C–H Activation

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Palladium-Catalyzed Enantioselective C–H Arylation for the Synthesis of P-Stereogenic Compounds**

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Abstract: *A palladium-catalyzed enantioselective C–H arylation of N-(o-bromoaryl)-diarylphosphinic amides is described for the synthesis of phosphorus compounds bearing a P-stereogenic center. The method provides good enantioselectivities and high yields. The products were readily transformed into P-chiral biphenyl monophosphine ligands.*

P-stereogenic phosphorus compounds are of great interest in the fields of agrochemicals, insecticides, and materials, and they are especially important ligands for catalysis.[1,2] The conventional methods of constructing P-chiral compounds are mostly based on optical resolution methods with stoichiometric amounts of chiral reagents.[3] Recently, a few examples of the construction of P-chiral compounds through asymmetric catalysis have been reported.[4] Typical examples include either palladium/platinum- or ruthenium-catalyzed arylation/alkylation of secondary phosphines[5] and palladium/platinum-catalyzed asymmetric addition of phosphorus nucleophiles to electrophiles,[6] thus affording P-stereogenic compounds with good to excellent enantioselectivities. Despite such impressive progress, the development of new pathways to construct P-chiral phosphines remains a challenging problem and is highly desired.

Transition-metal-catalyzed C–H bond activation has received extensive attention over the past few decades, and great advances in this area have recently been made.[7] A tremendous number of compounds have been constructed from simple, unfunctionalized molecules with high efficacy. However, enantioselective C–H activation reactions are still in their infancy, likely because of the lack of efficient protocols to control stereoselectivity during the reaction.[8] Recently, a few successful examples of asymmetric C–H activation based on the use of transition metals (e.g., Pd,[9] Rh,[10] and Ir[11]) in combination with suitable chiral ligands have been reported. In the case of a palladium catalyst, Yu et al. described an elegant and highly successful strategy using a monoprotected amino acid as the ligand in enantioselective C–H activation reactions.[8c,9b] Other efficient pathways have been focused primarily on palladium(0)-catalyzed intramolecular arylation or cyclization reactions using either chiral phosphines[9d,j,m,p] or N-heterocyclic carbenes[9i,l,u] as ligands, thus resulting in the construction of complex molecules with good to excellent enantioselectivities.[9] However, enantioselective C–H activation has been rarely involved in reactions for P-chiral phosphine synthesis.[12,13]

Biphenyl-based monophosphine ligands developed by Buchwald et al. have attracted extensive attention because of their wide application in an array of reactions, including C–C and C–X bond formation and gold-catalyzed cyclization processes.[14] However, chiral biphenyl monophosphorus ligands have received less attention with respect to their investigation and synthesis.[15] Inspired by elegant works involving enantioselective C–H activation reactions,[9] and as a continuation of our interest in the synthesis of chiral phosphines,[16] we herein report a palladium-catalyzed C–H arylation reaction for the synthesis of enantioenriched P-chiral compounds. These compounds can be useful precursors for chiral biphenyl monophosphine ligands.

We began by examining the intramolecular cyclization reaction of *N*-(*o*-bromophenyl)-*N*-methyl-diphenylphosphinic amide (**1a**) with a palladium catalyst in the presence of various phosphorus ligands. The use of (*R*)-binap and $Pd(OAc)_2$ as the catalyst in the presence of K_2CO_3 in toluene at 120 °C successfully generated the desired product in 90% yield, but with only 3% enantiomeric excess (*ee*; Table 1, entry 1). Further screening of an array of bidentate phosphine ligands, including DIPAMP, TangPhos, Me-DuPhos, and Chiraphos, was slightly successful, and up to 7% *ee* of the product was obtained (entries 2–5). Next, the monophosphorus ligand (*S*)-methoxy-MOP (**L6**) and phosphoramidite **L7** were examined, and the *ee* values of the products were increased slightly to 12 and 19% (entries 6 and 7), respectively. The use of the readily available TADDOL-based *N*-Et phosphoramidite ligand **L8a** improved the *ee* value to 78%. The examination of other bases revealed that K_3PO_4 provided comparable results to K_2CO_3 and that others afforded inferior *ee* values and yields (entries 9–14). Changing the solvent to 1,2-dichloroethane (DCE), 1,4-dioxane, *t*-AmOH, and DMF did not enhance the stereoselectivity (entries 15–18). However, changing the substituent groups on the nitrogen atom of the TADDOL ligands revealed that the N-methyl-substituted ligand **L8b** generated 82% *ee* of the product in 95% yield (entries 20–23). Furthermore, when the reaction temperature was reduced to 80 °C, the *ee* value of the product was improved to 90% (entry 26). In contrast, at 60 °C, almost similar stereoselectivity was observed (entry 28). Lastly, when $[Pd_2(dba)_3]$ was used as the palladium precursor or an *N*-(*o*-iodophenyl)-substituted amide was used as the starting

