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Catalytic Asymmetric Addition of Arylboronic Acids to Isatins using C_2-Symmetric Cationic *N*-Heterocyclic Carbenes (NHCs) Pd^{2+} Diaqua Complexes as Catalysts

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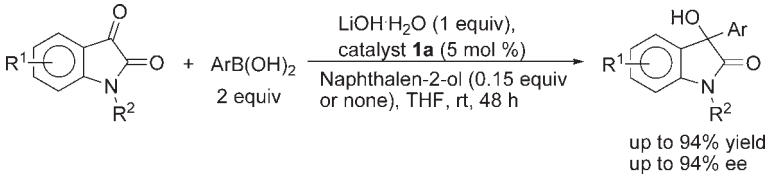
ABSTRACT



A catalytic asymmetric addition of arylboronic acids to isatins has been achieved by using chiral cationic C_2-symmetric *N*-heterocyclic carbene (NHC) Pd^{2+} diaqua complexes as the catalysts. The reaction can be performed under convenient conditions to give the corresponding adducts in good to high yields (79−94%) and moderate to excellent enantioselectivities (up to 94% *ee*) in the presence of LiOAr as the promoter which was generated *in situ*.

In the past decade, *N*-heterocyclic carbenes (NHCs) have been widely used as ancillary ligands in organometallic and catalytic chemistry because these ligands have several significant advantages over their phosphine counterparts. For example, they serve as stronger σ-donor and weaker π-acceptors than phosphine ligands while their air/moisture stability remains; this makes it very convenient for them to be stored and transferred.[1,2] In fact, Pd−NHC complexes have emerged as effective catalysts for a variety of coupling reactions recently.[3] Several transition-metal-mediated coupling processes have shown that it is possible to develop enantioselective reactions by using these complexes.[4−6] To the best of our knowledge, a highly reactive and

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(1) (a) Bourisou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39. (b) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290. (c) Hillier, A. C.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang, C.; Nolan, S. P. *J. Organomet. Chem.* **2002**, *653*, 69. (d) Clavier, H.; Nolan, S. P. *Annu. Rep. Prog. Chem., Sect. B* **2007**, *103*, 193. (e) Glorius, F.; Stahl, S. S.; Nolan, S. P.; Peris, E.; Bellemin-Laponnaz, S.; Louie, J.; Ritter, T. *Top. Organomet. Chem.* **2007**, *21*, 1. (f) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2768.

(2) (a) Scholl, M.; Dong, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Choi, T. -L.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1743. (c) Navarro, O.; Kelly, R. A., III.; Nolan, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 16194. (d) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101. (e) Navarro, O.; Marion, N.; Mei, J.; Nolan, S. P. *Chem.—Eur. J.* **2006**, *12*, 5142. (f) Albrecht, M.; Crabtree, R. H.; Mata, J.; Peris, E. *Chem. Commun.* **2002**, 32. (g) Albrecht, M.; Miecznikowski, J. R.; Samuel, A.; Faller, J. W.; Crabtree, R. H. *Organometallics* **2002**, *21*, 3596.

(3) (a) Herrmann, W. A.; Elison, M.; Fisher, J.; Koecher, C.; Artus, G. R. J. *Angew. Chem., Int. Ed.* **1995**, *34*, 2371. (b) Albert, K.; Gisdakis, P.; Rosch, N. *Organometallics* **1998**, *17*, 1608. (c) Huang, J.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 9889. (d) Grasa, G. A.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 119. (e) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 3690. (f) Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642. (g) Clyne, D. S.; Jin, J.; Genest, E.; Gallucci, J. C.; RajanBabu, T. V. *Org. Lett.* **2000**, *2*, 1125.

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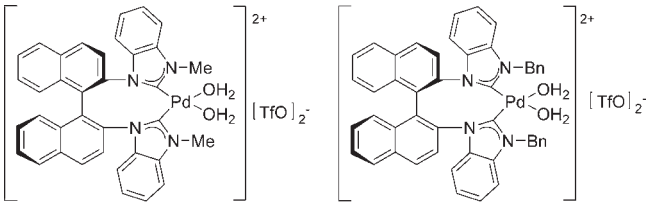
enantioselective Pd−NHC catalyst for asymmetric catalytic processes has not been well documented. Therefore, the search for new chiral catalysts and catalytic systems involving chiral NHC−metal complexes still remains challenging and in high demand.

