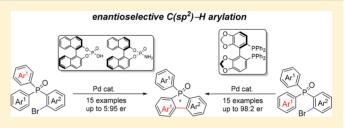
Pd-Catalyzed Asymmetric C—H Bond Activation for the Synthesis of P-Stereogenic Dibenzophospholes

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Supporting Information

ABSTRACT: Pd-catalyzed asymmetric C-H bond activation for the synthesis of P-stereogenic dibenzophospholes was efficiently achieved via two types of catalytic systems. Chiral phosphoric amides/acids as ligands provided the products with up to 5:95 er, and (R)-segphos as ligand resulted in enantioselectivities of up to 98:2.



P-stereogenic phosphorus compounds have attracted considerable interest because of their inherent property as useful chiral ligands¹ in asymmetric catalysis. Although P-stereogenic compounds are efficient in several catalytic reactions, their application in catalysis has been less explored in comparison with phosphorus ligands with chiral carbon centers or axial chirality, probably because of the difficulty in the preparation and accessibility of P-chiral ligands.² Pd-catalyzed asymmetric C-H bond activation has emerged as an effective method to synthesize chiral phosphorus compounds.^{3,4} Our group⁵ and Liu, Ma, and co-workers⁶ independently reported Pd-catalyzed enantioselective C-H arylation to synthesize P-stereogenic phosphinic amides by using TADDOL-derived phosphoramidites with excellent stereoselectivities (Scheme 1aa). Tang and co-workers⁷ also presented an efficient method for the synthesis of a series of P-chiral biarylphosphonates with good enantioselectivities from P-chiral biaryl monophosphorus ligands (Scheme 1ab). Cui, Xu, et al.8 demonstrated the desymmetrization of o-bromoaryl diarylphosphine oxides to provide P-stereogenic phosphole oxides with 4-94% ee by using Me-DuPhos as a ligand (Scheme 1ac); the success of this transformation built a solid foundation for further improving the enantioselectivity by the change of ligand or additive in the reaction. In the above examples (Scheme 1a), trivalent chiral phosphorus ligands were used in combination with palladium to control the enantioselectivity in reaction.

In 2015, we first described the Pd-catalyzed enantioselective arylation of β -C(sp³)-H bonds in 8-aminoquinoline amides, and a chiral phosphoric amide/acid¹⁰ was used as the only chiral source to control stereoselectivity in the reaction. In this new protocol, 11 ligands not only coordinate with metals but also directly participate in the concerted metalation—deprotonation 2 step to control the enantioselectivity of the reaction, which is different from the reaction involving Pd/ chiral phosphine catalysts (Scheme 1a). We further used Pd/ chiral phosphoric acid (CPA) systems to carry out the

Scheme 1. Synthesis of P-Stereogenic Phosphorus Compounds

(a) Controlling enantioselectivity with chiral phosphine ligands

$$Ar^1$$
 Ar^2

X: Br

aa) $Z = NMe$, Duan group and Liu, Ma groups ab) $Z = 0$, Cu, Tang group ac) $Z = 0$, Cu, Xu groups

(b) Controlling enantioselectivity with chiral phosphoric acids

(c) This work

asymmetric C-H arylation of ferrocenyl ketones through Pd(0)/Pd(II) catalysis (Scheme 1ba). Baudoin et al. 4 also developed an asymmetric intramolecular arylation to synthesize indolines with Pd/chiral phosphoric acid (Scheme 1bb).

Phosphole compounds have attracted considerable attention because of their π -conjugated systems, which is useful for the

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construction of optical electronic materials.¹⁵ To continue our interest in the area of synthesis of chiral phosphorus compounds.⁵ Herein, we report the development of two catalytic systems for the Pd-catalyzed asymmetric C–H arylation of phosphine oxides, thereby constructing P-stereogenic dibenzophospholes with good to excellent enantiose-lectivities (Scheme 1c).

