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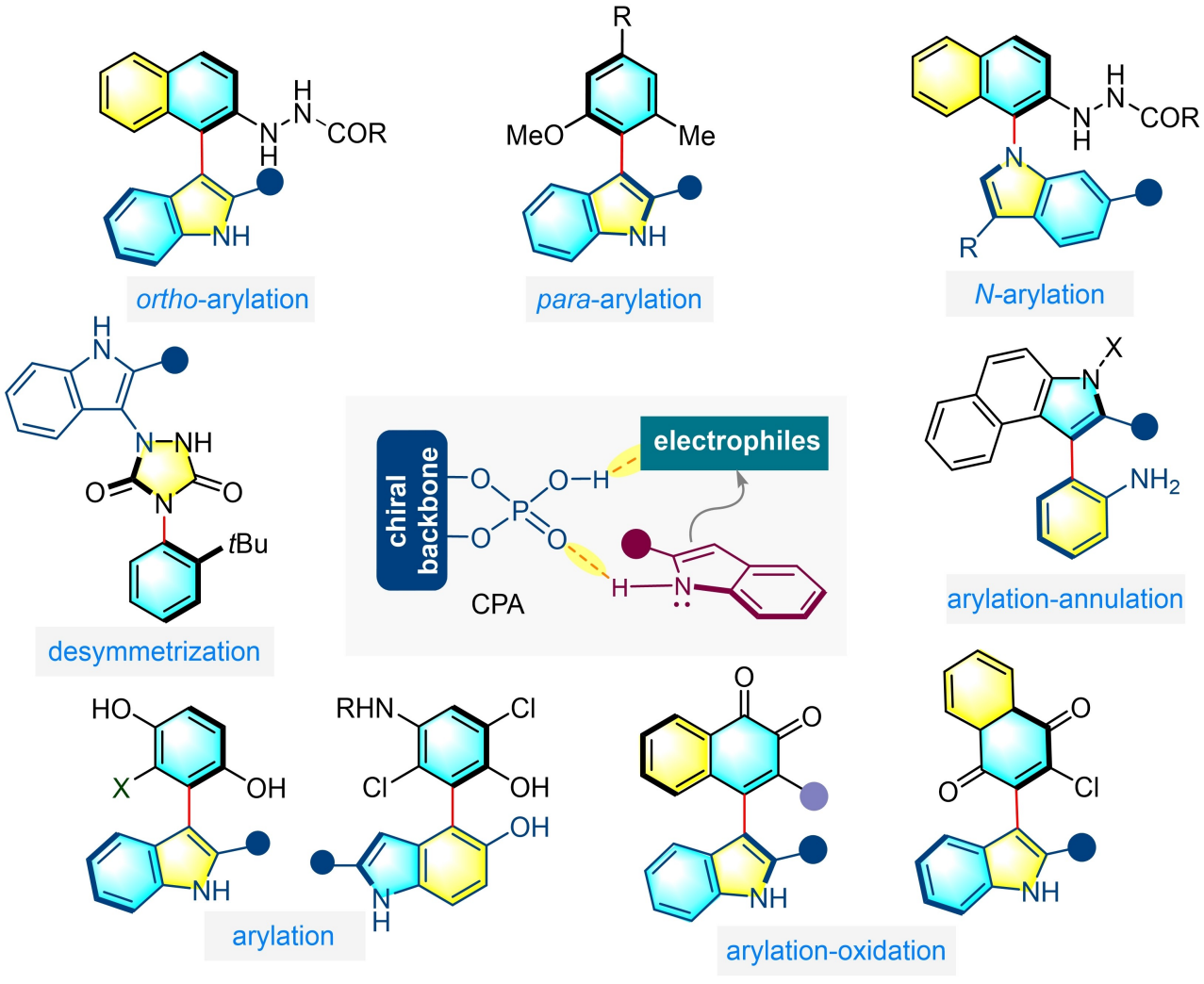
Chiral Phosphoric Acid-Catalyzed Enantioselective Synthesis of Axially Chiral Compounds Involving Indole Derivatives

Jun Kee Cheng and Bin Tan*[a]

Dedicated to Professor Keiji Maruoka on the occasion of his 70th birthday



Abstract: Indoles are one of the most ubiquitous subclass of N-heterocycles and are increasingly incorporated to design new axially chiral scaffolds. The rich profile of reactivity and N–H functionality allow chemical derivatization for enhanced medicinal, material and catalytic properties. Although asymmetric C–C coupling of two arenes gives the most direct access of axially chiral biaryl scaffolds, this chemistry has been the remit of metal catalysis and works efficiently on limited substrates. Our group has devoted special interest in devising novel organocatalytic arylation reactions to fabricate biaryl atropisomers. In this realm, indoles and derivatives have been reliably used as the arylation partners in combination with azoarenes, nitrosonapthalenes and quinone derivatives. Their efficient interaction with chiral phosphoric acid catalyst as well as the tunability of electronics and sterics have enabled excellent control of stereo-, chemo- and regioselectivity to furnish diverse scaffolds. In addition, indoles could act as nucleophiles in desymmetrization of 1,2,4-triazole-3,5-diones. This account provides a succinct illustration of these developments.

Keywords: organocatalysis, chiral phosphoric acid catalysis, axial chirality, indoles, direct arylation

1. Introduction

Indoles and derivatives thereof are widely represented within naturally occurring alkaloids, chiral ligands and compounds with diverse bioactivities.[1] The tunable electronic nature and the N–H functionality give a promising ground to decorate this scaffold for achieving structural and stereochemical diversity.[2] In line with recent interest in axial chirality, which has now made widespread appearance in medicinal,[3] material[4] and asymmetric chemistry,[5] our group has devoted special interest to incorporate this scaffold in our organocatalytic atroposelective synthesis programme for expanding the library of axially chiral molecules.[6] The rich chemistry of indoles gives unique opportunities to optimize catalytic performance and coordination properties for uses as chiral ligands and catalysts. Indeed, as their synthetic methods mature, their promising uses in this field have gradually come to light (Figure 1).[7] Medicinal chemists are also more equipped to modulate the properties of lead compounds through implementation of atropisomerism with indole nucleus.[3]

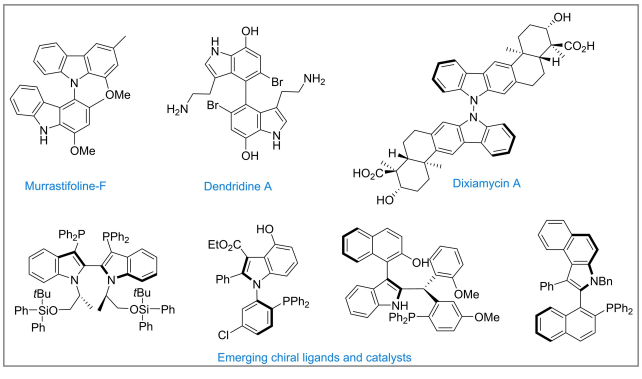


Figure 1. Indole-containing atropisomers in various settings.

In fact, indole compounds containing a stereogenic axis are not unknown in nature.[8] However, presumably due to the lack of synthetic capability to construct axial chirality and their lower conformational stability compared to the six-membered biaryl analogues, the catalytic asymmetric synthesis of axially chiral indole derivatives has emerged more slowly. The first catalytic approach could trace to Kitagawa's 2010 Pd-catalyzed annulation method that employed *ortho*-alkynyl aniline building blocks.[9] The inspiring contributions of many researchers have since enriched the synthetic toolbox to prepare axially chiral indoles, which have been summarized in pertinent reviews.[10] Here, we wish to discuss our findings on using indoles as the versatile arylation partners to assemble diverse classes of axially chiral compounds. In these reactions, the modularity of chiral phosphoric acid (CPA) catalysts and their ability to form effective interactions with these N-heterocycles have allowed remarkable stereo-, regio- and chemoselectivity control.