Meanwhile, much interest has been directed toward the study of 3-hydroxyoxindoles possessing substituents at their 3-positions due to their important biological activities.[7] Compounds containing this structural unit have been widely serving as targets for drug design and synthesis. Several methods have been developed for the preparation of 3-substituted oxindoles,[8] but the asymmetric addition of nucleophiles to isatins is still the most straightforward approach to this structural scaffold. Even though asymmetric additions of nucleophiles including arylboronic acids to isatins catalyzed by transition metals have shown promising progress,[9] there has been a very limited number of successful examples using the Pd catalytic complexes in the literature.[10] Previously, we have reported the synthesis of a series of the chiral cationic NHC−Pd^{2+} diaqua complexes and their applications in catalytic enantioselective arylation reactions of imines with arylboronic acids.[11] Herein, we would like to report our preliminary results on the use of these chiral cationic NHC−Pd^{2+} diaqua complexes for the enantioselective arylation of isatins with arylboronic acids.

Initially, we utilized the reaction of isatin **2a** with phenylboronic acid (2.0 equiv) as the model reaction in the presence of 1.0 equiv of K_2CO_3 as the base and NHC−Pd complex **1a** (Figure 1, 5 mol %) as the catalyst. We found that the use of K_2CO_3 as the base led to the

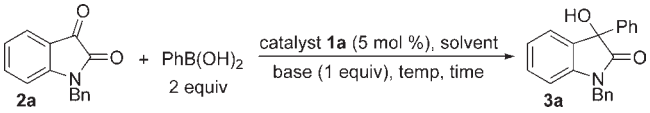


(*R*)-*N*-Me-NHC-Pd^{2+} **1a** (*R*)-*N*-Bn-NHC-Pd^{2+} **1b**

Figure 1. Chiral cationic NHC−Pd^{2+} diaqua complexes **1a** and **1b**.

adduct **3a** in 71% yield and 50% *ee* in THF at room temperature (Table 1, entry 1). Various bases were next screened for this catalytic system; it was found that when $LiOH \cdot H_2O$ was used as the base, the product **3a** was generated in 88% yield and 81% *ee* (Table 1, entries 2−14). We anticipated that the reactivity of isatin **2a** would be enhanced when Brønsted base $LiOH \cdot H_2O$ was added into the reaction system leading to the formation of the desired product in higher yield and enantioselectivity.[12a] We then utilized the complex **1b** to replace **1a** as the catalyst under identical conditions and found that the

Table 1. Optimization of the Reaction Condition for Catalytic Enantioselective Addition of Arylboronic Acids to Isatins



entry	base	solvent	temp	time	yield (%)[a]	*ee* (%)[b]
1	K_2CO_3	THF	rt	48 h	71	50 (*R*)[c]
2	$K_3PO_4 \cdot 3H_2O$	THF	rt	48 h	73	51 (*R*)
3	KOH	THF	rt	48 h	70	43 (*R*)
4	Cs_2CO_3	THF	rt	48 h	53	42 (*R*)
5	KO^{t}Bu	THF	rt	48 h	61	54 (*R*)
6	Pyridine	THF	rt	48 h	57	51 (*R*)
7	Et_3N	THF	rt	48 h	37	48 (*R*)
8	$LiOH \cdot H_2O$	THF	rt	48 h	88	81 (*R*)
9	Li_2CO_3	THF	rt	48 h	70	51 (*R*)
10	LiOAc	THF	rt	48 h	63	57 (*R*)
11	$Ca(OH)_2$	THF	rt	48 h	51	74 (*R*)
12	$Mg(OH)_2$	THF	rt	48 h	60	57 (*R*)
13	$Al(OH)_3$	THF	rt	48 h	58	61 (*R*)
14	$Ba(OH)_2 \cdot 8H2O$	THF	rt	48 h	63	43 (*R*)
15[d]	$LiOH \cdot H_2O$	THF	rt	48 h	81	73 (*R*)
16[e]	$LiOH \cdot H_2O$	THF	rt	48 h	51	65 (*R*)
17[f]	$LiOH \cdot H_2O$	THF	rt	48 h	90	71 (*R*)
18	$LiOH \cdot H_2O$	THF	0 °C	72 h	47	70 (*R*)
19	$LiOH \cdot H_2O$	THF	45 °C	8 h	91	54 (*R*)
20	$LiOH \cdot H_2O$	Dioxane	rt	48 h	71	57 (*R*)

[a] Isolated yields. [b] Determined by chiral HPLC. [c] Determined by comparison of the sign of optical rotation to the literature value.[10] [d] Catalyst **1b** was used. [e] 0.5 equiv base was used. [f] 2.0 equiv base were used.

