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Palladium-Catalyzed Asymmetric Addition of Arylboronic Acids to Nitrostyrenes

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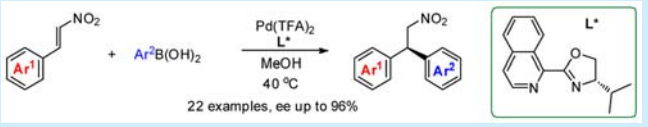
Supporting Information

ABSTRACT: A palladium-catalyzed asymmetric addition of arylboronic acids to nitrostyrene is reported. The catalytic system employing ***i*Pr-IsoQuinox** as a chiral ligand in MeOH solvent under an air atmosphere provides the chiral diarylsubstituted products in high yields with good enantioselectivities. A variety of functionalized nitrostyrenes can be used, and the method tolerates some variation in arylboronic acid scope. The stereochemical outcome can be explained using a stereochemical model.



Transition-metal-catalyzed asymmetric additions of organometallic reagents to electron-deficient double bonds represent useful strategies for the construction of C−C bonds and chiral centers, and is widely applied in total syntheses of complex chiral molecules.[1] The addition of hard organometallic reagents to electron-deficient double bonds has been well-studied, with such procedures usually employing chiral copper complexes as catalysts.[2] For additions using soft organometallic nucleophiles such as arylboron reagents (e.g., Hayashi−Miyaura reactions), rhodium complexes using chiral diphoshpines, dienes, and sulfur-olefins etc. as ligands perform as efficient catalysts showing high activity and enantioselectivity.[3] Conversely, using palladium catalysts in such reactions represents an attractive alternative due to their lower cost compared to rhodium catalysts. Therefore, considerable effort has been directed toward the development of palladium-catalyzed asymmetric additions of arylboron reagents.[4] Although several palladium catalyst systems have been developed by Miyaura,[5] Minnard,[6] Lu,[7] Shi,[8] Stoltz,[9] Jiang,[10] Zhang,[11] Hayashi/Lu,[12] and Pullarkat,[13] the substrate scope is still limited.[14]

Nitroalkene compounds, of which the nitro group can be readily manipulated after addition reactions to construct important building blocks for the synthesis of pharmaceuticals as well as natural products, have been described as "synthetic chameleons".[15] Owing to their importance, transition-metal-catalyzed additions of arylboron reagents to nitroalkenes have attracted much attention. The Hayashi group developed the first rhodium-catalyzed highly enantioselective addition of arylboronic acids to α-substituted nitroalkenes employing a Rh/Binap catalyst.[16] Diaryl-substituted chiral ternary stereocenters are common structural motifs present in a number of natural products, pharmaceuticals, and bioactive compounds.[17] To construct these types of scaffolds, the Feringa group developed a Rh/phosphoramidite catalytic system for the addition of arylboron to nitrostyrene, but generally with low enantioinduction.[18] High enantioselectivity was first achieved for simple nitrostyrene by Lin/Xu and coworkers using a chiral diene/Rh catalytic system.[19] After this report, the Liao,[20a] Wan,[20b] Wu,[20c] and Iuliano[20d] groups reported their own highly efficient rhodium catalysts. The Lu group reported the first achiral catalytic system for the palladium-catalyzed addition of phenylboronic acid to nitrostryene, but the desired product was only obtained in modest yield (only one example was described).[21] The Gutnov group reported the enantioselective addition of arylboronic acids to strongly activated 2-nitroacrylate using Miyarua's cationic chiraphos/Pd catalytic system.[22] The procedures are far from optimal; thus, the development of efficient palladium-catalyzed asymmetric additions of arylboronic acids to nitrostyrenes is still highly desired.

Inspired by the work of the Lu and Stoltz groups,[7,9,23] we recently developed a [$Pd(TFA)_2$/**Nicox**/TFE] catalytic system for the highly enantioselective addition of arylboronic acids to cyclic ketimines.[11] In continuation of our research concerning asymmetric addition reactions with nitroalkenes,[24] we herein report the first palladium-catalyzed asymmetric addition of arylboronic acids to nitrostyrenes (Scheme 1).