2. Arylation Reaction with Azoarenes

Ligands and catalysts built on axially chiral biaryl frameworks have been used reliably for diverse reactions but their syntheses are still not straightforward. The direct asymmetric coupling of two non-functionalized arenes represents the most direct disconnection, but only naphthols, naphthylamines and carbazoles adorned with specific substitutions are amenable to highly selective metal-catalyzed oxidative coupling.[11] Very recently, Smith's team achieved the direct oxidative cross-coupling between naphthols and indoles with a chiral Fe/

[a] *Dr. J. Kee Cheng, Prof. B. Tan*
Department of Chemistry and Shenzhen Grubbs Institute
Southern University of Science and Technology
Shenzhen 518055, China
E-mail: tanb@sustech.edu.cn

PyBox system. The reaction occurs through interception of a chiral Fe-bound naphthoxy radical by indole nucleophile.[12]

On the other hand, organocatalysis could enable distinctive reaction modes to couple two nucleophilic arene components. In 2017, Shi, Li and co-workers demonstrated the use of CPA to activate 2-indolylmethanols **1** for atroposelective arylation with aromatic alcohols to form 3-aryl-indoles **3** that contain a C–C chiral axis (Scheme 1a).[13] After dehydration, the nucleophile adds selectively to the C3-electrophilic carbon. Reaction at dibenzylic carbon is prohibited by steric congestion. CPA anion establishes hydrogen bonding with both reactants for the stereocontrolled addition. This is followed by aromatization with central-to-axial chirality transfer to reveal the chiral axis. By installing an alkyne group on C3 of the indolylmethanols and by using aromatic alcohols as the 1,3-dinucleophiles, the group furnished another class of axially chiral aryl-alkene-indole frameworks **5**, through sequential nucleophilic addition onto the alkyne and the dibenzylic carbon (Scheme 1b).[14]

In our approach, we envisioned the installation of a functional group on the arenes to modulate its reactivity towards organocatalytic arylation. First, it could withdraw electron density from the arene substrates, favorably by conjugation, and able to accept the hydride from (i.e. oxidize) the σ^H adduct intermediate formed after nucleophilic addition (Scheme 2a). Besides, it should serve as an interaction point for the catalyst to enable control of regio-, chemo- and stereoselectivity. These criteria guided our identification of azo group as the suitable directing/activating group for the redox-neutral arylation reaction. As an electron-withdrawing group mainly operates by conjugation, the formal nucleophilic aromatic substitution at *ortho* position was presumably enabled by synergistic catalyst control and resonance effect.

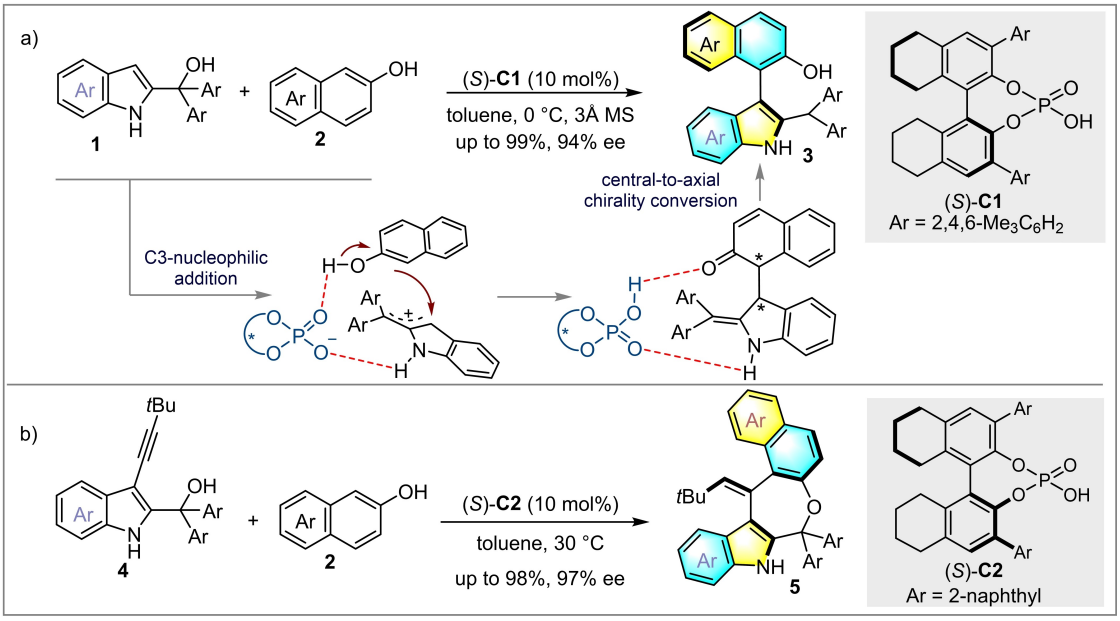
2.1. Regio- and Enantioselective C-Arylation with Azoarenes

This strategy was first exemplified in the arylation of azonaphthanelenes by indoles under the auspices of chiral phosphoric acid catalyst (Scheme 2b).[15] A modulation of C2-substituent on indoles led to two classes of axially chiral skeletons, namely, naphthyl indoles **7** and aniline indoles **8** in remarkable yields and stereoselectivities. The CPA operates in a bifunctional activation mode, which orients both substrates through hydrogen bonding and promotes a stereoselective 1,4-addition onto the *ortho*-carbon of azonaphthalene (**Int-A**). After rearomatization, a bifurcated reaction pathway commences from **Int-B**. Indole substrates with bulky C2-substituent such as *tert*-butyl and phenyl group readily undergo β-H elimination to afford naphthyl indoles **7**. On the other hand, the small steric block imposed by methyl or *iso*-propyl group promotes the addition of hydrazine to the tethering iminium carbon. An ensuing ring-opening/aromatization *via* β-H elimination releases the aniline product **8**. Notably, this pathway involves the deconstruction and re-assembly of an indole ring.

This reactivity portfolio was shown to be general and modular. In analogy to biocatalysis, where amino acid residues in active sites of enzymes cooperatively effect regiospecific chemical reactions, the tuning of CPA structure could switch the regioselectivity to realize *para*-selective arylation of azobenzenes by indoles (Scheme 3).[16] CPA with SPINOL backbone catalyzes the arylation of 3,5-disubstituted azobenzene **9** with various C2-substituted indoles. Modifications at C2 (i.e. the rotation-impeding groups), C5 and ester moiety on indoles were accommodated. This method constitutes an advance in remote control of stereoselectivity by structural fine-tuning of organocatalyst. Within metal catalytic framework, the Davies team achieved enantioselective differentiation of the non-activated Csp^3–H bonds through spatial arrangement of a chiral dirhodium catalytic system.[17] Based on the mechanistic experiments, the CPA catalyst should control the stereodetermining nucleophilic addition by establishing hydrogen bonding with both azoarene and indole substrates. The observed *para*-selectivity arises from steric differentiation, where the bulky backbone of catalyst hinders the formation of *N*- and *ortho*-products. It is worth noting that, compared to bicyclic naphthalene reactants, this transformation has to

Bin Tan is currently a chair Professor and vice-chair of Department of Chemistry in Southern University of Science and Technology (SUSTech). He received his Ph.D. in organic chemistry from Nanyang Technological University in 2010. He then did postdoctoral studies at The Scripps Research Institute. At the end of 2012, he started his independent research career at SUSTech. His research focuses on catalytic asymmetric axial chirality chemistry.

