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Synthesis of structurally diversified BINOLs and NOBINs *via* palladium-catalyzed C–H arylation with diazoquinones

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Privileged biaryl frameworks, BINOL and NOBIN, were efficiently constructed with sole 1-DNQs as arylation reagents under one set of reaction conditions. The judicious selection of palladium catalytic system plays a pivotal role in the excellent selectivities. This transformation accommodated fairly broad substrate generality for both 2-naphthol and *N*-Boc-2-naphthylamine and afforded the structurally diversified BINOLs and NOBIN derivatives in high efficiency. Notably, the bromo substituent which cannot be survived in conventional palladium catalyzed reactions were well-compatible with this set of conditions, providing an effective handle for further enriching the library of BINOLs and NOBINs. Preliminary attempts on the asymmetric variant of this reaction were also performed with up to 80:20 er for BINOLs synthesis.

BINOLs, NOBINs, high selectivity, C–H arylation, palladium-catalysis

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1 Introduction

1,1′-Bi-2-naphthol (BINOL) and 2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN) constituting the core structure of various axially chiral biaryls are widely applied in asymmetric transformations as chiral ligands or organocatalysts [1]. The significance of such backbones is further illustrated by their prevalence in natural products, biologically active molecules and functional materials (Scheme 1(a)) [2]. Given the well-explored resolution methods, the synthesis of racemic BINOLs and NOBINs attracted extensive attention in recent years. Conventional coupling between arylboronic acid and aryl halides under transition metal catalysis necessitated the tedious pre-functionalization of both arenes and then seriously influenced the reaction efficiency. Meanwhile, the potential of the oxidative dehydrogenative or the reductive dehalogenation cross-coupling of two aryl counterparts was restricted by the confined substrate generality and poor chemoselectivity [3]. Accordingly, a direct and universal approach to access BINOL and NOBIN derivatives, ideally from only one type of arylation reagents, remained highly desirable. In this context, quinones as well as iminoquinones were elegantly exploited as a class of convenient pre-oxidized surrogates towards the biaryl atropisomers possessing a phenol moiety. Undoubtedly, this discovery provided an efficient solution to acquire both biaryldiols [4], and biaryl amino alcohols [5], particularly with asymmetric aryl structures. Nonetheless, the extension to the synthesis of biaryls with BINOL and NOBIN scaffolds was rarely involved. Following this line, diarylhalonium salts were then employed by our group as efficient naphthylation reagents for the reaction with naphthylhydroxylamines to construct NOBIN derivatives [6]. However,

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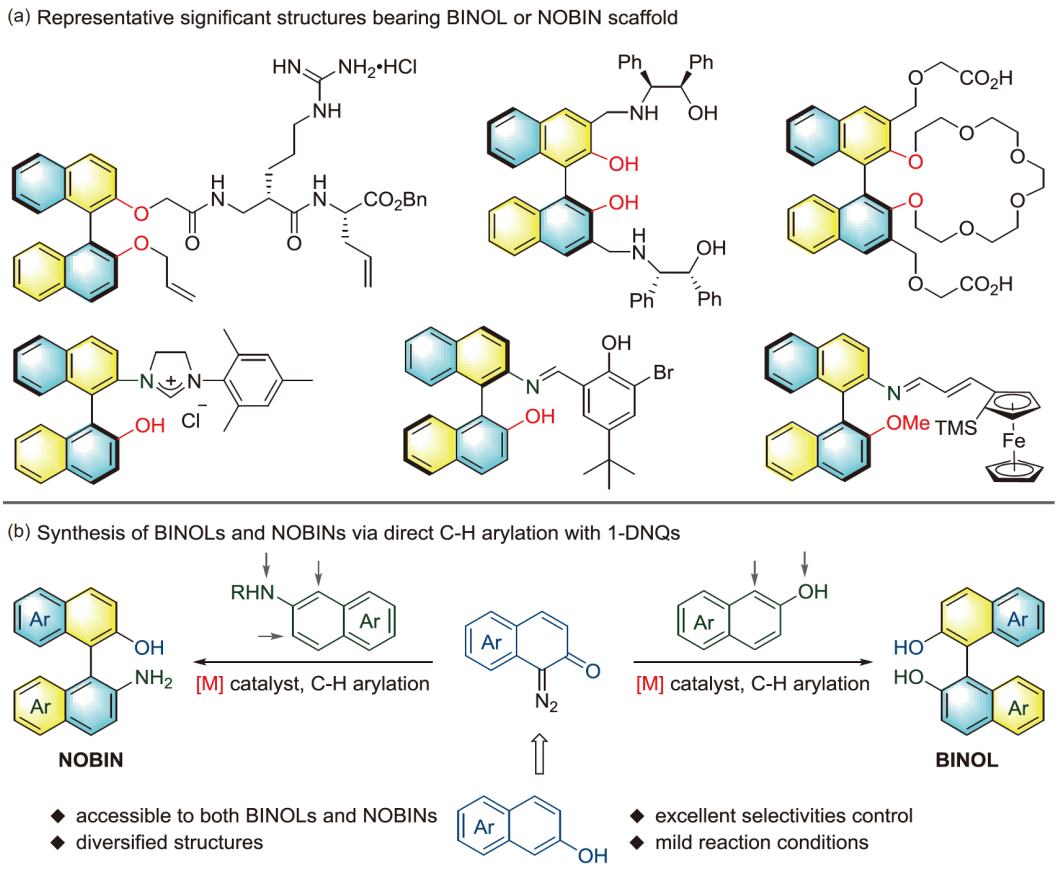


