depicted. The thermal ellipsoids correspond to 30% probability.

Thus, compound (±)-**6a** was adsorbed on activated silica gel and heated at 100 °C for overnight to give the desired product (±)-**8a**. This is in agreement with our hypothesis that the epoxide ring-opening reaction proceeds much faster than the deprotection of the Boc-protecting groups. Structure of (±)-**8a** was confirmed again by X-ray crystal structural analysis (Fig. 3). This method was successfully employed to all the other epoxide ring opened products to give the desired products in 56–75% yield (Table 2, entries 2–6).

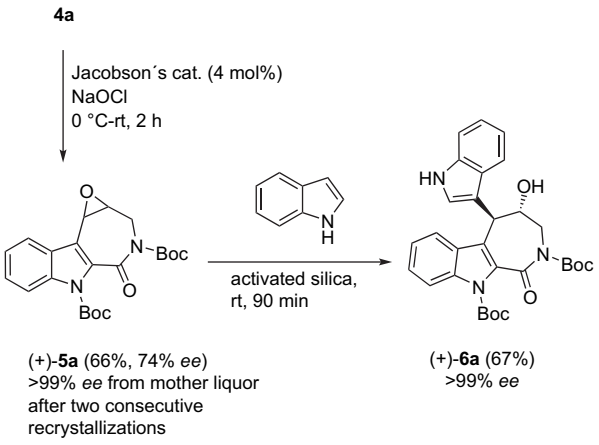
The selective epoxidation and subsequent ring opening prompted us to explore a synthetic route to prepare the enantiomerically pure epoxide of the Boc-protected olefin **4a**. For this purpose, we tested Shi's catalyst[25] using Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as the oxidant. But with our substrate, the conversion was negligible. Next, we checked the feasibility of Jacobson's protocol[26] for the epoxidation of olefin **4a**, for its simple work up procedure.[26b] When **4a** was treated with 4 mol % Jacobson's catalyst using NaOCl as the oxidant, the desired epoxide was yielded in 66% with 74% ee. The product was recrystallized using a mixture of hexane/ethyl acetate (9:1). After two consecutive recrystallizations, (+)-**5a** was obtained in >99% ee from the mother liquor in 34% yield. Subsequently, this enantiopure epoxide was subjected to the ring-opening reaction with indole. Indeed, the desired bisindole (+)-**6a** was obtained with 99% ee and 67% yield (Scheme 3).

Table 2
Deprotection of Boc groups of (±)-**6**[a]



Entry	R	Product	Yield[b] (%)
1		(±)-**8a**	75
2		(±)-**8b**	66
3		(±)-**8c**	65
4		(±)-**8d**	71
5		(±)-**8e**	56
6		(±)-**9a**	65

[a] Reaction conditions: (±)-**6a–e** and **7a** (0.415 mmol), activated silica (0.040–0.063 mm, 0.92 g), argon, 100 °C, overnight.
[b] Isolated yield.



Scheme 3. Synthesis of enantiomerically pure bisindoles.

3. Conclusions

In conclusion, we developed a convenient method for the opening of epoxide with indoles and pyrrole on solid support to synthesize novel unsymmetrical bisindoles. The advantages of the present protocol are the ease of work up, solvent-free conditions and the high selectivity. This method can also be extended to synthesize enantiomerically pure bisindole-type hymenialdisine analogues.

4. Experimental section

4.1. General

All solvents and chemicals were obtained commercially and were used as-received. NMR spectra were measured using a Bruker

ARX 300 or ARX 400 spectrometer at 300 or 400 MHz (^{1}H) and 75 or 100 MHz (^{13}C). All spectra were recorded in DMSO-d_6 or $CDCl_3$ and chemical shifts (δ) are reported in parts per million relative to tetramethylsilane referenced to the residual solvent peaks. Spectra were recorded at room temperature unless otherwise stated. Mass spectra were in general recorded on an AMD 402/3 or an HP 5989A mass selective detector. In each case characteristic fragments with their relative intensities in percentages are shown. Infrared spectra were recorded on a Nicolet 6700 spectrometer using KBr plates or on the same machine equipped with a smart endurance (Thermo Electron Corporation) for ATR-IR. Wave numbers (ν) are reported in cm^{-1}. HPLC analysis was performed on an HP 1090 machine with DAD detector. Melting points were measured with a Stuart melting point apparatus (SMP3) and are not corrected. Activated silica gel was obtained by heating silica gel (0.040–0.063 mm) at 140 °C in vacuum overnight.

4.2. X-ray diffraction

Diffraction data were collected with an STOE-IPDS diffractometer using graphite-monochromated Mo Kα radiation. The structures were solved by direct methods[27] and refined by full-matrix least-squares techniques on F^2.[28] XP (BRUKER AXS) was used for graphical representations. Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 681249 [(±)-**5a**] and CCDC 682863 [(±)-**8a**]. Copies of the data can be obtained free of charge from www.ccdc.cam.ac.uk or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk.

*4.2.1. Crystal data for (±)-**5a***

Space group $P\bar{1}$, triclinic, a=7.791(2), b=9.354(2), c=14.997(3) Å, α=96.86(3), β=102.25(3), γ=98.00(3)°, V=1045.1(4) Å^3, Z=2, ρ_{calcd}=1.317 g cm^{-3}, 15,688 reflections measured, 4551 were independent of symmetry, of which 3120 were observed ($I>2\sigma(I)$), R_1=0.042, wR_2 (all data)=0.113, 271 parameters.

*4.2.2. Crystal data for (±)-**8a***

Space group $P\bar{1}$, triclinic, a=12.1668(7), b=13.1234(7), c=14.0402(9) Å, α=70.049(5), β=84.851(5), γ=64.600(4)°, V=1899.3(2) Å^3, Z=4, ρ_{calcd}=1.327 g cm^{-3}, 29,081 reflections measured, 8062 were independent of symmetry, of which 4604 were observed ($I>2\sigma(I)$), R_1=0.051, wR_2 (all data)=0.131, 539 parameters.

4.3. Synthesis

*4.3.1. Epoxidation of (Z)-di-tert-butyl 1-oxoazepino[3,4-b]indole-2,10(1H,3H)-dicarboxylate (±)-**5a***

To a vigorously stirred mixture of olefin **4a** (0.80 g, 2.0 mmol) and $NaHCO_3$ (1.68 g, 20.0 mmol) in acetone (200 mL) at 0 °C was added dropwise a solution of Oxone® (3.71 g, 6.0 mmol) in H_2O (120 mL) over a period of 30 min. The ice bath was removed and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was filtered, the solid residue was washed with acetone and the filtrate was concentrated in vacuum. The aqueous layer was extracted with ethyl acetate (3×50 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated in vacuum. The crude compound was purified by column chromatography (silica gel 70–230 mesh, *n*-hexane/ethyl acetate 9:1) to yield a white fluffy solid (692 mg, 83%). Crystals suitable for X-ray analysis were obtained by recrystallizing with ethyl acetate.Mp R_f=0.27 (*n*-hexane/ethyl acetate 8:2). Mp: 164 °C (ethyl acetate). HPLC analysis: column, Chiralcel OD-H; solvent, heptane/ethanol 97:3; flow=1.0 mL/min, t_R=10.11, 13.97 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)=8.09 (1H, d, J=8.5 Hz), 7.75 (1H, d, J=7.8 Hz), 7.48 (1H, unresolved dd), 7.34 (1H, unresolved dd), 4.46–4.23 (1H, m), 4.18 (1H, unresolved d), 4.06–3.90 (1H, m), 3.90–3.79 (1H, m), 1.59 (18H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)=160.0, 152.0, 148.9, 137.8, 129.6, 127.6, 127.3, 123.6, 120.0, 119.0, 114.6, 85.1, 84.0, 47.1, 28.0, 27.6. ^{1}H NMR (400 MHz, 323 K, $CDCl_3$): δ (ppm)=8.14–8.07 (1H, m), 7.78–7.72 (1H, m), 7.46 (1H, unresolved ddd), 7.33 (1H, unresolved ddd), 4.30 (1H, unresolved d), 4.16 (1H, d, J=3.9 Hz), 4.02–3.91 (1H, m), 3.87–3.81 (1H, m), 1.6 (18H, m). ^{13}C NMR (100 MHz, 323 K, $CDCl_3$): δ (ppm)=159.9, 152.2, 149.0, 138.0, 129.9, 127.5, 127.5, 123.6, 119.9, 119.0, 114.9, 85.1, 83.9, 54.6, 47.2, 45.5, 28.1, 27.7. ATR-IR (cm^{-1})=3057w, 2980w, 2935w, 1768m, 1720s, 1559m, 1477w, 1448m, 1368s, 1322s, 1290m, 1258w, 1226w, 1206m, 1145s, 1119m, 1079s, 1024w, 985m, 944m, 894w, 851s, 780s, 746s. MS (EI): *m*/*z* (rel int.) 69 (20), 70 (18), 71 (22), 83 (19), 84 (24), 85 (11), 86 (10), 97 (14), 102 (12), 112 (10), 128(16), 129 (91), 130 (11), 157 (51), 158 (10), 169 (31), 170 (11), 185 (28), 186 (22), 197 (23), 198 (52), 214 (100), 215 (12), 414 (6). HRMS (EI): calcd for $C_{22}H_{26}N_2O_6$ (M^+) 414.1785, found 414.1782.

*4.3.2. Asymmetric epoxidation of (Z)-di-tert-butyl 1-oxoazepino[3,4-b]indole-2,10(1H,3H)-dicarboxylate (+)-**5a***

A solution of 0.05 M Na_2HPO_4 (5 mL) was added to a 6 mL aqueous solution of bleach (~14% NaOCl). The pH value of the resulting buffered solution (~1 M in NaOCl) was ~12.0 and was adjusted to pH 11.5 by addition of a few drops of 5% HCl solution. The solution was cooled to 0 °C from which 8.7 mL were added at once to a 0 °C solution of **4a** (1.0 g, 2.5 mmol) and Jacobson's catalyst (64.0 mg, 0.10 mmol) in 4 mL of dichloromethane. The reaction mixture was stirred at room temperature for 2 h. Ethyl acetate (20 mL) was added to the mixture, the organic phase was separated, dried over $MgSO_4$ and concentrated in vacuum. The crude product was purified by column chromatography (silica gel 70–230 mesh, *n*-hexane/ethyl acetate 9:1) to afford a white fluffy solid (671 mg, 66%, 74% ee). The product was recrystallized with hexane. White solid precipitated out with 33% ee and the enantiomerically enriched compound with 82% ee was obtained after drying the mother liquor. It was again recrystallized using hexane/ethyl acetate mixture (9:1) to produce (+)-**5a** in >99% ee from mother liquor with 34% yield as a fluffy solid. Mp: 78 °C (ethyl acetate/hexane). HPLC analysis: >99% ee (Chiralcel OD-H, solvent: heptane/ethanol 97:3, flow=1.0 mL/min); t_R=13.97 min (major). $[\alpha]_D^{22}$ +4.65 (*c* 1.0, $CHCl_3$).

4.4. General procedure for the ring-opening reaction of the epoxide (±)-5a with indoles (general procedure A)

Epoxide (±)-**5a** (300 mg, 0.72 mmol) and an indole derivative (7.2 mmol) were dissolved in dichloromethane and activated silica (1.56 g, 0.040–0.063 mm) was added. The solvent was removed under reduced pressure at room temperature and the solid mixture was kept under argon for 90 min. Purification by column chromatography (silica gel 70–230 mesh, *n*-hexane/ethyl acetate 9:1 to *n*-hexane/ethyl acetate 8:2 as the gradient eluent) yielded the pure product. It was then washed or recrystallized as described below.

*4.4.1. Di-tert-butyl 4-hydroxy-5-(1H-indol-3-yl)-1-oxo-4,5-dihydroazepino[3,4-b]indole-2,10(1H,3H)-dicarboxylate (±)-**6a***

The desired product was obtained following general procedure A (287 mg, 74%). This was recrystallized from ethyl acetate/hexane to yield pure analytical sample as an off-white solid. Mp R_f=0.35 (ethyl acetate/hexane 4:6). Mp: 190 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=8.21 (1H, br s), 8.13 (1H, d, J=9.1 Hz), 7.71–7.68 (1H, m), 7.43 (1H, unresolved ddd), 7.38–7.32 (2H, m), 7.23–7.20 (2H, m), 7.14–7.09 (1H, m), 6.71 (1H, unresolved d), 5.19–5.13 (1H, m), 4.98–4.95 (1H, m), 4.76 (1H, d, J=3.6 Hz), 3.68–3.60 (1H, m), 2.96–2.87 (1H, m), 1.69 (9H, s), 1.43 (9H, s). ^{13}C

NMR (75 MHz, $CDCl_3$): δ (ppm)=157.6, 156.1, 149.2, 139.9, 136.1, 135.6, 129.0, 126.7, 124.3, 123.9, 123.5, 123.4, 122.6, 121.2, 120.5, 118.3, 115.3, 111.6, 109.1, 85.1, 80.6, 79.8, 42.7, 32.5, 28.4, 27.9. ATR-IR (cm^{-1})=3369br, 2978w, 2931w, 1711s, 1611w, 1506m, 1444m, 1415m, 1392w, 1354s, 1315m, 1280m, 1250m, 1152s, 1083s, 1015m, 964w, 942w, 907w, 854w, 836m, 740s. MS (EI): *m*/*z* (rel int.) 41 (100), 43 (30), 44 (99), 55 (43), 56 (74), 57 (25), 60 (10), 69 (18), 71 (10), 83 (15), 97 (12), 272 (26), 531 (1). HRMS (EI): calcd for $C_{30}H_{33}N_3O_6$ (M^+) 531.2364, found 531.2368. HPLC analysis: column, Chiralcel OD-H; solvent, heptane/isopropanol 90:10; flow=1.0 mL/min; t_R=7.81, 9.95 min.

4.4.2. Di-tert-butyl 4-hydroxy-5-(1H-indol-3-yl)-1-oxo-4,5-dihydroazepino[3,4-b]indole-2,10(1H,3H)-dicarboxylate (+)-**6a**

Enantiomerically pure (+)-**6a** was obtained as a white solid from (+)-**5a** following the same procedure as described for (±)-**6a** (258 mg, 67%). Mp: 136 °C (ethyl acetate/hexane). HPLC analysis: >99% ee; column, chiracel OD-H; solvent, heptane/ethanol 90:10; flow=1.0 mL/min; t_R=9.54 min major. $[\alpha]_D^{22}$ +409.5 (*c* 0.097, $CHCl_3$).

4.4.3. Di-tert-butyl 4-hydroxy-5-(7-methyl-1H-indol-3-yl)-1-oxo-4,5-dihydroazepino[3,4-b]indole-2,10(1H,3H)-dicarboxylate (±)-**6b**

The desired product was obtained as a white solid following general procedure A (252 mg, 64%).Mp R_f=0.51 (ethyl acetate/hexane 2:3) Mp: 154 °C (ethyl acetate/hexane).. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=8.07–8.04 (2H, m), 7.49 (1H, d, *J*=8.1 Hz), 7.36 (1H, unresolved ddd), 7.26 (1H, d, *J*=7.9 Hz), 7.11–6.93 (3H, m), 6.62 (1H, unresolved d), 5.11–5.06 (1H, m), 4.89–4.85 (1H, m), 4.68 (1H, d, *J*=3.5 Hz), 3.59–3.49 (1H, m), 2.88–2.78 (1H, m), 2.38 (3H, s), 1.62 (9H, s), 1.36 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=157.6, 156.0, 149.1, 139.8, 135.7, 135.7, 129.0, 126.3, 124.3, 123.5, 123.5, 123.3, 123.0, 121.2, 120.8, 120.6, 116.0, 115.2, 109.5, 85.0, 80.5, 79.7, 42.7, 32.5, 28.3, 27.8, 16.5. ATR-IR (cm^{-1})=3342br, 3054w, 2976w, 2930w, 1711s, 1612w, 1505m, 1444m, 1416w, 1392w, 1365s, 1354s, 1315m, 1280m, 1245m, 1153s, 1088s, 1016w, 967w, 943w, 928w, 906w, 853w, 835m, 785m, 768m, 744s, 633w. MS (EI): *m*/*z* (rel int.) 41 (94), 43 (14), 44 (100), 55 (31), 56 (77), 57 (13), 286 (36), 545 (3). HRMS (ESI^+): calcd for $C_{31}H_{35}N_3O_6$+Na^+ (M+Na^+) 568.2418, found 568.2416.

4.4.4. Di-tert-butyl 5-(5-bromo-1H-indol-3-yl)-4-hydroxy-1-oxo-4,5-dihydroazepino[3,4-b]indole-2,10(1H,3H)-dicarboxylate (±)-**6c**

The desired product was obtained following general procedure A (318 mg, 72%). This was recrystallized from ethyl acetate/hexane to yield pure analytical sample as a white solid. R_f=0.44 (ethyl acetate/hexane 2:3). Mp: 207 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=8.35 (1H, br s), 8.13 (1H, d, *J*=8.5 Hz), 7.87 (1H, unresolved d), 7.45 (1H, ddd, *J*=8.5, 7.2, 1.3 Hz), 7.34–7.22 (3H, m), 7.17–7.12 (1H, m), 6.69 (1H, unresolved d), 5.20–5.14 (1H, m), 4.96–4.92 (1H, m), 4.68 (1H, d, *J*=3.4 Hz), 3.60–3.51 (1H, m), 2.96–2.86 (1H, m), 1.68 (9H, s), 1.44 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=157.5, 155.9, 149.0, 139.9, 135.4, 134.6, 129.1, 128.5, 125.5, 125.1, 124.1, 123.6, 123.2, 121.1, 120.6, 115.3, 113.8, 113.1, 85.1, 80.2, 79.9, 42.5, 32.0, 28.1, 27.8. ATR-IR (cm^{-1})=3424s, 2978w, 2925w, 1742w, 1727s, 1689m, 1561w, 1508w, 1458m, 1446m, 1417w, 1393w, 1368s, 1354m, 1316m, 1280m, 1256w, 1195m, 1157s, 1100s, 1056w, 1016w, 945w, 905w, 886w, 835w, 797w, 770w, 750m, 626w, 472w, 424w. HRMS (EI): calcd for $C_{30}H_{32}Br_1N_3O_6$ (M^+) 609.1469, found 609.1477.

