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Asymmetric Synthesis of P-Stereogenic Phosphinic Amides via Pd(0)-Catalyzed Enantioselective Intramolecular C−H Arylation

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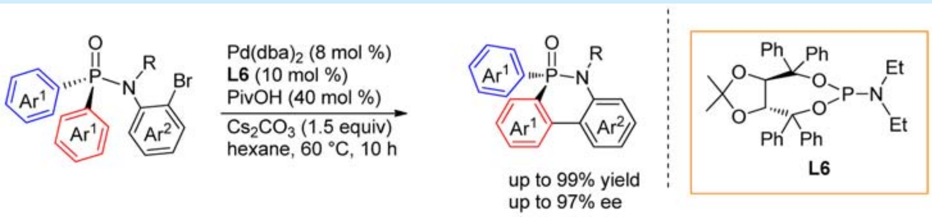
Supporting Information

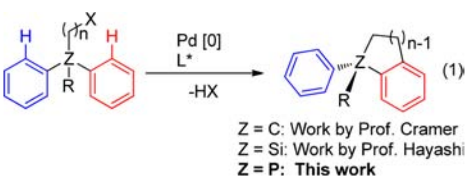


ABSTRACT: The palladium-catalyzed enantioselective intramolecular C−H arylation of *N*-(2-haloaryl)-*P,P*-diphenylphosphinic amides furnishes *P*-stereogenic phosphine oxide derivatives in 61−99% yield with 88−97% ee. The catalyst generated in situ from a TADDOL-derived phosphoramide ligand and $Pd(dba)_2$ is optimum in terms of yield and enantioselectivities.

Chiral phosphorus compounds constitute a class of prominent compounds typically used as versatile ligands or organocatalysts in asymmetric catalysis.[1] Particularly attractive are those possessing chiral centers at phosphorus atoms (P-stereogenic phosphines) which exhibit excellent enantioselectivities in asymmetric catalysis, and some have also been applied in the pharmaceutical industry. The usefulness of the P-stereogenic phosphines has made their stereoselective synthesis the subject of extensive research.[2]

Significant methods for stoichiometric asymmetric synthesis of P-stereogenic phosphines have been developed on the basis of the use of chiral auxiliaries[3] and enantioselective deprotonation of prochiral phospines.[4] More efficient and atom-economical pathways become accessible with the advent of transition-metal-catalyzed methods such as enantioselective cycloaddition of symmetrical dialkynylphosphine oxides,[5] asymmetric ring-closing metathesis of symmetrical dialkenylphosphine oxides,[6] asymmetric alkylation,[7] and arylation[8] of secondary phosphines as well as their catalytic asymmetric conjugate addition to electron-deficient olefins.[9] Very recently, chiral Brønsted acid catalyzed phosphoramidic acid additions to alkenes have been reported for the synthesis of C- and P-chiral phosphoramidates.[10] Despite these elegant approaches, catalytic asymmetric methods for highly enantioselective synthesis of P-stereogenic phosphines, especially the methods for P-stereogenic phosphorus heterocycles, remain undeveloped.[11]

Asymmetric C−H direct functionalization has been a challenging task in asymmetric catalysis.[12] Recently, Pd(0)-catalyzed enantioselective functionalization of enantiotopic C−H bonds has been successfully applied to asymmetric construction of quaternary carbon-stereogenic centers,[13] silicon-stereogenic centers[14] and planar chirality[15] (eq 1).



