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Chiral-Phosphoric-Acid-Catalyzed Atroposelective C-H Amination of Arenes

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Dedication ((optional))

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Abstract: *N*-arylcarbazole structures are of significant importance due to their wide prevalence in natural products and functional OLED materials. C-H amination of arene has been widely recognized as the most efficient approach to access these structures. Conventional strategies involving transition metal catalyst always suffered from confined substrate generality and the requirement of exogenous oxidants. Organocatalytic enantioselective *C-N* chiral axis construction remains elusive. Here we present the first organocatalytic strategy for the synthesis of novel axially chiral *N*-arylcarbazole frameworks via the assembly of azonaphthalenes and carbazoles. This reaction accommodates broad substrate scope and gives atropisomeric *N*-arylcarbazoles in good yields with excellent enantiocontrol. This approach not only offers an alternative to metal-catalyzed *C-N* cross-coupling, but also brings about opportunities for the exploitation of structurally diverse *N*-aryl atropisomers and OLED materials.

Organic molecules possessing *N*-aryl framework are ubiquitous in natural products, pharmaceuticals, agrochemicals, and functional materials.[1] Among these structures, *N*-arylcarbazoles featuring high triplet energies and competitive hole transport ability have been emerged as one of the most widely used host materials for OLEDs in the recent years (Figure 1A).[2] Rapid progress in such fields stimulates a continuous exploration of structurally novel *N*-arylcarbazoles, particularly those bearing distinct chiral elements. Therefore, the pursuit of catalytic and enantioselective strategy to assemble such molecules has been and continues to be highly enthralling. Conventional transition-metal-catalyzed *N*-arylation protocols such as Ullmann, Buchwald-Hartwig, and Chan-Lam-Evans coupling reactions have become indispensable tools in *C-N* bond formation regime (Figure 1B).[3] However, pre-functionalization of the arene substrate and the superfluous waste production largely hampered their efficiencies. To circumvent these drawbacks, a series of strategies based on arene oxidative amination reactions were successively exploited using hypervalent iodine[4] or transition metal[5] as the facilitator (Figure 1C). The amine-arene coupling was further elegantly complemented by means of novel photocatalysis[6] and electrocatalysis[7] established by Nicewicz,[6a,b] Ackermann[7a] and their coworkers very recently. Despite abovementioned contributions, confined substrate scope significantly restricted their applications and harsh conditions were adverse to enantiocontrol. On the other hand, organocatalytic enantioselective arene C-H amination with *N*-nucleophiles remains hard to access due to the low activity of aromatic ring and limited catalytic modes of asymmetric organocatalysis.