Jun Kee Cheng earned her B.S. in 2012 and Ph.D. in 2016 from Nanyang Technological University under the supervision of Professor Loh Teck Peng. She joined Southern University of Science and Technology in 2020 with research interests on atroposelective synthesis.



Scheme 1. CPA-catalyzed arylation and (4 + 3)-cyclization of indolylmethanols.

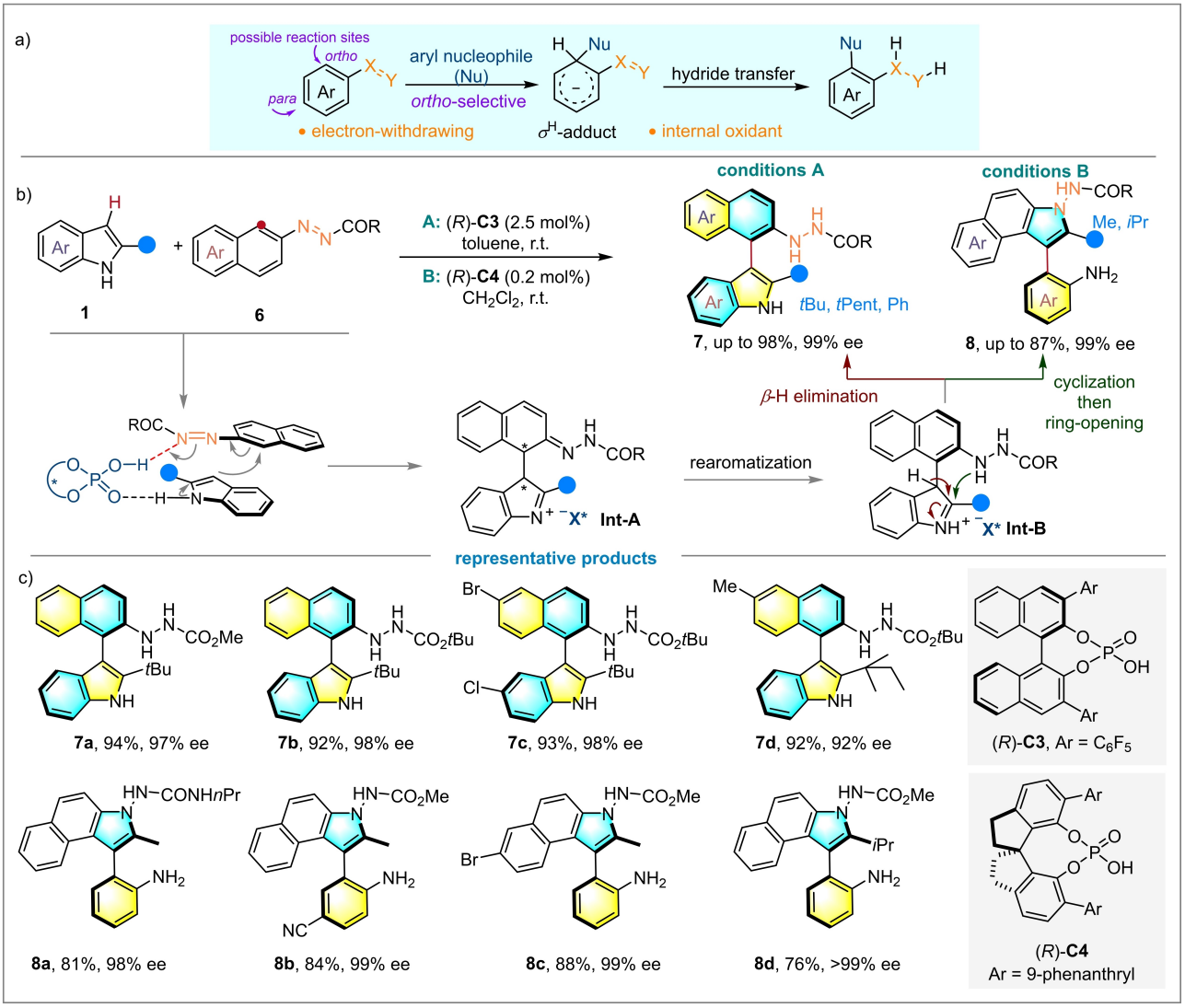
surmount a higher energy barrier due to dearomatization of a single aromatic ring system upon nucleophilic attack.

2.2. Catalytic Asymmetric Dearomatization Reaction

By structural optimization of substrates, this organocatalytic arylation strategy could be extrapolated to catalytic asymmetric dearomatization reaction (CADA) to fabricate an underexplored class of axially chiral molecules with cyclohexadienylidene backbone (Scheme 4).[18] The axial chirality in **12** is derived from the perpendicular arrangement between terminal substituents of C=N double bond and C4 of the cyclohexadienylidene moiety. The initial design that installs a methoxy substituent at C4-position led to an exclusive *N*-addition. To override this reactivity, a 3,4,5-trisubstitution on the benzene substrate could favorably localize the positive charge and yields dearomatizative *para*-adduct. In general, the more electron-deficient ester groups on azo (e.g. **12a** versus **12b**) gave rise to higher reaction efficiencies. Various functionalities including hydroxyl, amine, halogen and cyano group were compatible. Due to poor solubility of product, compound **12a** could be obtained in 99% yield and 99.6% ee from a gram-scale reaction after simple filtration process. Mechanistically, the protonation of azobenzene substrate first generates arylnitrenium ion and double bond conjugation leads to the more stable *para*-carbocation. The chiral phosphate ion establishes hydrogen bonding with the N–H entity on indole and azobenzene for the regio- and stereoselective nucleophilic addition.