The application of the asymmetric C−H functionalization process to construct P-chiral phosphines would be highly desirable but remains undeveloped.[16] Herein, we report asymmetric synthesis of phosphorus heterocycles with P-stereogenic center through palladium-catalyzed enantioselective intramolecular C−H arylation of *N*-(2-haloaryl)-*P,P*-diphenyphosphinic amides with excellent enantioselectivity under mild conditions.[17]

The achiral substrate *N*-(2-bromophenyl)-*N*-methyl-*P,P*-diphenylphosphinamide (**1a**) was prepared by the acylation of 2-bromoaniline with diphenylphosphinic chloride and the subsequent *N*-methylation with methyl iodide. When **1a** was treated with $Pd(dba)_2$ (8 mol %), Cy_3P (10 mol %), PivOH (30 mol %), and Cs_2CO_3 (1.5 equiv) in toluene at 100 °C for 10 h, the C−H bond of the phenyl ring was cleaved and arylated intramolecularly to generate racemic **2a** in 98% isolated yield (Scheme 1).

A plausible mechanistic pathway for the formation of **2a** is depicted in Scheme 2. Initially, oxidative addition of the $C(sp^2)$−Br bond onto palladium(0) generates arylpalladium bromide **A**. The pivalate anion replaces the bromide ligand on palladium to afford palladium pivalate **B**. Then, a C−H bond

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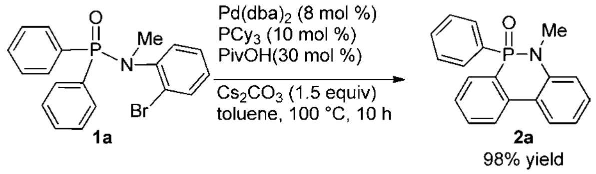
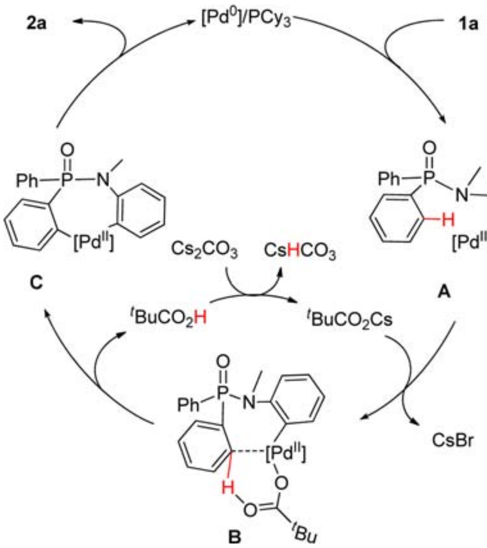
Scheme 1. Intramolecular C−H Arylation Reaction of 1a



Scheme 2. Proposed Mechanism

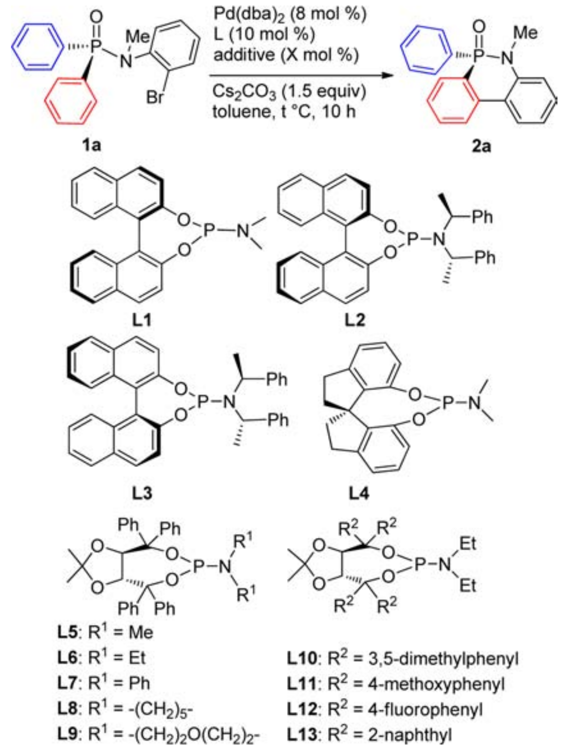


on the phenyl ring is cleaved to generate the seven-membered di(aryl)palladium species **C**.[17] Reductive elimination ensues to furnish phosphorus heterocycle **2a** possessing P-stereogenic center along with regeneration of the palladium(0) species.