4.4.5. Di-tert-butyl 4-hydroxy-5-(5-(methoxycarbonyl)-1H-indol-3-yl)-1-oxo-4,5-dihydroazepino[3,4-b]indole-2,10(1H,3H)-dicarboxylate (±)-**6d**

The desired product was obtained following general procedure A (235 mg, 55%). This was recrystallized from methanol to yield pure analytical sample as a white solid.Mp R_f=0.23 (ethyl acetate/hexane 4:6). Mp: 205 °C (methanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm)=11.50 (1H, unresolved d), 8.40 (1H, br s), 8.00 (1H, d, *J*=8.5 Hz), 7.73 (1H, dd, *J*=8.5, 1.5 Hz), 7.56–7.51 (1H, m), 7.46–7.30 (2H, m), 7.23–7.18 (1H, m), 7.11 (1H, unresolved dd), 6.99 (1H, m), 5.23 (1H, d, *J*=3.4 Hz), 5.11–5.06 (1H, m), 3.85 (3H, s), 3.30–3.21 (1H, m), 2.83–2.71 (1H, m), 1.62 (9H, s), 1.34 (9H, s). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm)=167.2, 156.8, 155.5, 148.6, 139.1, 138.8, 135.9, 129.1, 126.5, 126.3, 124.1, 123.6, 123.2, 122.2, 121.6, 121.3, 120.8, 114.5, 111.8, 109.5, 84.6, 79.5, 78.0, 51.7, 42.4, 31.3, 28.1, 27.3 ATR-IR (cm^{-1})=3340br, 2978w, 2931w, 1708s, 1619m, 1508m, 1442m, 1416w, 1392w, 1355s, 1314m, 1279m, 1241s, 1189w, 1153s, 1090s, 1016w, 964w, 905m, 835m, 767w, 746s. HRMS (ESI^+): calcd for $C_{32}H_{35}N_3O_8$+Na^+ (M+Na^+) 612.2317, found 612.2316.

4.4.6. Di-tert-butyl 5-(5-(benzyloxy)-1H-indol-3-yl)-4-hydroxy-1-oxo-4,5-dihydroazepino[3,4-b]indole-2,10(1H,3H)-dicarboxylate (±)-**6e**

The desired product was obtained following general procedure A (258 mg, 56%). This was recrystallized from ethyl acetate/hexane to yield pure analytical sample as an off-white solid. R_f=0.32 (ethyl acetate/hexane 4:6). Mp: 142 °C (hexane/ethyl acetate) ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=8.13 (1H, d, *J*=8.5 Hz), 8.10 (1H, br s), 7.55–7.48 (2H, m), 7.47–7.36 (3H, m), 7.35–7.21 (2H, m), 7.20–7.08 (3H, m), 6.97 (1H, dd, *J*=8.7, 2.3 Hz), 6.77–6.67 (1H, m), 5.20 (3H, br s), 5.02–4.91 (1H, m), 4.70 (1H, d, *J*=3.4 Hz), 3.62–3.50 (1H, m), 3.04–2.92 (1H, m), 1.70 (9H, s), 1.44 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=156.0, 153.8, 149.2, 140.0, 137.5, 135.7, 131.4, 129.0, 128.6, 127.9, 127.7, 127.1, 124.6, 124.4, 123.6, 123.4, 121.2, 115.3, 113.6, 112.4, 108.9, 101.5, 85.1, 80.4, 79.8, 70.8, 32.5, 28.4, 27.9. ATR-IR (cm^{-1})=3367br, 2975w, 2928w, 2857w, 1713s, 1624w, 1581w, 1499w, 1483w, 1446m, 1415w, 1392w, 1365s, 1315m, 1280m, 1249w, 1153s, 1092s, 1016w, 966w, 938w, 907w, 836m, 744s, 696s. HRMS (ESI^+): calcd for $C_{37}H_{39}N_3O_7$+Na^+ (M+Na^+) 660.2680, found 660.2676.

4.4.7. Di-tert-butyl 4-hydroxy-1-oxo-5-(1H-pyrrol-2-yl)-4,5-dihydroazepino[3,4-b]indole-2,10(1H,3H)-dicarboxylate (±)-**7a**

The desired product was obtained following general procedure A (240 mg, 69%). This was recrystallized from ethyl acetate/hexane to yield pure analytical sample as an off-white solid. R_f=0.60 (ethyl acetate/hexane 2:3). Mp: 175 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)=8.58 (1H, br s), 8.15–8.13 (1H, m), 7.50–7.45 (2H, m), 7.25–7.21 (1H, m), 6.67–6.66 (1H, m), 6.08 (1H, dd, *J*=5.6, 2.9 Hz), 6.01–5.95 (1H, m), 4.98–4.91 (2H, m), 4.55 (1H, d, *J*=3.6 Hz), 3.67–3.59 (1H, m), 3.14–3.07 (1H, m), 1.67 (9H, s), 1.45 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=157.0, 156.3, 149.0, 139.8, 133.4, 129.2, 124.3, 123.8, 123.7, 123.5, 121.2, 118.9, 115.3, 109.1, 108.6, 85.2, 80.3, 42.2, 34.8, 28.4, 27.8. ATR-IR (cm^{-1})=3342br, 2978w, 2931w, 1733s, 1611w, 1512m, 1445m, 1414w, 1392w, 1356s, 1314s, 1279m, 1248m, 1153s, 1089s, 1016w, 979w, 945w, 906w, 853w, 835m, 768w, 746m, 722m. MS (EI): *m*/*z* (rel int.) 41 (99), 43 (15), 44 (97), 55 (36), 56 (83), 57 (38), 192 (10), 193 (64), 194 (17), 207 (11), 220 (10), 221 (30), 222 (100), 223 (41), 263 (16), 264 (30), 280 (10), 281 (14), 325 (10), 481 (4). HRMS (EI): calcd for $C_{26}H_{31}N_3O_6$ (M^+) 481.2207, found 481.2222.

4.4.8. Di-tert-butyl 4-hydroxy-1-oxo-5-(1H-pyrrol-3-yl)-4,5-dihydroazepino[3,4-b]indole-2,10(1H,3H)-dicarboxylate (±)-**7b**

The desired product was obtained following general procedure A (53 mg, 15%). This was recrystallized from ethyl acetate/hexane to yield pure analytical sample as an off-white solid. R_f=0.40 (ethyl acetate/hexane 2:3). Mp: 100 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=8.20 (1H, br s), 8.15–8.10 (1H, m), 7.52–7.42 (2H, m), 7.23 (1H, unresolved ddd), 6.66 (1H, dd, *J*=4.7, 2.4 Hz), 6.46 (1H, unresolved dd), 6.03–5.98 (1H, m), 5.07–4.93 (2H, m), 4.37 (1H, d, *J*=3.6 Hz), 3.66–3.54 (1H, m), 3.16–3.03 (1H, m), 1.67 (9H, s), 1.45 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=157.5, 156.1, 149.2, 139.9, 136.0, 128.7, 124.6, 123.5, 123.1, 121.2, 118.6, 116.7, 116.5, 115.3, 108.7, 85.0, 80.4, 79.8, 43.0, 34.5, 28.4, 27.9. MS (EI): *m*/*z* (rel int.) 41

(93), 55 (26), 56 (73), 57 (25), 193 (32), 194 (14), 221 (26), 222 (100), 223 (37), 234 (13), 239 (24), 251 (5), 264 (19), 280 (20), 281 (14), 324 (13), 325 (13). 481 (1). ATR-IR (cm^{-1})=3322m, 2983w, 2935w, 1728s, 1685s, 1530s, 1478w, 1446m, 1409m, 1366m, 1350s, 1313m, 1275s, 1251s, 1227w, 1192w, 1154s, 1124w, 1087s, 1042m, 1008m, 976w, 944m, 902w, 871w, 854w, 838w, 829w, 805w, 784m, 767w, 752s, 739w, 694w. HRMS (ESI^+): calcd for $C_{26}H_{31}N_3O_6+Na^+$ ($M+Na^+$) 504.2110, found 504.2104.

4.5. General procedure for the deprotection of Boc groups (general procedure B)

Compounds (±)-**6a–e** and **7a** (0.415 mmol) were dissolved in dichloromethane, and activated silica (0.92 g, 0.040–0.063 mm) was added. The solvent was removed under reduced pressure and the solid mixture was heated at 100 °C overnight. Purification by column chromatography (silica gel 70–230 mesh, methanol/dichloromethane 0.5:9.5 as the gradient eluent) yielded the pure product. It was then washed or recrystallized as described below.

*4.5.1. 4-Hydroxy-5-(1H-indol-3-yl)-2,3,4,5-tetrahydroazepino[3,4-b]indol-1(10H)-one (±)-**8a***

The desired product was obtained following general procedure B (93 mg, 75%). This was recrystallized from methanol to yield pure analytical sample as colourless crystals. R_f=0.31 (methanol/dichloromethane 0.5:9.5). Mp: 306 °C (methanol, dec). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm)=11.24 (1H, br s), 10.80 (1H, unresolved d), 7.96 (1H, unresolved dd), 7.43(1H, d, J=7.9 Hz), 7.36 (1H, d, J=8.1 Hz), 7.31 (1H, d, J=8.1 Hz), 7.12–6.97 (3H, m), 6.93–6.88 (2H, m), 6.74 (1H, unresolved dd), 5.22 (1H, d, J=4.9 Hz), 4.73 (1H, d, J=5.1 Hz), 4.24–4.10 (1H, m), 3.29–3.20 (1H, m). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm)=164.3, 136.4, 136.2, 127.8, 127.2, 126.0, 124.0, 123.4, 120.8, 118.5, 118.3, 118.3, 117.6, 116.6, 112.0, 111.6, 71.4, 44.1, 42.6. ATR-IR (cm^{-1})=3281br, 2924w, 2851w, 1626s, 1548m, 1483m, 1454m, 1338m, 1069s, 1013m, 740s, 681m. MS (EI): m/z (rel int.) 44 (13), 117 (15), 128 (11), 129 (24), 130 (10), 144 (27), 188 (100), 189 (16), 214 (10), 216 (14), 242 (15), 243 (37), 244 (11), 245 (12), 257 (18), 258 (15), 271(35), 272 (76), 273 (24), 286 (15), 313 (30), 331 (68), 332 (14). HRMS (EI): calcd for $C_{20}H_{17}N_3O_2$ (M^+) 331.1315, found 331.1315.

*4.5.2. 4-Hydroxy-5-(7-methyl-1H-indol-3-yl)-2,3,4,5-tetrahydroazepino[3,4-b]indol-1(10H)-one (±)-**8b***

The desired product was obtained as a white solid following general procedure B (83 mg, 66%). R_f=0.26 (methanol/dichloromethane 0.5:9.5). Mp: 168 °C (methanol/dichloromethane). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm)=11.23 (1H, br s), 10.76 (1H, unresolved d), 7.95 (1H, unresolved dd), 7.36 (1H, d, J=8.2 Hz), 7.30–7.25 (1H, m), 7.12–7.04 (2H, m), 6.86–6.80 (3H, m), 6.76 (1H, unresolved dd), 5.20 (1H, d, J=4.6 Hz), 4.72 (1H, d, J=5.2 Hz), 4.18–4.07 (1H, m), 3.27–3.18 (1H, m), 2.40 (3H, s). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm)=164.3, 136.2, 135.8, 127.8, 127.2, 125.7, 123.7, 123.4, 121.3, 120.8, 120.7, 118.5, 118.1, 116.6, 116.0, 112.0, 71.3, 44.0, 42.8, 16.7. ATR-IR (cm^{-1})=3375m, 3288s, 2973w, 2917w, 1633s, 1579w, 1537m, 1480s, 1452m, 1398w, 1375w, 1338s, 1286w, 1228m, 1181w, 1155w, 1129w, 1105m, 1076s, 1003m, 970m, 936w, 914w, 870m, 834w, 816w, 778w, 773w, 741s, 680m, 653w. MS (EI): m/z (rel int.) 41 (14), 43 (30), 44 (81), 55 (12), 57 (11), 60 (10), 69 (17), 71 (15), 73 (18), 128 (16), 129 (10), 130 (12), 131 (22), 256 (11), 257 (26), 259 (12), 271 (25), 272 (16), 284 (10), 285 (33), 286 (94), 287 (23), 300 (15), 327 (33), 345 (100), 346 (18). HRMS (EI): calcd for $C_{21}H_{19}N_3O_2$ (M^+) 345.1472, found 345.1472.

*4.5.3. 5-(5-Bromo-1H-indol-3-yl)-4-hydroxy-2,3,4,5-tetrahydroazepino[3,4-b]indol-1(10H)-one (±)-**8c***

The desired product was obtained following general procedure B (87 mg, 65%). This was washed with diethyl ether and hexane to yield pure analytical sample as an off-white solid. R_f=0.26 (methanol/dichloromethane 0.5:9.5). Mp: 234–238 °C (ether/hexane, dec). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm)=11.28 (1H, br s), 11.02 (1H, unresolved d), 8.00 (1H, unresolved dd), 7.62 (1H, d, J=1.9 Hz), 7.37 (1H, d, J=8.4 Hz), 7.29 (1H, d, J=8.5 Hz), 7.19–7.03 (3H, m), 6.91 (1H, d, J=2.3 Hz), 6.77 (1H, unresolved dd), 5.28 (1H, d, J=4.5 Hz), 4.69 (1H, d, J=5.3 Hz), 4.14–4.01 (1H, m), 3.32–3.20 (1H, m). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm)=164.2, 136.2, 135.0, 128.0, 127.7, 127.2, 125.7, 123.5, 123.2, 120.7, 120.6, 118.7, 117.6, 116.1, 113.7, 112.0, 111.0, 71.7, 44.1, 42.5. ATR-IR (cm^{-1})=3401m, 3286w, 3054w, 2920w, 1630s, 1546s, 1478s, 1451s, 1408w, 1335s, 1286w, 1242w, 1154w, 1079s, 1003w, 971w, 931w, 909w, 883m, 791m, 768w, 740s, 660w. MS (EI): m/z (rel int.) 44 (18), 59 (10), 69 (12), 102 (12), 103 (19), 115 (10), 123 (19), 128 (15), 129 (44), 144 (77), 188 (100), 189 (46), 409 (5). HRMS (EI): calcd for $C_{20}H_{16}Br_1N_3O_2$ (M^+) 409.0420, found 409.0412.

*4.5.4. Methyl 3-(4-hydroxy-1-oxo-1,2,3,4,5,10-hexahydroazepino[3,4-b]indol-5-yl)-1H-indole-5-carboxylate (±)-**8d***

The desired product was obtained following general procedure B (92 mg, 71%). This was recrystallized from methanol to yield pure analytical sample as colourless crystals. R_f=0.21 (methanol/dichloromethane 0.5:9.5). Mp: 201 °C (methanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm)=11.30 (1H, br s), 11.23 (1H, unresolved d), 8.32 (1H, unresolved d), 7.98 (1H, unresolved dd), 7.73 (1H, dd, J=8.7, 1.7 Hz), 7.44–7.35 (2H, m), 7.11–6.98 (2H, m), 6.90 (1H, d, J=2.3 Hz), 6.75 (1H, unresolved ddd), 5.34 (1H, d, J=4.7 Hz), 4.80 (1H, d, J=5.3 Hz), 4.17–4.08 (1H, m), 3.83 (3H, s), 3.31–3.20 (1H, m). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm)=167.3, 164.1, 138.9, 136.2, 127.6, 127.3, 125.9, 125.8, 123.5, 122.0, 121.2, 120.6, 120.0, 119.5, 118.6, 116.0, 112.0, 111.5, 71.4, 51.6, 43.8, 42.3. ATR-IR (cm^{-1})=3296br, 3059w, 2924w, 2854w, 1691m, 1616s, 1546m, 1480m, 1435m, 1336m, 1282w, 1242s, 1214w, 1147w, 1102w, 1078w, 1003w, 972w, 932w, 870m, 768m, 742s, 668w, 661w. MS (EI): m/z (rel int.) 43 (11), 44 (35), 121 (22), 129 (13), 144 (17), 149 (13), 175 (16), 214 (21), 215 (15), 216 (12), 241 (18), 242 (31), 243 (31), 256 (15), 257 (10), 269 (12), 270 (14), 271 (65), 272 (86), 273 (17), 299 (11), 300 (15), 301 (23), 302 (10), 303 (16), 304 (13), 315 (20), 316 (13), 328 (16), 329 (38), 330 (100), 331 (39), 332 (10), 344 (20), 357 (13), 358 (24), 371 (70), 372 (14), 389 (97), 390 (31). HRMS (EI): calcd for $C_{22}H_{19}N_3O_4$ (M^+) 389.1370, found 389.1380.

*4.5.5. 5-(5-(Benzyloxy)-1H-indol-3-yl)-4-hydroxy-2,3,4,5-tetrahydroazepino[3,4-b]indol-1(10H)-one (±)-**8e***

The desired product was obtained following general procedure B (77 mg, 56%). This was recrystallized from ethyl acetate/hexane to yield pure analytical sample as an off-white solid. R_f=0.20 (methanol/dichloromethane 0.5:9.5). Mp: 203 °C (ethyl acetate/hexane, dec). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm)=11.27 (1H, br s), 10.63 (1H, unresolved d), 8.00 (1H, unresolved dd), 7.48–7.27 (6H, m), 7.19 (1H, d, J=8.9 Hz), 7.14–7.04 (3H, m), 6.83 (1H, unresolved d), 6.81–6.71 (2H, m), 5.22 (1H, d, J=4.7 Hz), 5.00 (2H, s), 4.69 (1H, d, J=4.9 Hz), 4.17–4.06 (1H, m), 3.30–3.17 (1H, m). ^{13}C NMR (75 MHz, DMSO-d_6): 164.4, 151.7, 137.6, 136.2, 131.6, 128.4, 127.8, 127.7, 127.6, 127.5, 127.2, 126.3, 124.7, 123.4, 120.8, 118.5, 117.4, 116.6, 112.2, 112.0, 111.3, 102.0, 71.2, 69.7, 44.0, 42.6, 38.7. ATR-IR (cm^{-1})=3292br, 3060w, 2956w, 2924w, 2855w, 1722m, 1622s, 1579w, 1545m, 1478s, 1451m, 1378w, 1335m, 1285s, 1219w, 1182m, 1154w, 1074m, 1044w, 1003w, 846w, 786m, 739s, 696m, 666w. MS (EI): m/z (rel int.) 71 (13), 73 (25), 91 (40),149 (11), 223 (10), 243 (11), 259 (30), 260 (11), 261 (31), 271 (10), 272 (18), 273 (9), 285 (13), 287 (33), 288 (12), 289 (11), 328 (17), 346 (32), 419 (25), 437 (100), 438 (28). HRMS (EI): calcd for $C_{27}H_{23}N_3O_3$ (M^+) 437.1734, found 437.1733.

