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## Enantioselective palladium-catalyzed arylation of *N*-tosylaryl-imines with arylboronic acids using a chiral 2,2'-bipyridine ligand

Received 00th January 20xx,  
Accepted 00th January 20xx

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DOI: 10.1039/x0xx00000x

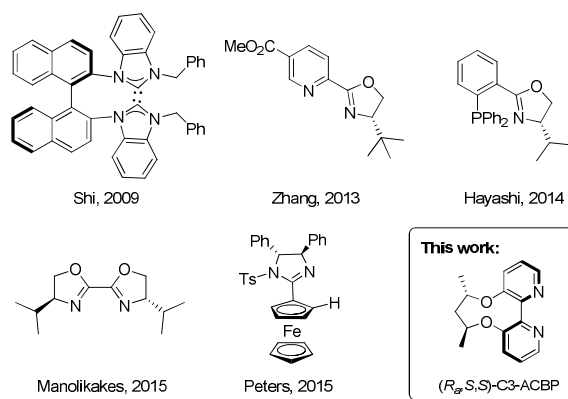
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**With the aid of an axially chiral 2,2'-bipyridine ligand, we have successfully developed a palladium-catalyzed method for the enantioselective arylation of *N*-tosylaryl-imines, furnishing the chiral diarylmethamines with high yields and enantioselectivities under very mild conditions. Exogenous base was avoided and imine hydrolysis was inhibited in this transformation.**

Transition-metal-catalyzed asymmetric addition of organo-metallic reagents to imines represents one of the most straightforward approaches for the construction of chiral diarylmethamines, which are synthetically important chiral building blocks for pharmaceutically active compounds.<sup>1</sup> Thanks to the seminal work by Hayashi,<sup>2</sup> Carreira<sup>3</sup> and Lin,<sup>4</sup> the chiral dienes flourished as steering ligands in rhodium-catalyzed asymmetric reactions, especially the arylation of imines with excellent yields and enantioselectivities.<sup>5</sup> Pioneered by these works, ene-based ligands were extensively studied, *P*-olefin, *N*-olefin and *S*-olefin ligands were developed and applied in rhodium-catalyzed asymmetric addition of arylboronic acids to enones or imines with excellent stereocontrol.<sup>6</sup> Therefore, rhodium complexes coordinated with ene-based ligands have emerged as the most versatile catalysts for the asymmetric arylation of imines by arylboronic acids.

In contrast to rhodium, other transition-metals received relatively less attention. Several reports have described the copper- or zirconium-catalyzed asymmetric addition of allylboronates or dialkylzinc reagents to ketimines.<sup>7</sup> Recently, palladium-catalyzed addition of arylboronic acids to imines has become a subject of keen interest due to the high efficacy and robustness of palladium catalysts.<sup>8</sup> A wide array of palladium catalysts coordinated with *N*-heterocyclic carbenes,<sup>9</sup> pyridine-oxazolines,<sup>10</sup> phosphinoxazolines,<sup>11</sup> bisoxazolines,<sup>12</sup> and imidazolines<sup>13</sup> ligands have been reported in the asymmetric arylation of imines (Scheme 1).<sup>14</sup> These elegant works by

Zhang, Hayashi and Peters authenticate that the catalytic proficiency of palladium catalysts has been comparable to that of the best rhodium catalysts in terms of enantioselectivity and activity. Despite these valuable progresses made in this area, highly-efficient ligands occupied in this asymmetric transformation are limited and developing new ligands is still desirable. Herein, we report an example of using palladium complexes coordinated with axially chiral 2,2'-bipyridine ligands for the enantioselective arylation of *N*-tosylaryl-imines with arylboronic acids, affording the chiral diarylmethamines with up to 94% ee.



**Scheme 1. Representative Ligands in Palladium-Catalyzed Asymmetric Arylation of Imines**

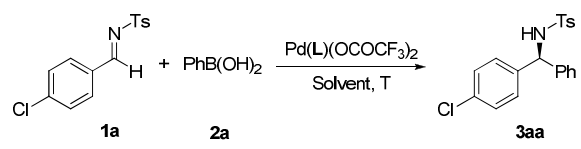
In 2007, Lu and co-workers disclosed a palladium-catalyzed arylation of *N*-tosylaryl-imines promoted by an achiral 2,2'-bipyridine ligand.<sup>15a</sup> They found the 2,2'-bipyridine ligand was crucial in the reaction by enabling the arylpalladium species to become more nucleophilic, thus making the addition reaction possible. However, without easily accessible chiral bipyridine ligands in hand, they turned to use chiral pyridine-oxazoline ligands to study the asymmetric version and moderate ee values could be obtained.<sup>15b</sup> Recently, we have reported the design and synthesis of a series of axially chiral 2,2'-bipyridine ligands Cn-ACBP, they exhibited excellent stereocontrol in