Diphenyl(2-bromo-4-fluorophenyl)phosphine oxide (1a) as a model substrate was subjected to cyclization. The chiral phosphoric acid was initially examined as the ligand in the reaction. The desired product was generated in 85% yield and 12:88 er with L1 and Pd(PCy₃)₂ as a catalyst in the presence of Cs₂CO₃ in toluene (Table 1, entry 1). An array of R substituents (steric and electronic influence) at the 3,3'position of CPAs was examined. As the steric hindrance increased, the enantioselectivity of the product became relatively lower than the initial result (entries 2-7). The chiral phosphoric amides of the binaphthyl skeleton with different N-substituents achieved high enantioselectivity and yields except for L12, which had N-(R)CHMePh (entries 8-12). The use of a CPA-bearing nitro substituent at the 6,6'position, L13, generated a product with 25:75 er (entry 13). The TADDOL-derived chiral phosphoric acid L14 produced a racemized product (entry 14). The solvent was changed to DME, t-amylOH, 1,4-dioxane, DMF, o-xylene, and p-xylene. Among them, p-xylene provided the highest enantioselectivity (entries 15-20). The use of chiral phosphoric amides/acids L1/L8 = 1/1 slightly improved the er to 8:92 (entry 21). ¹⁶ The enantioselectivity of the product could be maintained even when the loading of Pd catalyst was reduced to 3 mol % (entries 22 and 23). Moderate yields and high enantioselectivity could be achieved without the addition of phosphine ligands to the reaction (entry 24), possibly indicating that the coordination of the phosphorus ligand with the Pd catalyst is not essential in this reaction. Finally, L1/L8 was used as a ligand in 2 mL of m-xylene to furnish the product in 95% yield and 6:94 er (entry 25). For comparison with CPAs, a chiral phosphine ligand was applied to control the enantioselectivity in the current reaction. A survey of different chiral bisphosphine ligands revealed that (R)-segphos as a chiral ligand generated a product with 90% ee and 38% yield (entries 26-28). When the amount of ligand was increased to 15 mol % (5 mol % Pd), the product yield improved to 68%, and the enantioselectivity was maintained (entry 29).

Under the optimized reaction conditions, the scope of the substrate was examined using chiral phosphoric amides/acids as ligands (Table 2). Various substituents on the bromoaryl ring, such as fluoro, chloro, methyl, and tert-butyl (2a-d), were used to produce P-stereogenic dibenzophospholes in high yields with up to 5:95 er. Substrate-bearing and electrondonating and -withdrawing groups, such as OMe (2e), CN (2f), and ester (2g), were also examined. The cyclization products were isolated in good yields and enantioselectivities. The product having a naphthyl substituent, 2h, was also isolated in 16.5:83.5 er. A series of substituents on the diphenyl rings was also tested. Substrates with a methyl substituent at the ortho, meta, and para positions (2i-k) produced Pstereogenic dibenzophospholes with good yields and moderate enantioselectivities. Fluoro, chloro, trifluoromethyl, and methoxy groups at the para position (21-o) were tolerated well, and the enantioselectivity of the product bearing electronwithdrawing substituents was higher than that of the substrates containing electron-donating substituents. In addition, a 2

Table 1. Optimization of Reaction Conditions^a

L7. R = 3,5-(GF ₃) ₂ -G ₆ F ₃					(R)-segphos	
entry	Pd cat.	ligand (mol %)	solvent	yield ^b (%)	er ^c	
1	$Pd(PCy_3)_2$	L1 (10)	toluene	85	12:88	
2	$Pd(PCy_3)_2$	L2 (10)	toluene	34	57:43	
3	$Pd(PCy_3)_2$	L3 (10)	toluene	51	40:60	
4	$Pd(PCy_3)_2$	L4 (10)	toluene	49	49:51	
5	$Pd(PCy_3)_2$	L5 (10)	toluene	34	47:53	
6	$Pd(PCy_3)_2$	L6 (10)	toluene	59	35:65	
7	$Pd(PCy_3)_2$	L7 (10)	toluene	62	49:51	
8	$Pd(PCy_3)_2$	L8 (10)	toluene	75	19:81	
9	$Pd(PCy_3)_2$	L9 (10)	toluene	92	17:83	
10	$Pd(PCy_3)_2$	L10 (10)	toluene	72	14:86	
11	$Pd(PCy_3)_2$	L11 (10)	toluene	59	16:84	
12	$Pd(PCy_3)_2$	L12 (10)	toluene	24	54:46	
13	$Pd(PCy_3)_2$	L13 (10)	toluene	34	25:75	
14	$Pd(PCy_3)_2$	L14 (10)	toluene	17	51:49	
15	$Pd(PCy_3)_2$	L1 (10)	DME	65	28:72	
16	$Pd(PCy_3)_2$	L1 (10)	t-amylOH	75	26:74	
17	$Pd(PCy_3)_2$	L1 (10)	dioxane	75	13:87	
18	$Pd(PCy_3)_2$	L1 (10)	DMF	48	53:47	
19	$Pd(PCy_3)_2$	L1 (10)	o-xylene	98	12:88	
20	$Pd(PCy_3)_2$	L1 (10)	p-xylene	95	11:89	
21	$Pd(PCy_3)_2$	L1 (10) L8(10)	<i>p</i> -xylene	97	8:92	
22 ^d	$Pd(PCy_3)_2$	L1 (6), L8 (6)	<i>p</i> -xylene	96	8:92	
23 ^{d,e}	$Pd(PCy_3)_2$	L1 (6), L8 (6)	<i>p</i> -xylene	95	7:93	
24	$Pd(CH_3CN)_2Cl_2$	L1 (6), L8 (6)	<i>p</i> -xylene	58	9:91	
25 ^{d,e}	$Pd(PCy_3)_2$	L1 (6), L8 (6)	m-xylene	95	6:94	
26 ^f	$Pd(OAc)_2$	(<i>R</i>)-binap (10)	toluene	25	87:13	
27 ^f	$Pd(OAc)_2$	(R)-segphos (10)	toluene	38	95:5	
28 ^f	Pd(OAc) ₂	(S,S)-Me- Duphos (10)	toluene	88	63:37	
29 ^f	$Pd(OAc)_2$	(R)-segphos (15)	toluene	68	95:5	