Using simple nitrostyrene **1a** as the standard substrate and *p*-tolylboronic acid as the boron reagent, conditions were investigated employing 5 mol % of $Pd(TFA)_2$ and 7.5 mol % of ligand (Table 1). Initially, different alcohol solvents were investigated since these types of solvents had shown special effects in our previous studies (entries 1−4).[11] We were pleased to find that the addition proceeded smoothly in MeOH to give the desired product in 85% yield with 90% ee (entry 1). The reaction showed lower enantioselectivity in EtOH; however, poor results were obtained when using TFE and *t*-AA as solvents (entries 2−4). DCE was previously found to be the best solvent for the palladium-catalyzed asymmetric addition of arylboronic acids to cyclic enones;[9] however, very low reactivity was observed

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Scheme 1. Asymmetric Addition of Arylboron to Nitrostyrene

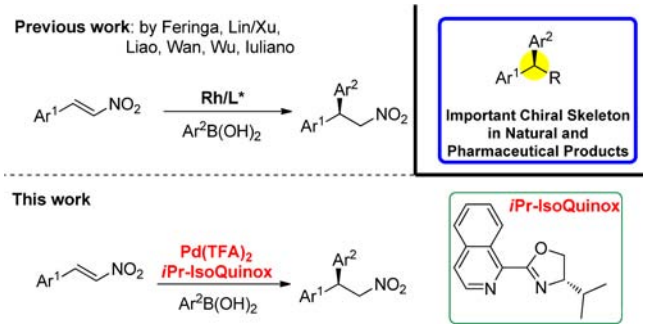
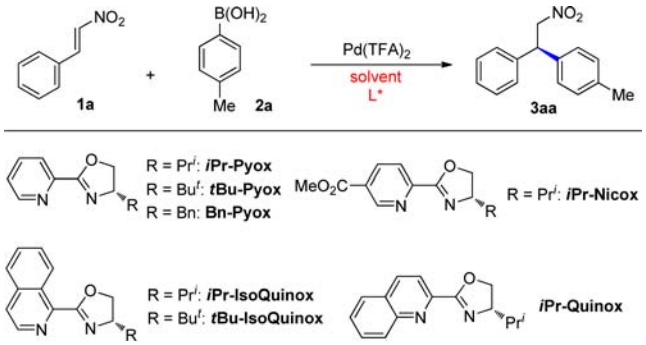


Table 1. Condition Screening[a,g]



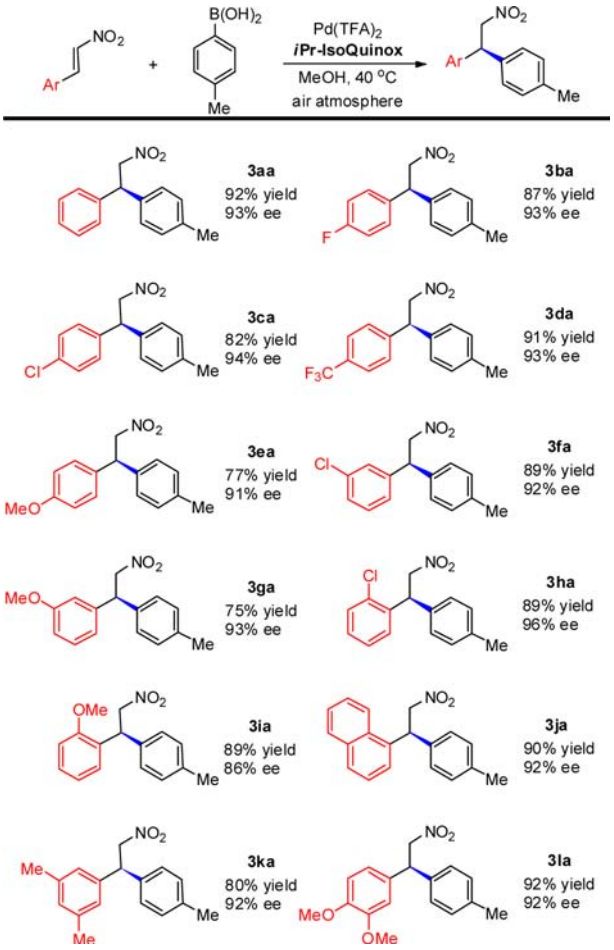
entry	solvent	ligand	yield (%)[b]	ee (%)[c]
1	MeOH	***i*Pr-Pyox**	85	90
2	EtOH	***i*Pr-Pyox**	86	86
3	TFE	***i*Pr-Pyox**	43	60
4	*t*-AA	***i*Pr-Pyox**	16	75
5	DCE	***i*Pr-Pyox**	19	71
6	toluene	***i*Pr-Pyox**	NR	–
7	DMF	***i*Pr-Pyox**	42	60
8	DMSO	***i*Pr-Pyox**	NR	–
9	MeOH	***t*Bu-Pyox**	82	81
10	MeOH	**Bn-Pyox**	91	85
11	MeOH	***i*Pr-Nicox**	84	87
12	MeOH	***i*Pr-Quinox**	NR	–
13[d]	MeOH	***t*Bu-IsoQuinox**	91	91
14	**MeOH**	***i*Pr-IsoQuinox**	**92**	**93**
15[e]	MeOH	***i*Pr-IsoQuinox**	92	93
16[f]	MeOH	***i*Pr-IsoQuinox**	86	93