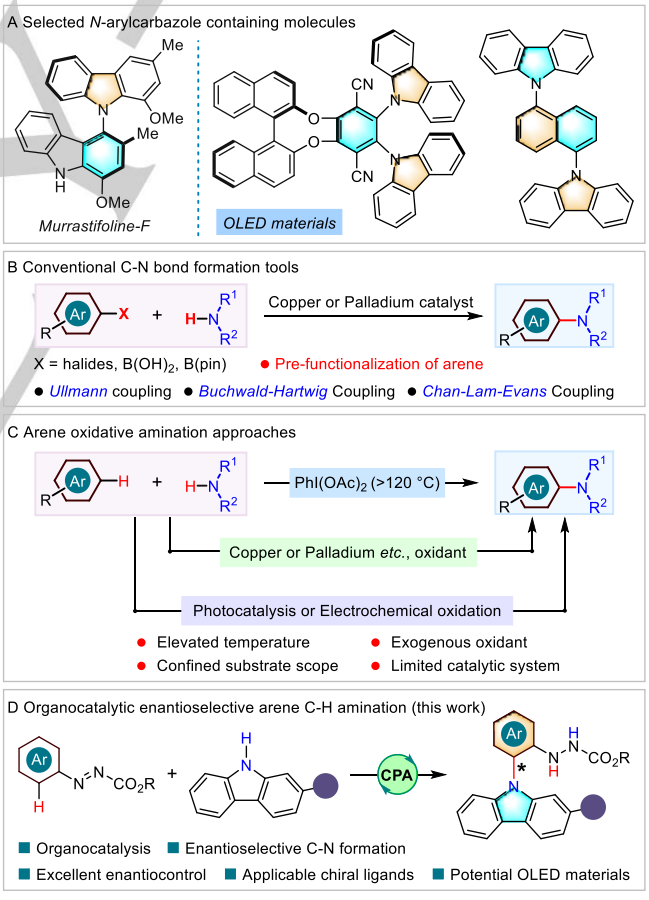


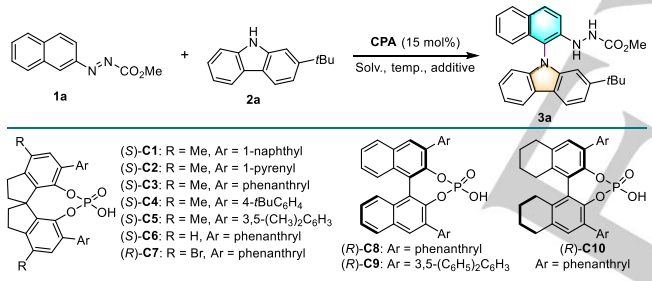
Figure 1. Significance of *N*-arylcarbazole, conventional C-N bond formation approaches to access *N*-aryl structures and our design for atroposelective construction of novel *N*-arylcarbazoles.

We have formerly discovered that an azo group serves aptly for aryl ring activation thus warrants organocatalytic C-H arylation of arene.[8] This strategy realized the scarce aromatic nucleophilic substitution with a couple of *C*-nucleophiles for the production of privileged biaryl atropisomers with chiral

phosphoric acid (**CPA**) catalysis,[9] while the employment of typical *N*-nucleophiles remains absent. Given the importance of the *N*-arylcarbazoles in chemical and material science, engaging the carbazoles as competent *N*-nucleophiles for this organocatalytic strategy to enable an alternative *N*-aryl enantioselective cross-coupling became highly appealing (Figure 1D). Notably, azo group could be transformed to an amine readily and offer an effective functional handle for the downstream diversity-oriented synthesis. Herein, we would like to present our recent endeavors on the construction of atropisomeric *N*-arylcarbazoles in line with our long-standing research interest in exploiting axially chiral frameworks through the first **CPA**-catalyzed atroposelective C-H amination of arenes.

Based on recent achievements in axial chirality domain[10] and our understandings in organocatalytic construction of atropisomeric frameworks,[11] azonaphthalene derivative **1a** and 2-*tert*-butyl-9*H*-carbazole **2a** were selected as model substrates. We aimed to control the rotation of *C*-*N* axis by the installation of a sterically hindered group on C2 position of carbazole substrate. Delightfully, the desired axially chiral *N*-arylcarbazole **3a** was delivered in 64% isolated yield with 65% enantiomeric excess (ee) when the reaction was facilitated by SPINOL-derived phosphoric acid (*S*)-**C1** (15 mol%) in CH_2Cl_2 at 40 °C (Table 1, entry 1). Despite moderate enantioselectivity, this proof-of principle result verified the feasibility of stereoinduction from CPA to *C*-*N* axis *via* arene C-H amination. We then set out to evaluate the substitution effect on the **CPA** and found that

Table 1. Optimization of the reaction conditions.[a]

