CHEMICAL REVIEWS

Review

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Indoles in Multicomponent Processes (MCPs)

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CONTENTS

1. INTRODUCTION

Indoles are widely distributed in nature, many of which display important biological activities; moreover, a vast number of natural and synthetic indoles have found applications as pharmaceuticals and agricultural chemicals.[1] Therefore, the synthesis[2] and functionalization[2b,3] of indoles have been the object of research for over one and half century.

In the last two or three decades the emphasis on and applications of green chemical principles, introduced some significant advances in organic synthesis, such as combinatorial chemistry, multicomponent processes (MCPs), organofluorine chemistry, organocatalysis, microwave synthesis and sonochemistry, etc. Among these new developments MCP techniques (including multicomponent reactions (MCRs) and one-pot multicomponent reactions) played a leading role and the field experienced tremendous developments.[4] MCR is defined as a process in which three or more different starting materials react together and/or sequentially to yield ideally a major product. Another variation of MCPs involves sequential addition of three or more different compounds in two or more steps to the same reaction vessel, entitled one-pot multicomponent reactions.

In the process consequent target molecules are isolated without purification and with minimal side products. Some advantages of MCPs involve minimization of the requisite reagents, solvents, cost, and time. Other advantages, which make MCPs an effective tool for synthetic chemists, are ease of separation and also minimizing the formation of chemical waste.

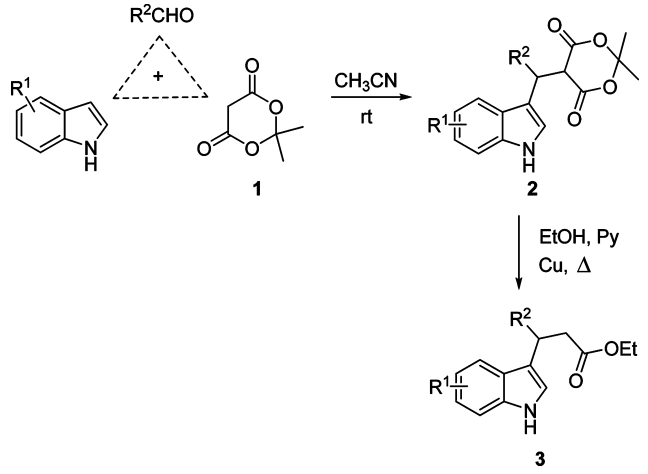
It appears that the term "MCR" was coined by Tsepalov in 1961.[5] Nevertheless, the principle was already applied as far back as 1850 in a Strecker report.[6] The first four-component reactions were developed in 1959 by Ugi et al. This appeared to have refreshed the interest in MCRs.[7] Since then MCRs have found useful applications in the construction of valuable organic molecules as well as in the construction and functionalization of indoles.[8] In this review, we wish to summarize the most important MCRs and one-pot MCR reactions in which either one of the starting materials or one of the product molecules are indole derivatives. The review will also present MCRs and one-pot reactions in the synthesis of indole alkaloids.[9]

2. FUNCTIONALIZATION OF INDOLES BY MCPS

Rediscovery of the MCR one-pot reaction initiated a flood of investigations to determine the possibility to apply MCR technology to some of the traditional reactions that require two or three steps, leading to very exciting and valuable results. Carbon−carbon bond formation reactions in the field of alkylation of indoles were mainly targeted utilizing different pathways. A large variety of substituents were investigated.

Yonemitsu et al. was the first group to report the successful 3-CRs of indoles with Meldrum's acid **1**[10] and various aldehydes (Scheme 1).[11] Subsequent decarboxylative ethanolysis of adducts

Scheme 1. Yonemitsu Reaction



2 led to various ethyl 3-substituted indolyl-propionates **3** used as intermediates in the synthesis of complex indole alkaloids (Scheme 1).[12]

Liu et al. conducted this reaction by means of solid-phase synthesis and they used a polymer-supported cyclic malonic acid ester, indole and aldehydes in the MCR.[13] Upon completion of condensation reaction, the trimolecular adducts

Received: October 13, 2011
Published: March 5, 2012

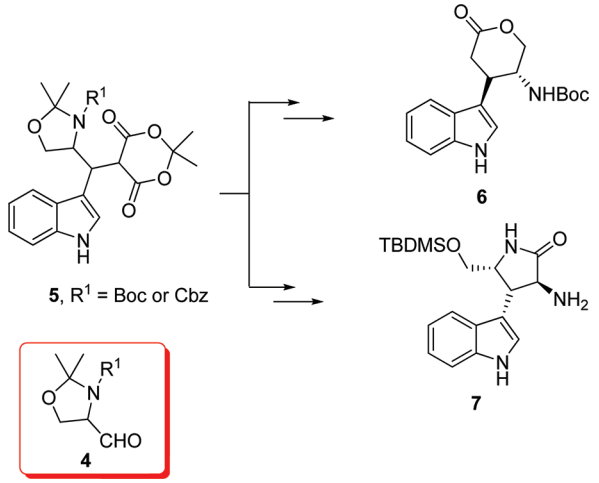
   dx.doi.org/10.1021/cr2003954 | Chem. Rev. 2012, 112, 3508–3549

were cleaved with pyridine/EtOH to release the final products in good yield and with high purity.

As a result, the Yonemitsu reaction was successfully applied and extended to various complexes of alkyl- or phenyl-ring-substituted indole derivatives, which proved to be a useful method in the synthesis of complex indole alkaloid precursors.[14]

For example, employment of Garner's aldehydes **4** in this reaction with the corresponding indole derivatives **5** are converted through a series of different steps to the chiral 2′,3′-pyranone(pyrrolidinone)-fused tryptamines **6** and **7** (Scheme 2).[15]

Scheme 2. Application of the Yonemitsu Reaction to Synthesize Chiral Tryptamines 6 and 7



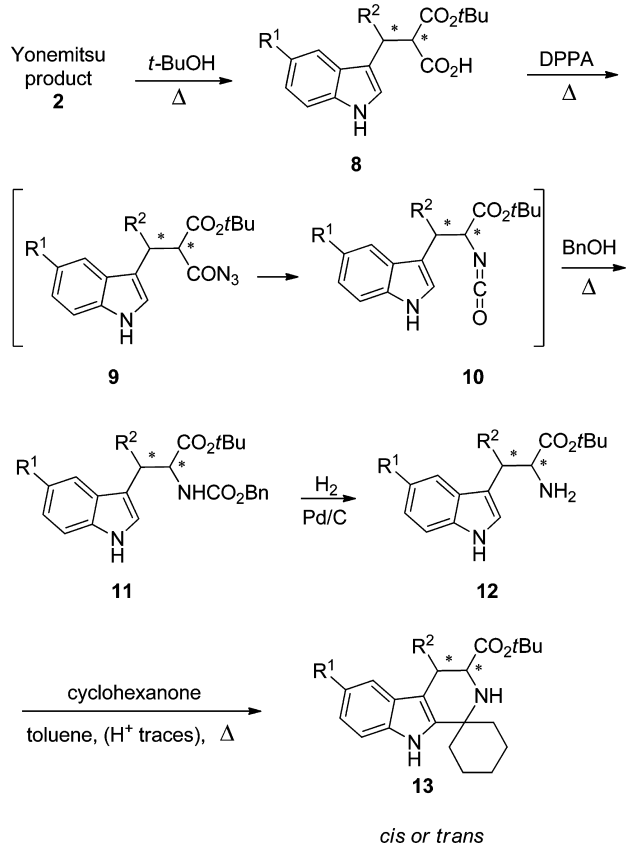
Also Nemes et al. found that the Yonemitsu products **2** are hydrolyzed by *t*-BuOH to the hemiacid esters **8** (Scheme 3).[16] The latter are transformed to carbamates **11** via a classical Curtius rearrangement mediated with diphenylphosphoryl azide (DPPA). The intermediate corresponding acylazides **9**, are subjected to a Curtius rearrangement to afford the isocyanates **10**. Isocyanate intermediates **10** are converted to carbamate esters **11** by the addition of benzyl alcohol in high yields. Debenzylation of the carbamate esters **11** through catalytic hydrogenation produces the amino esters **12**. Utilization of the Pictet-Spengler cyclization strategy with cyclohexanone affords *cis*- and *trans*-tetrahydro-carbolines **13** (Scheme 3).

Three-component condensation followed by cyclization of indoles, via the sugar aldehyde **14**, and Meldrum's acid catalyzed by proline lead to 7-(1*H*-3-indolyl)-2,3-dimethoxyperhydrofuro[3,2-b]pyran-5-ones **15** (Scheme 4).[17] Expectedly, when an *O*-protected sugar is used, the non-cyclized product **16** is isolated (Scheme 4). The reaction of chiral sugar-derived aldehydes takes place in good yield and with high diastereoselectivity.[18]

Deb and Bhuyan[14a] used barbituric acid **17** instead of Meldrum's acid in alternative strategy to obtain the Yonemitsu products **18** while bisindolyl methanes (BIMs) **19** form as side products (Scheme 5). In the presence of protic solvent the yield of BIMs is increased.[14a,19]

A plausible mechanism for the acid catalyzed-condensation of indole with aldehydes to BIMs **19** via the formation of

Scheme 3. Synthesis of Tetrahydro-carbolines



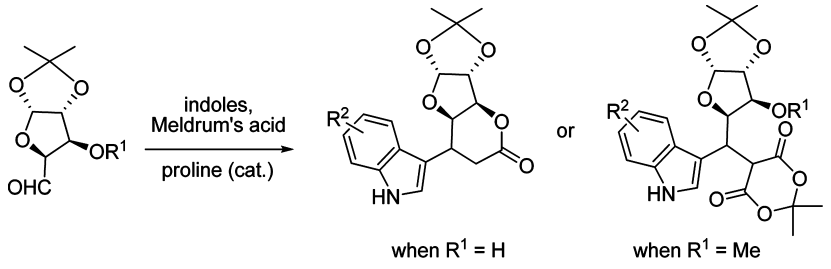
azafulvenium **20** are presented in Scheme 6.[3a] Azafulvenium **20** may be subject to additional nucleophilic attack by indoles or also to other nucleophiles present in the reaction media. It is noteworthy to mention that indoles and aldehydes in the presence of TFA/Et_3SiH give 3-alkylindole which is most probably converted to intermediate **20** via elimination of water.[20] However when indoles and aldehydes and imines are exposed to H_2, 2,3- chiral disubstituted indolines[21] and 2-alkyl indole[22] are isolated via an efficient Pd catalized tandem reaction. The reactions of indoles with ethers give a variety of symmetric and unsymmetric 1,1-bis-indolylmethane derivatives via iron-catalyzed C−H bond oxidation and C−O bond cleavage.[23] In addition manganese chloride tetrahydrate was found to be effective for the selective transformation of indole, 3,4-dihydropyran and *β*-keto ester to the corresponding BIM.[24]

The Yonemitsu methodology was extended to the synthesis of polyfunctionalized indole derivatives by a $TiCl_4$/Et_3N-promoted trimolecular condensation of aldehydes, indoles,and various activated carbonyl compounds by Renzetti et al. (Scheme 7).[25] Rationalization of these reactions and extension of it to other heterocyclic systems were also described.The same condensation of indoles, aldehydes and dimethyl malonate,[26] ethyl acetoacetate,[27] or nitroalkanes[28] were reported.

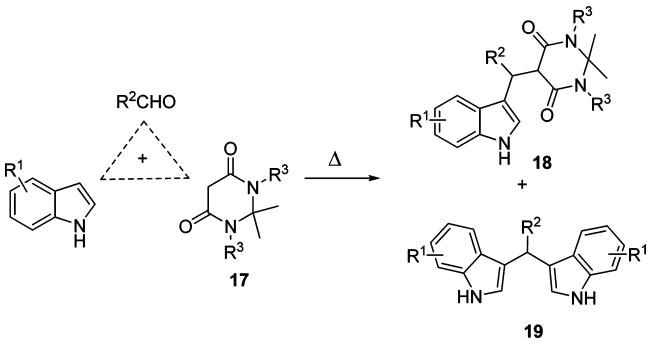
The variation in product distribution of trimolecular condensation of indoles with aldehydes and methyl acetoacetate in the presence of Ti(IV) and under different conditions were investigated.[29] Catalyzing the reaction with $TiCl_4/Et_3N$ or $TiCl_2(O\text{-}iPr)_2/Et_3N$ gives only Yonemitsu product **21** but with $TiCl_4/Et_3N$ and extended reaction time, the tricyclic

dx.doi.org/10.1021/cr2003954 | *Chem. Rev.* 2012, 112, 3508–3549

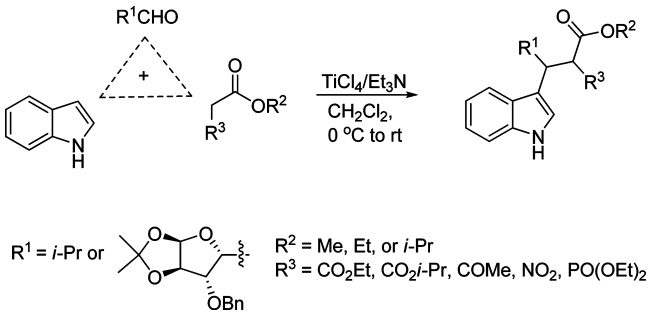
Scheme 4. Sugar Aldehydes in Yonemitsu Reaction



Scheme 5. Formation of BIMs 19 as By-product in a Yonemitsu-type Reaction



Scheme 7. Extension of the Yonemitsu Reaction to Other Activated Carbonyl Compounds



cyclopenta[*b*]indole **22** is the dominant product (Scheme 8). It appears that the intermolecular Friedel–Crafts reaction of **21** is efficiently catalyzed with $TiCl_4$ to yield the tricyclic compound **22**.

The reaction of *β*-dicarbonyl compounds such as 4-hydroxycoumarin or triacetic acid lactone, and indole in the presence of an aldehyde lead to the corresponding trimolecular condensed materials **23** and **24** respectively (Figure 1).[30] The reaction shows a surprising dependence on the solvent, with 1:1 chloroform-water giving the best yield of **23** and **24**.[30] Earlier, the same method was employed to convert special 3-substituted indoles such as **23** and **24** to form the corresponding adducts **25**. The product exhibits antibacterial activity (Figure 1).[31]

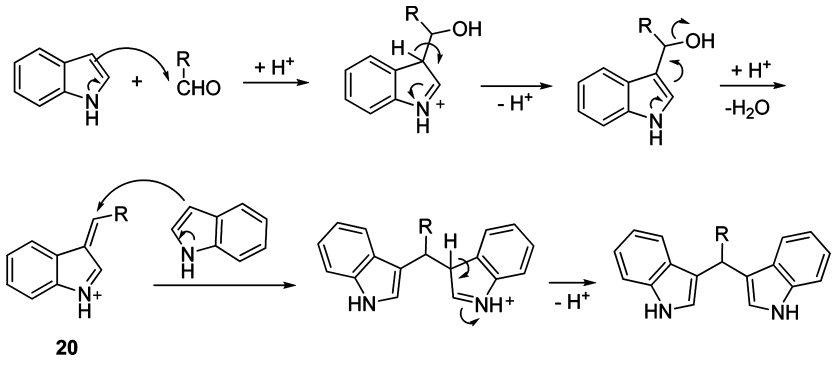
In a two-step sequential strategy involving green chemistry principles arylhydrazine reacts with methyl aroylacetate to form 1,3-disubstituted 5-pyrazolones in glycerol at 110 °C for several hours. Treatment of indoles and paraformaldehyde under the same conditions leads to the isolation of the corresponding indolyl derivatives **26**–**28** in good yield (Figure 2).[32]

Sapi and co-workers successfully prepared 1,2,3,4-tetrahydrocarbazoles **29** utilizing condensation of 2-substituted indoles, Meldrum's acid and 2 equivalents of aldehydes in the presence of proline in high yields (Scheme 9).[33] This method was used for the synthesis of a large library of carbazols; their biological capacities were examined.[34]

Perumal reported an efficient approach in which a three-component condensation of salicaldehyde derivatives, malononitrile and indoles, catalyzed by $InCl_3$[35] or L-proline forms indolyl chromanes **30** (Scheme 10).[36] This protocol was extended to 2-hydroxynaphthalene-1-carboxaldehyde, indole and malononitrile. The effectiveness of the reaction of indoles, aldehydes and malononitrile in aqueous media was reported by Qu et al.[37] Also the enantioselective version of reaction have been reported.[38]

A method for the synthesis of *β*-indolylketones **32** in good yields via condensation of indoles, aromatic aldehydes, and

Scheme 6. Mechanism of BIMs Formation via Azafulven 20



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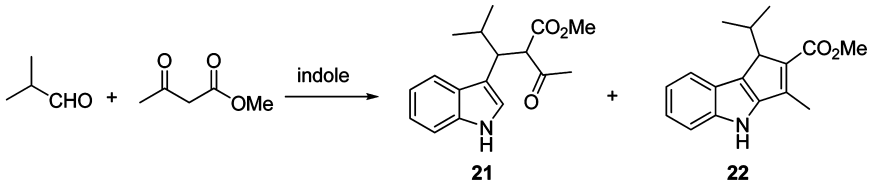
Scheme 8. Ti(IV)/Et_3N-Promoted Trimolecular Condensation



Conditions	Yield (%)	Yield (%)
$TiCl_4$, Et_3N, CH_2Cl_2, 3 Å, 0 °C to rt, 30 min	45	0
$TiCl_4$, Et_3N, CH_2Cl_2, 3 Å, 0 °C to rt, 3 h	trace	48
$TiCl_2(O\text{-}iPr)_2$, Et_3N, CH_2Cl_2, 3 Å, 0 °C to rt, 3 h	40	0
$TiCl_2(O\text{-}iPr)_2$, Et_3N, CH_2Cl_2, 3 Å, 0 °C to rt, overnight	45	0

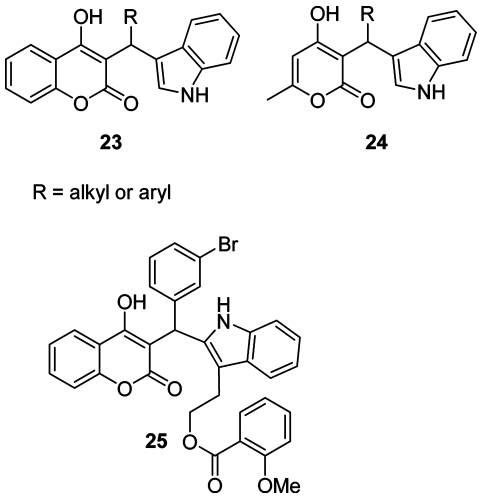


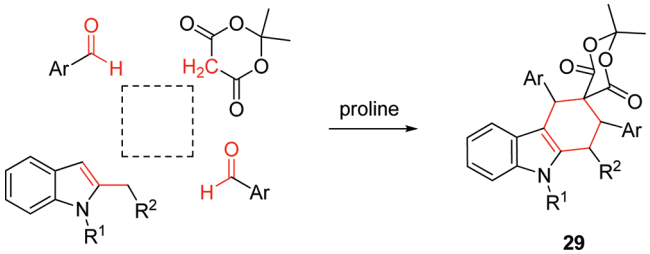
Figure 1. Cyclic β-dicarbonyl in Yonemitsu reaction.

deoxybenzoin **31** with ultrasonic irradiation was described by Shen et al. (Scheme 11).[39] This one-pot process proceeds smooth and efficient in alkaline ethanolic solution.

3-(1-Arylsulfonylalkyl) indoles **35** were generated from the three-component condensation of indoles, aldehydes or ketones, and arenesulfinic acids **33** (Scheme 12).[40] *para*-Toluenesulfonic acid-mediated azafulvenium **34** formation *via* condensation of carbonyls and indoles followed by the addition of arenesulfinic acids **33** sufficiently yield 67−95% 3-(1-arylsulfonylalkyl) indoles **35** (Scheme 12). The obtained products **35** undergo a Reformatsky reaction leading to alkyl 3-(3-indolyl) ketones **36**.

The reaction of isoxazole **37**, aldehydes and indoles in the presence of BuLi leads to the formation of indole derivatives **40**. The latter are easily hydrolyzed in aqueous alkaline media in a one-pot process to form valuable compounds such as indole 3-propionic acids **39** in good yield (Scheme 13).[41] The

Scheme 9. Synthesis of Carbazoles 29



reaction most probably leads to the formation of styrylisoxazole **38** via activation of the methyl group in the oxazole **37** with BuLi followed by a condensation reaction with aldehyde. This method also works well for 7-azaindoles.

Alternatively, El Kaim et al. demonstrated that phenols react with aldehydes and *N*-benzylpiperazine **41** in toluene at 110 °C to give the Mannich adduct **42** as intermediate. The adduct can without isolation directly be converted to indolyl derivatives **43** in moderate yields when it is refluxed in toluene with 1,2-dibromoethane and 1-methylindole (Scheme 14).[42]

In a sequential process hemiaminal ether **44** and ene-carbamate **45** in the presence of the chiral catalyst (*R*)-**46** (binaphthol derived phosphoric acid), form the hemiaminal product **46** which undergoes reaction with indole to afford the syn-product (**48**) in good yield and in nearly optically pure form; albeit with moderate syn diastereoselectivity (Scheme 15).[43] The extremely high enantioselectivity observed for syn-**48** could be attributed to double asymmetric induction arising from an ideal matching between the respective chiralities of the optically active product (**47**) and the catalyst (*R*)-**46**.

Condensation of indoles, formaldehyde, and tertiary aromatic amines catalyzed by silica-supported perchloric acid ($HClO_4$−SiO_2) to form dialkylaminoarylated indoles were described by

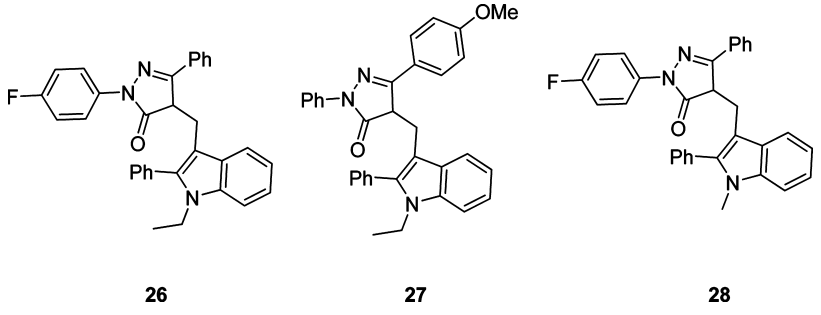


Figure 2. Structure of indolyl derivatives **26**−**28**.

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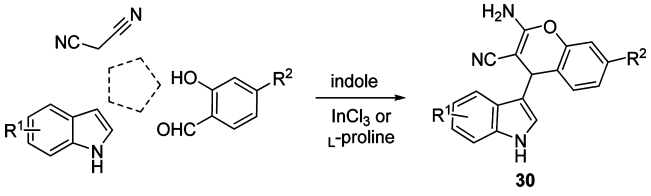
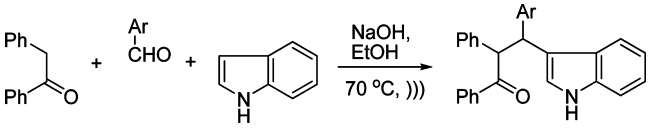
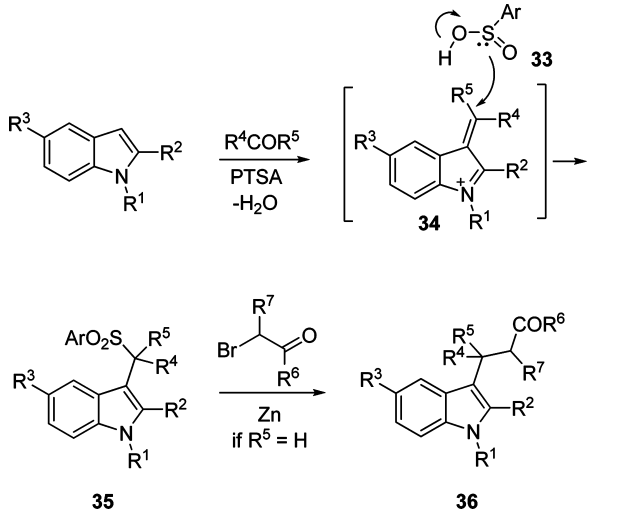
Scheme 10. Indolyl Chromanes 30 Formation Through MCRs



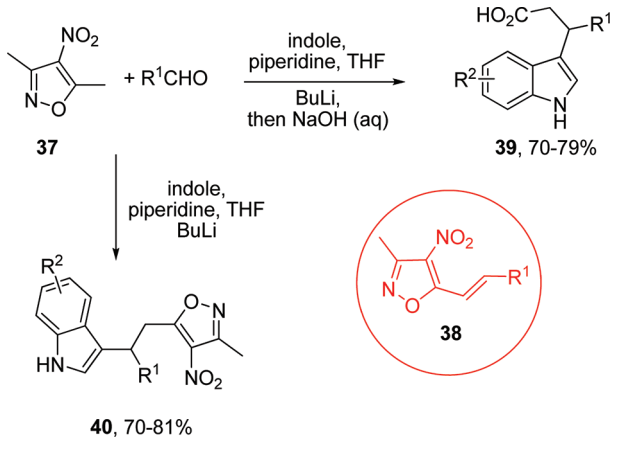
Scheme 11. Deoxybenzoin Formation in a Yonemitsu Reaction



Scheme 12. 3-(1-Arylsulfonylalkyl) Indoles

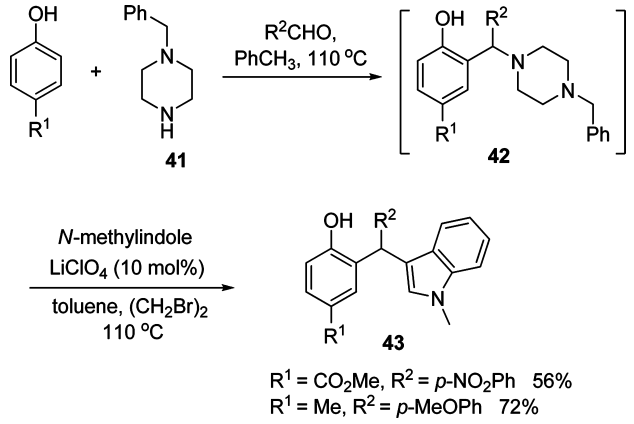


Scheme 13. One-Pot Synthesis of Indole 3-Propionic Acids 39 and Indole Derivatives 40

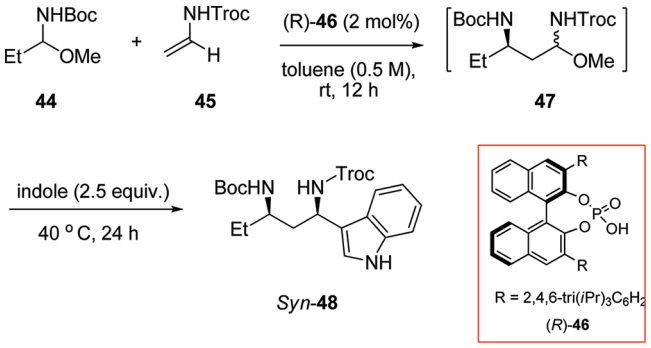


Kumar et al.[44] The proposed mechanism shows that the arylamine in the *para*-position is condensed with formaldehyde to give the iminium salt **49**. The latter is then subjected to

Scheme 14. *N*-Methylindole and Mannich Products

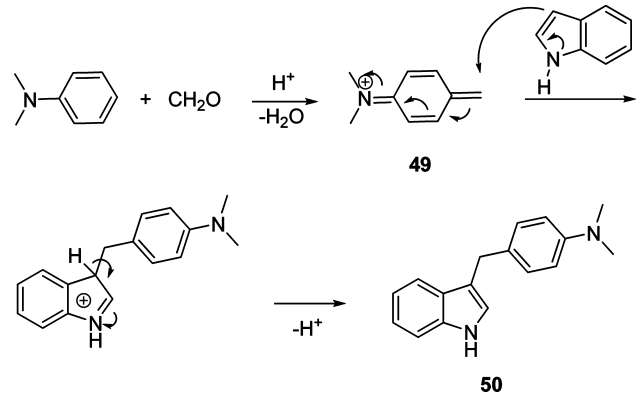


Scheme 15. Access to Enantio-Enriched 1,3-Diamine Derivatives of Indole



nucleophilic attack by an indole unit that finally produces the 3-alkylated indole **50** in good yield (Scheme 16). The

Scheme 16. Mechanism for Indole, *N,N*-Dimethylaniline, and Formaldehyde Condensation



promotion of this reaction by ruthenium was reported,[45] and Liu et al. extended this reaction to other aldehydes using $FeCl_3$ as catalyst.[46]

In a modification of the Mannich reaction (condensation of amines, aldehydes, and activated aryls), Petasis successfully used aromatic or alkenylboronic acids instead of activated aryl compounds.[47] The Petasis reaction provides a selective approach to the synthesis of special molecules. After that indoles were proposed as substrates for the Petasis boronic acid-Mannich reaction, providing a practical synthetic route for

dx.doi.org/10.1021/cr2003954 | *Chem. Rev.* 2012, 112, 3508–3549

C−C bond formation in α-(*N*-substituted indole)carboxylic acids **51**−**56** from corresponding indoles, ethyl glyoxylic acid and aromatic or alkenylboronic acids (Figure 3).[48] In this

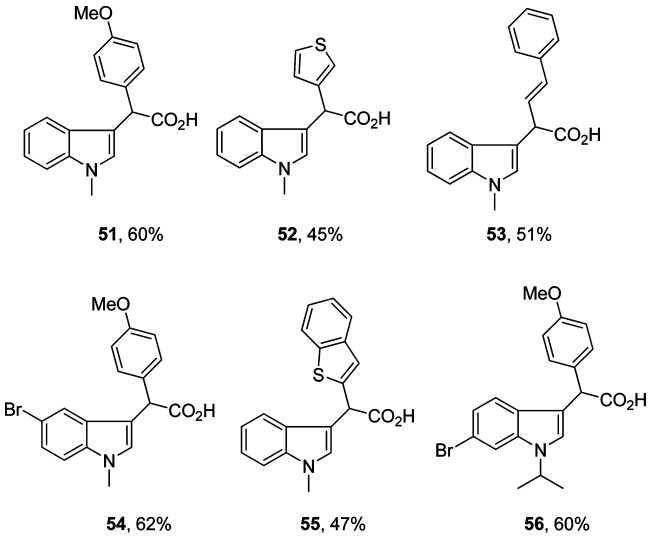
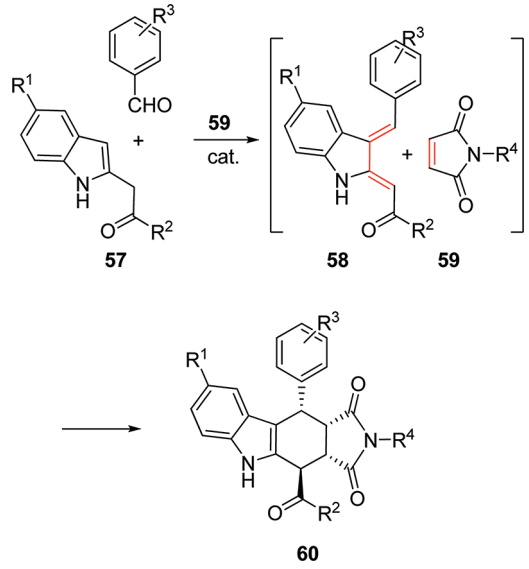


Figure 3. Products from condensation of indoles, aryl or alkenylboronic acids, and glyoxylic acid.

reaction a *N*-substituted indole replaces the amine component in the original Mannich reaction, yielding products in which two carbon−carbon bonds are formed during the multicomponent condensation.