*4.5.6. 4-Hydroxy-5-(1H-pyrrol-2-yl)-2,3,4,5-tetrahydroazepino[3,4-b]indol-1(10H)-one (±)-**9a***

The desired product was obtained following general procedure B (76 mg, 65%). This was recrystallized from ethyl acetate/hexane to yield pure analytical sample as a brown solid. R_f=0.33 (methanol/dichloromethane 0.5:9.5). Mp: 209 °C (hexane/ethyl acetate). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm)=11.24 (1H, br s), 10.55 (1H, unresolved d), 7.91 (1H, unresolved dd), 7.38–7.33 (1H, m), 7.13–7.06 (2H, m), 6.86–6.79 (1H, m), 6.53–6.51 (1H, m), 5.84 (dd, 1H, J=3.0, 2.6 Hz), 5.61–5.59 (1H, m), 5.16 (1H, d, J=4.7 Hz), 4.48 (1H, d, J=5.8 Hz), 4.06–3.99 (1H, m), 3.29–3.16 (1H, m). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm)=164.1, 136.0, 134.0, 127.8, 127.3, 123.4, 120.7, 118.6, 116.3, 115.2, 111.9, 107.0, 105.8, 71.9, 44.4, 44.3. IR (KBr) (cm^{-1})=3533w, 3321s, 2876w, 1619s, 1552s, 1483s, 1455m, 1412w, 1367w, 1334s, 1299m, 1250w, 1217m, 1196w, 1156w, 1131w, 1093w, 1069s, 1027w, 1012w, 1003w, 977w, 930w, 913w, 875w, 846w, 802s, 785w, 768m, 745w, 733s, 633m, 612m, 550m, 481w, 449w, 432w. MS (EI): m/z (rel int.) 44 (32), 166 (11), 192 (17), 193 (63), 194 (17), 195 (17), 207 (19), 208 (10), 220 (22), 221 (36), 222 (98), 223 (24), 262 (11), 263 (100), 264 (15), 281 (39). HRMS (EI): calcd for $C_{16}H_{15}N_3O_2$ (M^+) 281.1159, found 281.1161.

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Supplementary data

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3.4. A highly selective Ir-catalyzed borylation of 2-substituted indoles: a new access to 2,7- and 2,4,7-substituted indoles

Tetrahedron Letters **2007**, *48*, 371-375.

Wei Fun Lo, Hanns Martin Kaiser, Anke Spannenberg, Matthias Beller, and Man Kin Tse*

H.M.K. planned and performed experiments for the borylation of natural product derivatives. H.M.K. was involved in the interpretation of the experimental data, during the preparation of the manuscript and contributed to discussions. The work of H.M.K. to this publication accounts to approximately 40 %.

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A highly selective Ir-catalyzed borylation of 2-substituted indoles: a new access to 2,7- and 2,4,7-substituted indoles

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Abstract—The selective CH-functionalization of 2-substituted indoles is presented. Using bis(pinacolato)diboron (**2**) in the presence of iridium complexes, a novel catalytic mono-borylation is observed preferentially at the 7-position of the indole. This allows for an efficient synthesis of various 2,7-di- and 2,4,7-trisubstituted indoles, which are otherwise difficult to access. The scope and limitation of the method is demonstrated.

Indoles are an important class of heterocycles not only because they are among the most ubiquitous compounds in nature, but also because they have a wide range of biological activities.[1,2] Hence, it is not surprising that indoles act as lead compounds and are key building blocks in numerous pharmaceuticals.[3] In the past, a multitude of synthetic methods for indoles have been developed since its first chemical synthesis.[3,4] Nowadays, the choice of the synthetic method for a desired indole derivative depends highly on the availability of the starting materials and the functional group tolerance. Despite all known procedures, the synthesis of indoles with non-conventional substitution patterns remains a challenging task. In fact, such unusually substituted indoles are highly interesting for the preparation of new biologically active compounds.

We have been interested in the application of catalytic reactions for the synthesis of potential pharmaceuticals for some time.[5] In this regard, recently metal-catalyzed borylation on aromatic C–H bonds has drawn our attention.[6] In general, this method is complimentary to traditional electrophilic aromatic substitution and has been used to synthesize otherwise not easily accessible phenols[7] and anilines.[8]

In addition, aromatic and heteroaromatic boronates are valuable intermediates for Suzuki-Miyaura cross-coupling reactions,[10,11] for Cu-catalyzed C–N and C–O bond-forming reactions,[12] and for other reactions.[13] Clearly, the direct C–H bond activation and functionalization provides a straightforward synthetic route to access these arylboronates and avoid the use of halide substrates and lithium or Grignard reagents in conventional boronic acid synthesis.

Noteworthy, as potential pharmaceuticals, boronic acids exhibit various biological activities.[9] For example, some of them have been used in boron neutron capture therapy (BNCT) (Scheme 1).

In light with these issues, here we report a regioselective borylation reaction towards 2,7-di- and 2,4,7-trisubstituted indoles, which are otherwise difficult to obtain.

As a proto-typical reaction, ethyl indole-2-carboxylate (**1a**) is borylated in an inert solvent with 0.75 mol % of $[Ir(COD)OMe]_2$ and 1.5 mol % 4,4′-di-*tert*-butyl-2,2′-bipyridine as the catalyst (Table 1).[14] Only trace of product is observed by GC–MS at room temperature both in *n*-heptane and 1,4-dioxane (Table 1, entries 1 and 3). However, by increasing the temperature to 50 °C, a good yield (67%) of the mono-borylated product is obtained. Further optimization of the ratio of **1a** to **2** gave **3a** in excellent yield (92%). It should be noted that this reaction works better in *n*-heptane than in

Keywords: Iridium; Borylation; CH-activation; Indole.
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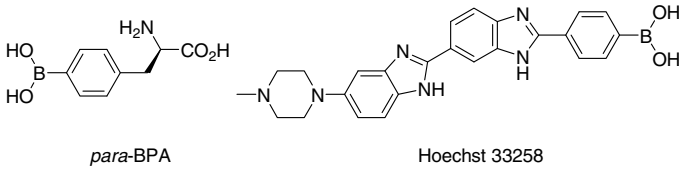
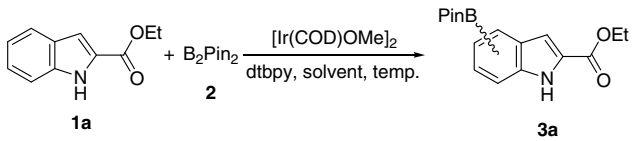


Scheme 1. Selected boron neutron capture therapy agents (BNCT).[9]

Table 1. Influence of stoichiometry of ethyl indole-2-carboxylate (**1a**) to bis(pinacolato)diboron (**2**), B_2Pin_2, temperature and solvent to the borylation reaction



1a **2** **3a**

Entry	**1a**:**2**[a]	Solvent	Temp (°C)	Yield[b] (%)
1	1:0.5	*n*-Heptane	rt	Trace
2	1:0.5	*n*-Heptane	50	67
3	1:0.5	1,4-Dioxane	rt	No reaction
4	1:0.5	1,4-Dioxane	50	Trace
5	1:0.5	1,4-Dioxane	100	59
6	1:0.7	*n*-Heptane	50	92

Standard reaction conditions: **1a** (0.50 mmol), **2** (0.25–0.35 mmol), $[Ir(COD)OMe]_2$ (0.0038 mmol) and 4,4′-di-*tert*-butyl-2,2′-bipyridine (0.0075 mmol) were charged into a schlenk tube with Teflon screwed stopper under Ar. Freshly distilled solvent (1.5 mL) and dodecane (GC internal standard, 432 μL) were added. The reaction mixture was then heated for ~16 h at rt–100 °C.

[a] Molar ratio of **1a** to **2**.

[b] GC yield.

1,4-dioxane (Table 1, entries 2 and 4). However, at higher reaction temperature (100 °C) both solvents gave comparative results. Hence, 1,4-dioxane can be used for less soluble substrates instead.

As two C–H bonds are not hindered in **1a**, non-selective borylation was initially expected. Different from our expectation, a single regioisomer **3a** was obtained, the structure of which was assigned based on 2D-^{1}H NMR and further confirmed by X-ray crystallography (Fig. 1).

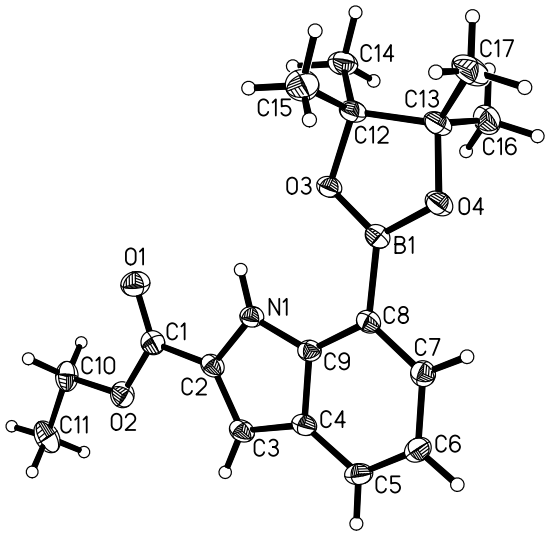
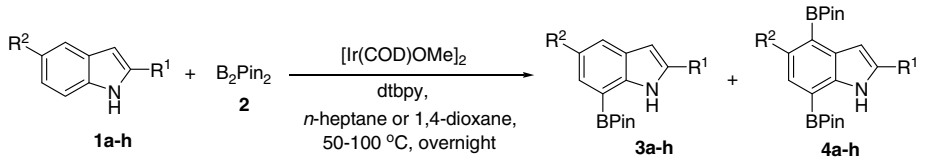


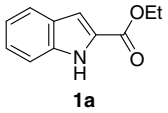
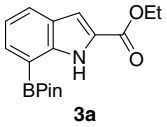
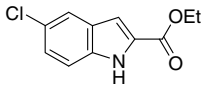
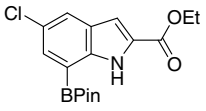
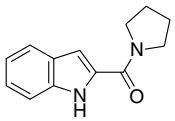
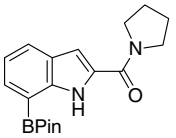
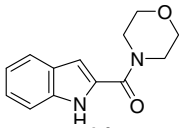
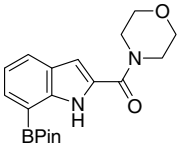
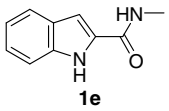
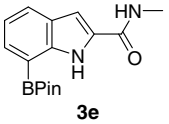
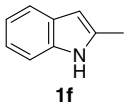
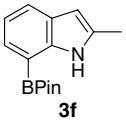
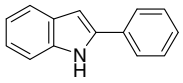
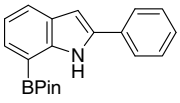
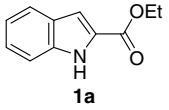
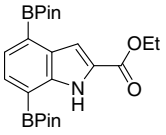
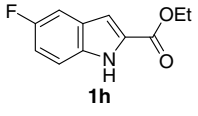
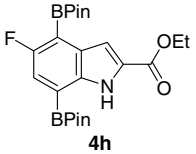
Figure 1. Molecular structure of **3a**. The thermal ellipsoids correspond to 30% probability.[15]

To demonstrate the scope and limitation of this reaction, various 2-substituted indoles were subjected to the typical reaction conditions,[16] which, to our delight, provided 2,7-disubstituted indole products in moderate to excellent yields (Table 2, entries 1–7). Various functional groups, such as halogen, ester, mono- and di-N-substituted amides, as well as aromatic rings (phenyl) are tolerated. From the GC–MS analysis of the crude reaction mixture, the mono-borylated product usually has >97% selectivity at the 7-position. Lower product yields obtained were due to isolation problems and subsequent diborylation. In fact, the diborylated compounds can be obtained as major products when more B_2Pin_2 (**2**) is employed (Table 2, entries 8 and 9). It is noteworthy that the second catalytic borylation reaction proceeds also with high regioselectivity (>85%). ^{1}H NMR of the isolated regioisomers showed that the major diborylated product contains a 2,4,7-substitution pattern.

We surmise that the high selectivity towards the 7-position is due to an *ortho*-directing effect. Although the regioselectivity of the borylation process for arenes is mainly controlled by steric effects,[6] a few examples showed the involvement of an electronic or coordination effect.[6b,17] For unprotected pyrrole and indole it is known that borylation occurs preferentially at the

Table 2. [Ir(COD)OMe]$_2$/dtbpy-catalyzed borylation of various 2-substituted indoles[14]



Entry	Substrate	Product	1:2[a]	Temp (°C)	Solvent	Yield[b] (%)
1	 **1a**	 **3a**	1:0.7	50	*n*-Heptane	83 (92)[c]
2	 **1b**	 **3b**	1:0.6	100	1,4-Dioxane	45
3	 **1c**	 **3c**	1:0.7	100	1,4-Dioxane	93
4	 **1d**	 **3d**	1:0.7	100	1,4-Dioxane	99[d]
5	 **1e**	 **3e**	1:0.7	100	1,4-Dioxane	50[c]
6	 **1f**	 **3f**	1:0.7	50	*n*-Heptane	54
7	 **1g**	 **3g**	1:0.7	50	*n*-Heptane	58
8	 **1a**	 **4a**	1:2.5	50	*n*-Heptane	75[c,e]
9	 **1h**	 **4h**	1:1.2	50	*n*-Heptane	48

Standard reaction conditions: **1a** (0.50 mmol), **2** (0.30–1.25 mmol), [Ir(COD)OMe]$_2$ (0.0038 mmol) and 4,4′-di-*tert*-butyl-2,2′-bipyridine (0.0075 mmol) were charged into a schlenk tube with Teflon screwed stopper under Ar. Freshly distilled solvent (1.5 mL) and dodecane (GC internal standard, 432 μL) were added. The reaction mixture was then heated for ~16 h at 50 °C for *n*-heptane and 100 °C for 1,4-dioxane.

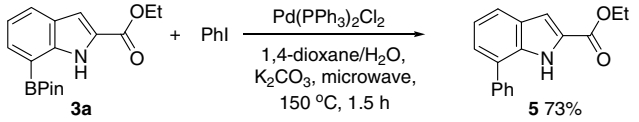
[a] Molar ratio of **1a** to **2**.

[b] Isolated yield.

[c] GC yield.

[d] NMR yield.

[e] The ratio of 4,7-diborylated product to 5,7-diborylated product is 85:15 determined by ^{1}H NMR.



Scheme 2. Suzuki-Miyaura cross-coupling of **3a** with PhI.[6a]

2-position,[6,18] while borylation of *N*-methylindole gave a mixture of 2- and 3-borylated products in a ratio of 56:44.[18a] Thus, it is likely that the indole N–H group is a directing group for the borylation reaction.

In most of the reported borylation procedures, the arenes are usually used in excess with respect to **2** when more than one unhindered C–H bond exists in order to obtain the mono-boronate in good yield.[6,18] However, 2-substituted indoles gave full conversion with high selectivity towards 7-borylated indoles in the presence of an equimolar or a slight excess amount of **2** (Table 2, entries 1, 3 and 4). This is an important advantage because more expensive starting materials may also be further functionalized through the boronate using our protocol. It is noteworthy that in principle both boronate groups in bis(pinacolate)diborane (**2**) are effective to the borylation reaction and generate only hydrogen as by-product (Tables 1 and 2). Hence this reaction is a clean, atom efficient and direct method towards 2,7-disubstituted indoles.

As a demonstration for the use of the borylated indoles, the Suzuki-Miyaura cross-coupling reaction was performed with **3a** and PhI, which yielded the phenyl-substituted product **5** in 73% yield under microwave conditions (Scheme 2).[6a]

Since 2-substituted phenylhydrazines are less accessible, relatively few examples for the synthesis of 2,7-disubstituted indoles are known via the most commonly used Fischer indole synthesis.[19]

Clearly, the method presented here provides a more general access to this substitution pattern and may contribute to medicinal chemistry and pharmaceutical industry in the future.

In conclusion, we have shown the application of the iridium-catalyzed borylation reaction to 2-substituted indoles. Excellent regioselectivity towards 7-borylated indoles was observed. In the presence of an excess of the borylation reagent, 2,4,7-trisubstituted indoles are obtained preferentially. The scope and limitation of the catalytic system are demonstrated on indoles with various functional groups with moderate to excellent yields. Further functionalization of the 7-borylated indoles to potentially bioactive compounds is in progress in our group.

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References and notes

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14. All experiments were carried out under an inert gas atmosphere (argon) with exclusion of air. For the standard reaction procedure, **1a** (0.50 mmol), **2** (0.25–0.35 mmol), $[Ir(COD)OMe]_2$ (0.0038 mmol) and 4,4′-di-*tert*-butyl-2,2′-bipyridine (0.0075 mmol) were charged into a schlenk tube with Teflon screwed stopper under Ar. Freshly distilled solvent (1.5 mL) and dodecane (GC internal standard, 432 μL) were added. The reaction mixture was then heated for ~16 h at 50 °C for *n*-heptane and 100 °C for 1,4-dioxane. Compound **3a**: $R_f = 0.24$ (hexane–ethyl acetate 10:1); mp 68–71 °C; ^{1}H NMR (300.1 MHz, $CDCl_3$): $\delta = 1.33$ (m, 12H), 1.35 (t, $J = 6.98$ Hz, 3H), 4.40 (q, $J = 7.1$Hz, 2H), 7.09 (dd, $J = 7.8$, 7.0 Hz, 1H), 7.14 (d, $J = 2.25$Hz, 1H), 7.77 (m, 2H), 9.70 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 14.40$, 24.99, 60.92, 84.10, 108.20, 120.39, 126.07, 126.49, 127.44, 132.79, 141.65, 162.14; IR (KBr, cm^{-1}): 3447, 3060, 2986, 2930, 1717, 1593, 1538, 1421, 1368, 1287, 1234, 1146, 1128, 1028, 976, 850, 822, 750, 677; EIMS *m*/*z* 315.2 (M^+); Elemental Anal. Calcd for $C_{17}H_{22}BNO_4$: C, 64.78; H, 7.04; B, 3.43; N, 4.44; O, 20.31. Found: C, 64.66; H, 7.16; N, 4.46.
15. X-ray crystallographic study of **3a**: Data were collected with a STOE-IPDS diffractometer using graphite-monochromated Mo Kα radiation. The structure was solved by direct methods [SHELXS-97: Sheldrick, G. M. University of Göttingen, Germany, 1997.] and refined by full-matrix least-squares techniques against F^2 [SHELXL-97: Sheldrick, G. M. University of Göttingen, Germany, 1997.] XP (BRUKER AXS) was used for structural representation. Space group $P\bar{1}$, triclinic, $a = 8.389(2)$, $b = 10.099(2)$, $c = 11.479(2)$ Å, $\alpha = 114.43(3)°$, $\beta = 92.60(3)°$, $\gamma = 106.58(3)°$, $V = 833.6(3)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.256$ g cm^{-3}, 13,135 reflections measured, 3809 were independent of symmetry, of which 2723 were observed ($I > 2\sigma(I)$), $R1 = 0.0384$, wR^2 (all data) = 0.1032, 212 parameters.
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3.5. Palladium-mediated fluorination of arylboronic acids

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H.M.K. planned, executed and analyzed experiments for the development of the palladium complexes and the fluorination reactions. H.M.K. was further involved during the compilation of the supporting information, contributed to the preparation of the manuscript and was involved in discussions. The work of H.M.K. to this publication accounts to approximately 40 %.