2.3. N-Arylation with Azonaphthalenes

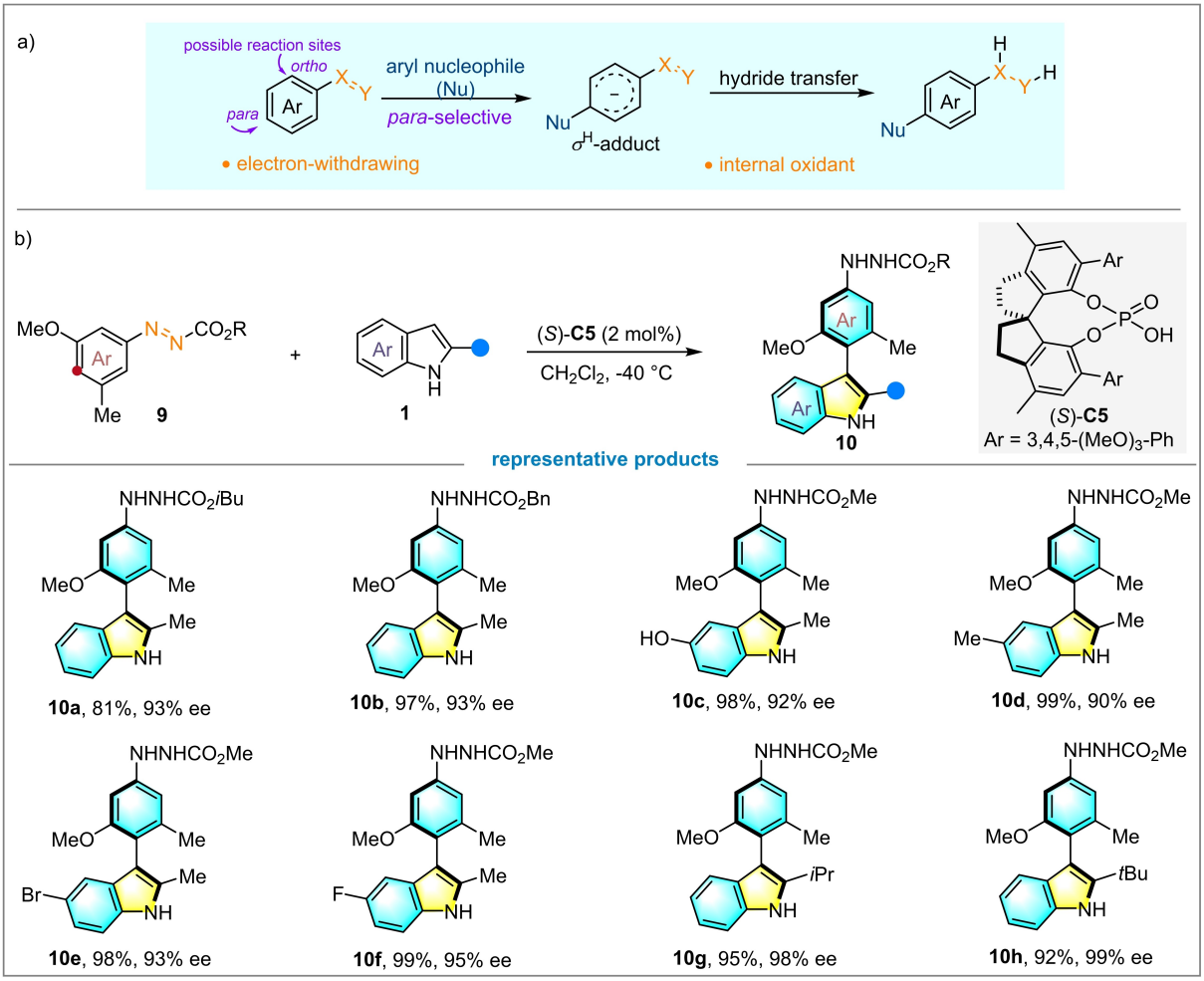
Although the examples above showcased a prevailing C-nucleophilic reactivity of indoles, we envisioned the possibility to exploit the reactivity of indole nitrogen to achieve arene amination within organocatalytic framework. The realization of this chemistry would be a meaningful addition to the C–N coupling toolbox that is predominated by metal-catalyzed methodologies. This reaction was enabled by introducing sterically demanding substituent at the usual C3 reaction site. The *N*-arylation of indoles **1** by azonaphthalenes **6** generated an array of axially chiral *N*-arylindole adducts **13** with excellent stereocontrol and modest yields (e.g. **13a–e**) in the presence of CPA **C7** (Scheme 5).[19] Intriguingly, C3-methyl-substituted azo substrates were transformed with notable increment in yield (>90%) and 99% ee. (**13f**, **13g**). In this study, the carbazoles were also found to participate in atroposelective C–H amination reactions (**14**) as well as double C–H amination to afford 1,5-dicarbazole naphthalene derivatives **15**. The CPA catalyst likely forms hydrogen bond with azo nitrogen and N–H of the indole/carbazole substrates for the stereoselective addition, followed by rearomatization with central-to-axial chirality transfer. The *N*-arylcarbazole scaffold could be elaborated into monophosphine **16** and thiourea **17**, whose stereoinduction capability has been preliminarily verified.



Scheme 2. Atroposelective arylation with azonaphthalenes.

3. Arylation Reaction with Nitrosonaphthalenes

The demonstrated utility of azo functionality to activate arenes towards chemo-, regio- and atroposelective arylation under effective control of CPA catalyst motivates us to extend this formal nucleophilic aromatic substitution strategy. By reasoning that the activating/directing group should be capable of drawing electron density away from arenes, we commenced the investigation by computing electron affinity (EA) and lowest unoccupied molecular orbital (LUMO) energies of representative naphthalenes that contain ester, cyano, aldehyde and sulfonyl substituents.[20] In addition to the azo group (1.72 eV) investigated in our previous studies, other nitrogen functional groups such as nitroso (1.50 eV) and nitro (1.41 eV) also show high EA (Scheme 6a). This trio also possesses the lowest LUMO energies and effective lowering of LUMO energies upon association with phosphoric acid could be seen for nitroso and azo group. Nonetheless, a formidable control of chemoselectivity was anticipated for nitroso substrates, in view of their established reactivity at the nitrogen and oxygen centers.[21] The initial trial with 2-*tert*-butyl-indole **1a** and nitrosonaphthalene **18a** indeed attested to the predicted cross-coupling reactivity, but the oxidized product (**20a** instead of **19a**) and aniline-indole **21a** formed from intramolecular nucleophilic attack of hydroxylamine, red arrow) were generated alongside (Scheme 6b). Compared to using nitroso as the internal oxidant and the aerobic conditions, the inclusion of dibromo-substituted quinone **Oxd1** as oxidant gave rise to the nitroso product **20** in most



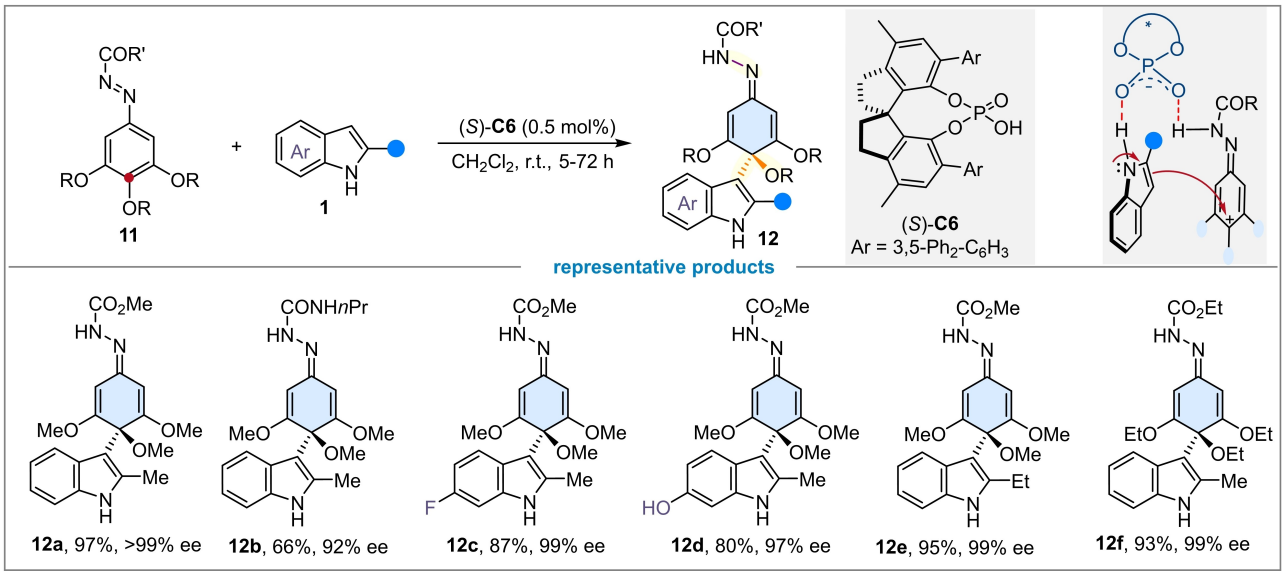
Scheme 3. Atropo- and *para*-selective arylation with azonaphthalenes.

optimal results (Scheme 6c). Under these conditions, the substrate generality and functional group tolerance were high with respect to both coupling partners. Remarkably, by excluding the external oxidant and slight modification of reaction conditions, formation of aniline-indole atropisomeric **21** from a broad range of 2-nitrosonaphthalenes and indoles in good yields and excellent ee (mostly 98–99%) could be achieved.