Aryl-pyrrolo-tetrahydrocarbazoles **60** are isolated with ease from the three-component reaction of 2-substituted indoles **57**, aldehydes and maleimides **59** in the presence of $CuSO_4$ as a catalyst (Scheme 17).[49] It appears that the diene **58**, generated

Scheme 17. Synthesis of Pyrrolo-tetrahydrocarbazoles



from the condensation of indole **57** and aldehyde followed by H-shift,[50] reacts with the dienophile **59**. By changing the starting materials and through some modification of the sequence of the reaction a large diversity of compounds **60** was generated. These compounds disrupt protein−protein interactions and its activity was evaluated.[51]

Similarly indole **61**, 3,4,5-trimethoxyacetophenone **62** and maleimides **63** participate in a multicomponent reaction in protic media to yield tetrahydrocarbazoles **64** and the corresponding carbazoles **65** (Scheme 18).[52] Tetrahydrocarbazoles **64** in the presence of dichlorodicyanoquinone (DDQ) are oxidized to carbazoles **65** (Scheme 18).[53] Ty et al. have investigated the biological activity of **64** and **65** in terms of antivascular action, the cytotoxicity against murine B16 melanoma cells, the rounding up of endothelial cells (EA.hy 926) and the inhibition of tubulin polymerization.[53]

The eco-friendly and one-pot Mannich reaction of aldehydes, primary amines, and indoles in water is catalyzed by $C_9H_{19}COOH$ as a surfactant-type catalyst,[54] and was reported by Shirakawa and Kobayashi (Scheme 19).[55] Catalyst and solvent free version of this reaction but under thermal condition has been reported.[56]

However, the majority of these reactions involved the use of catalysts including phosphomolybdic acid (PMA) on silica gel under solvent-free conditions,[57] $ZnCl_2$ in ethanol,[58] acidic alumina under microwave irradiation,[59] acetic acid with reflux conditions,[60] ionic liquids,[61] $Yb(OTf)_3$-SiO_2,[62] bromodimethylsulfonium bromide (BDMS),[63a] L-proline,[63b] and also by 2,4,6-trichloro-1,3,5-triazine (TCT) in CH_3CN.[64] Under high pressure conditions indoles react with dichloromethane and secondary amines to give the corresponding Mannich products of 2-aminomethylindoles **66** in moderate to good yields (Figure 4).[65] Aldehydes in the presence of $LiClO_4$ react with Me_3SiNMe_2 to give the corresponding iminium salts that undergo addition of electron-rich aromatic compounds, leading to Mannich type products.[66] Zhang demonstrated the functionalization of resin-bound indoles utilizing the same process.[67]

McFarland et al. used the Mannich product of **67**, obtained from the condensation of 3-methylindole, formaldehyde and aniline in a phosphate buffer at pH = 6.5, as a model for characterization of proteins by isotopic labeling and NMR-based studies (Figure 5).[68] Adduct **67** is formed by the addition of 3-methylindole in position 1 to the imine from corresponding amine and formaldehyde.

Similarly to this unique Mannich type reaction, the trimolecular condensation of 2-methylindole, benzaldehyde and ethanol in basic solution gives the ether **68** (Scheme 20).[69] The latter is unstable and is converted to the fulvalene **69** in free-base media (Scheme 20).[3a]

3-CR of indole, ethyl glyoxylate **70** and anilines to form the acetate **71** was first reported by Passerini (Scheme 21).[70] Since valuable products are obtained through this method, it became quite a prominent reaction. It is well worth to mention the condensation of indoles, aniline and glyoxyl acid catalyzed with ytterbium triflate,[71] also under catalyst-free conditions in water[72] as well as solvent-free conditions.[73]

Secondary indolyl amines **72** are isolated in excellent yields from indole, 3-formyl chromone and corresponding anilines catalyzed by indium triflate under microwave irradiation while the corresponding bisindolyl methane **73** is obtained in poor yields (Figure 6).[74] Indium triflate was recovered after the reaction and reused in the subsequent experiments.

Zhang et al. developed a highly enantioselective organocatalytic process employing the Friedel−Crafts aminoalkylation of indoles with imines generated in situ from trifluoroacetaldehyde methyl hemiacetal and aniline.[75] They employed the chiral phosphoric acid **74** as an efficient catalyst (Figure 7). A series of fluorinated indole derivatives **75**−**79** were obtained

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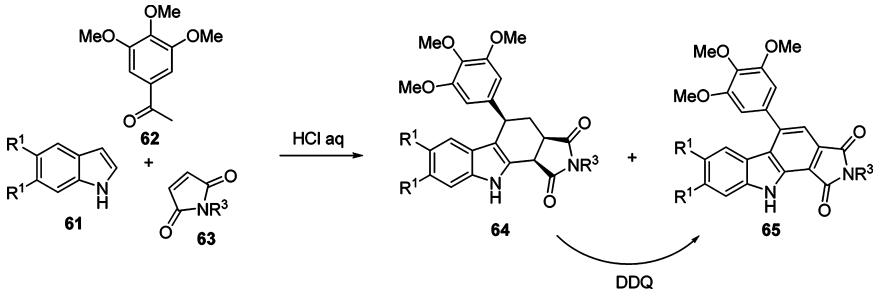
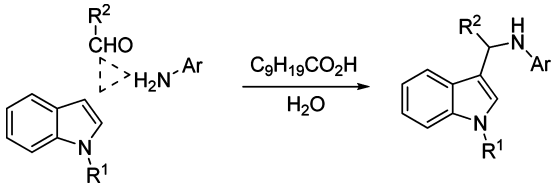
Scheme 18. Synthesis of Tetrahydrocarbazoles 64 and Carbazoles 65



Scheme 19. Modified One-Pot Mannich Reaction



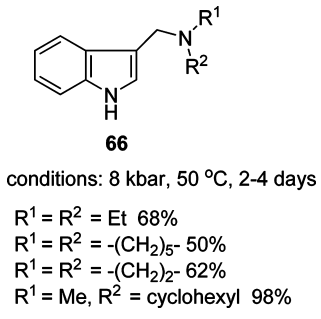


Figure 4. Mannich products under high pressure conditions.

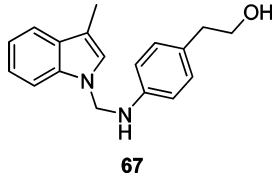
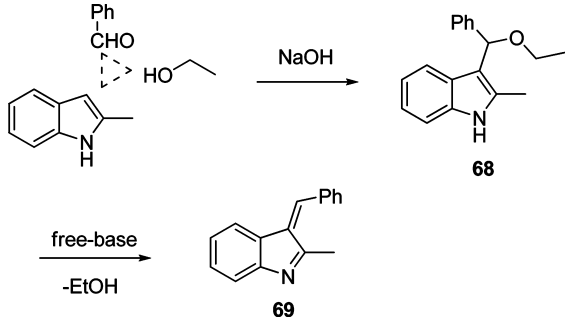


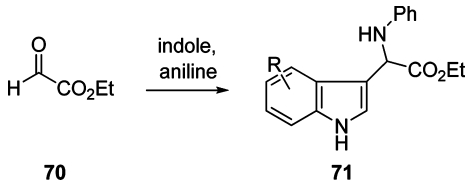
Figure 5. Structure of the Mannich product **67**.

Scheme 20. Base-Catalyzed Condensation of 2-Methylindole, Benzaldehyde, and Ethanol



in high yields with excellent enantioselectivities (Figure 7). This methodology was further extended to include difluoroacetaldehyde methyl hemiacetal which enable a broad scope of new

Scheme 21. Indoles in a Mannich-Type 3-CR



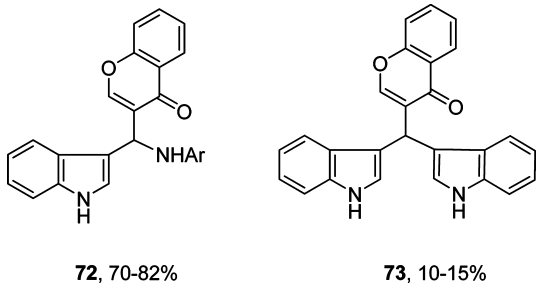


Figure 6. Products of indole, 3-formyl chromone, and anilines.

substrates. This reaction also with another chiral binaphthol phosphoric acid **74** (9-phenanthryl instead of 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$) also gives promising results.[76]

Desimmoni and his group discovered that the reaction of aniline, indole and ethyl glyoxylate in the presence of Sc(OTf)$_3$ gives a mixture of complicated products such as **80**, **81**, and **82** (Table 1), depending on the reaction time and temperature.[77] As shown in Table 1, when aniline, indole and ethyl glyoxylate react at −50 °C for 8 h mainly produced the product **80** in 95% yield (Table 1, entry 1). The same reaction at room temperature and also after 8 h gives a lower overall yield, and **82** (48%) is the major product even though an appreciable amount of **80** (38%) is still isolated (Table 1, entry 2). The behavior of o-anisidine at different temperatures is quite different. After 30 min and at low temperature it solely gives the product **80**, but at room temperature and after 3 h the ethyl 2-(4-amino-3-methoxyphenyl)-2-(1*H*-indol-3-yl)acetate (**82**, R = OMe, Table 1) is isolated in 65% yield as the sole product (Table 1, entries 3 and 4). Successful rearrangements of **80** and **81** to **82** in the presence of Sc(OTf)$_3$ was also investigated.[77]

This group also reported the MCR of indole, ethyl glyoxylate and 3,4-dimethoxy- or 3,4-methylenedioxyanilines where the reactions are catalyzed by scandium triflate. This MCR gives two pairs of diastereomeric aza-Diels−Alder adducts (**84** and **85**). This appears to be a reaction in which the imines **83** behave as heterodienes and the indole as the dienophile (Scheme 22).[78]

dx.doi.org/10.1021/cr2003954 | *Chem. Rev.* 2012, 112, 3508−3549

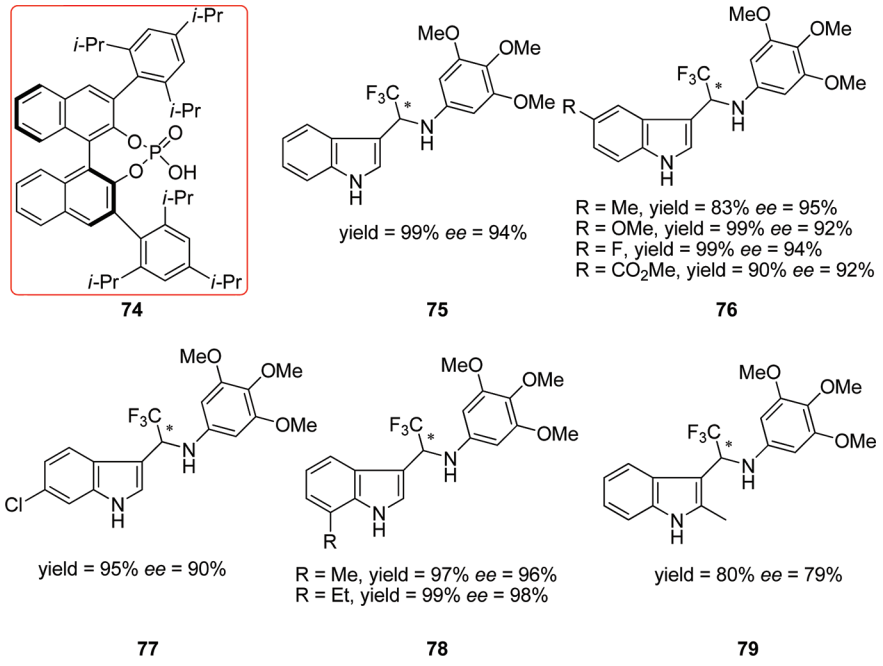
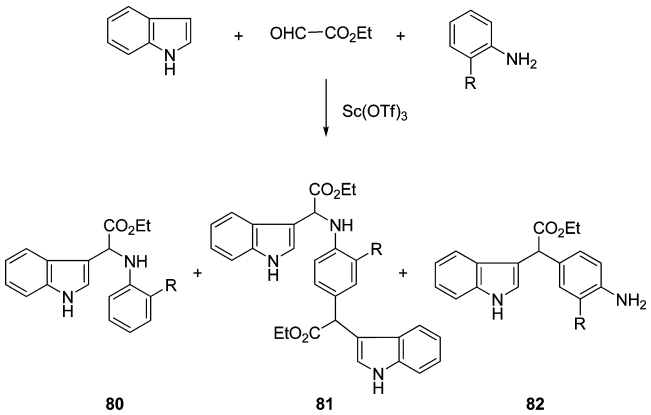


Figure 7. Asymmetric Mannich products via the chiral Brønsted acid **74**.

Table 1. $Sc(OTf)_3$ Mediated Reaction of Aniline, Indole, and Ethyl Glyoxylate

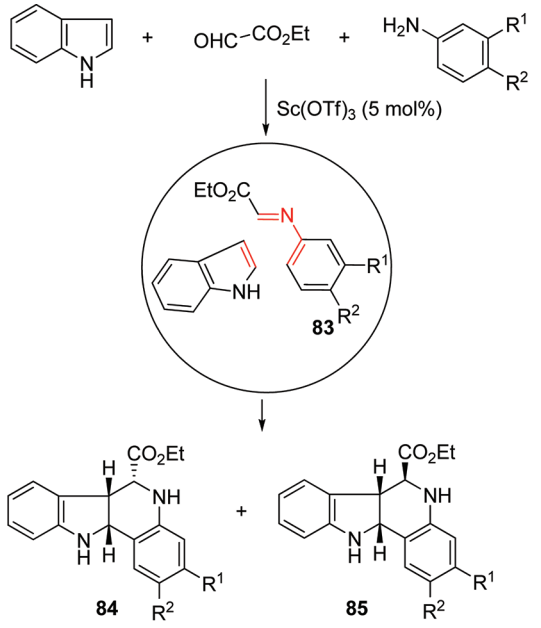


					product distribution (%)		
entry	R	time (h)	temp. (°C)	overall yield (%)	**80**	**81**	**82**
1	H	8	−50	92	95	2	3
2	H	8	rt	73	38	14	48
3	OMe	0.5	−50	92	100	–	–
4	OMe	3	rt	65	–	–	100

The aza-Friedel−Crafts reaction of indoles with aldehydes and thiourea gives compound **86** in good to high yields. The reactions is efficiently catalyzed by thiamine/HCl or $TiCl_4$ (Scheme 23).[79] The thiourea derivative **86** forms various polysubstituted 2-amino-1,3-thiazoles **87** during the Hantzsch cyclization of α-chloroketones (Scheme 23). The reaction is simple and allows for the introduction of at least three diverse functional groups which can be explored for the synthesis of multiple different compounds.

Ethyl glyoxylate, ethyl-4-amino-benzoate, and dihydropyridine-indole **88** unexpectedly yielded an indoloquinolizidine derivative **89** isolated as a racemic mixture and in 66% yield (Scheme 24).[80]

Scheme 22. Povarov Adducts 84 and 85 from 3-CR



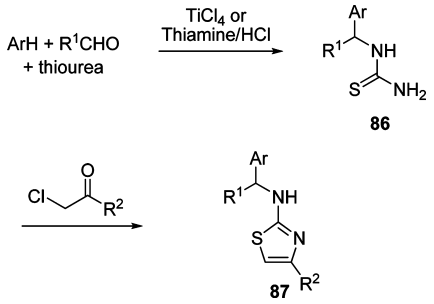
$R^1 = R^2$ = OMe, overal yield 83% (ratio **84**:**85** (7:3)) in 0.5 h at rt
$R^1 = R^2 = OCH_2O$, overal yield 75% (ratio **84**:**85** (85:15)) 1 h at -50 °C

The tetrahydropyridinium ion **91** is generated from the [4 + 2] cycloaddition of the *N*-alkenyl compound **90** and cyclohexene in a one-pot process. Further functionalization through nucleophilic addition of *N*-methylindole was achieved to yield the highly stereoselective adduct **92** in 53% (Scheme 25).[81]

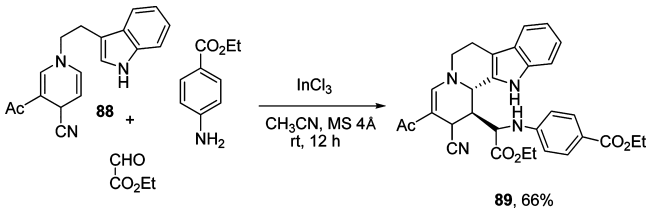
2-Alkynylbenzaldehyde **93**, *p*-toluidine and indole in the presence of Ag(I), Cu(II) and Pd(II) effectively yield 1-(1*H*-indol-3-yl)-1,2-dihydroisoquinoline **94** but with $FeCl_3$ and triflate

dx.doi.org/10.1021/cr2003954 | *Chem. Rev.* 2012, 112, 3508–3549

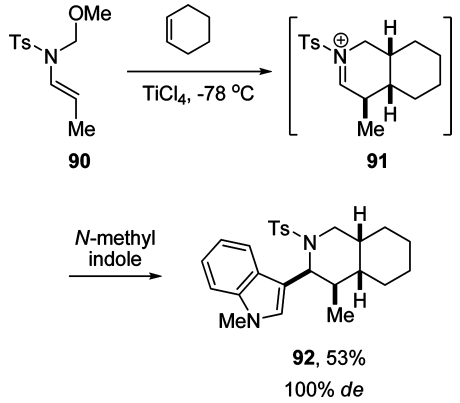
Scheme 23. Polysubstituted 2-Amino-1,3-thiazoles



Scheme 24. Intramolecular Approach to Indoloquinolizidine

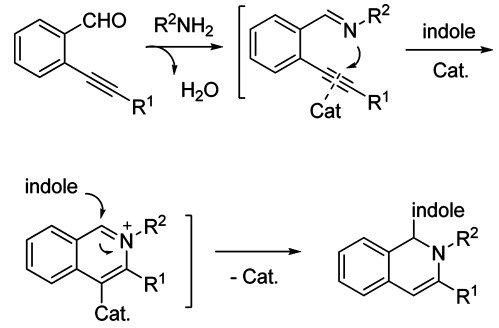


Scheme 25. One-Pot Diels–Alder and Mannich Reactions

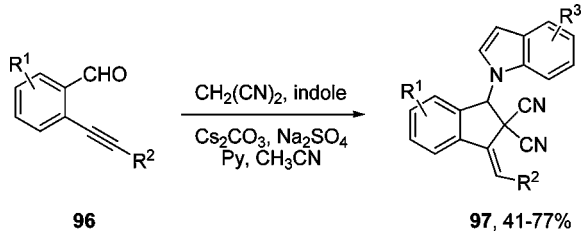


salts of Zn(II), Yb(III), Bi(III) and Dy(III) it solely gives the corresponding bisindolyl methane (BIMs) **95** (Scheme 26).[82a,b] The reaction of **93** with different heteroarenes in the presence

Scheme 27. Proposed Mechanism for the Condensation of 2-Alkynylbenzaldehyde, *p*-Toluidine, and Indole to the 1,2-Dihydroisoquinoline



Scheme 28. 3-CR of 2-Alkynylbenzaldehyde 96, Malononitrile, and Indole



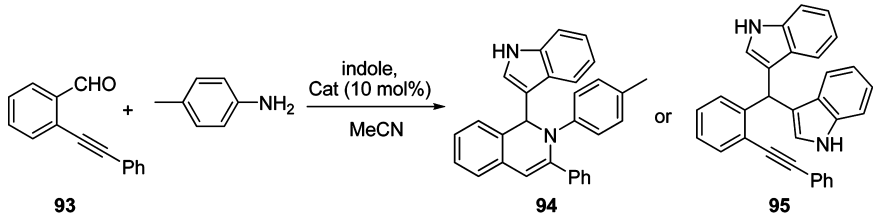
of bis(pyridine) iodonium tetrafluoroborate (IPy_2BF_4) gave functionalized 4-iodo-1H-isochromenes.[82c]

As shown in Scheme 27, the synthesis of 1,2-dihydroisoquinoline **94** most possibly occurs in two steps, first imine formation and then attack of the imine nitrogen to the alkyne followed by addition of indole to the carbon terminal of the imine group.[82a] Ag(I), Cu(II), and Pd(II) ions activate the alkyne in second step while several other salts are not effective catalysts.

In basic media, the indole nitrogen is deprotonated and then adds to the Knoevenagel adduct of aldehyde **96** and malononitrile (Scheme 28).[83] (*Z*)-1-Benzylidene-3-(1*H*-indol-1-yl)-1*H*-indene-2,2(3*H*)-dicarbonitriles **97** is selectively generated in moderate to good yields via tandem condensation, nucleophilic addition, and 5-exocyclization.

Yadav discovered coupling of indoles to quinoline and isoquinolines which are activated by dimethyl acetylenedicarboxylate

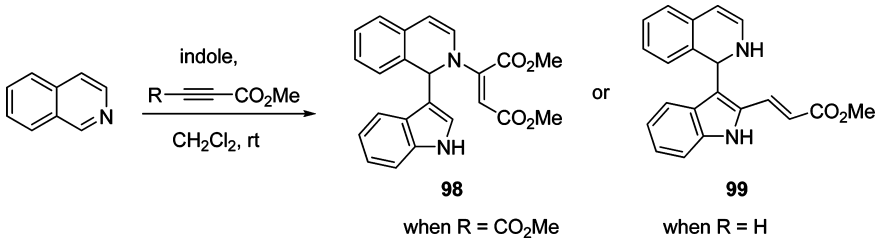
Scheme 26. Selective 1,2-Dihydroisoquinoline and BIMs Formation



Cat.	yield (%)	yield (%)
AgOTf	58	-
CuI	48	-
$Cu(OTf)_2$	48	-
$Pd(OAc)_2$	46	-
$FeCl_3$	-	86
$Zn(OTf)_2$	-	82
$Yb(OTf)_3$	-	83
$Bi(OTf)_3$	-	88
$Dy(OTf)_3$	-	85

dx.doi.org/10.1021/cr2003954 | *Chem. Rev.* 2012, 112, 3508–3549

Scheme 29. Coupling of Indoles and Isiquinolines



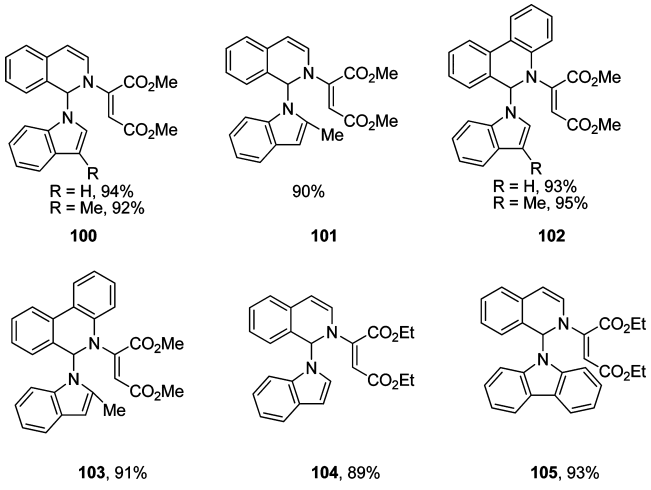
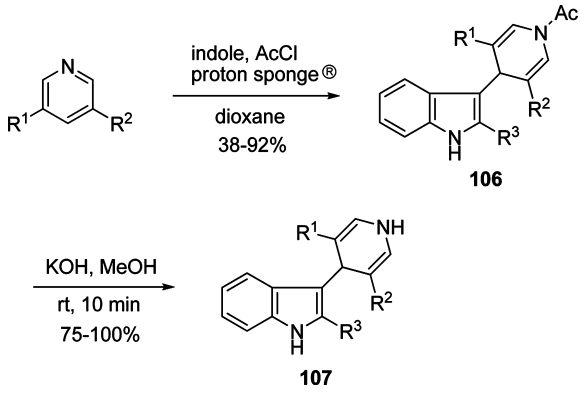


Figure 8. Compounds isolated from the condensation of dialkyl acetylenedicarboxylate, indoles, and isoquinoline or phenanthroline.

Scheme 30. 4-(Indolyl)dihydropyridines 107



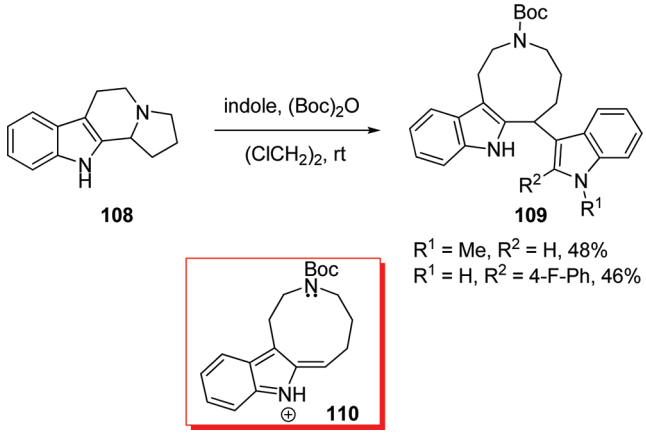
at room temperature without a catalyst to produce indolyl-dihydroquinoline and isoquinolines (Scheme 29).[84] Isoquinolines, dimethyl acetylenedicarboxylate, and indoles give dimethyl (*E*)-2-[1-(1*H*-3-indolyl)-1,2-dihydro-2-isoquinolinyl]-2-butenedioates **98** in excellent yields and with high selectivity (Scheme 29). When a terminal acetylene and methyl propiolate are used the major product is an indolyl compound **99** (Scheme 29).

In contrast to this report, it was found that indoles are added to the 1-position of isoquinoline or phenanthroline with similar starting materials but through C–N bond formation.[85] For example structures **100**–**105** have been reported for the condensation of the corresponding dialkyl acetylenedicarboxylate, indoles and isoquinoline or phenanthroline (Figure 8).