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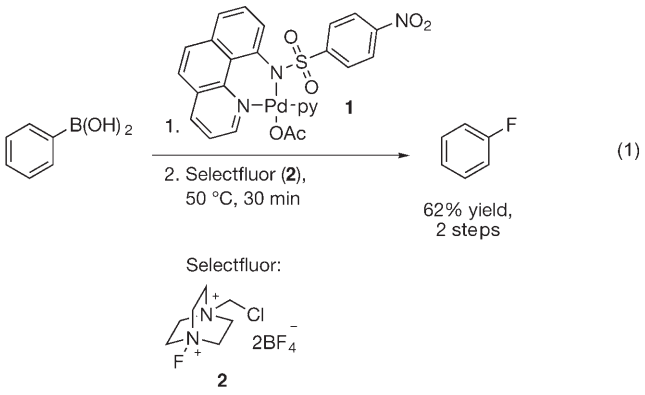
Fluorination

Palladium-Mediated Fluorination of Arylboronic Acids**

*Takeru Furuya, Hanns Martin Kaiser, and Tobias Ritter**

Fluorinated organic molecules have become increasingly important as pharmaceuticals[1] and tracers for positron-emission tomography (PET), a powerful technology for noninvasive molecular imaging.[2] The nucleus of choice for PET is fluorine-18 (^{18}F), which is typically introduced into PET tracers through the formation of carbon–fluorine bonds using nucleophilic fluoride ($^{18}F^-$) under harsh reaction conditions.[3] The short half-life of ^{18}F (109 minutes) requires that carbon-fluorine bond formation occurs at a late stage in the PET tracer synthesis, ideally as the last step. Many promising PET tracers for imaging are currently inaccessible owing to the lack of suitable chemistry for the general, late-stage introduction of fluorine into complex, functionalized molecules.[3,4] Herein, we present a new strategy for carbon–fluorine bond formation that relies on the fluorination of arylboronic acids using palladium complexes [Eq. (1)]. The



(1)

reaction permits a general, regiospecific late-stage formation of carbon–fluorine bonds in the presence of a large variety of functional groups found in biologically active molecules. Ultimately, we anticipate our new fluorination reaction will provide a chemical solution for the synthesis of currently inaccessible PET tracers to increase both knowledge and understanding of basic, biomedical, and pharmaceutical research through molecular imaging.[5–8]

Carbon–fluorine bond formation is a challenging chemical transformation, and no general, functional-group-tolerant fluorination reaction of arenes is currently available for the synthesis of complex molecules. Simple fluoroarenes are typically synthesized by pyrolysis of diazonium tetrafluoroborates,[9] direct fluorination using highly reactive elemental fluorine,[10] or nucleophilic aromatic substitution reactions of electron-poor aromatic molecules.[11,12] Common aromatic organometallic compounds, such as aryl lithium and aryl Grignard reagents, can afford arylfluorides if using electrophilic fluorine sources; however, neither aryl lithium nor aryl Grignard reagents can be used for the late-stage fluorination of arenes bearing electrophiles, such as aldehydes, or protic functionalities, such as alcohols, limiting their general utility.[13] Organometallic compounds with lower basicity, such as aryl zinc halides, aryl silanes, aryl stannanes, and aryl boronic acids, afford fluorobenzenes in less than 10% yield (see the Supporting Information). The electrophilic fluorination of specific carbon–hydrogen bonds of phenylpyridine derivatives and related structures was reported in 2006 by Sanford et al., and uses catalytic palladium (II) acetate and *N*-fluoropyridinium salts.[14] The reaction takes advantage of a covalently attached pyridine directing group and affords fluorinated aryl pyridine derivatives using microwave irradiation (100–150 °C, 1–4 h, 33–75% yield). A different approach, the reductive elimination of aryl fluorides from palladium(II) fluoride complexes, would obviate the use of directing groups, and has been investigated over the past decade by Grushin and Yandulov.[15,16] Carbon–fluorine bond formation to form aryl fluorides by reductive elimination from a palladium(II) fluoride complex has not yet been substantiated.[16,17] In general, all methods mentioned above cannot be employed for late-stage fluorination of structurally complex molecules owing to either harsh reaction conditions or limited substrate scope.

We have sought a new regiospecific, late-stage fluorination reaction of arenes that encompasses a larger substrate scope than is currently accessible, tolerates the presence of a variety of functional groups, is not limited to a particular class of arenes, and is not dependent on a directing group. Our strategy is illustrated in Equation (1), and consists of the synthesis of new aryl palladium complexes that react with the electrophilic fluorination reagent selectfluor[18] to afford fluoroarenes.

Our initial investigations for the design of transition-metal complexes that afford efficient fluorination was guided by the observation that palladium has been successfully employed in several carbon–heteroatom bond formations,[19,20] including carbon–fluorine bonds for specific substrates.[14,21] Additionally, the development of our methodology was directed by the

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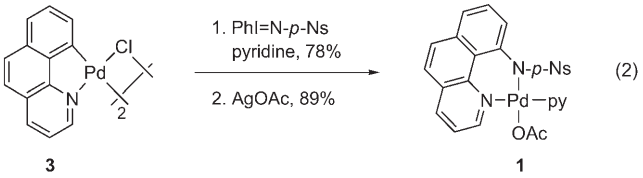
necessity to predict and control the exact location of fluorination and the need to introduce fluorine at any desired aromatic position. Therefore, the target molecules for fluorination are pre-functionalized with boronic acids at the position at which fluorine is desired. Boronic acids are readily accessible, compatible with a variety of functional groups present in PET tracers, competent nucleophiles for transmetallation to palladium, and can be introduced into complex molecules.[22]

Several aryl palladium complexes based on ligands that are commonly used for palladium chemistry did not lead to carbon–fluorine bond formation when evaluated for fluorination. We therefore designed new aryl palladium complexes that are derived from a bidentate ligand that contains a neutral and an anionic nitrogen donor atom for coordination to palladium. Our design was based on the assumptions that nitrogenous ligands resist oxidation by electrophilic fluorination reagents, can support high-valent aryl palladium fluorides for subsequent carbon–fluorine reductive elimination, and do not induce competing nitrogen–fluorine reductive elimination. We prepared the new palladium acetate complex **1** by known sulfonamide insertion[23] into the palladium–carbon bond of benzoquinoline-derived palladacycle **3**,[24] followed by chloride–acetate ligand exchange [Eq. (2)]. The

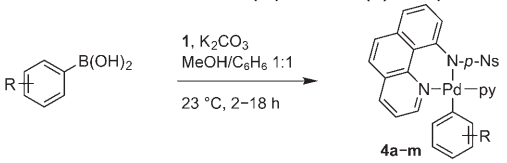


3 1 (2)

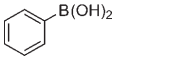
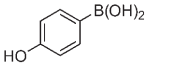
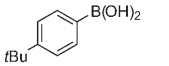
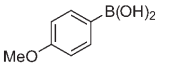
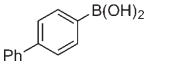
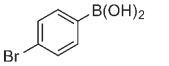
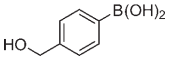
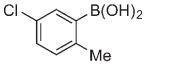
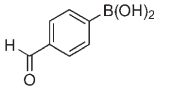
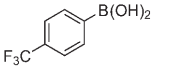
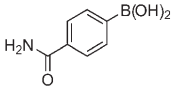
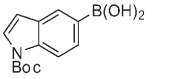
aryl palladium complexes **4a**–**m** were prepared by transmetallation using twelve different arylboronic acids (Table 1). Transmetallation proceeded at 23 °C in a basic methanol/benzene solution and afforded the palladium complexes as moisture- and air-stable yellow solids in 65–91 % yield on a 400 mg scale after purification by chromatography on silica gel. The aryl palladium complexes derived from **1** are tolerant toward the presence of a variety of functional groups found in biologically active compounds, including alcohols, an indole, and a primary amide. The phenyl palladium sulfonamide **4a** (R = H) crystallized in a square-planar geometry with the aryl group *trans* to the κ^1-sulfonamide ligand (Figure 1). The *trans* relationship may be crucial to prevent undesired carbon–nitrogen bond formation through reductive elimination of the aryl and sulfonamide substituents.[25]

Fluorination of the aryl palladium complexes **4a**–**m** using the electrophilic reagent selectfluor (**2**) afforded the arylfluorides **5a**–**m** regiospecifically in 31–82 % isolated yield (Table 2). The fluorination reaction tolerates the presence of a variety of functional groups, most notably protic functionalities that are not typically compatible with nucleophilic aromatic substitution methods owing to the high basicity of fluoride ion in anhydrous solvents suitable for nucleophilic displacement.[10] Additionally, electron-rich fluoroarenes (**5b**, **5g**, **5h**), which cannot be synthesized through late-stage fluorination using nucleophilic displacement, are accessible

Table 1: Transmetallation to form aryl palladium(II) complexes.



4a–m

Boronic acid		Yield [%]	Boronic acid		Yield [%]
	**4a**	76		**4g**	70
	**4b**	85		**4h**	79
	**4c**	91		**4i**	65
	**4d**	80		**4k**	90
	**4e**	71		**4l**	88
	**4f**	73		**4m**[a]	76

[a] Boc = *tert*-butyloxycarbonyl.

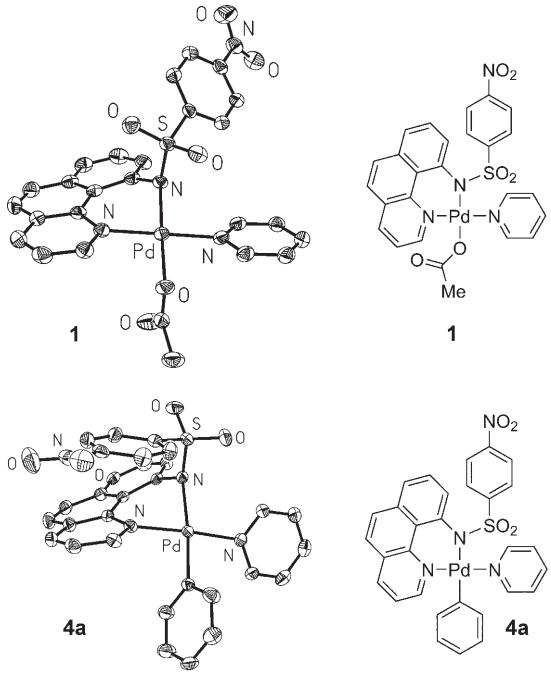
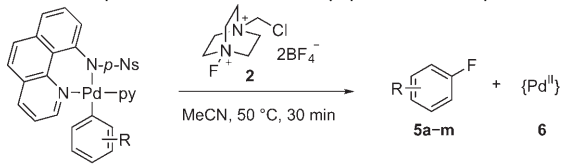
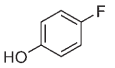
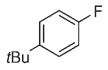
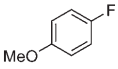
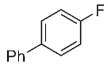
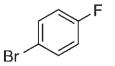
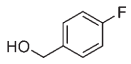
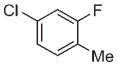
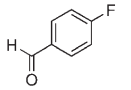
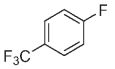
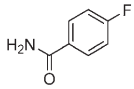
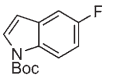


Figure 1. ORTEP diagrams of **1** and **4a**, with thermal ellipsoids set at 50 % probability, showing the *trans* relationship of the sulfonamide nitrogen atom to the acetate and to the aryl ligands.

regiospecifically. The scope of the reaction was further extended to electron-poor (**5e**, **5l**), heterocyclic (**5m**), and *ortho*-substituted arenes (**5k**). Fluorination proceeds in 30 minutes when performed in acetonitrile or acetone at 50 °C. Although fluorination was observed at 23 °C, the highest

Table 2: Electrophilic fluorination with aryl palladium complexes.

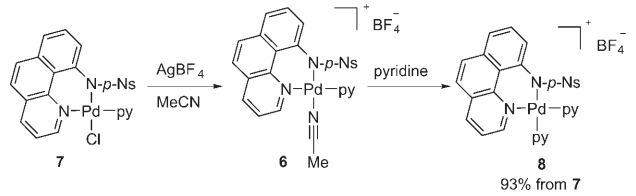


4	Product	Yield [%]	4	Product	Yield [%]
4a		**5a**[a] 81	**4g**		**5g**[b] 31
4b		**5b**[a] 79	**4h**		**5h**[b] 46
4c		**5c** 72	**4i**		**5i** 73
4d		**5d** 70	**4k**		**5k** 82
4e		**5e** 61	**4l**		**5l**[a] 54
4f		**5f** 74	**4m**		**5m**[b] 60

[a] Yield for this entry determined by ^{19}F NMR analysis because of low boiling point of product. [b] Acetone used as solvent.

yields were obtained at a reaction temperature of 50 °C. Yields of isolated products were identical when the fluorination reactions were performed under rigorous exclusion of air and moisture or open to the atmosphere.

The fate of the palladium moiety after fluorination was determined to be cationic palladium complex **6**, which was independently synthesized by treatment of palladium chloride **7** with silver tetrafluoroborate in acetonitrile (Scheme 1). Subsequent reaction of **6** with one equivalent of pyridine afforded the stable palladium tetrafluoroborate salt **8**, which was isolated and characterized. Addition of pyridine after termination of the reaction shown in Table 2 also afforded **8**, which suggests that the pyridyl sulfonamide ligand remained coordinated to palladium throughout the reaction. The stability of the ligand–metal complex is advantageous for a prospective catalytic version of the presented fluorination reaction.



Scheme 1. Independent synthesis of palladium byproduct **6**. *p*-Ns = *para*-nitrobenzenesulfonyl.

Transition-metal catalysis for carbon–fluorine bond formations is a valuable goal in itself. However, for the synthesis of PET tracers, a fluorination reaction using stoichiometric amounts of transition metal is advantageous, as stoichiometric reactions are faster than the corresponding catalyzed reactions, and time is the most important factor for the efficient preparation of PET tracers owing to the short half-life of ^{18}F. Moreover, price and toxicity of palladium are of lesser importance for applications in molecular imaging because PET tracers are used in picomolar quantities and are purified by HPLC before injection in vivo.

Two possible mechanisms for the fluorination reaction presented herein are electrophilic palladium–carbon bond cleavage and carbon–fluorine reductive elimination from a discrete, high-valent palladium fluoride.[21] The redox activity of palladium (II) may play a crucial role for fluorination, which suggests a high-valent, discrete palladium fluoride complex as an intermediate before carbon–fluorine reductive elimination.[26]

In conclusion, we report a fluorination reaction of aryl boronic acids mediated by palladium, in which carbon–fluorine bond formation is the final synthetic step. The functional group tolerance, broad substrate scope, and regiospecificity of the reaction provide a general method for the late-stage fluorination of functionalized arenes. This new chemistry may become the basis for the development of a general solution for the synthesis of PET tracers for biomedical applications. Electrophilic ^{18}F sources are available, but from a biomedical perspective nucleophilic $^{18}F^-$ is the preferred source of fluorine for PET imaging because it can be prepared in high specific activity.[3] A subsequent goal is therefore the development of an electrophilic fluorine source originating from nucleophilic fluoride ($^{18}F^-$). Further development of the transformation presented herein, in combination with known or new electrophilic fluorine sources, may deliver promising PET tracers to impact biomedical research in the fields of cancer, neurodegenerative diseases, gene therapy, and drug development.

Experimental Section

Representative fluorination (4-fluorobiphenyl, **5c**): Aryl palladium complex **4c** was added as a solid (143 mg, 0.200 mmol, 1.00 equiv) in 10 portions over 10 min to a solution of selectfluor (**2**; 85.0 mg, 0.240 mmol, 1.20 equiv) in acetonitrile (6.0 mL) at 50 °C. The reaction mixture was subsequently stirred at 50 °C for 20 min. After cooling to 23 °C, pyridine was added to the reaction mixture (8.1 μL, 0.10 mmol, 1.0 equiv), and the reaction mixture filtered through a plug of celite. The filtrate was concentrated in vacuo and the residue purified by chromatography on silica gel, eluting with hexane/ethyl acetate 99:1 (v/v) to afford 24.8 mg of **5c** as a white solid (72% yield).

CCDC-675999 (**1**) and CCDC-676000 (**4a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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3.6. A general copper-catalyzed sulfonylation of arylboronic acids

Organic Letters **2007**, *9*, 3405-3408.

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H.M.K. planned and performed experiments for the sulfonylation of natural product derivatives. H.M.K. was involved in the interpretation of the experimental data, during the preparation of the manuscript and contributed to discussions. The work of H.M.K. to this publication accounts to approximately 15 %.

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A General Copper-Catalyzed Sulfonylation of Arylboronic Acids

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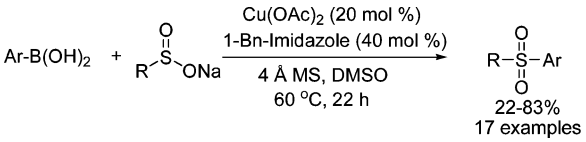
ABSTRACT



A general copper-catalyzed method for the sulfonylation of arylboronic acids with sulfinate salts is described. A variety of alkyl–aryl, diaryl, and alkyl–heteroaryl sulfones were synthesized in good yield.

