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UMPOLUNG OF ELECTRON-RICH HETEROARENES WITH HYPERVALENT IODINE REAGENTS

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Abstract – Five-membered heterocycles are well known for their innate nucleophilicity. In contrast, reaction of these heterocycles as electrophiles is less established and has become only recently an intensively investigated research area in synthetic chemistry. The use of hypervalent iodine reagents for the umpolung of the nucleophilic reactivity has been especially successful. This review provides a comprehensive overview regarding the generation of electrophilic intermediates from electron-rich heterocycles using hypervalent iodine reagents. The functionalization with different heteroatoms, arenes or heteroarenes nucleophiles is then described.

In Celebration of Professor Yasuyuki Kita for His 77th Birthday

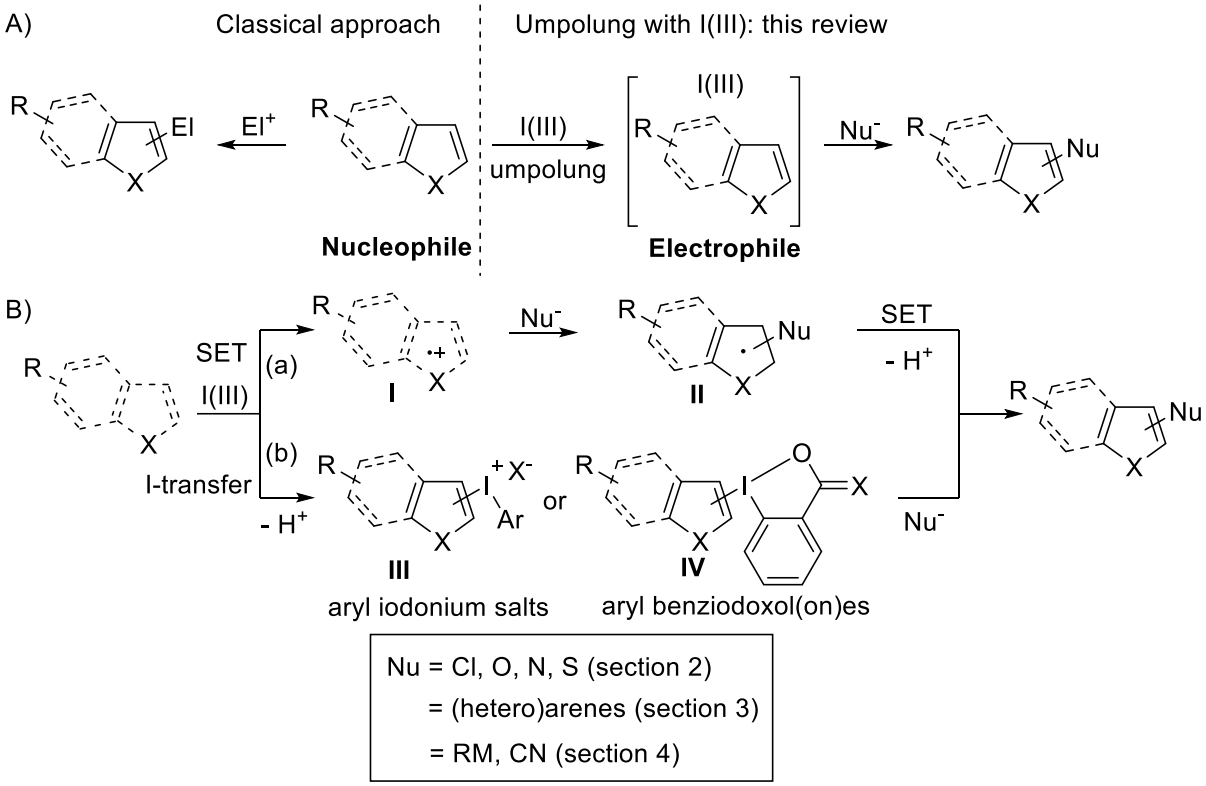
CONTENTS

1. INTRODUCTION

Heteroarenes are among the most important building blocks of drugs, agrochemicals and organic materials.[1] Among them, five-membered heterocycles and their derivatives fused to benzene rings such as pyrroles, indoles, furans and thiophenes occupy a privileged position. It is therefore not surprising that the synthesis and modification of these heterocycles has been the focus of synthetic organic chemistry since its beginning. Five-membered heterocycles are inherently nucleophilic, so that electrophilic aromatic substitutions have been especially successfully used to modify them (Scheme 1A). However, this approach limits the structural diversity of products that can be synthesized. The combination of electron-rich heterocycles with nucleophilic partners requires a umpolung (i.e. reversal of polarity) of the heterocycles. However, such a reversal of reactivity is difficult to achieve, unless strong electron-withdrawing groups are present on the heterocycles.[2]

In this context, hypervalent iodine reagents are now well-established for their capacity to achieve a formal umpolung of the reactivity of diverse nucleophiles.[3] Whereas iodine(V) reagents have been especially successful as oxidants (Dess-Martin periodinane, IBX), iodine(III) reagents have enabled the transfer of numerous inherently nucleophilic groups such as heteroatoms, alkynes, alkenes, arenes or trifluoromethyl groups as electrophiles. Recently, they have led to important breakthroughs for the umpolung of electron-rich arenes also (Scheme 1A).[3g] The group of Kita has been leading this research for over three decades. Their contribution towards metal free cross coupling of different heterocycles, especially pyrroles and thiophenes, with hypervalent iodine reagents is one of the most impressive achievements in the area. Mechanistically, the umpolung of heterocycles with hypervalent iodine reagents has been proposed to follow either a single electron transfer (SET) or an iodine transfer pathway ((a) and (b) in Scheme 1B). The former leads to the formation of highly electrophilic radical cation **I**, which reacts rapidly with nucleophiles. The formed radical **II** can then be further oxidized in a second SET step, and deprotonation leads to the product. In the iodine transfer pathway, new hypervalent iodine reagents are formed: either aryliodonium salts **III**, or recently introduced more stable cyclic benziodoxol(on)e reagents **IV**. Reaction with the nucleophile then gives the product. In this review, we will describe the use of these two approaches for the umpolung of electron-rich heteroarenes, classifying the reaction in dependence of the used nucleophilic partner. We will start with the coupling of electron-rich heterocycles with heteroatom nucleophiles (section 2, halogens, oxygen, nitrogen and sulfur) and then move to C-C

coupling reactions with electron-rich (hetero)-arenes (section 3). Finally, rare examples of other transformations, such as alkylation and cyanation will be described (section 4).



Scheme 1. A) Umpolung of the reactivity of electron-rich (hetero)arenes. B) Mechanisms for umpolung with hypervalent iodine reagents and reported nucleophilic partners.

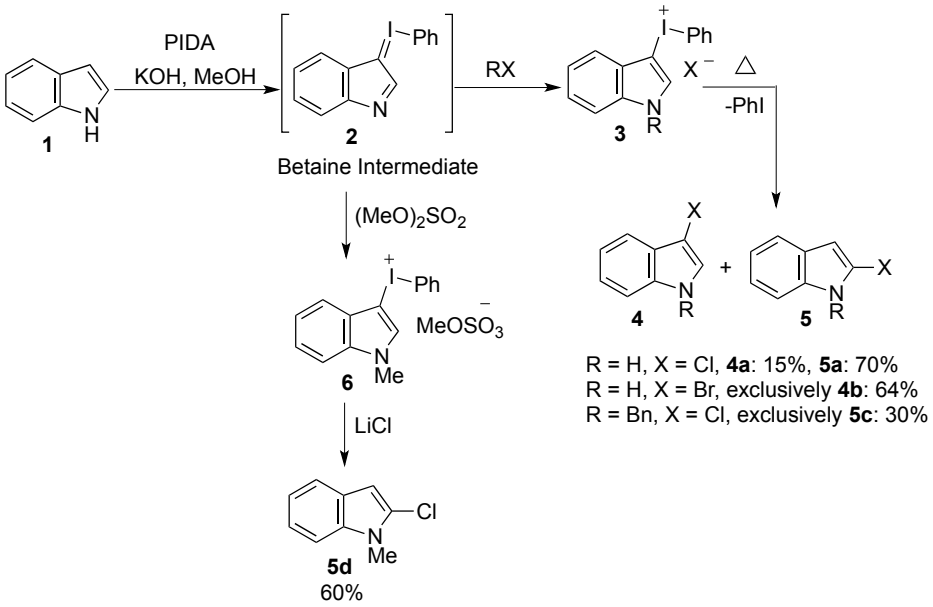
2. FUNCTIONALIZATION OF ELECTRON RICH HETEROCYCLES WITH HETEROATOM NUCLEOPHILES

When considering the coupling of an electron-rich heterocycle with a nucleophilic heteroatom, a umpolung of the reactivity is needed. By far the most common approach is by inverting the reactivity of the heteroatom nucleophile. For this approach, hypervalent iodine reagents are well suited and have been often used.[3] In this review, we will focus on the alternative reverse approach: inverting the reactivity of the heterocycles for reaction with unchanged heteroatom nucleophiles.

2.1. HALOGENATION

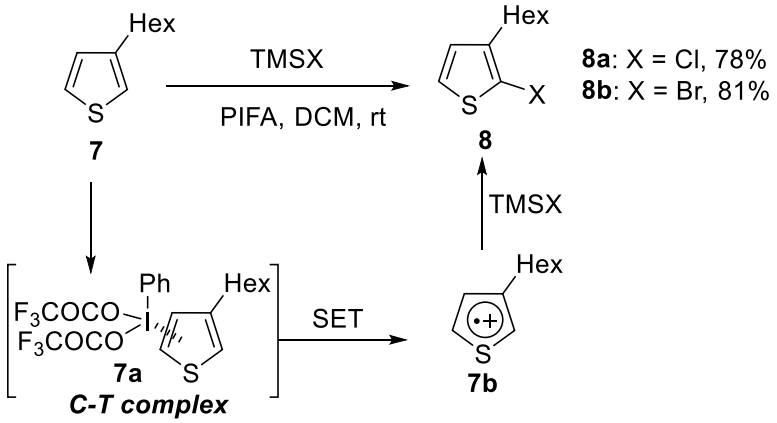
A nucleophilic halogenation of indoles (at both C2 and C3 position) was reported via indole-based iodonium reagents as early as 1981.[4] Indole-based iodonium salts were first reported in the 70s by Neiland and coworkers[5] followed by the groups of Kost,[6] and Moriarty.[7] Starting from indole (**1**) a two step procedure involving oxidation using iodobenzene diacetate (PIDA) via a spontaneously detonating

betaine intermediate **2** was required to access iodoniums **3** (Scheme 2). Among a few reported transformations, a halogenation was achieved by Kost and co-workers.[4] Treatment of intermediate **2** by halo acids (HCl and HBr) followed by heating furnished halogenated indoles **4** and **5** via iodonium **3**. A mixture of products (halogenated at both C2 and C3, **4** and **5**) were obtained for HCl, but with HBr exclusively 3-bromoindole **4b** was isolated in 64% yield. 2-Chloroindole derivative **5c** was obtained exclusively via *N*-benzylation followed by heating in 30% yield. Methylation followed by reaction with LiCl afforded **5d** as only regioisomer in 60% yield via iodonium **6**. It is interesting to note that methods based on electrophilic chlorination would lead to the formation of products such as **4** as major outcome.



Scheme 2. Halogenation of indoles involving betaine intermediate **2**

In 2009, Kita et al. reported a PIFA mediated halogenation of 3-hexylthiophene **7** using 2 equivalents of trimethylsilyl halide (Scheme 3).[8] 2-Chloro derivative **8a** was obtained in 78% yield by using TMSCl, whereas the use of TMSBr gave 2-bromo derivative **8b** in 81% yield. The single-electron-transfer (SET) oxidation ability of phenyliodine(III) bis(trifluoroacetate) (PIFA) is believed to lead to the formation of radical cation **7b** via charge-transfer (C-T) complex **7a**. Radical **7b** then reacts with chloride. A second SET step followed by rearomatization then gives product **8**.

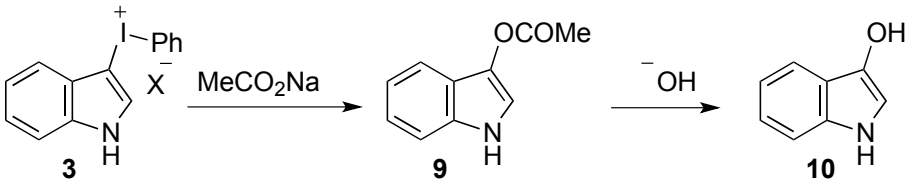


Scheme 3. PIFA mediated halogenation of thiophene derivatives **7**

In addition, Moriyama, Togo and coworkers reported a halo amino functionalization,[9] which will be discussed in details in Section 2.3.

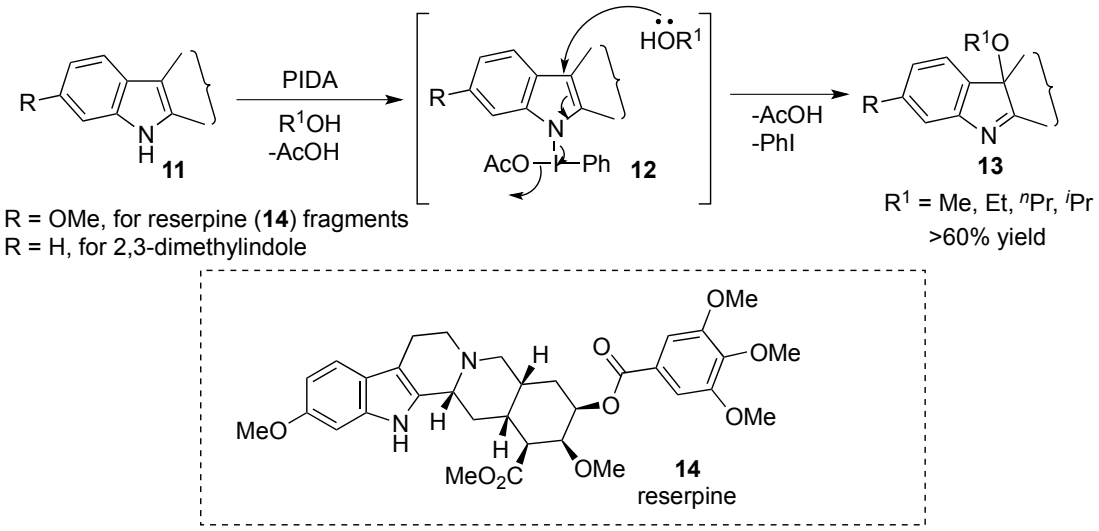
2.2. FUNCTIONALIZATION WITH OXYGEN NUCLEOPHILES

The introduction of hydroxy functional group in indole heterocycles was also reported by Neiland and coworkers in their first article on indole-based iodonium reagents.[5a] Treatment of **3** with sodium acetate and subsequent alkaline hydrolysis of acyloxy derivative **9** affords 3-hydroxyindole **10** (Scheme 4). As **10** was directly used for indigo synthesis by oxidation, no yield was reported for its formation.