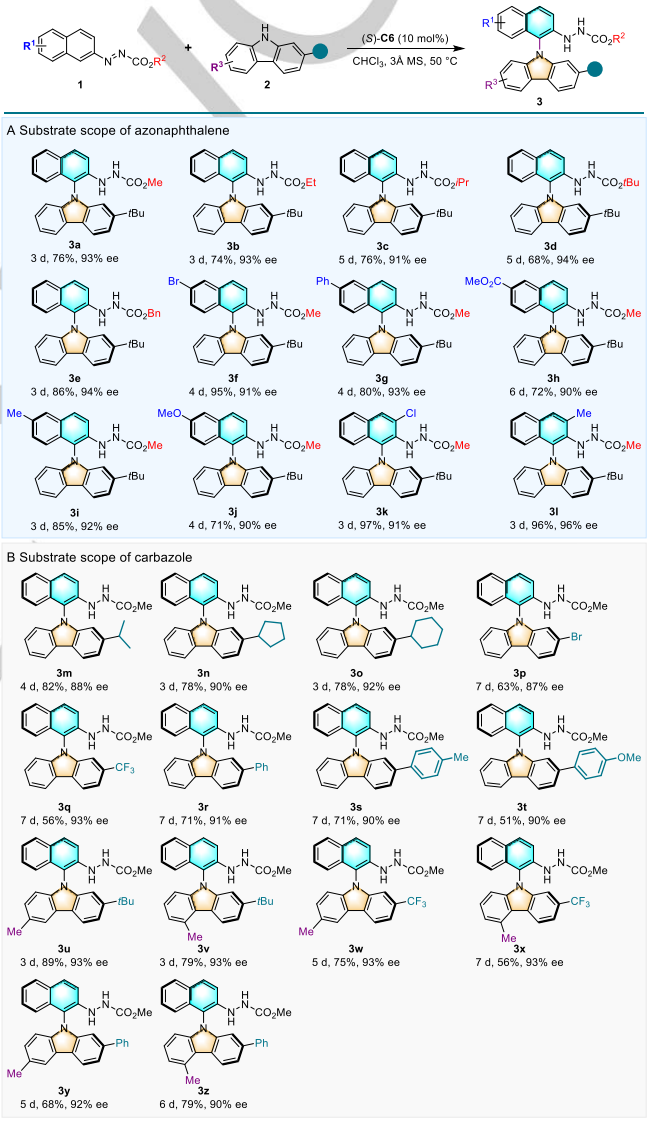


Entry	CPA	Solvent	T (°C)	Time (day)	Yield (%)[b]	Ee (%)[c]
1	(*S*)-**C1**	CH_2Cl_2	40	2.0	64	65
2	(*S*)-**C2**	CH_2Cl_2	40	2.0	78	74
3	(*S*)-**C3**	CH_2Cl_2	40	2.0	78	87
4	(*S*)-**C4**	CH_2Cl_2	40	2.0	9	62
5	(*S*)-**C5**	CH_2Cl_2	40	2.0	32	72
6	(*S*)-**C6**	CH_2Cl_2	40	2.0	79	90
7	(*R*)-**C7**	CH_2Cl_2	40	2.0	71	-88
8	(*R*)-**C8**	CH_2Cl_2	40	2.0	30	-25
9	(*R*)-**C9**	CH_2Cl_2	40	2.0	23	-37
10	(*R*)-**C10**	CH_2Cl_2	40	2.0	5	-24
11	(*S*)-**C6**	$CHCl_3$	40	2.5	71	92
12	(*S*)-**C6**	CCl_4	40	2.5	68	67
13	(*S*)-**C6**	DCE	40	2.5	64	90
14	(*S*)-**C6**	toluene	40	2.5	51	77
15[d]	(*S*)-**C6**	$CHCl_3$	50	3.0	73	91
16[d],[e]	(*S*)-**C6**	$CHCl_3$	50	3.0	76	93

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), **CPA** (15 mol%) in 2 mL of solvent at 40 °C or 50 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] 10 mol% of **CPA** was used. [e] 3Å molecular seive (MS) was added. DCE, 1,2-dichlorethane.

(*S*)-**C6** with phenanthryl on 6,6'-position was a superior facilitator, boosting the enantioselectivity to 90% ee. Meanwhile, the chemical yield was improved to 79% (Table 1, entry 6). Ensuring optimization through the alternation of axially chiral backbones of the catalyst met with failure (Table 1, entries 8-10). Subsequent investigations revealed that chloroform was a beneficial solvent to this reaction, producing the adduct **3a** in similar yield with 92% ee (Table 1, entries 11-14). Reduction of catalyst loading to 10 mol% resulted in negligible effect on the reaction outcome (Table 1, entry 15). Finally, the best results were concluded with slight elevation of the temperature and the introduction of 3Å MS (Table 1, entry 16).