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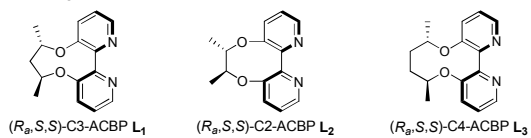
palladium-catalyzed asymmetric carbene migratory insertion reactions.<sup>16</sup> Therefore, we envisioned that our chiral bipyridine ligands could effectively promote the palladium-catalyzed asymmetric arylation of *N*-tosylarylimines with arylboronic acids.

We began our investigation on the addition of phenylboronic acid to (*E*)-*N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide **1a** catalyzed by Pd(L<sub>1</sub>)(OCOCF<sub>3</sub>)<sub>2</sub> in trifluoroethanol (TFE) at 60 °C. Gratifyingly, the reaction proceeded smoothly without exogenous base and furnished **3aa** in 99% yield and 82% ee (Table 1, entry 1). Notably, imine hydrolysis couldn't be detected even when the reaction was performed under the air. Lowering the reaction temperature resulted in slight improvement of enantioselectivities (Table 1, entries 2-4). To our satisfaction, the reaction even proceeded well at 0 °C, affording **3aa** in 99% yield and 89% ee within 12 h (Table 1, entry 5). Next, a solvent screening revealed that dichloromethane and 1,2-dichloroethane led to a drastic decrease in both reactivity and enantioselectivity (Table 1, entries 6-7). Surprisingly, no product was detected when employing MeOH as the solvent (Table 1, entry 8). While reactivity retained, there was a significant drop in enantioselectivity when utilizing C2-ACBP L<sub>2</sub> as ligand (Table 1, entry 9), and the low enantioselectivity might be ascribable to the small dihedral angle.<sup>17</sup> C4-ACBP L<sub>3</sub> was also examined and a slightly lower ee value was obtained (Table 1, entry 10). Therefore, the optimal reaction conditions were established: using Pd(L<sub>1</sub>)(OCOCF<sub>3</sub>)<sub>2</sub> as catalyst, TFE as solvent to perform the reaction at 0 °C.

**Table 1.** Optimization of Reaction Parameters<sup>a</sup>



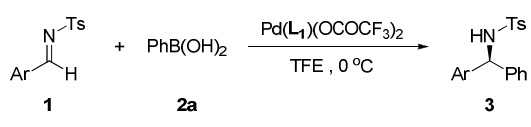
Entry	L	Solvent	T (°C)	Yield (%) <sup>b</sup>	Ee (%) <sup>c</sup>
1	L <sub>1</sub>	TFE	60	99	82
2	L <sub>1</sub>	TFE	40	99	83
3	L <sub>1</sub>	TFE	25	99	86
4	L <sub>1</sub>	TFE	10	99	87
5	L <sub>1</sub>	TFE	0	99	89
6	L <sub>1</sub>	DCM	0	41	89
7	L <sub>1</sub>	DCE	0	59	88
8	L <sub>1</sub>	MeOH	0	N/R	--
9 <sup>d</sup>	L <sub>2</sub>	TFE	0	99	4
10 <sup>d</sup>	L <sub>3</sub>	TFE	0	99	88



(*R,R,S,S*)-C3-ACBP L<sub>1</sub>      (*R,R,S,S*)-C2-ACBP L<sub>2</sub>      (*R,R,S,S*)-C4-ACBP L<sub>3</sub>

<sup>a</sup> Reaction conditions: Pd(L)(OCOCF<sub>3</sub>)<sub>2</sub> (5.0 mol%), **1a** (0.20 mmol), **2a** (0.30 mmol), Solvent (3 mL), 5-96 h. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by HPLC. <sup>d</sup> The catalyst was prepared *in situ*. N/R: no reactivity. DCM: dichloromethane. DCE: 1,2-dichloroethane.