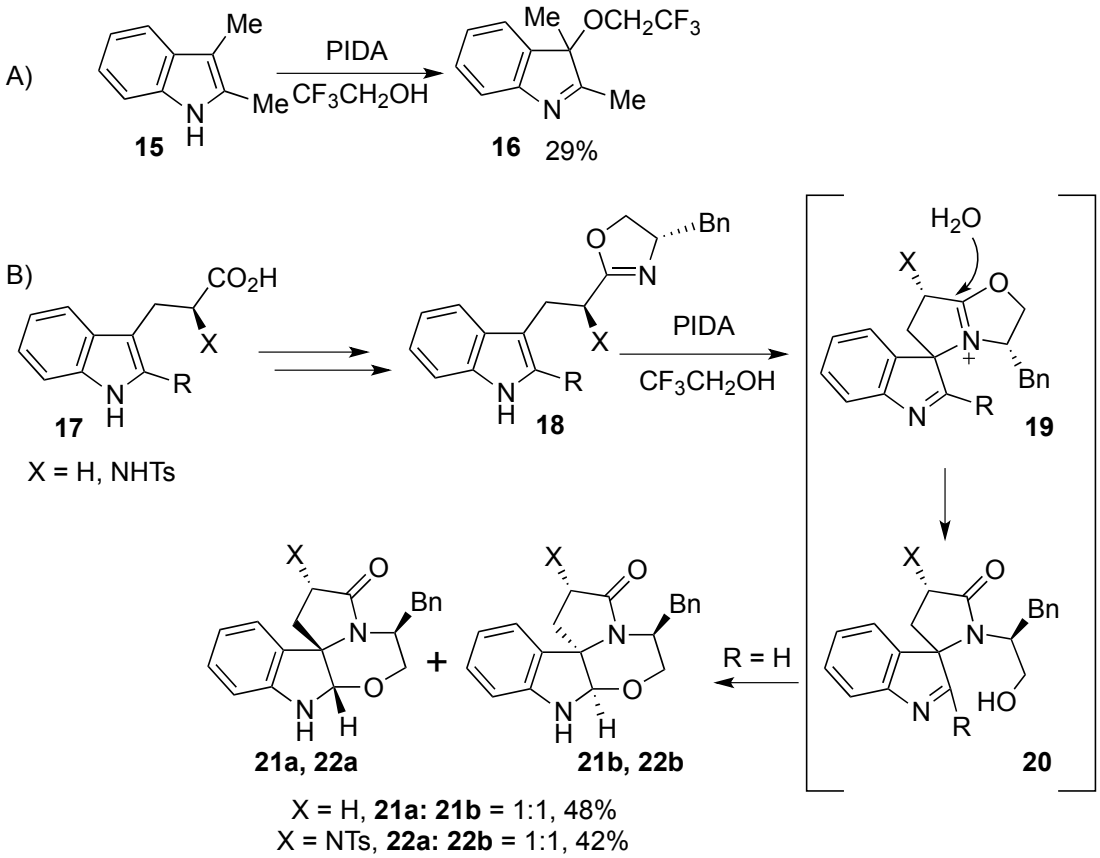
Scheme 4. Acetylation of indoles involving indolyl iodane reagent **3**, followed by hydrolysis

In 1980, Awang and Vincent introduced alkoxy groups on the C3 position of 2,3-disubstituted indoles **11**, especially fragments of the alkaloid reserpine (**14**), using PIDA in alcoholic solvents to give 3-alkoxyindolenines **13** (Scheme 5).[10] Primary and secondary alkoxy groups could be incorporated, but the reaction of *tert*-butanol led to a complex mixture. The nucleophilic attack at β-position is believed to proceed via hypervalent iodine intermediate **12**. For reserpine (**14**) itself, isopropanol failed to give the corresponding product due to severe 1,3-diaxial interactions with the C-6 and C-3 hydrogens. In case of unsubstituted or monosubstituted indoles, a complex mixture of products was obtained.



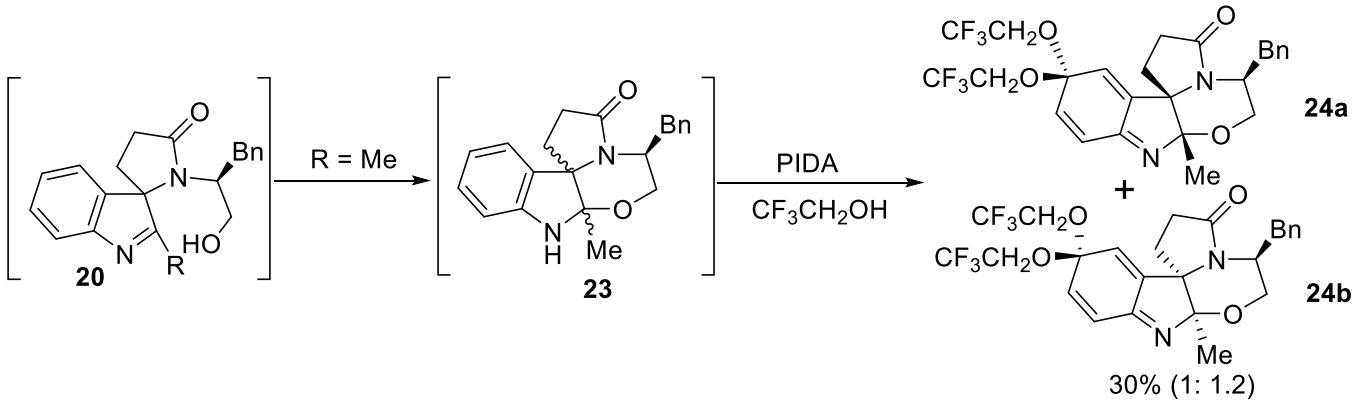
Scheme 5. Introduction of alkoxy groups at the C3 position of indole derivatives using PIDA

Ciufolini and co-workers observed that the reaction of dimethyl indole **15** with PIDA in CF_3CH_2OH afforded oxidation product **16** (Scheme 6A).[11] This result was interesting as it showed the successful addition of barely nucleophilic CF_3CH_2OH onto electrophilic indole intermediates generated with hypervalent iodine reagents. This reactivity was used for the synthesis of various indole-based spirolactams from indolic acids- and tryptophan-derived oxazolines (Scheme 6B). Reaction of C2-unsubstituted **18**, synthesized from tryptophan derivatives **17**, with hypervalent iodine reagents proceeded with no stereoselectivity to provide a 1:1 mixture of both indolic acid derived tetracycles **21a,b** and tryptophan-derived tetracycles **22a,b** with 48% and 42% yields respectively. These products probably originated from the initially formed spiro-3*H*-indoles **19**, which subsequently undergo rapid water addition to give amides **20**. Intramolecular nucleophilic addition of the alcohol to the imino function of indolenines **20** finally gives **21** and **22**.



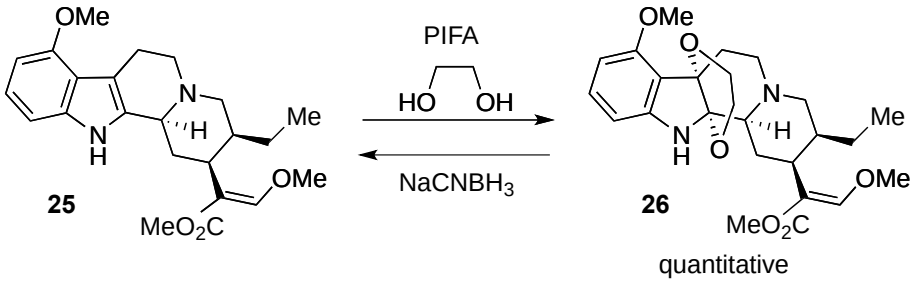
Scheme 6. A) Oxidation of dimethylindole **15** with PIDA in CF_3CH_2OH and B) Synthesis of tetracyclic indolines **21** and **22** via oxazoline derivatives **18**

In contrast, the 2-methylindole derivatives **20** gave quinonimine monoketals **24 a,b** in a 1: 1.2 ratio via oxidation of the benzene ring followed by attack of the solvent as nucleophile (Scheme 7). It seems that in this case a further oxidation of the assumed primary products **23** occurred faster than oxidative cyclization of the oxazoline. Using 3 equivalents of PIDA allowed complete oxidation of the substrate to give **24a,b** in 30% isolated yield.



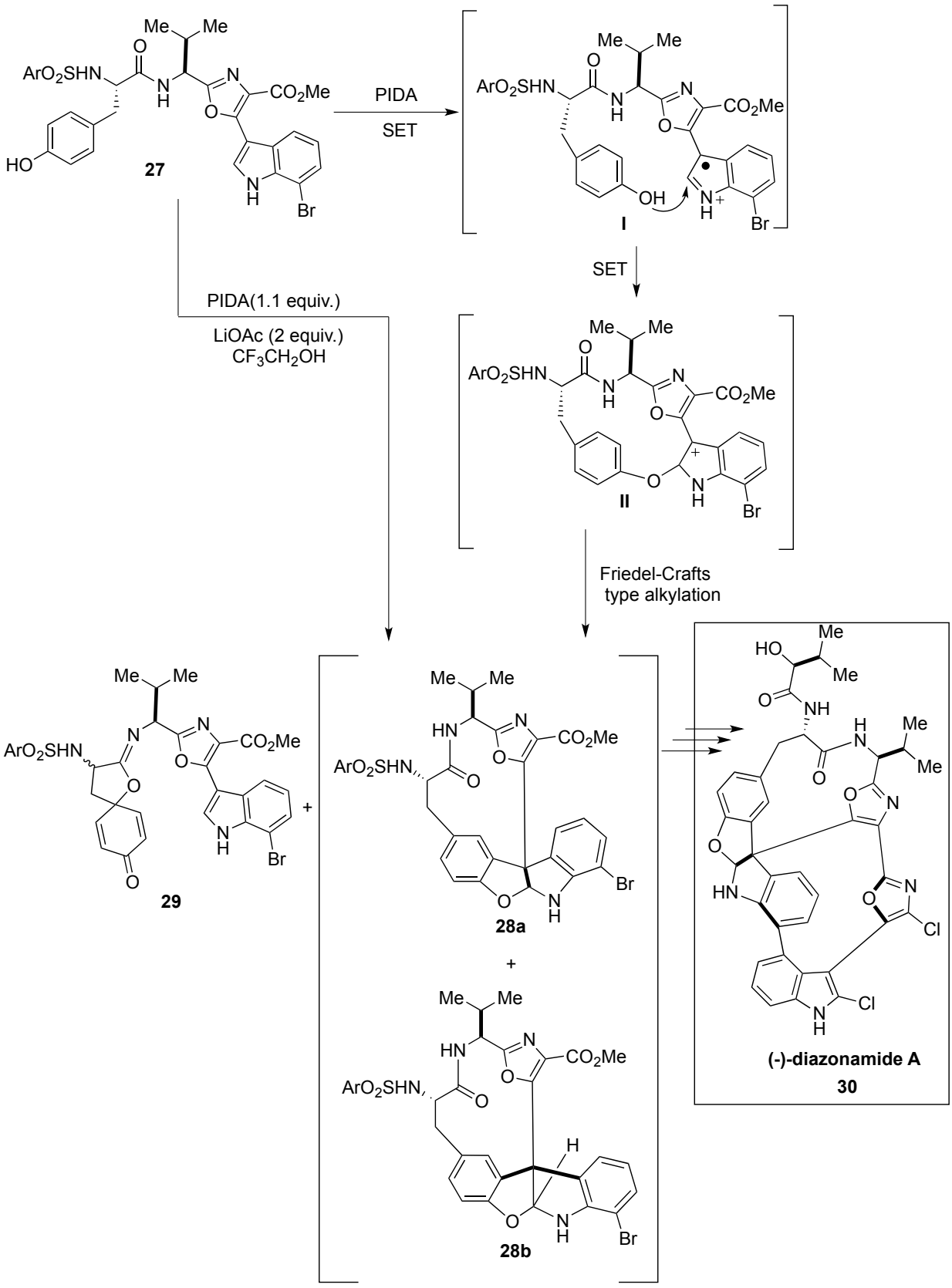
Scheme 7. Formation of quinonimine monoketals **24**

Takayama and co-workers reported a dearomatization reaction of indole alkaloid **25** on treatment with PIFA in the presence of ethylene glycol to give 2,3-ethylene glycol bridged adduct **26** (Scheme 8).[12] This umpolung dearomatization was used to mask the C3 reactivity of indole alkaloid **25**. After modification of the aryl ring, the ethylene glycol bridge could be removed under mild reductive conditions to regenerate the indole ring.



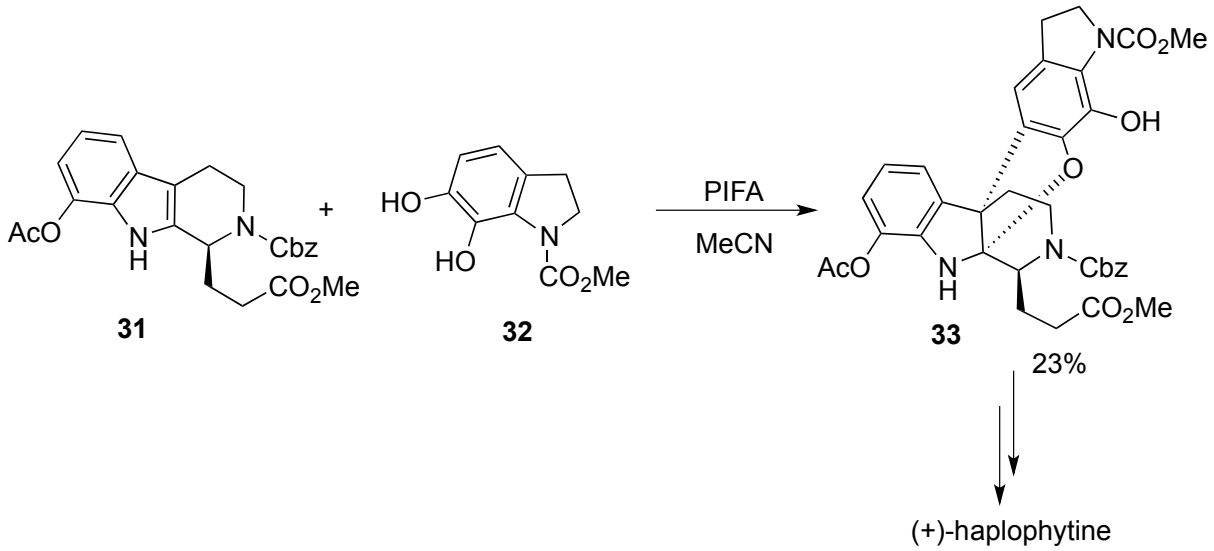
Scheme 8. Reversible PIFA mediated dearomatization of indole alkaloid **25**

Harran and coworkers reported a PIDA mediated intramolecular oxidative marcocyclization between an indole and a phenol in compound **27** to afford benzofuroindoline scaffolds **28** in their total synthesis of (-)-diazonamide A (**30**).[13] Addition of **27** to a cold trifluoroethanol solution of PIDA was sufficient to generate the targeted lactam **28a** and its C10-(*R*), C11-(*S*) diastereoisomer **28b** in an overall yield of 27-33% with 3:1 dr along with comparable amounts of diastereomeric mixture of spirodienones **29** (Scheme 9). In their article, Harran and coworkers proposed a SET oxidation of the indole by PIDA, which would produce radical cation **I**. This species could trap the tethered phenol, and a second SET (to either I(III) or I(II)) would then occur. The resulting carbocation **II** would then undergo an internal Friedel-Crafts type alkylation to afford **28a**/**28b**.