[a]Reactions were carried out on a 0.20 mmol scale using 5 mol % $Pd(TFA)_2$, 7.5 mol % ligand and *p*-Me-$C_6H_4B(OH)_2$ (0.30 mmol) in unpurified solvent (1.0 mL) at 40 °C for 24 h under an air atmosphere. [b]Yield of isolated product. [c]Determined by HPLC using a chiral Daicel column. The absolute configuration was determined by comparing the optical rotation and retention time of **3aa** with that of the literature.[19,20] [d]Reaction time was 45 h. [e]The reaction was carried out in O_2 (balloon). [f]The reaction was carried out in N_2. [g]TFA = trifluoroacetic acetate, TFE = trifluoroethanol, *t*-AA = *tert*-Amyl alcohol; DCE = 1,2-dichloroethane.

for the linear nitrostyrene substrate (entry 5). DMF, DMSO, and toluene inhibited the addition reaction, either completely or partially (entries 6–8). Subsequently, ligand screening was conducted (entries 9–14). An *i*Pr group at the chiral position showed the best chiral inducing ability (entries 1 vs 9,10). **Nicox** bearing a CO_2Me group on the pyridine gave the desired product with lower enantioselectivity (entry 11). No reaction occurred using the sterically hindered ligand **Quinox** (entry 12). Interestingly, the **IsoQuinox** chiral ligand performed well with higher enantioselectivities (entries 13 and 14). Finally, reaction under an O_2 atmosphere gave comparable results to that of reactions carried out under air, but slightly lower yields were obtained under a N_2 atmosphere (entries 15 and 16). Thus, the optimized reaction conditions were found to include using ***i*Pr-IsoQuinox** as the chiral ligand in MeOH solvent under an air atmosphere.

With the optimized conditions in hand, we tested the substrate scope using *p*-tolylboronic acid as a nucleophile (Scheme 2).

Scheme 2. Substrate Scope[a,b,c]



[a]Reactions were carried out on a 0.20 mmol scale using 5 mol % $Pd(TFA)_2$, 7.5 mol % ligand, and *p*-Me-$C_6H_4B(OH)_2$ (0.30 mmol) in MeOH (1.0 mL) at 40 °C for 24 h under an air atmosphere. [b]Yield of isolated product. [c]Ee was determined by HPLC using a chiral Daicel column.

Both electron-withdrawing and -donating groups are well tolerated (**3aa**–**3ia**). Substrates bearing electron-withdrawing groups at the *para* or *meta* positions showed higher reactivity than those bearing electron-donating groups, although the enantioselectivities are similar (**3aa**–**3ga**). The highest ee was obtained when the *ortho* position was substituted with a Cl group (**3ha**). However, substitution at the *ortho* position with an OMe group gave the lowest ee (**3ia**). Fused-ring substrates and disubstituted substrates are also compatible with the reaction conditions and gave their corresponding products in high yields with high enantioselectivities (**3ja**–**3la**). However, no reaction occurred using aliphatic nitroalkene as the substrate.

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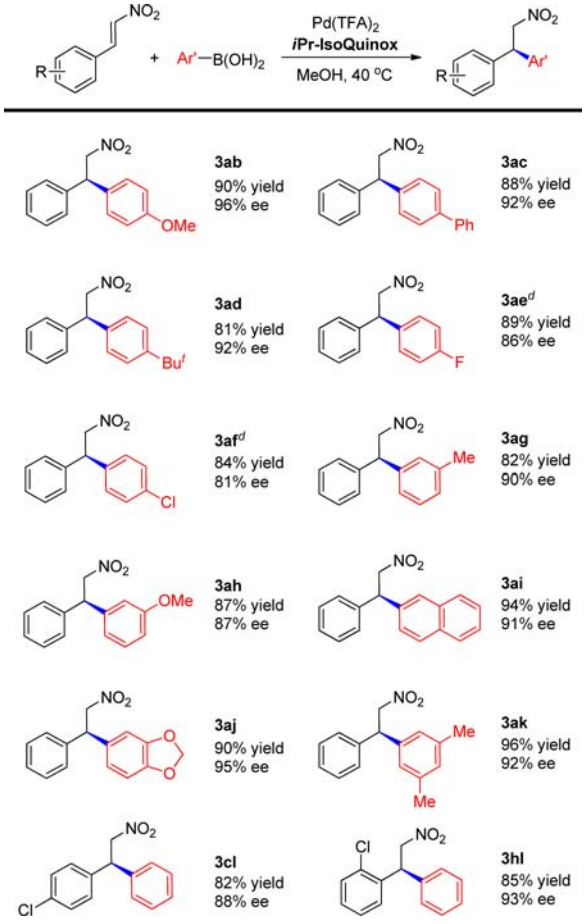
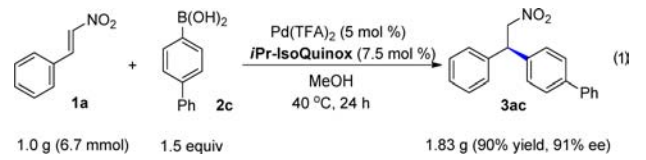
The arylboronic acid scope was also investigated (Scheme 3). Electron-rich arylboronic acids are more reactive than electron-deficient ones due to the higher nucleophilicity of the more electron-rich aryl group (**3ab**–**3af**). The ee decreased when using eletron-deficient arylboronic acids (**3ae** and **3af**). Arylboronic acids possessing *meta*-substituents also gave the addition products in high yields, but with slightly lower ee's (**3ag**, **3ah**). The addition of naphthyl boronic acid also showed high reacitivity and enantioselectivity (**3ai**). The use of piperonyl boronic acid resulted in the highest ee (**3aj**). A good yield and ee were also obtained for a diMe-substituted arylboronic acid (**3ak**). Additions of phenylboronic acid were examined using *p*-Cl and *o*-Cl nitrostyrene. Both substrates were converted to the desired products with good results (**3cl** and **3hl**).