Scheme 1 (a) Selected applications of the molecules carrying BINOL or NOBIN backbone; (b) our strategies for highly selective synthesis of BINOL and NOBIN derivatives *via* direct C–H arylation with 1-DNQs under transition metal catalysis (color online).

BINOL and its derivatives remained untouchable through this approach. Considering the importance of both BINOLs and NOBINs, the exploration of more versatile aryl partners is still necessary.

On the other hand, diazo quinones have received increasing attention because of their application in C–H arylation reactions under transition metal catalysis recently. A series of biaryl compounds have been effectively assembled through the carbene transfer process with arene substrates containing directing group or electron-rich arenes [7]. Based on these achievements and our continuous research interest in constructing biaryl atropisomers [8], we envisaged that 1-diazo-2-naphthoquinones (1-DNQs) might be competent arylation candidates for coupling with both 2-naphthol and 2-naphthylamine to afford the desired BINOL, NOBIN and their derivatives. However, the major challenge in this scenario would be the chemoselectivity issue that originated from the competitive X–H (X=N or O) bond insertion, which has been clearly revealed in the previous investigations [9]. Additionally, it was found that satisfactory results were only obtained for the arenes carrying a single reactive site for most cases. Inspired by the exquisite work by Zhang's group [10] on the catalyst-controlled site-selective C–H arylation with unmasking phenols, we initiated our studies on the expedite synthesis of the most representative biaryl atropisomers, BINOLs and NOBINs, from one type of substrates 1-DNQs (Scheme 1(b)).

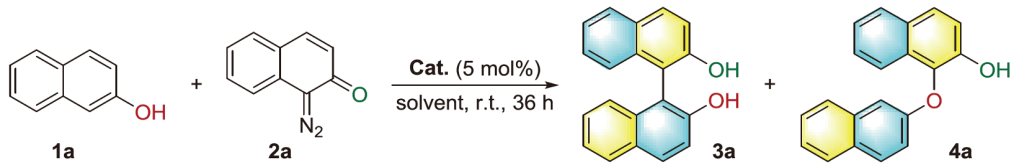
2 Experimental

Under an argon atmosphere, an oven-dried Schlenk tube equipped with a magnetic stir bar was charged with **1** or **5** (0.20 mmol), **2** and $Pd(OAc)_2$. Anhydrous dichloromethane (DCM) (2 mL) was added and the reaction mixture was stirred for 36 h at room temperature till **1** or **5** was completely consumed (monitored by thin layer chromatography (TLC)). After evaporating the solvent, the residue was purified by flash chromatography to afford the corresponding product **3** or **6**. The details are listed in the Supporting information online.