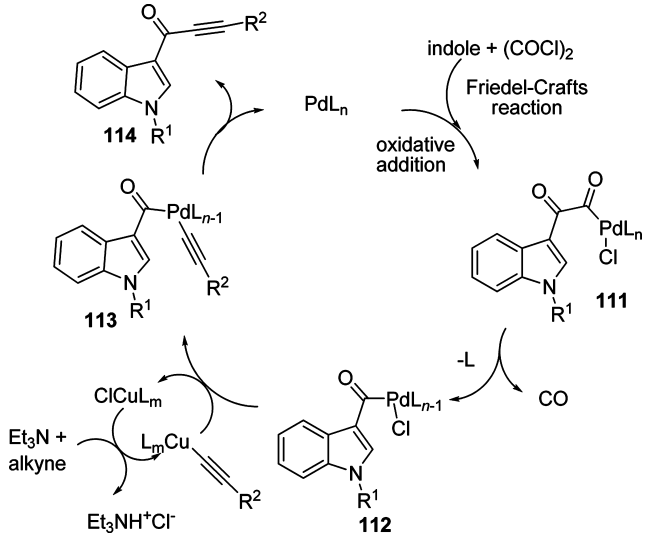
Pyridines in the presence of acetyl chloride and a proton sponge were activated to react with nucleophiles such as indole and is then converted to *N*-acyl dihydropyridines **106** (Scheme 30).[86] Subsequent treatment of **106** with alkaline methanol successfully yields (indolyl)dihydropyridines **107** in good to high yields. Similarly 1,4-diazines react with indole in the presence of acyl halides.[87] Such reaction could be promoted in the presence of triflic anhydride.[88]

Treatment of **108**[89] with Boc anhydride as the acylating agent, in the presence of *N*-methyl indole as well as 2-(4-fluoro)phenyl indole, allows for access to the corresponding *N*-Boc protected azonino[5,4-*b*]indoles **109** (Scheme 31).[90] Formation of the intermediate **110** is plausible by the activation

Scheme 31. *N*-Boc-azonino[5,4-*b*]indoles 109 via the Rearrangement of 108 with $(Boc)_2O$



Scheme 32. Mechanistic Rationale of the Decarbonylative Sonogashira Coupling



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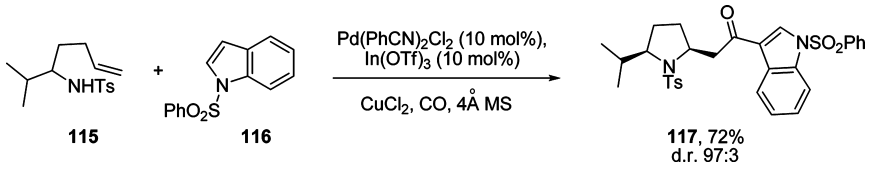
Scheme 33. One-Pot Synthesis of α-Pyrrolidinyl Ketones



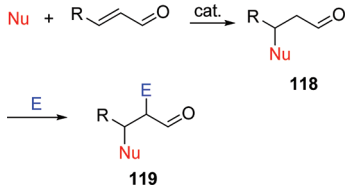
of **108** with $(Boc)_2O$; followed by addition of indole to **110**, forming product **109** (Scheme 31).

Müller and co-workers demonstrated a new consecutive trimolecular preparation of alkynones **114** *via* glyoxylation of indole, 7-aza-indole, and pyrrole derivatives with oxalyl chloride and subsequent Pd/Cu-catalyzed decarbonylative alkynylation of the heteroaryl glyoxylyl chlorides with terminal alkynes (Scheme 32).[91] The alkynones **114** are converted to pyrimidines in a subsequent transformation. The mechanistic pathway after Friedel–Crafts reaction of indole and $(COCl)_2$ and the oxidative addition of indole-3-glyoxylyl chloride to [Pd], adduct **111** involves a migratory deinsertion and elimination of carbon monoxide to furnish the acyl–Pd species **112** (Scheme 32). Then, transmetalation of the in situ generated copper acetylide to **112** gives rise to the formation of the acyl-alkynyl-Pd complex **113**, which undergoes Sonogashira coupling (reductive elimination) to yield the alkynone **114**. Previously in an alternative process starting from 3-iodoindoles, carbon monoxide and trimethylsilyl acetylene were also utilized for the preparion of similar compounds but in lower yields (see Figure 21).[92]

Cernak and Lambert disclosed a new multicatalytic system in which both an aminochlorocarbonylation and Friedel–Crafts acylation reaction are utilized for the synthesis of α-pyrrolidinyl ketones (Scheme 33).[93] For instance aminoalkene **115** and indole **116** in the presence of $Pd(PhCN)_2Cl_2$, $CuCl_2$, $In(OTf)_3$ under a carbon monoxide atmosphere give α-pyrrolidinyl ketone **117** in 72% yield (Scheme 33). Rh-catalyzed C–H carbonylation of indoles under 1 atm of CO has been achieved.[94] Various substituted indoles and indole with free N–H could be carboxylated with linear- or cyclic-alcohol to give the desired indole-3-carboxylates with up to 92% yield.

In a Michael-type addition of nucleophiles to α,β-enals, an α-methylene group of the produced aldehyde **118** is activated for reaction with electrophiles leading to a series of new model compounds **119** (Scheme 34).[95]

Scheme 34. Cascade Reaction of α,β-Enals with Nucleophiles and Electrophiles



MacMillan's group used this basic reaction in an impressive design of an effective organocatalytic synthetic approach. They established the highly enantioselective synthesis of indole derivatives **122–124** by employing an indoles as the nucleophile and Cl^+ as the electrophile (in situ generated from chlorinated

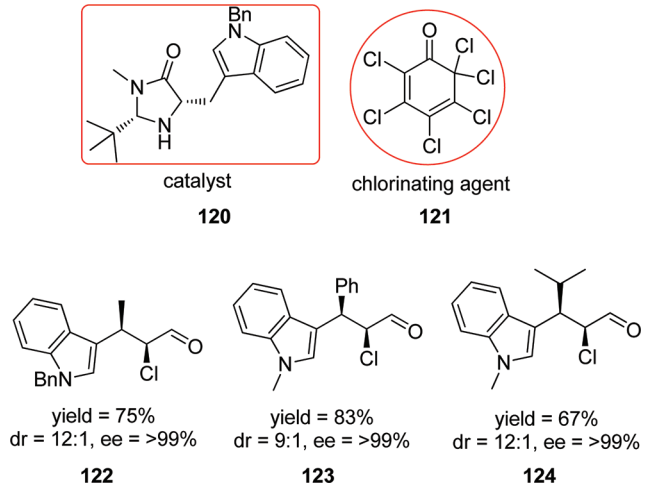


Figure 9. Products from a cascade of reactions via organocatalysis.

quinone **121**). They used imidazolidinone **120** as the organocatalyst (Figure 9).[95] The Amine **120** mediated chiral catalytic cascade reaction via formation of an iminium/enamine is presented in Figure 1.

After that, the group of Frechet proposed an iminium catalytic Michael addition of *N*-methylindole to hexenal and enamine addition of the intermediate to methyl vinyl ketone as outlined in the Figure 10.[96] They found that the combination of immobilized catalysts **125** (the salt of imidazolidinonium with polystyrene sulfonate) and polymer supported diphenylprolinol methyl ether **126** sufficiently catalyzed MCRs of *N*-methylindole, hexenal and methyl vinyl ketone. Also by addition of a *H*-bonding catalyst such as **127** dramatically increases the yield from 33% to 89% while the enantiomeric excess stay >99%.

Similarly, another organocatalytic based reaction was reported by Melchiorre and co-workers where indoles, α,β-enals and azocarboxylate react (Scheme 35).[97] Compounds **129** are efficiently prepared through the aminocatalytic activation of α,β-disubstituted enals. The use of catalyst **128** in which chiral induction though a primary amine facilitates the fusion of these substrates into valuable precursors for α-amino acids with very high enantiomeric purity. The amino acids have two adjacent stereogenic centers.

In a related study, Arai and Yokoyama developed a three-component tandem reaction with indoles, nitroalkenes and aldehydes to construct acyclic products with three contiguous stereocenters **131** (Scheme 36).[98] They found that the asymmetric ligand **130** when complexed to CuOTf efficiently catalyzes the domino reaction of a Michael-type addition of indole to nitrostyrene followed by the Henry reaction of the Michael-adduct with benzaldehyde. Diastereomer **131** is mainly isolated and **132** is also observed as minor product (Scheme 36). The addition of 1,1,1,3,3,3-hexafluoro-2-propanol

dx.doi.org/10.1021/cr2003954 | *Chem. Rev.* 2012, 112, 3508–3549

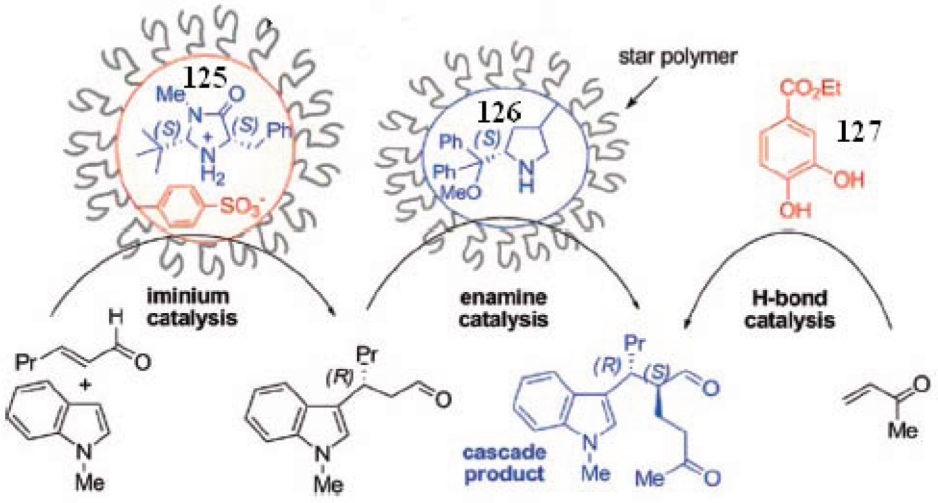
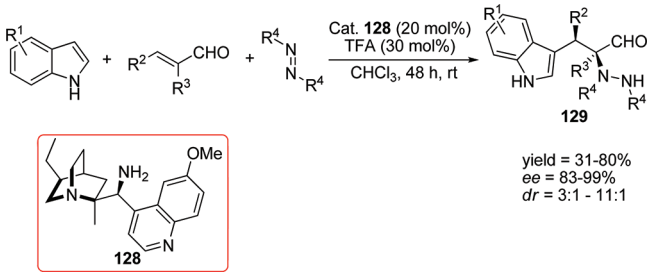
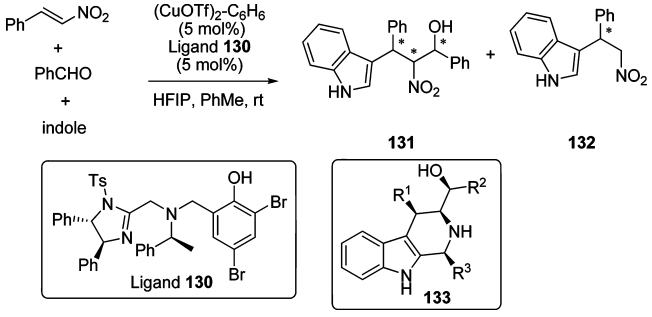


Figure 10. Polymer-based chiral catalysis for MCRs.

Scheme 35. Primary Amine 128 Catalyzed Cascade Reaction



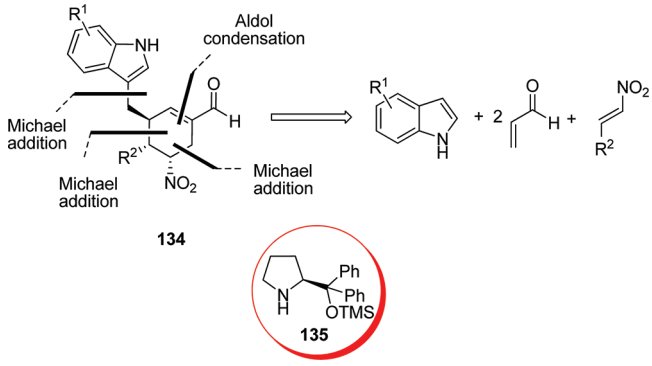
Scheme 36. Synthesis of a Three Contiguous Stereocenter Compound 131



(HFIP) was effective in enhancing the yield and to dramatically promote the stereoselectivity of the major product **131**. They also demonstrated that reduction of the nitro group in **131**, followed by Pictet–Spengler cyclization provided an efficient route for the synthesis of fully substituted chiral tetrahydro-β-carbolines (THBCs) **133** (Scheme 36).[99]

Enders' group reported an innovative asymmetric organocatalytic scenario in which various indoles, nitroalkenes and 2 equivalents of acrolein are condensed to yield 3-(cyclohexenylmethyl)-indoles **134** bearing three stereogenic centers in moderate to excellent yields (23–82%) and with excellent stereoselectivities (dr = 91: 9 to >95: 5, *ee* = 94 to >99%) (Scheme 37).[100] The diphenylprolinol TMS-ether **135**

Scheme 37. Retrosynthetic Analysis of the Domino Friedel–Crafts-type/Michael/Michael/Aldol Condensation Reaction



efficiently catalyzed this cascade reaction by an iminium/enamine/iminium/enamine activation sequence.

A similar cascade reaction was reported by Kobayashi et al. Indole reacts with two different vinyl ketones in the presence of 5–8 mol % of $Fe(BF_4)_2.6H_2O$ or $Fe(ClO_4)_3.nH_2O$ to give 2,3-dialkylated products **136–138** (Figure 11).[101] The first alkylation step proceeds very quickly, while the reaction rate of the second alkylation is very slow.

Bandini et al. in an innovative strategy have added indoles to the chalcones and then without purification, protected the Michael adduct with Me_3SiCN (Figure 12).[102a] This reaction is efficiently catalyzed by $InBr_3$ and opened a new route for the one-pot 1,4 and 1,2 addition of indoles to α,β-unsaturated ketones. With the optimized atom-efficient protocol, several polyfunctionalized α-silyloxy cyanohydrins were synthesized in good to excellent yields (up to 97%) (Figure 12). Applicability of such reaction in the presence of nanocrystalline titanium(IV) oxide has been examined.[102b]

para-Toluenesulfonic acid (PTSA) efficiently catalyzes the three-component coupling of indoles, styrenes and *N*-phenylselenophthalimide **139** yielding the corresponding seleno bearing indolyl compounds **140** in 63–95% yield (Scheme 38).[103]

Also, the organophosphosphorus compound **141** is obtained in excellent yield from indole, dialkyl acetylenedicarboxylate and triphenyl or trialkyl phosphite (Figure 13).[104] Although there are a few reactions of indole in the 1-position in this

dx.doi.org/10.1021/cr2003954 | *Chem. Rev.* 2012, 112, 3508–3549

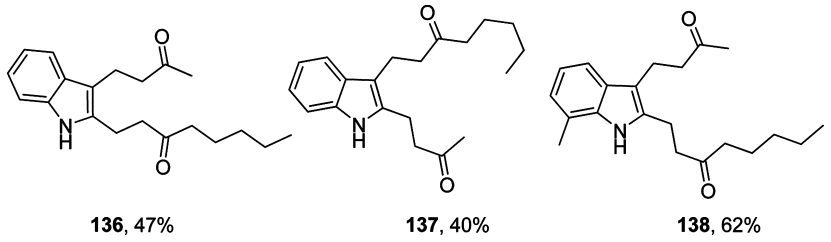


Figure 11. 2,3-Dialkylated indole via cascade Michael addition.

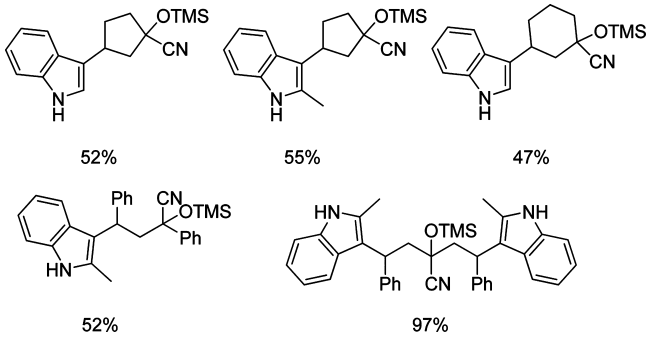
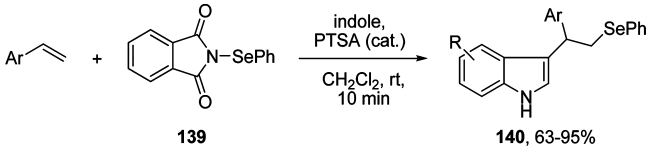


Figure 12. One-pot synthesis of polyfunctionalized α-silyloxy cyanohydrins.

Scheme 38. Indole-Containing Selenium Product



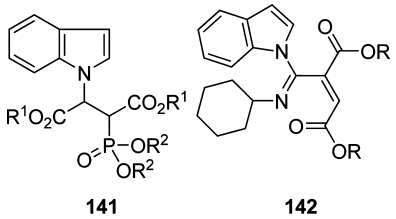


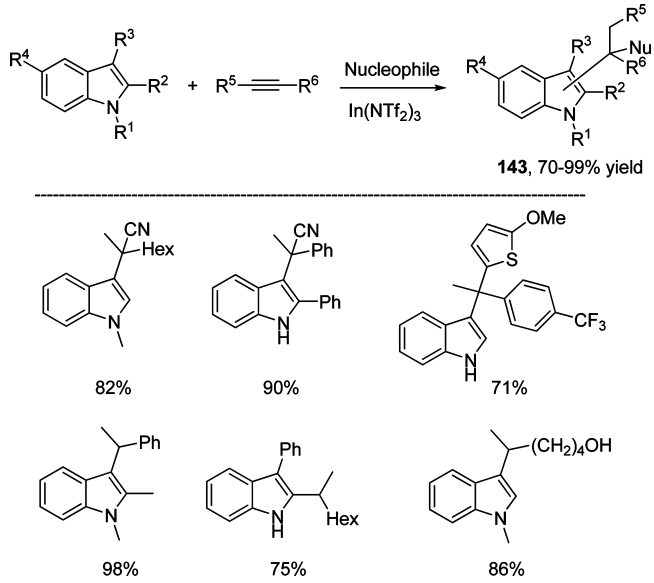
Figure 13. Examples of 1-indole type products.

context[104] an appropriate example is the reaction of indole, dialkyl acetylenedicarboxylate and cyclohexyl isocyanide to produce the aldimines **142** (Figure 13).[105]

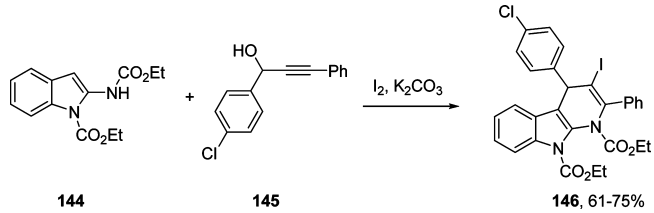
Alkynes activated by indium react with indoles and nucleophiles such as hydride, CN^- generated from $HSiMePh_2$ and Me_3SiCN to form alkylindole **143** in 70–99% yield (Scheme 39).[106] 2-Methoxythiophene is also used as a nucleophile in this reaction. When the 3-position on the indoles is blocked, then position-2 is functionalized. Also copper catalyzed reaction of indoles, sufonyl azides, and terminal alkynes led to the 3-functionalized indoles.[107]

A three component tandem reaction for the synthesis of diversified N^a N^b dicarbamate-4,9-dihydro-3-iodo-a-carbolines **146** have been described by Sharma et al. (Scheme 40).[108] The reaction involves a one-pot condensation of bis-carbamate indole **144** with disubstituted propargyl alcohols **145**, followed by iodocyclo-elimination of the N^b-linked carbamate under mild conditions in the final step. In the presence of ICl the full aromatic form of **146** was generated.

Scheme 39. Indium-Catalyzed Alkylation of Indoles with Alkynes and Carbon Nucleophiles



Scheme 40. Synthesis of Dihydro-α-carbolines 146

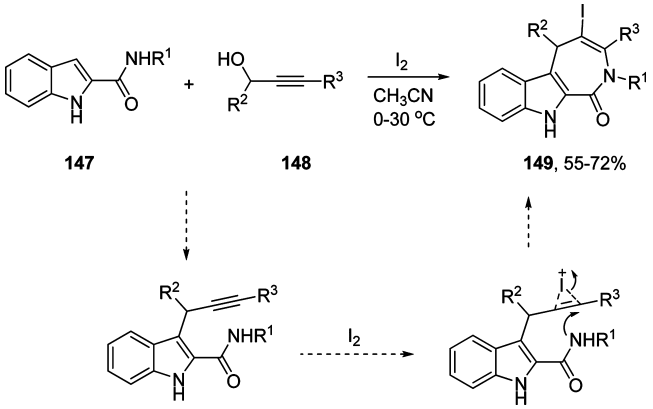


The same group also reported several other iodinemediated MCRs yielding the indoloazepinone scaffold **3** *via* a three component reaction of indole-2-carboxamides **147**, 1,3-disubstituted propargyl alcohols **148**, and I_2 (Scheme 41).[109] The proposed mechanism for this reaction involves activation of the hydroxyl group toward electrophilic substitution reaction by indole with iodine. Addition of iodine across the alkyne triple bond facilitates subsequent amide intramolecular cyclization to afford **149** in 55–72% yield (Scheme 41). Similarly, Rossi's group has reported the reaction of 2-acetyl indole, 1,3-disubstituted propargyl alcohols and amines in the presence of $InCl_3$ to yield 1-aminocarbazoles in 58–89%.[110]

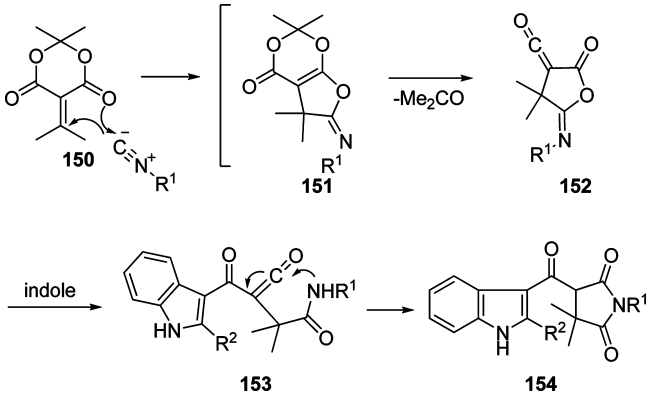
Yavari and Habibi provided a novel procedure for the synthesis of 2-oxo-pyrrole and 3-oxo-indole derivatives **154** (Scheme 42).[111] In this methodology isopropylidene Meldrum's acid **150** and isocyanide react via a [4 + 1] cycloaddition forming the intermediate iminolactone **151**. The latter looses

dx.doi.org/10.1021/cr2003954 | *Chem. Rev.* 2012, 112, 3508–3549

Scheme 41. MCR Involving Indole-2-carboxamide, 1,3-Disubstituted Propargyl Alcohol, and I_2



Scheme 42. 3-Component Approach to Obtain 3-Oxo-indole Derivatives 154



acetone to give the acyl ketene **152**. Addition of an indole to the lactone **152** induces cyclization of intermediate **153** to produce indolyl compounds **154** in 66−75% yield. Ren et al. have discovered that *N*-methylindoles are selectively transformed to their corresponding cyano derivatives in the 3-position via a palladium-catalyzed system in the presence of NH_4HCO_3 and DMSO.[112] It is worthy to note that the cyano group appears to originate from both DMSO and NH_4HCO_3 under these conditions. This novel approach serves as a safe source for cyanide and it can potentially be used in other cyano addition reactions.

N-Substituted indoles in the presence of Selectfluor as the electrophilic fluorinating reagent and some nucleophiles such as H_2O via difluorohydroxylation and alcohols via difluoroalkoxylation respectively led to the 3,3-difluoroindolin-2-ols **155**−**157** and their alkoxy derivatives **158**−**160** in good yields (Figure 14).[113]

3. SYNTHESIS OF INDOLE DERIVATIVES VIA MCPS

The MCRs technique caused significant advances in the construction of indoles, first by effective modification of traditional reactions such as the Fischer indole synthesis and second by planning new pathways for the synthesis of indoles. For example, a protocol described by Simoneau and Ganem involves formation of imines or ketones from nitriles or carboxylic acids. These intermediates then react with organometallic reagents and subsequent Fischer indole cyclization with an arylhydrazine hydrochloric acid salt to yield various

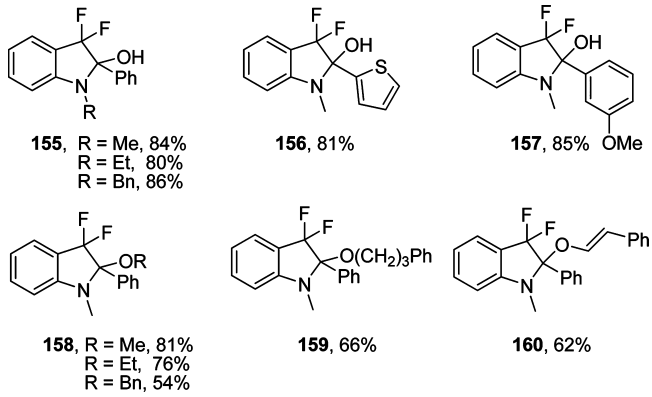
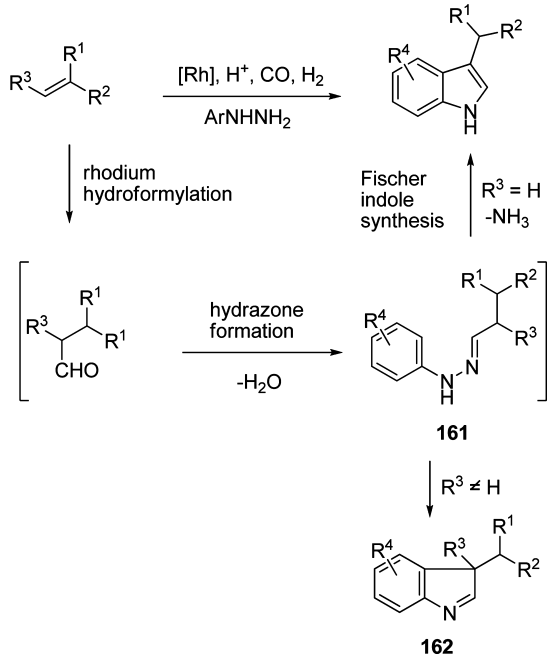


Figure 14. Difluorohydroxylation of indoles.

indole derivatives.[114] A modified approach to obtain *N*-arylindoles was developed by successive coupling of two different aryl bromides to arylhydrazones, followed by cyclization with an enolizable ketone in a 3-component process.[115]

A novel tandem rhodium-mediated reaction involving hydroformylation of olefins in an atmosphere containing both CO and H_2, followed by the Fischer indole synthesis with arylhydrazines **161**, was the key to the synthesis of highly desirable indolyl structural motifs (Scheme 43).[116]

Scheme 43. One-Pot Hydroformylation and Fischer Indole Synthesis



Following this methodology it was found that if 1, 2-substituted alkenes were used, then indolenine intermediates **162** form. An acid-catalyzed Wagner−Meerwein-type rearrangement of the latter results in selective substitution at the 3-position. Selective substitution of the 2- and 3-position, lead to 2,3-disubstituted indoles **163** or **164** in good to excellent yields (Scheme 44).[117]

Another modification *via* titanium-catalyzed regioselective hydroamination of alkynes **165** with aryl hydrazines followed

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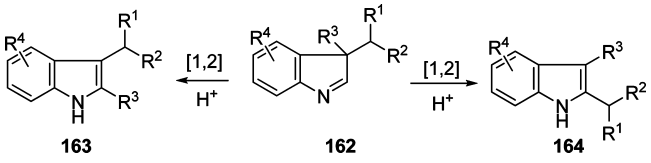
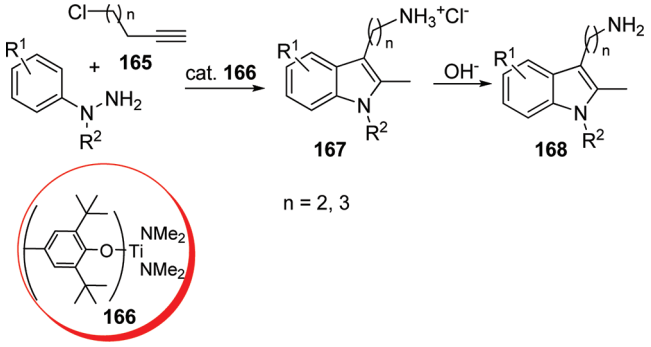
Scheme 44. Wagner−Meerwein-Type Rearrangement



by Fischer cyclization gives the indolyl hydrochloride salt **167** in good yield (Scheme 45).[118] It is worthwhile to point out that

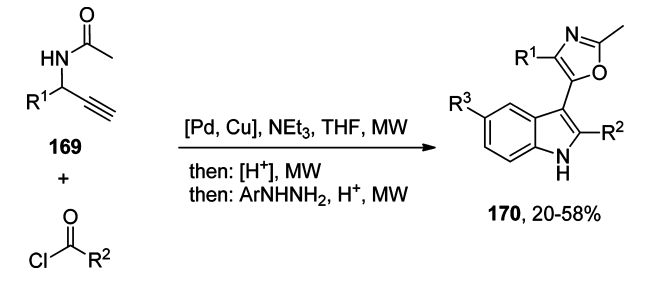
Scheme 45. Titanium-Mediated Indole Synthesis



ammonia separates from hydrazine in the course of the cyclization. Substitution of chlorine is then subsequently achieved by ammonia floating in solution. Neutral substituted 3-(2-aminoethyl)- and 3-(3-aminopropyl)indoles **168** products are readily obtained when the salts **167** are washed in alkaline media. Three-component coupling between acyl chlorides, diazonium salts, and alcohols or amines allows the formation of α-hydrazono carboxylic acid derivatives which may be directly converted to indoles by means of a Fischer-type cylization.[119] In addition, highly functionalized tryptamine derivatives via a Fischer indole type pathway using 2-methyl-1-pyrroline, acetyl chloride, phenylhydrazine, has been reported.[120]

Müller and co-workers have established a novel method for the preparation of aryl substituted 5-(3-indolyl)oxazoles **170** involving Sonogashira coupling of **169** and acyl chlorides, sequentially cycloisomerization followed by Fischer indole synthesis under microwave irradiation (Scheme 46).[121] Interestingly aryl substituted 5-(3-indolyl)oxazoles **170** exhibit blue luminescence.