Scheme 3. Arylboronic Acid Scope[a,b,c]



[a]Reactions were carried out on a 0.20 mmol scale using 5 mol % $Pd(TFA)_2$, 7.5 mol % ligand, and arylboronic acid (0.30 mmol) in MeOH (1.0 mL) at 40 °C for a certain time under an air atmosphere. [b]Yield of isolated product. [c]Ee was determined by HPLC using a chiral Daicel column. [d]Reaction time was 65 h.

To test the practicality of our methodology, a gram-scale reaction using substrate **1a** and boronic acid **2c** was carried out (eq 1). The product **3ac** was obtained with results comparable to those shown in Scheme 3 using the same reaction conditions. When 1 mol % of catalyst was used, the reactivity was lowered but the ee was still high (57% yield with 92% ee; see Supporting Information).



The chiral induction can be explained using the model shown in Figure 1.[25] The nucleophilic aryl group coordinated to the Pd center is *trans* to the oxazoline of **IsoQuinox**, and the nitrostyrene is *cis* to the oxazoline. The sterically disfavored intermediate (**B**), in which the substrate coordinates to the palladium with the $-NO_2$ group oriented downward (*si*-face) close to the isopropanyl group of **IsoQuinox**, leads to the optically minor product (*S*)-**3aa**. DFT calculations showed that the energy of the transition state $\mathbf{Ts}^S$ was 8.3 kcal/mol. The intermediate **A** is more sterically favored. The energy of the corresponding transition state $\mathbf{Ts}^R$ is 4.5 kcal/mol.

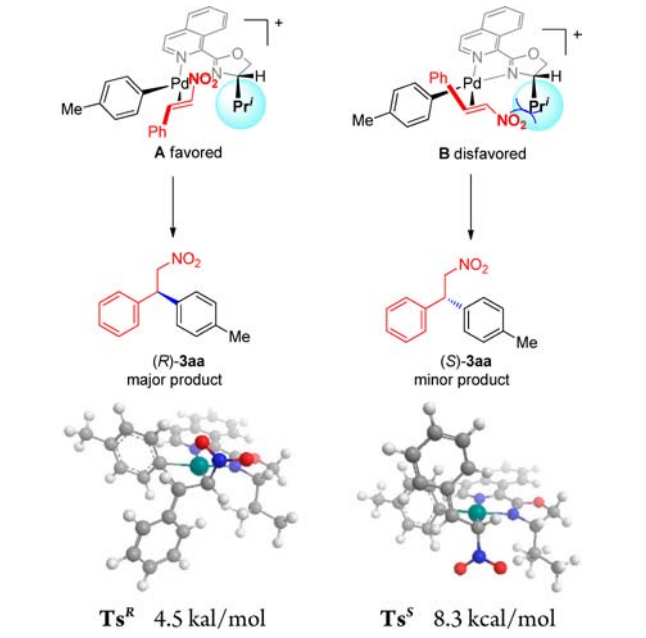


Figure 1. Stereochemical model.

In conclusion, a palladium-based catalytic system was developed for the asymmetric addition of arylboronic acids to nitrostyrenes. The catalyst system provided the desired chiral nitro products with good enantioselectivities and yields (up to 96% ee and 96% yield). A range of nitrostyrenes and arylboronic acids are tolerant to the reaction conditions. A stereochemical model was also proposed to explain the chiral induction during the catalytic cycle.

■ ASSOCIATED CONTENT

Supporting Information

Experimental section and copies of NMR and HPLC spectra. 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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