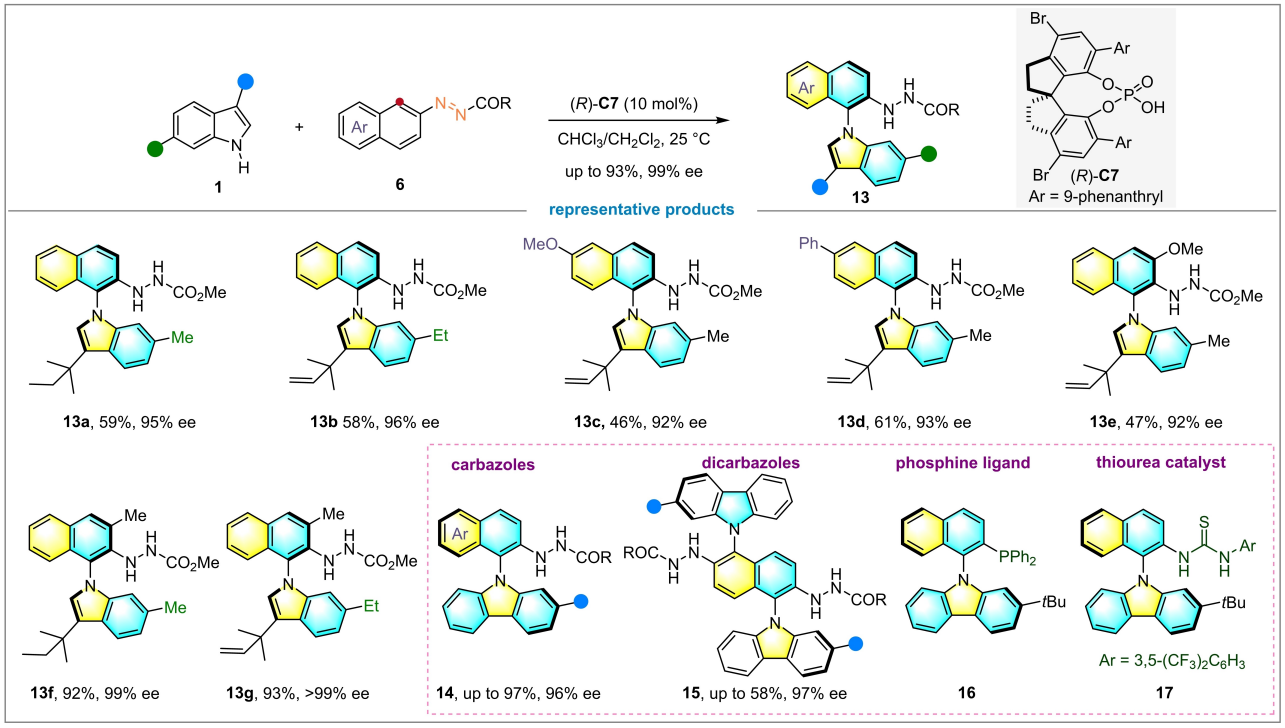
4. Arylation with Quinone Derivatives

4.1. Redox Neutral Arylation with (Imino) Quinones

Axially chiral biaryls that contain aromatic alcohol structure are commonly found among privileged ligands. The hydroxyl functionality is also a convenient handle to facilitate their further conversion into other organocatalysts or ligands. Progress has been made to construct NOBIN and BINOL-type compounds **22** *via* oxidative coupling conditions (Scheme 7a).[11c–g] These conditions were found to be less compatible with phenols due to higher oxidation potential of phenols and complicated chemoselectivity caused by the presence of multiple reactive centers.[22] To bypass this synthetic hurdle, our group and others have developed quinone and derivatives as pre-oxidized precursors of phenols for direct arylation with 2-naphthols and 2-naphthylamines to generate axially chiral biaryl amino alcohols and diols **23**.[23] The rising interest in diversifying the collection of axially chiral biaryls led us to contemplate the applicability of indoles as nucleophiles to selectively fabricate two classes of axially chiral phenylindole frameworks *via* reaction at heterocyclic (C3) or carbocyclic ring (C4) (Scheme 7b). However, a literature survey revealed that [3+2] annulation between quinones and indoles could compete to form benzofuroindolines, which could occur in oxidative cross-coupling of indoles and phenols.[24]