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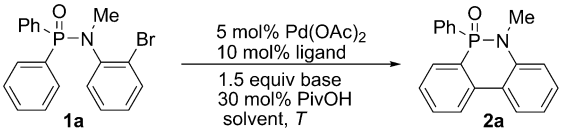
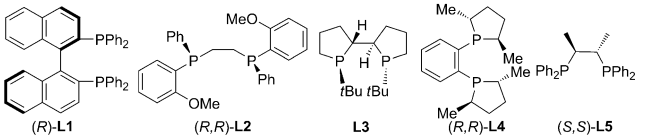
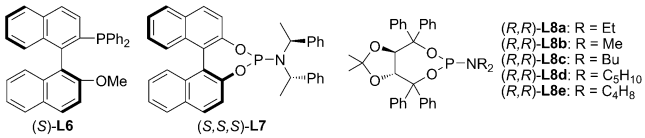
Table 1: Palladium-catalyzed cyclization of *N*-(*o*-bromophenyl)-*N*-methyl-diphenylphosphinic amide (**1a**).







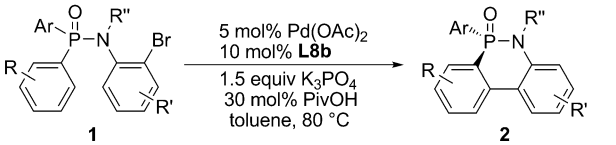
Entry	Ligand	Base	Solvent	*T* [°C]	*t* [h]	Yield [%][a]	*ee* [%][b]
1	**L1**	K_2CO_3	toluene	120	12	90	3
2	**L2**	K_2CO_3	toluene	120	12	94	7
3	**L3**	K_2CO_3	toluene	120	12	90	3
4	**L4**	K_2CO_3	toluene	120	12	84	0
5	**L5**	K_2CO_3	toluene	120	12	92	7
6	**L6**	K_2CO_3	toluene	120	12	94	12
7	**L7**	K_2CO_3	toluene	120	12	21	19
8	**L8a**	K_2CO_3	toluene	120	12	90	78
9	**L8a**	Cs_2CO_3	toluene	120	12	43	71
10	**L8a**	Na_2CO_3	toluene	120	12	32	59
11	**L8a**	KF	toluene	120	12	37	73
12	**L8a**	CsF	toluene	120	12	64	71
13	**L8a**	K_3PO_4	toluene	120	12	77	79
14	**L8a**	K_2HPO_4	toluene	120	12	21	79
15	**L8a**	K_2CO_3	DCE	120	12	75	63
16	**L8a**	K_2CO_3	1,4-dioxane	120	12	91	73
17	**L8a**	K_2CO_3	DMF	120	12	53	27
18	**L8a**	K_2CO_3	*t*AmOH	120	12	76	43
19[c]	**L8a**	K_2CO_3	toluene	120	12	39	78
20	**L8b**	K_2CO_3	toluene	120	12	95	82
21	**L8c**	K_2CO_3	toluene	120	13	66	78
22	**L8d**	K_2CO_3	toluene	120	13	69	58
23	**L8e**	K_2CO_3	toluene	120	12	88	81
24	**L8b**	K_3PO_4	toluene	100	20	88	86
25	**L8b**	K_2CO_3	toluene	100	20	90	85
26	**L8b**	K_3PO_4	toluene	80	22	90	90
27	**L8b**	K_2CO_3	toluene	80	22	74	88
28	**L8b**	K_3PO_4	toluene	60	37	64	90
29[d]	**L8b**	K_3PO_4	toluene	60	23	90	90
30[d]	**L8b**	K_3PO_4	toluene	40	42	12	n.d.
31[d,e]	**L8b**	K_2CO_3	toluene	60	21	11	n.d.
32[d,e]	**L8b**	Cs_2CO_3	toluene	60	21	81	90
33[d,e]	**L8b**	Cs_2CO_3	toluene	40	42	28	n.d.

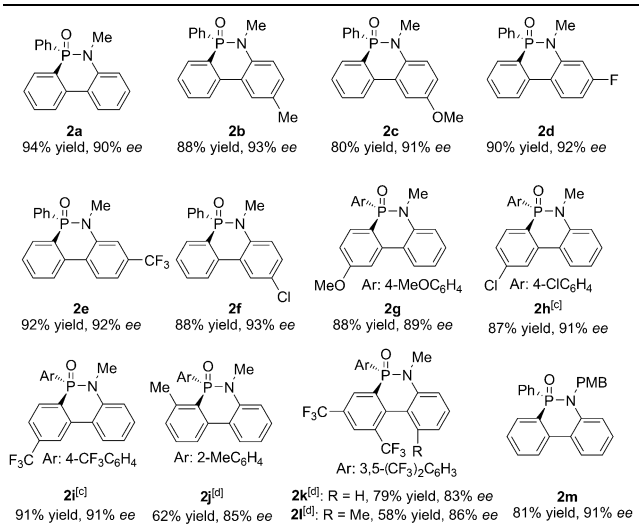
[a] Yield of isolated product. [b] The *ee* value was determined by HPLC analysis using a chiral stationary phase and hexane/2-propanol. [c] Without addition of PivOH. [d] 2.5 mol% $[Pd_2(dba)_3]$ was used instead of $Pd(OAc)_2$. [e] The bromine atom of **1a** was changed to an iodine atom. DCE = 1,2-dichloroethane, DMF = *N*,*N*-dimethylformamide, Piv = pivaloyl.

material at a lower reaction temperature, no further improvement of the *ee* values was achieved (entries 29–33).