Scheme 46. One-Pot Three-component Synthesis of Indolo-oxazoles



Boruah and his group have developed a modified Nenitzescu reaction for the synthesis of 5-hydroxy-2,3-disubstituted-benzo-[g]indoles **171**−**174** (Figure 15).[122] In this reaction naphthoquinone and acetophenones bearing aza-heterocycles are present, however the NH groups of indole originates from urea

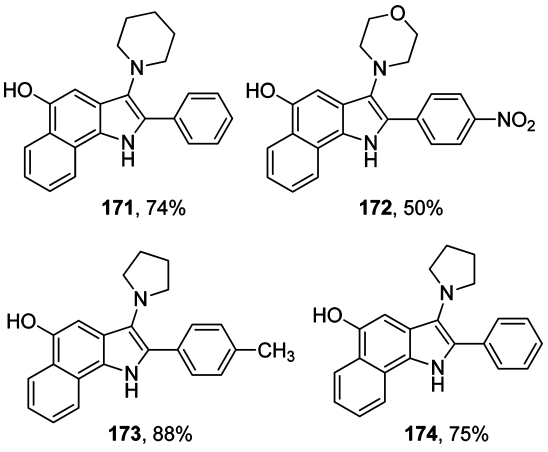
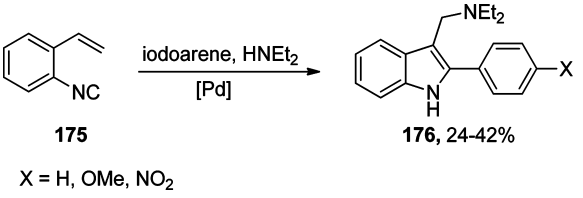


Figure 15. Benzo[*g*]indoles formation.

under microwave irradiation without solvent. The reaction is efficiently catalyzed with BF_3OEt_2. Very recently a multicomponent reaction leading to polyfunctionalized indoles and bis-indoles was established by Jiang et al.[123]

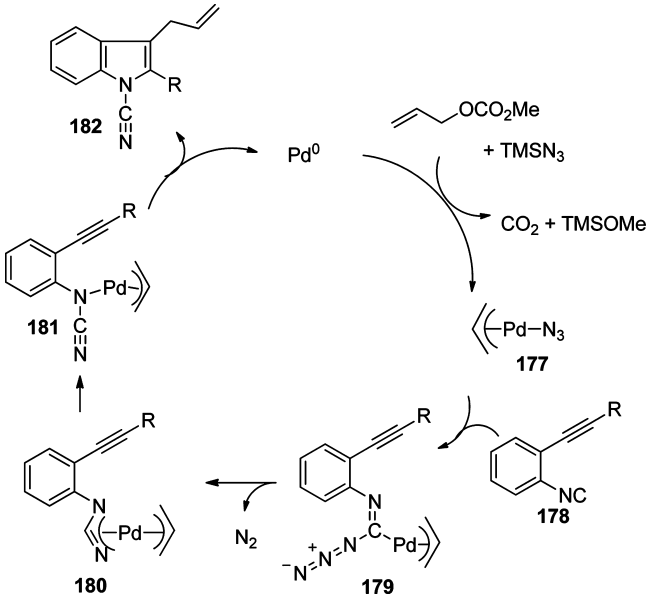
A new MCR approach was revealed involving the one-pot reaction of gramine derivatives **176**, *o*-alkenylphenyl isocyanide **175**, diethylamine, and iodoarenes catalyzed by palladium (Scheme 47).[124]

Scheme 47. Gramine Derivatives Formation



The palladium-catalyzed coupling of 2-alkynylisocyanobenzenes **178**, allyl methyl carbonate and trimethylsilyl azide leads to *N*-cyanoindoles **182** (Scheme 48).[125] A plausible mechanism

Scheme 48. Proposed Mechanism for the Formation of *N*-Cyanoindoles



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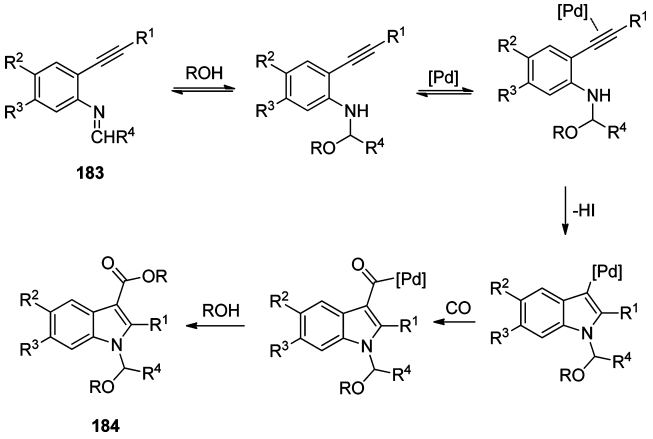
involves the generation of π-allylpalladium azide **177** from allyl methyl carbonate and $TMSN_3$ (Scheme 48). Insertion of isocyanide **178** between the Pd−N_3 bond in the π-allylpalladium azide **177** then yields the π-allylpalladium **179**. Elimination of N_2 and 1,2-migration of the π-allylpalladium moiety from the carbon atom to the α-nitrogen atom lead to the formation of **180**. The palladium-carbodiimide complex **181** forms via intermediate **180** and subsequent insertion of the alkyne moiety to the Pd−N bond. Finally at 100 °C the *N*-cyanoindoles **182** are isolated via intermediate **181** followed by the reductive elimination of Pd^0.

A novel multicomponent cascade process was reported by Gabriele et al. involving a sequential combination of an initial nucleophilic attack (ROH) to an imine moiety **183** and a palladium-catalyzed oxidative heterocyclization-alkoxycarbonylation process (Scheme 49).[126] In this new process, four simple

Scheme 49. Proposed Reaction Mechanism for the Formation of 1-(Alkoxyarylmethyl) indole-3-carboxylic Esters 184 from 2-Alkynylaniline Imines 183



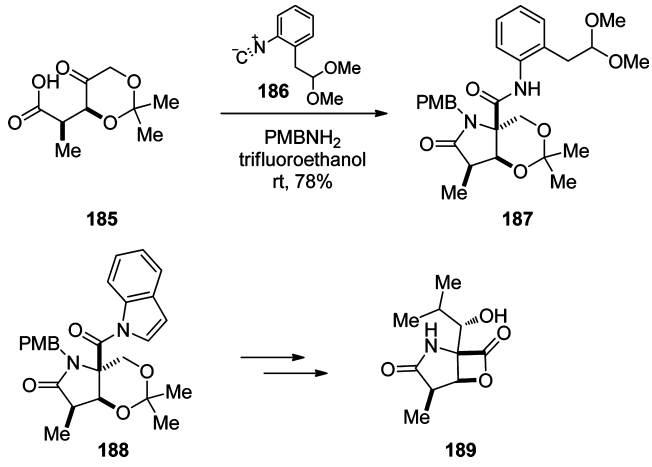
183 **184**

molecules [alcohol, carbon monoxide, alcohol, and oxygen] sequentially and selectively react with the 2-alkynylaniline imine starting structure, leading to high value-added functionalized indole derivatives **184** in a single operation catalyzed by oxygen activated Pd^0. A chemo- and the regio-selectives tandem hydroformylation of substituted alpha nitrocinnamaldehydes leading to indoles has been reported.[127a] Acetoxyindoles were obtained by cyclocarbonylation of 3-pyrrolyl acetates in the presence of Ac_2O and a catalytic amount of $PdCl_2$ under 50−70 atm of CO.[127b]

In a careful study, construction and elimination of indole played an important role in the synthesis of highly functionalized lactones (Scheme 50).[128] For example, the Ugi stereocontrolled condensation of acid **185**, isocyanide **186**, and *p*-methoxybenzylamine ($PMBNH_2$) leads to the formation of **187**. Cyclization of the latter under thermal conditions forms the *N*-acylindole intermediate **188** and hydrolysis of the hindered amide **188** facilitates the preparation of the omuralide **189**.[129] Rhoden et al. successfully used this strategy in the synthesis of *N*-substituted diketopiperazines.[130]

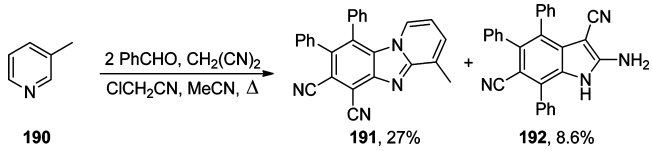
A four-component strategy was designed for the synthesis of polysubstituted pyrido[1,2-*a*]benzimidazole derivatives **191** from 3-picoline **190**, chloroacetonitrile, malononitrile, and benzaldehyde in refluxing acetonitrile. Interesting byproduct such as polysubstituted indole **192** forms in 8.6% yield (Scheme 51).[131] The mechanism of this novel reaction appears to involve the

Scheme 50. Construction and Elimination of Indole in the Synthesis of Omuralide 189



185 **187** **188** **189**

Scheme 51. Polysubstituted Indole 190 as By-product in the Synthesis of the Benzimidazole 189

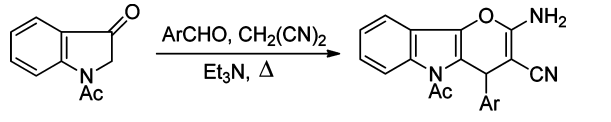


190 **191**, 27% **192**, 8.6%

formation of polysubstituted benzenes with a subsequent substitution and annulation reaction of pyridine.

Condensation of acetylindol-3(2*H*)-one **193**, malononitrile and aldehydes leads to 5-acetyl-2-amino-4-aryl-3-cyano-4*H*-pyrano-[3,2-*b*]indole **194** in the presence of Et_3N[132] and NH_4OAc (Scheme 52).[133]

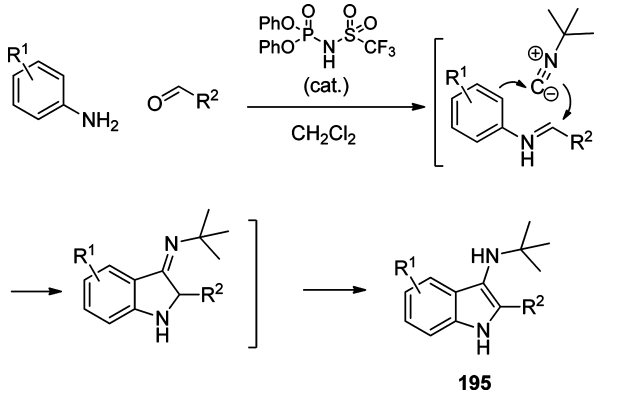
Scheme 52. Formation of Pyrano[3,2-*b*]indole 194



193 **194**

Preparation of a wide variety of 3-aminoindoles **195** was accessed by Brønsted acid mediated imine formation of anilines and aldehydes followed by cyclization with *tert*-butyl isocyanide (Scheme 53).[134] When the aldehyde is changed to a ketone, the

Scheme 53. 3-Aminoindoles



195

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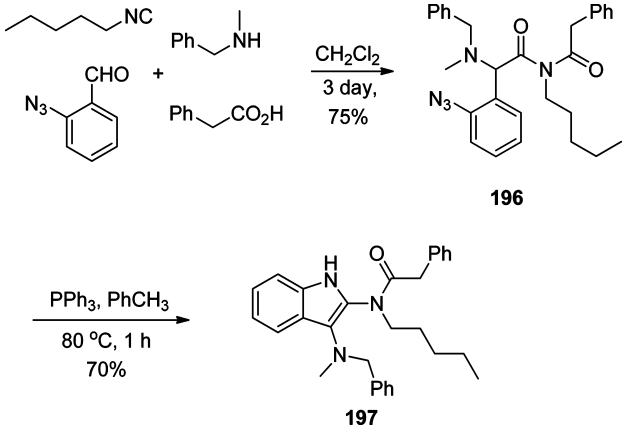
reaction leads to the preparation of substituted indoxyls. The similar reaction was previously reported by Deyrup et al.[135]

Mossetti et al. during an attempt with an Ugi condensation found that 2-azidobenzaldehyde, phenylacetic acid, pentylisocyanide and *N*-methyl benzylamine, led to the imide intermediate **196** in 75% yield. When the reaction is performed under aza-Wittig conditions, the 2,3-diamino indole derivative **197** is

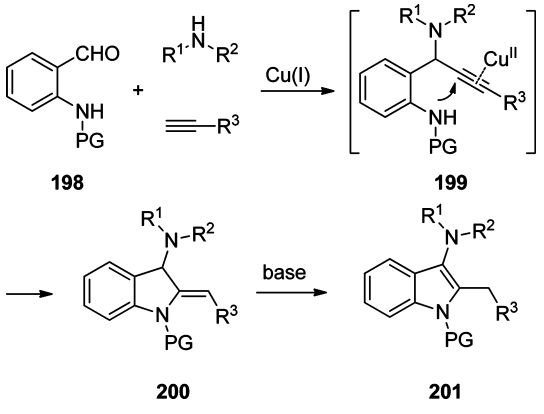
Scheme 54. Formation of the 2,3-Diaminoindole Derivative



isolated in 70% yield (Scheme 54).[136] Aza-Wittig conditions with 2-azidobenzoic acid as starting material generate quinazolinones derivatives.

Alternatively 3-aminoindoles can be prepared using an efficient Cu-catalyzed three-component coupling reaction with 2-aminobenzaldehyde **198**, a secondary amine, and an alkyne leading to a propargylamine intermediate **199**. Under these reaction conditions **199** undergoes cyclization generating the indoline core **200** (Scheme 55).[137] The latter, upon treatment

Scheme 55. Three-Component Coupling Towards Indoles

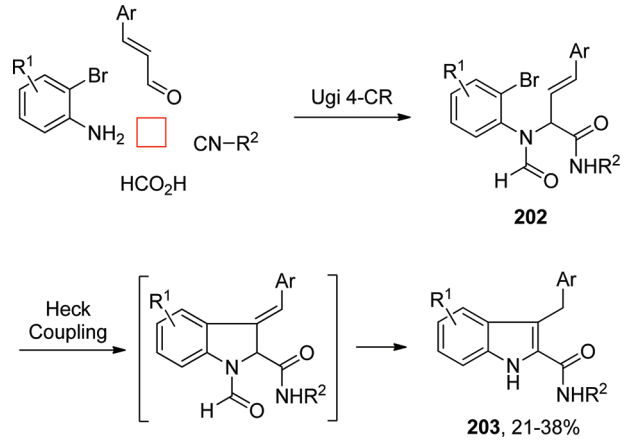


with a base, smoothly isomerizes into the indole **201**. The asymmetry version of this reaction with a chiral ligand complexed to copper was also reported in the same study.

A new strategy was reported in which a combination of a Ugi 4-CR and a Heck reaction was utilized. *o*-Bromoanilines, cynamaldehydes and isocyanides in the presence of formic acid form the intermediate **202**. An intramolecular Heck reaction of **202** produces the desired indoles **203** in yields between 21 and 38% (Scheme 56).[138]

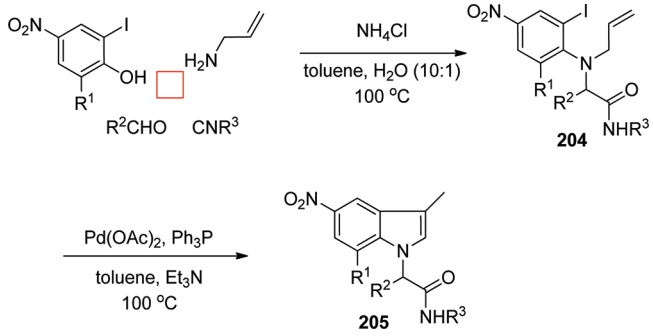
A novel combination of the Smiles,[139] Ugi[7c] and Heck[140] reactions was used for the synthesis of indoles. In the Ugi-Smiles

Scheme 56. Combination of the Ugi and Heck Reactions



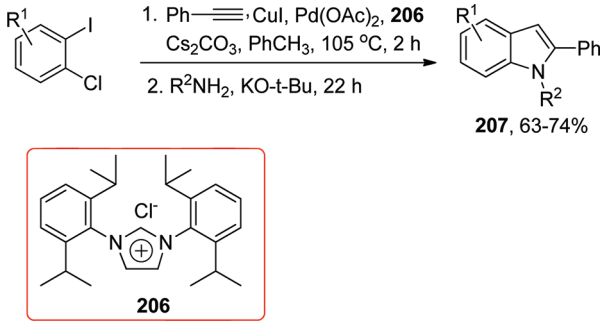
and Heck reaction *ortho*-iodonitrophenol reacts with aldehydes, amines and isocyanide to form **204**. The latter in the presence of $Pd(OAc)_2$ gives indole **205** in good yield (Scheme 57).[141]

Scheme 57. Combination of Ugi-Smiles and Heck Reactions



Ackermann described the efficient construction of indoles **207** using the sequential coupling of ortho-dihaloarenes with phenyl acetylene and various amines (Scheme 58). The reaction proceeds by

Scheme 58. Employment of ortho-Dihaloarenes in Indole Formation

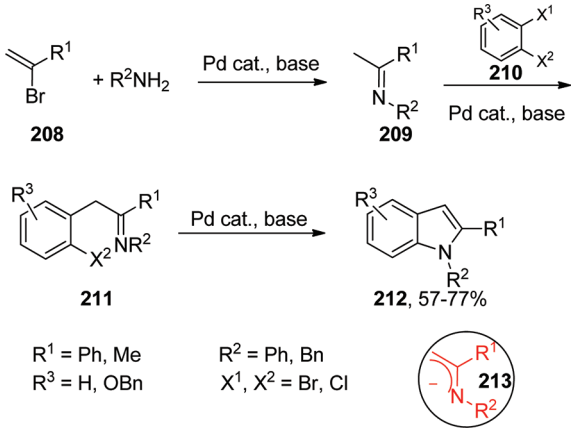


means of a multicatalytic system consisting of a *N*-heterocyclic carbine[142a,b] or tri-tert-butylphosphine[142c] palladium complex and CuI.

Barluenga discovered a new domino type three component strategy for the synthesis of 2,3-disubstituted indoles (Scheme 59).[143] Primary amines in the presence of palladium and base are inserted into the bromoalkene **208** to give imines **209**. The latter in basic media generates the azaallylic anion **213** which couples with the dihaloarene **210** (Scheme 59). In the

dx.doi.org/10.1021/cr2003954 | *Chem. Rev.* 2012, 112, 3508–3549

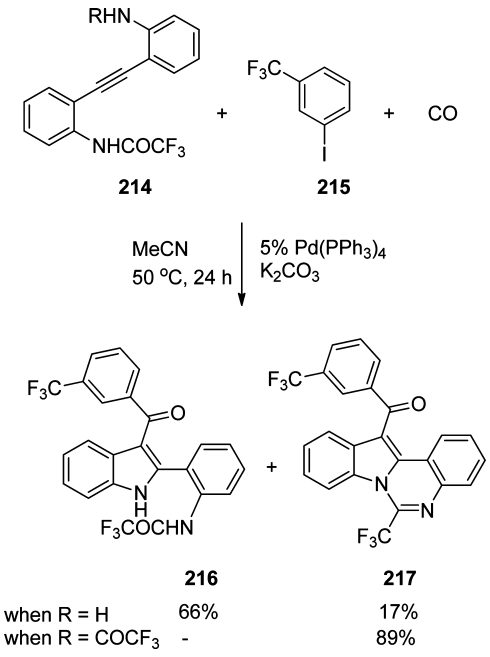
Scheme 59. Pd-Catalyzed Construction of Indoles from Primary Amines, Bromoalkenes, and Dihalobenzenes



last step efficient intramolecular *N*-arylation of **211** occurs with the aid of the same catalyst to form the indoles **212** in 57−77% yield. High yield synthesis of furo[2,3-b]indole derivatives have been achieved utilizing 2-aminofurans formation via the reaction of isocyanide, cyclicketones and *o*-halobenzaldehydes followed by a copper-catalyzed intramolecular Ullmann reaction sequence.[144]

The palladium-mediated reaction of 2-alkynyltrifluoroacetanilides with aryl halides in a carbon monoxide atmosphere leads to the isolation of 3-acylindoles **216**. This reaction was first reported by Arcadi et al.[145] Similarly *o*-(*o*-aminophenylethynyl)-trifluoroacetanilide **214** (R = H) reacts with aryl iodide **215** and carbon monoxide in the presence of $Pd(PPh_3)_4$. To produce 3-acylindole **216**[146] (66%) along with the indoloquinazoline byproduct **217** (17%) (Scheme 60).[147] Replacement of acyl

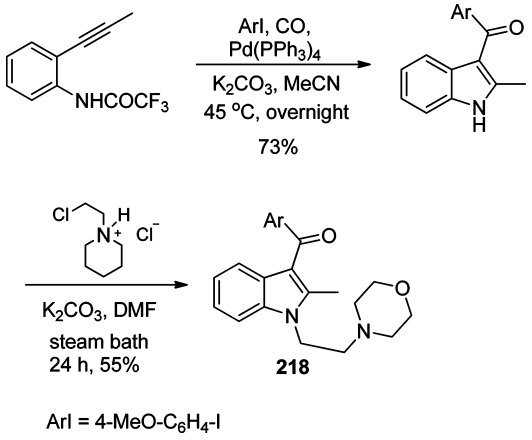
Scheme 60. Selective Synthesis of 3-Acylindole versus 12-Acylindolo[1,2-*c*]quinazoline



amine with **214** (where R = $COCF_3$) leads to an improved yield of indole. 6-Trifluoromethyl-12-acylindolo[1,2-*c*]quinazoline **217** is formed in 89% yield (Scheme 60).[148] This method can also be applied to other aryl halides as well as triflates.

The methodology was also applied to the synthesis of pravadoline **218**, an indole derivative designed as a nonacidic analogue of nonsteroidal antiinflammatory drugs (NSAIDs) (Scheme 61).[149] In the another study 2-aroylindoles using a

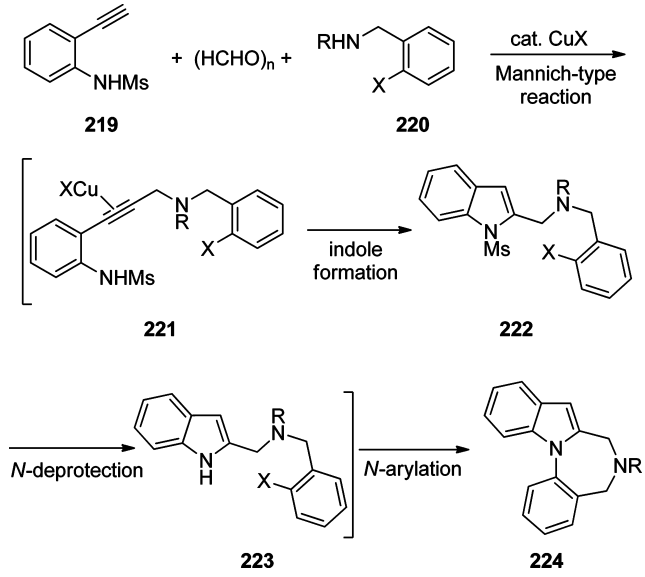
Scheme 61. Synthesis of Pravadoline 218



domino palladium-catalyzed C,N-coupling/carbonylation/C,C-coupling sequence easily prepared from 2-*gem*-dibromovinylanilines and boronic acids under carbon monoxide.[150] If methanol be used instead of boronic acid the previous reaction the corresponding ester could be obtained.[151]

Copper was found to be a suitable catalyst in the domino process for the formation of Mannich-products **221** from 2-ethynylanilines **219**, formaldehyde and *o*-bromobenzylamines **220**. Subsequent indole formation of **222**[152] follows, but if *N*-deprotection is introduced (to form *N*-arylation of **223**) then the indole-fused benzo-1,4-diazepines **224** are isolated (Scheme 62).[153] Nonstandard amines are used to construct

Scheme 62. Copper(I)-Catalyzed Domino Coupling−Cyclization−N-Arylation Reaction



more complex molecules such as carbolines,[154] tetrahydropyridine-fused indoles,[155] and benzoazepines[152] with the same process. Au(III)-supported on ZrO_2 also efficiently catalyzes the reaction affording compound **222**.[156] An alternative method

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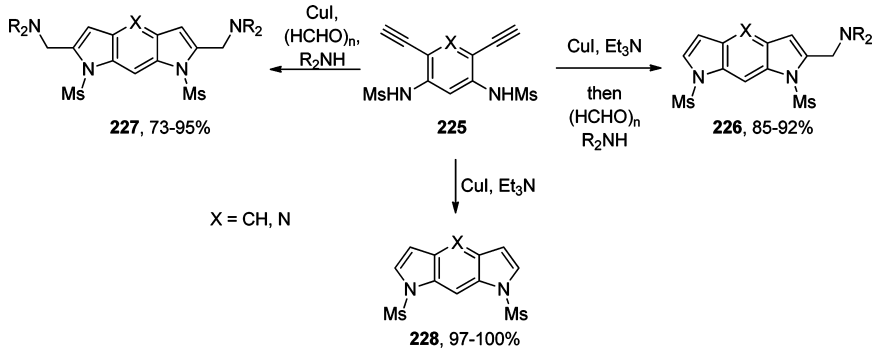
Scheme 63. Synthesis of Aminomethylated Pyrroloindoles and Dipyrrolopyridines

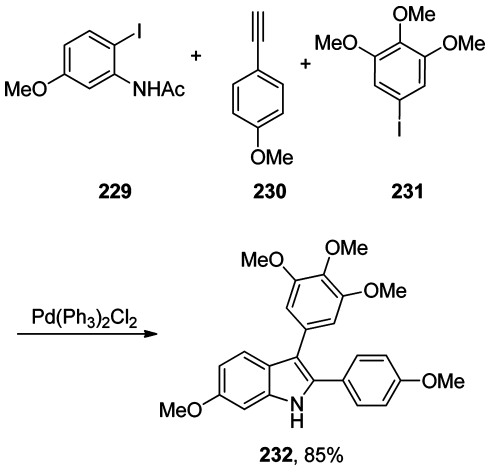


that produces 2-(aminomethyl) indole derivatives **222** is the palladium−copper-catalyzed three-component assembling of propargyl halides, aryl halides, and secondary amines.[157]

Ohta and co-workers have modified the route for the synthesis of pyrrole-fused indole derivatives **226**, **227**, and **228** (when X = CH) utilizing a domino copper-catalyzed multicomponent coupling and bis-cyclization reaction (Scheme 63).[158] They discovered that the Mannich-type cyclization reaction of 4,6-diethynyl-1,3-phenylenediamine **225** (X = CH) can be controlled with paraformaldehyde and a secondary amine to selectively form the mono- or bis-aminomethylated pyrroloindoles. The high-yielding bis-cyclization of terminal alkynes occurs in absence of Mannich-conditions to generate **227**.