Scheme 1. Generality of enantioselective arene C-H amination with carbazole nucleophiles.[a]



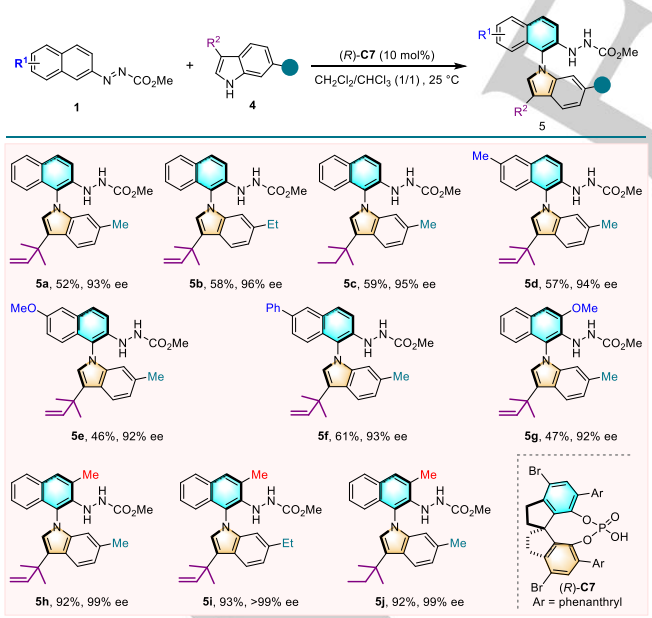
[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), (*S*)-**C6** (10 mol%) and 3Å MS (64 mg) in $CHCl_3$ (4 mL) at 50 °C. Isolated yield. Ee was determined by chiral HPLC analysis.

Having established the optimal conditions, the substrate generality of this reaction was then evaluated. First, various azonaphthalene derivatives were tested and the reaction results were summarized in Scheme 1A. Replacement of methyl ester group by ethyl, *iso*propyl, *tert*-butyl or benzyl derivative could give the expected product **3b**-**3e** in similar yield with remarkable

enantiocontrol, respectively. The electronic nature of substituents and substitution patterns resulted in limited effect on enantioselectivity of **3f**-**3l**. Notably, excellent yields were obtained when substrates bearing a C3 substitution were employed (**3k** and **3l**). Subsequently, the substrate scope of 9*H*-carbazole **2** was explored for this enantioselective **CPA**-catalyzed arene C-H amination reaction (Scheme 1B). Aside from the *tert*-butyl group in the model substrate, a wide range of sterically hindered groups were substantiated to effect restricted rotation of *C*-*N* axis, including *iso*propyl, cyclohexyl, bromine, CF_3 and aryl (**3m**-**3t**). C5 and C6 methyl substituted carbazoles were also well tolerated for this reaction, furnishing axially chiral *N*-arylcarbazoles **3u**-**3z** in moderate to good yields with excellent ee values (90-93%).

Noteworthy, indole substrate **4a** with multiple reactive sites commonly perceived as *C*-nucleophile in organocatalysis[12] was validated to be applicable *N*-nucleophile for this transformation by subtle modifications of standard reaction conditions (Table S1), to generated the corresponding axially chiral *N*-arylindole adducts **5a** with remarkable enantiocontrol (93% ee), albeit with low yield (Scheme 2). It should be noted that the bulky substitution on C3 position of indole was crucial to allow the formation of the desired *N*-aryl axis. Next, the substitution effect on azonaphthalene was examined and most substrates gave *N*-arylindole atropisomers in moderate yields with an enantiomeric excess range from 92-96%, respectively (**5d**-**g**). Interestingly, the introduction of a methyl group on C3 position of azonaphthalene significantly boosted the yield to over 90% with enhanced enantioselectivity (**5h**, 99% ee). This positive substitution effect was further substantiated by the reaction with **4b** or **4c** as the nucleophile (**5i** and **5j**).