"Reaction conditions unless specified otherwise: phosphine oxide 1a (0.10 mmol, 1.0 equiv), $Pd(PCy_3)_2$ or $Pd(OAc)_2$ (5 mol %), L (6–15 mol %), Cs₂CO₃ (2 equiv), solvent (1 mL), 120 °C, 24 h. ^bIsolated yield. Determined by chiral HPLC. ^d3 mol % Pd cat. at 110 °C. ^eIn 2 mL solvent with 3 equiv of Cs₂CO₃. ^f30 mol % PivOH, 1.5 equiv of Cs₂CO₃.

Table 2. Substrate Scope Using Chiral Phosphoric Amides/Acids as Ligands a,b

"Reaction conditions: phosphine oxide 1 (0.10 mmol), $Pd(PCy_3)_2$ (3 mol %), L1 (6 mol %), L8 (6 mol %), Cs_2CO_3 (3 equiv), *m*-xylene (2 mL), 110 °C, 24 h. ^bIsolated yield and er were determined with chiral HPLC.

mmol scale of reaction was also conducted and the product **2d** was isolated with 2.5:97.5 er after recrystallization (eq 1).

Next, we examined the reaction scope by using (R)-segphos as the ligand (Table 3). The substrates bearing various functional groups, such as fluoro, chloro, methyl, tert-butyl, methoxy, cyano, and ethyl ester, on the bromoaryl ring exhibited compatibility and yielded P-chiral phosphine oxides with a relatively high er (2a-g). The product 2h with a naphthyl substituent was obtained with a low yield and a moderate ee. The methyl substituents at different positions of diphenyl rings were tolerated well with good yields and high er (2i-k). Aromatic rings bearing fluoro (2l) had the highest enantioselectivity (98:2). Finally, the compounds bearing chloro, trifluoromethyl, and methoxy substituents delivered dibenzophospholes in useful yields and enantioselectivities (2m−o). The X-ray crystal diffraction analysis of the product 2a (Table 3) indicated that the absolute configuration of 2a is R, and other absolute configurations were assigned through analogy with 2a.1

Table 3. Substrate Scope with (R)-segphos as a Ligand^{a,b}

"Reaction conditions: phosphine oxide 1 (0.10 mmol), $Pd(OAc)_2$ (5 mol %), (R)-segphos (15 mol %), PivOH (30 mol %), Cs_2CO_3 (1.5 equiv), toluene (1 mL), 120 °C, 24 h. ^bIsolated yield and er were determined with chiral HPLC.

In summary, we have developed two protocols to achieve Pd-catalyzed asymmetric C–H bond activation for the synthesis of P-stereogenic dibenzophospholes; both chiral phosphoric acids/amides and trivalent phosphorus P(III) compounds are effective ligands for the reaction. The suitability for gram-scale reactions further enhances the utility of these methods.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.9b00216.

Experimental procedures, analysis data for all new compounds, and details of X-ray crystallographic analysis for 2a (PDF)

Accession Codes

CCDC 1870685 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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- (17) See the Supporting Information for X-ray data.