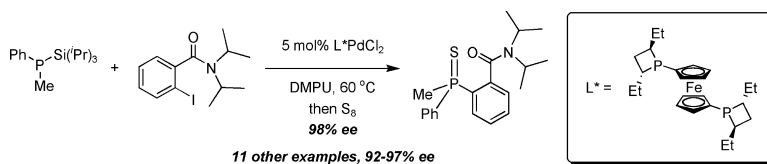Communication

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Pd-Catalyzed Dynamic Kinetic Enantioselective Arylation of Silylphosphines

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Chiral phosphines are essential ligands for asymmetric transition-metal-catalyzed transformations.[1] In 1972, Knowles and co-workers reported the first practical and highly asymmetric hydrogenation using P-stereogenic phosphines,[2] yet planar chiral and point chiral phosphines are the most commonly employed ligands today. P-Stereogenic phosphines are less often utilized, in part due to the lack of efficient and general methods for their enantioselective synthesis. Traditionally, these molecules are prepared by resolutions or the use of chiral auxiliaries.[3] Recently, there have been reports of asymmetric metal-catalyzed approaches to P-stereogenic phosphines via alkene hydrophosphination[4] and the arylation[5] or alkylation[6] of secondary phosphines. Herein, we describe a new route to P-stereogenic phosphines that proceeds through the dynamic kinetic[7] enantioselective arylation of tertiary racemic silylphosphines catalyzed by palladium.

The Pd-catalyzed coupling of achiral silylphosphines with aryl iodides was first reported by Stille.[8] The mechanism is believed to proceed via oxidative addition, followed by transmetalation of the silylphosphine, and reductive elimination to form a P−C bond (Scheme 1). In rendering this transformation enantioselective, we envisioned exploiting the low barrier to pyramidal inversion of metal phosphido complexes.[9] Rapid epimerization of the Pd(II) phosphide (relative to reductive elimination) enables the dynamic kinetic arylation of chiral racemic silylphosphines.[5e]

Optimization of the silylphosphine arylation was performed with 3-iodoanisole.[10] After extensive screening, the highest levels of enantioselectivity were achieved at 60 °C when methylphenyl-(triisopropylsilyl)phosphine **1** was cross-coupled using 5 mol % of ((R,R)-Et-FerroTANE)PdCl$_2$[5b] **2** in N,N′-dimethylpropylene urea (DMPU) (eq 1). Under these conditions, (3-anisyl)methylphenylphosphine **3**, which was isolated as the air-stable borane adduct, was obtained in 56% ee and 91% yield. A variety of inorganic[11a] and organic[11b] additives were evaluated, and none was found to have a beneficial effect on the enantioselectivity. When the coupling partner was modified such that 3-bromoanisole or 3-methoxyphenyl trifluoromethanesulfonate was employed, similar enantioselectivity was observed, but the reactions proceeded in much lower yields.
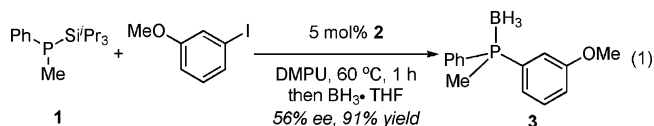
Using catalyst **2**, *ortho*-functionalized iodoarenes were evaluated in the arylation with **1**. In a recent report by Glueck,[5e] *ortho*-substituted arenes were coupled to secondary phosphines using an Et-FerroTANE catalyst in low enantiomeric excess. As shown in Table 1, an array of coordinating substituents was tolerated in the "phospha-Stille" reaction with modest to excellent enantioselectivities. Whereas 2-iodoanisole afforded the corresponding phosphine **4a** in 52% ee (entry 1), the more π-releasing 2-iodothioanisole furnished **4b** in 63% ee (entry 2). The amine directing group,
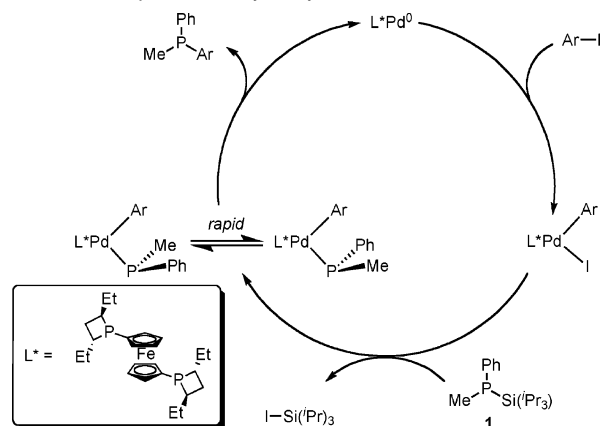
Scheme 1. Proposed Catalytic Cycle

Table 1. Enantioselective Arylation with Iodoarenes

entry	Ar-I		product	% yield^a	% ee^b
1		R = OMe	**4a**	74	55 (R)
2		R = SMe	**4b**	73	63 (R)
3		R = NMe$_2$	**4c**	77	43
4		R = ^{t}Bu	**4d**	83	78
5		R = 2,6-Me$_2$-Ph	**4e**	76	82
6		R = 2,6-^{i}Pr$_2$-Ph	**4f**	77	75
7		R = Me(OMe)	**4g**^{c}	65	81
8		R = Et	**4h**^{c}	63	79
9		R = ^{i}Pr	**4i**^{c}	53	98
10			**4j**^{c}	82	32