3 Results and discussion

Our investigation was commenced with the reaction of 1-DNQ **2a** and 2-naphthol **1a** with commonly used catalyst

Table 1 Optimization of the reaction conditions [a] (color online)



Entry	Solvent	Cat.	**3a**/**4a** [b]	Yield (%) [b]
1	DCM	$Rh_2(OAc)_4$	1/12	82[c]
2[d]	DCM	$Fe(ClO_4)_2$	–	trace
3	DCM	$CuCl_2$	–	trace
4	DCM	AgOTf	–	trace
5[d]	DCM	IPrAuCl[e]	9/1	41
6[d]	DCM	$[Cp^*IrCl_2]_2$	4/1	19
7	DCM	$Pd(OAc)_2$	12/1	87
8	DCM	$Pd(TFA)_2$	11/1	81
9	DCM	$PdCl_2$	10/1	82
10	DCM	$[(\eta^3\text{-}C_3H_5)PdCl]_2$	11/1	83
11	DCM	$Pd_2(dba)_3$	9/1	60
12	DCE	$Pd(OAc)_2$	11/1	83
13	toluene	$Pd(OAc)_2$	10/1	66
14	EtOAc	$Pd(OAc)_2$	10/1	80
15[f]	DCM	$Pd(OAc)_2$	12/1	93 (92)[g]

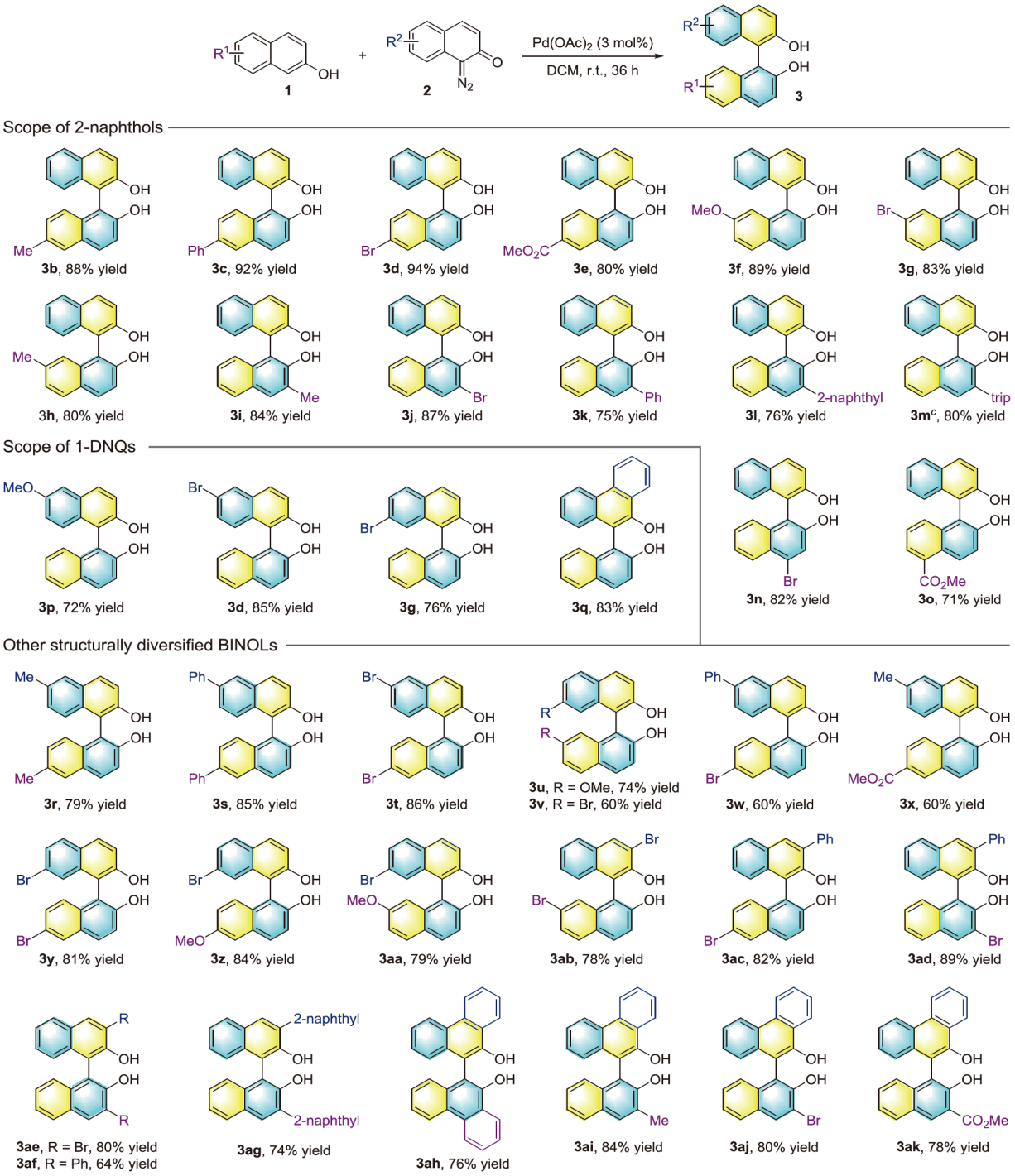
a) Unless otherwise specified, reactions were performed with **1a** (0.10 mmol), **2a** (0.10 mmol) and Cat. (5 mol%) in solvent (1.0 mL) at room temperature for 36 h. b) Yield of **3a** and the ratio of **3a**/**4a** were determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard. c) Yield of **4a**. d) Reaction was performed at 80 °C with sodium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (NaBArF, 6 mol%) as the additive. e) IPr=1,3-bis(2,6-di-ipropyl-phenyl)imidazol-2-ylidene. f) $Pd(OAc)_2$ (3 mol%) was used with **1a**/**2a**=1/1.2. g) Reaction was performed at 0.20 mmol scale, isolated yield.