(4) (a) Glorius, F.; Altenhoff, G.; Goddard, R.; Lehmann, C. *Chem. Commun.* **2002**, 2704. (b) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402. (c) Arao, T.; Kondo, K.; Aoyama, T. *Tetrahedron Lett.* **2006**, *47*, 1417. (d) Bertogg, A.; Camponovo, F.; Togni, A. *Eur. J. Inorg. Chem.* **2005**, 347.

(5) (a) Bonnet, L. G.; Douthwaite, R. E.; Kariuki, B. M. *Organometallics* **2003**, *22*, 4187. (b) Flahaut, A.; Baltaze, J. P.; Roland, S.; Mangeney, P. *J. Organomet. Chem.* **2006**, *691*, 3498.

(6) (a) Sato, Y.; Imakuni, N.; Mori, M. *Adv. Synth. Catal.* **2003**, *345*, 488. (b) Sato, Y.; Imakuni, N.; Hirose, T.; Wakamatsu, H.; Mori, M. *J. Organomet. Chem.* **2003**, *687*, 392.

(7) (a) Nicolaou, K. C.; Hao, J.; Reddy, M. V.; Rao, P.; Rassias, G.; Synder, S. A.; Huang, X.; Chen, D. Y.-K.; Brenzovich, W. E.; Giuseppone, N.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2004**, *126*, 15316. (b) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (c) Rasmussen, H. B.; MacLeod, J. K. *J. Nat. Prod.* **1997**, *60*, 1152. (d) Kohno, J.; Koguchi, Y.; Nishio, M.; Nakao, K.; Kuroda, M.; Shimizu, R.; Ohnuki, T.; Komatsubara, S. *J. Org. Chem.* **2000**, *65*, 990. (e) Hibino, S.; Choshi, T. *Nat. Prod. Rep.* **2002**, *19*, 148.

(8) (a) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402. (b) Dounay, A. B.; Hatanaka, K.; Kodanko, J. J.; Oestreich, M.; Overman, L. E.; Pfeifer, L. A.; Weiss, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 6261. (c) Hills, I. D.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921. (d) Trost, B. M.; Frederiksen, M. U. *Angew. Chem., Int. Ed.* **2005**, *44*, 308. (e) Jia, Y.-X.; Hillgren, J. M.; Watson, E. L.; Marsden, S. P.; Kündig, E. P. *Chem. Commun.* **2008**, *34*, 4040. (f) Jia, Y.-X.; Kündig, E. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1636.

(9) (a) Toullec, P. Y.; Jagt, R. B. C.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Org. Lett.* **2006**, *8*, 2715. (b) Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3353. (c) Shintani, R.; Takatsu, K.; Hayashi, T. *Chem. Commun.* **2010**, *46*, 6822.

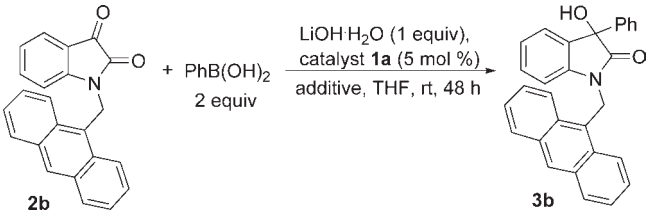
(10) Lai, H. S.; Huang, Z. Y.; Wu, Q.; Qin, Y. *J. Org. Chem.* **2009**, *74*, 283.

(11) (a) Chen, T.; Jiang, J. J.; Xu, Q.; Shi, M. *Org. Lett.* **2007**, *9*, 865. (b) Ma, G. N.; Zhang, T.; Shi, M. *Org. Lett.* **2009**, *11*, 875. (c) Liu, Z.; Shi, M. *Organometallics* **2010**, *29*, 2831. (d) Liu, Z.; Shi, M. *Tetrahedron* **2010**, *66*, 2619.

product **3a** was obtained in 81% yield and 73% *ee* (Table 1, entry 15). Decreased or increased amounts of the base did not improve the enantioselectivity (Table 1, entries 16 and 17). The best results were achieved when the reaction was controlled at room temperature (20 °C) in THF in the presence of **1a** as the catalyst (Table 1, entries 18, 19, and 20). Other organic solvents, such as dichloromethane, toluene, and acetonitrile, have also been used for this reaction, but they were proven not as efficient as THF or dioxane. This reaction was also performed on a 0.5 mmol scale giving **3a** in a similar yield and enantioselectivity.