Scheme 2. Generality of the atroposelective arene C-H amination with indole nucleophiles.[a]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), (*R*)-**C7** (10 mol%) in $CHCl_3/CH_2Cl_2$ (2/2 mL) at 25 °C for 1.5 days. Isolated yield. Ee was determined by chiral HPLC analysis.

To verify the practicality of this protocol, a preparative-scale synthesis of product **3a** was carried out under the standard conditions. As displayed in Figure 2A, negligible deterioration of yield and identical stereochemical integrity were observed, indicating the potential in large-scale chemical production. The configurational stability of the generated products was exemplified by heating a solution of product **3a** in toluene at 110 °C for 48 h. HPLC analysis illustrated that no erosion of enantiopurity in **3a** was detected (Table S2). The high stability of the chiral axis motivated us to extend their applications in asymmetric catalysis as organocatalysts or ligands. Thus, atropisomeric thiourea **7** and mono-phosphine **10** were successively synthesized from **3a** as shown in Figure 2B. The two-step synthesis provided product **7** in 74% yield with no loss of stereochemical purity. Meanwhile, mono-phosphine **10** was afforded in 43% overall yield in 3 steps from **6** bearing a free amine group on the naphthalene ring. The optical purities of both products could be improved to >99% ee by means of semi-preparative high-performance liquid chromatography purification. Gratifyingly, thiourea **7** promoted the reaction of phosphorus ylide **11** and *N*-Boc imine **12** smoothly to give the expected product **13** in 71% yield with 80% ee after subjection to formalin (Figure 2C).[13] *N*-arylcarbazole **10** could serve as an efficient ligand for palladium catalyzed enantioselective allylic alkylation of racemic **14** with malonate **15** nucleophiles. In the presence of palladium catalyst (2 mol%) and **10** (4 mol%), these reactions proceeded efficiently, to furnish the desired products **16a**-**c** in excellent yields with commendable stereoselectivity (85-95% ee).[14] The absolute configuration of compound **8** was determined as (*aS*) by X-ray crystallographic analysis (CCDC: 1963374) and those of other products were assigned by analogy. A plausible stereochemical model featuring bifunctional **CPA** facilitated H-bond activation and rearomatization-enabled central to axial chirality transfer pathway were also provided in Figure 2D for current arene C-H enantioselective amination reaction.[10j,k]

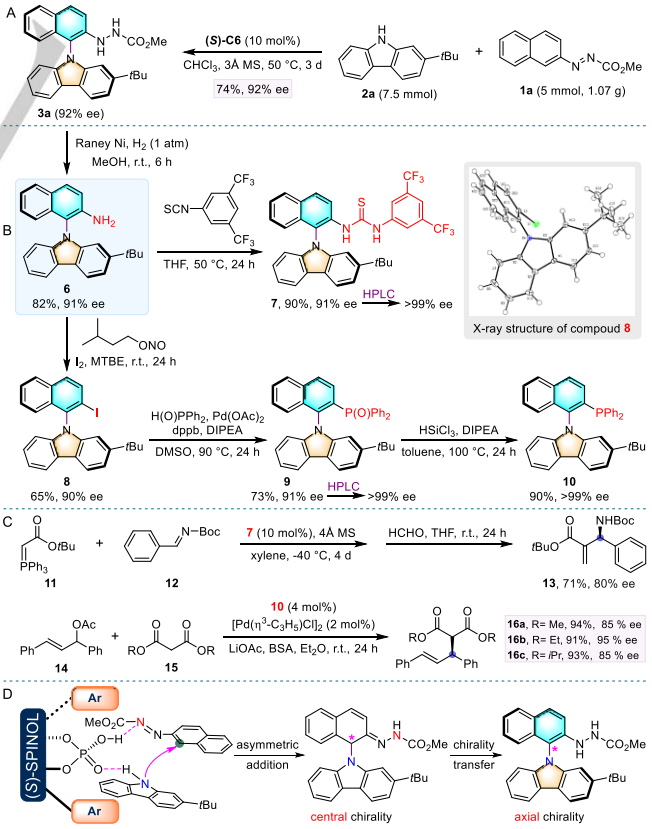
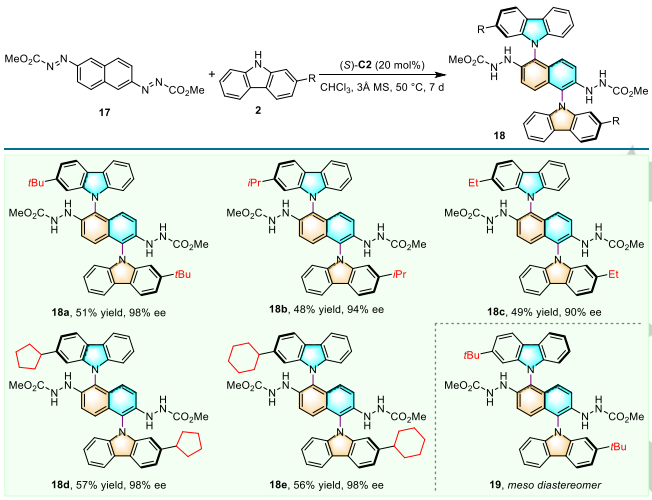