$Rh_2(OAc)_4$ (5 mol%) in dichloromethane at room temperature. Unsurprisingly, the O–H bond insertion product **4a** dominated the reaction system after 36 h and less than 10% of the target product **3a** was detected (Table 1, entry 1). Following examination of other reported conditions for the reaction with 1-DNQs met with failure (entries 2–6), although Ir(III) and Au(I) dramatically increase the proportion of **3a** in the mixture under elevated temperature with $NaBAr_{F4}$. Delightfully, the formation of the competitive O–H insertion product **4a** could be effectively inhibited when $Pd(OAc)_2$ was utilized as catalyst (entry 7). Other screened Pd(II) catalysts also gave **3a** in about 80% yield with more than 10:1 ratio of **3a**:**4a** (entries 8–10), while the use of Pd(0) led to slight erosion on both chemical yield and chemoselectivity (entry 11). With $Pd(OAc)_2$ as the superior catalyst, the next optimization through the evaluation of various solvents proved DCM as the best solvent. Finally, the optimal results were obtained with a 92% isolated yield of **3a** and 12:1 ratio of **3a**:**4a** through fine-tuned stoichiometry of reactants and catalyst loading (entry 15).

With the optimized conditions in hand, the generality of this transformation was then firstly explored with respect to 2-naphthols **1**. As illustrated in Table 2, all these examined 2-naphthol substrates were completely transformed within 36 h and afforded the respective non-C_2 symmetric BINOLs in generally good efficiency with the recorded yield up to 94% (**3b**–**3o**). The electronic property of the substituents as well as the substitution patterns exerted limited influence on the reaction results. Notably, 2-naphthols possessing a sterically bulky group at the C3 position was also amendable to give the desired product in good yields (**3l**–**3m**). In addition, the bromo substituent which cannot be survived in conventional palladium catalyzed reactions was well-tolerated for this set of conditions, offering an efficient handle for further transformations (**3d**, **3g**, **3j** and **3n**).

Subsequently, the generality of 1-DNQs **2** was evaluated. First, the reaction of 1-DNQs **2** and model 2-naphthol **1a** was performed and the desired BINOLs were obtained in 72%–85% yields (**3d**, **3g** and **3p**–**3q**). It should be noted that **3d** and **3g** were also formed effectively *via* the reverse of coupling partner. Following examination on 1-DNQs revealed that the electronic nature and position of the substituents imposed a negligible effect on the reaction efficiency and a wide range of C_2 symmetric and non-C_2 symmetric BINOLs were synthesized in up to 89% yield through the selection of coupling partners (**3r**–**3ak**). A variety of functional groups

Table 2 Substrate scope of 2-naphthols and 1-DNQs [a),b)] (color online)