**Table 2.** Palladium-Catalyzed Asymmetric Addition of Phenylboronic Acid **2a** to *N*-tosylarylimines **1**<sup>a</sup>



Entry	Ar	t (h)	Yield (%) <sup>b</sup>	Ee (%) <sup>c</sup>
1	4-ClC <sub>6</sub> H <sub>4</sub> ( <b>1a</b> )	12	99 ( <b>3aa</b> )	89 (S)
2	4-BrC <sub>6</sub> H <sub>4</sub> ( <b>1b</b> )	35	96 ( <b>3ba</b> )	89 (S)
3	2-BrC <sub>6</sub> H <sub>4</sub> ( <b>1c</b> )	24	90 ( <b>3ca</b> )	90 (S)
4	4-MeC <sub>6</sub> H <sub>4</sub> ( <b>1d</b> )	22	91 ( <b>3da</b> )	90 (S)
5	4-MeOC <sub>6</sub> H <sub>4</sub> ( <b>1e</b> )	35	99 ( <b>3ea</b> )	91 (S)
6 <sup>d</sup>	2-HOC <sub>6</sub> H <sub>4</sub> ( <b>1f</b> )	35	76 ( <b>3fa</b> )	91 (-)
7	2-MeOC <sub>6</sub> H <sub>4</sub> ( <b>1g</b> )	24	95 ( <b>3ga</b> )	91 (S)
8	3,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> ( <b>1h</b> )	42	94 ( <b>3ha</b> )	92 (-)
9	3,5-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> ( <b>1i</b> )	22	90 ( <b>3ia</b> )	90 (-)
10	3,4,5-(MeO) <sub>3</sub> C <sub>6</sub> H <sub>2</sub> ( <b>1j</b> )	36	99 ( <b>3ja</b> )	92 (-)
11	2-Br-4,5-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>2</sub> ( <b>1k</b> )	21	99 ( <b>3ka</b> )	93 (-)
12	1-Naphthyl ( <b>1l</b> )	24	99 ( <b>3la</b> )	90 (S)

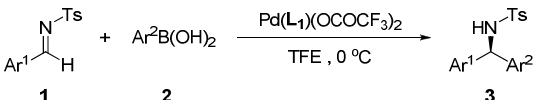
<sup>a</sup> Reaction conditions: Pd(L<sub>1</sub>)(OCOCF<sub>3</sub>)<sub>2</sub> (5.0 mol%), **1** (0.20 mmol), **2a** (0.30 mmol), TFE (3.0 mL), 0 °C. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by HPLC. <sup>d</sup> Determined by HPLC of product after being protected by benzoyl chloride.

Having identified the optimal reaction conditions, we turned to investigate the substrate scope, and the results were summarized in Table 2. Excellent yields could be obtained regardless of electronic properties of *N*-tosylarylimines (Table 2, entries 1-12). Though a slight decrease in reactivity was observed when electron-deficient *N*-tosylarylimines were used (Table 2, entries 2-3), enantioselectivities were consistently maintained (89-90% ee). It is noteworthy that electron-rich *N*-tosylarylimines gave relatively higher ee values than electron-deficient ones (Table 2, entries 4-12), excellent enantioselectivities were generally obtained (90-93% ee). *ortho*-Substituents on the *N*-tosylarylimines dramatically decreased the activity, but excellent yields and enantioselectivities could still be achieved after a prolonged time (entries 6-7).

In addition, a variety of arylboronic acids were examined for addition to different *N*-tosylarylimines (Table 3). Steric properties of the substrates obviously affected the reaction activity (Table 3, entries 1-6), the reaction could complete within 24 h when using *p*-tolylboronic acid (Table 3, entry 1), however, when *o*-tolylboronic acid was used, it would take 10 days before the total consumption of **1** (Table 3, entry 3). It's amazing to see that the catalyst kept active in such long reaction time and no imine hydrolysis or aryl-aryl coupling was

detected during this period. The desired product was obtained with 97% yield and 94% ee. It was also found that the electronic properties of the arylboronic acids had little influence on enantioselectivities (Table 3, entries 1-10), arylboronic acids bearing electron-withdrawing group Br and F all gave excellent yields and enantioselectivities (Table 3, entries 7-8). Extending reaction time could give complete conversion for all cases, furnishing the corresponding adducts in excellent enantioselectivities (90-94% ee). Additionally, we also employed pyridine-3-boronic acid and furan-2-boronic acid as reaction partners, but unfortunately, neither of the two heteroaryl boronic acids fitted in this protocol and no product was detected, which might attribute to deactivation of catalyst caused by coordination of heteroatom with palladium.