Encouraged by these results, we then studied the reactions of phenylboronic acid with various isatin substrates bearing a sterically hindered 1-anthracen-9-ylmethyl substituent on their nitrogen atoms under the above conditions. This resulted in the addition product **3b** in 90% yield and 53% *ee* (Table 2, entry 1). We next turned our attention to the use of alcoholic additives. Among these additive promoters, we found that aromatic phenols were promising in giving the product **3b** in higher enantioselectivity, in which naphthalen-2-ol showed the best results with a 94% yield and 94% *ee* (Table 2, entry 10).

Table 2. Additive Effects on the Reaction of Isatin **2b** with Phenylboronic Acid



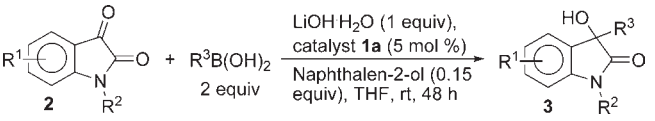
entry	additive	equiv	yield (%)[a]	*ee* (%)[b]
1	–	–	90	53 (+)
2	Anthracen-9-yl-methanol	0.15	92	75 (+)
3	9-Bromomethyl-anthracene	0.05	trace	–
4	Anthracene-9-carbaldehyde	0.15	79	74 (+)
5	Phenol	0.15	92	91 (+)
6	4-*tert*-Butyl-phenol	0.15	92	56 (+)
7	2,3,4,5,6-Pentafluoro-phenol	0.15	91	65 (+)
8	Benzene-1,2-diol	0.15	93	57 (+)
9	Naphthalen-1-ol	0.15	93	78 (+)
10	Naphthalen-2-ol	0.15	94	94 (+)

[a] Isolated yields. [b] Determined by chiral HPLC.

Since aromatic alcohols can be deprotonated by lithium hydroxide, LiOAr was readily generated and believed to act as a coadditive *via* coordination of the hard Brønsted acidic lithium with carbonyl groups of isatins; this would benefit the catalytic cycles and asymmetric outcomes.[12a]

Having established the optimal catalytic condition, a variety of isatins **2** having diverse substituents on the aromatic rings were evaluated for the reaction with various arylboronic acids. The corresponding adducts **3** were produced in high yields (up to 91%) and good enantioselectivity (up to 80% *ee*) whether they had electron-donating or electron-withdrawing substituents on their aromatic rings (Table 3, entries 1–6). Furthermore, the position of the substituents on the aromatic rings did not have a significant influence on this asymmetric addition reaction, giving the corresponding adducts in good *ee* values (Table 3, entries 2, 3, and 4–6). Moreover, isatins bearing different protection groups on the nitrogen atom can be reacted effectively under the standard conditions (Table 3, entries 7–10).