Scheme 9. Intramolecular oxidative coupling of indole and phenol in the total synthesis of diazonamide A (**30**) reported by Haran and coworkers

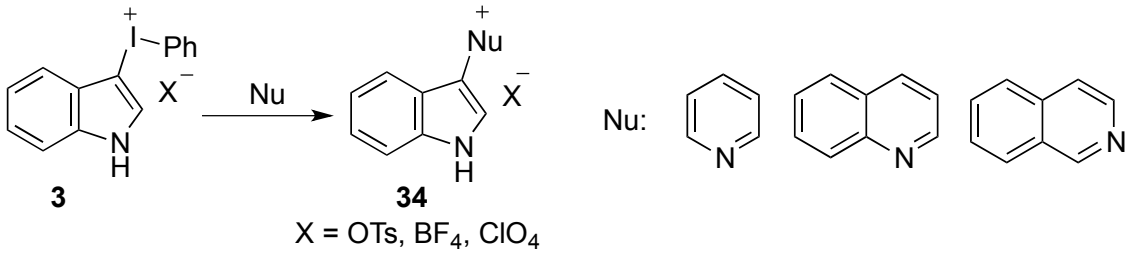
A similar type of oxidative coupling reaction of enantiopure tetrahydro-β–carboline **31** and diphenol **32** was also used in the total synthesis of (+)-haplophytine by the Nicolaou group.[14] (Scheme 10). After considerable experimentation, they observed that treatment of a mixture of **31** and **32** with PIFA (1.1 equiv.) in MeCN effected the desired coupling and provided the propellane-like hexacycle **33** in 23% yield, based on 23% conversion of **31** (the more valuable component). Whilst the reaction could not be driven to completion, tetrahydro-β-carboline **31** was successively recycled to provide sufficient quantity of material for completion of the synthesis.[14a]



Scheme 10. Intermolcular coupling of indole **31** and catechol **32** in Nicolaou's total synthesis of haplophytine

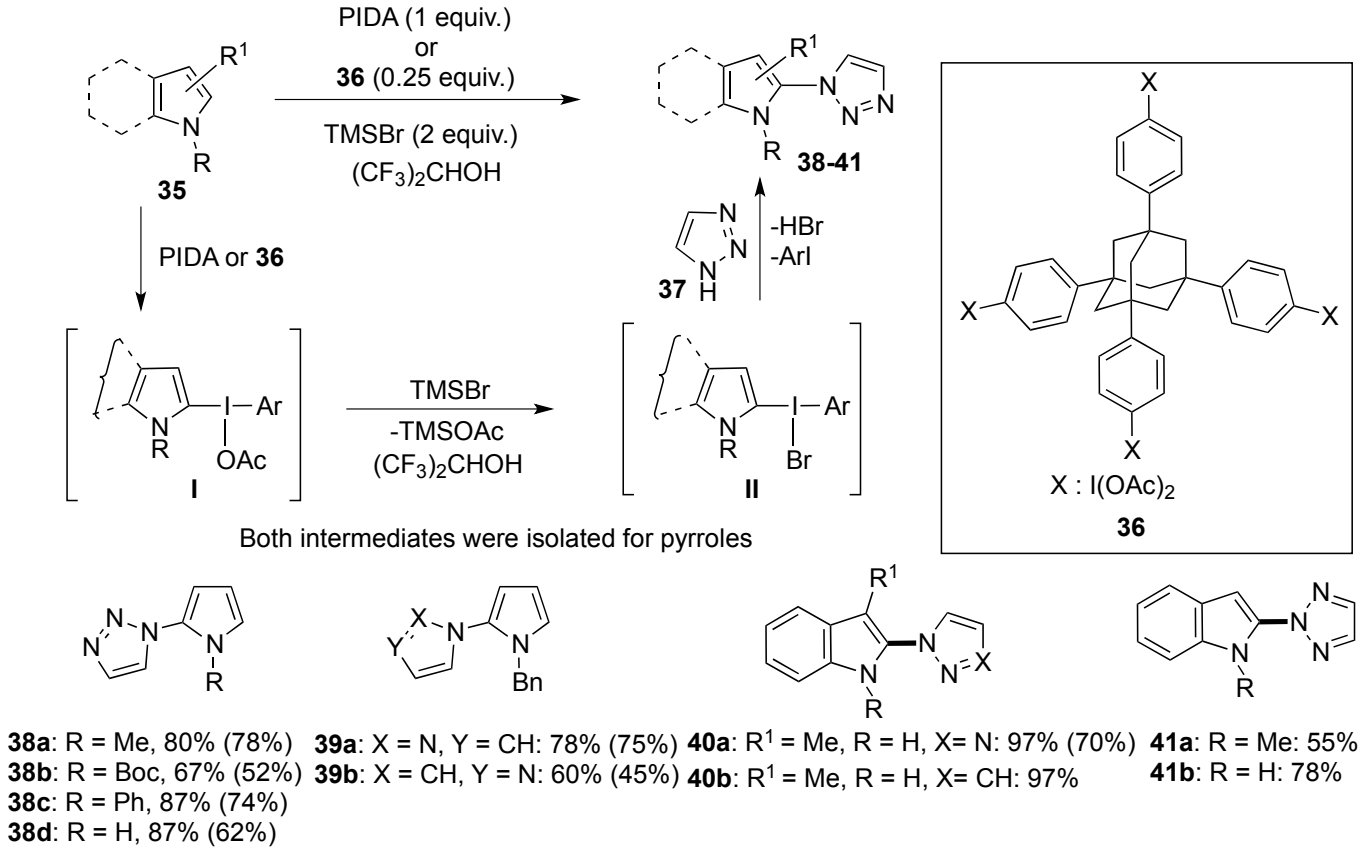
2.3. FUNCTIONALIZATION WITH NITROGEN NUCLEOPHILES

Nitrogen containing heterocycles were introduced at the C3 position of indole in the seminal report of Neiland and coworkers on indole-based iodonium reagents.[5a] On treatment of compound **3** (R = H) with various heterocycles like pyridine, quinoline and isoquinoline, the corresponding quaternary salts **34** were obtained (Scheme 11).



Scheme 11. Addition of N-heterocycles to iodonium salt **3**

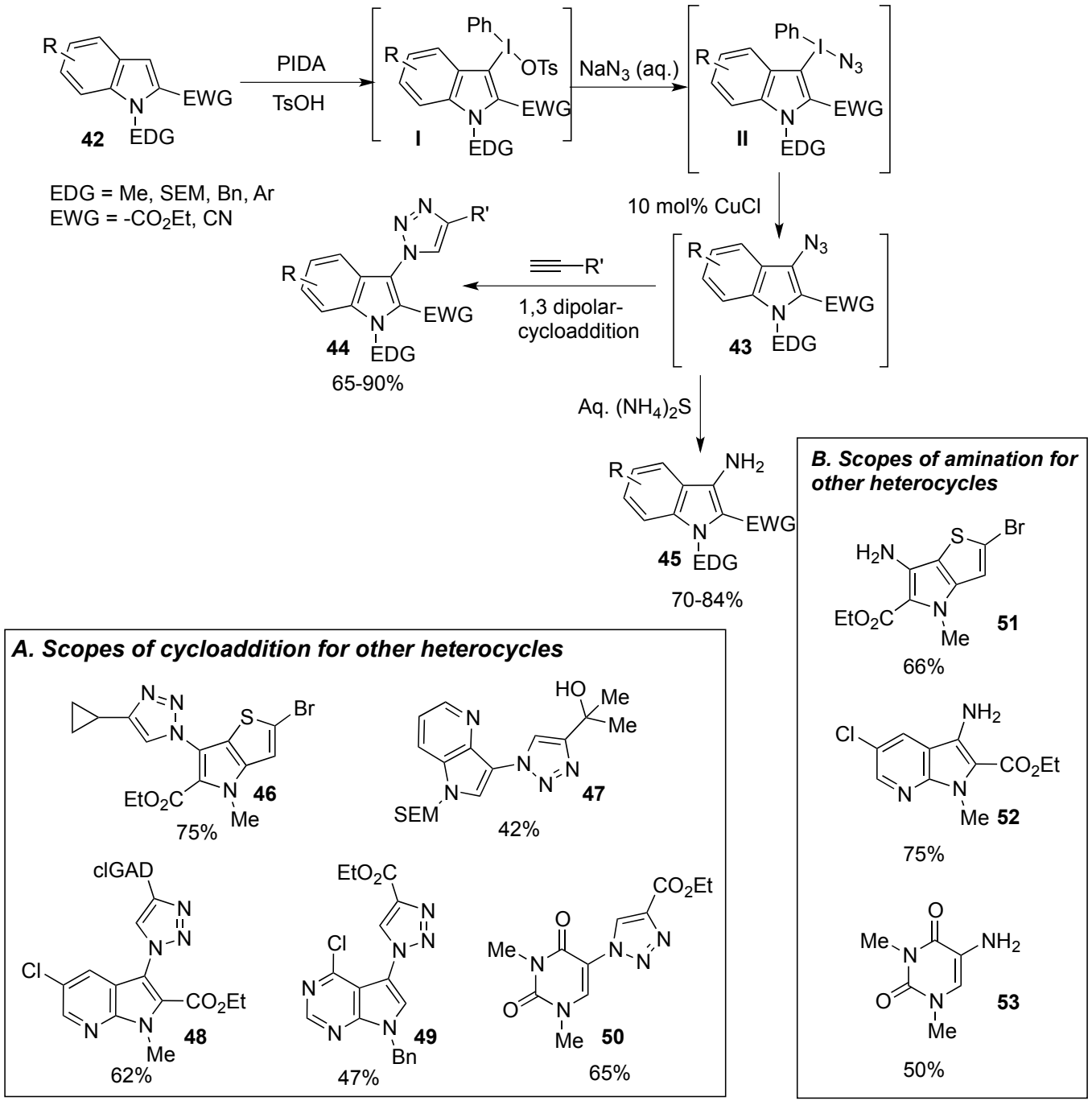
In 2014, Kita and coworkers reported an oxidative coupling to form the C-N bond directly from CH and NH bonds. They developed the C2 selective cross coupling between triazole **37** and pyrroles, as well as a limited number of indoles (only 3 examples) with PIDA and TMSBr in 1,2-dichloroethane to give C-N coupling products **38-41** in 55-97% yields (Scheme 12).[15] Notably, the reaction was found to be N1-selective for triazoles and tolerant to a broad range of substrates and functional groups. Electron-rich pyrroles/indoles **35** reacted selectively at the C2-position with aryl iodine diacetates to form iodonium(III) salts **I**. The formed σ-aryl trivalent iodine intermediates **I** are usually inert toward neutral aromatic nucleophiles, but they could be activated by addition of TMSBr in hexafluoroisopropanol (HFIP) as solvent, probably through formation of the more reactive bromide salts **II**. The same transformation could be achieved with recyclable hypervalent iodine reagent **36** with slightly lower yields (52-78%).[15b]



Scheme 12. Iodine(III)-reagents mediated C-N coupling of pyrroles/indoles with azoles **37**. Yields in parenthesis are obtained with reagent **36**.

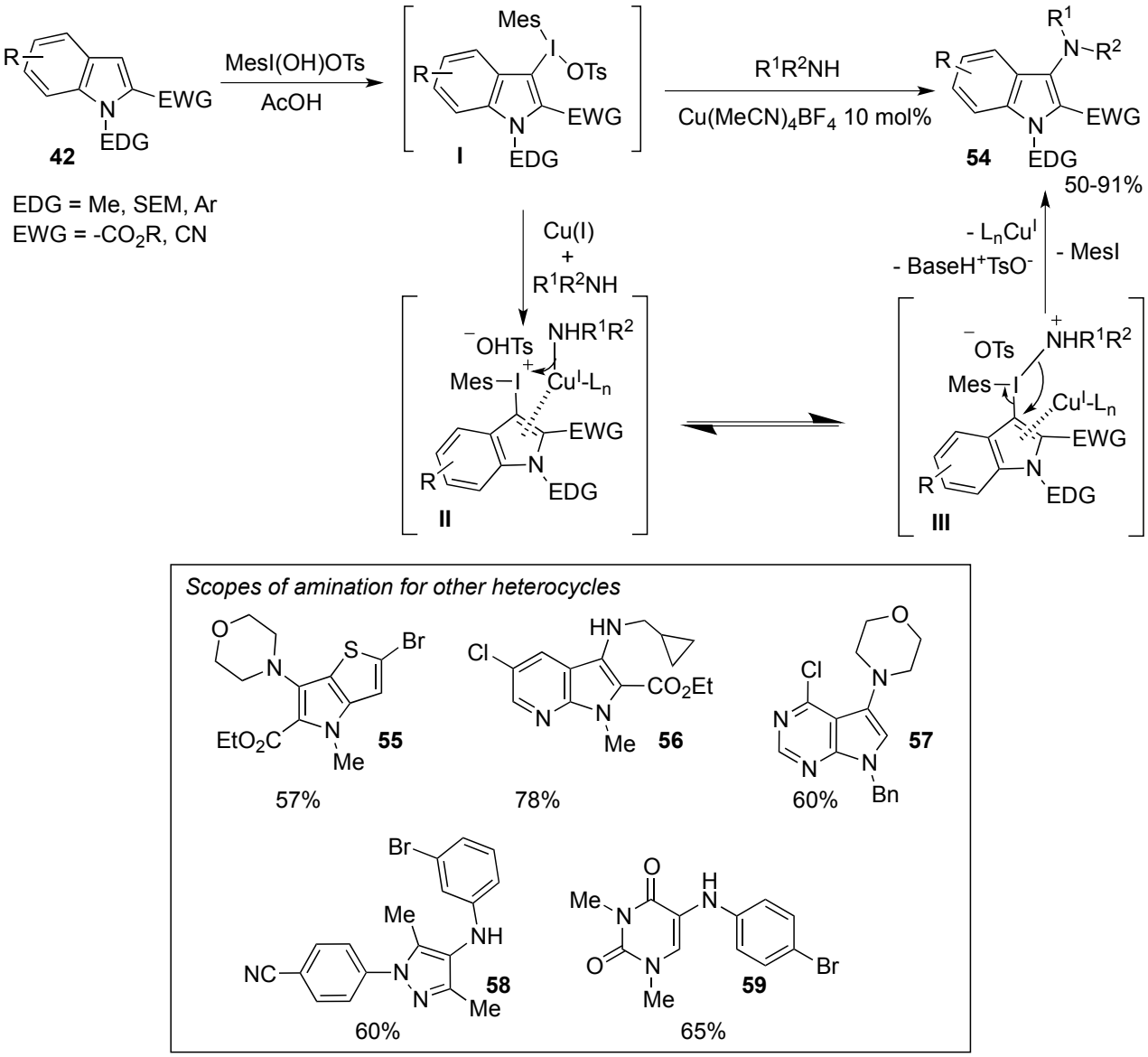
In order to stabilize the indole-based iodonium reagents, an electron-withdrawing group can be introduced at the C2 or the electron donating group at N1 position of indole (**42**).[16] With this class of reagents, Suna and coworkers reported an umpolung azidation at the C3 position (Scheme 13).[17] Unstable heteroaryl azides **43** were formed via Cu(I) catalyzed *in situ* regioselective fragmentation of

heteroaryl(phenyl)iodonium azides **II**, obtained by ligand exchange from tosylates **I**. Further modifications of the azide products **43** were made via 1,3-dipolar cycloaddition with acetylenes to afford stable triazoles **44** in 65 to 90% yields. Azides **43** could also be reduced to heteroaryl amines **45** in 70-84% yields using aqueous ammonium sulfide. This procedure could be applied to a variety of other electron-rich heterocycles such as thienopyrroles, pyrrolopyridines, pyrrolopyrimidines and uracil to give either cycloaddition products **46**-**50** (Scheme 13a) or amines **51**-**53** (Scheme 13B).