Then, various types of ligands were employed to realize the asymmetric transformation, and the selected examples are listed in Table 1. The commercial available bidentate ligand (*R*)-BINAP gave **2a** in 66% yield with only 4% ee (Table 1, entry 1). However, no promising result was observed when other bidentate ligands, such as (*R*)-H_8-BINAP, (*R*)-SEGPHOS, (*R,R*)-DIOP, and (*R,S*)-PPFA, were used as chiral ligands (Table 1, entries 2−5). We then turned our attention to monodentate phosphoamidites ligands. To our disappointment, BINOL-derived phosphoamidites **L1−3** showed no enantioselectivity either (Table 1, entries 6−8). Pleasingly, when TADDOL-derived phosphoamidite **L5** (R^1 = Me) was used as ligand, the reaction proceeded smoothly to afford **2a** in 64% yield with 82% ee (Table 1, entry 12). The better result (75% yield with 86% ee) was obtained when **L6** (R^1 = Et) was used as ligand (Table 1, entries 11). However, **L7** (R^1 = Ph) exhibited poor reactivity and enantioselectivity (Table 1, entry 10), which indicates that the amine portion of the phosphoamidites also has important influence on the reactivity and enantioselectivity of the reaction. Further modification of the amine portion with cylic substituents (piperidine or morpholine) gave ligands **L8** and **L9** that were comparable to **L7** (Table 1, entries 13 and 14). Replacement of the phenyl substituents by other aryl groups (3,5-dimethylphenyl, 4-methoxyphenyl, 4-fluorophenyl, 2-naphthyl) had no positive or even negative influence on the reactivity and enantioselectivity (Table 1, entries 15−18).

The substrate scope was investigated under the optimized conditions and the results are summarized in Table 2. Although

Table 1. Selected Optimization of Reaction Conditions[a]



entry	L	addtive (mol %)	*t* (°C)	yield[b] (%)	ee[c] (%)
1	(*R*)-BINAP	PivOH (30)	100	66	4
2	(*R*)-H_8−BINAP	PivOH (30)	100	33	2
3	(*R*)-SEGPHOS	PivOH (30)	100	34	13
4	(*R,R*)-DIOP	PivOH (30)	100	73	3
5	(*R,S*)-PPFA	PivOH (30)	100	28	4
6	**L1**	PivOH (30)	100	0	0
7	**L2**	PivOH (30)	100	50	1
8	**L3**	PivOH (30)	100	0	0
9	**L4**	PivOH (30)	100	30	42
10	**L5**	PivOH (30)	100	64	82
11	**L6**	PivOH (30)	100	75	86
12	**L7**	PivOH (30)	100	26	9
13	**L8**	PivOH (30)	100	84	77
14	**L9**	PivOH (30)	100	73	85
15	**L10**	PivOH (30)	100	40	73
16	**L11**	PivOH (30)	100	75	53
17	**L12**	PivOH (30)	100	50	86
18	**L13**	PivOH (30)	100	69	82
19	**L6**	PivOH (30)	60	60	92
20	**L6**	PivOH (30)	50	52	92
21	**L6**	PivOH (40)	60	98	93
22	**L6**	AdOH (40)	60	56	91
23	**L6**	TMBA (40)	60	13	97
24[d]	**L6**	PivOH (40)	60	99	95

[a]Reaction conditions: **1a** (0.05 mmol) in 3 mL of toluene at the indicated temperature. [b]Isolated yield. [c]The ee values were determined by HPLC analysis. [d]In hexane. dba = (*E,E*)-dibenzylideneacetone, PivOH = pivalic acid, AdOH = adamantoic acid, TMBA = 2,4,6-trimethylbenzoic acid.