^{a} Isolated yield of the protected phosphine. ^{b} Measured by chiral HPLC. ^{c} Phosphine protected as the sulfide after heating at 60 °C for 2.5 h.

$$\text{(1)}$$

however, was less satisfactory (entry 3). *o*-Iodobenzoates (entries 4−6) and -benzamides (entries 7−9) were particularly selective substrates; with 2-iodo(2,6-dimethylphenyl)benzoate, phosphine **4e** was isolated in 82% ee (entry 5). A clear steric limitation was observed with the more bulky 2,6-diisopropylphenyl benzoate, as the product was isolated in 75% ee (entry 6). However, a dramatic change was observed with N,N-diisopropyl-2-iodobenzamide: when coupled with **1**, this substrate furnished the resulting phosphine sulfide **4i** in 98% ee (entry 9).[12,13] The tether length of the amide directing group was found to be crucial, as the benzylic N,N-diisopropylamide provided the product in only 32% ee (entry 10).

Subsequent experiments took advantage of the apparently privileged properties of the diisopropylbenzamide (Table 2). Changing the electronics *para* to the iodide had no effect on the enantioselectivity (entries 1 and 2): both methyl- (**5a**) and chloro-substituted (**5b**) amides give 97% ee. Varying the electronics *para* to the amide also had no effect on the outcome (entries 3−5). Both

Table 2. Enantioselective Arylation with Iodobenzamides

entry	Ar-I		product	% yield[a]	% ee[b]
1		R = Me	**5a**	61	97
2		R = Cl	**5b**	83	97
3		R = OMe	**5c**	55	97
4		R = CF$_3$	**5d**	79	97
5		R = Cl	**5e**	80	95
6		R = Me	**5f**[c]	67	97
7		R = -CH$_2$-	**5g**[c]	66	97
8			**5h**	89	93
9			**5i**	75	94
10			**5j**[d]	44	92
11			**5k**	52	93
12			**5l**	62	86

[a] Isolated yield of the phosphine sulfide. [b] Measured by chiral HPLC. [c] Reaction mixture heated at 60 °C for 4.5 h. [d] Reaction proceeded to completion after 8 h at 60 °C.

Table 3. Phosphine Scope in Enantioselective Arylation

entry	R^1	R^2	product	% yield[a]	% ee[b]
1	Me	3,5-F$_2$-C$_6$H$_3$	**6a**	72	46
2	Ph	CH$_2$Ph	**6b**	76	92
3	Ph	OMe	**6c**	69	92
4	Ph		**6d**	89	93

[a] Isolated yields of the phosphine sulfide. [b] Measured by chiral HPLC.

scenario, formation of the five-membered palladacycle, through binding of the amide oxygen, is instrumental in conferring the high enantioselectivities observed.

In conclusion, we have developed a Pd-catalyzed arylation of silylphosphines, which represents a powerful method for the asymmetric synthesis of P-stereogenic phosphines. The method relies on the unique ability of the *ortho*-benzamide substituent to enhance the enantioselectivity of these coupling reactions. Studies toward the elucidation of the role of the directing group and its application to other transition-metal-catalyzed coupling processes are currently underway.

Supporting Information Available: Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) (a) Representative inorganic salts added: LiBr (42% ee), K$_3$PO$_4$ (52% ee), CsF (52% ee), CuI (28% ee). (b) Some organic additives which were evaluated: TBAF (12% ee), MeOH (51% ee).
(12) Coupling with methylphenyl(trimethylsilyl)phosphine furnished **4i** in 93% ee and 31% yield.
(13) Under conditions reported in ref 5b, no reaction was observed.
(14) The cross-coupling of 3-iodothiophene with **1** under the optimized conditions afforded the corresponding phosphine in only 43% ee.

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the methoxy (**5c**) and trifluoromethyl substrates (**5d**) yielded the product in 97% ee. Comparison of phosphines **5c** and **3** clearly demonstrated the beneficial effect of the *ortho*-amide group. More electron-rich iodides required prolonged heating but proceeded equally enantioselectively: 4,5-dimethoxy- and piperonyl-derived benzamides reacted with **1** in 97% ee (entries 6 and 7). Extended conjugation was also tolerated as phosphinonaphthamide **5h** was recovered in 93% ee. Electron-rich heteroarenes were also discovered to be competent coupling partners; a pyridine carboxamide furnished the product in 94% ee (**5i**, entry 9), and the thiophenyl[14] substrate reacted in 92% ee (**5j**, entry 10). Even the sterically encumbered amide (entry 11) proved effective for the arylation of **1**, proceeding at 93% ee. As an extension of the benzamide directing effect, the *N,N*-diisopropylcarbamoyl moiety was used as a N-protecting group for 2-iodoindole, yielding phosphine **5l** in 86% ee (entry 12).

The phospha-Stille coupling was also extended to other phosphines (Table 3). Coupling of the electron-poor (3,5-difluorophenyl)methylphosphine afforded a dramatic decrease in the enantioselectivity (entry 1). Variation of the alkyl substituent, however, was well-tolerated: the less sterically differentiated benzylphenyl-(triisopropylsilyl)phosphine was coupled to *N,N*-diisopropylbenzamide to give phosphine sulfide **6b** in 92% ee (entry 2). Oxygenated alkyl groups were also tolerated, furnishing products **6c** and **6d**, potential P,O-bidentate ligands, in 92 and 93% ee, respectively.

Given the significant dependence of the enantioselectivity on the amide substituents and tether length (Table 1, entries 7−10), we postulate the coordination of the amide to the Pd center. In this