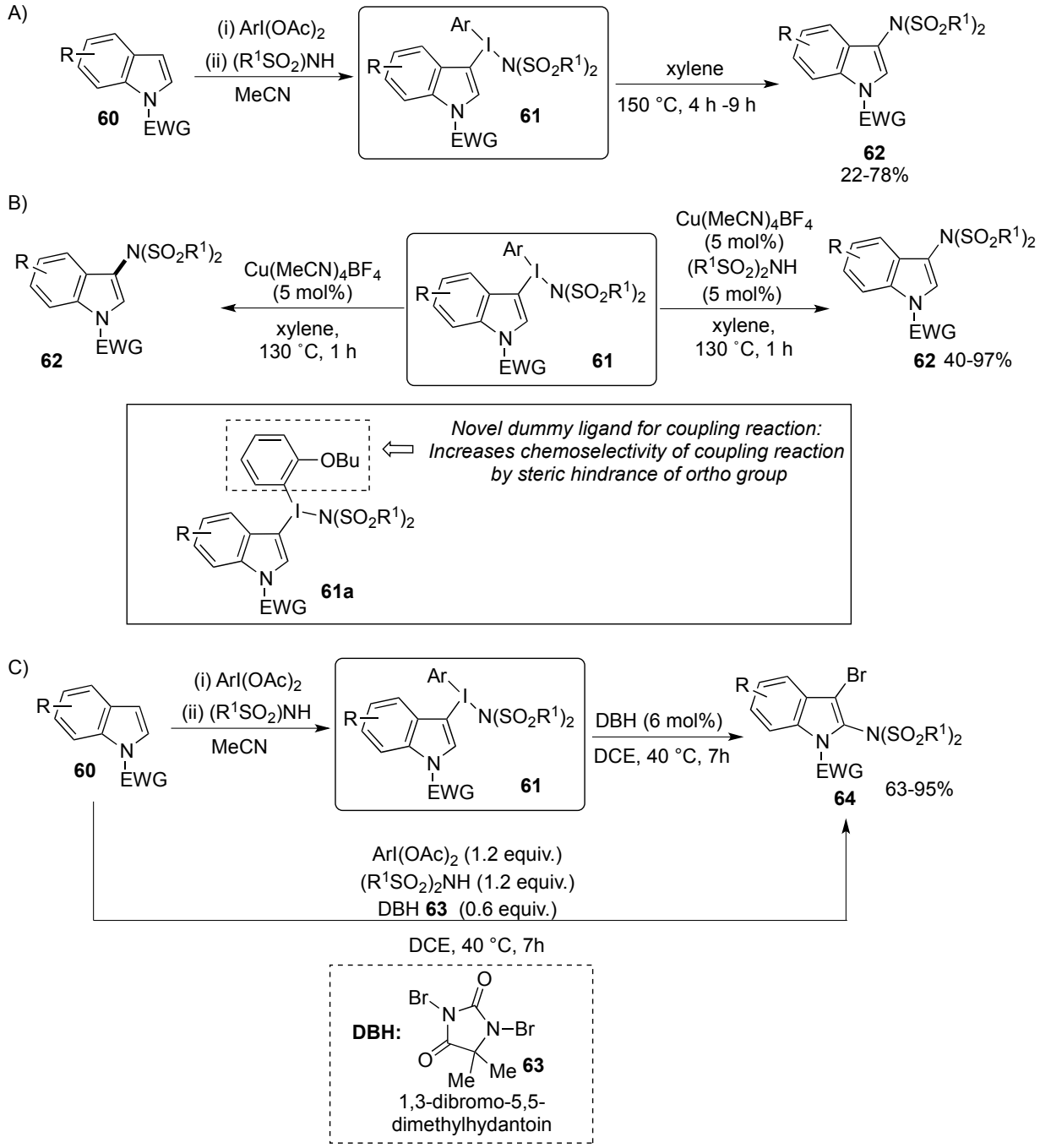
Scheme 13. C3 Azidation of heterocycles via hypervalent iodine reagents followed by amine and triazole formation

Using a similar protocol, the same group reported a C3 amination of indoles **42** in 30-91% yields via hypervalent iodine intermediate **I** (Scheme 14).[18] The approach was based on a room-temperature copper(I)-catalyzed regioselective reaction of the *in situ* formed unsymmetrical heteroaryl(mesityl)iodonium tosylate **I** with a wide range of primary and secondary aliphatic amines and anilines. The reaction was proposed to proceed via a Cu(I)−amine complex L_nCu^I-NHR^1R^2, which coordinates to the electron-rich heterocycles moiety in λ^3 -iodane **I**, forming a η^2-complex **II**. Subsequent substitution of tosylate by amine in intermediate **II** and reductive elimination from the highly unstable λ^3 -iodane **III** would lead to 3-amino indoles **54**. A variety of other electron-rich heterocycles such as thienopyrroles, pyrrolopyridines, pyrrolopyrimidines, azole and uracil also afforded the corresponding amine derivatives **55-59** in 57-78% yields.



Scheme 14. C3 Amination of electron-rich heterocycles via hypervalent iodine intermediates

A C3-selective amidation of indoles was also reported by Moriyama and coworkers (Scheme 15).[19] They introduced indolyl(aryl)iodonium imides **61**, obtained by reacting electron-withdrawing group *N*-protected indoles **60** with bissulfonimides and (diacetoxyiodo)arenes. This indolyl(aryl)iodonium imides underwent reductive elimination to give C3-amino indoles **62** in 22–78% yields under refluxing conditions in xylene (Scheme 15A).[19a]



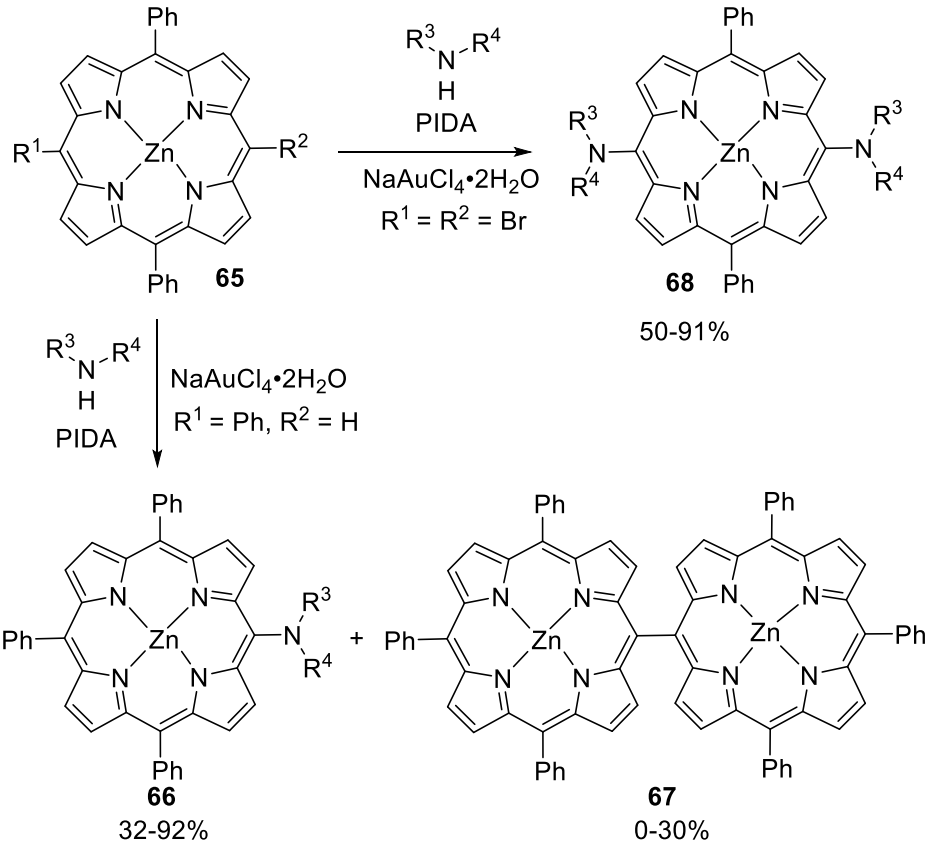
Scheme 15. Regioselective amidation processes based on iodonium imide salts **61**

This protocol led to moderate yields of products, long reaction times and amination at the aryl part of

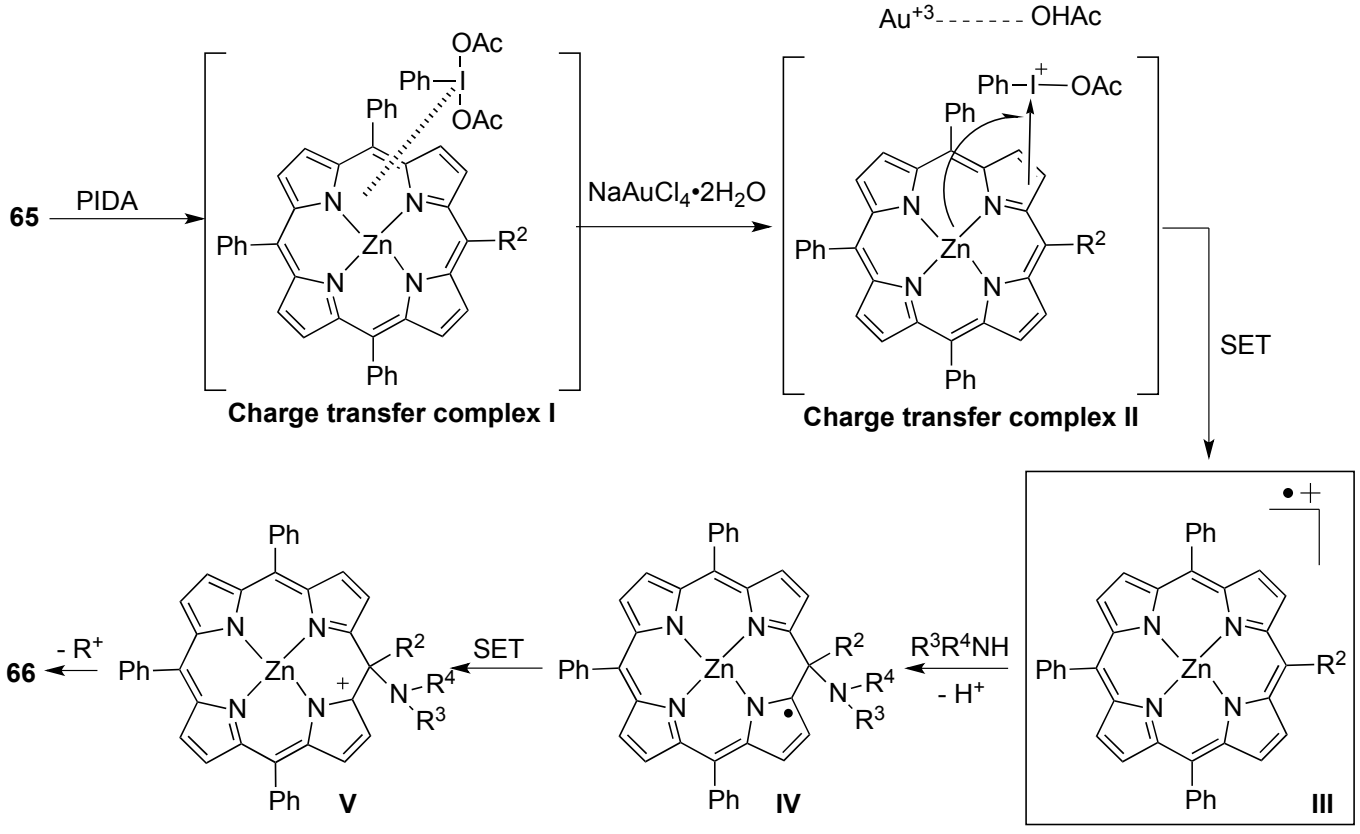
indolyl(aryl)iodonium imides **61** as side products. These limitations could be overcome by using a Cu(I) catalyst and indolyl(2-alkoxyphenyl)iodonium imide **61a** as reagent (Scheme 15B). The authors proposed that the alkoxy group of **61a** prevented amination of the aryl substituent due to steric hinderance at the *ortho* position.[19b] This C-N coupling was best performed with 5 mol% $Cu(MeCN)_4BF_4$ with or without a catalytic amount of bissulphonyl imide $(RSO_2)_2NH$ to give compounds **62** in 40-97% yields.

They also developed a metal free methodology for the imidobromination of indoles via indolyl(aryl)-iodonium imides **61** using 1,3-dibromo-5,5-dimethylhydantoin (DBH, **63**) as reagent (Scheme 15C).[9] This bromo-amination proceeded via 1,3-migration of the imide groups on **61** to provide 2-bis(sulfonyl)amino-3-bromoindoles **64** in 63-95% yields. A one pot reaction using $ArI(OAc)_2$, $(R^1SO_2)_2NH$ and DBH (**63**) could also be developed.

In 2009, Chen and co-workers reported a *meso*-amination of porphyrins with PIDA and a stoichiometric amount of $NaAuCl_4$ as activator.[20] This PIDA mediated direct nucleophilic substitution reactions of porphyrin **65** with different amines was proposed to occur via a radical cation intermediate. $NaAuCl_4 \cdot 2H_2O$ was a superior activator, giving good yields of the desired nucleophilic substitution products **66** and a small amount of dimers **67** in a short reaction time (30 min). When [5,15-dibromo-10,20-diphenylporphyrinato]zinc(II) **65** ($R^1 = R^2 = Br$) was used as the starting porphyrin under similar conditions, the double nucleophilic substitution products **68** were obtained in 50-91% yields (Scheme 16). The authors proposed the following mechanism for this transformation (Scheme 17): The reaction of PIDA with the porphyrin macrocycle generates the charge-transfer complex **I**, which further forms the activated charge-transfer complex **II** by coordination of gold(III) to the acetate anion. The key intermediate porphyrin radical cation **III** is subsequently produced via SET oxidation. *In situ* trapping of radical cation **III** by nucleophiles followed by further oxidation and deprotonation/debromination results in the formation of nucleophilic substitution products **66**.