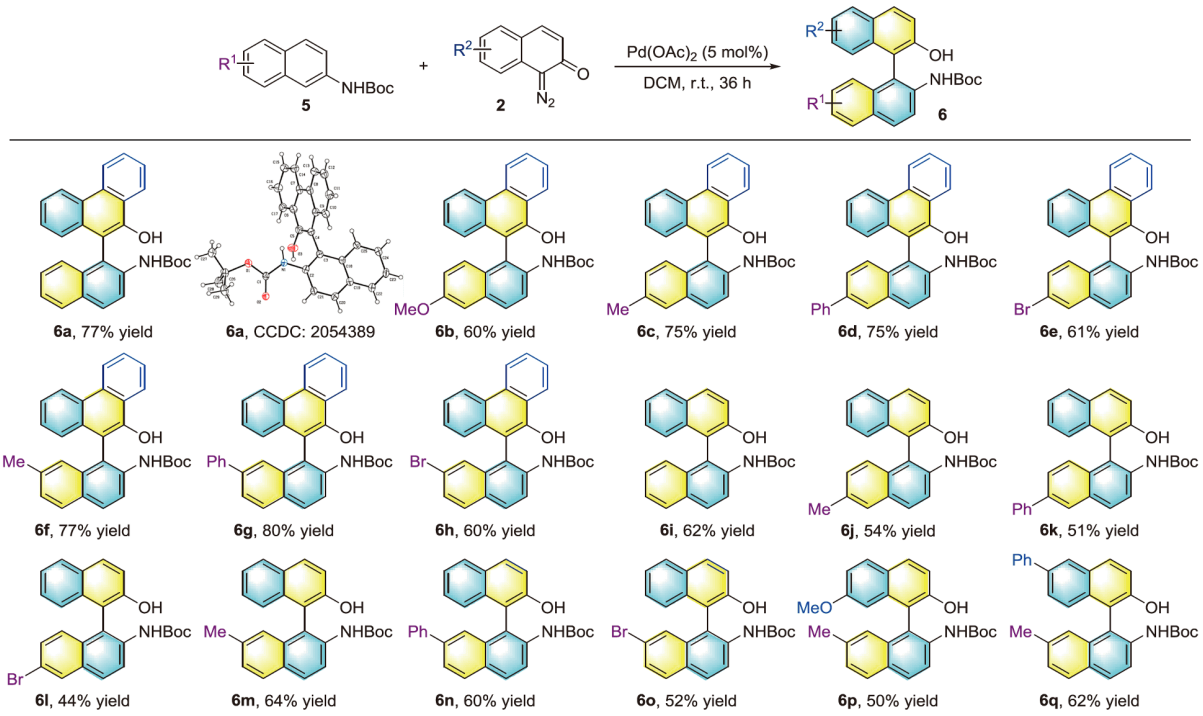


a) Unless otherwise specified, reactions were performed with **1a** (0.20 mmol), **2a** (0.24 mmol) and $Pd(OAc)_2$ (3 mol%) in DCM (2.0 mL) at room temperature for 36 h; b) isolated yield; c) trip=2,4,6-triisopropyl-C_6H_2.

including phenyl, 2-naphthyl and bromo were well compatible for this reaction, similarly. Noteworthy, 1-DNQ with an extended fused ring system was also an efficient substrate and the reactions with different 2-naphthols could produce the corresponding BINOLs in about 80% yield (**3q** and **3ah**–**3ak**). Moreover, C_2 symmetric 3,3′-diaryl BINOLs (**3af**–**3ag**) which have been recognized as the preferred backbone of various ligands were obtained in synthetically useful yields.

Successful establishment of a highly efficient and selective approach to construct BINOLs encouraged us to explore the feasibility of procuring NOBINs, another type of privileged biaryl atropisomers, to further extend the applicability of the developed method. As compared with 2-naphthol, the reaction with 2-naphthylamine was considered to be more chal-

Table 3 The substrate scope of N-Boc-naphthylamines and 1-DNQs [a),b)] (color online)