Table 3. Catalytic Asymmetric Arylation of Isatins with Arylboronic



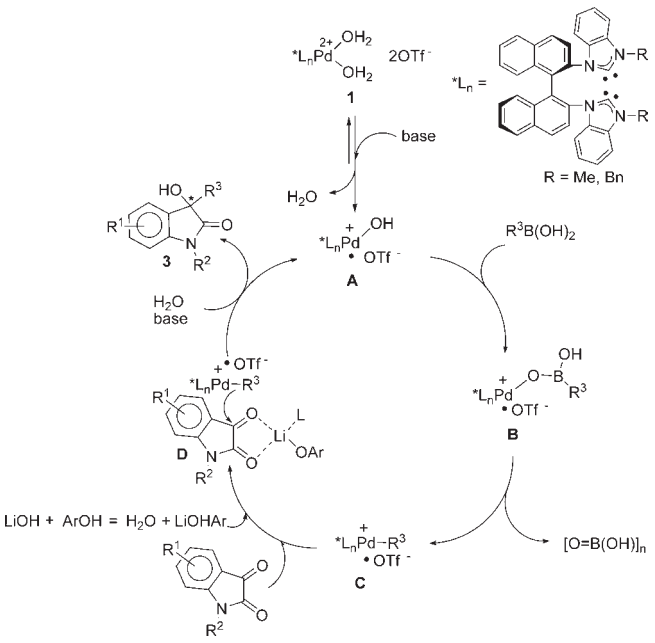
entry	R^1	R^2	R^3	yield (%)[a]	*ee* (%)[b]
1	5-Cl	1-Anthracen-9-ylmethyl (**2c**)	C_6H_5	88 (**3c**)	71 (+)
2	5-Me	1-Anthracen-9-ylmethyl (**2d**)	C_6H_5	91 (**3d**)	80 (+)
3	7-Me	1-Anthracen-9-ylmethyl (**2e**)	C_6H_5	90 (**3e**)	70 (+)
4	5-MeO	1-Anthracen-9-ylmethyl (**2f**)	C_6H_5	91 (**3f**)	60 (+)
5	6-MeO	1-Anthracen-9-ylmethyl (**2g**)	C_6H_5	89 (**3g**)	61 (+)
6	7-MeO	1-Anthracen-9-ylmethyl (**2h**)	C_6H_5	90 (**3h**)	60 (+)
7[c]	H	Bn (**2a**)	4-MeC_6H_4	89 (**3i**)	63 (+)
8[c]	H	Bn (**2a**)	4-PhC_6H_4	85 (**3j**)	60 (+)
9[c]	H	Bn (**2a**)	4-ClC_6H_4	79 (**3k**)	60 (+)
10	H	1-Trityl (**2i**)	C_6H_5	86 (**3l**)	50 (+)
11	H	1-Anthracen-9-ylmethyl (**2b**)	4-MeC_6H_4	92 (**3m**)	70 (+)
12	H	1-Anthracen-9-ylmethyl (**2b**)	4-$MeOC_6H_4$	90 (**3n**)	71 (+)
13	H	1-Anthracen-9-ylmethyl (**2b**)	4-PhC_6H_4	92 (**3o**)	82 (+)
14	H	1-Anthracen-9-ylmethyl (**2b**)	4-ClC_6H_4	90 (**3p**)	62 (+)
15	H	1-Anthracen-9-ylmethyl (**2b**)	3-MeC_6H_4	90 (**3q**)	70 (+)
16	H	1-Anthracen-9-ylmethyl (**2b**)	3-$MeOC_6H_4$	90 (**3r**)	87 (+)
17	H	1-Anthracen-9-ylmethyl (**2b**)	2-naphthyl	91 (**3s**)	65 (+)
18	H	1-Anthracen-9-ylmethyl (**2b**)	3-thienyl	90 (**3t**)	60 (+)
19	H	1-Anthracen-9-ylmethyl (**2b**)	2-trans-phenylvinyl	82 (**3u**)	60 (+)

[a] Isolated yields. [b] Determined by chiral HPLC. [c] Naphthalen-2-ol was not added.

Encouraged by these results, we finally utilized the substrates of various arylboronic acids to react with isatin **2b** under the optimal conditions. We found that the corresponding adducts **3m**–**3t** were produced in good to excellent yields (up to 92%) and moderate to good enantioselectivities (up to 87% *ee*) with a variety of aromatic

boronic acids attached by diverse substituents on their phenyl rings; even heterocyclic 3-thienylboronic acid was proven to be a suitable reactant for this reaction (Table 3, entries 11−18). In addition, phenylvinylboronic acid also resulted in the desired product **3u** in 82% yield and 60% *ee* (Table 3, entry 19).

Scheme 1. A Plausible Reaction Mechanism



A possible mechanism was proposed as shown in Scheme 1. As the first step, the cationic NHC−Pd^{2+} diaqua complex **1** was converted into the Pd hydroxo complex **A** in the presence of bases. Transmetalation of arylboronic acid with palladium species **A** gave the corresponding palladium boronate complex **B**, which underwent β-aryl elimination to acids, resulting in the palladium−aryl complex **C**. The coordination of the *in situ* generated LiOAr with isatins led to the formation of intermediate **D**. The subsequent addition of the aryl group to intermediate **D** from the favored face furnished the corresponding adduct **3** upon hydrolysis in a highly stereoselective manner along with regeneration of the active species **A** to serve the catalytic cycles.[11,12]

In conclusion, we have successfully established a new catalytic system for the enantioselective arylation of isatins with arylboronic acids by using chiral C_2-symmetric cationic NHC−Pd^{2+} diaqua complexes as the catalysts under mild conditions. This system provides easy access to biologically relevant 3-aryl-3-hydroxy-2-oxindoles in good to high yields (up to 94%) and moderate to high enantioselectivities (up to 94% *ee*). The hard Lewis acidic species, LiOAr, which was generated in situ substantially benefited the catalytic efficiency through the coordination of LiOAr with the two carbonyl groups of isatins. Further optimization of this new catalytic system and probing of the detailed mechanism are in progress in our group.

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Supporting Information Available. Experimental details and characterization data as well as the chiral HPLC. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) (a) Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 5522. (b) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240. (c) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474. (d) Tomita, D.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 6946.