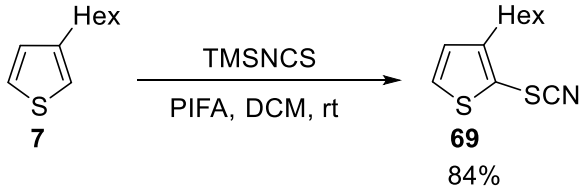
Scheme 16. PIFA mediated *meso*-amination of porphyrins



Scheme17. Reported plausible mechanism for the *meso*-amination of porphyrins

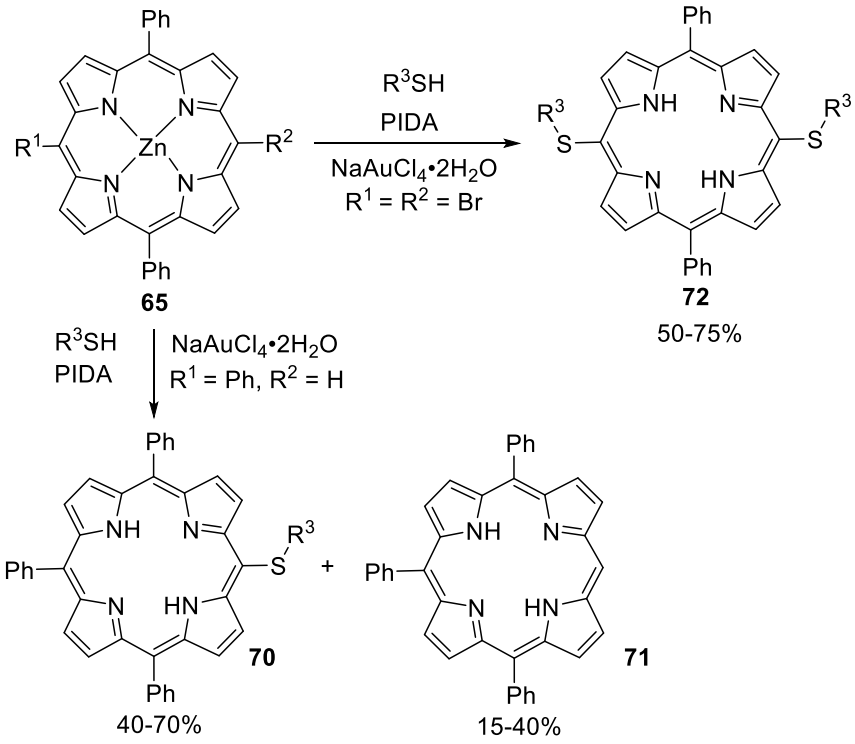
2.4. FUNCTIONALIZATION WITH SULFUR NUCLEOPHILES

Very few examples were reported in literature regarding sulfur-based nucleophilic functionalization of electron rich heterocycles with hypervalent iodine reagents. The PIFA mediated SET oxidative thiocyanation of 3-hexylthiophene (**7**) was reported by Kita (Scheme 18).[8] TMSCN was used as source of $^{-}$SCN nucleophile and thiocyanate **69** was obtained in 84% yield.



Scheme 18. PIFA mediated thiocyanation of 3-hexylthiophene (**7**)

The thiolation of porphyrins was also reported by Chen and coworkers including *meso* functionalization with different thiophenols as nucleophiles (Scheme 19).[20] This reaction was promoted by a PIDA-$NaAuCl_4•2H_2O$ combination and also occurred via a porphyrin cation radical intermediate. Thiophenols with both electron-donating and electron-withdrawing substituents were reacted with **65** (R^1 = Ph, R^2 = H) resulting in 40-70% yields of the desired mono nucleophilic substitution products **70** without formation of the oxidative coupling product. Demetalated starting porphyrin **71** was recovered in 15-40% yields. In case of bromo substituted porphyrins the corresponding demetalated di-thiolated porphyrin derivatives **72** were obtained in 50-75% yields.

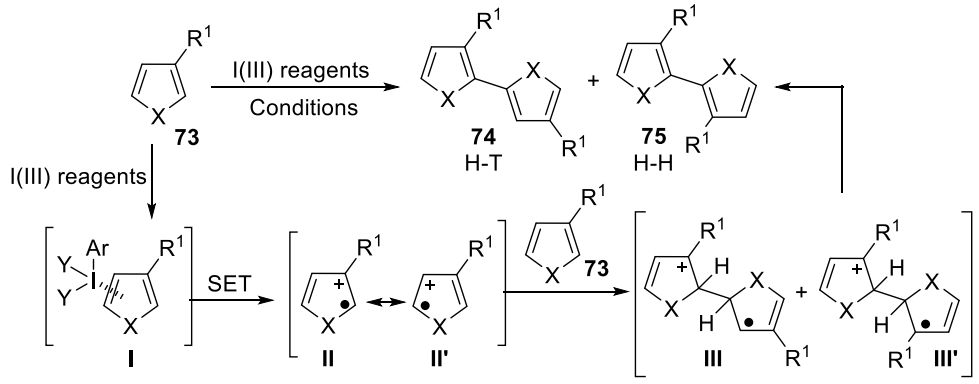


Scheme 19. PIDA mediated thiolation of porphyrins

3. UMPOLUNG (HETERO-)ARYLATION OF ELECTRON RICH HETEROCYCLES

3.1 REACTION INVOLVING A SET MECHANISM

At the beginning of the 1990's, Kita and coworkers first demonstrated the single-electron-transfer (SET) oxidation ability of PIFA toward phenyl ethers, affording the corresponding aromatic cation radicals.[21] Throughout the first decade of the 21st century, they then extended this approach to a series of heteroaromatic compounds such as thiophenes, pyrroles and indoles.[22] Reaction of the cation radicals with electron-rich (hetero)aryls enabled overall C–H functionalization under mild conditions. A challenge for this approach is the formation of oligomers by reaction of the starting heteroarene with the formed radical cation. In the case of pyrroles and thiophenes, this reaction potentially leads to the formation of a mixture of C2-C5 (Head to tail connection, H-T) and C2-C2 (Head to Head connection, H-H) dimers **74** and **75** respectively (Scheme 20).



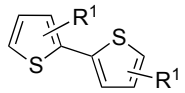
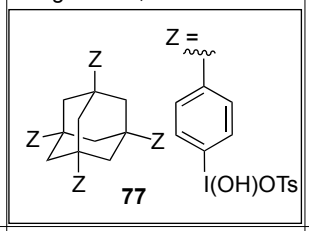
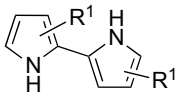
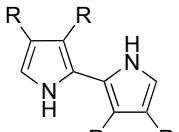
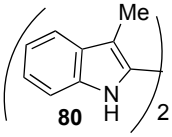
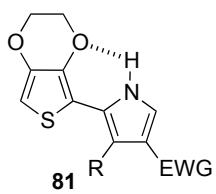
Scheme 20. Homo-dimerization of heterocycles **73**

In this process, the heteroaryl cation radicals are formed by SET from PIFA, often further activated by Lewis acids, via the CT-complex **I**. The formed radicals **II** then react with the neutral heterocycles. Kita and coworkers have shown that this process selectively occurred at the 2-position of the cation to give dimer radical cation **III** and **III'**. Coupling between the 2-position of the cation radicals and the 5-position of the neutral heterocycle accounts for the formation of the H–T linked **III**, and reaction with the 2-position leads to the H–H dimers **III'**. Finally, the reactions are completed by one-electron oxidation and deprotonation to afford **74** and **75**. Further reaction of the dimers usually does not occur: probably the initial SET oxidation process is faster than the heterocycle addition step. The addition of Lewis acids was essential for initiating the SET oxidation process. Both BF_3•OEt_2 and TMSX (X = OTf, Br) were used to enhance the electrophilicity of the iodine center of PIFA by coordinating to the trifluoroacetoxy ligand. The added Lewis acids thus facilitated the initial interaction of PIFA with heterocycles to form the CT-complexes **I** leading to SET.

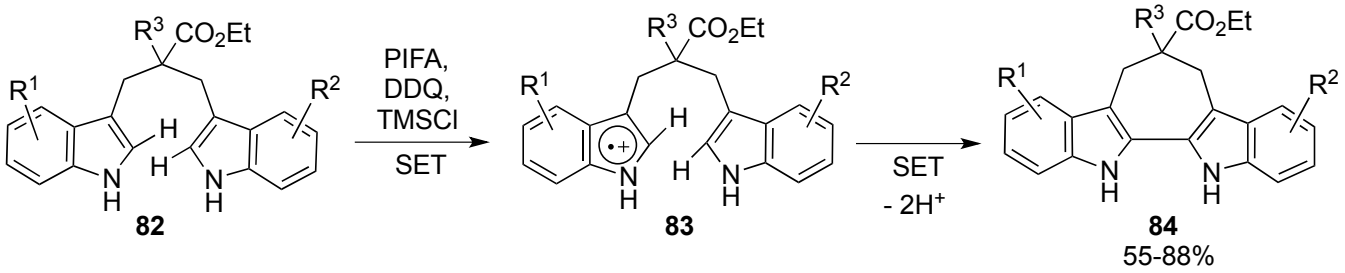
The work of the Kita group on this type of biheteroaryl synthesis is summarized in Table 1. Compounds **76** and **78** were obtained from both 3-substituted thiophene[22a, b] and pyrroles[22c, d] respectively as a mixture

of the two regiosomers (Head-Tail (H-T) and Head-Head (H-H)). With recyclable hypervalent iodine reagents **77**, it was possible to maximize the formation of the H-T regioisomer and in some cases it was obtained exclusively.[22e] Symmetrical 3,4-di-substituted pyrroles and 3-substituted indoles gave dimers **79** and **80** in 60-78% yields respectively with PIFA and TMSBr at low temperature (-78 °C). Interestingly, these reaction conditions could be extended to the cross coupling of 3,4-ethylenedioxythiophene (EDOT) and pyrroles to give EDOT-pyrroles **81** in 33-85% yields.[22f]

Table 1. Summary of SET oxidative couplings of electron rich heterocycles

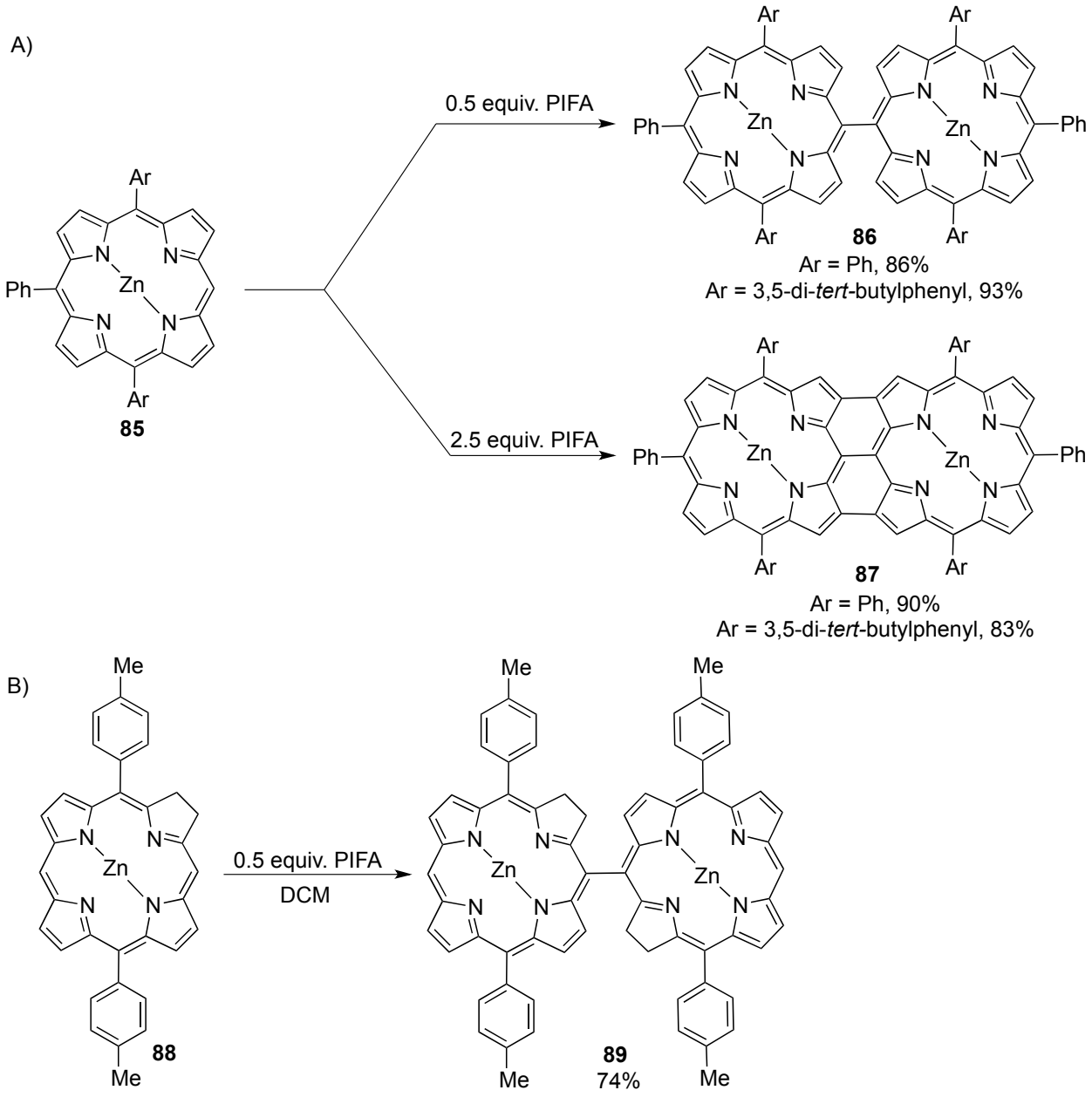
Biaryls	Conditions	Substituents	Yield range	H-T : H-H
 **76**	(i) PIFA, BF_3•OEt_2, DCM, -78 °C	^{n}Hexyl, ^{n}Butyl, ^{n}Octyl, Me, Cyclopentyl	50-72%	(46-60%): (40-54%)
	(ii) 2-$MeC_6H_4I(O_2CCF_3)_2$, TMSOTf, DCM, -78 °C	^{n}Hexyl, ^{n}Butyl, ^{n}Octyl, Me, ^{n}Heptyl, Cyclohexyl, ^{i}Butyl, $(CH_2)_6Br$	30-98%	(77-95%): (5-23%)
	(iii) Recyclable Hypervalent reagents **77**, TMSBr  **77**	^{n}Hexyl, ^{n}Butyl, ^{n}Octyl, Me, ^{n}Heptyl, Cyclohexyl, ^{i}Butyl, $(CH_2)_6Br$, OMe	50-75%	(93- 99%): (7:1%)
 **78**	(i) PIFA, TMSBr, DCM, -78 °C	Me, Heptyl, $(CH_2)_3CO_2Me$, Ph, 4-$MeOC_6H_4$, 4-BrC_6H_4	53-95%	(82-98%): (2-18%)
	(ii) Recyclable Hypervalent reagents **77,** TMSBr		78%, 70%	(90-100%): (00-10%)
 **79**	PIFA, TMSBr, DCM, -78 °C	H, Octyl	60-78%	--
 **80**	PIFA, TMSBr, DCM, -78 °C	H, Ethyl, ^{i}Butyl	74%	--
 **81**	PIFA, TMSBr, HFIP, rt	R = H, Me, Ph; EWG = -CO_2R, CN, SO_2Ph	33-85%	

Recently, Zhang and co-workers reported a synthesis of 6,7,12,13-tetrahydro-5*H*-cyclohepta[2,1-*b*:3,4-*b*']diindoles **84** through intramolecular oxidative coupling of 1,3-di(1*H*-indol-3-yl)propanes **82** with moderate to excellent yields (55-88%) (Scheme 21).[23] This transformation followed the same SET mechanism via indolyl cation **83** in the presence of PIFA, DDQ and TMSCl.