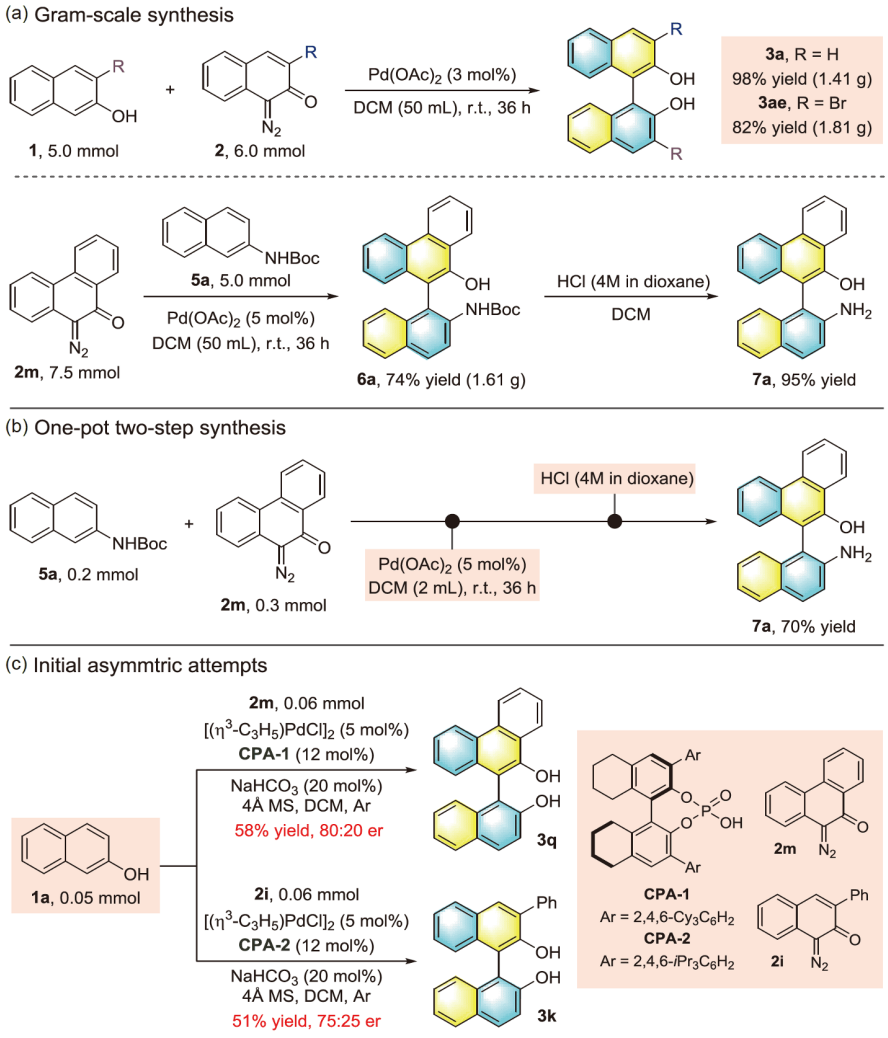
a) Unless otherwise specified, reactions were performed with **5** (0.20 mmol), **2** (0.30 mmol) and $Pd(OAc)_2$ (5 mol%) in DCM (2.0 mL) at room temperature for 36 h. b) Isolated yield.

lenging and complicated due to the disparate nucleophilicity as well as multiple reactive sites. Pleasingly, this set of conditions also adequate for the reaction of 2-naphthylamines and 1-DNQs and the optimal results with 77% isolated yield for **6a** were readily attained by subtle modulation of the loading of **2m** (1.5 equiv.) and $Pd(OAc)_2$ (5 mol%). It is worth noting that in Liu's work [11], the C–H arylation of *N*-phenylacetamide with diazo quinones in the presence of Ir (III)-catalyst occurred at C3-position of *N*-acetyl-naphthylamine, and thus hampered the application in NOBINs synthesis.

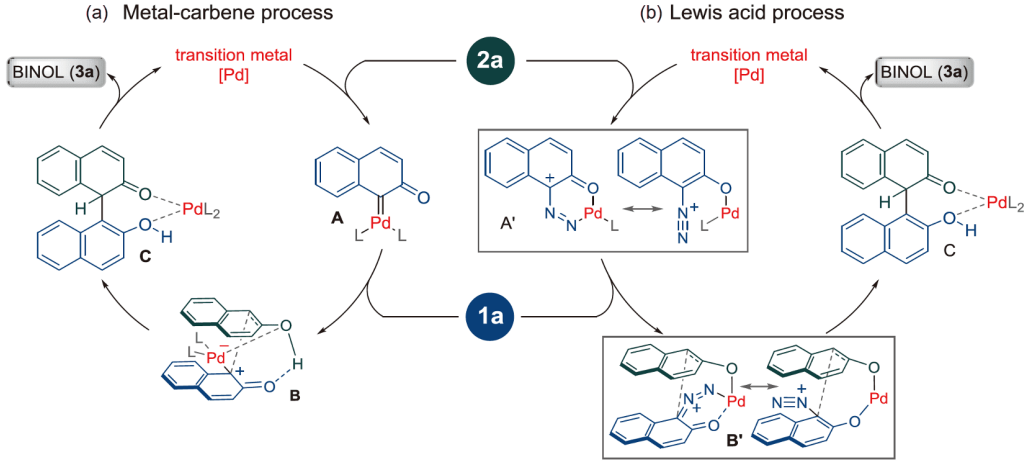
The re-optimized conditions were then applied to various 1-DNQs and 2-naphthylamines to extend the generality of the substrate. As shown in Table 3, all these reactions displayed high site-selectivity and furnished the desired NOBIN derivatives bearing different functional groups in moderate to good efficiency (**6a**–**6q**). Meanwhile, the experimental results revealed that 9-diazo-10-phenanthrone presented better reactivity than 1-DNQs with a naphthyl ring (**6a**–**6h** *vs.* **6i**–**6o**). Expectedly, the bromo substituent was successfully retained under our developed conditions.

