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Editorial

Phosphine ligands featuring C–N chiral axis applicable to tetra-*ortho*-substituted biaryl synthesis

Asymmetric catalysis has been one of the most effective strategies for building up a chirality in the favored stereoisomer. Over the past decades, various sophisticated chiral ligands and catalysts have been well-designed, which enable great advances in enantioselective chemical transformations, for achieving excellent selectivity and activity. Among them, biaryl phosphines possessing $C_{(Ar)}$–$C_{(Ar)}$ axial chirality have revealed outstanding performance [1–5]. In sharp contrast, the development of chiral ligands bearing axially chiral $C_{(Ar)}$–N backbones has been widely neglected so far because of its intrinsically less restricted rotational barrier [6]. Furthermore, the introduction of a N atom may also provide an additional coordination site for the metal center in controlling the catalytic behavior.

In view of its importance in biologically active natural products, pharmaceuticals, and privileged ligands, the enantioselective synthesis of atropisomeric biaryl skeletons has drawn considerable attention from chemists. Pd-catalyzed Suzuki-Miyaura cross-coupling reaction (SMR) has been regarded as one of the most practical methods [1,2]. Although impressive synthetic methods of tri-*ortho*-substituted biaryls were developed, only very limited examples on the inherently steric hindered tetra-*ortho*-substituted biaryls *via* enantioselective SMR pathway have been reported. For instance, Cammidge *et al.* [7] firstly described the asymmetric synthesis of binaphthalene derivatives by using a planar chiral ferrocenylphosphane ligand, followed by work reported by Espinet [8]. An amphiphilic resin supported chiral phosphine was reported by Uozumi and co-workers, which firstly facilitated the SMR in water delivering desired chiral binaphthyl skeleton in good selectivity, though a high excess of boron acid was used [9]. Kozlowski disclosed a detailed mechanistic study of Tang-type phosphine catalyzed enantioselective tetra-*ortho*-substituted biaryl synthesis [10]. Recently, Tang *et al.* presented an asymmetric SMR towards the synthesis of tetra-*ortho*-substituted biaryls, among which a hydrogen bonding interaction between the P-chiral monophosphine BaryPhos and coupling partners was critical for the stereoinduction [11]. To the best of our knowledge, this is the optimal catalytic system providing excellent enantioselectivity for various challenging tetra-*ortho*-substituted biphenyls to date. Besides phosphines, Shi and co-workers also developed an extremely bulky C_2-symmetric chiral *N*-heterocyclic carbene, but only four examples of tetra-*ortho*-substituted binaphthalene derivatives were shown [12]. Considering the remarkably steric congested environment from both coupling partners, the design of a chiral catalyst system featuring adaptable ligation is highly significant to help accommodate the steric crowding during the reaction process.

To address this challenge, Kwong and co-workers recently reported a novel type of atropisomeric phosphine bearing C–N axial chirality, termed as Kin-Phos, enabling an enantioselective SMR towards the assembly of tetra-*ortho*-substituted biaryls [13,14]. Ligands Kin-Phos were easily synthesized according to a four-step synthetic route (Fig. 1a). The carbazole unit to the phenyl ring at the *ortho*-position of P atom provided opportunities of an *in-situ* formed Pd-catalyst with two distinctive *ipso*-coordination modes, that is Pd–N and Pd–π (Fig. 1b). In such a way, this catalytic system is anticipated to allow adaptable coordination *via* "Pd-arene-walking" for attaining a lower energy-preferred transition state. Secondly, the introduction of 2,6-dimethoxyphenyl unit to one of the flanked arenes at the carbazole moiety not only realized the desymmetrization of Kin-Phos forming the C–N axial chirality, but also offered a transient hydrogen bonding interaction between the ligand and boronate complex for achieving stereo-communication.

Detailed evaluation of catalytic activity towards the asymmetric synthesis of tetra-*ortho*-substituted biaryls was conducted by using a model reaction of 2-(2–bromo-3-methoxyphenyl)-1,3-dioxolane **1** and 2-methoxyl naphthalen-1-ylboronic acid **2** (Fig. 1c). (*S*)-Cyp-Kin-Phos presented the best enantioselectivity among all Kin-Phos-type ligands surveyed, and delivered the desired tetra-*ortho*-substituted biaryl **3** in 94% *ee*. In comparison, well-established chiral phosphine ligands, such as Binap, DTBM-Segphos and Feringa's phosphoramidite ligand Monophos, showed no activity, but only a moderate *ee* value of 70% for the best phosphine Tang's BaryPhos under the stated reaction conditions. These quite different results intuitively proved the good catalytic performance of (*S*)-Cyp-Kin-Phos. Furthermore, good enantioselectivity was also obtained for different tetra-*ortho*-substituted biaryls possessing various substitution patterns, electronic properties, and steric bulkiness (26 examples, up to 96% *ee*, Fig. 1d). A one-pot sequential Miyaura borylation and enantioselective SMR was also successfully demonstrated, yielding the most steric bulky biaryl **8** (90%, 92:8 *er*) from this pathway to-date.