Chaplin and Flynn have described a one-pot, multicomponent coupling procedure for the synthesis of benzofuranes. They employed o-iodophenoles, alkynes and iodoarenes or alkenes.[159] They extended this methodology for the synthesis of 2,3-disubstituted indole **232**. The reaction involves the Sonogashira coupling[160] of *o*-iodoacetanilide **229** to the terminal alkyne **230** followed by addition of a suitable coupling partner such as **231** to give the indole **232** (Scheme 64). The same strategy

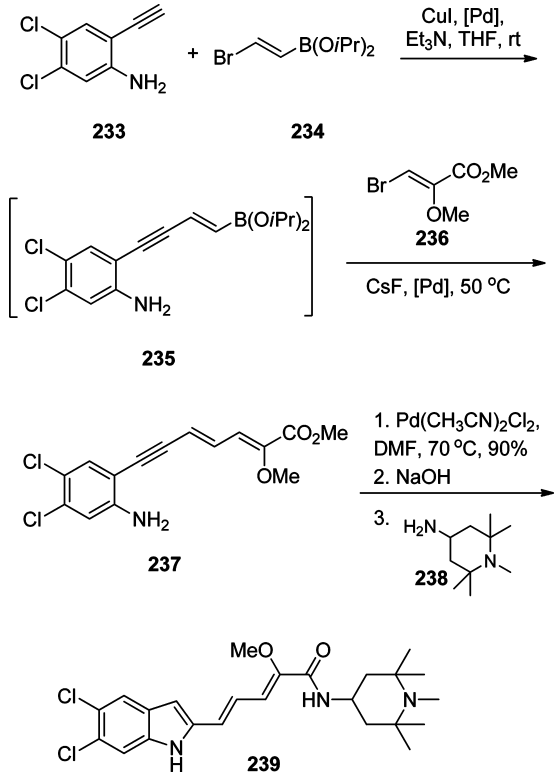
Scheme 64. One-Pot Synthesis of 2,3-Disubstituted Indole



was followed for the synthesis of a wide diversity of 2,3-disubstituted indoles by other groups.[161] Very recently Rao et al. have established a method for the synthesis of indoles involving the one-pot coupling of (trimethylsilyl)acetylene with iodoarenes in the presence of 10% Pd/C−CuI, followed by treatment of the reaction mixture with K_2CO_3 in aqueous MeOH, and finally coupling with *o*-iodoanilides.[162]

SB 242784 (**239**), a compound in development for the treatment of osteoporosis, is synthesized from the coupling of alkynyl aniline **233** with bromoalkene **234** to form **235**. A subsequent Suzuki coupling of **235** with **236** produces the ynediene **237** (Scheme 65).[163] Treatment of **237** with

Scheme 65. Tandem Reaction in the Synthesis of SB 242784 (239)



$Pd(CH_3CN)_2C1_2$ induces cyclization to give the indole ester. Hydrolysis of the ester group and reaction of the resulting acid with amine **238** give SB 242784 (**239**).

Leogane and Lebel have developed the first sequencial one-pot Curtius rearrangement/palladium-catalyzed indolization process for the direct synthesis of 2,3-disubstituted and 3-substituted indoles, as well as indole *N*-carboxamide derivatives **240**, starting from readily available 2-iodobenzoic acid (Scheme 66).[164]

A new and efficient copper(I)-catalyzed method was developed for the synthesis of 2-amino-3-alkylindole with the

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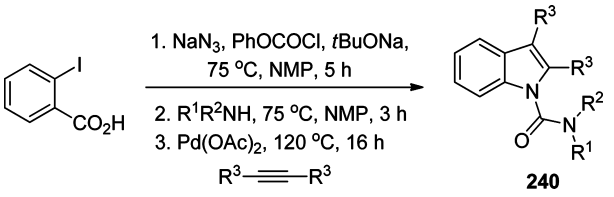
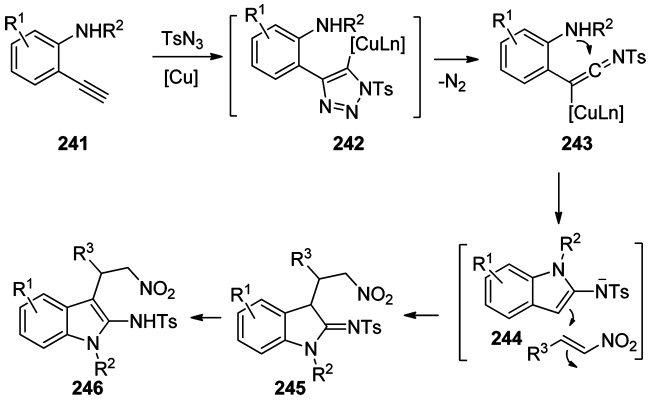
Scheme 66. Synthesis of Indole *N*-Carboxamides



participation of 2-ethynylaniline **241**, sulfonyl azide, and nitroolefin (Scheme 67).[165] As described in Scheme 67,

Scheme 67. Possible Mechanism for the Three-component Reaction of 2-Ethynylaniline, Sulfonyl Azide, and Nitroolefin



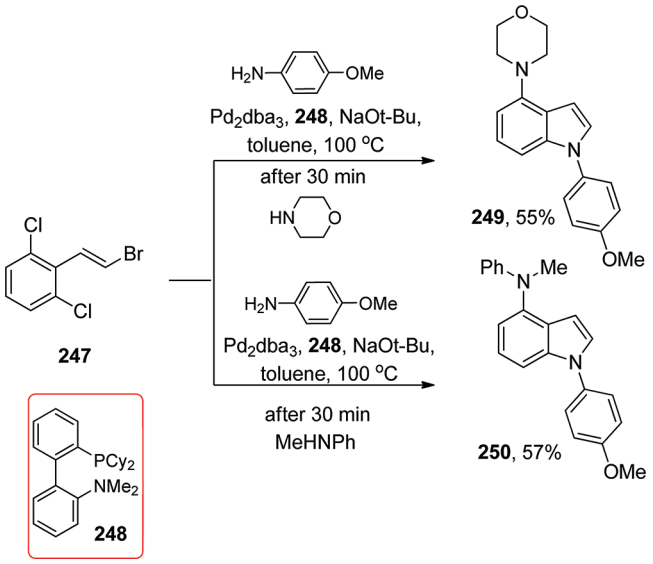
probably 2-ethynylaniline **241** reacts with the azide to form the reactive ketenimine **243** upon the ring-opening rearrangement of the triazole intermediate **242**. Subsequently intramolecular nucleophilic addition occurs, leading to the intermediate **244**. Afterward intermolecular Michael addition and tautomerization afford the desired product **246**. HCT-116 inhibition activity of the produced indolyl compounds **246** was evaluated and it showed satisfactory results.

2-(2-Haloalkenyl)-aryl halides such as **247**, react with amines with the aid of Pd catalysis to provide 1-substituted indoles.[166] When 1,3-dichloro substrate **247** reacts with different primary amines the corresponding three-component product 4-aminoindoles **249** and **250** in moderate yields were obtained (Scheme 68). A sequential metal-catalyzed C−N bond formation employing *ortho*-haloaryl acetylenic bromides and two different amines provides a facile access to 2-amido-indoles possessing a unique structural manifold.[167]

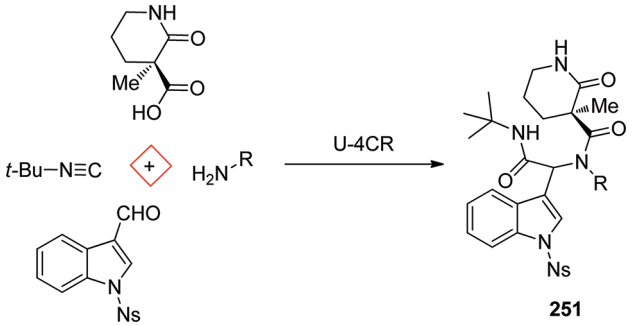
4. PARTICIPATION OF INDOLE FUNCTIONAL GROUPS IN MCPS

Using additional functional groups such as aldehydes, ketones, acids, amines, cyanides, etc., in MCRs makes it possible to prepare more complexes indole molecules. Mizoguchi et al. employed a Ugi 4-CR method to introduce indolyl derivatives **251**. They used these compounds successfully as starting materials in the synthesis of poly fused cyclic compounds (Scheme 69).[168] Two patents used 3-formylindole and tryptamine in the synthesis of Ugi-adducts and evaluated the antibiotic activity of several bioisosteres.[169] *N*-Alkyloxazolidines react in a multicomponent reaction with carboxylic acids and isocyanides to give *N*-acyloxyethylamino acid amides.[170] Waki et al. have investigated the racemization in peptide synthesis using the Ugi-4CR of *N*-boc-3-formylindole, isocyanates and two differ-

Scheme 68. Sequential Amination Reactions



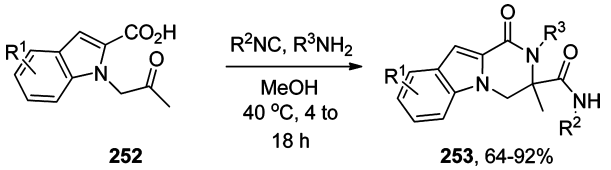
Scheme 69. 3-Formylindole in a Ugi-4CR



ent aminoacids.[171] We found that ethyl 3-formylindole 2-carboxylate participate in an Ugi-4CC with *N*-boc-amino acids to yield complex dipeptides which are potential biological active molecules.[172]

Another strategy to increase the diversity of the indole scaffold is to use bifunctional starting materials in which the participating functional groups of two components of the 4-CR are present in one structure.[173] With this idea in mind the bifunctional keto-acid indoles **252** (or pyrroles) react with isonitriles and amines to form the corresponding novel 3-carboxamide derivatives **253** (Scheme 70).[174] The reaction

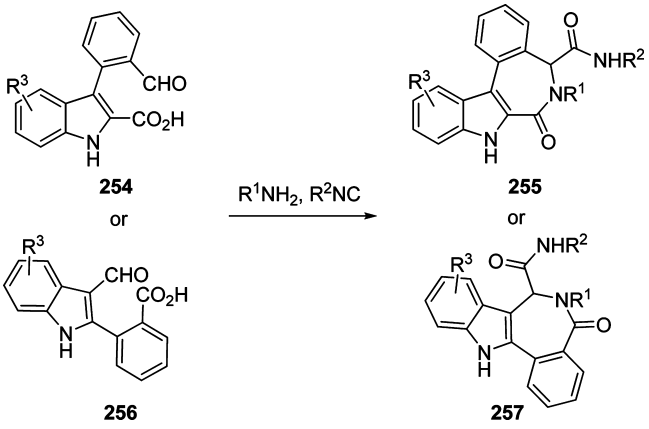
Scheme 70. Indole[1,2-*a*]pyrazin-1-one Heterocycles 253



proceeds smoothly in methanol at 40 °C to yield the desired products in 64−92% yield. 3-Formyl-1*H*-indole-4-carboxylic acid is another example of a bifunctional molecule which undergoes Ugi condensation to give the corresponding heterocycles.[8c]

dx.doi.org/10.1021/cr2003954 | *Chem. Rev.* 2012, 112, 3508−3549

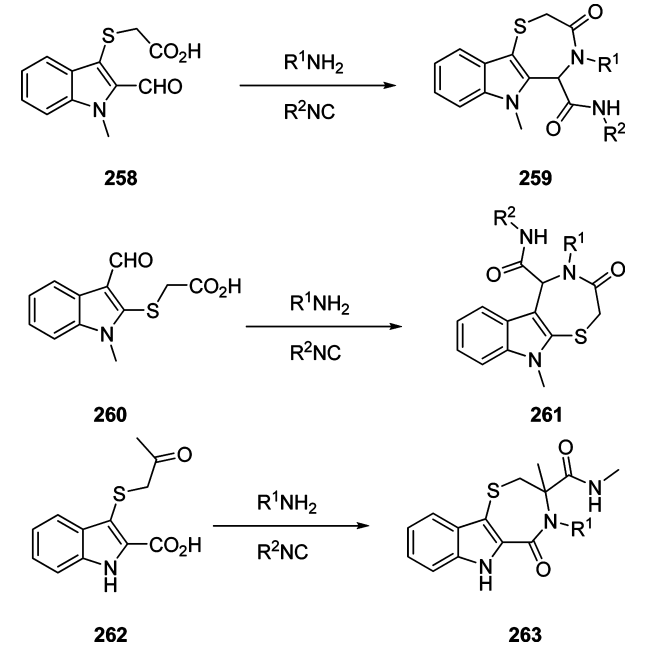
Scheme 71. Indolobenzazepinones 255 and 257 via the Ugi Reaction



Beaumont et al. have demonstrated an intramolecular isocyanide-based multicomponent design utilizing the reaction of oxo-acids **254** and **256** to get access to indolobenzazepinones **255** and **257** respectively in good yields (Scheme 71).[175]

A diversity of 1,4-thiazepine carboxamides **259**, **261**, and **263** were isolated utilizing a modified four-component Ugi condensation reaction with bifunctional aldehyde/keto acids **258**, **260**, and **262**, isonitriles, and amines (Scheme 72).[176]

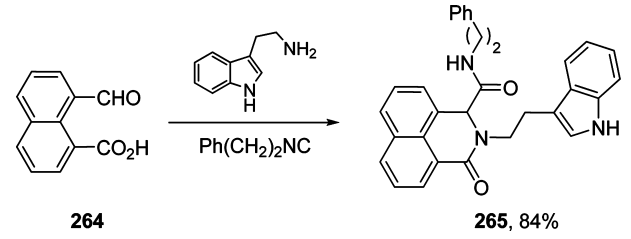
Scheme 72. Carbamoyl-Substituted Seteroannelated [1,4]Thiazepines



Considering the ease of the preparation of the initial starting materials, the convenient synthesis and isolation of the products, and the overall good chemical yields of the described transformations, this route provides a new and valuable entry to novel heterocycle-fused analogues of biologically active thiazepines.

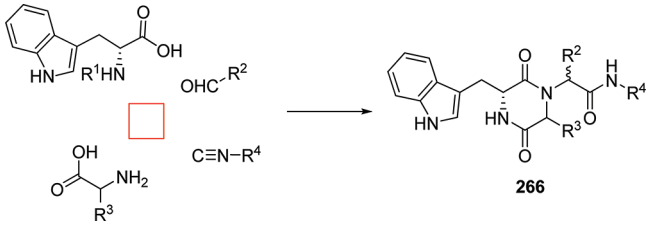
The unique lactam structure **265** was isolated from 1,8-naphthaldehydic acid **264** upon reaction with tryptamine and phenylethyl isocyanide in 84% yield (Scheme 73).[177] A reaction between levulinic acid, isocyanides and primary amines in distilled water was reported in which γ-lactams derivatives were formed.[178] The reaction proceeds with the aid of a surfactant.

Scheme 73. Indolyl Lactam 265



In an impressive design involving a six-functional group condensation from a four component one-pot process, the tryptophan-derived diketopiperazines **266** were obtained in good yield under heating or microwave conditions (Scheme 74).[179]

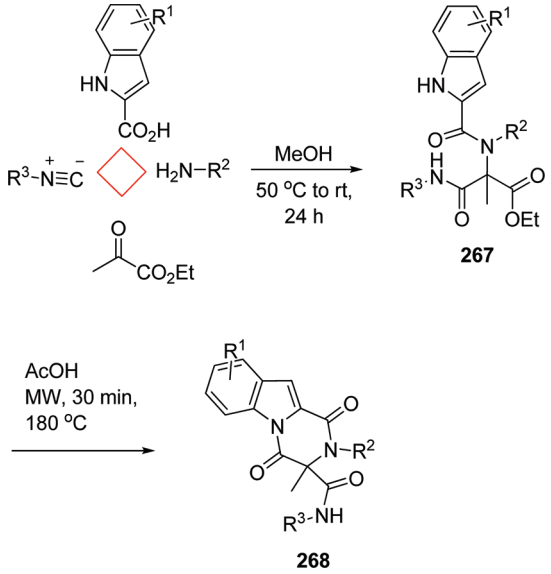
Scheme 74. Synthesis of Diketopiperazines 266



The four-component nature of the Ugi reaction contributes to the formation of complex molecules with high diversity. The programmed combination of this multicomponent reaction with sequential secondary transformations has already been recognized as a powerful approach to get access to molecules with high molecular complexity. Indeed, many cycloadditions, cyclocondensations or organometallic couplings have been reported in which post Ugi condensations took place.

Ivachtchenko and his group established a Ugi-4CR for the construction of drug-like 2,3-dihydropyrazino[1,2-a]indole-1,4-diones **268** from indole-2-carboxylic acids, ethyl pyruvate, isocyanides, and primary amines (Scheme 75).[180] In this procedure

Scheme 75. 2,3-Dihydropyrazino[1,2-*a*]indole-1,4-diones 2 via a One-Pot Two-Step Procedure

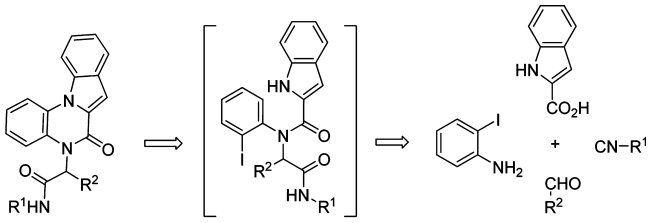


dx.doi.org/10.1021/cr2003954 | Chem. Rev. 2012, 112, 3508–3549

after the Ugi condensation of four mentioned compounds to form compound **267** at room temperature at 50 °C in methanol, the solvent is removed in vacuo and the resulting solid is redissolved in glacial acetic acid. The cyclized product **268** is isolated in moderate to good yield when the sealed reaction vessel is heated under microwave irradiation.

Construction of **269** via N-arylation of **270** would be access (Scheme 76). Diamide **2** is Ugi adduct indole-2-carboxylic acid,

Scheme 76. Combination of Ullmann and Ugi Reactions in the Construction of Indolo[1,2-a]quinoxalinones 269

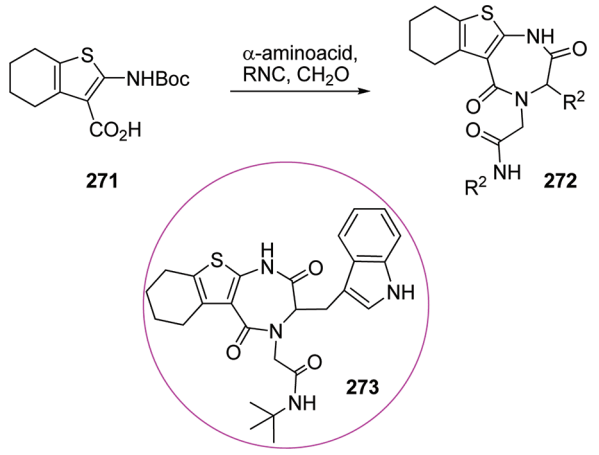


269 **270**

aldehyde, isocyanide and 2-iodoaniline (Scheme 76). Balalaie and co-workers by this strategy gave a practical method which came from combination of Ullmann N-arylation and Ugi 4CC to preparing indolo[1,2-a]quinoxalinones **269** in good overall yield (Scheme 76).[181] Ugi reaction was performed in methanol and N-arylation done in the presence of CuI/L-proline.

Dömling and his group used an Ugi-deprotection-cyclization strategy for the preparation of 1,4-thienodiazepine-2,5-diones **272** from 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid **271**, an α-amino acid, isocyanate and formaldehyde (Scheme 77).[182] For example when tryptophan (as the α-amino

Scheme 77. 1,4-Thienodiazepine-2,5-diones



271 **272** **273**

acid) and *t*-butyl isocyatate is used in this reaction the indolyl derivative **273** is isolated in 16% overall yield. The mechanism involves an Ugi condensation in methanol, followed by amine Boc-deprotection in TFA and treatment with triethyl amine in third step (Scheme 77). These hybrid peptidomimetic diazepine structures were evaluated for chemical space distribution and drug-like properties.

The Ugi–Hulme-modified condensation of monoboc protected *ortho*-phenylene diamine, glyoxylic acids, aldehydes, and isocyanide in a two-step procedure has produced several quinoxalinone derivatives (Figure 16).[183] In the first step Ugi-condensation occurs followed by simultaneous boc-deprotection

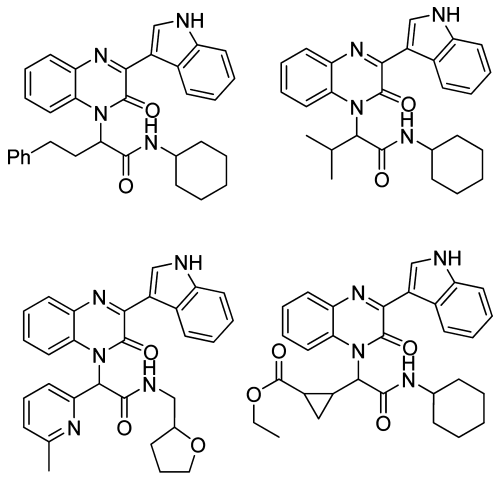
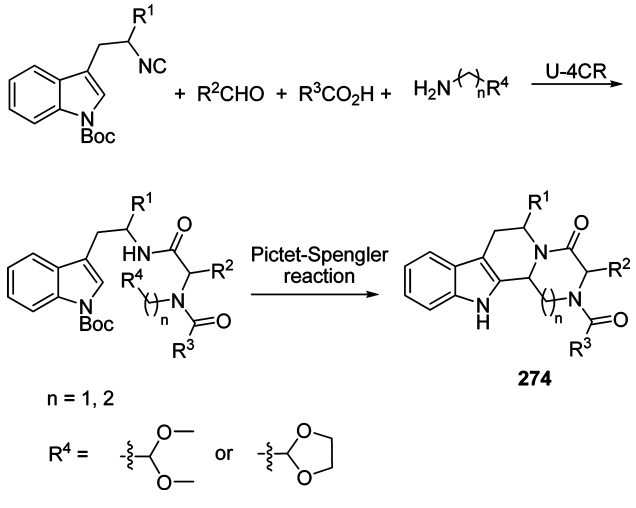


Figure 16. Indolyl quinoxalinones.

and cyclization in the presence of TFA in dichloroethane to yield the target molecules.

A two-step procedure involving an Ugi reaction preceding a Pictet–Spengler reaction allows for the isolation of the tetrahydro-β-carboline scaffold **274** (Scheme 78).[184]

Scheme 78. Combination of the Ugi and Pictet–Spengler Reactions



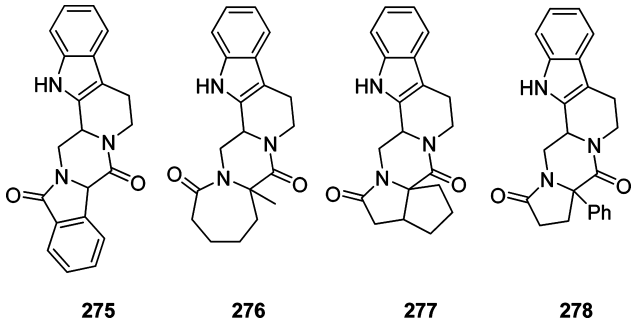
274

Alternatively, employment of bifunctional materials that have both aldehyde and acid groups react with aminoacetaldehyde dimethyl acetal and 2-isocyanoethylindole to afford some interesting polycyclic compounds such as **275–278** (Figure 17).[185]

Similarly a fantastic design was reported with the choice of imine **279**, α-ketoacid **280** and isocyanide **281** as starting materials, yielding Ugi adducts **282** which cyclizes to form 2,5-diketopiperazines **283** in the presence of TMSOTf in good yield (Scheme 79).[186]

Dömling prepared the pentacyclic compound **285** by means of the combination of the Ugi and Pictet–Spengler reactions of tryptophan (Trp) **284**, phthalic dialdehyde and *tert*-butyl isocyanide (Scheme 80).[4a]

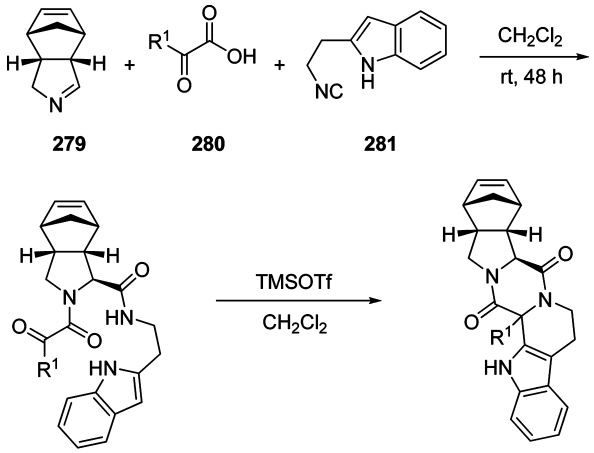
dx.doi.org/10.1021/cr2003954 | *Chem. Rev.* 2012, 112, 3508–3549



275 276 277 278

Figure 17. Polycyclic compounds via a two step Ugi condensation combined with the Pictet–Spengler reactions.