The synthesis of sulfones has drawn much attention over the years since they constitute useful building blocks in organic chemistry as well as in medicinal chemistry. Because of their chemical properties[1] and promising biological activities,[2] especially, aryl and diaryl sulfones have emerged as important synthetic targets in recent years. As an example, aryl sulfones are the main constituent of many drugs, such as the selective COX-2 inhibitor Vioxx[3] (**1**) and the prostaglandin D_2 (DP) antagonist MK-0524 (**2**),[4] whereas the diaryl sulfones **3** have been shown to inhibit the HIV-1 reverse transcriptase and represent an emerging class of substances able to address the toxicity and resistance problems of nucleoside inhibitors (Figure 1).[5]

Known procedures for aryl sulfone preparation are based on the oxidation of the corresponding sulfides,[6] the electro-

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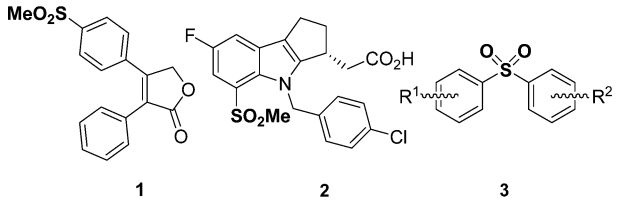
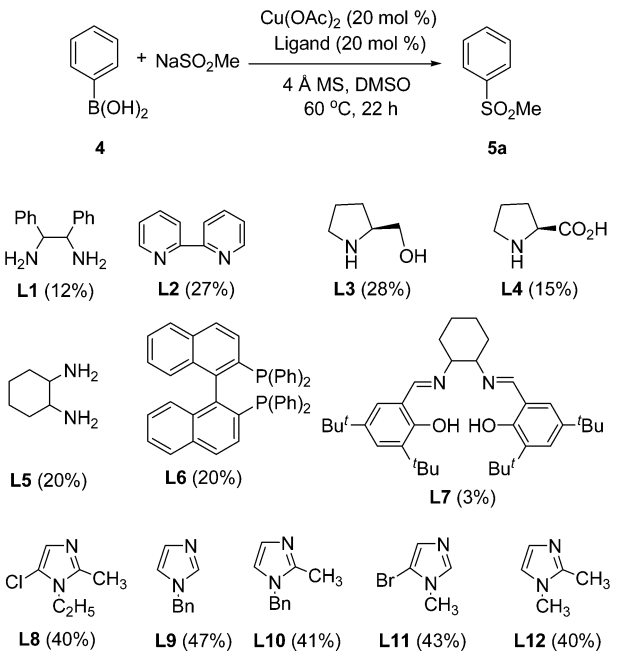


Figure 1. Structures of Vioxx (**1**), MK-0524 (**2**), and diaryl sulfones **3**.[3−5]

philic aromatic substitution of arenes with arenesulfonic acids in the presence of strong acids[7] or with arenesulfonyl halides,[8] the reaction of carbon electrophiles with sulfinate salts,[9] and the reaction of organomagnesium halides[10] or organolithium compounds[11] with sulfonate esters. All these simple and attractive procedures have their own drawbacks, mainly due to the incompatibility with numerous functional groups such as amines, olefins, and some nitrogen heterocycles. Over the past decade, there has been a significant improvement in metal-mediated coupling of sulfinic acid salts with aryl halides and triflates[12] as well as arylboronic acids with sulfonyl chlorides[13] as alternatives to these conventional methods. However, the scope is limited to aryl bromides/iodides or triflates, and the use of air- or moisture-sensitive reagents is sometimes not avoidable. Recently, a copper-mediated oxidative coupling reaction of arylboronic acid with sulfinic acid salt was described.[14] However, an excess of copper acetate (with respect to the arylboronic acid) was required. Hence, improved methods for the preparation of diaryl sulfones are therefore highly desirable. In recent years, we have applied catalytic reactions to the synthesis of new pharmacologically interesting compounds.[15] On the basis of our previous work on copper-catalyzed reactions,[16] we thought that the use of an appropriate ligand or additive would enable us to realize a catalytic version of the

Scheme 1. Catalytic Sulfonylation with Different Ligands (GC Yield)[a]



[a] Reaction conditions: see Supporting Information.

sulfonylation of boronic acids to synthesize aryl sulfones (Scheme 1). With the wide variety of commercially available boronic acids and esters as well as the metal-catalyzed direct C−H bond functionalization to the not easily accessible boronates,[17] catalytic sulfonylation of these boron-containing compounds should be very versatile for the preparation of sulfones. In light with these issues, here we report the first copper-catalyzed oxidative coupling of arylboronic acids with sulfinic acid salts. In our prototypical reaction, phenylboronic acid and sodium methanesulfinate were reacted at 60 °C in anhydrous DMSO in air in the presence of $Cu(OAc)_2$, a ligand, and K_2CO_3 as base. The initial screening of the

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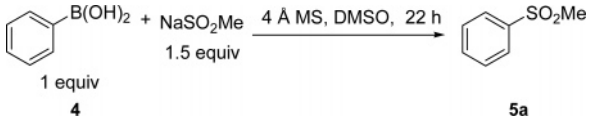
ligands clearly showed that the reaction can be performed catalytically with 20 mol % of $Cu(OAc)_2$. We have tested different ligand types in our model reaction. Among these ligands, tetradentate and bidentate N ligands gave poor results irrespective of their donor atom and capacity. We realized that only monodentate ligands can stabilize the generated copper species for the required transformation, and indeed, N-protected imidazoles were found to be the most suitable ligands for this reaction with a loading of 20 mol % with respect to the substrate.

In fact, when the ligand loading was increased to 40 mol %, a substantial amount of conversion was observed and the corresponding methyl sulfone was isolated in 64% yield (Table 1). Following a previously reported protocol using a

Table 1. Cross-Coupling Reaction between Arylboronic Acid and Sodium Methanesulfinate[a]



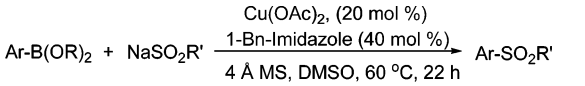
entry	$Cu(OAc)_2$	1-benzylimidazole	temp	GC yield (%)
1	1.1 equiv	–	rt	59
2	20 mol %	20 mol %	60 °C	47
3	20 mol %	40 mol %	60 °C	**64**

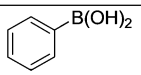
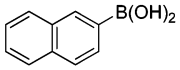
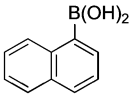
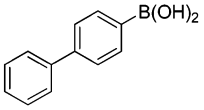
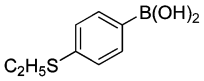
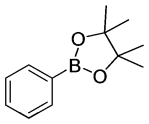
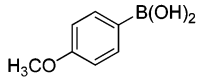
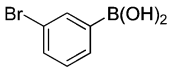
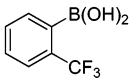
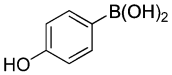
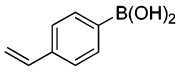
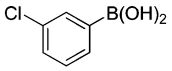
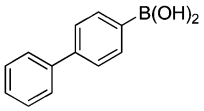
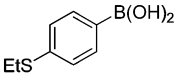
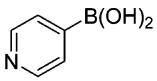
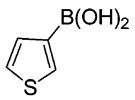
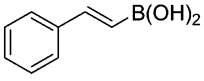
[a] Reaction conditions: see Supporting Information.

stoichiometric amount of copper at room temperature,[12] the same substrate gave only 59% of the desired product. These results indicate that our catalytic system is even slightly more efficient than the reported stoichiometric conditions. Reactions with different additives, such as $(CH_3)_4NBr$, CsF, chloramine-T, and 1,4-benzoquinone, were also performed in the presence or absence of ligand; however, none of them were able to improve the yield significantly. Further optimization showed the best catalytic system was defined as follows: 0.5 mmol of boronic acid, 1.5 equiv of sulfinic acid salt, 20 mol % of $Cu(OAc)_2$, 40 mol % of 1-benzylimidazole, 2 equiv of K_2CO_3, and 1.25 g of molecular sieves (4 Å) at 60 °C in anhydrous DMSO in a flask equipped with an air drying tube. To the best of our knowledge, this is the first example of copper-catalyzed sulfonylation of an arylboronic acid.

A variety of aryl sulfones have been prepared employing these reaction conditions, as shown in Table 2. This cross-coupling reaction is quite general and can be easily applied to a wide range of arylboronic acids. Both electron-rich and electron-deficient substrates reacted with almost similar ease, and the substrate variety indicates that the substitution pattern in the aromatic ring does not have significant influence in the reaction outcome. Bromo and chloro substituents on the boronic acid part are also tolerated under the reaction conditions, which could extend the scope of further functionalization on the aromatic ring. The reaction also proceeded with pinacol boronate ester with good yield (Table 2, entry 6). Reaction of the 2-trifluoromethylphenylboronic acid is noteworthy. In spite of the presence of a strong

Table 2. Catalytic Sulfonylation of Boronic Acids[a]



entry	substrate	R′	product	isolated yield (%)
1		Me	**5a**	64
2		Me	**5b**	70
3		Me	**5c**	64
4		Me	**5d**	69
5		Me	**5e**	83
6		Me	**5a**	71
7		Me	**5f**	68
8		Me	**5g**	70
9		Me	**5h**	43
10		Me	**5i**	27
11		Me	**5j**	50
12		Me	**5k**	52
13		Tol	**5l**	59
14		Ph	**5m**	44
15		Me	**5n**	22
16		Me	**5o**	54
17		Me	**5p**	65

[a] Reaction conditions: see Supporting Information.

electron-withdrawing group at the *ortho* position, it reacted smoothly to provide the corresponding sulfone (Table 2, entry 9). Of particular interest is the reaction with 4-vinylphenylboronic acid to the corresponding methyl sulfone. Although the starting material polymerized, we were able to obtain a moderate product yield (Table 2, entry 11). Under the same reaction conditions, we were able to couple 4-hydroxyphenylboronic acid to the corresponding methyl sulfone, but only with moderate yield, most probably because of the reduction of the in situ generated arylcopper species (Table 2, entry 10).[18]

The same method can also be extended to synthesize diaryl or heteroaryl substrates, which are of particular interest for potential drug applications. Arylsulfinate salts were efficiently coupled with arylboronic acids to provide diaryl sulfones in good yields following the same reaction procedure (Table 2, entries 13 and 14). Similarly, this reaction was also possible with heterocyclic substrates, such as thiophene-3-boronic acid and pyridine-4-boronic acid, though the yields were somewhat lower (Table 2, entries 15 and 16). This method is also applicable to a vinyl sulfone. As an example, phenylvinylboronic acid was coupled successfully to give the corresponding vinyl methyl sulfone in good yield (Table 2, entry 17).

In summary, we have developed an efficient and general method for a copper-catalyzed synthesis of methyl−aryl, aryl−aryl, and heteroaryl sulfones with various functional groups, which can also be extended to the preparation of vinyl sulfones. Further studies to increase the catalytic activity are currently underway in our laboratory.

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Supporting Information Available: A typical experimental procedure and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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3.7. Self-catalyzed oxidation of sulfides with hydrogen peroxide: a green and practical process for the synthesis of sulfoxides

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H.M.K. planned and analyzed experiments and was involved in the interpretation of the experimental data, during the preparation of the manuscript and contributed to discussions. The work of H.M.K. to this publication accounts to approximately 10 %.

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Self-Catalyzed Oxidation of Sulfides with Hydrogen Peroxide: A Green and Practical Process for the Synthesis of Sulfoxides

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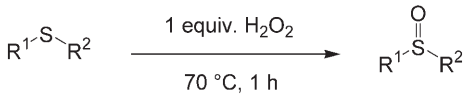
Abstract: A self-catalyzed selective oxidation of sulfides to sulfoxides has been developed. The scope of the protocol is demonstrated in the selective oxidation of 17 different substrates. High yields and chemoselectivity (in general >90%) are achieved in most cases.

Keywords: green chemistry; selective oxidation; self-catalyzed; solvent free; sulfoxide

For the sustainable development of our economy, the further use of green chemistry is an important issue. In this respect preventing waste, but not treating or cleaning it up, is a basic requirement.[1] In a given chemical process, reducing the use of toxic chemicals and waste remitting with high atom-efficiency are key points. One of the major challenges of organic synthesis is undoubtedly to develop more environmentally friendly oxidation processes.[2] As an example, herein we report an efficient oxidation of sulfides to sulfoxides.

The selective oxidation to give sulfoxides has attracted much attention over the years since sulfoxides constitute useful building blocks in organic synthesis for the preparation of biologically active compounds and activation of enzymes.[3] Traditionally, the synthesis is performed with a stoichiometric amount of organic or inorganic oxidant and a large amount of toxic waste is produced.[4] In order to run this transformation in a "greener" manner, there are three factors that can be improved: use of (i) environmentally benign oxidants, (ii) less or even no organic solvent and (iii) non-toxic catalysts. Hence, aqueous hydrogen peroxide has been used as the terminal oxidant since the beginning of the last century,[5] because it is cheap, environmentally benign, readily available, of high atom-efficiency (47%), and theoretically only generates water as the by-product.[6] Different kinds of catalysts including acids,[7] iron,[8] vanadium,[9] tungsten,[10] manganese,[11] copper,[12] titanium,[13] platinum,[14] and magnesium[15] based systems were used to obtain good yields.

During our continuous investigation for selective oxidation reactions using aqueous hydrogen peroxide as the terminal oxidant,[16] we found serendipitously that the sulfoxides themselves, produced during the reaction, can be very effective catalysts for the selective oxidation of sulfide to sulfoxide (Scheme 1). This



Scheme 1. Selective oxidation of sulfides to sulfoxides.

is one of the relatively few cases of self-catalyzed reactions.[17] This process needs no additional catalysts, solvents and proceeds highly selectively.

In our initial exploratory experiments applying thioanisole in the presence of different transition metal catalysts under solvent-free conditions, all reactions gave good yields of methylsulfinylbenzene after 12 h at room temperature. To our surprise, the control experiment without catalyst also showed high yield of the corresponding sulfoxide (>98%, GC yield). At 70°C, the oxidation of thioanisole to methylsulfinylbenzene with 1 equiv. 30 wt% H_2O_2 gave even full conversion within 1 h! When the reaction was carried out at room temperature, the yield to methylsulfinylbenzene was only 63% (GC yield) after 6 h. As shown in Figure 1 the reaction started at a very low rate. However, when a small amount of methylsulfinylbenzene is produced, the reaction is accelerated and became faster and faster. After the formation of 4.7% sulfoxide in the mixture (5 min), ~90% of thioanisole could be further converted into methylsulfinylbenzene in the next 15 min. It is clear that the concentration of methylsulfinylbenzene, but not the concentration of thioanisole or hydrogen peroxide determined the initial reaction rate. In order to clarify this

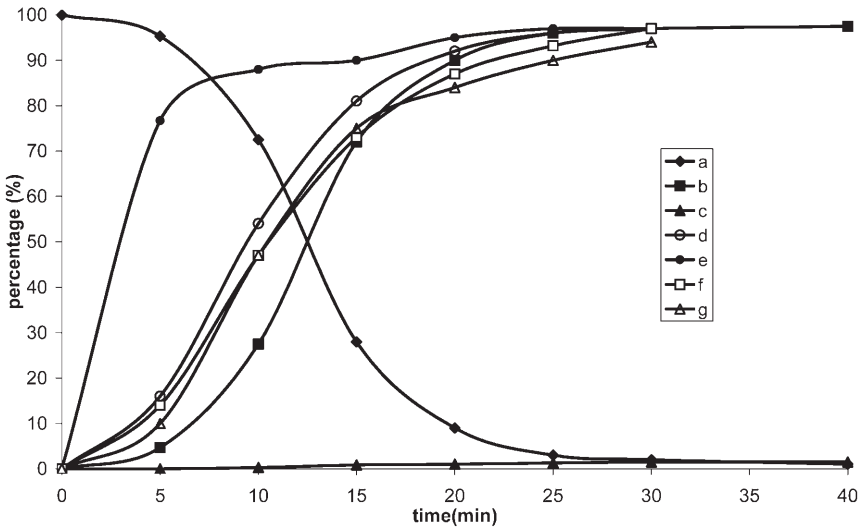


Figure 1. Typical reaction conditions: 5.0 mmol (620 mg) thioanisole and 5.0 mmol (0.50 mL) 30 wt% H_2O_2 and the appropriate catalyst [no sulfoxide or sulfone was added for (a)–(c), 5 mol% methylsulfinylbenzene, 20 mol% methylsulfinylbenzene, 20 mol% methylsulfonylbenzene, or 20 mol% dimethyl sulfoxide were initially present in (d), (e), (f) and (g) respectively] were heated at 68–70 °C. (a) thioanisole (%) *vs.* reaction time; (b) methylsulfinylbenzene (%) *vs.* reaction time; (c) methylsulfonylbenzene (%) *vs.* reaction time; (d), (e), (f) and (g) methylsulfinylbenzene (%) *vs.* reaction time.[18]

effect, methylsulfinylbenzene was further added to the reaction mixture. 16% or 76% of thioanisole are converted in 5 min with 5 or 20 mol% of added methylsulfinylbenzene. The reaction rates became similar after 20 min, because much more sulfoxide than the pre-added amount was produced. This is a direct evidence for the acceleration of the sulfide oxidation by the self-generating sulfoxide. Interestingly, both phosphine oxides and nitroxyl radicals decrease the rate of the sulfide oxidation. Hence, the addition of 20 mol% of trioctylphosphine oxide and 20 mol% TEMPO gave a significantly lower yields (50–60% after 30 min) compared with the blank experiment (90% after 30 min). Also the corresponding sulfone is not the catalyst in the reaction system because up to 60 min, only ~1% of methylsulfonylbenzene is observed by GC-FID and GC-MS. In fact, the reaction in the presence of 20 mol% sulfone is much slower than that with sulfoxide. The addition of dimethyl sulfoxide exhibited comparable activity to methylsulfonylbenzene but it was much lower than with methylsulfinylbenzene, Figure 1 (h). Therefore, the structure of sulfoxide but not only the functional group itself has a great effect on its activity.

In order to explore the generality for this protocol, we further tested this selective oxidation with various sulfides (Table 1). Typical sulfides, such as thioanisole, methyl *p*-tolyl sulfide and ethyl phenyl sulfide gave the corresponding sulfoxides in excellent yields, 92–97% (Table 1, entries 1–3). It is noteworthy that only 1% sulfones formed in the oxidation of thioanisole and methyl *p*-tolyl sulfide. This indicates that the present protocol is very selective and easily controllable. Functional groups are also tolerated in this procedure. Methyl phenyl sulfide derivatives with −OMe, −Cl, −CN, $-CH_2Br$ and $-CH_2CH_2Cl$ substituents re-

Table 1. Selective oxidation of sulfides to sulfoxides with hydrogen peroxide.[a]

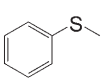
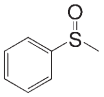
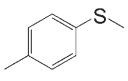
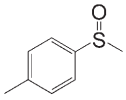
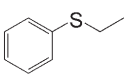
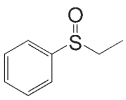
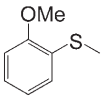
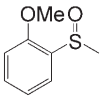
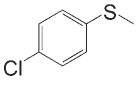
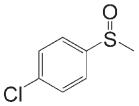
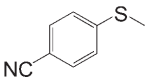
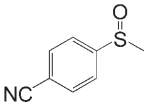
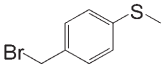
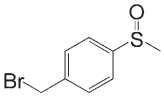
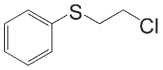
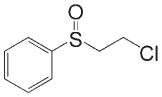
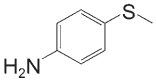
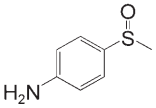
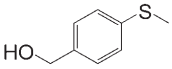
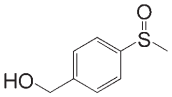
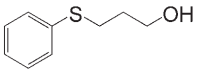
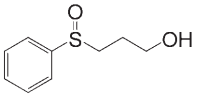
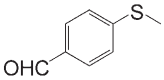
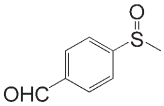
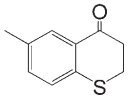
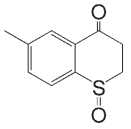
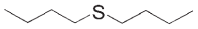
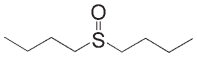
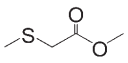
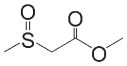
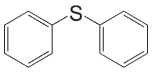
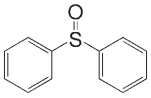
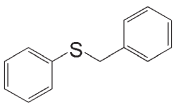
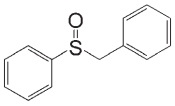
Entry	Substrate	Product	Sulfoxide:Sulfone[b]	Yield[c] [%]
1			99:1	97
2			99:1	94
3			94:6	92

Table 1. (Continued)

Entry	Substrate	Product	Sulfoxide:Sulfone[b]	Yield[c] [%]
4			99:1	98
5			97:3	91
6			98:2	88
7			91:9	52
8			94:6	90
9			91:1	90
10			99:1	90
11			99:1	87
12			88:12	69
13			99:1	93
14			96:4	87
15			96:4	81
16[d]			83:17	80
17[e]			86:14	84

[a] 2.0 mmol sulfide, 2.0 mmol H_2O_2 (30 wt% in water, 1 equiv., VWR), 70 °C (oil bath temperature), 1 h.
[b] Determined by GC-MS.
[c] Isolated yield for sulfoxide.
[d] 24.0 mmol H_2O_2, 12 h.
[e] 16.0 mmol H_2O_2, 2 h.

sulted in excellent yields (Table 1, entries 4–8). With 2-(methoxyphenyl)methylsulfane, the isolated yield reached 98% (Table 1, entry 4). However, a lower yield (52%) is obtained with 4-(methylthio)benzyl bromide. Here, GC-MS analysis showed that hydrolysis of the bromomethyl group to the corresponding 4-methylthiobenzyl alcohol and oxidation of the benzyl bromide group to 4-methylthiobenzylaldehyde are the major side reactions.