Scheme 21. Synthesis of bisindole derivatives **84** via PIFA mediated oxidative cyclisation

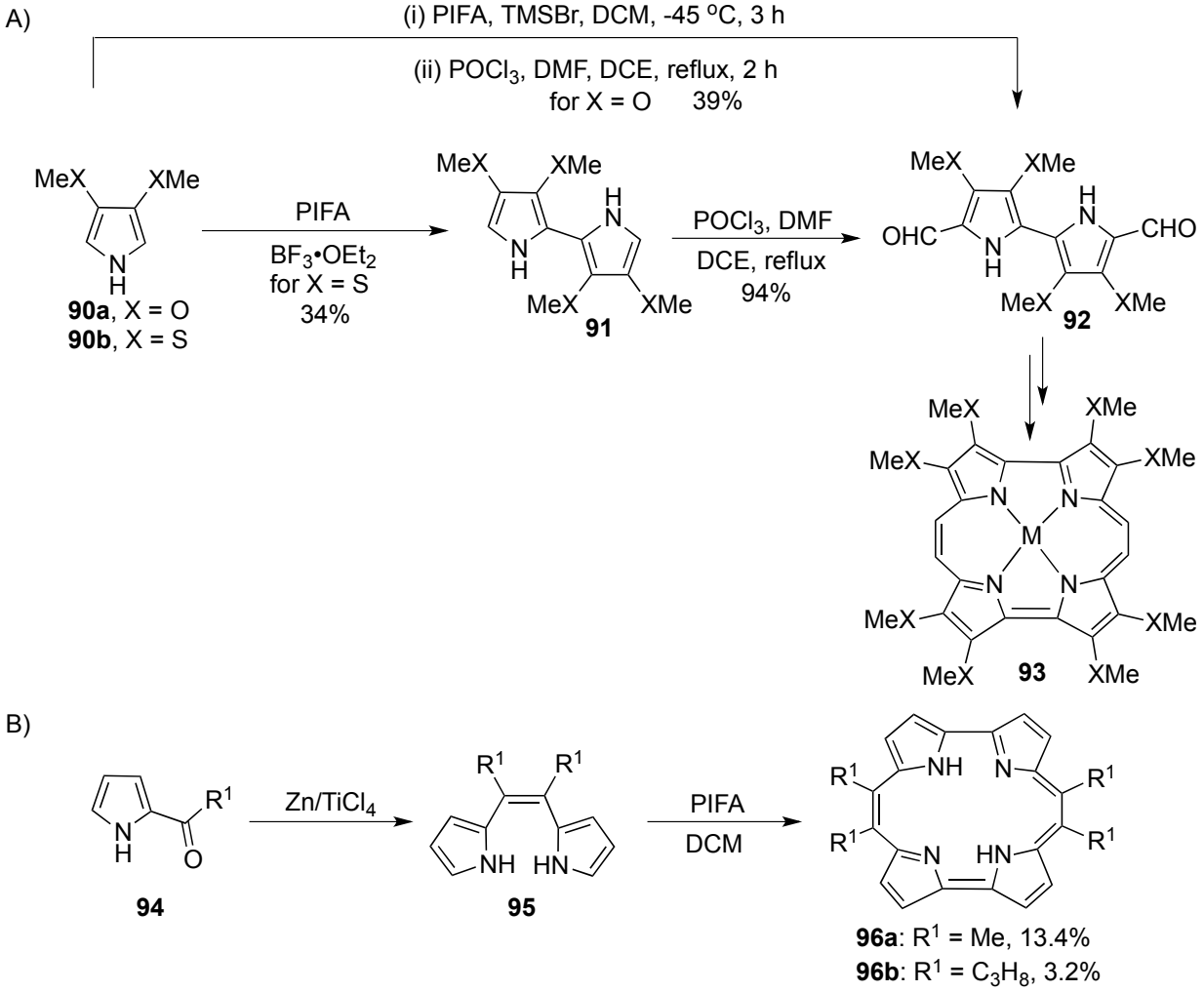
The PIFA mediated SET-oxidative coupling was also used for porphyrins by Zheng and coworkers (Scheme 22).[24a] A single bond linked diporphyrines **86** was obtained in 86-93% yields when compounds **85** was treated with 0.5 equivalent of PIFA (Scheme 22A). With an excess of PIFA (2.5 equiv.) fused diporphyrin derivates **87** were obtained in 83-90% yields. This reaction occurred only for Zn(II) porphyrins **85**. When other metals were used, e.g Cu(II), Ni(II) or Pd(II), then only single linked diporphyrins were observed even on treatment with 2.5 equiv. of PIFA. The same group also extended this methodology to the synthesis of a directly linked (single linked) zinc chlorin dimer (Scheme 22B).[24b] In this reaction, PIFA is more efficient and faster than PIDA. The reaction shows high regioselectivity at the 20-position near the hydrogenated pyrrole ring producing selective dichlorin **89** in 74% yield and oxidation of the pyrroline ring could be avoided.



Scheme 22. Oxidative coupling of porphyrins and chlorins

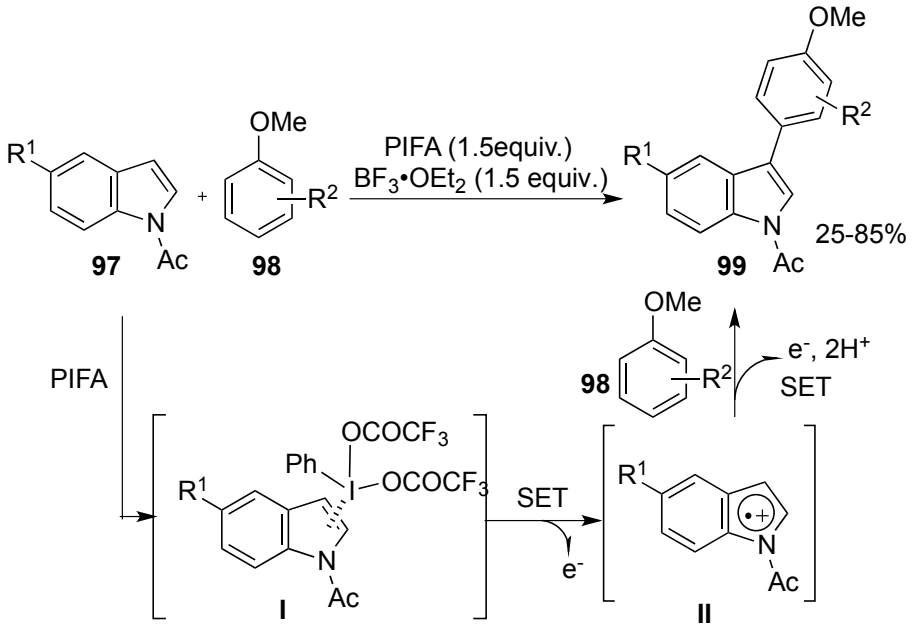
The PIFA-mediated homodimerisation of pyrroles was also used by Panda and coworkers in the synthesis of β-octa-substituted porphycenes (Scheme 23A).[25] The bispyrroles **91** were subjected to formylation, followed by McMurry coupling to afford the porphycenes skeleton **93**. For the synthesis of β-octamethoxyporphycenes, a one pot dimerization-formylation protocol was developed as the dimer underwent decomposition during purification. The desired product **92** was obtained in 39% yield. An alternative approach for the synthesis of porphycenes was reported by Ono and co-workers.[26] In this approach the McMurry coupled product **95**, obtained from formylated pyrrole **94**, was reacted with PIFA

to afford the corresponding *meso*-tetraalkylporphycenes **96** in 13.4% (R^1 = Me, **96a**) and 3.2% yield (R^1 = C_3H_8, **96b**) (Scheme 23B).



Scheme 23. Synthesis of porphycenes derivatives via PIFA mediated oxidative coupling

In comparison to homo-coupling, cross coupling via SET process are very rare. In addition to Kita's example with EDOT, a coupling of *N*-acetylindoles **97** with electron-rich anisoles **98** was reported by Gu and Wang in 2010 (Scheme 24).[27] In this protocol the *N*-acetylindoles **97** and PIFA formed a charge transfer complex **I**. A SET then generates indolyl radical cation **II**, which is trapped by the electron-rich arene to afford C3 arylated indoles **99** in 25-85% yields.



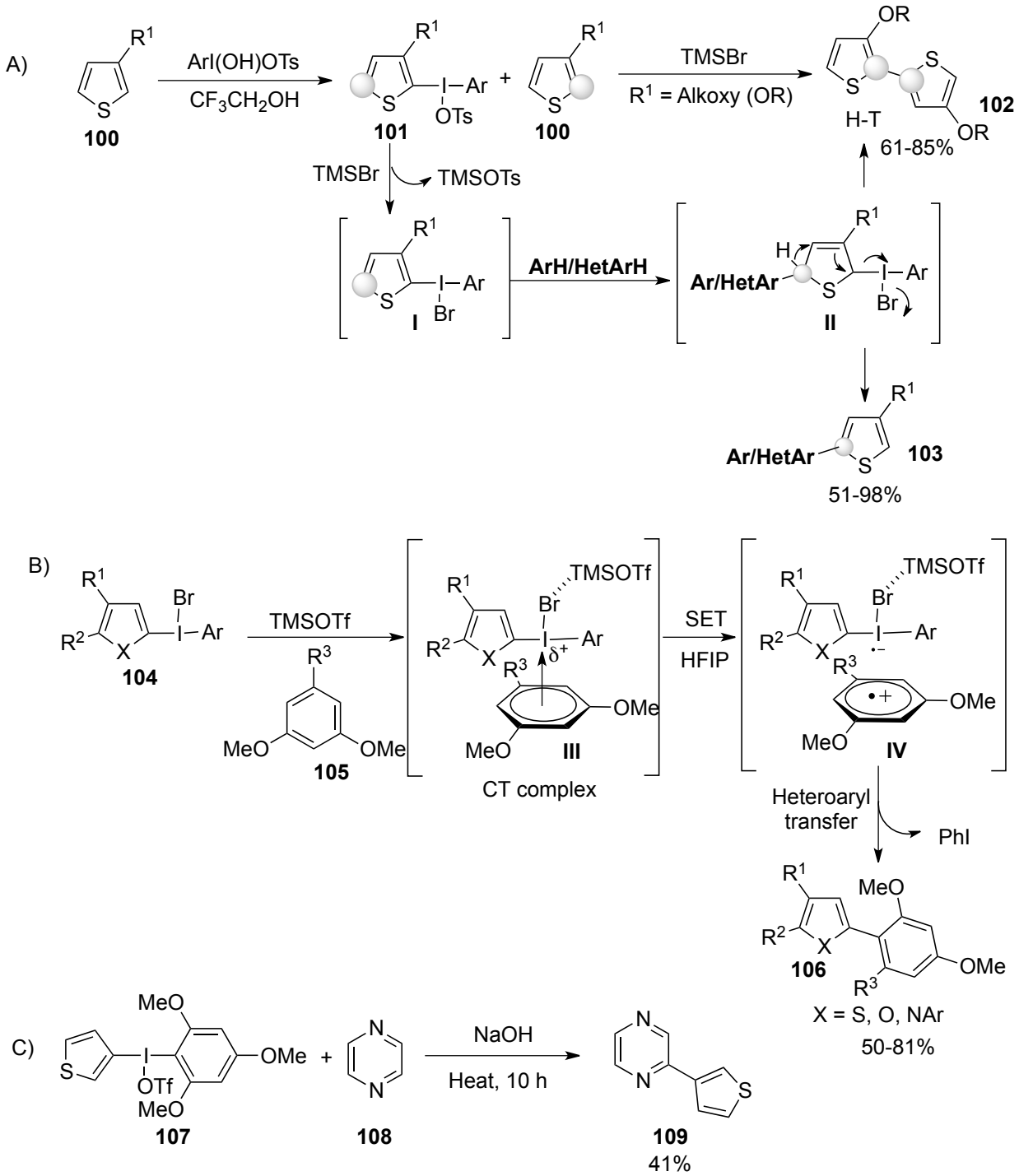
Scheme 24. Arylation of *N*-acetylindoles **97** using PIFA

3.2 REACTION INVOLVING STABLE OR PROPOSED (HETERO-)ARYLATED-HYPERVALENT IODINE REAGENTS

One of the major drawback of SET based approaches is the difficulty to prevent homo-dimerization when cross-coupling processes are desired. This can be overcome if a stable hypervalent iodine reagent is first formed from the heteroarene, prior to addition of the nucleophilic partner. In addition to the PIFA mediated single-electron-transfer (SET) oxidation, Kita also developed a method for the synthesis of heteroaryliodonium(III) salts by the dehydrative condensation of heteroaromatic compound and Koser-type hypervalent iodine reagents (Scheme 25A).[28] The formation of the σ-heteroaromatic iodonium(III) species such as **101** as intermediates then enabled the development of cross-coupling reactions. In addition, they were able to obtain better regioselectivity (H-T vs H-H) for thiophenes **100** when compared with the SET approach, with the exclusive formation of H-T products.[29] This selectivity was rationalized by reaction of the more nucleophilic C2 position of thiophene **100** with the vinylogous C5 position of activated iodonium **I**. Subsequent elimination from **II** leads to product **102**. This methodology was also used for the synthesis of oligothiophenes in photovoltaic dyes.[30] Iodonium salts **101** were also used in metal-free cross-coupling reactions with different electron-rich arenes and heteroarenes in presence of TMSBr and afforded **103** in 51-98% yields.[31]

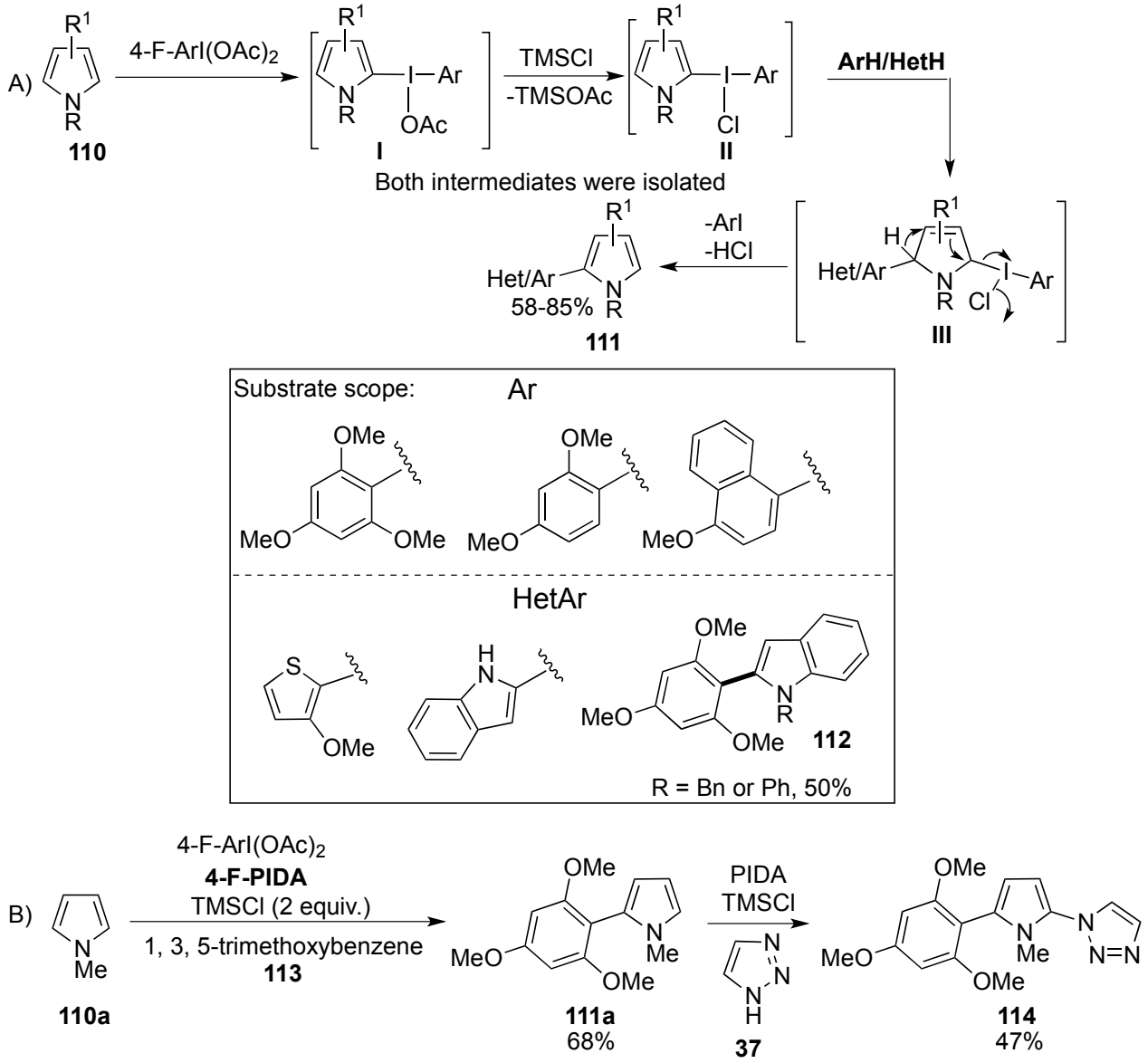
The Kita group also reported that another mechanism is possible for this transformation when stable heteroaryliodonium salts derived from thiophenes, furans or pyrroles are activated by TMSOTf in hexafluoroisopropanol (HFIP) (Scheme 25B).[32] In this case, *ipso* substitution of iodonium salts **104** to

give **106** was observed. Kita proposed the formation of a charge transfer complex **III**, followed by SET to give radical pair **IV**. The role of HFIP would be to accelerate this SET process. Simultaneous heteroaryl transfer to the radical cation and carbon-iodine bond cleavage affords then *ipso*-arylated heterocycles **106**. Finally, a selective transfer of the thienyl group from stable thienyl iodonium (III) salts **107** to pyrazine **108** was also reported in 41% yield, although the mechanism is less clear in this case (Scheme 11C).[33]