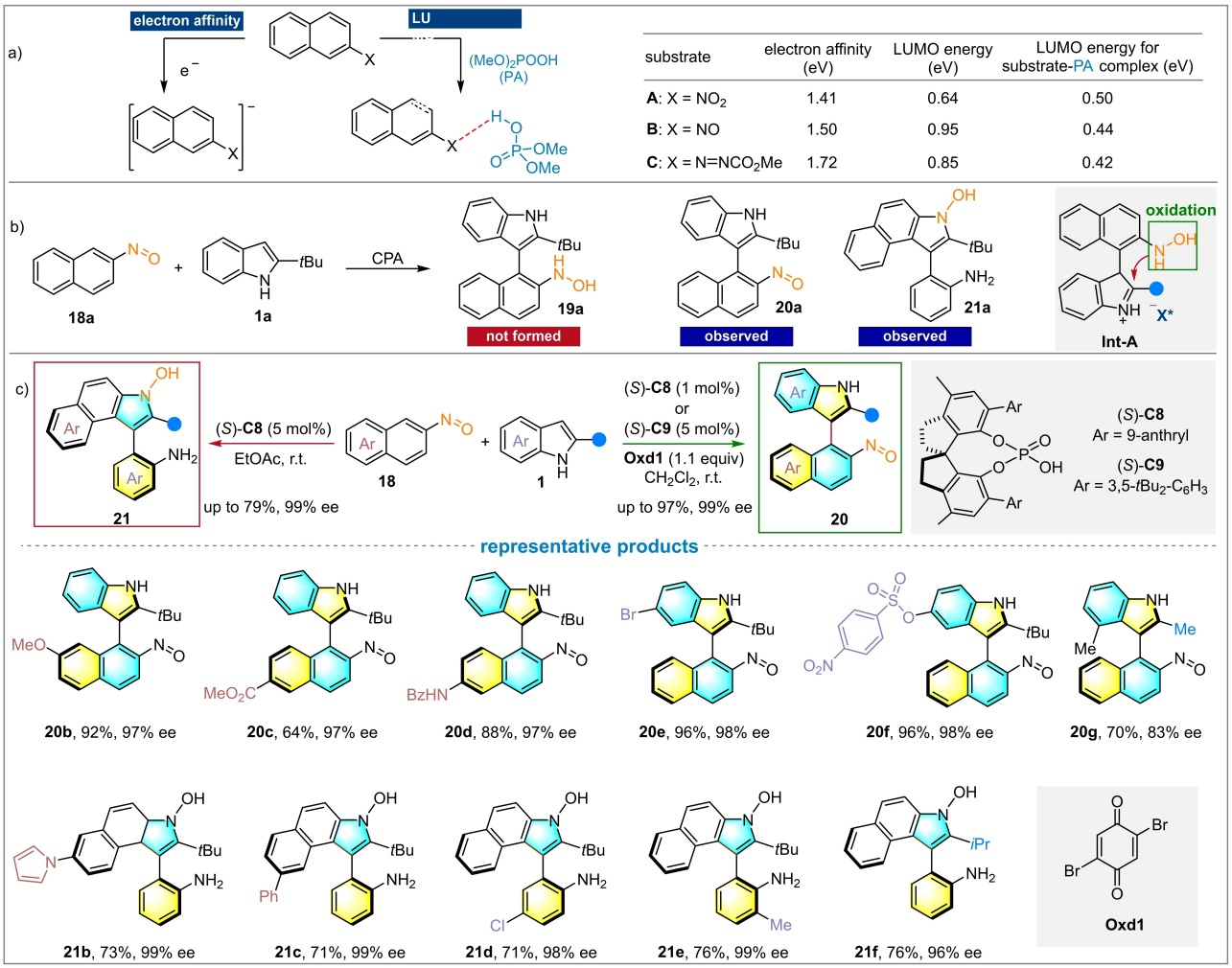


Scheme 4. Catalytic asymmetric dearomatization reaction of azobenzenes.



Scheme 5. Atroposelective C–H amination of azonaphthalenes.

To override the cyclization pathway, we sought to adopt steric bias by installing bulky groups at C2-positon of indole or at the quinone moiety. Differently, electronic differentiation was leveraged to suppress the nucleophilic reactivity of 5-hydroxyindoles at the nitrogen, C3, C4 and hydroxyl group.[25] In the presence of catalyst **C10**, ester quinones could undergo arylation with indoles with differing electronics (**26**) but the steric size of C2-substituent would affect the rigidity of chiral axis, where smaller group such as 1-methylcyclopropyl led to greatly diminished ee. Pleasingly, the employment of diiodo-

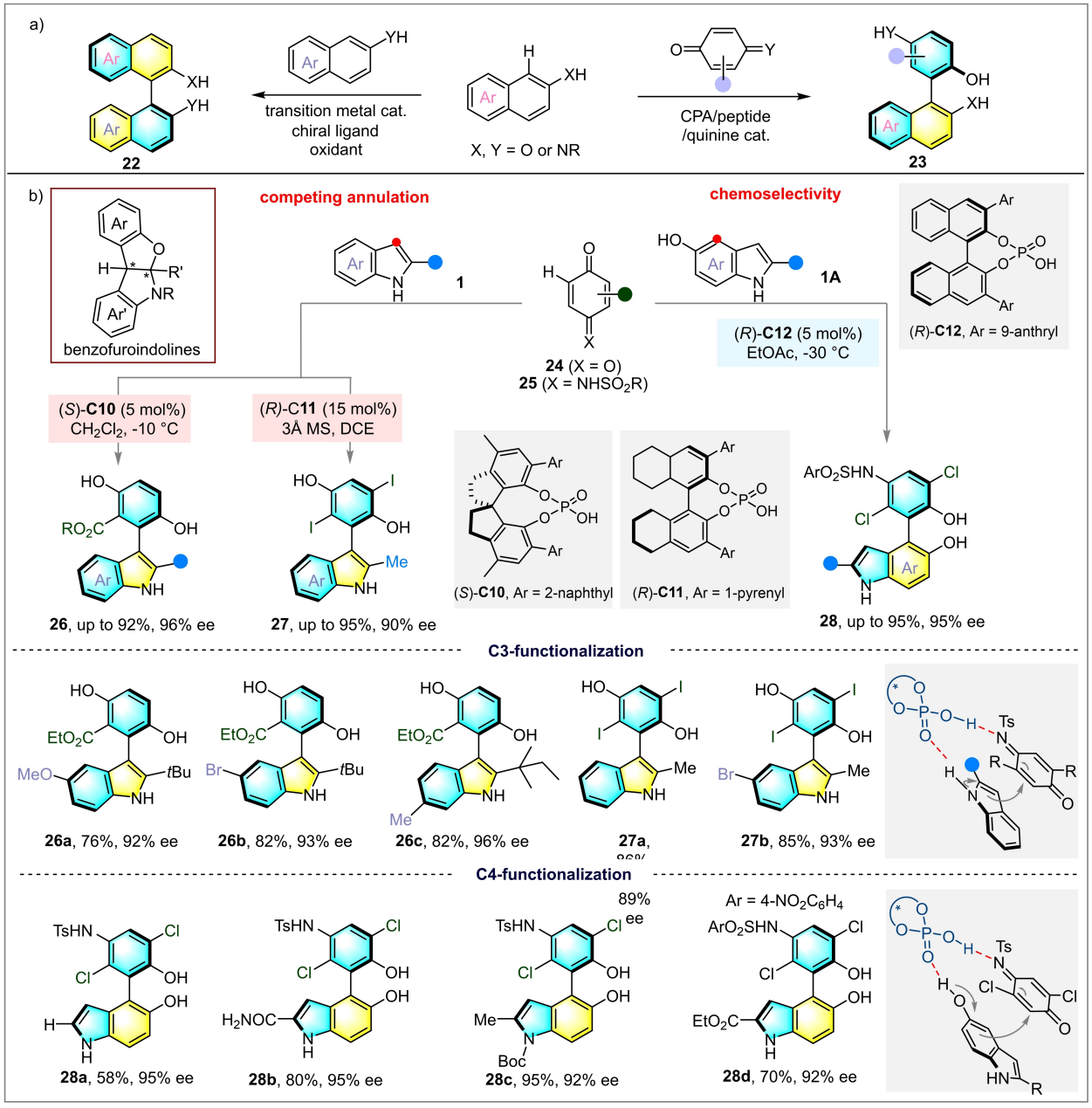


Scheme 6. Atroposelective arylation of nitrosonapthalenes.

quinone enabled arylation with the smaller 2-methylindole substrate (**27**).

Differently, when ester quinone was treated with 5-hydroxyindole, the reduced phenol product was obtained. To avoid reduction of quinone reactants, we turned to using iminoquinones with lower redox potential. This switch of reactant and a re-optimized set of catalytic conditions have allowed formation of biaryl diols **28**. This transformation showed good tolerance towards the nature of C2-substituents and the nitrogen protecting groups. Intriguingly, both N–H (**28 c**) and C2-substituents (**28 a**) were not necessary for product formation and stereocontrol. Therefore, it is likely that the OH group is hydrogen bonded to the CPA catalyst during the stereocontrolling addition step for this reaction class. The atropostability and chirality induction properties of the product have also been verified in the application of **28 d** in asymmetric addition of diethylzinc to 2-naphthaldehyde.

o-Quinones are co-factors in quinoproteins and this structure could also be found in natural products. However, the synthesis of axially chiral *o*-quinone-arenes, which could constitute an unexplored class of biomimetic catalysts, was unknown despite their structural resemblance to biaryl atropisomers. Our design blueprint centered on organo-catalytic arylation of *o*-naphthoquinones **29**, which occurs through initial addition of arene nucleophiles (**Int-1**), and is succeeded by aromatization (**Int-2**) and oxidation with central-to-axial chirality conversion (Scheme 8). Owing to a lack of related studies, the substrate design to confer suitable reactivity and atropostability became the foremost task. On the other hand, a suitable bifunctional chiral organocatalyst that could establish effective interactions with substrates to confer reactivity and stereoselectivity control has to be identified. Finally, the oxidation conditions at the final step also have to