The selective oxidation of compounds with two functional groups within one molecule is always an interesting topic in oxidation chemistry. Hence, sulfides containing oxidizable $-NH_2$, $-CH_2OH$, $-CHO$ and $-C(O)-$ groups were tested (Table 1, entries 9–13). To our delight, for compounds containing amine and alcohol groups, the oxidation occurred selectively on the sulfur atom. Even with 4-methylthiobenzaldehyde, a good isolated yield of 69%, was obtained.

Moreover, for the selective oxidation of aliphatic sulfides, good yields are also achieved (Table 1, entries 14 and 15). Methyl (methylthio)acetate was easily oxidized into methyl methylacetate sulfoxide, a synthetically useful reagent, in 81% yield.[19] Notably, this protocol can be easily scaled up. As a demonstrationof a 200-mmol scale reaction, 29.2 g of di-*n*-butyl sulfide were oxidized to di-*n*-butyl sulfoxide. Merely by extracting the reaction mixture was a quantitative yield of product obtained with >93% purity.

The formation of sulfoxides from diphenyl sulfide and benzyl phenyl sulfide are more difficult to achieve under the known standard oxidation procedures. Even in the presence of highly active catalysts, much more hydrogen peroxide and longer reaction times were necessary in order to accomplish satisfactory results.[10b] In the presence of an excess of hydrogen peroxide, the yield for diphenyl sulfoxide reached 80% (Table 1, entry 16) and the yield of benzyl phenyl sulfoxide reached 84% (Table 1, entry 17).

In conclusion, a self-catalyzed selective oxidation of sulfides to sulfoxides has been developed for the first time. The scope of the protocol is demonstrated in the selective oxidation of 17 different substrates. High yield and chemoselectivity (in general >90%) are achieved in most cases. Compared with the previous protocols, this system has the advantage that no organic solvents or any additional catalyst is necessary. This makes the reaction environmentally benign, more practical and easily manageable. The study of the reaction mechanism and the development of a stereoselective version of this reaction are now undergoing in our laboratory.[20]

Experimental Section

General Procedure for the Self-Catalyzed Selective Oxidation of Sulfide to Sulfoxide

All reactions were carried out in an oil bath (69–70°C, oil bath temperature). To a glass reactor (40 mL), 2.0 mmol (0.292 g) di-*n*-butyl sulfide and 2.0 mmol H_2O_2 (30 wt% in water, from VWR, 0.20 mL) were added, respectively. The reaction was vigorously stirred (500–750 rpm) at 70°C for 1 h. The mixture was then cooled to room temperature and extracted by CH_2Cl_2 (20 mL×3). After drying with anhydrous Na_2SO4, the organic mixture was removed in vacuum and a colorless liquid (0.301 g) was obtained. The sample was analyzed by GC-MS, which indicated that the ratio between sulfoxide and sulfone was 96:4. $_1$H NMR analysis showed that the ratio between sulfoxide and sulfone was 95:5.

Analytically pure dibutyl sulfoxide was obtained by column chromatography (silica gel 60, 70–230 mesh) using CH_2Cl_2 to ethyl acetate as the gradient eluent. After removal of the solvent and drying under high vacuum for 2 h, a white solid was obtained; yield: 282 mg (87%).

Example of a Scaling-Up for the Selective Oxidation of Dibutyl Sulfide

To a round-bottom flask (250 mL), 200 mmol (29.2 g) of di-*n*-butyl sulfide and 200 mmol H_2O_2 (30 wt% in water, from VWR, 20 mL) were added respectively. The reaction mixture was vigorously stirred (500–750 rpm) at 70°C for 1 h. During the reaction, the system should be open to air and well cooled with a condenser.[21] The mixture was then cooled to room temperature and extracted by ethyl acetate (200 mL×4). After drying with anhydrous Na_2SO_4, the organic mixture was removed in vacuum and a colorless liquid (34.6 g) was obtained. The sample was analyzed by GC-MS, which indicated that the ratio between sulfoxide and sulfone was 93:7. ^{1}H NMR analysis showed that the ratio between sulfoxide and sulfone was 93:7. *1-(Butylsulfinyl)butane:* R_f= 0.84 (ethyl acetate); colorless semi-solid; ^{1}H NMR (300.1 MHz, $CDCl_3$): δ=0.93 (6H, t, J=7.3 Hz), 1.35–1.54 (4H, m), 1.66–1.76 (4H, m), 2.54–2.70 (4H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=13.7, 22.1, 24.6, 52.1; GC-MS (E.I., 70 eV): *m/z* (rel. int.)=162 (M^+, 1), 106 (12), 89 (32), 63 (16), 57 (35), 56 (12), 55 (22), 41 (100), 39 (36).

Acknowledgements

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[18] Typical reaction conditions: 5.0 mmol (620 mg) thioanisole and 5.0 mmol (0.50 mL) 30 wt% H_2O_2 and the appropriate catalyst [no sulfoxide or sulfone was added for (a)–(c), 5 mol% methylsulfinylbenzene, 20 mol% methylsulfinylbenzene, 20 mol% methylsulfonylbenzene, or 20 mol% dimethyl sulfoxide were initially present in (d), (e), (f) and (g),] were heated at 68–70 °C. A small aliquot (~20 μL) was taken out during the reaction and quenched with CH_2Cl_2 (~1.5 mL) and the reaction was monitored by GC-FID. All the reactions were performed in a multi-reactor in parallel (Carousel 12 station, RADLEYS). The methylsulfinylbenzene added at beginning was subtracted by analyzing the sample before addition of hydrogen peroxide. Thioanisole does not react with 30 wt% H_2O_2 in CH_2Cl_2 at room temperature. In a control experiment, thioanisole (12.4 mg, 0.10 mmol) and 30 wt% H_2O_2 (10.0 μL) were dissolved in 2 mL CH_2Cl_2 and monitored by GC-MS. After 6 h, only < 0.1% of thioanisole was converted to methylsulfinyl benzene.
[19] For volatile aliphatic sulfide oxidation, the system should be well cooled during the reaction to prevent severe vapourization.
[20] It should be noted that the present procedure can be combined with known resolution protocols for chiral sulfoxides to give enantiomerically pure sulfoxides: a) A. Scettri, F. Bonadies, A. Lattanzi, A. Senatore, A. Soriente, *Tetrahedron: Asymmetry* **1996**, *7*, 657–658; b) P. Kiełbasiński, B. Zwanenburg, T. J. G. Damen,

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[21] Even on this scale, we did not observe any explosion during the reaction. For safety reason, the system should be open to air and well cooled with a condenser.

3.8. A general gold-catalyzed direct oxidative coupling of non-activated arenes

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H.M.K. was involved in the interpretation of the experimental data, during the preparation of the manuscript and contributed to discussions. The work of H.M.K. to this publication accounts to approximately 10 %.

A general gold-catalyzed direct oxidative coupling of non-activated arenes†

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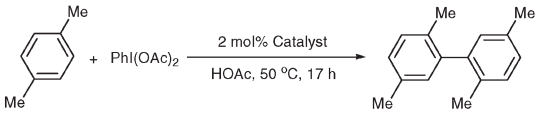
A gold-catalyzed mild and general oxidative homo-coupling of arenes using $PhI(OAc)_2$ as the oxidant is described (13 examples, 31–81% yield).

Biaryls constitute an important structural component in natural products, pharmaceuticals, agrochemicals and materials.[1] In recent decades there have been rapid advances in $C(sp^2)$–$C(sp^2)$ bond formation reactions to construct biaryls. Traditionally, the arene being coupled needs to be 'pre-activated', such as by halogenation, prior to metal-mediated coupling reactions.[2] Alternatively, halogenated arenes are converted to organometallic reagents and homo- or hetero-coupling reactions are performed in the next step. Transition metal-catalyzed cross-coupling reactions are undoubtedly the most versatile protocols to connect electrophilic reagents (ArX) with nucleophilic organometallic derivatives (ArM).[3] One drawback of these reactions is the necessity for an activating group on both the coupling partners. Though elegant C–H bond functionalization methods to obtain the organometallic reagents save one synthetic step,[4] direct metal (*e.g.* Pd, Rh, Ru *etc.*) catalyzed regioselective C–H bond activation with subsequent C–C bond formation with ArX or ArM has a better atom efficiency.[5] Very recently, significant advances have been made in the development of arylation of arenes, such as indole, benzofuran and naphthalene, with benzenes in metal-catalyzed reactions in the presence of oxidants.[6] Light mediated Ar–H substitution[7] and Lewis acid[8] mediated oxidative coupling of arenes are also impressive. However, these reactions typically take place under an inert atmosphere or drastic conditions and have limited substrate scope. Hence, the improvement of C–H bond transformations to biaryls through direct oxidation under practical and mild conditions is highly desired.

Gold has been under the spotlight of the chemistry stage as a catalyst in recent years.[9] Both heterogeneous and homogeneous gold catalysts showed excellent results in diversified reactivities. With regard to homogeneous catalysis, on the one hand gold shows reactivity as a 'soft' Lewis acid to perform C–C,[10] C–N,[11] C–O[12] and C–F[13] bond formation reactions with multiple bonds. On the other hand redox-type reactions such as reduction,[14] oxidation,[15] diboration,[16] homo-coupling of boronic acids,[17] cross-coupling reactions[18] and coupling of alkyl triflates with electron-rich arenes[19] have been demonstrated. Novel structures have been made smoothly with gold catalysts *via* cascade reactions.[20]

Notably, gold has a rich organometallic chemistry.[21] Its aryl complexes have been synthesized from Au(I)/(III) complexes.[22] Alternatively, C–H bond activation of arenes with Au(III) complexes to form gold aryl complexes is possible[23] and these gold aryl complexes can produce aryl acetylenes with concomitant formation of Au(I) species.[21a] Though the catalytic version of this interesting transformation has been attempted, it gave only the hydroarylation of alkynes.[24] Coupling of the ligands on gold complexes was also reported.[25] Thus, gold is a good candidate to act as a catalyst for biaryl synthesis from arenes with a suitable oxidant.[26] Based on our experience with C–H functionalization of arenes[27] and oxidation reactions,[28] here we report the first general gold-catalyzed oxidative coupling of arenes to yield biaryls.

Our screening started with a model reaction, using *p*-xylene to form 2,2′,5,5′-tetramethylbiphenyl catalyzed by various catalysts using $PhI(OAc)_2$ as the oxidant. 2 mol% of catalyst was employed in our primary investigations (eqn (1)). To our delight, $HAuCl_4$ catalyzed the reaction smoothly to yield the biphenyl in 74% yield at 55 °C (Table 1, entry 1). Other gold catalysts such as $Au(OAc)_3$ and $AuCl(PPh_3)$ also showed significant activity (39 and 76% yield respectively). Although Lewis acid mediated oxidative coupling of electron-rich arenes in an overstoichiometric amount has been reported, typical Lewis acids like $FeCl_3$ and $BF_3{\cdot}OEt_2$ did not work under our catalytic reaction conditions. Further solvent screening revealed that acetic acid is a good solvent for this reaction. Non-coordinative solvents like 1,2-dichloroethane (42% yield) and the substrate, *p*-xylene (58% yield), can also be used as the reaction medium (see ESI†).



(1)

Even though a slightly higher concentration (10 equiv. to the oxidant) of arene is used to get an optimized yield, the excess starting material can be recovered and reused. It should be noted that strong acids [*e.g.* TFA (>1% yield)] gave inferior results, possibly due to the formation of polymers. It is noteworthy that our protocol can be easily managed in ambient conditions. It is not necessary to use inert conditions and no pre-treatment of solvent or substrate is needed. When acetic anhydride was used (71% yield) instead of HOAc, no improvement was observed. This result implies that water in the reaction mixture does not affect our system very much. Among the several oxidants used ($K_2S_2O_8$,

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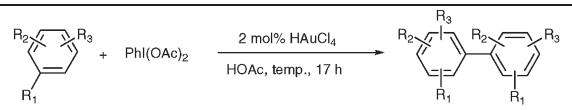
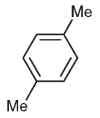
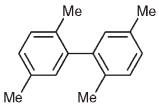
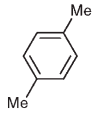
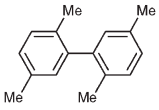
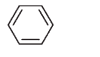
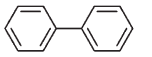
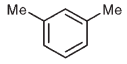
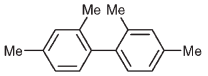
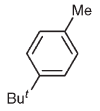
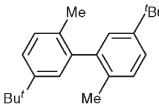
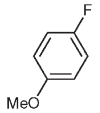
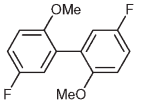
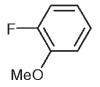
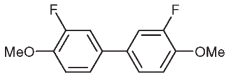
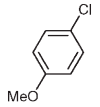
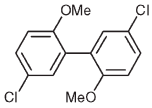
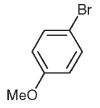
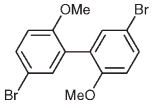
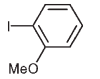
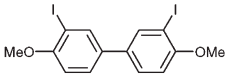
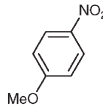
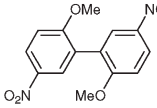
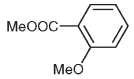
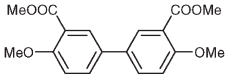
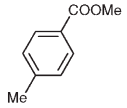
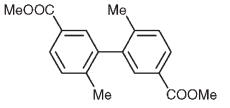
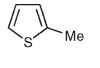
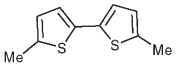
† Electronic supplementary information (ESI) available: Effect of solvent, oxidant and catalyst in oxidative homo-coupling of *p*-xylene and spectral data of compounds synthesized. See DOI: 10.1039/b714928j

Table 1 Au-catalyzed oxidative homo-coupling of arenes[a]



Entry	ArH	Major product	Temp./°C	Yield (%)[b]
1			55	74[c]
2[d]			55	81[c]
3[d]			95	71[c]
4			55	75[e]
5			95	62
6			95	68[c]
7[c]			55	63[f]
8			95	68
9			95	56
10			95	79[g]
11			95	38
12			95	74[h]
13			95	78
14			95	31

[a] Reaction conditions: oxidant (1.0 mmol), *p*-xylene (10.0 mmol), dodecane (55 μL, internal standard) and $HAuCl_4$ (0.02 mmol, 2.0 mol%) were heated in the appropriate solvent (1.0 mL) at 55 °C in air for 17 h. [b] Isolated yields based on the oxidant used. [c] GC yields; trimers were observed. [d] 2 mL of solvent were used. [e] An isomer mixture was isolated; product ratio = 89 : 11 by GC-FID. [f] 54% of *para–para* coupled product and 9% of *para–ortho* coupled product were isolated. [g] 69% of *para–para* coupled product and 10% of *para–ortho* coupled product were isolated. [h] 74% of *para–para* coupled product was isolated and the *para–ortho* coupled product was observed.

Oxone®, 35% CH_3CO_3H, $Cu(OAc)_2$, see ESI†), $PhI(OAc)_2$ proved to be the best oxidant for this reaction.

$PhI(OCOCF_3)_2$ is a suitable reagent for Lewis acid mediated biaryl formation reactions, however it gives slightly lower productivity in our model reaction (69% yield).

To test the effectiveness of the gold catalytic system, a range of arenes was examined using the preliminary optimized reaction conditions (Table 1). In general, the reaction shows a typical electrophilic aromatic substitution pattern. Notably, a variety of arenes work comparably well (Table 1). Even 4-nitroanisole, which gave no product in Lewis acid mediated oxidative coupling,[8g] furnished the corresponding biaryl in moderate yield (Table 1, entry 11).

The reaction protocol tolerates a wide range of functional groups. All halogens survive after the reaction. To the best of our knowledge, neither palladium- nor Lewis acid-catalyzed reactions can maintain the reactivity with tolerance to all halogens. Only a few C–H functionalization reactions exhibit such high halogen group preservation (Table 1, entries 7–10).[4b–e] Other functional groups such as methoxide and esters work equally well in our reaction conditions (Table 1, entries 12 and 13). It is worth mentioning that electron-rich heterocycles, such as thiophene, also gave the corresponding products in moderate yield.

Interestingly, a decrease of reactivity from $HAuCl_4$ to $Au(OAc)_3$ was observed. It suggests that some chloride ions may still coordinate to the catalytic center. As a trace amount of chlorinated product was detected by GC-MS, it is likely that the gold reaction center contains both acetate and chloride ions. Though arene cationic radical has been observed in Lewis acid mediated oxidative coupling reactions of electron-rich arenes at −78 °C,[8e] no biaryl was observed with 2 mol% $BF_3{\cdot}OEt_2$ in the present system. Moreover, nitro-substituted anisole did not work in the Lewis acid systems while it worked moderately in our case. Since $AuCl(PPh_3)$ worked as well as $HAuCl_3$ under our oxidative conditions, Au(III) is suggested as the CH–functionalization catalyst.[29] The substrate with the weakest carbon–halogen bond (C–I) coupled smoothly in our conditions (Table 1, entry 10). It further implies that high valent Au(III) is the major catalyst.[18,30] A typical electrophilic aromatic substitution pattern has been observed in our reaction conditions. Hence, participation of a free cationic radical is not likely, but the possibility of an auration reaction, a Friedel–Crafts type substitution or the participation of a coordinated cationic radical cannot be ruled out.

In summary, a new general gold-catalyzed oxidative homo-coupling of arenes is reported. It can be simply handled in air and no pre-treatment of substrate and solvent is necessary. Interestingly, our reaction protocol does not require any Ag salt to enhance the reactivity.[31] Remarkable functional group tolerance has been shown in our reaction conditions. The results shown represent the first successful example of Au-catalyzed oxidative homo-coupling of simple arenes. In principle the double CH-functionalization is the most efficient process for the synthesis of biaryls. Improved systems for direct cross-coupling of arenes are under investigation and mechanistic studies of this reaction are in progress in our laboratory.