Scheme 25. (Hetero-)arylation of electron rich heterocycles through stable heteroaylated iodonium salts

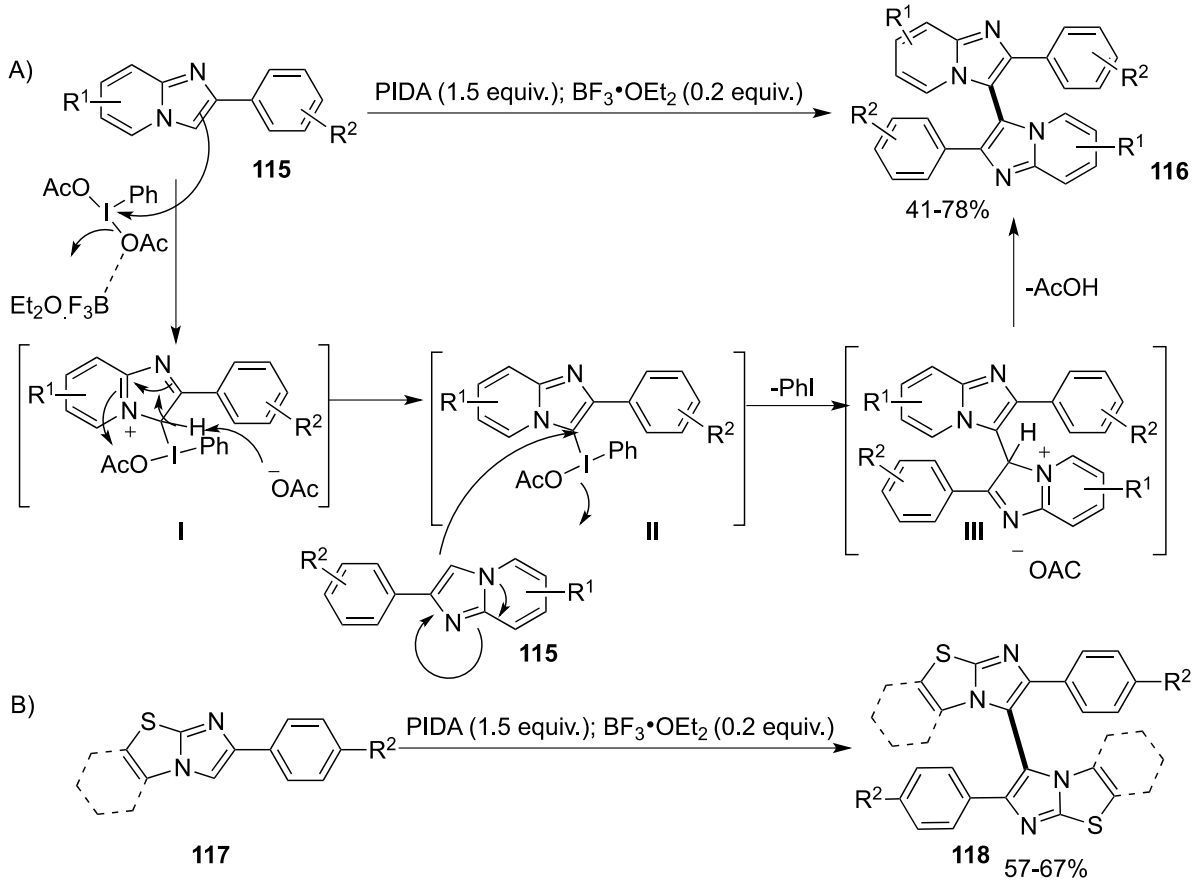
The same approach was also successful for the umpolung of pyrroles (Scheme 26).[31,32,34] In this case, the hypervalent iodine reagents were prepared by reaction with aryl iodine diacetates instead of Koser-type reagents to form stable iodonium(III) salts **I** (Scheme 26A).[34]



Scheme 26. Arylation of nitrogen heterocycles via iodonium salts

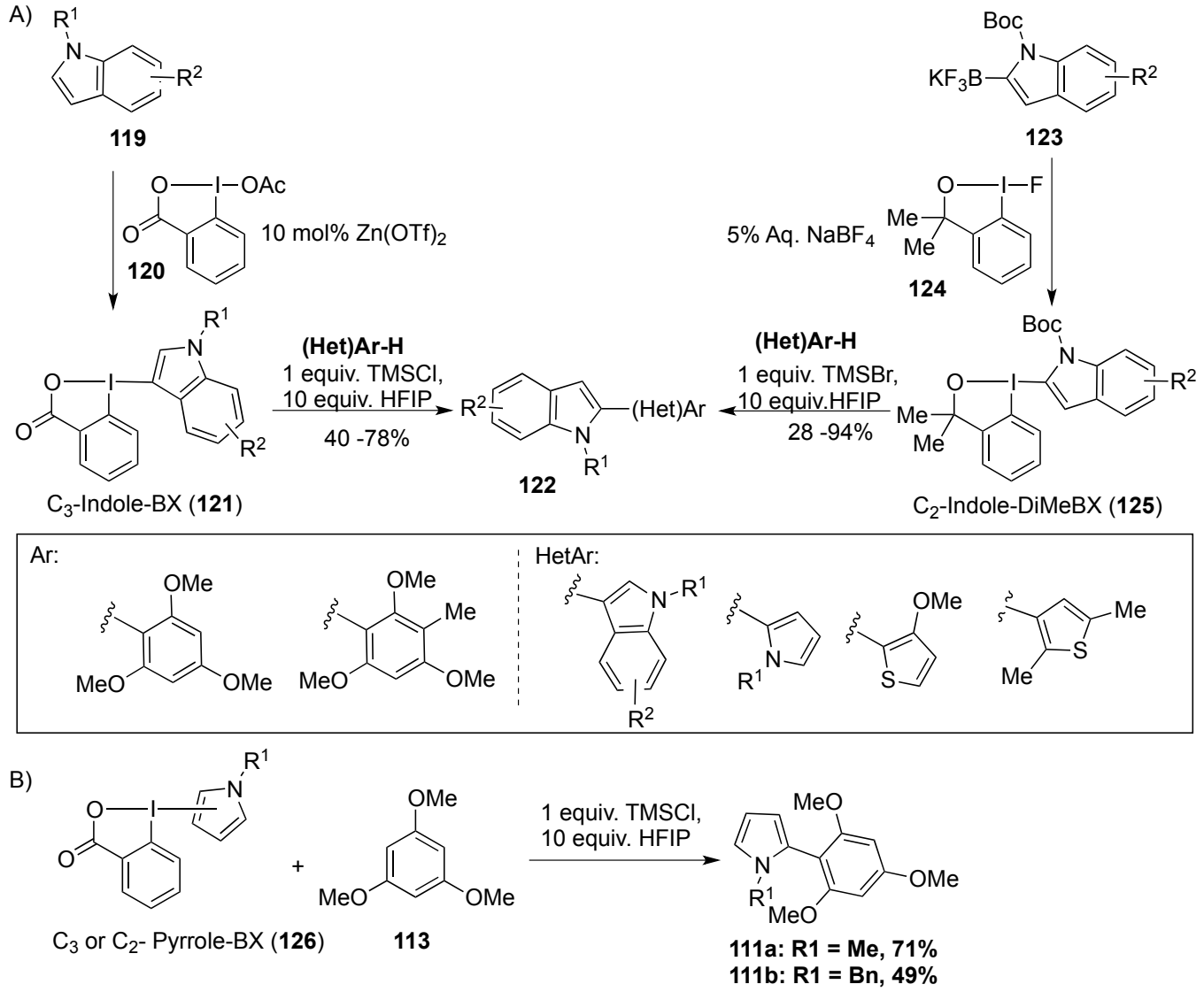
Again, salts **I** are usually inert toward neutral aromatic nucleophiles, but they could be activated by addition of TMSBr/TMSCl in HFIP as solvent, probably through formation of more reactive bromide or chloride salts **II**. Arylation products **111** would then be formed by the same mechanism as proposed for thiophene-based reagents: vinylogous addition followed by elimination of iodobenzene through intermediate **III**. Cross coupling with electron-rich benzene derivatives, thiophenes and indoles was possible using this protocol. It could be also extended to the cross coupling of 1,3,5-trimethoxybenzene (**113**) with indole-based iodonium salts (only *N*-phenylindole and *N*-benzylindole) using 4-fluoro-PIDA and TMSCl in HFIP to afford **112** in 50% yield. The limited scope for indoles was due to the instability of indole-based iodonium salts. The Kita group also reported a consecutive two cross coupling process of *N*-methylpyrrole **110a** with 1,3,5-trimethoxybenzene (**113**) and triazole **37** affording doubly substituted pyrrole derivative **114** in 47% yield (Scheme 26B).[34]

Sakuja and coworkers reported a PIDA-mediated homocoupling of 2-arylimidazo[1,2-*a*]pyridines **115** in 2017.[35] A series of homocoupled 2,2′-diaryl-3,3′-biimidazo[1,2-*a*]pyridines **116** were synthesized in 41-78% yields at room temperature (Scheme 27A). This hypervalent iodine(III) mediated cross-dehydrogenative protocol was also applicable to the homocoupling of other imidazo-heterocycles, including imidazo[2,1-*b*]thiazoles and benzo[*d*]imidazo[2,1-*b*]thiazoles **117** (Scheme 27B). The reaction was proposed by the authors to proceed through BF_3•OEt_2-accelerated C-3 nucleophilic attack of imidazo[1,2-*a*]pyridine **115** on PIDA, forming intermediate **II** through an electrophilic aromatic substitution mechanism. The author proposed a rare S_N2' attack of a second heterocycle on the sp^2 center of **II** to generates species **III**. Elimination of acetic acid then generates biimidazo[1,2-*a*]pyridine derivatives **116**. However, a mechanism involving SET processes cannot be excluded for this transformation.



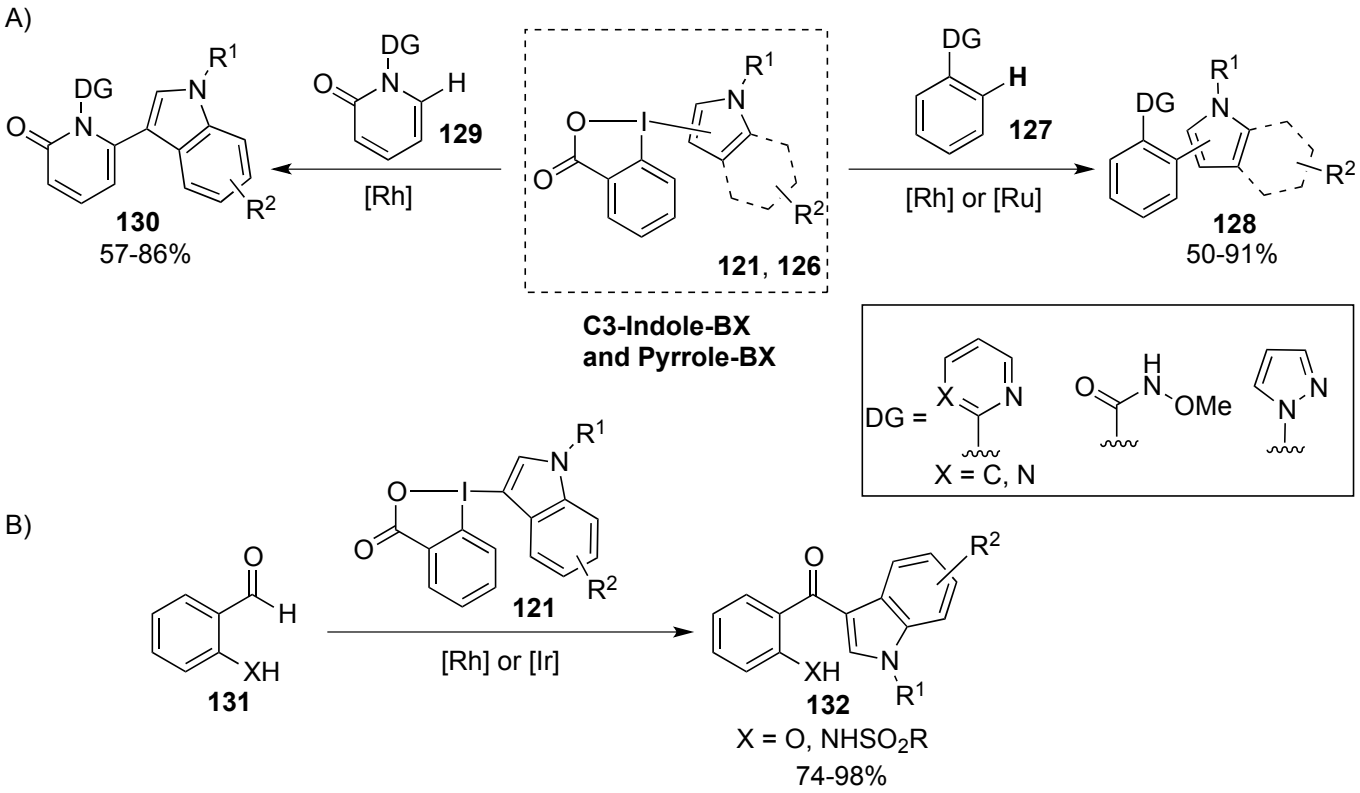
Scheme 27. PIDA mediated homocoupling of imidazole-derived heterocycles (**115** &**117**)

Finally, a more general cross coupling of indoles with electron-rich arenes/heteroarenes was reported by Waser and co-workers based on the use of bench-stable cyclic hypervalent iodine-indole reagents.[36] They developed a straightforward synthesis of C3-indole carrying benziodoxolones (BX) **121** and C2-indole carrying benziodoxoles (DiMeBX) **125** that were stable up to 150/170 °C (Scheme 28A). Reagent **121** could be obtained from acetoxy-benziodoxolone **120** using zinc triflate as Lewis acid catalyst, whereas **125** was accessed by reaction of trifluoroborate salt **123** with fluorobenziodoxole **124**. Both reagents gave C2 arylated product **122** in 28-94% yields in the cross-coupling reaction with electron-rich (hetero)arenes in presence of TMSX (X = Cl, Br) and HFIP. TMSBr was superior for the cross coupling of C2-Indole-DiMeBX **125**, whereas nucleophilic arylation of C3-Indole-BX **121** took place already with less reactive TMSCl. Both C2- and C3-Pyrrole-BX **126** afforded exclusive C2-arylated product **111** when reacting with 1,3,5-trimethoxybenzene **113** (Scheme 28B). These cyclic hypervalent iodine reagents were also employed for cross coupling reactions with different heterocycles like pyrroles, thiophenes and indoles for the synthesis of non-symmetrical electron-rich bi-heteroaryls. These new reagents therefore allowed to overcome the previous limitations of homo-dimerization observed for SET approaches and the insufficient stability of indole based iodonium salts.