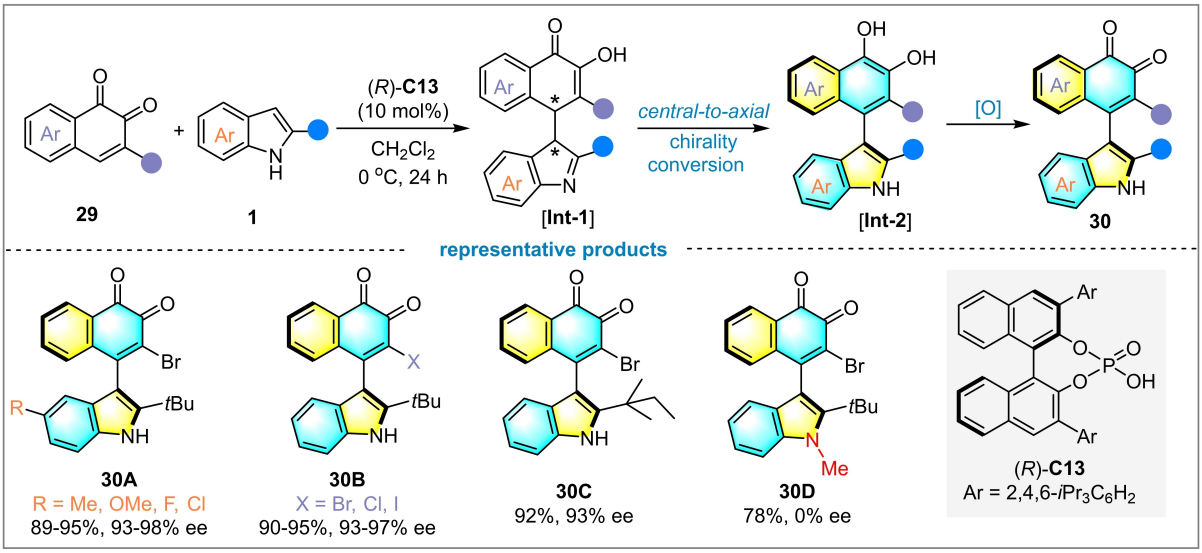
Scheme 7. Regioselective arylation of indoles with quinones and iminoquinones.

be sufficiently mild to prevent free rotation of the chiral axis during the conversion.

With *o*-naphthoquinones **29** playing a dual role as oxidant and **C13** as the catalyst, the envisioned pathway could proceed for indoles that bear electron-rich or halogen functionality (**30A**) in combination with halogen-substituted *o*-naphthoquinones **29**.[26] The CPA works in a bifunctional activation mode to establish hydrogen bonding through the N–H entity. This was corroborated by the complete loss of ee for N-methylated substrate (**30D**). Other than indoles, 2-naphthylamines and 2-naphthols could engage in this atroposelective synthesis in good yields and excellent enantioselectivities.

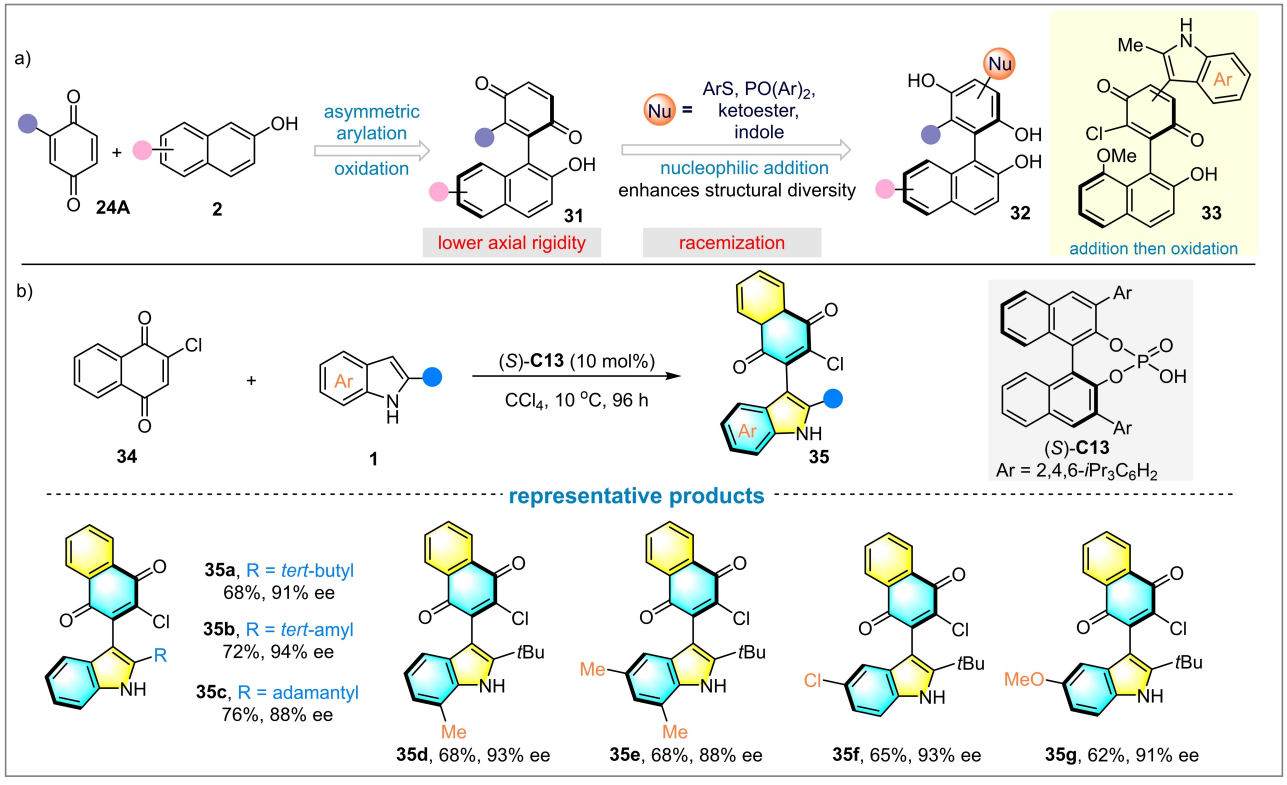
4.2. Atroposelective Synthesis of Arylquinones via Arylation-Oxidation Sequence

The propensity of quinone to undergo nucleophilic addition prompted us to investigate generation of novel axially chiral



Scheme 8. Axially chiral indolyl-*o*-naphthoquinone *via* arylation–oxidation sequence.

aryl *p*-quinones **31** as precursors to non-C_2 symmetric biaryldiols **32** through the arylation-oxidation-addition sequence (Scheme 9a).[27] This scheme would not only circumvent the difficulty faced in direct employment of phenols for asymmetric oxidative coupling reactions (*vide supra*), but the nucleophilic addition step would also offer a convenient



Scheme 9. Axially chiral indole-*p*-quinones *via* arylation–oxidation sequence.