Scheme 79. Preparation of 2,5-Diketopiperazines



279 280 281

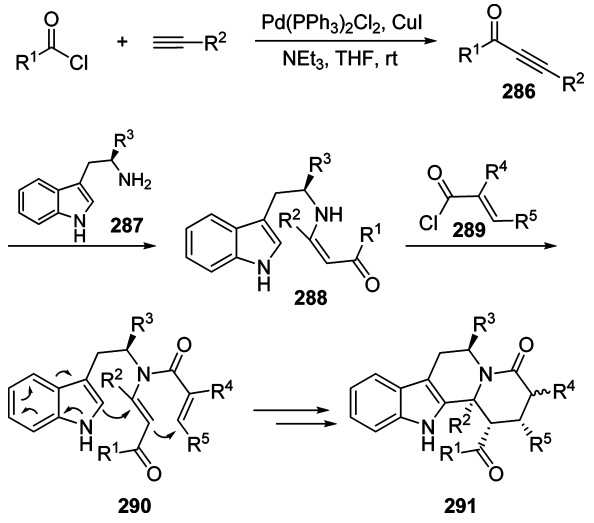
282, 48-77% **283**, 71-92%

Scheme 80. Tryptophan in the Synthesis of Pentacyclic Derivative 285

284 285

The Müller group reported an impressive method to prepare highly substituted tetrahydro-β-carbolines **291** with five stereocenters utilizing a coupling-amination-aza-annulation-Pictet–Spengler MCR (Scheme 81).[187] In this one-pot reaction an acyl halide reacts with a terminal alkyne in the presence of palladium and copper to give the ynones **286**. The later undergoes an aza-Michael addition of (*R*)-tryptamines **287** to form **288**. The intermediate **290** forms form the condensation reaction of the indolyl amines **288** and α,β-unsaturated chlorides **289**, followed by cyclization to the tetrahydro-β-carbolines **291** in 32–59% yield (Scheme 81). Similarly Gupta et al have prepared α-carboline derivatives *via* a three-component tandem reaction using acid chlorides, terminal alkynes, and 2-aminoindole hydrochlorides.[188] Via *N*-acyliminium Pictet–Spengler reaction of tryptamine, cinnamaldehyde derivatives, and alkynoyl chlorides sequence by an intramolecular Diels–Alder cycloaddition a diverse polycyclic alkaloid-like compounds were prepared.[189a] Another modification on the Pictet–Spengler

Scheme 81. Formation of Five Stereocenters in the Tetrahydro-β-carbolines 291

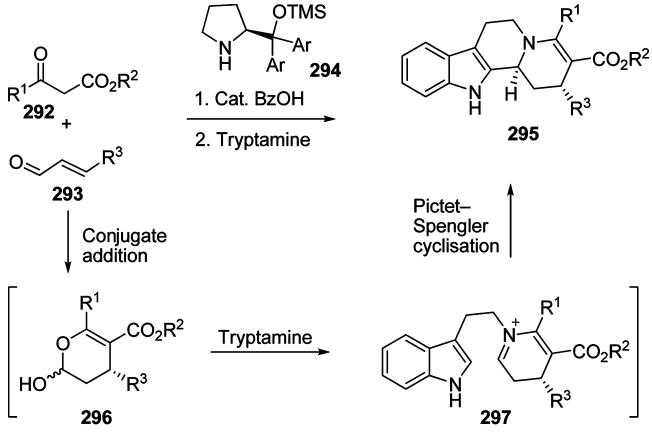


286 287 288 289 290 291

reaction is one-pot preparation of aldehydes came from alkenes and carbon monoxide (see Scheme 43).[189b,c]

The synthesis of asymmetric indoloquinolizidines **295** from β-ketoesters **292**, α,β-unsaturated aldehydes **293** and tryptamines was reported by Wu et al.[190] Both organocatalysts and prolinol ether **294** efficiently catalyzed this reaction to give **295** in moderate to excellent yields and good to excellent enantioselectivities. The mechanism for the formation of the cyclic hemiacetal intermediate **296** appears to involve the conjugated addition of β-ketoesters to α,β-unsaturated aldehydes followed by treatment with tryptamine to yield the indoloquinolizidine **295** (Scheme 82). Alternatively similar products **295** were

Scheme 82. Michael and Pictet–Spengler Reaction in the Synthesis of Indoloquinolizidine



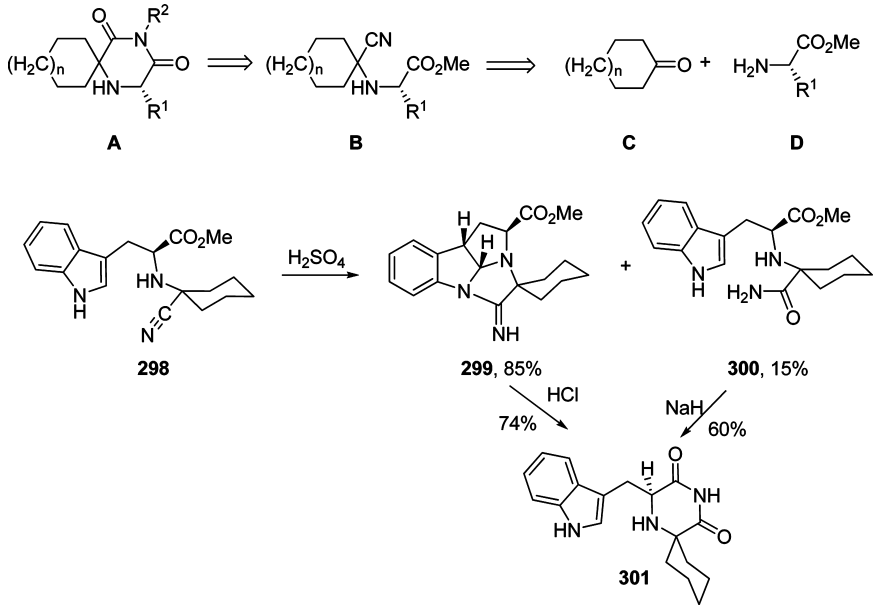
292 293 294 295 296 297

achieved by employing an asymmetric organocatalyzed one-pot three-component cascade reaction of tryptamines, alkyl propiolates, and α,β-unsaturated aldehydes.[191]

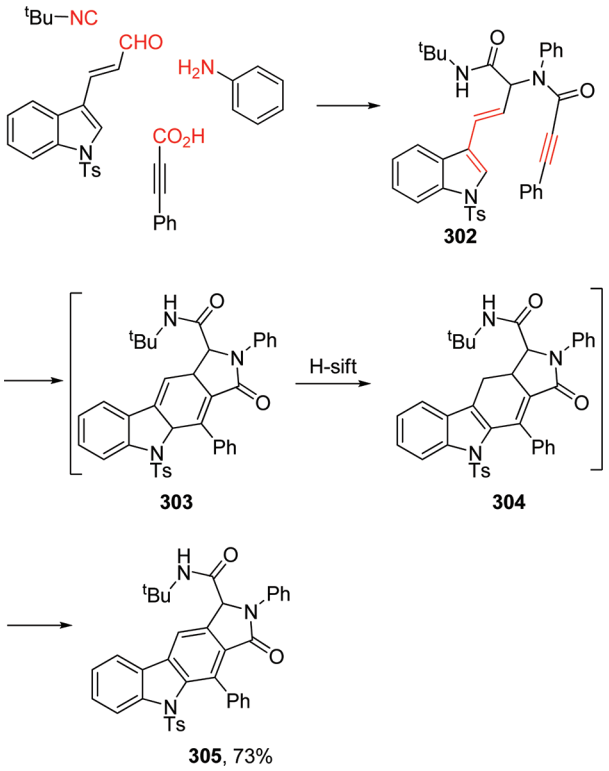
Chiral spirocyclic 2,6-dioxopiperazines **A** are prepared from normal amino acids as outlined in Scheme 83.[192] Condensation of (L)-Trp-OMe, cyclohexanone and trimethylsilylcyanide leads to the α-amino nitrile **298** (Scheme 83). The Trp-derived amino nitrile **298** when treated with H_2SO_4 gives a new

dx.doi.org/10.1021/cr2003954 | *Chem. Rev.* 2012, 112, 3508–3549

Scheme 83. Chiral Spirocyclic 2,6-Dioxopiperazines 301



Scheme 84. Combination of Ugi and Diels–Alder Reaction for the Synthesis of 305



tetracyclic indoline derivative **299** (85%) and the carboxamide **300** (15%). Both **299** and **300** can be converted to **301**. The indoline derivative **299** requires refluxing in 1 N HCl and the carboxamide **300** requires treatment with NaH to lead to the Trp-derived 2,6-dioxopiperazine **301**. Further functionalization of the dioxopiperazine derivatives **301** to the corresponding derivatives **A** is achieved through alkylation of the latter with alkyl halides.

In another scenario Lu et al, via an sequential Ugi 4-CR, followed by an intramolecular Diels–Alder reaction, and oxidative aromatization made a wide diversity of benzofurans and indoles.[193] For instance 3-(1-tosyl-1H-indol-3-yl)acrylaldehyde **303** reacts with aniline, *tert*-butylisocyanide and phenylpropiolic acid producing the substituted indole derivative **302**. Removal of the solvent (methanol) and stirring of the intermediate at 50 °C under nitrogen atmosphere for 4 h, after which DDQ was added as oxidant at room temperature, compound **305** was isolated in 73% (Scheme 84). As shown in Scheme 84, the Ugi intermediate **302** undergoes an intramolecular Diels–Alder reaction leading to **303**. Product **305** is formed via a H-shift and subsequent oxidation reaction.

The Quinolino scaffold **307** and its derivatives were constructed in a combinatorial approach via the Ugi four-component reaction (U-4CR) and a Pd-catalyzed intramolecular arylation reaction (Scheme 85).[194] In this context, iodoindole **306**, 4-chloroaniline, *tert*-butylisocyanide, and 2-methoxybenzaldehyde in methanol were condensed and their Ugi-adduct was isolated in 88% yield which in the presence of palladium was cyclized to the quinolino-indole **307** in 92% yield. This method gives access to a large diversity of quinoline derivatives.

El Kaim and co-workers exposed the Ugi-adducts **308** to $Cu(OAc)_2$ in a novel method for the synthesis of spiroindolines **311** (Scheme 86).[195] This copper-catalyzed spirocyclization reaction probably proceeded *via* a radical mechanism starting with the generation of enolates **309** (Scheme 86). This simple procedure produces final structures of remarkable complexity because of four points of molecular diversity for the first step. This is a rare example of cyclization of a radical species which only gives one diastereomer. It may be explained either by a degradation of the isomer unable to cyclize with the pendant amide or by a ring-opening of the spiro iminium **310** leading to an epimerization of the peptidyl position.

Treatment of indoles with 5-hydroxyfuran-2(5*H*)-one **312** in the presence of catalyst **313** followed by addition of isocyanide and benzylamine give lactams **314** as a mixture of two diasteromers (Scheme 87).[196] 5-Hydroxyfuran-2(5*H*)-one **312** reacts with the diphenylprolinol silyl ether **313** to yield the activated intermediate **315** which undergoes Michael addition of indole in the beta position to form the acid aldehyde **316** in high enantioselectivity. The latter was precipitated successfully in an Ugi-condensation to yield lactams **314** in 75–95%.

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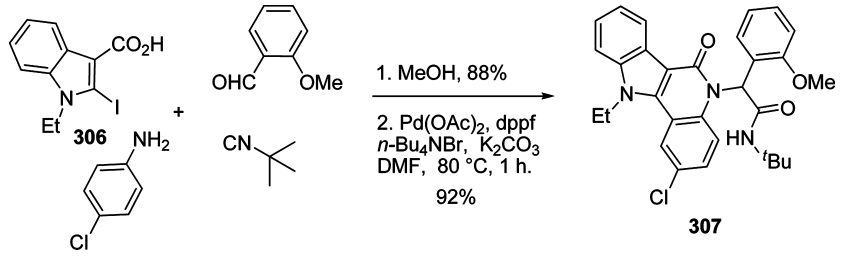
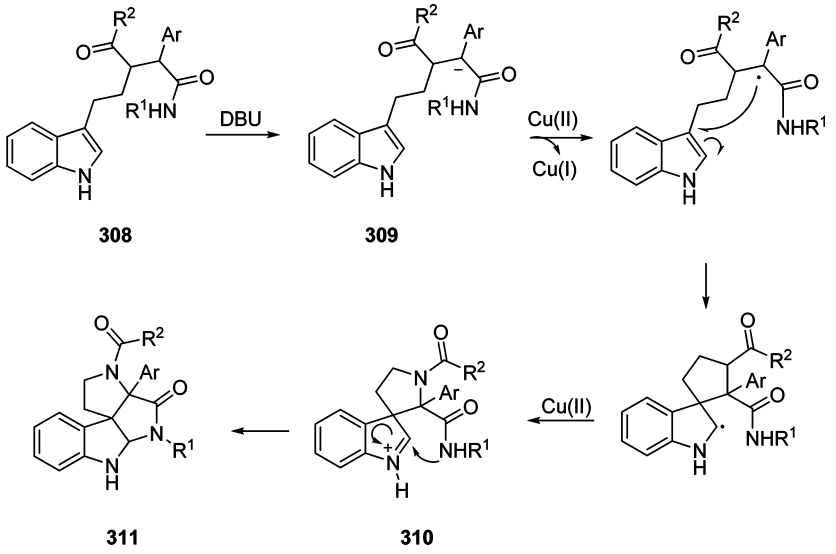
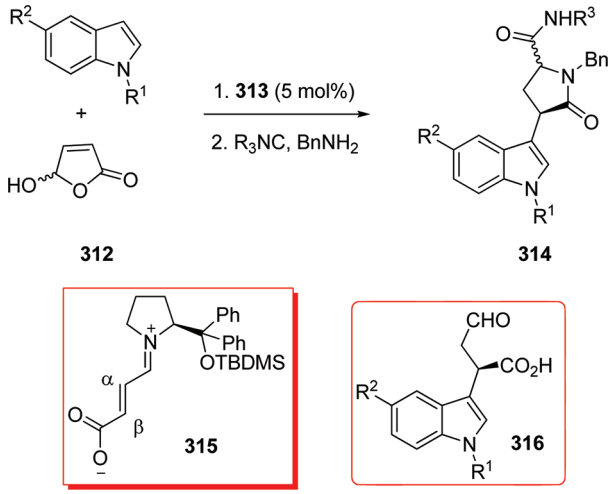
Scheme 85. Combination of Ugi-4CR and Pd-Catalyzed Cyclization Reaction



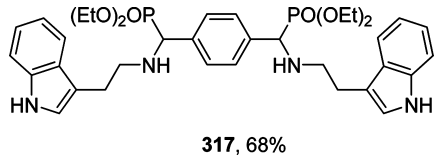
Scheme 86. One-Pot Conditions for the Preparation of Spiroindolines



Scheme 87. Combination of Michael Addition and Ugi Reaction



In a study toward the $FeCl_3$ mediated synthesis of α-aminophosphonates, via a Kabachnic–Fields reaction between an aldehyde, amine and phosphite, the bis(α-aminophosphonate) **317** (68%) was isolated. In this specific case the condensation of terephthaldialdehyde, tryptamine and $P(OEt)_3$, leads to the formation of **317** (Figure 18).[197] In a biological investigation supported with docking studies, the indole derived **317** was shown to exhibit high activity on the cell lines RAJI, JURKAT and MCF-7. The observed activity was comparable to that of doxorubicin. N-alkylated α-methyltryptamine derivatives was generated by simple reductive amination of α-methyltryptamines with ketones using catalytic hydrogenation conditions (3 atm H_2 and 10% Pd on carbon).[198] This method was also applied to other primary and secondary amines using ketones and aldehydes.

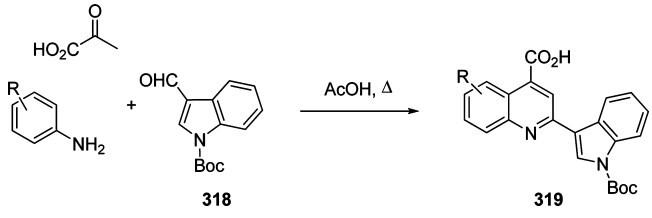


317, 68%

Figure 18. Bis(α-aminophosphonates) **317**.

In a one pot procedure *N*-boc protected 3-formyl indole **318** is first condensed with the aldol form of pyruvic acid and then cyclized with aniline derivatives to yield 2-indolyl-4-carboxylic acid quinolines **319** (Scheme 88).[199] It is certainly also possible

Scheme 88. One-Pot Formation of 2-Indolyl Quinolines

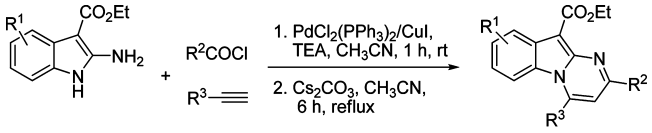


dx.doi.org/10.1021/cr2003954 | *Chem. Rev.* 2012, 112, 3508–3549

that the indole-aldehyde first form the imine with aniline, followed by attack of the pyruvic acid aldol form, and subsequent cyclization. These compounds were then further functionalized and their antibacterial activities were evaluated on Gram-positive bacteria.

Gupta et al. have prepared a novel structure of pyrimido[1,2-*a*]-indoles **321** utilizing a three component reaction of functionalized indoles **320**, alkynyl derivatives and acyl chlorides (Scheme 89).[200a] The reaction must probably start with alkynone

Scheme 89. Sequential Sonogashira and [3 + 3]-Cyclocondensation Reactions



320 **321**, 63-87%

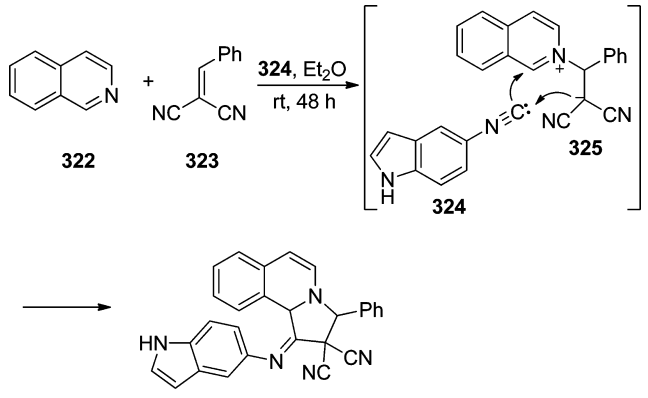
formation from acyl chloride and alkynes which efficiently catalyzed with palladium and cupper then produced alkynone and indole **320** undergoes cyclocondensation to form **321** in 63−82% yield (Scheme 89). Palladium also has catalyzed cyclization/carboalkoxylation of alkenyl indoles.[200b]

Mironov et al. reported the synthesis of 5-substituted indoles. Isoquinoline **322** attacks the alkene **323** to yield the zwitterion **325**, which subsequently cyclizes with indole-5-isocyanide **324** to give the 2,3-dihydro-10*H*-pyrrolo[2,1-*a*]isoquinoline-1-one **326** in 76% yield (Scheme 90).[201]

Van Leusen's imidazole approach involves the activation of tosylmethyl isocyanides **327** in which the acidic α-hydrogen is abstracted under these basic conditions to form **328**. In situ condensation of the amine and aldehyde to an intermediate imine then facilitates the cyclization reaction yielding **329**. Elimination of toluenesulphinic acid led to the imidazole **330** (Scheme 91).[202] When indole functionalized aldehydes or amines are used in this one pot approach, the corresponding imidazoles **331**−**334** are efficiently obtained. The biological activities of some of these products were examined for instance against NCI-H460 and HCT-15 cancer cell lines gave good results (Scheme 91).[203]

3-Formylindoles react with glycine, potassium thiocyanate to give two related products, believed to form from different mechanistic pathways.[204] *N*-methyl, *N*-*n*-butyl, or *N*-*p*-cyano-

Scheme 90. Pyrrolo[2,1-*a*]isoquinoline-1-ones 326 via 3-CR



322 **323** **325** **324** **326**, 76%

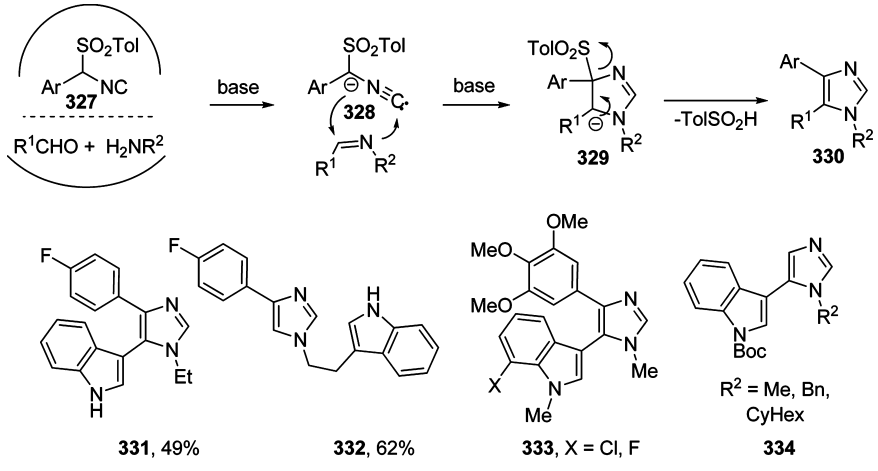
phenoxypentyl-3-formylindole **335**, glycine, and potassium thiocyanate in the presence of acetic anhydride form the *gem*-diacetylthio derivative **336** in 63−68% yield (Scheme 92). Acetic anhydride promotes the cyclization of **336** to 1-acetyl-2-thiohydantoin **337**, with the generation of one equivalent water molecule. Condensation of *N*-acetyl protected indole-aldehyde **338** with hydantoin **337** followed by partial *N*-deacetylation yields indolylmethylene 2-thiohydantoins **339** and **340** in 7% and 25% yield, respectively (Scheme 92).

Indium-mediated reaction of indole-3-carboxaldehydes, allyl bromide and electron-rich heteroarenes, electron-rich aromatics, or stabilized enols deliver a large diversity of interesting products such as unsymmetrical bisindolyl methanes **341** and **342**, indolyl-uracil **343**,[205] indoly arylmethanes **344**−**347**,[206] and indolyl-pyrazoles **348** and indolyl-imidazoles **349** (Figure 19).[207]

The reduction reaction of 3-alkynyl-indole-2-carbaldehydes **350** in the presence of alkoxides, generated from alcohols and sodium metal, under mild reaction conditions leads to intramolecular cyclization and the isolation of the novel [1,4]-oxazino[4,3-α]indole nucleus **351** (Scheme 93).[208]

Indole-3-carbaldehyde derivatives were used in the three-component aza-Diels−Alder reaction with *N*-vinyl-2-pyrrolidinone **352** and aniline to give the corresponding products **353** (Scheme 94).[209] Only 1-tosylindole-3-carbaldehyde proceeds well in this reaction with good yields while other indole-3-carbaldehydes such as indole-3-carbaldehyde and 1-methyl-indole-3-carbaldehyde did not give the desired products.

Scheme 91. Van Leusen's Synthesis of Indolyl Imidazoles



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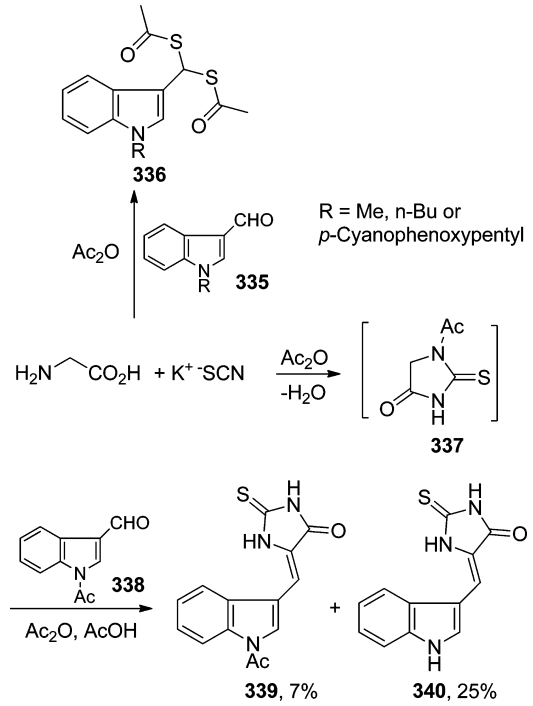
Scheme 92. Hydantoin Derivatives of Indole



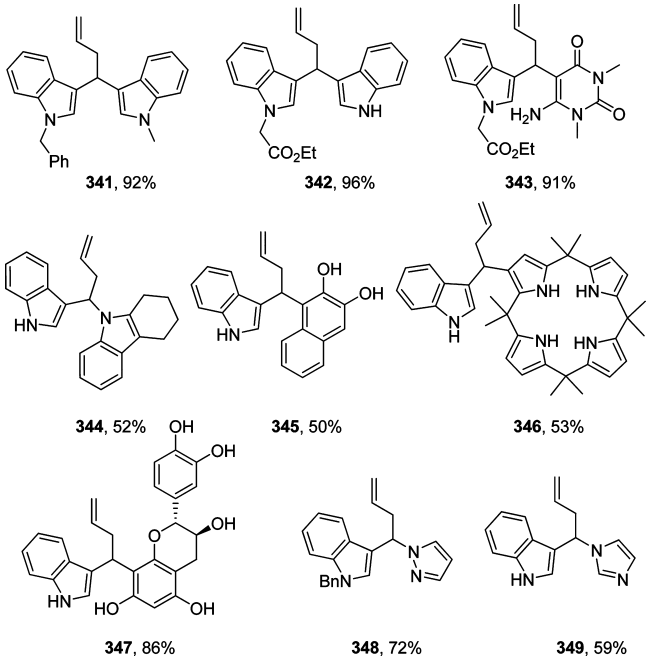
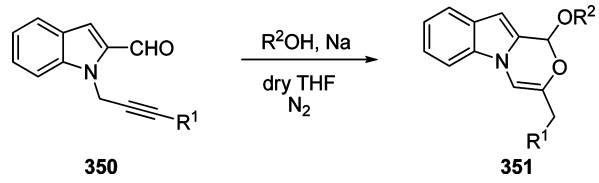


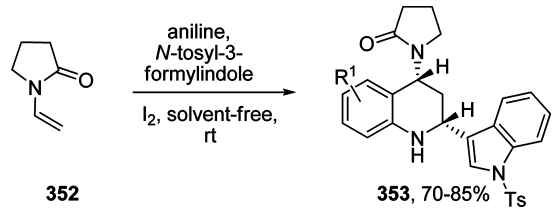
Figure 19. Allylic indolyl compounds.

Zhu et al. established a new synthetic protocol for the efficient and regiospecifc assembly of pyrido[1,2-α]indoles **354** or indolizines (Table 2). They employed indole-2-carbaldehyde or pyrrole-2-carbaldehyde, α-bromoketones, and alkynes in this novel protocol.[210] The mechanism of this reaction in basic media involves activation of the indole to N-alkylation by alkyl bromide and carbon between nitrogen and R^3 as second nucleophilic attacks to β-position of eynone. The formed intermediate subsequently undergoes intramolecular cycloisomerization to afford the desired product **354**.

Scheme 93. Nucleophilic Cyclization of δ-Acetylenic Aldehydes



Scheme 94. Indole-3-carbaldehydes in 3-C Aza-Diels–Alder Reactions



Majumder and Bhuyan have designed a novel reaction for the synthesis of α-carbolines **356** from indoles **355**, which undergoes a Knoevenagel condensation with nitriles and then an intramolecular [3 + 2]-dipolar cycloaddition reaction by azides (Scheme 95). The last step consists of an aromatic nucleophilic substituted reaction.[211]

The *N*-boc-3-amido indole **357** when treated with a range of aryl aldehydes and aromatic alkynes under acidic media and with microwave irradiation leads to the synthesis of a wide array of δ-carbolines **358** (Scheme 96).[212] This reaction probably starts with boc-deprotection of **357** followed by imine formation with the aldehyde. The in situ produced indole imine acts as a heterodiene in a Diels–Alder cyclization reaction with the alkyne. Oxidation of the latter yields the δ-carbolines **358**.

Huber et al. provided a facial method for the preparation of 3-substituted 4-cyano-1,2,3,4-tetrahydro-1-oxo-β-carbolines **360**, by treating ethyl 3-(cyanomethyl)indole-2-carboxylate **359** with ammonia and addition of aldehydes or ketones to the reaction mixture (Scheme 97).[213] When cyclic ketones are used, the procedure allows a convenient synthesis of tetracyclic spiro compounds.

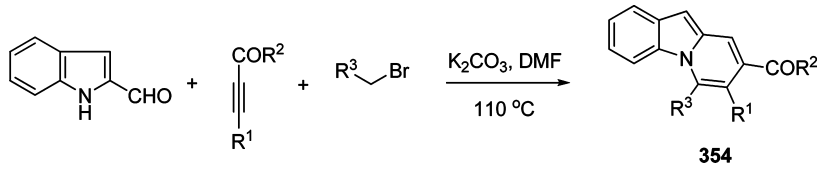
Substituted gramines **361**, in the presence of *t*BuOK, react with acrolein and β-keto-phosphonates, via a novel sequence involving a multicomponent condensation reaction followed by an anionic polycyclisation cascade, to afford the highly functionalized tetracyclic structures **362** (Scheme 98) in excellent overall yields and diastereoisomerically pure.[214] In this unique process, up to eight elementary transformations take place with remarkably high chemo- and stereocontrol.