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3.9. Gold-catalyzed direct oxidative coupling reactions of non-activated arenes

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Gold-catalyzed Direct Oxidative Coupling Reactions of Non-activated Arenes

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In recent decades, transition metal catalyzed coupling reactions to construct aromatic C-C and C-X (X = N, O, S) bonds have been gained great attention of the scientific community and presently reached a highly advanced status.[1] The classical way to this type of transformation is the metal-mediated coupling reactions of the "pre-activated" compounds, such as halogenated arenes.[2] The most simple and convenient method to connect the electrophilic reagents (ArX) with the nucleophilic counter part, such as organometallic derivatives (ArM), or amines, alcohols and thiols, is undoubtedly transition metal-catalyzed cross-coupling reactions.[1,3] The major drawback of these reactions is the necessity of an activating group on both or at least one of the coupling partners, which may not be always easily available. Also this "pre-activation", such as halogenation, sulfonate formation or preparation of organometallic reagents, usually refers to an extra step towards the final product.

Biaryls as well as aromatic amines constitute important structural motifs in natural products, pharmaceuticals, agrochemicals and materials. Owing to the numerous appealing applications, many efforts have been devoted to providing direct and efficient processes for their preparation. Organometallic reagents from elegant C-H bond functionalization methods save one synthetic step[4] and direct metal, such as Pd, Rh and Ru etc., catalyzed regioselective C-H bond activation with subsequent coupling reaction has better atom efficiency.[5] However,

direct aromatic C-H functionalization has not been reached its optimum level because practical synthetic utility demands less expensive, highly efficient and environmentally friendly catalytic systems. Recently, significant advances have been made in the development of arylation of arenes, such as indole, benzofuran and naphthlene, with benzenes in metal-catalyzed reactions in the presence of oxidants.[6] Light mediated Ar-H substitution[7] and Lewis acid[8] mediated oxidative coupling of arenes are also impressive. On the other hand, metal mediated direct aromatic C-H activation followed by coupling with amines[9] or Lewis acid catalyzed amination of electron rich arenes with electrophilic nitrogen source to produce aromatic amines has been well documented in the literature.[10] In general, use of inert atmosphere or drastic conditions and limited substrate scope often renders the practicability of industrial usage of these types of reactions. Therefore, the improvement of aromatic C-H bond transformations under practical and mild conditions is one of the priority tasks for modern organic chemists.

In recent years, gold has emerged as a most discussed topic of the catalysis community.[11] Gold catalysts are known to produce extraordinary results both in the fields of heterogeneous and homogeneous catalysis. Although in the last few years, there is a significant increase in scientific publication using gold as homogeneous catalysts, especially as a "soft" Lewis acid to perform C-C,[12] C-N,[13] C-O[14] and C-F[15] bond formation reactions with multiple bonds, heterogeneous gold catalysts are still dominant. Gold catalysts also have been employed in redox-type reactions such as reduction,[16] oxidation,[17] diboration,[18] homo-coupling of boronic acids,[19] cross coupling reactions[20] and coupling of alkyl triflates with electron-rich arenes.[21] They have been used fruitfully for multi-component and cascade reactions to generate complex structures.[22] Mechanistically, there is still a concern associated with the role of proton in reactions catalyzed by gold and other Lewis acids.[23]

Simple gold salts are known to react with arenes to produce stable aryl-gold complexes. In early landmark reports, these aryl complexes used to be synthesized from Au(I)/(III)

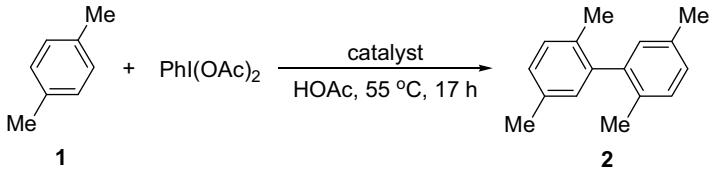
complexes with Grignard reagents or organo-mercury compounds.[24] These Au(I) aryl complexes can be further oxidized to their Au(III) derivatives.[24b,e] C-H bond activation of arenes with Au(III) complexes to produce gold aryl complexes has also been reported in the literature, which is often stabilized by *N*-donating ligands.[25] In stoichiometric reactions, this gold complex reacts with acetylenes to produce aryl acetylenes and Au(I) species.[26] However, when this reaction was performed in catalytic amount of gold in the presence of various oxidants, only hydroarylation of alkynes was observed.[27] It should be noted that C-H bond activation and homocoupling of the coordinating ligand itself was determined.[28] On the basis of these observations it was thought for long times that switching between two distinct oxidation states of gold in catalytic reaction conditions will be fruitful to the chemical enterprise. Very recently, it has been demonstrated that with a suitable ligand system gold can also perform Suzuki-Miyaura[29] as well as Cu-free Sonogashira[20a] coupling reactions. In our long term searching for efficient C-H functionalization of arenes[30] and oxidation reaction systems,[31] we thought that gold can be a good candidate to act as catalyst for biaryl synthesis from arenes with a suitable oxidant.[32]

Herein we present more detailed studies of the homo- and hetero-coupling of nonactivated arenes on the basis of aromatic C-H bond functionalization catalyzed by gold,[33] and some intial experiments on aromatic electrophilic amination reaction. These results give us some insights on the diverse reaction mechanism.

We started investigating the oxidative homocoupling reaction of *p*-xylene to form 2,2',5,5'-tetramethylbiphenyl using $PhI(OAc)_2$ as the oxidant (Table 1). Initially we started with 5 mol% of $HAuCl_4$ as catalyst with respect to the oxidant employed. This reaction went smoothly to yield the biphenyl in 65% at 55 °C (Table 1, entry 2) but remained unreactive in the absence of the catalyst (Table 1, entry 1). As substantial amount of chlorination of *p*-xylene also observed with 5 mol% of $HAuCl_4$, reduction of the catalyst loading to 2 mol% slightly enhanced the product yield by decreasing the amount of chlorine source (Table 1,

entry 3). Further experiments show that catalyst loading can be reduced down to 1 mol% with a slight decrement in yield but with accretion in TON and TOF of the reaction (Table 1, entry 4).

Table 1. Catalyst screening of oxidative homo-coupling of *p*-xylene[a]



1 **2**

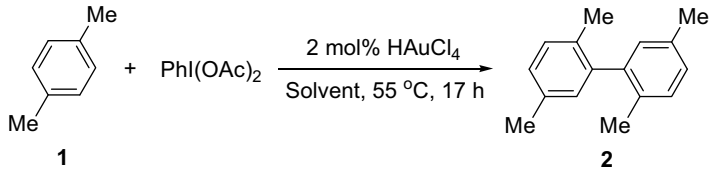
entry	catalyst	yield [%][b]	TON[c]	TOF [h^{-1}][d]
1	nil	0	0	0
2[e]	$HAuCl_4$	65	13	0.8
3	$HAuCl_4$	**74**	37	2.2
4[f]	$HAuCl_4$	57	57	3.4
5	$Au(OAc)_3$	39	20	1.1
6	AuCN	0	0	0
7	$AuCl(PPh_3)$	**76**	38	2.2
8	$FeCl_3$	0	0	0
9	NH_4FeCl_4	0	0	0
10	$AgNO_3$	0	0	0
11	$CuCl_2$	0	0	0
12	BF_3•OEt_2	0	0	0

[a] Reaction conditions: $PhI(OAc)_2$ (1.0 mmol), *p*-xylene (10.0 mmol), dodecane (55 μL, internal standard) and catalyst (0.02 mmol, 2.0 mol%) were heated in HOAc (1.0 mL) at 55 °C in air for 17 h. [b] Calibrated GC yields were reported; % yield = (no. of moles of biaryl)/(no. of moles of oxidant) x 100%. [c] Turnover number (TON) = (no. of moles of biaryl produced)/(no. of moles of catalyst). [d] Turnover frequency (TOF) = (no. of moles of biaryl produced)/[(no. of moles of catalyst) x (reaction time in hour)]. [e] 5 mol% of catalyst used. [f] 1 mol% of catalyst used.

With 2 mol% of the catalyst loading, other gold catalysts such as $Au(OAc)_3$ and $AuCl(PPh_3)$ also showed moderate activity, whereas AuCN remained completely inactive (Table 1, entries 5,6 and 7). It suggests that catalytic activity depends not only on the oxidation state of the catalyst, but also on the counter anion employed. Though Lewis acid mediated oxidative coupling of electron rich arenes has been reported, low temperature

(-78 °C), inert gas (N_2) and overstoichiometric amount of the Lewis acid ($BF_3{\cdot}Et_2O$) are necessary.[8] Typical Lewis acids like $FeCl_3$ and $BF_3{\bullet}OEt_2$ did not work under our catalytic reaction conditions (Table 1, entries 8 and 12). Catalysts like NH_4FeCl_4, $AgNO_3$, $CuCl_2$ also remained unreactive (Table 1, entries 9, 10 and 11). These results reveal that the reaction do not follow a simple electrophilic substitution reaction pathway through a non-stabilized cationic radical.[8]

Table 2. Solvent screening of oxidative homo-coupling of *p*-xylene[a]



entry	solvent	yield [%][b]	TON[c]	TOF [h^{-1}][d]
1	*p*-xylene	58	29	1.7
2	CH_3CN	0	0	0
3	CH_3NO_2	12	6	0.4
4	$ClCH_2CH_2Cl$	42	21	1.2
5	MeOH	3	2	0.1
6	TFA	<1	<1	<0.1
7	HOAc	**74**	37	2.2
8	Ac_2O	71	36	2.1

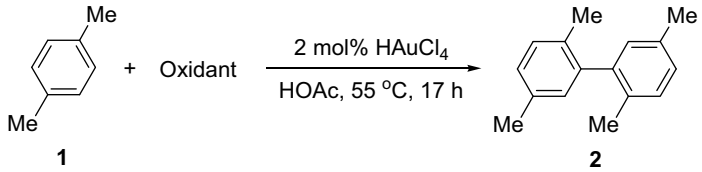
[a] Reaction conditions: $PhI(OAc)_2$ (1.0 mmol), *p*-xylene (10.0 mmol), dodecane (55 μL, internal standard) and $HAuCl_4$ (3.2 mg, 0.02 mmol, 2.0 mol%) were heated in an appropriate solvent (2.0 mL) at 55 °C in air for 17 h. [b] Calibrated GC yields were reported; % Yield = (no. of moles of biaryl)/(no. of moles of oxidant) x 100%. [c] Turnover number (TON) = (no. of moles of biaryl produced)/(no. of moles of catalyst). [d] Turnover frequency (TOF) = (no. of moles of biaryl produced)/[(no. of moles of catalyst) x (reaction time in hour)].

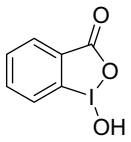
Solvent shows pivotal effects to this reaction and acetic acid came out as the best solvent. Acids activate the gold catalyst. Only small amount of HOAc (56 μL) provided sufficient activity (66%) for the reaction. For a more practical reaction protocol for solid substrates, 1-2 mL of HOAc proved to be convenient. When strong acid (TFA) was used as the solvent, the reaction furnished rapidly but produced inferior results, possibly due to the formation of

polymers (Table 2, entries 6). Both acetic anhydride and HOAc produced the desired biaryl in comparable yields (Table 2, entry 7 and 8). These results imply that water in the reaction mixture does not affect our system very much. The reaction can also be carried out in the presence of non-coordinative solvents like 1,2-dichloroethane and the substrate, *p*-xylene itself but with comparatively lower yield (Table 2, entries 1 and 4). As HOAc was generated during the reaction, the reaction may activate itself. With strongly coordinative solvent like CH_3CN and $MeNO_2$ (Table 2, entries 2 and 3), either there was no reaction or the yield was very poor, suggesting that the reduced Lewis acidity may be the reason for this.

Amongst the oxidant used, $PhI(OAc)_2$ showed to be the best oxidant of this reaction (Table 3, entries 1). $PhI(OCOCF_3)_2$, a suitable reagent for Lewis acid mediated biaryl formation reactions, gave slightly lower productivity in our model reaction (Table 3, entry 2). Hypervalent iodine seems participating in the reaction as well. Indeed only very low yield of product was detected, PhI with peracetic acid, a formal *in-situ* generation method for $PhI(OAc)_2$, gave 3% of the biphenyl while peracetic acid alone did not produce any coupling product. Other conventional oxidant such as $K_2S_2O_8$, Oxone® and $Cu(OAc)_2$ did not work at all (Table 3, entries 2-6).

Table 3. Solvent screening of oxidative homo-coupling of *p*-xylene[a]



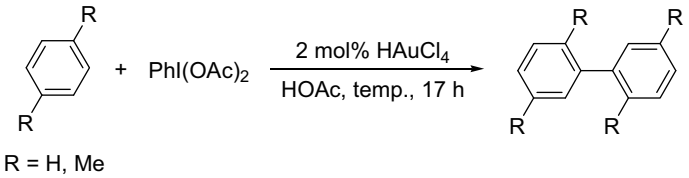
entry	oxidant	yield [%][b]	TON[c]	TOF [h^{-1}][d]
1	$PhI(OAc)_2$	**74**	37	2.2
2	$PhI(OCOCF_3)_2$	69	35	2.1
3		0	0	0
4	45% IBX	<1	<1	<0.1
5	Dess-Martin	1	<1	<0.1
6	35% CH_3CO_3H	0	0	0
7	PhI + 35% CH_3CO_3H	3	2	<0.1
8	DMSO	0	0	0
9	$K_2S_2O_8$	0	0	0
10	Oxone®	0	0	0
11	$Cu(OAc)_2$	0	0	0

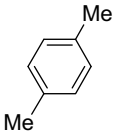
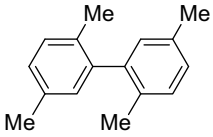
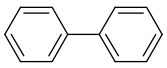
[a] Reaction conditions: Oxidant (1.0 mmol), *p*-xylene (10.0 mmol), dodecane (55 μL, internal standard) and $HAuCl_4$ (3.2 mg, 0.02 mmol, 2.0 mol%) were heated in HOAc (1.0 mL) at 55 °C in air for 17 h. [b] Calibrated GC yields were reported; % yield = (no. of moles of biaryl)/(no. of moles of oxidant) x 100%. [c] Turnover number (TON) = (no. of moles of biaryl produced)/(no. of moles of catalyst). [d] Turnover frequency (TOF) = (no. of moles of biaryl produced)/[(no. of moles of catalyst) x (reaction time in hour)].

To improve the effectiveness of the gold catalytic system, the concentration effect was examined using the preliminary optimized reaction conditions (Table 4). The reaction is dependent on the concentration of substrate, mainly because of the formation of undesired oligomers observed on GC-MS (Table 4, entries 1, 4-6). When the concentration of the substrate such as *p*-xylene and benzene was increased to 20 fold compared to the oxidant, the yield of the corresponding homo-coupled product was also increased substantially especially in the latter case (Table 4, entries 6 and 9). While temperature effect is insignificant to

electron-rich *p*-xylene (Table 4, entries 1-3), it is beneficial to non-activated benzene (Table 4, entries 7 and 8). With these reaction conditions, various non-activated arenes were coupled to test the effectiveness of the gold catalytic system.

Table 4. Concentration effects on Au-catalyzed oxidative homo-coupling of arenes[a]



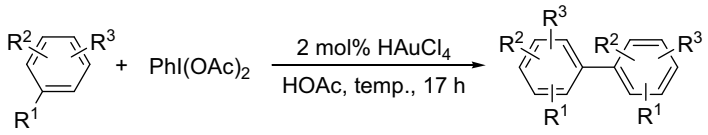
entry	ArH	ArH:PhI(OAc)$_2$:HOAc[b]	major product	temp. [°C]	yield [%][c]
1	 **1**	10:1:17	 **2**	55	74
2	**1**	10:1:17	**2**	75	74
3	**1**	10:1:17	**2**	95	70
4	**1**	10:1:3	**2**	55	31
5	**1**	10:1:9	**2**	55	52
6	**1**	20:1:17	**2**	55	81
7	 **3**	10:1:17	 **4**	55	34
8	**3**	10:1:17	**4**	95	54
9	**3**	20:1:17	**4**	95	71

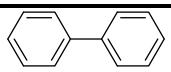
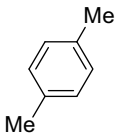
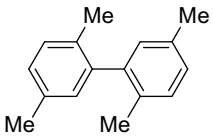
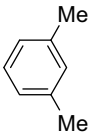
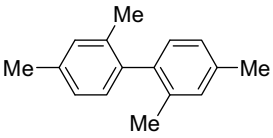
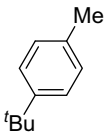
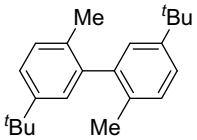
[a] Reaction conditions: Oxidant (1.0 mmol), *p*-xylene (10.0 mmol), dodecane (55 μL, internal standard) and $HAuCl_4$ (0.02 mmol, 2.0 mol%) were heated in the appropriate solvent (1.0 mL) and temperature in air for 17 h. [b] Molar ratio. [c] GC yields.