The gram-scale reactions were performed to demonstrate the utility of this strategy. Under the standard conditions, **3a**, **3ae** and **6a** all delivered with high efficiency, implying that this protocol should be well suited for large-scale chemical production (Scheme 2(a)). Furthermore, the Boc protecting group of **6a** could be readily removed by the treatment with HCl, to give NOBIN **7a** in a 95% yield. The one-pot two-step synthesis of **7a** was performed and inconspicuous change in yield was observed (Scheme 2(b)). The catalytic asymmetric variant of this transformation was also attempted to approach optically active BINOLs. After extensive investigations of the palladium/chiral ligand system, we found that chiral phosphoric acids (CPA) [12] could effectively induce the enantiocontrol in the presence of $[(\eta^3\text{-}C_3H_5)PdCl]_2$. Although only moderate yields and enantiopurities were obtained for both **3q** and **3k** at the present stage, the good compatibility between CPA and palladium catalyst created the possibility for highly enantioselective arylation of 2-naphthols of 1-DNQs (Scheme 2(c)).

On the basis of previous reports [7f, 7g,10c,13] concerning the reaction with diazo compounds and our understandings on the construction of biaryl atropisomers, two plausible pathways were rationalized as follows (using **1a** as a model; Scheme 3): pathway a is the metal-carbene process. The catalytic cycle commences with the generation of metal-carbenoid **A** from 1-DNQ **2a** and metal catalyst along with the releasing of N_2. The multiple interactions between **A** and 2-naphthol **1a** enable the C–C bond formation to afford intermediate **C** *via* **B**. Following re-aromatization of intermediate **C** produces the desired product BINOL **3a** and meanwhile regenerates the catalyst. In pathway b, palladium species serves as a Lewis acid and the catalytic cycle is initiated from the coordination between metal center and the



Scheme 2 (a) Gram-scale preparation of **3a**, **3ae** as well as **6a** and their transformation; (b) one-pot two-step synthesis of **7a**; (c) initial asymmetric attempts of BINOLs (color online).



Scheme 3 Proposed reaction pathways (color online).

oxygen and/or nitrogen of 1-DNQ **2a** (intermediate **A'**). Subsequent ligand change with 2-naphthol **1a** generates **B'** and then the intramolecular nucleophilic addition occurs to give the same intermediate **C**.

4 Conclusions

In summary, we have established an efficient approach for the synthesis of BINOLs and NOBIN derivatives employing 1-DNQs as arylation reagents under mild conditions. Palladium catalyst was verified to be most effective to inhibit the undesired X–H insertion reactions for both 2-naphthols and *N*-Boc-2-naphthamines. This approach demonstrated fairly good functional group compatibility to give the structurally diversified BINOLs and BONIN derivatives with up to 94% yield. Particularly, the amendable substituents bearing bromo substituent for this set of conditions offered efficient platform molecules for downstream coupling reactions under transition metal catalysis. The enantioselective variant for the BINOLs synthesis was also conducted and moderate atroposelectivities could be obtained at the present stage. Further applications on the construction of other biaryl skeletons and the exploitation of highly enantioselective variants are ongoing in our group.

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Conflict of interest The authors declare no conflict of interest.

Supporting information The supporting information is available online at http://chem.scichina.com and http://link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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