With the optimized reaction conditions in hand, we began to examine the substrate scope of the reaction using a range of phosphinic amides bearing different substituent groups (Table 2). Various moieties on the aniline ring, such as

Table 2: Palladium-catalyzed intramolecular cyclization of *N*-disubstituted-diarylphosphinic amides **1**.[a,b]



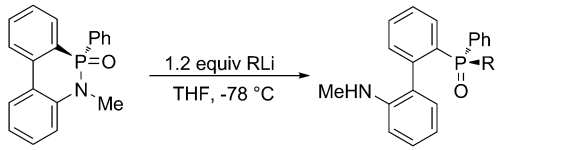


[a] Yield of isolated product. [b] The *ee* value was determined by HPLC analysis using a chiral stationary phase and hexane/2-propanol. [c] The reaction was conducted with 5 mol% $[Pd_2(dba)_3]$ and 20 mol% **L8b** at 25 °C for 72 h. [d] 10 mol% $Pd(OAc)_2$ and 20 mol% ligand **L8b** were used.

methyl, methoxy, fluoro, chloro, and trifluoromethyl groups, were well tolerated and resulted in good yields and excellent enantioselectivities (Table 2, **2a**–**f**). With respect to the substituent effects on the diaryl rings of the phosphinic amides, the substrate with a methoxy moiety generated an 89% *ee* for the product **2g** under the standard reaction conditions. Compounds bearing electron-withdrawing groups, such as chloro and trifluoromethyl groups, were converted into the corresponding products with 91% *ee* even at ambient temperature (25 °C; **2h** and **2i**). Furthermore, sterically hindered substrates containing a methyl group *ortho* to the phosphorus or bromine atoms, or containing a 3,5-bis(trifluoromethyl) moiety on the aryl ring, were tested in this reaction. The desired P-chiral compounds (**2j**–**l**) were successfully obtained with slightly decreased *ee* values and yields. Aside from the methyl group on the nitrogen atom, the substrate bearing a *para*-methoxybenzyl moiety can also be transformed into the phosphinic amide **2m** in 91% *ee* with 81% yield, and thus further extends the applicability of the current catalytic system. X-ray crystal diffraction analysis of the product **2f** indicated that the absolute configuration of the product is *R* and that no axial chirality is present in this

molecule, as suggested by the small dihedral angle (8.3°) between the two aryl rings (see the Supporting Information).[17]

To demonstrate the utility of the current protocol, the P–N bond cleavage was examined using various nucleophiles (Scheme 1). Methyllithium can react with **2a** smoothly, thus



2a, 90% *ee*

R: Me, 73% yield, 1.3:1 atropisomers
R: *i*Pr, 59% yield, 2.2:1 atropisomers

Scheme 1. Transformation of the product **2a** into biaryl monophosphine oxides.

generating a mixture of two atropisomers[18] in 73% yield without erosion of the enantiomeric ratio.[19] The use of isopropyllithium afforded the corresponding products in decreased yield. *tert*-Butyllithium generated relatively complicated mixtures, and this reagent may require further optimization of the reaction conditions or adjustment of the substituent groups on the nitrogen atom to enhance the substrate reactivity. Grignard reagents, such as isopropylmagnesium chloride or cyclohexylmagnesium chloride, did not react with **2a** at all, possibly because of their relatively low reactivity compared to that of lithium reagents.

In summary, we have described a palladium-catalyzed intramolecular C–H arylation reaction furnishing P-chiral phosphorus compounds in good yields and excellent stereoselectivities. Further transformation and application of the obtained phosphorus compounds as ligands in catalysis is ongoing.

Experimental Section

General experimental procedures for Table 2: $Pd(OAc)_2$ (2.2 mg, 5 mol% Pd), **L8b** (10.8 mg, 10 mol%), PivOH (6.0 mg, 30 mol%), diarylphosphinic amides **1** (0.20 mmol), and potassium phosphate (63.6 mg, 0.30 mmol) were weighed into a Schlenk tube, which was then sealed with a rubber septum. The tube was put under vacuum and then backfilled with nitrogen (×3). Toluene (0.8 mL) was added, and the reaction mixture was stirred at 80°C for 10 to 48 h. Then, the reaction mixture was cooled to room temperature, and evaporated under vacumm. The residue was directly purified by chromatography column on silica gel using hexane/EtOAc = 1:1 to afford the desired products.

Keywords: asymmetric catalysis · C–H activation · chirality · palladium · P ligands

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