Figure 2. Synthetic transformations, applications and reaction pathway.

Given the central role of di-carbazole substituted arenes in the OLEDs materials, we then explored the synthesis of such structural motifs possessing two chiral *N*-aryl axes[15] with the developed strategy. Accordingly, 2,6-diazonaphthalene **17** was prepared and subjected to the standard conditions with carbazole as the nucleophile. Pleasingly, this double atroposelective C-H amination reaction occurred to give the desired 1,5-dicarbazole naphthalene derivative **18** with excellent enantiocontrol (98% ee). However, only 27% yield was obtained for this one-week reaction with the formation of mesomeric byproduct **19** (16%) and about 10% of mono-amination product. After evaluating a set of **CPA** catalysts, it was delightful to identify 20 mol% of (*S*)-**C2** with 1-pyrenyl group on 6,6'-position of spiro-backbone greatly improved the yield to 51% without ee erosion.[16] Meanwhile, a satisfactory diastereoselectivity (**18**:**19** = 4:1) could be noted. To demonstrate the generality of this transformation, other carbazoles with varied substituents on C2 position were then tested. As displayed in Scheme 3, all the desired products (**18b**-**d**) were generated in moderate yields with >90% ee values.

Scheme 3. Generality evaluation of double enantioselective arene C-H amination reaction.[a]



[a] Reaction conditions: **17** (0.2 mmol), **2** (0.6 mmol), (*S*)-**C2** (20 mol%) and 3Å MS (64 mg) in $CHCl_3$ (6 mL) at 50 °C. Isolated yield. Ee was determined by chiral HPLC analysis.

In summary, we have developed the first chiral phosphoric acid-catalyzed atroposelective arene C-H amination. This nucleophilic aromatic substitution reaction represents as a straightforward and alternative C-N bond formation method to conventional metal-involved cross-couplings, delivering axially chiral *N*-arylcarbazoles in good yields with remarkable enantiocontrol through a rearomatization-enabled central to axial chirality transfer pathway. Indoles as commonly known *C*-nucleophiles in organocatalysis were also effective for this transformation to give expected products possessing *N*-aryl chiral axes with superior optical purities. Gram-scale synthesis, versatile transformations and asymmetric catalytic attempts as chiral organocatalyst and ligand substantiated the utility of the generated constructs. Moreover, highly enantioenriched 1,5-dicarbazole naphthalene derivatives with significant potential in OLED materials were assembled *via* this protocol. Further investigations about the synthesis of novel OLED materials and exploitation of their underlying applications are ongoing in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: *N*-arylcarbazole • C-N chiral axis • chiral phosphoric acid • asymmetric catalysis • amination

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[17] CCDC 1963374 (**8**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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