A new indolyl fullerenopyrrolidine **363** was synthesized with a three-component reaction of fullerene C_{60}, *N*-methylglycine, and indole-3-carbaldehyde in 40% yield (Scheme 99).[215] It is probably the aldehyde and amine which condensed to form an iminium salt followed by decarboxylation and a subsequent [3 + 2] cycloaddition reaction to give **363**. A similar reaction with ketones and chalcones has been reported.[216]

Fang and co-workers made a series of tetracyclic compounds **366** bearing indole and thiophene rings.[217] The key step is this three-component coupling of methyl thiophene-2-carboxylate with *N*-alkylindole-2-carbaldehyde and 4-methoxyacetophenone. The reaction is promoted by samarium diiodide (Scheme 100). This one-pot operation presumably proceeds

dx.doi.org/10.1021/cr2003954 | *Chem. Rev.* 2012, 112, 3508–3549

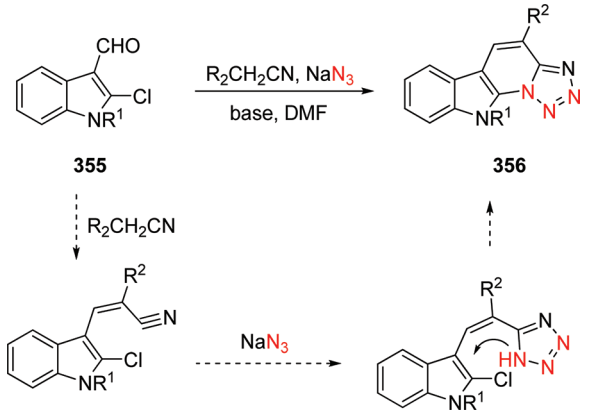
Table 2. Synthesis of Pyrido[1,2-a]indoles



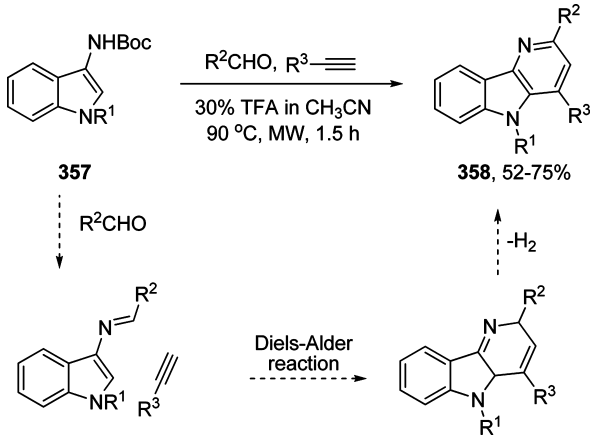
354

R^1	R^2	R^3	yield (%)
CO_2Me	OMe	PhCO	46
CO_2Me	OMe	4-BrC_6H_4CO	41
CO_2Me	OMe	4-$MeOC_6H_4CO$	58
CO_2Me	OMe	C_3H_3CO	40
CO_2Et	OEt	PhCO	49
H	OMe	PhCO	45

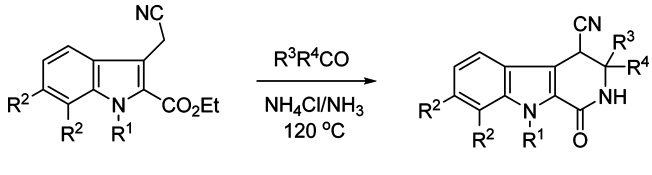
Scheme 95. Proposed Mechanism for the Formation of 356



Scheme 96. Synthesis of δ-Carbolines

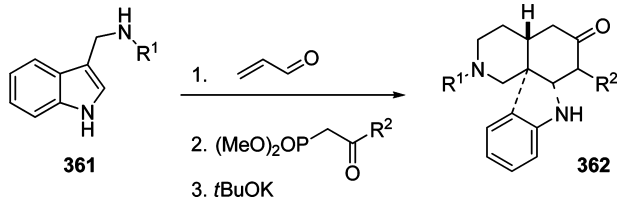


Scheme 97. β-Carbolines Synthesis via MCRs



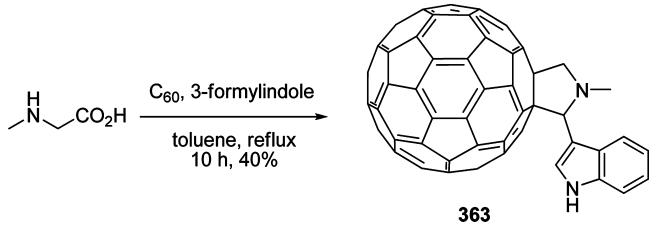
359 **360**, 21-95%

Scheme 98. Preparation of Substituted Tetracycles 362



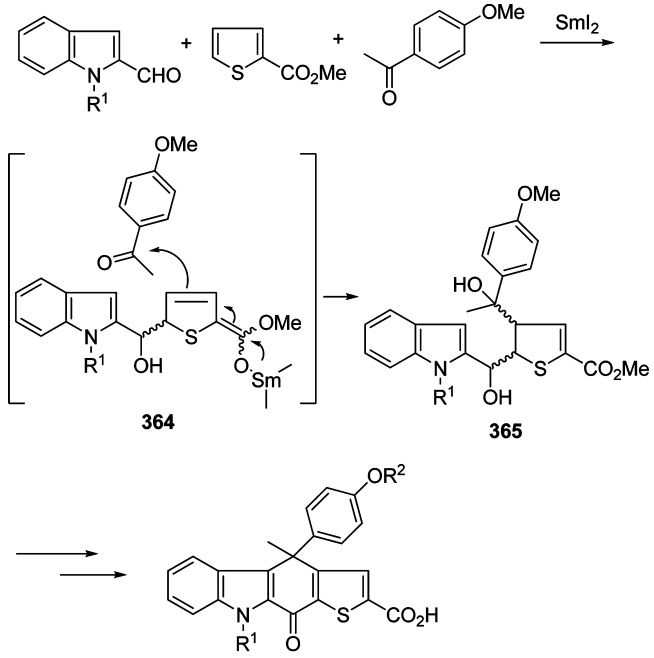
361 362

Scheme 99. C_{60}-Containing Indole



363

Scheme 100. Carbazolothiophene-2-carboxylic Acid Derivatives 366



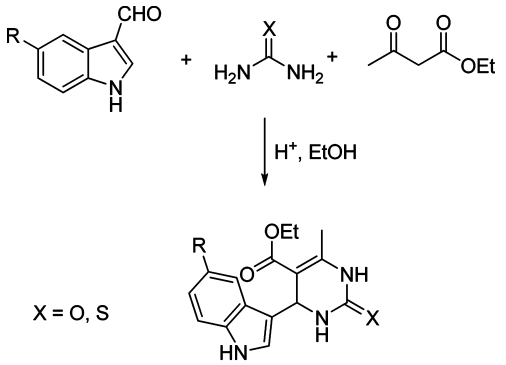
364 365 366

dx.doi.org/10.1021/cr2003954 | Chem. Rev. 2012, 112, 3508–3549

through the initial coupling of the ester with aldehyde to give a dienolate intermediate **364** which is then trapped by the acetophenone leading to compound **365**. 9-Benzyl-4-methyl-4-(4-hydroxyphenyl)-10-oxo-4,10-dihydro-carbazolo[2,3-*b*]thiophene-2-carboxylic acid (**366**, when R^1 = benzyl and R^2 = H) show the most potent inhibition of the endothelin-1 induced increase of intracellular calcium ion concentration.

3,4-Dihydropyrimidine-2 (1*H*)-ones **367** form via the Biginelli three-component condensation of 3-formylindoles, urea or thiourea and ethyl acetoacetate. The antimicrobial activities of these compounds were evaluated (Scheme 101).[218] The reactions of

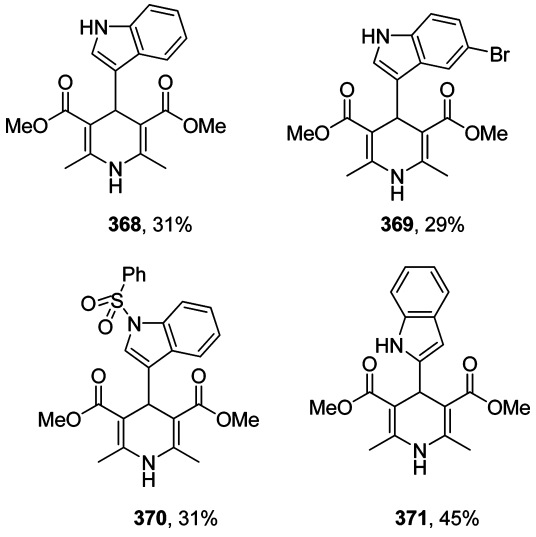
Scheme 101. Indolyl-pyrimidinone 367



367

benzocyclic α-ketoacids as carbonyl components in the Biginelli reaction have been investigated.[219]

A series of indolyldihydropyridines **368**−**371** were synthesized via the Hantzsch reaction of methyl acetyl acetate, 2- or 3-formylindoles under reflux conditions with methanol or ethanol and a solution of 30% NH_4OH (Figure 20). The



368, 31% **369**, 29%

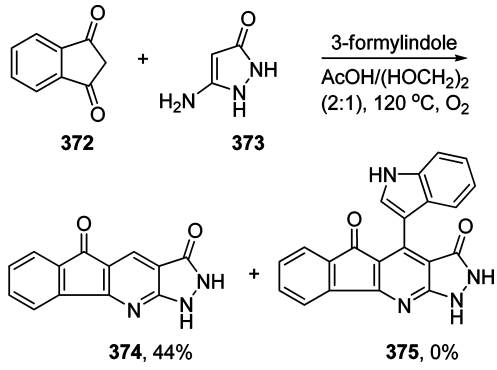
370, 31% **371**, 45%

Figure 20. 2- and 3-Formylindoles in Hantzsch 1,4-Dihydropyridine Synthesis.

calcium channel blocking activity of these compound **368**−**371** were also evaluated.[220a,b] One-pot transition-metal-catalyzed methylenation-hydroboration-Suzuki cross-coupling process with aldehydes has been reported by Lebel et al.[220c]

Surprisingly, the 3-CR of indane-1,3-dione **372**, 5-amino-1,2-dihydropyrazol-3-one **373**, and indole-3-carbaldehyde results in

Scheme 102. 3-Formylindole in Pyridine Synthesis



372 **373**

374, 44% **375**, 0%

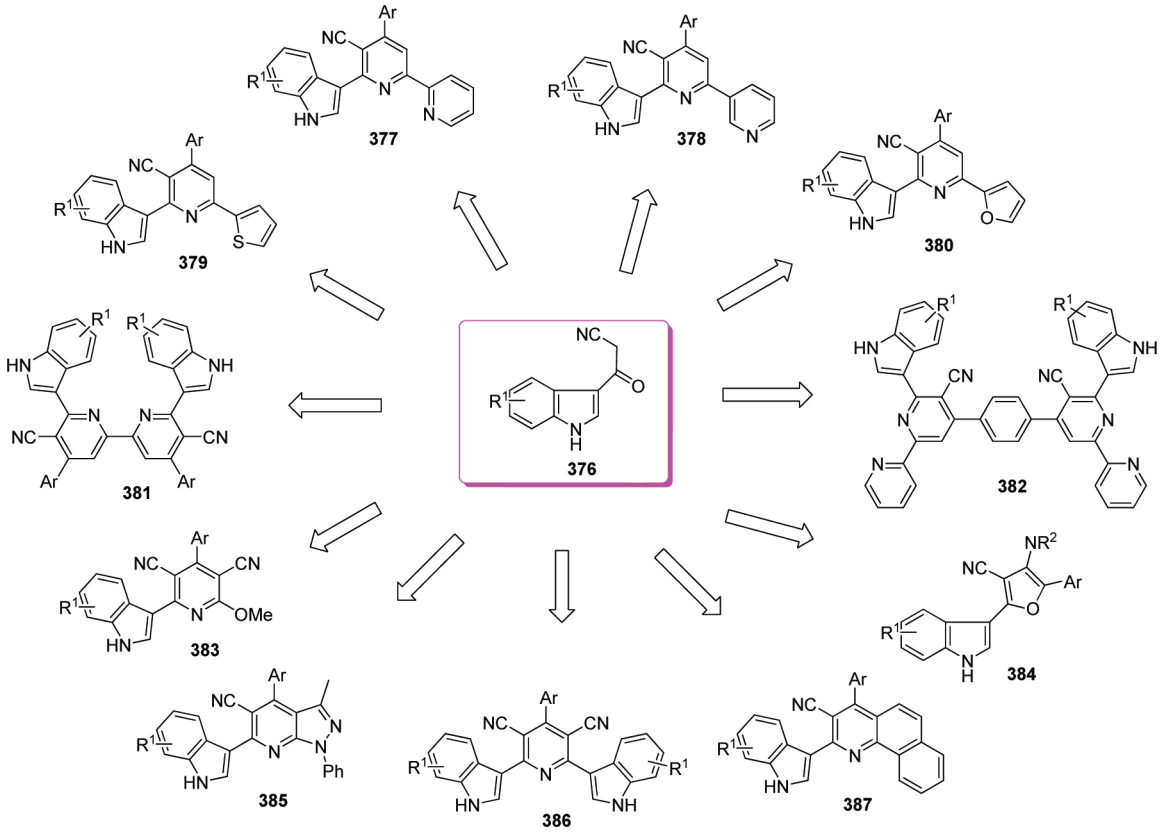
the isolation of tetracycle **374** in 44% yield instead of the expected indolyl derivative **375** (Scheme 102).[221] Compound **374** are also smoothly obtained in 34% yield when formaldehyde is used as the aldehyde. It appears that oxidation of the indole subunit with oxygen occurs before oxidation of the dihydropyridine portion of the molecule resulting in C−C bond cleavage. A simple and efficient direct aldol reaction via the double activation of both aldehydes and ketones by ammonia to afford 2,2-dimethyl-6-aryl-4-pyrilidinones has been developed.[222]

3-(Cyanoacetyl)indoles **376**[223] are prepared from indoles and cyanoacetic acid.[224] These indoles were recently used as starting substrates in the synthesis of a variety of valuable azaheterocyclic compounds (Scheme 103). 2-Acylthiophene, 2- or 3-acylpyridine reacts with indole **376**, aldehyde and NH_4OAc and the 3-CR is cyclized to the corresponding pyridine derivatives **377**−**379** under thermal conditions. The addition of DDQ improves the yield of the products (Scheme 103).[225] A similar reaction under MW irradiation was investigated.[226] Enamines, **376** and aldehydes in the Hantzsch 1,4-dihydropyridine synthesis was reported by Chen et al.[227] Some heterocyclic scaffolds including 6-(2-furyl)-2-(1*H*-indol-3-yl)-4-arylpyridine-3-carbonitriles **380** are made utilizing the same method (Scheme 103).[228] Similarly the poly functional compound **381** is synthesized from cinnamil, compound **376** and ammonium acetate. Compound **382** also forms due to the condensation of terephthaldialdehyde, 2-acylpyridine, **376**, and ammonium acetate at 120 °C or with microwave conditions (Scheme 103).[228,229] Perumal extended the use of 3-cyanoacetyl indole **376** to the $InCl_3$ catalyzed preparation of pyridines derivatives **383** through four-component reactions of aldehydes, **376** and malononitrile in methanol (Scheme 103).[230] Ji and co-workers described the efficient synthesis of 3-(2-furanyl)indole derivative **384** using a three-component reaction between **376**, isocyanides and aromatic aldehydes (Scheme 103).[231] 3-(Cyanoacetyl)indoles **376** also react with arylaldehydes and ammonium acetate under microwave irradiation to form 2,6-diindolyl pyridine derivatives **386** (Scheme 103).[232]

A series of polysubstituted (3-indolyl)pyrazolo[3,4-*b*]pyridines **385** and (3′-indolyl)benzo[*h*]quinoline derivatives **387** are synthesized from **376**, aldehydes or ketones, 3-aminopyrazol or 1-aminonaphthylamine with microwave irradiation in good yield (Scheme 103).[233] When ketones are used in this reaction, the corresponding 1,4-dihydropyridines are generated.[234] 3-Pyranyl indoles are also prepared in the same manner. These 3-pyranyl indoles were evaluated for antimicrobial, antioxidant, and anticancer activities.[235a,b] Compounds **376** were also employed in the synthesis of spiroindolyls.[235c] Some of the compounds also

dx.doi.org/10.1021/cr2003954 | *Chem. Rev.* 2012, 112, 3508−3549

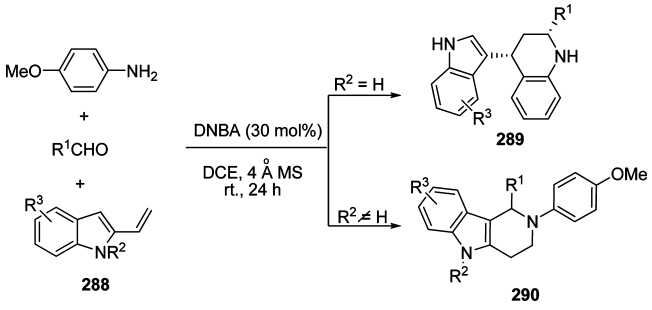
Scheme 103. 3-(Cyanoacetyl)indoles 376 in the Synthesis of Azaheterocyclic Compounds



showed good anticancer activity against MCF-7 breast cancer cell lines in comparison with Doxorubicin that was used as the control drug.

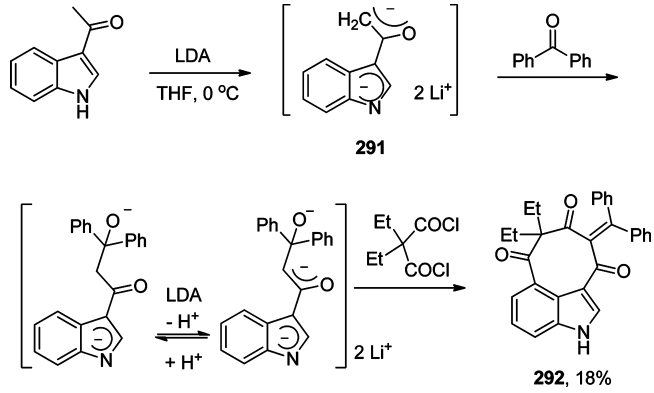
It was found that 2-vinylindoles **388** (R^2 = H) react with aldehydes and *p*-methoxyaniline to form tetrahydroquinoline derivatives **389** in good yield (Scheme 104).[236a] On the other hand when nitrogen protected analogues of **388** are used, tetrahydro-γ-carbolines **390** are isolated as sole product (Scheme 104). These regio- and chemoselective reactions are efficiently catalyzed with 3,5-dinitrobenzoic acid (DNBA) in 1,2-dichloroethane (DCE). Cobalt-catalyzed hydrohydrazination reaction of olefins has been reported.[236b]

Scheme 104. Chemoselective Three-component Reaction of Aldehydes, *p*-Methoxyaniline and 2-Vinylindoles 288



3-Acetylindole in the presence of lithium diisopropylamine (LDA) yields the dianion **291**. The later reacts with benzophenone and subsequent addition of $Et_2C(COCl)_2$ results in the isolation of 1,3,5-triketooctene **292** in 18% yield (Scheme 105).[237] When an excess of LDA is used, regeneration of the enolate anion appears to be possible after condensation of **291** with benzophenone. The carbon center of the enolate reacts with the dielectrophile, and subsequent ring closure involves attack at C-4 of the indole system, as attack at the nitrogen atom would lead to a highly strained product (Scheme 105). The exocyclic double bond C=CPh_2 is formed by elimination of water during the aqueous workup.

Scheme 105. Reaction of the Dianion of 3-Acetylindole with Benzophenone and Diethylmalonic Dichloride



Perumal and his group have prepared 1,4-disubstituted 1,2,3-bis-triazoles **294**. Products **294** were obtained from a variety of *N*-propargyl derivatives **293**, benzyl bromides and sodium azide. CuI was employed as the catalyst in the presence of PEG-400 (Scheme 106).[238a] These triazoles have also been screened for their biological activity. In addition the one-pot process reaction of

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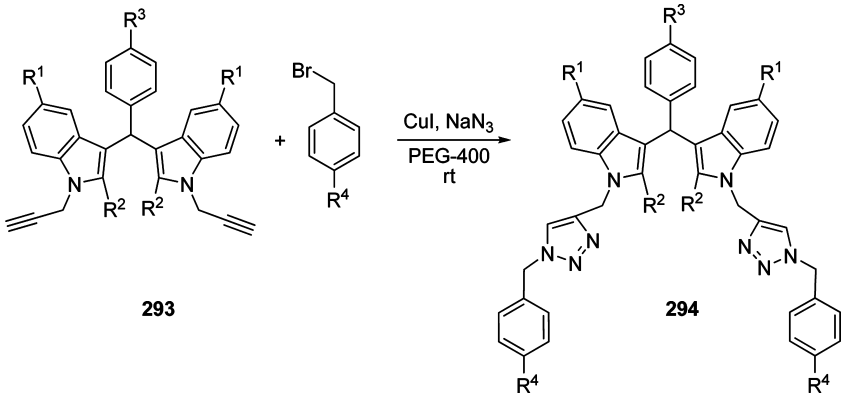
Scheme 106. Triazole BIM Derivatives

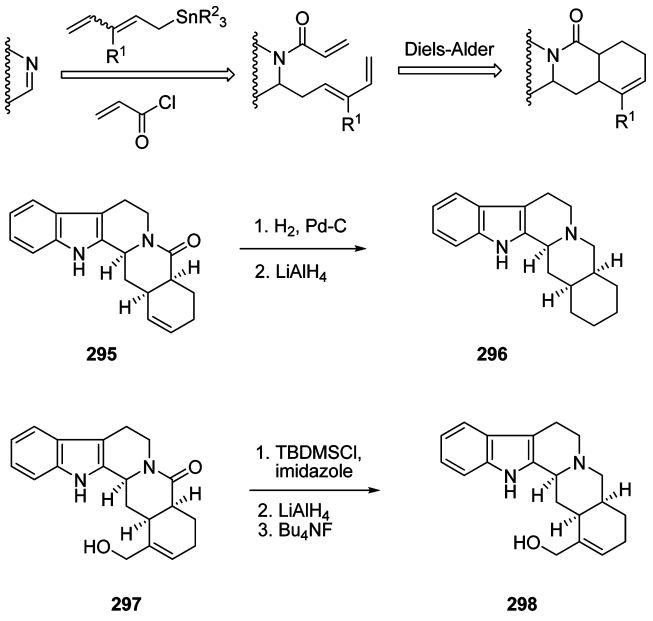


conjugated enyne, carbene complex and 2,3-dihydrofuran leading to polycyclic compounds have been reported.[238b]

5. SYNTHESIS OF INDOLE BEARING NATURAL PRODUCTS VIA MCPS

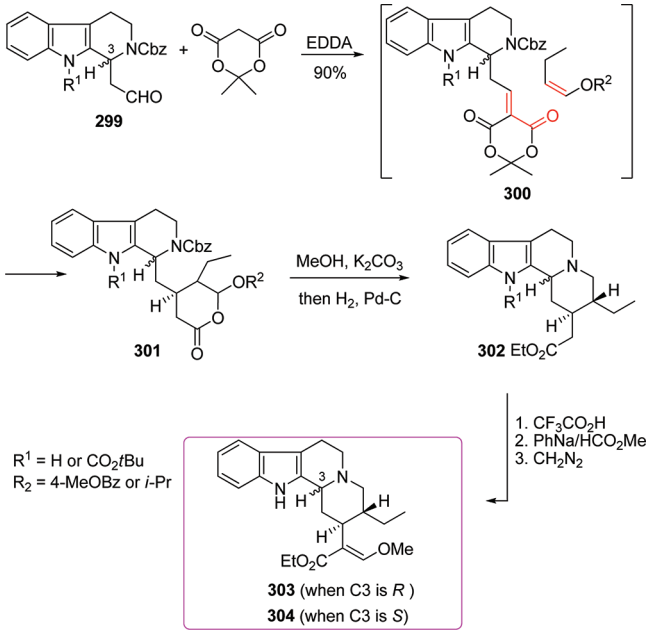
Indole alkaloids usually have complex structures and chemists normally prefer to synthesize them by means of multistep processes. However, MCRs methodology offers an alternative method with a reduced number of steps.[239a] For example, the schematic plan for the one-pot synthesis of compounds **295** and **297** is shown in Scheme 107. These products are precursors for (±)-*allo*-yohimban **296** and (±)-nitraraine **298**, respectively (Scheme 107).[239b,c] In this method the C=N bond of the cyclic imines, acryloyl chloride, and 2,4-pentadienyltin are coupled together, followed by the spontaneous intramolecular Diels–Alder cycloaddition reaction (Scheme 107).

Scheme 107. MCRs in the Synthesis of (±)-*allo*-Yohimban 296 and (±)-Nitraraine 298



Tietze[240] and Zhou have demonstrated that the biologically interesting hirsutine **303**, an alkaloid, can be obtained with high selectivity and efficiency from simple precursors such as **299** (when R^1 = CO_2tBu and C3 has *R* configuration), Meldrum's acid and 4-methoxybenzyl butenyl ether (*E*:*Z* ≈ 1:1). The MCR consists of a sequence of domino reactions, namely a Knoevenagel–hetero-Diels–Alder reaction in the presence of ethylene diammonium diacetate (EDDA). Solvolysis of the formed lactone **301** with methanol/K_2CO_3 and subsequent hydrogenation to **302** is followed by the condensation of the latter with methyl formate and treatment with diazomethane lead to the desired product **303** (Scheme 108).[241] Dihydrocorynantheine **304** is also analogously formed from **299** (when R^1 = H and C3 is *S* configuration), Meldrum's acid and *iso*-propyl butenyl ether (Scheme 108).

Scheme 108. MCRs in the Synthesis of Hirsutine 303 and Dihydrocorynantheine 304



Hirsutine **303** was successfully obtained by means of an alternative 3-component process in which dihydrocarboline **305** is treated with allyltributyltin and acryloyl chloride to furnish **306** in 75% yield. Cyclization of **306** in the presence of 4 mol % of Grubbs' catalyst **307**, produced **308** in 87% yield. Several more steps are required for the ultimate preparation of Hirsutine **303** (Scheme 109).[242] Precursor **305** was also used in an enantioselective manner for the synthesis of azaeburnane analogue.[243a] In situ preparation of **305** and participation in Ugi-condensation has been reported.[243b]

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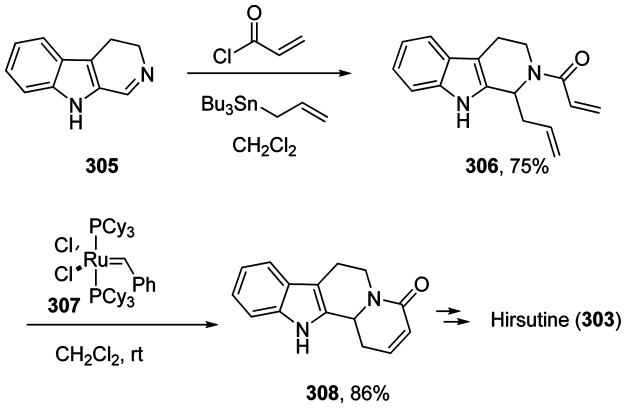
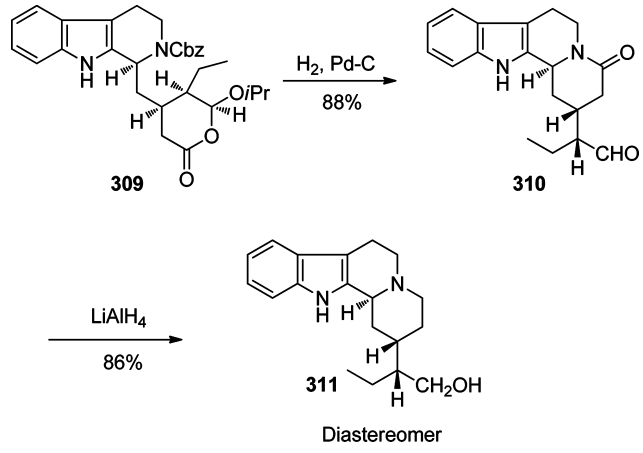
Scheme 109. Grubbs' Catalyst 307 in Hirsutine 303 Preparation



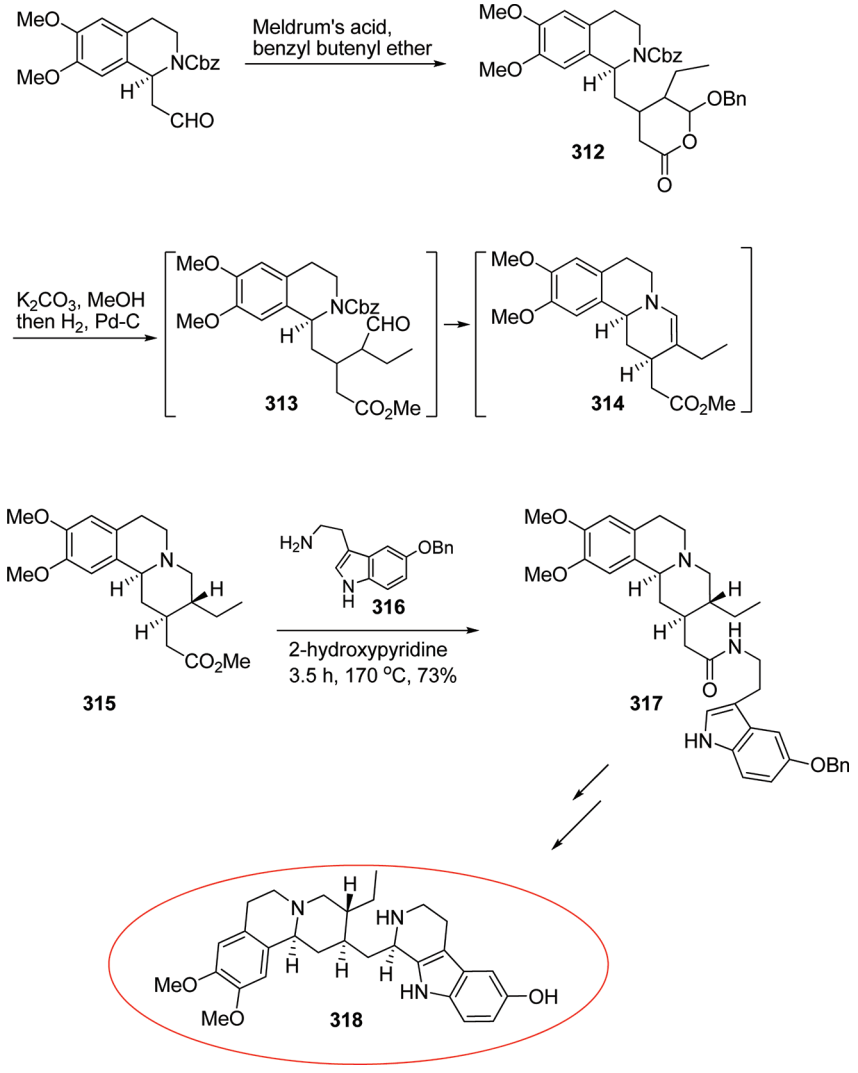
Scheme 110. Synthesis of (−)-Dihydroantirhine 311



Tietze et al. have prepared compound **309** via a 3-CR (Scheme 110). The latter is converted to **310** in the presence of H_2 catalyzed by Pd (Scheme 110).[244] Reduction of the lactam **310** with $LiAlH_4$ gives the indole alkaloid (−)-dihydroantirhine **311**.