aryl chloride (X = Cl) failed to take part in this reaction, aryl iodide (X = I) reacted smoothly to give **2a** in 95% yield with 93% ee which is comparable with the result of aryl bromide, whereas no reaction occurred when unprotected amide (R = H) was subjected to the optimized reaction conditions, the

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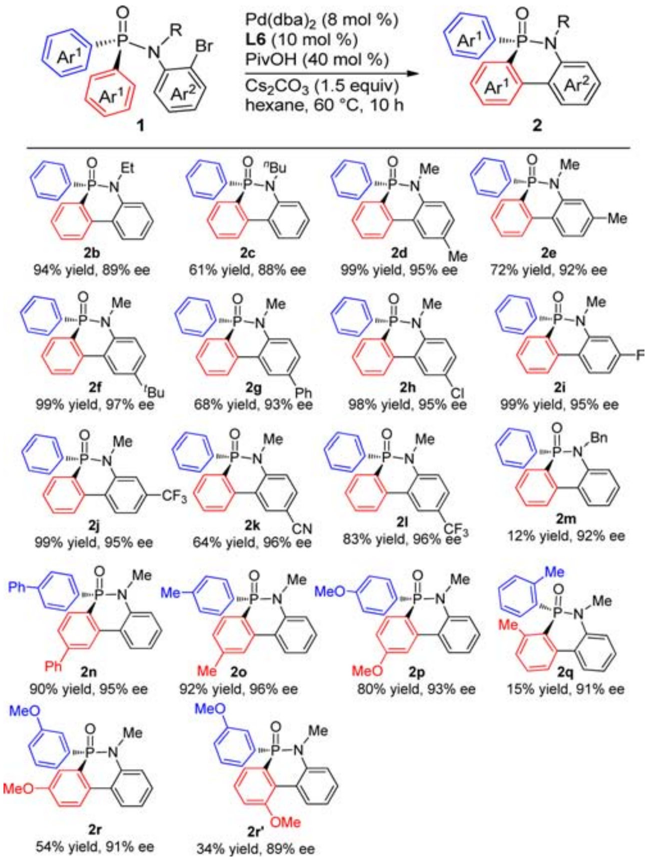
Table 2. Substrate Scope[a−c]



[a]Reaction conditions: amide 1 (0.05 mmol, 1.0 equiv), Pd(dba)$_2$ (8 mol %), L6 (10 mol %), Cs$_2$CO$_3$ (1.5 equiv), PivOH (40 mol %), hexane (3 mL), 60 °C, 10 h. [b]Isolated yield. [c]Determined by chiral HPLC.

amides with bulkier N-protecting groups furnish the desired cyclic products **2b,c** in good yield albeit with slightly lower enantioselectivity. The substrates derived from substituted 2-bromoanilines successfully took part in the reaction affording the products **2d−l** with excellent enantioselectivities ranging from 92 to 97% ee. Compound **2m** with an *N*-benzyl group was obtained in excellent enantioselectivity but with poor yield. Products **2n−p** bearing groups at the para-position of the P-phenyl ring can also be prepared by this method. Product **2q** containing a methyl group ortho to the phosphorus atom was obtained with poor yield and excellent ee. Two isomers, **2r** and **2r′**, were obtained when substrate containing a methyl group meta to the phosphorus atom was tested. Notably, various useful substituents including −F, −CF$_3$, −CN, and −Cl are well tolerated. The absolute configuration of **2f** was assigned as *R* by X-ray crystallographic analysis.[18]

In conclusion, we have developed a concise way to synthesize cyclic P-chiral phosphinic amides through Pd-catalyzed enantioselective C−H bond arylation of prochiral *N*-(2-haloaryl)-*P*,*P*-diphenylphosphinc amides. The method presents an example of catalytic asymmetric construction of P-stereocenters with excellent enantioselectivity by enantioselective C−H bond functionalization.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data for new compounds, and details of X-ray crystallographic analysis for **2f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(18) CCDC1042046 (**2f**) contains the supplementary crystallographic data for this paper.

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