Scheme 28. Synthesis of indole-based cyclic hypervalent iodine reagents and their applications in metal-free cross coupling reactions

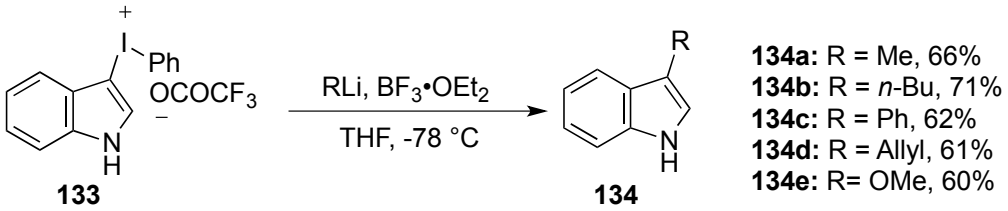
With C3-Indole(/pyrrole)-BX **121** and **126**, the Waser group also reported the Rh or Ru catalyzed arylation of arenes **127**[37a, b] and pyridones **129**.[37c] Complete regioselectivity was achieved by mean of a directing group strategy with excellent yields for arenes (products **128**, 50-91%) and for pyridones (products **130**, 57-86%) (Scheme 29A). They also extended this methodology to the selective Ir or Rh-catalyzed C-H functionalization of the formyl group of *ortho*-substituted benzaldehydes **131** to give ketones **132** in 74-98% yields (Scheme 29B).[37d] This umpolung approach allowed the direct installation of benzoyl at the C3 position of indoles in high yields that are difficult to achieve via classical Friedel-Crafts benzoylation reactions.



Scheme 29. Transition-metal catalyzed C-H functionalizations with Indole- and Pyrrole-BX reagents

4. MISCELLANEOUS

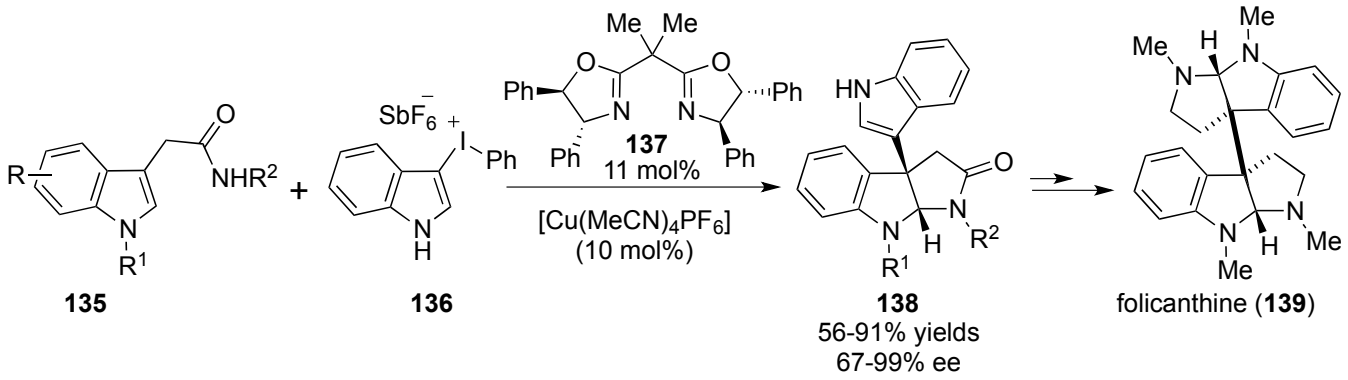
Most methods reported so far have focused on heteroatom nucleophiles or (hetero)arenes as partners. Only few other transformations have been reported. In 1987, Moriarty and co-workers reported the addition of aliphatic organometallic reagents to indole-based iodonium salts.[7] Treatment of **133** with organolithium reagents and BF_3•OEt_2 as Lewis acid afforded regioselectively C3 alkylated and arylated products **134** in 60-71% yields (Scheme 30).



Scheme 30. Alkylation and arylation of indole iodonium salt **133** using organolithium reagents

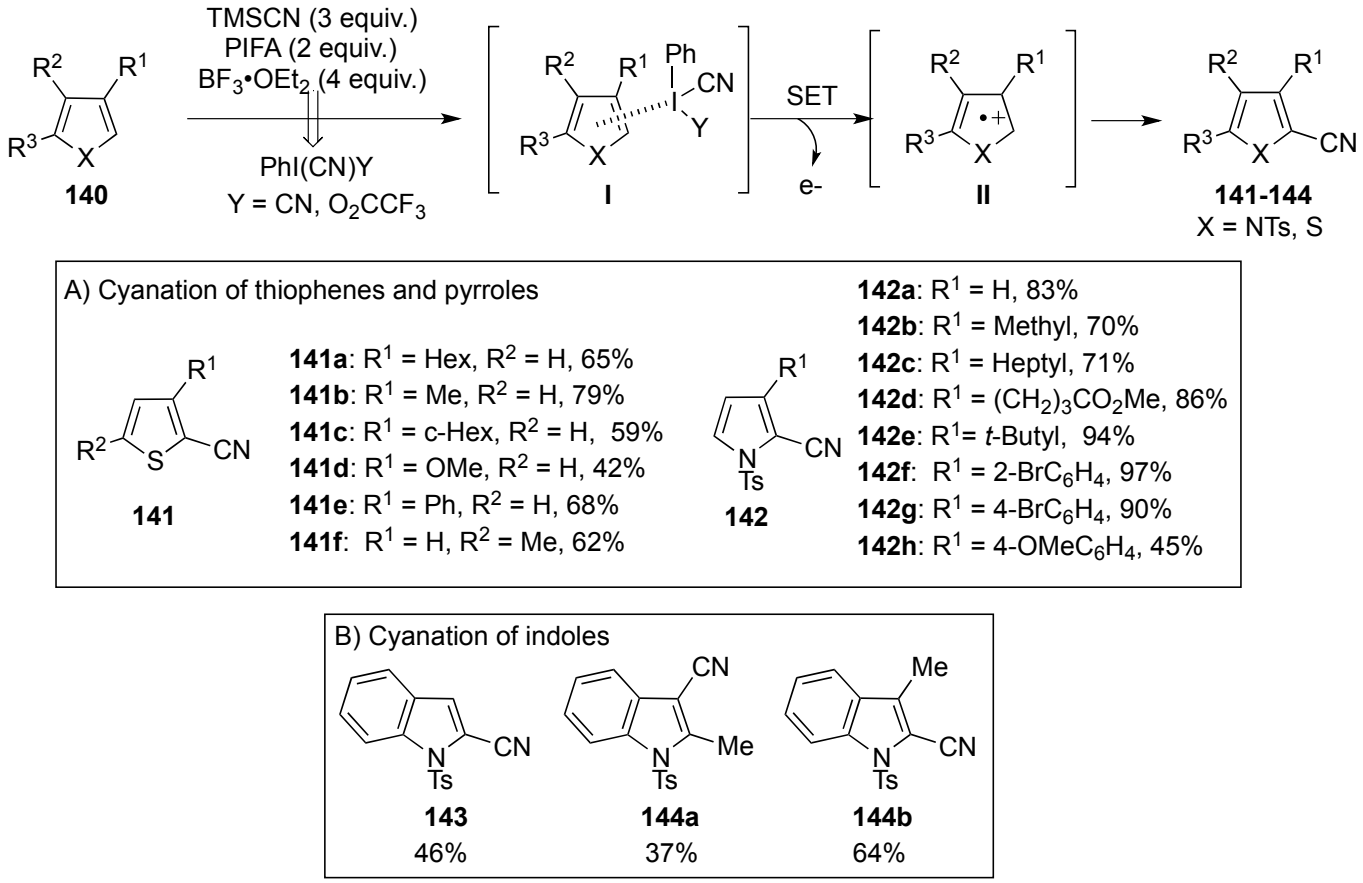
In 2016, an intermolecular asymmetric cascade dearomatization reaction of indole acetamides **135** with 3-indolylphenyliodonium salts **136** was developed by You and co-workers (Scheme 31).[38] The combination of chiral (4*R*,5*R*)-bis-oxazoline ligand **137** (11 mol%) and $[Cu(MeCN)_4]PF_6$ (10 mol%) provided a straightforward access to 3-(3a-indolyl)hexahydropyrroloindolines **138** bearing an all-carbon

quaternary stereocenter at the C3 position of indoline in high yield (55-91%) and *ee* up to 99%. This transformation also resulted in the rare formation of a $C(SP^2)$-$C(SP^3)$ bond. This protocol was used in a formal asymmetric synthesis of folicanthine (**139**).



Scheme 31. Copper-catalyzed enantioselective cascade dearomatization reaction of indole acetamides with indole-based iodonium salts applied in the total synthesis of folicanthine (**139**)

Finally, a PIFA mediated SET oxidative cyanation of electron-rich heterocycles has been reported by Kita and coworkers (Scheme 32).[39] For 3-substituted thiophenes, the 2-cyanated products **141a-f** were selectively obtained (Scheme 32A). The reaction is sensitive to the electronic character of the thiophenes. The presence of some donating groups, e.g., OMe, on the thiophene ring was tolerated, but no reaction was observed for thiophenes possessing electron-withdrawing groups such as an ester or cyano functionality.[39b] The cyanation reaction was also applicable to a wide range of substituted pyrroles. The reaction of pyrroles having aliphatic or aromatic substituents at their 3-position afforded the corresponding 2-cyanated products **142a-h** in 45-97% yields. This cyanation protocol was also extended to *N*-tosylindoles, but led to moderate yields (37-64%) (Scheme 32B). For unsubstituted *N*-Ts indole, C2-cyanated product **143** was obtained, with trace amount of the C3-isomer. For 3-methylindole and 2-methylindole, the corresponding C2-cyanated and C3 cyanated derivatives **144a** and **144b** were obtained respectively.



Scheme 32. Cyanation of electron-rich heterocycles using PIFA and TMSCN

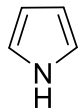
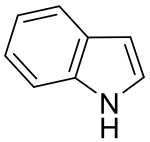
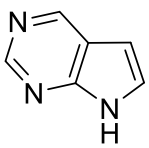
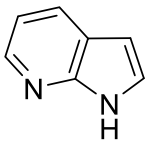
The authors proposed a SET oxidation process initiated by iodine(III) cyanide reagents [PhI(CN)Y (Y = CN, O_2CCF_3)] generated *in situ* from PIFA and TMSCN. This reagent would form a charge-transfer complex I with heterocycles **140**. A single electron transfer (SET) then affords heteroaryl radical cation **II,** which is trapped by the cyanide ion to form cyanated heterocycle derivatives **141-144** after a second SET and rearomatization.

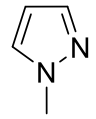
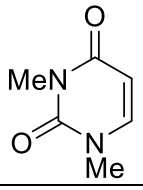
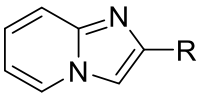
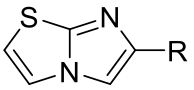
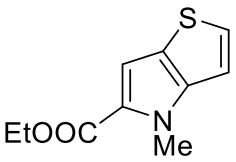
5. CONCLUSION AND OUTLOOK

In conclusion, the umpolung of the reactivity of electron-rich heteroarenes using hypervalent iodine reagents has emerged in the last decade as an interesting alternative for the functionalization of heterocycles. Thanks especially to the work of the Kita group, numerous homo- and cross-coupling methods were developed for both C-X and C-C bond formation. Both direct single electron processes (SET) and the formation of defined heteroaryl-based hypervalent iodine reagents have been achieved. The former allows achieving direct C-H, C-H coupling in a single step, but is often limited to homo-coupling. The latter requires the formation of defined hypervalent iodine reagents, but then enables a broad range of selective cross-coupling reactions, which were not possible before. A further advantage of these

transformations is that they occur under metal-free conditions. A summary of the transformations described in this review organized by heteroarene classes is given in Table 2.

Table 2. Summary of the transformations described in this review

Heteroarene Core	Reaction type	Scheme
	Arylation with electron-rich arenes[32]	Scheme 25B
	(i) Dimerization[22c,d] (ii) Arylation with electron-rich arenes[31, 32, 34] (iii) Cyanation[39] (iv) Amination[15]	Table 1 Scheme 25B Scheme 32 Scheme 12
	(i) Halogenation[8] (ii) Thiocyanation[8] (iii) Dimerization[22a,b] (iv) Arylation and Heteroarylation[22f, 28-33]	Scheme 3 Scheme 18 Table 1 Table 1, Scheme 25
	(i) Halogenation[4] (ii) Hydroxylation[5a] (iii) Alkoxylation[10-14] (iv) Azidation[17] (v) Amination[5a, 15-19] (vi) Dual Haloamination[9] (vii) Dimerization[22e, 23] (viii) Arylation/Heteroarylation[27, 36, 37] (ix) C3- Benzoylation[37d] (x) Alkylation[7] (xi) Dearomatization[38] (xii) Cyanation[39]	Scheme 2 Scheme 4 Scheme 5-10 Scheme 13 Scheme 11-15 Scheme 15C Table 1, Scheme 21 Scheme 24, 28, 29A Scheme 29B Scheme 30 Scheme 31 Scheme 32
	(i) Azidation[17] (ii) Amination[18]	Scheme 13 Scheme 14
	(i) Azidation[17] (ii) Amination[18]	Scheme 13 Scheme 14

	Amination[18]	Scheme 14
	(i) Azidation[17] (ii) Amination[18]	Scheme 13 Scheme 14
	Dimerization[35]	Scheme 27A
	Dimerization[35]	Scheme 27B
	(i) Azidation[17] (ii) Amination[18]	Scheme 13 Scheme 14

Despite its success, the umpolung approach has been so far mostly limited to the reaction with heteroatom nucleophiles and (hetero)arenes and the regioselectivity is dictated by the electron density on the reaction partner. Only two examples of the formation of C(SP^2)-C(SP^3) bonds have been reported and major efforts are still needed in this area. Combining hypervalent iodine-based activation with transition metal catalysis has been also rarely exploited. Although this approach has the disadvantage to lose the "metal-free" aspect, it has the potential for accessing a much broader range of transformations, not limited to the innate reactivity of the nucleophilic partners. The time is now ripe for a new generation of researchers to build upon the impressive pioneering work of the Kita group to develop new useful synthetic methods for heterocycle functionalization based on hypervalent iodine chemistry.

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