They also used this methodology in the preparation of the lactone **312** (Scheme 111).[245] The cycloadduct **312** is directly treated with K_2CO_3/MeOH and a catalytic amount of Pd−C in methanol under a nitrogen atmosphere for 50 min. After that the mixture is stirred under a H_2-atmosphere for 2 h at room temperature to give the benzoquinolizidine **315** via **313** and **314** with the correct stereochemistry at all stereogenic centers (Scheme 111). The alkaloid tubulosine **318** was successfully

Scheme 111. Synthesis of Tubulosine 318



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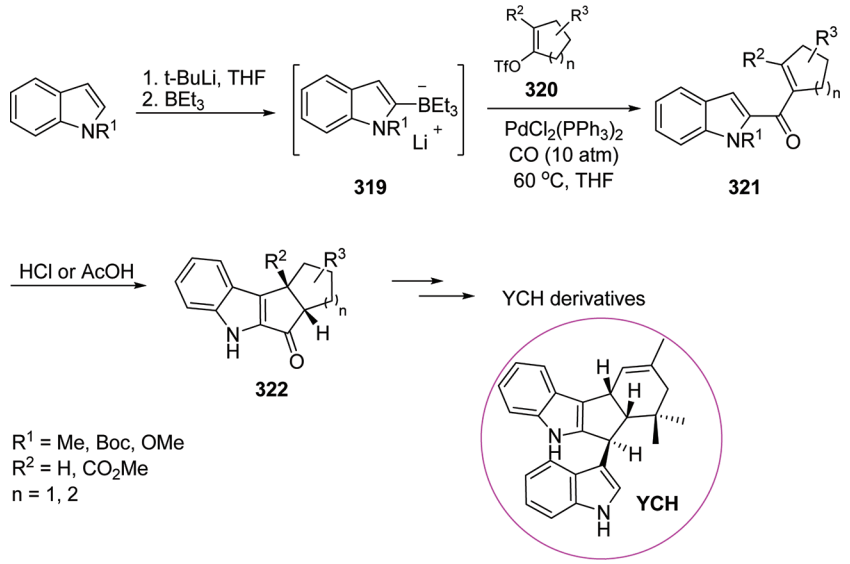
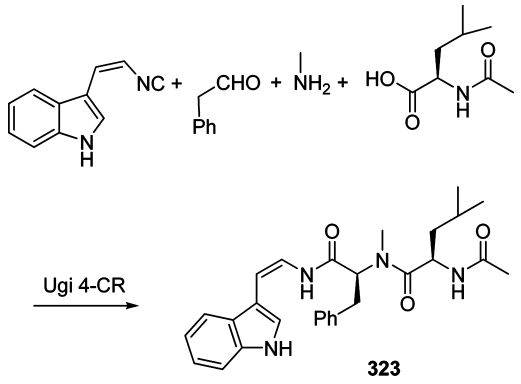
Scheme 112. Palladium Cross-Coupling in the Synthesis of YCHs



Scheme 113. Spergillamide 323 Formation via a Ugi Reaction



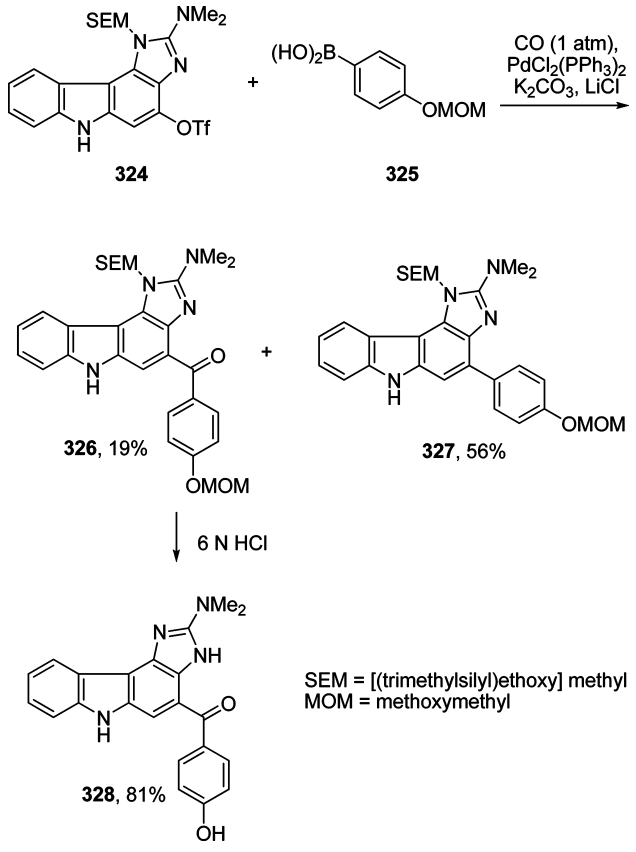
synthesized by reacting benzoquinolizidine **315** with *O*-benzyl seretonine **316** to form the amide **317**; further transformations lead to **318**.

Ishikura et al. employed a palladium catalyst for the one-pot carbonylation and cross-coupling reaction of indolylborates **319** with vinyl triflates **320** in the presence of carbon monoxide to prepare 2-acylindole **321**. Compound **321** is converted to **322** by acid catalysis and then used as precursor for the synthesis of Yuehchukene (YCH)[246] (Scheme 112).[247] A highly efficient diastereoselective and enantioselective one-pot multistep reaction for the construction of cyclopenta[b]indoles has been reported by Guo and co-workers.[248]

A typical natural products such as spergillamide **323** and its analogues are synthesized with MCRs (Scheme 113).[249] Dömling and co-workers reported a solution phase Ugi 4-CR method to get access to these compounds. The antibiotic and cytotoxic activities of these compounds were measured. Several of the synthetic analogues are more potent than the original natural product.

Choshi et al. have prepared **324** and used it as a convenient starting material for the synthesis of grossularine-2 **328** via a three-component cross coupling reaction (Scheme 114).[250] The reaction of the triflate **324**, carbon monoxide and

Scheme 114. Synthesis of Grossularine-2

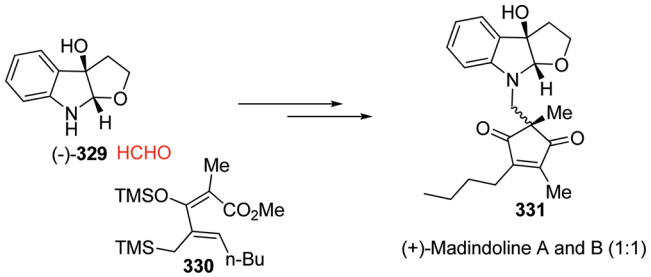


phenylboronic acid **325** is carried out at 80 °C in the presence of $PdC1_2(PPh_3)_2$ in anisole to provide the tetracyclic 2-benzoylpyrido[2,3-b]-indole **326** (19%) along with 2-phenylpyrido[2,3-blindole **327** (58%). Subsequent hydrolysis of the *N*-SEM group of **326** with diluted acid gives a natural grossularine-2 (**328**) in 81% yield (Scheme 114).

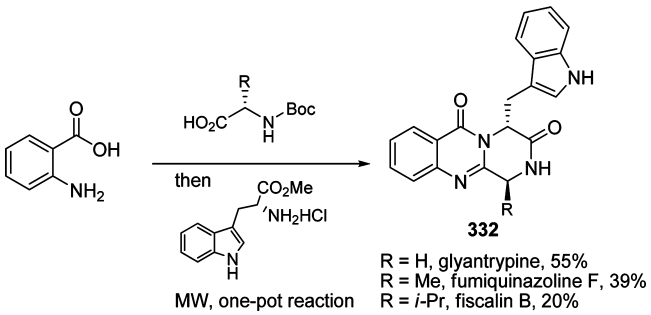
A Mannich three-component reaction of hydroxyfuroindoline (−)-**329**, formaldehyde and silylenolether **330** as the key

dx.doi.org/10.1021/cr2003954 | *Chem. Rev.* 2012, 112, 3508–3549

Scheme 115. (+)-Madindolines A and B 331



Scheme 116. MW in the Construction of 4-Quinazoline-3,6-diones (332) Scaffold



step is used for the construction of (+)-Madindolines A and B **331** as potent IL-6 inhibitors (Scheme 115).[251]

A microwave promoted 3-CR of *o*-amino benzoic acid, D-tryptophan methylester hydrochloride and related amino acid leads to the corresponding natural products **332**, glyantrypine (R = H), fumiquinazoline F (R = CH_3) and fiscalin B (R = *i*-Pr) in overall yields of 55%, 39%, and 20%, respectively (Scheme 116).[252]

Recently, Takiguchi et al. reported the asymmetric total synthesis of two anticancer natural products **334** and **335** employing a common tricyclic imine precursor **333** and an Ugi reaction (Scheme 117).[253] Thus *N*-acetylardeemin was accessed by the Ugi-3CR of **333** with anthranilic acid, isocyanide, and N-protected D-Ala in toluene followed by deprotection and polycondensation, whereas fructigenine was synthesized by the Ugi-3CR of **333** with *p*-methoxybenzyl isocyanide and Boc-Phe with subsequent deprotection and diketopiperazine ring closure under basic conditions. In both cases, the Ugi reaction was highly stereoselective and the isocyanide attack takes place preferentially from the side opposite the bulky reverse-prenyl group of imine **333**.

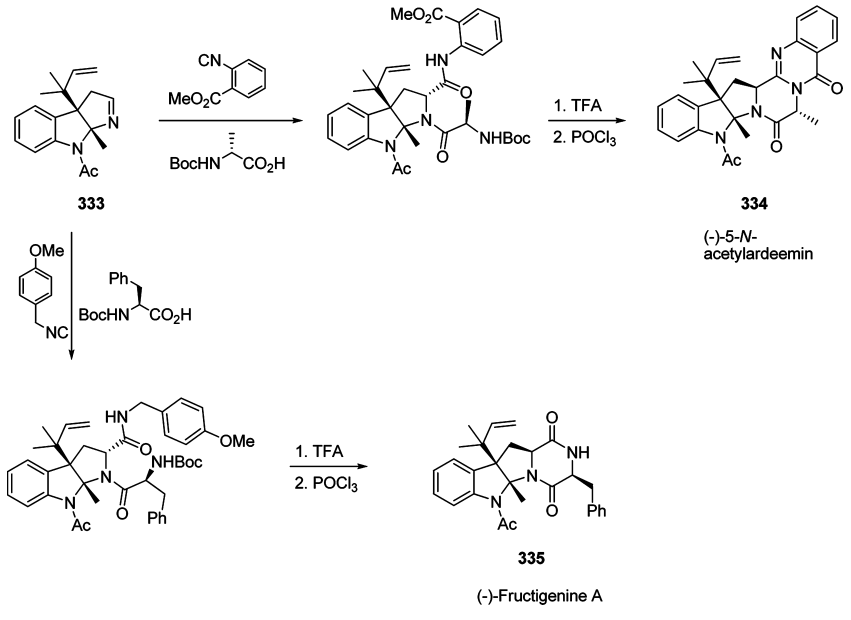
Kobayashi et al. have prepared tetracyclic chiral aminoacetals **339** via a one-pot procedure involving a Stille–Migita coupling, a 6π-azaelectrocyclization, and aminoacetal formation from vinylstannanes **338**, vinyliodides **337**, and cis-aminoindanol derivatives **336** (Scheme 118).[254] The same group also reported a modified strategy for the successful synthesis of indole alkaloids (−)-20-epiuleine **340**,[255] (−)-corynantheidol **341**, and (−)-corynantheidine **342** (Scheme 118).[256] In a combine vinylogous Mukaiyama–Mannich and Diels–Alder reactions stereoselectively some hexahydroindoles were synthesized which are represent precursors of complex natural products.[257]

6. MISCELLANEOUS REACTIONS

Petasis et. al employed indolyl boronic acids, amines and aldehydes to open a new route for the highly selective functionalization of indoles.[47] The Petasis method was also used by Jiang et al. to prepare optically pure 3-indolyl *N*-substituted glycines **343** in 61 to 77%. They employed a chiral amine as the chiral auxiliary in the absence of any catalyst (Scheme 119).[258]

In the course of a tandem alkylation/alkenylation reaction of 3-iodothiophene to construct trisubstituted thiophenes via a palladium-catalyzed system, Lautens and his group discovered that this methodology can also be extended to include indoles.[259] After screening of the reaction parameters, compound **345** was isolated in 81% yield from **344** and *tert*-butyl acrylate and 1-iodobutane (Scheme 120). It is worthy to note that the nature of the nitrogen protecting group is crucial for the efficiency of the reaction. The use of a methyl protecting group yields only the direct Heck product.

Scheme 117. Ugi Reaction as a Key Step in the Asymmetric Total Syntheses of Two Pyrazino-pyrroloindole Alkaloids, Fructigenine A, and 5-*N*-Acetylardeemin



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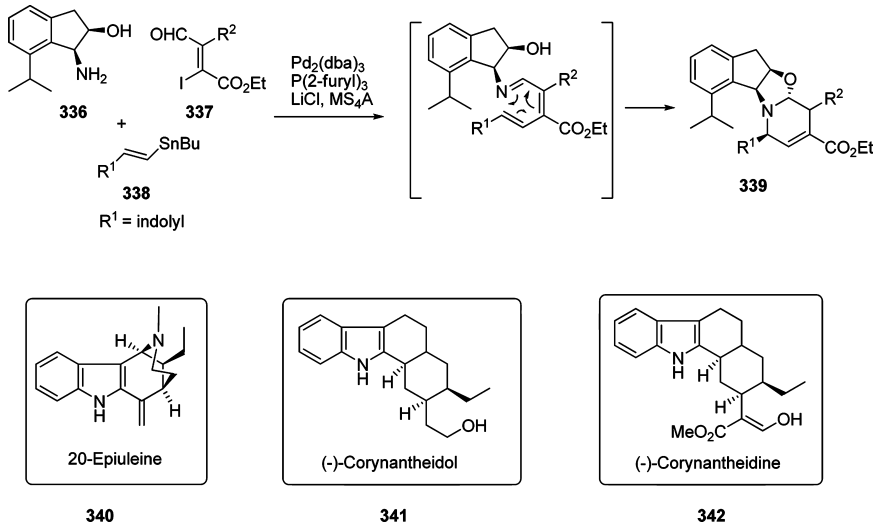
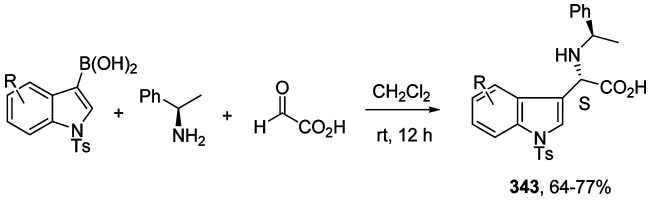
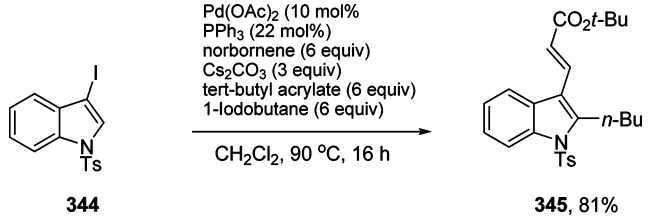
Scheme 118. Synthesis of (−)-20-Epiuleine, (−)-Corynantheidol, and (−)-Corynantheidine



Scheme 119. Asymmetric Synthesis 3-Indolyl Substituted via Petasis Reaction



Scheme 120. Tandem Alkylation/Alkenylation of Indole 344



Müller and co-workers have developed a new method for the synthesis of naturally occurring indolyl pyrimidinones, such as meridianins and variolins via carbonylation/alkynylation of 3-iodoindoles and subsequent cyclocondensation.[92] They have utilized a mixture of (5% $[Pd(PPh_3)_2Cl_2]$) (**E**) and (1% $[Pd(dppf)Cl_2]$) (**F**) as the catalytic system for efficient coupling of 3-iodoindole, carbon monoxide and trimethylsilyl acetylene. The corresponding TMS-ethynylindoles **346**−**348** were isolated in good yields (Figure 21). But for the pyrrolopyridine **349** it turned out that a 0.05 equiv of $[Pd(PPh_3)_2Cl_2]$ provides a better yield than with the mixture of catalysts.

In a sequential reaction the protected indolecarboxaldehyde **350** is condensed with allyl amine to generate an intermediate imine that is treated with acetyl chloride and allylmagnesium bromide to furnish adducts **351** in a one pot process (Scheme 121).[260] The latter is converted to the bridged bicyclic tetracycle **353** upon sequential ring closing metathesis (RCM) and Heck reactions and treatment with ruthenium **352** and $Pd(OAc)_2$ respectively (Scheme 121). In another strategy the indolic aldehyde **350** is reacted with bis(trimethylsilyl)allylamine providing an intermediate imine that is treated in situ with acetyl chloride and the silyl ketene acetal **354** to furnish the amide **355** in 72% yield (Scheme 121).[260] Bromoindole **355** is subjected to an intramolecular Heck cyclization reaction under microwave irradiation in the presence of $Pd(OAc)_2$, to give **356** as two isomers $\Delta^{4,5}$ and $\Delta^{3,4}$ in 85% and 12% yield, respectively.

Langer and co-workers started from *N*-methyl-2,3-dibromoindole **357** and utilized a Suzuki−Miyaura reaction with two different arylboronic acids. This one-pot approach is selective for the synthesis of unsymmetrical 2,3-diarylindoles **358** (Scheme 122).[261] Because position two of the indole ring is more electron-deficiencient than position three, the oxidative addition of palladium to indole **357** occurs first at position two.

In a three component cyclization-anion transfer process the alkene **359** and stannyl indole **360** are undergoing concomitant carbonylation with carbon monoxide to produce 2-oxoindolyl derivatives **361** in good yield (Scheme 123).[262] Palladium catalyzed aminocarbonylation of aryl halides with an amine and carbon monoxide[263] and carbonylation of indolylborate with carbon monoxide and alkenes have been reported.[264]

Chataigner and Piettre have described the feasibility of a multicomponent domino [4 + 2]/[3 + 2] cycloaddition reaction with electron-poor nitroheteroaromatics.[265a] 3-Nitroindole is used

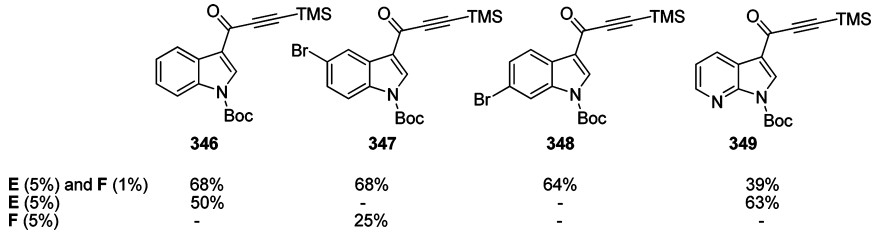


Figure 21. Products via carbonylation/alkynylation of iodoindoles.

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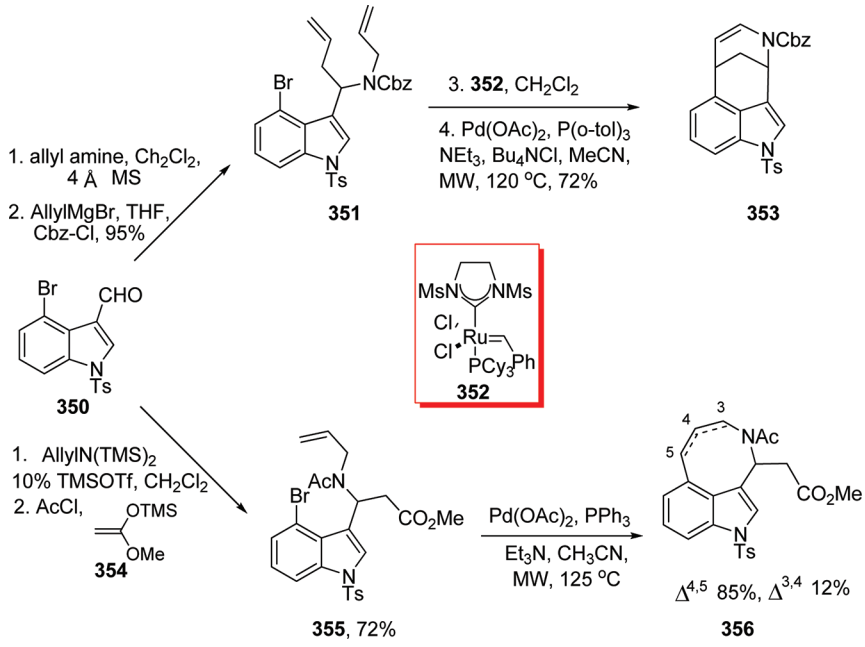
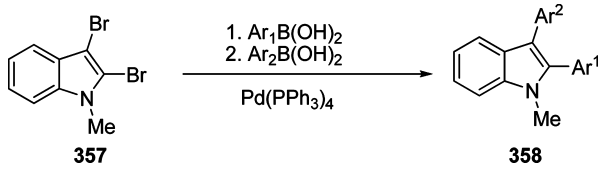
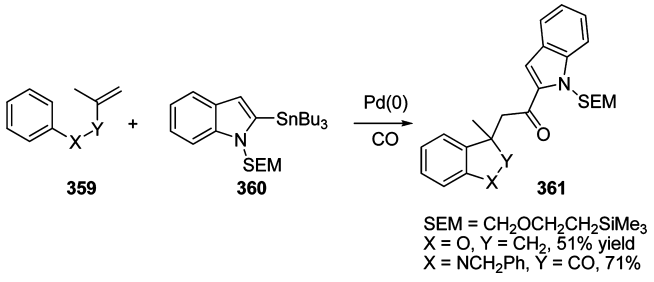
Scheme 121. Ru and Pd in the Formation of Tetracyclic 353 and Tricyclic 356, Respectively



Scheme 122. Synthesis of Unsymmetrical 2,3-Diarylindoles 358



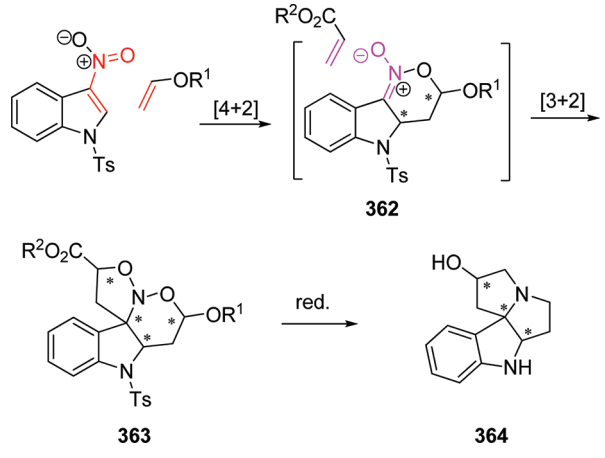
Scheme 123. 2-Oxoindolyl Derivatives



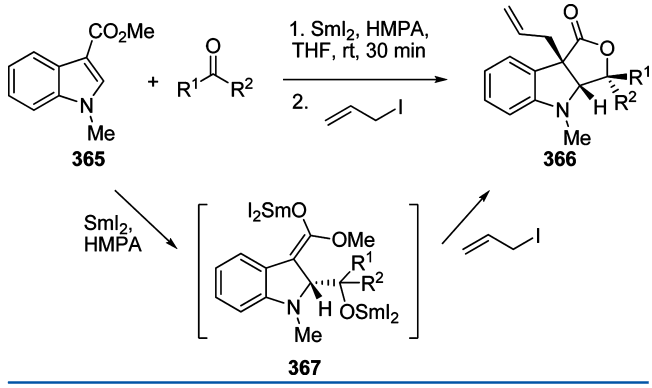
for the rapid and efficient generation of tetracyclic dearomatized diamines **363** featuring a quaternary center at one of the ring junctions (Scheme 124). It is clear that it would be quite difficult to prepare these novel structures with alternative synthetic methods. The reduction products of **364** are considered to be potential candidates for the design and preparation of novel catalysts in the context of asymmetric synthesis. Activation of 3-nitroindole at high pressure allows it to behave as electron-poor heterodienes for a [4 + 2] cyclization with vinyl ethers to form **362**. The latter participates in a [3 + 2] cycloaddition process with acrylate to give **363** in good yield. Already similar sequence cycloaddition has been reported for *β*-nitrostyrenyl compounds.[265b]

The Samarium-mediated reaction of indole **365** with carbonyl compounds followed by trapping of the intermediate **367** with allyl iodide leads to the synthesis of the highly stereoselective lactone **366** in 42−94% yield (Scheme 125).[266]

Scheme 124. Domino [4 + 2]/[3 + 2] Cycloaddition Reaction



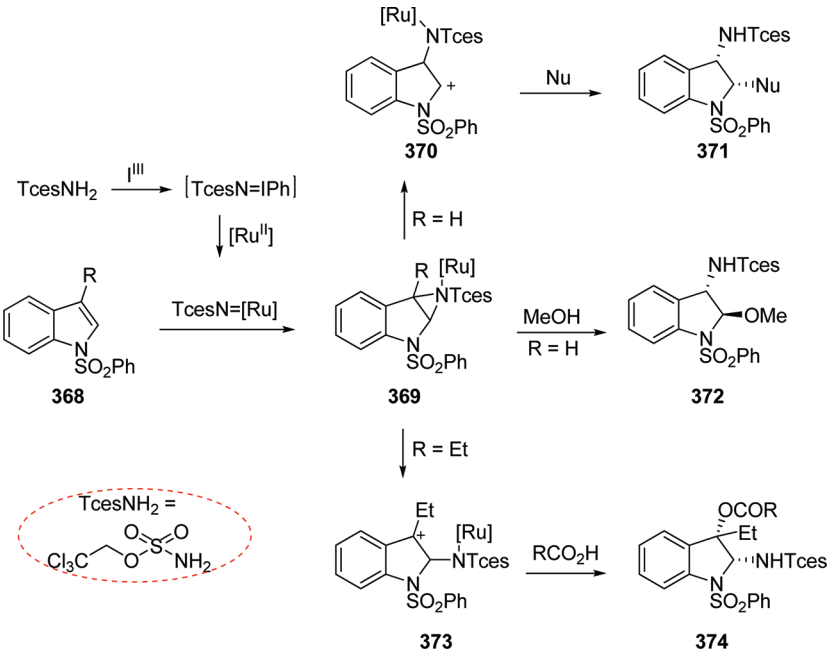
Scheme 125. Highly Stereoselective Substitution in the Dihydroindole Derivatives 366



Rhodium catalyzed nitrene addition to indolic derivatives has been reported.[267] In the proposed mechanism for this reaction, amine and iodine(III) yield iminoiodane which is transferred to

dx.doi.org/10.1021/cr2003954 | Chem. Rev. 2012, 112, 3508−3549

Scheme 126. Access to 2,3-Substituted Indolines



[Ru^{III}] (Scheme 126). The produced metalonitrene is added to pi-bond of indole **368** to yield the aziridine intermediate **369**. The latter undergoes fast ring-opening to give rise to a carbocation, the nature of which depends on the substitution pattern at the C3 position. In the case of **369** (R = H), formation of cation **370** is favored, whereas aziridine **369** (R = Et) preferentially affords the more stable tertiary benzylic cation **373**.

Both intermediates (**370** and **373**) are then attacked in a cis manner by nucleophiles, presumably owing to conformational effects, however, aziridine **369** (R = H), in the presence of methanol as nucleophile gives the trans-product **372**. A key feature of this transformation is the ability to control either its stereoselectivity by changing the nucleophile or its regioselectivity by the introduction of a substituent at C3.

7. CONCLUSIONS

It was demonstrated that the MCR technology has emerged as a valuable tool in the synthesis of natural and synthetic indole derivatives. This method offers the opportunity of synthesizing molecules via novel routes, which may be difficult or impossible with traditional methods. It also offers the possibility for the rapid synthesis of potential drugs without tedious and time-consuming purification.

This technology depends mainly on the polycondensation of a large diversity of functional groups such as acids, isocyanides, amines, aldehydes, ketones, methylenes, aryls etc. or also a combination of two or three well-known reactions such as the Heck, Diels–Alder, Knoevenagel, Mannich, Ugi, Smile, Petasis reactions, etc.

In addition, research on MCRs opened exciting opportunities in the field of green organic reactions or green chemistry by minimizing waste, cost, and time. These are valuable factors in the chemical and pharmaceutical industries. The continued evolution of such methodologies promises new routes to readily synthesize complex molecules previously thought to inaccessible.

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Notes

The author declares no competing financial interest.

Biography

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

ACKNOWLEDGMENTS

The author thanks Alzahra University and Iran National Science Foundation (INSF) for financial support to our research group. Professor H. G. Kruger from UKZN in South

Africa is also greatly appreciated for proof-reading the manuscript and giving valuable suggestions.

DEDICATION

Dedicated to Prof. Mohammad Ali Zolfigol

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