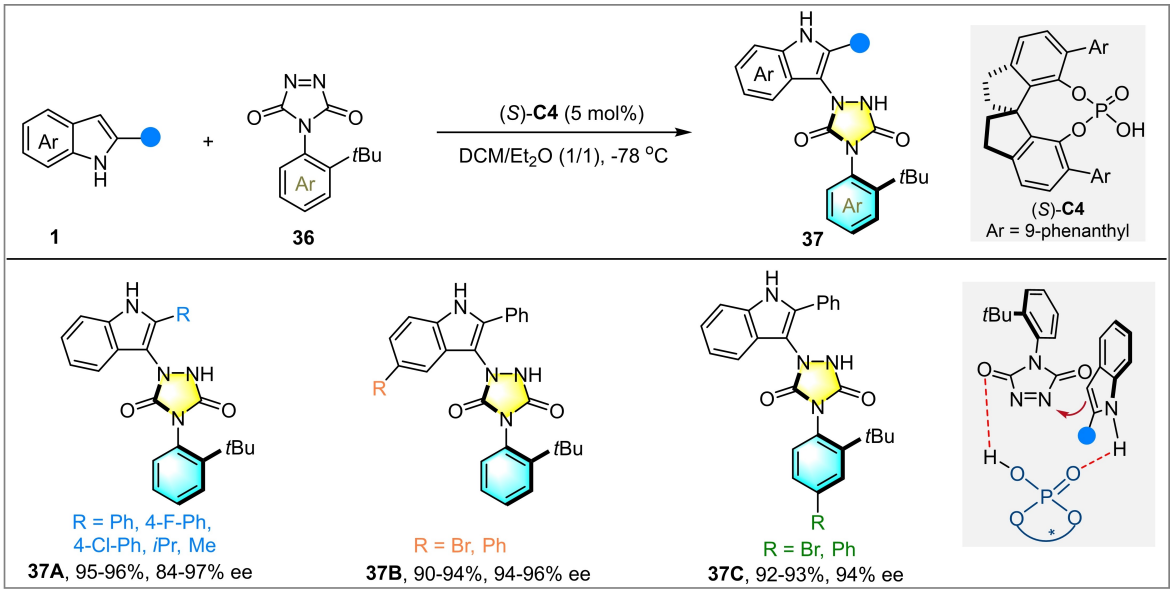
platform to further enhance the structural diversity of products. However, compared to naphthoquinones used previously, this proposal could be hindered by rapid racemization, due to lower rotational barrier of the arene-benzoquinone axis and conditions used in the final oxidation-reduction steps. After careful substrate design, we were delighted to find that atropisomeric aryl-*p*-quinones **31** constructed from 1,4-benzoquinone and 2-naphthols could readily be intercepted by various nucleophiles to form diverse biaryl diol atropisomers **32**. However, instead of the reduced diol form, the addition of indole to these quinone atropisomers would give rise to regioisomeric and highly functionalized indole-aryl-*p*-quinone atropisomers **33**, due to their lability towards aerobic oxidation. The treatment with DDQ post-reaction could facilitate this oxidation process and improve product yield. These observations inspired us to examine the direct formation of axially chiral indole-*p*-quinones from quinones and indoles as a new class of heteroaryl-*p*-quinone structures. By rationalizing that such structures would possess an even more labile chiral axis due to the five-membered N-heterocycle ring, C2-substituted indole and bulkier 2-chloro-1,4-naphthoquinone **34** were evaluated (Scheme 9b). Pleasingly, the target heteroaryl-p-quinones **35** were obtained with accommodation of different substitutions on indole substrates. Aside from *tert*-butyl group, the C2-substituents could be occupied by *tert*-amyl and adamantyl group without substantial loss of ee.

5. Desymmetrization Reaction

Aside from acting as the direct arylation partners, indoles have been successfully employed in a desymmetrization of 4-aryl-1,2,4-triazole-3,5-dione (ATAD) electrophiles to construct N–C chiral aryl urazoles **37** (Scheme 10). CPA **C4** promotes a rapid tyrosine click reaction (within 20 mins) of indoles through a bifunctional activation mode with excellent stereocontrol, despite the remoteness of the incipient chiral axis from reaction site.[28] As the N–C biaryl axis is rotationally restricted by the *tert*-butyl group, the catalyst controls the facial selective nucleophilic addition to break the symmetry of the triazoledione ring. Variations of C2- and C5- substituents on indoles as well as *para*-substituents on ATADs were possible. The indole urazole products were furnished in excellent yields and enantioselectivities.

6. Conclusion

Axially chiral biaryls have shown overarching and increasing uses in various chemistry settings. This emphasizes the need to improve their synthetic accessibility and skeletal diversity. In addition to their omnipresence in biologically active compounds, indoles and derivatives are highly amenable to chemical derivatization, an attribute that would allow modulation of properties of catalyst and ligands derived from them. As part of our efforts in organocatalytic atroposelective research, we have established indoles as robust building blocks to construct axially chiral compounds. Aside from (hetero)biaryl frameworks, these transformations have also



Scheme 10. Desymmetrization of ATADs with indoles by CPA catalyst.

unlocked underexplored structures that display axial chirality such as cyclohexadienylidenes and aryl urazoles. A salient feature of these reaction systems lies in the excellent control of regio-, chemo- and stereoselectivity through chiral phosphoric acid catalysis as well as flexibility to modulate steric and electronic effects. Notably, the synthetic toolbox that incorporates indoles to construct axially chiral compounds is expanding rapidly to enhance the chemical space. For instance, Ackermann and Wencel-Delord have recently disclosed synthesis of the rare atropoisomeric C2-aryl indoles by a cobalt-catalyzed direct arylation protocol.[29] Zhang and Shi explored the formal (3 + 2) cycloadditions of indole-based enaminones and diketoesters with CPA catalyst to prepare axially chiral *N*,*N*'-bisindoles.[30] These illustrative examples portend that more diversified axially chiral scaffolds would be soon accessible. This advancement could be further accelerated with merging of photoredox catalysis and electrocatalysis in their synthesis, which could establish unique reaction modes.

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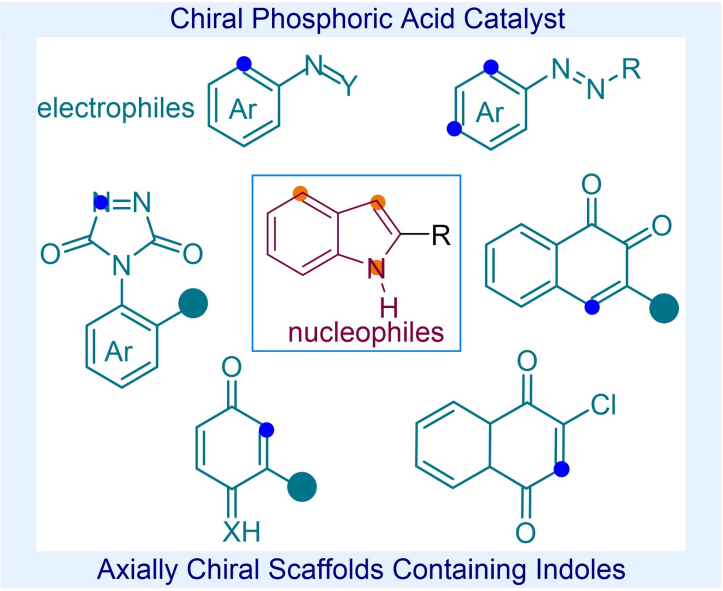

*Dr. J. Kee Cheng, Prof. B. Tan**

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Chiral Phosphoric Acid-Catalyzed Enantioselective Synthesis of Axially Chiral Compounds Involving Indole Derivatives

Indoles serve as versatile building blocks in constructing various axially chiral scaffolds in the presence of chiral phosphoric acid catalysts. The transformations are enabled by tunability of both indole substrates and catalysts for high chemo-, regio- and atroposelectivities.