To comprehensively investigate the reaction mechanism and key intermediates, DFT calculations were carried out. Particularly noteworthy is that the interesting "Pd-arene-walking" coordination mode was proved to have a crucial role in the catalytic cycle. The resultant multi-swapping coordination between Pd–N and Pd–π

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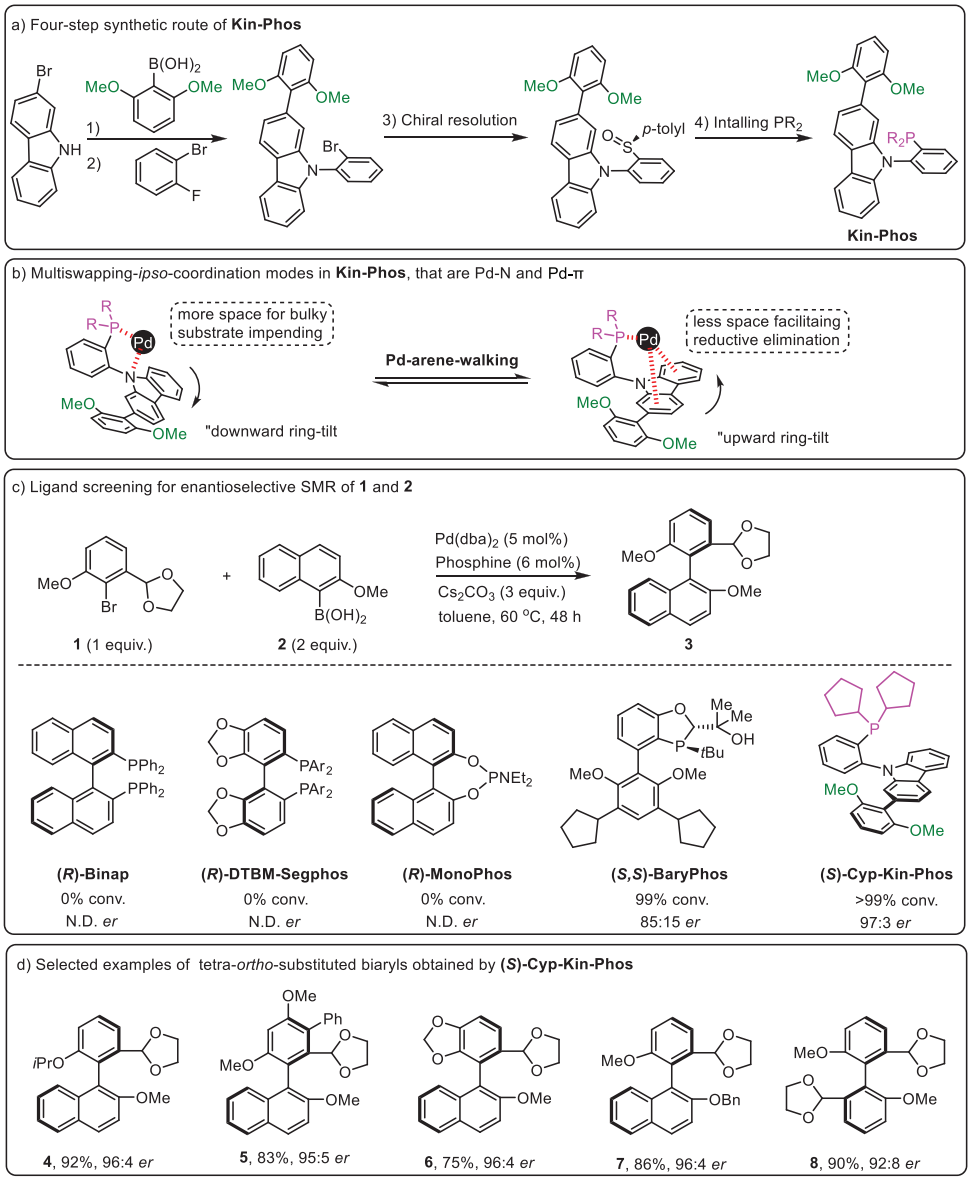

Fig. 1. (a) Ligand synthesis, (b) multi-swapping-ipso-coordination modes, (c) ligand screening for enantioselective SMR towards tetra-ortho-substituted biaryls, and (d) substrate scope.

sufficiently relieved the steric bulk of the overly crowded Pd intermediates and transition states. Furthermore, the transient hydrogen bonding observed between the 2,6-dimethoxyphenyl unit and O–H of the boronate complex contributed a lower energy barrier for facilitating the transmetalation process. The reductive elimination was suggested as the rate-determining step by converting two favored transition states exclusively to the (*S*)-biaryl isomer.

Kwong's group presented a "Pd-arene-walking" catalytic system based on C–N axially chiral atropisomeric phosphines, and revealed their applications in SMR for accessing enantioenriched tetra-*ortho*-substituted biaryls. This work provides an efficient approach to accommodate the highly steric hindered substrates *via* tuning the *ipso*-coordination mode of Pd to phosphine ligand. Additionally, we are confident that these interesting results will impact further chiral ligand design, for instance *N*-heterocyclic carbene featuring adaptable coordination fashion and with potential applications in frontier transition metal catalysis.

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