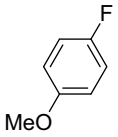
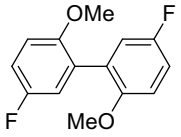
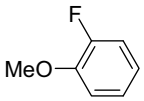
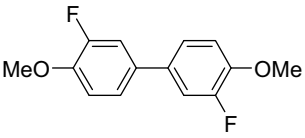
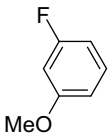
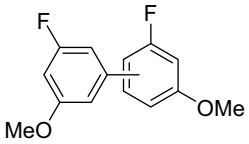
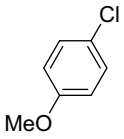
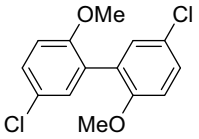
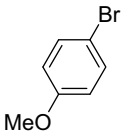
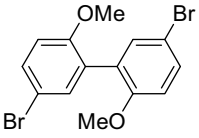
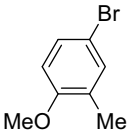
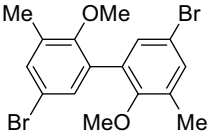
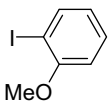
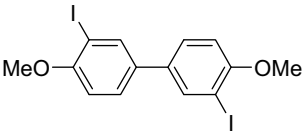
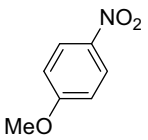
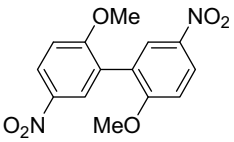
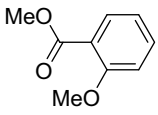
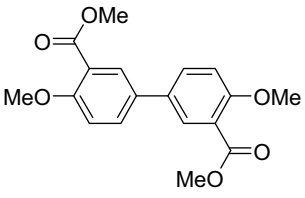
While electron-rich substrates work well at 55 °C, neutral or electron deficient substrates react at slightly higher temperature (95 °C). In general, the reaction works smoothly in good to excellent yield. Even though slightly higher concentration (10 equivalents to the oxidant) of arene is used to get optimized yield, the excess starting material can be recovered and reused. For example, 7.5 equivalents of 4-bromo-2-methylanisole with respect to PhI(OAc)$_2$ were

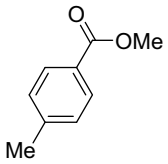
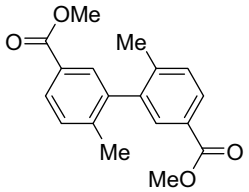
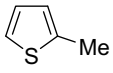
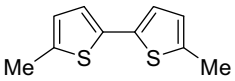
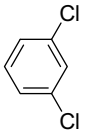
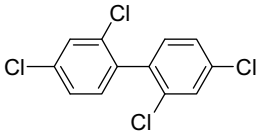
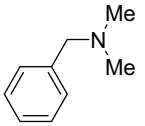
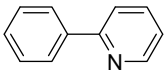
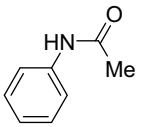
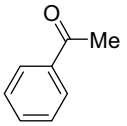
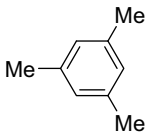
recovered after the reaction (Table 5, entry 10). The regioselectivity of the reaction follows typical electrophilic aromatic substitution pattern. A range of arenes worked comparably well under our reaction conditions to give the corresponding biaryls in moderate to good yields (Table 5). Even difficult substrates such as 4-nitroanisole, which was reported to be unreactive in Lewis acid mediated oxidative coupling,[34] produced the corresponding biaryl in moderate yield (Table 5, entry 12). Highly electron deficient substrates like 1,3-dicholorobenzene also reacted at elevated temperature (Table 5, entry 16).

Table 5. Au-catalyzed oxidative homo-coupling of arenes[a]



entry	ArH	major product	temp. [°C]	yield [%][b]
1[c]	 **3**	 **4**	95	71[d]
2[c]	 **1**	 **2**	55	81[d]
3	 **5**	 **6**	55	75[e]
4	 **7**	 **8**	95	62

5	 **9**	 **10**	95	68[d]
6	 **11**	 **12**	55	63[f]
7	 **13**	 **14**	95	63[g]
8	 **15**	 **16**	95	68
9	 **17**	 **18**	95	56
10	 **19**	 **20**	95	56[h]
11	 **21**	 **22**	95	79[i]
12	 **23**	 **24**	95	38
13	 **25**	 **26**	95	86[j]

14	 **27**	 **28**	95	78
15	 **30**	 **31**	95	31
16	 **32**	 **33**	95	15[k]
17	 **34**	-	95	0
18	 **35**	-	95	0
19	 **36**	-	95	0
20	 **37**	-	95	0
21	 **38**	-	95	0

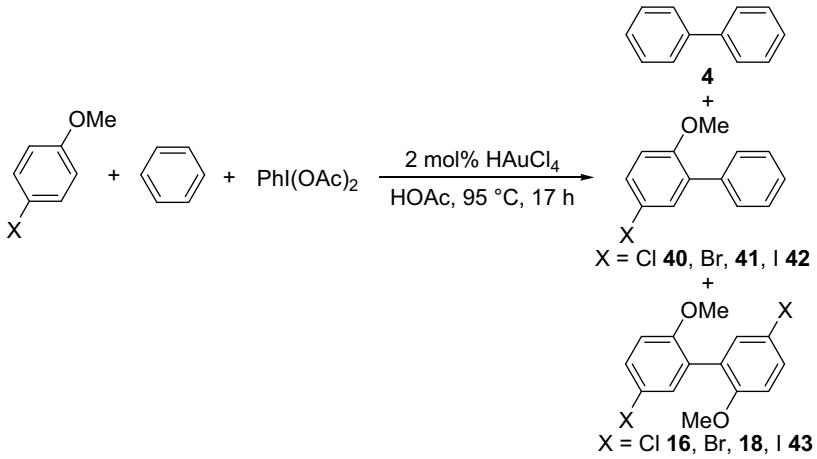
[a] Reaction conditions: Oxidant (1.0 mmol), arene (10.0 mmol), dodecane (55 μL, internal standard) and $HAuCl_4$ (0.02 mmol, 2.0 mol%) were heated in HOAc (1.0 mL) at 55 °C in air for 17 h. [b] Isolated yields based on the oxidant used. [c] GC yields. [d] 20.0 mmol of arene was used. [e] An isomer mixture was isolated; product ratio = 89:11 on GC-FID. [f] 54% of *para-para* coupled product and 9% of *para-ortho* coupled product were isolated. [g] An isomer mixture was isolated; product ratio = 24:49:27 on GC-FID. [h] An isomer mixture was isolated; product ratio = 88:12 (^{1}H NMR). [i] 69% of *para-para* coupled product and 10% of *para-ortho* coupled product were isolated. [j] 74% of *para-para* coupled product was isolated and 12% of *para-ortho* coupled product were observed. [k] An isomer mixture was isolated; product ratio = 94:6 on GC-FID.

A wide range of functional groups has been tolerated by the present reaction protocol. All halogens survived and kept intact during the course of the reaction. To the best of our

knowledge, neither palladium- nor Lewis acid-catalyzed reactions can maintain the reactivity tolerating all halogens (Table 5, entries 5-11). Some C-H functionalization reactions exhibit such high halogen group preservation.[4b-e] Methoxide and ester groups also survived and worked equally well in our reaction conditions (Table 5, entries 13 and 14). The electron rich heterocycle, thiophene also coupled to the corresponding product in single regioisomeric form in moderate yield (Table 5, entry 15). One of the drawbacks for this protocol is the compatibility with strong coordinating groups. Substrates containing functionalization such as *N*,*N*-dimethylbenzyl amine, 2-phenyl pyridine, *N*-acetyl aniline, aliphatic aromatic ketones did not give any desired product. Electron rich mesitylene did not produce the desired homo-coupled product possibly due to the increased steric bulk in the substrate. Nevertheless, the present protocol is very easy to handle. It can be managed in ambient conditions and is not necessary to protect the mixture under inert atmosphere or pre-treat the solvent or substrate.

Exploration of oxidative hetero-coupling of arenes using our protocols showed interesting results. Concentration effect plays a crucial role in this reaction. With equal amounts of *para*-haloanisole and benzene, nearly equal amount of the homo-coupling product of biphenyl and the hetero-coupling product of phenylanisole was observed, whereas the yield of bis-anisole was only in a few percent (Table 6, entries 3, 9, 15). Clearly it can be imagined that the activation of benzene occurs in the initial step and the reactive intermediate is then trapped by another arene. Hence the biphenyl to phenylanisole ratio is close to the concentration ratio of benzene and anisole. Increasing the amount of benzene from 1 to 10 equivalents to $PhI(OAc)_2$ caused increment of biphenyl, as expected (Table 6, entries 1-4).

Table 6. Au-catalyzed oxidative hetero-coupling of arenes[a]



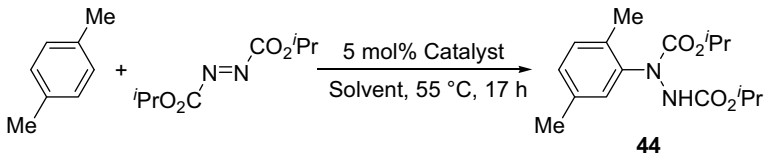
entry	X	halo-anisole :benzene[b]	hetero-coupled product (**40**, **41** or **42**) [%][c]	homo-coupled product (**16**, **18** or **43**) [%][c]	biphenyl (**4**) [%][c]	hetero: homo:**4** [%][d]
1	Cl	5:1	23	17	4	49:40:11
2	Cl	5:2	32	7	18	52:12:36
3	Cl	5:5	30	3	32	41:5:53
4	Cl	5:10	23	0	41	32:0:68
5	Cl	10:4	43	10	19	56:15:29
6	Cl	15:6	46	11	22	54:15:31
7	Br	5:1	27	15	9	45:37:18
8	Br	5:2	42	7	27	48:13:39
9	Br	5:5	37	3	43	38:4:58
10	Br	5:10	29	1	60	27:2:71
11	Br	10:4	50	8	30	50:13:37
12	Br	15:6	55	11	30	51:14:35
13	I	5:1	15	nd[e]	3	48:40:12
14	I	5:2	26	nd	16	51:16:33
15	I	5:5	25	nd	29	41:7:52
16	I	5:10	20	nd	54	25:2:73
17	I	10:4	36	nd	17	53:21:26
18	I	15:6	41	nd	15	48:13:39

[a] Reaction conditions: Oxidant (1.0 mmol), appropriate amounts of arenes, dodecane (55 μL, internal standard) and $HAuCl_4$ (0.02 mmol, 2.0 mol%) were heated in HOAc (1.0 mL) at 95 °C in air for 17 h. [b] No. of moles of anisole:no. of moles of benzene. [c] Calibrated GC yields based on the oxidant used. [d] GC peak area ratio of corresponding products. [f] Not determined.

Higher concentration of arenes resulted in a better total yield. The best result was obtained when a ratio of 15:6:1 of *para*-bromoanisole:benzene:$PhI(OAc)_2$ was performed, in which a total yield of 95% was attained with 55% of cross coupling product (Table 6, entry 12). On the other hand, in the case of *para*-iodoanisole, *ortho*-acetoxylated product with respect to the methoxy goup, which was the major product in homocouplig reaction conditions, was not at all observed (according to GS-MS spectra of the crude reaction mixtures). The formation of such acetoxylated product with hypervalent iodine salt and a Lewis acid was already reported in the literature,[35] which supports our observation during the homo-coupling experiments with *para*-iodoanisole. But surprisingly, the same substrate in hetero-coupling conditions produced different amount of homo- and hetero-coupling product of *para*-iodoanisole together with the formation of biphenyl (**4**) but not the acetoxylated product.

Gold catalysts can be extended to C-N bond formation. The same type of amination reaction of electronrich arenes was reported in the literature promoted mainly with stoichiometric amount of Lewis acids.[10] In a model reaction amination of *p*-xylene catalyzed by gold catalysts using diisopropylazodicarboxylate (DIAD) as an amine source was performed (Table 7). To our delight, 5% $HAuCl_4$ catalyzed the reaction smoothly to yield the major aminated product in 31% at 55 °C using $MeNO_2$ as solvent (Table 7, entry 1).

Table 7. Catalyst and solvent screening of electrophilic amination of *p*-xylene [a]



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entry	catalyst	solvent	yield of major isomer [%][b]	major:minor [%][c]
1	$HAuCl_4$	CH_3NO_2	31	85:15
2	$AuPPh_3Cl$	CH_3NO_2	0	0:0
3	$AuCl_3$	CH_3NO_2	30	85:15

4	$Au(OAc)_3$	CH_3NO_2	0	0:0
5	AuCN	CH_3NO_2	0	0:0
6	$HAuCl_4$	CH_3CN	14	80:20
7	$HAuCl_4$	*p*-xylene	11	83:17
8	$HAuCl_4$	$ClCH_2CH_2Cl$	14	84:16
9	$HAuCl_4$	AcOH	22	84:16
10	$HAuCl_4$	MeOH	0	0:0
11	$BF_3.OEt_2$	CH_3NO_2	31	85:15

[a] Reaction conditions: DIAD (1.0 mmol), *p*-xylene (10.0 mmol), dodecane (55 μL, internal standard) and catalyst (0.05 mmol, 5.0 mol%) were heated in the appropriate solvent (1.0 mL) at 55 °C in air for 17 h. [b] Calibrated GC yields. [c] GC peak area ratio of corresponding products.

But in sharp contrast to the C-C bond formation reaction, amination did not proceed when $Au(OAc)_3$, $AuCl(PPh_3)$ or AuCN were used as catalyst, whereas $AuCl_3$ showed comparable reactivity (Table 1, entries 2, 3, 4 and 5). Further solvent screening revealed that, $MeNO_2$ is the solvent of choice, whereas polar protic solvent like AcOH and MeOH, coordinative CH_3CN, and non-polar aprotic 1,2-dichloroethane gave inferior results (Table 1, entries 6-10). However, using 5 mol% of $BF_3{\cdot}Et_2O$ instead of $HAuCl_4$, a similar yield was given (Table 1, entry 11), which suggests the present aromatic amination passes through a Lewis acid catalyzed reaction mechanism. This type of gold catalyzed electrophilic aromatic C-H functionalization is mechanistically entirely different from the forementioned oxidative homocoupling of arenes.

Some mechanistic insights can be drawn from this diverse reactivity of gold catalysts. We have observed that the reactivity of $Au(OAc)_3$ was lower than that of $HAuCl_4$ and $AuCl_3$ in C-C bond formation. By close monitoring the reaction mixture by GC-MS, in the initial stage of the reaction, a substantial amount of chlorinated product was formed with a rate faster than the formation of homo-coupled product. This implies that some chloride ion remained attached to the catalytic center during the course of the reaction and the actual catalyst contains both acetate and chloride ions. Lewis acid mediated oxidative coupling reactions of electron rich arenes using hypervalent iodine salts was performed at as low temperature as

-78 °C and a cationic radical species has been proposed as the reaction intermediate.[8e] In the aromatic amination process both $BF_3{\cdot}OEt_2$ and $HAuCl_4$ worked equally well, establishing that it is likely a Lewis acid catalyzed process, while no biaryl was observed with 2 mol% $BF_3{\cdot}OEt_2$ in the present oxidative homo-coupling system. Moreover, nitro-substituted anisole did not work in the Lewis acid systems while it worked moderately in our case. Hence, direct participation of cationic radicals is not very likely. But the regioselectiviy in the present homo-coupling reaction protocol strictly follows typical electrophilic aromatic substitution pattern. Moreover during the screening process of homo-coupling of *p*-xylene, a trace amount of an unidentified compound with a molecular mass of 212, which corresponds to the unoxidized intermediate to bixylyl was observed. Participation of gold stabilized cationic radical species or electrophilic metalation like conventional Pd(II) or Pt(II) cannot be entirely ruled out. It has been recently reported that oxidative addition of aryliodides is possible with Gold(I) complexes. But under our conditions, the substrate with the weakest carbon halogen bond (C-I) coupled smoothly with intact preservation of iodo-group in the product (Table 5, entry 11), which implies that high valent Au(III) is the major catalyst.[20, 36] It should be noted that both $AuCl(PPh_3)$ and $HAuCl_3$, worked with same efficacy under our oxidative conditions and this also further supports the fact that Au(III) may be the C-H functionalization catalyst.[37] Knowing the distinct difference of reactivity between the C-C bond formation and amination process, it strongly suggests that rather than a simple aromatic electrophilic substitution, it follows a complicated pathway.

In summary, a new general gold-catalyzed oxidative coupling of arenes was reported. Hetero-coupling was shown for the first time possible. This reaction can be simply handled in air and no pre-treatment of substrate and solvent is necessary. Interestingly our reaction protocol activated by a suitable acidic solvent and does not require any Ag salt to enhance the reactivity.[38] Remarkable functional groups tolerance has been shown in our reaction conditions. This double CH-functionalization reaction is in principle the most efficient

process for the synthesis of biaryls. From the reaction pattern showed by electrophilic amination of *p*-xylene, the mechanism of gold catalyzed CH-functionalization is still unclear and an interesting area. Studies of the reaction mechanism are undoubtedly a currently fruitful area for the next generation of gold catalysis.

General Procedure for $HAuCl_4$ Catalyzed Homo-coupling of Arenes: To a 10 mL vial arene (10 mmol), $PhI(OAc)_2$ (1 mmol), $HAuCl_4$ (0.02 mmol) and acetic acid (1 mL) were added. The mixture was stirred for 17 h at 55 ºC and then quenched with water (10 mL). The reaction mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layer was washed with saturated $NaHCO_3$ (2 x 20 mL), brine (10 ml), dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography to afford the desired product.

General Procedure for $HAuCl_4$ Catalyzed Hetero-coupling of Arenes with Benzene: To a 10 mL vial arene (5-15 mmol), benzene (1-10 mmol), $PhI(OAc)_2$ (1 mmol), $HAuCl_4$ (0.02 mmol) and acetic acid (1 mL) were added. The mixture was stirred for 17 h at 95 ºC and then quenched with water (10 mL). The reaction mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layer was washed with saturated $NaHCO_3$ (2 x 20 mL), brine (10 ml), dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography to afford the desired product. Analytically pure sample was obtained by thin layer chromatography of the purified product.

General Procedure for Catalytic amination of Arenes: To a 10 mL vial arene (10 mmol), diisopropylazodicarboxylate (1 mmol), catalyst (0.05 mmol) and appropriate solvent (1 mL) were added. The mixture was stirred for 17 h at 55 ºC, cooled and quenched with water (10 mL). The reaction mixture was added dodacane (internal standard, 55 μL), stirred for 15

minutes, extracted with EtOAc and the organic layer was to GC analysis to determine the yield. The analytically pure sample of **44** was prepared by known literature method[39] to calibrate the GC machine.

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Abstract

This dissertation deals with the synthesis of novel bioactive derivatives of the natural occurring hymenialdisine. As a part of this project, a solvent-free, efficient, and easy to handle diversification strategy for annulated hymenialdisine-type bisindoles was developed. A C-C bond-formation reaction on activated silica under mild reaction conditions starting from aziridines, epoxides or hydroxyl compounds is the key technology. The versatility of different aziridines as key building blocks was demonstrated with H-, O-, and N-nucleophiles in a diversity oriented synthesis to build up a focused chemical library. Furthermore, novel transition metal mediated introduction and transformation of functional-groups for potential application in the synthesis of novel drug candidates were developed.

Die vorliegende Dissertation beschäftigt sich mit der Synthese von neuartigen biologisch-aktiven Derivaten des Naturstoffes Hymenialdisin. Dafür wurde eine lösungsmittelfreie, effiziente und einfach zu handhabende Diversifizierungsstrategie für die Synthese von Hymenialdisin-artigen Bisindolen entwickelt. Durch den Aufbau von C-C Bindungen auf aktiviertem Kieselgel unter milden Reaktionsbedingungen wurden die Zielprodukte ausgehend von Aziridinen, Epoxiden oder Alkoholen erhalten. Der flexible Einsatz verschiedener Aziridine als Schlüsselbausteine konnte durch Umsetzungen mit H-, O-, und N-Nukleophilen beim Aufbau einer fokussierten Substanzbibliothek gezeigt werden. Ein zweiter Schwerpunkt der Arbeit lag in der Entwicklung neuer Übergangsmetall-vermittelter Reaktionen für die Einführung und Transformation von funktionellen Gruppen für deren potentielle Anwendung in der Synthese biologisch aktiven Verbindungen.