**Table 3.** Palladium-catalyzed Asymmetric Addition of Arylboronic Acids **2** to *N*-tosylarylimines **1**<sup>a</sup>

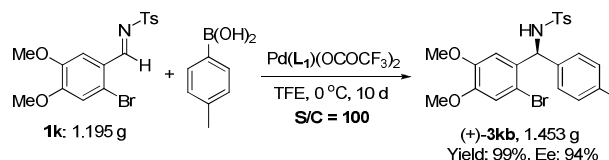


Entry	<b>1</b>	Ar <sup>2</sup>	t (h)	Yield (%) <sup>b</sup>	Ee (%) <sup>c</sup>
1	<b>1k</b>	4-MeC <sub>6</sub> H <sub>4</sub> ( <b>2b</b> )	24	98 ( <b>3kb</b> )	93 (+)
2	<b>1k</b>	3-MeC <sub>6</sub> H <sub>4</sub> ( <b>2c</b> )	36	99 ( <b>3kc</b> )	93 (+)
3	<b>1k</b>	2-MeC <sub>6</sub> H <sub>4</sub> ( <b>2d</b> )	240	97 ( <b>3kd</b> )	94 (+)
4	<b>1k</b>	4-MeOC <sub>6</sub> H <sub>4</sub> ( <b>2e</b> )	24	98 ( <b>3ke</b> )	92 (+)
5	<b>1k</b>	3-MeOC <sub>6</sub> H <sub>4</sub> ( <b>2f</b> )	36	99 ( <b>3kf</b> )	93 (+)
6	<b>1k</b>	2-MeOC <sub>6</sub> H <sub>4</sub> ( <b>2g</b> )	24	99 ( <b>3kg</b> )	94 (+)
7	<b>1k</b>	4-FC <sub>6</sub> H <sub>4</sub> ( <b>2h</b> )	120	99 ( <b>3kh</b> )	94 (+)
8	<b>1k</b>	4-BrC <sub>6</sub> H <sub>4</sub> ( <b>2i</b> )	144	95 ( <b>3ki</b> )	93 (+)
9	<b>1k</b>	4-BnOC <sub>6</sub> H <sub>4</sub> ( <b>2j</b> )	24	99 ( <b>3kj</b> )	92 (+)
10	<b>1k</b>	1-Naphthyl ( <b>2k</b> )	168	99 ( <b>3kk</b> )	92 (+)
11	<b>1d</b>	4-MeC <sub>6</sub> H <sub>4</sub> ( <b>2b</b> )	24	87 ( <b>3db</b> )	90 (S)
12	<b>1d</b>	2-MeOC <sub>6</sub> H <sub>4</sub> ( <b>2g</b> )	36	77 ( <b>3dg</b> )	90 (R)
13	<b>1h</b>	4-MeC <sub>6</sub> H <sub>4</sub> ( <b>2b</b> )	24	98 ( <b>3hb</b> )	90 (-)
14	<b>1h</b>	2-MeOC <sub>6</sub> H <sub>4</sub> ( <b>2g</b> )	48	80 ( <b>3hg</b> )	90 (+)
15	<b>1j</b>	4-MeC <sub>6</sub> H <sub>4</sub> ( <b>2b</b> )	24	99 ( <b>3jb</b> )	92 (+)
16	<b>1j</b>	2-MeOC <sub>6</sub> H <sub>4</sub> ( <b>2g</b> )	48	99 ( <b>3jg</b> )	90 (+)

<sup>a</sup> Reaction conditions: Pd(L<sub>1</sub>)(OCOCF<sub>3</sub>)<sub>2</sub> (5.0 mol%), **1** (0.20 mmol), **2** (0.30 mmol), TFE (3.0 mL), 0 °C. <sup>b</sup> Isolated yields based on imines. <sup>c</sup> Determined by chiral HPLC.

To further demonstrate the practicality, 1 mol% catalyst was used in the addition of 4-methylphenylboronic acid to imine **1k** on a gram scale, and the desired product was obtained in 94% ee and 99% yield (Equation 1). The corresponding product **3kb** could be conveniently converted into chiral 3-substituted isoindolinone derivatives, a useful framework frequently found in bioactive molecules.<sup>18</sup>

**Equation 1.** Scale-up of Substrate **1k**



## Conclusions

In conclusion, we have successfully established a new catalytic protocol by employing Pd-bipyridine complexes as catalysts for asymmetric arylation of *N*-tosylarylimines, the corresponding chiral diarylmethamines could be obtained with up to 94% ee. This represents the first example of palladium-catalyzed arylation of *N*-tosylarylimines promoted by a chiral 2,2'-bipyridine ligand. Highlights of this methodology involve an exogenous-base-free transmetalation process, inhibition of imine hydrolysis, mild reaction condition. Studies to extend the scope of this methodology and probe the reaction mechanism are currently underway in our laboratory.

We are grateful for the financial support from National Natural Science Foundation of China (21372220 & 21532006).

## Notes and references

#Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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