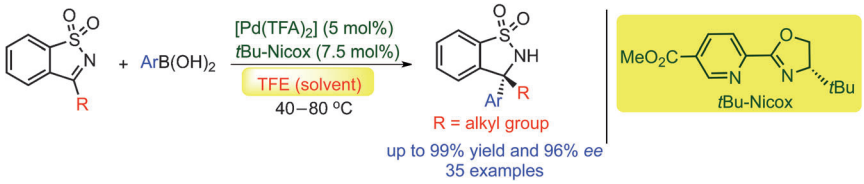
Communications

Asymmetric Catalysis

G. Yang, W. Zhang* _____ ■■■■–■■■■

A Palladium-Catalyzed Enantioselective Addition of Arylboronic Acids to Cyclic Ketimines



Sly as Nicox: A palladium-catalyzed addition of arylboronic acids to ketimines has been developed to efficiently provide products in up to 99% yield and 96% *ee*. The reactions could be run under aerobic conditions and with unpurified trifluoroethanol (TFE). A pyrrolidine compound bearing a chiral α-tertiary amine was synthesized in several steps without loss of enantioselectivity. TFA = trifluoroacetate.

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A Palladium-Catalyzed Enantioselective Addition of Arylboronic Acids to Cyclic Ketimines**

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The construction of chiral quaternary stereocenters by asymmetric catalysis remains a challenging proposition for chemists.[1,2] Chiral α-tertiary amines reside within a wide assortment of potent drugs and bioactive natural products, therefore considerable effort has been directed toward their asymmetric synthesis.[2] Among reactions involving the construction of chiral α-tertiary amines,[3–9] asymmetric addition to ketimines is a powerful strategy. Organocatalytic and chiral Lewis acid catalyzed nucleophilic additions to ketimines have been reported for the synthesis of chiral α-tertiary amines.[4,5] Another convenient method involves the transition metal catalyzed enantioselective addition of organometallic nucleophiles. Despite the great advances in asymmetric transition metal catalyzed additions of organometallic reagents to imines,[10,11] the development of such reactions towards the construction of chiral α-tertiary amines has had limited success because of the steric and electronic factors.[2,6–9] Several reports have described the copper- or zirconium-catalyzed asymmetric addition of allylboronates or dialkylzinc reagents to ketimines.[7] Alternatively, Hayashi and coworkers pioneered rhodium-catalyzed asymmetric additions for several kinds of ketimines and arylboron reagents with various functional groups.[8,9] Although valuable progress has been made, the asymmetric addition of arylboron reagents to ketimines to give chiral α-diaryl alkyl amines (important components of potent drugs)[12] suffers from limited substrate scope.[8a,b] The asymmetric addition of arylboronic acids to ketimines, is therefore still highly desired.

Palladium catalysis is a very attractive area for both academia and industry. Although it has been applied to conjugate addition reactions involving arylboron reagents,[13] the palladium-catalyzed addition of arylboronic acids to imines has become feasible only recently.[14] Subsequently, several asymmetric approaches have been developed for aldimine substrates,[14c–h] and chiral bidentate N-heterocyclic carbene palladium catalysts have shown excellent catalytic activity.[14e] However, there are still no reports concerning the palladium-catalyzed addition of arylboronic acids to ketimines (including the reaction producing racemic products), and this may be due to the less nucleophilic nature of the arylpalladium species compared with that of the arylrhodium species.[15] Herein, we report the first ligand- and solvent-assisted palladium-catalyzed addition of arylboronic acids to ketimines, thus representing a practical enantioselective synthesis of chiral α-diaryl alkyl amines under either an air or oxygen atmosphere.

Recently, saccharin-derived cyclic ketimines bearing aryl or carboxy substituents have been studied in the rhodium-catalyzed addition of arylboron reagents because of the stable geometry and low electron density of the C=N bond.[8c,d] However, the addition of boronic acids to the slightly electron-donating, alkyl-substituted, saccharin-derived cyclic ketimines has never been explored. Additionally the sultam products are an intriguing class of synthetic targets.[16] Thus, the alkyl-substituted ketimine **1** was chosen as the substrate for our palladium-catalyzed addition reaction. Using the *n*-butyl-substituted **1a** as the standard substrate, reaction conditions for the palladium-catalyzed enantioselective addition of phenylboronic acid to the cyclic ketimine were investigated (Table 1). Initial solvent screening showed that catalysis in MeOH provided the most promising result (entry 1; and see the Supporting Information). This may be due to the beneficial effect MeOH has on the rate of the transmetalation and protonation steps of the catalytic cycle.[13m,p] Palladium black was formed in most of the other tested solvents. Subsequently, different chiral pyridine-oxazoline-type ligands were screened (entries 1–8). *i*Pr-Pyrox provided the best results compared to *i*Pr-Quinox and *i*Pr-Pyrim (entry 1 versus entries 2 and 3). The highest enantioselectivity was achieved when a *t*Bu substituent was attached to the oxazoline ring of Pyrox (92% *ee*), however reaction yield was poor because of the steric hindrance (entry 7 versus entries 1 and 4–6). It has been reported that an electron-deficient ligand may improve palladium-catalyzed addition reactions.[13q,14d] Therefore, *t*Bu-Nicox was tested and a slightly higher *ee* value and yield were obtained (entry 8).[17] Considering the formation of palladium black was due to the low rate of the addition reaction and high rate of homocoupling, two simple methods were considered to resolve this problem. One method involved using oxygen to oxidize the Pd^0 species to regenerate the catalyst Pd^{II} with the help of a pyridine-oxazoline-type ligand.[3i,18] The other method involved performing the catalysis in the more polar and protic solvent, TFE, which can stabilize the intermediates and transition state of addition by decreasing the charge density, and

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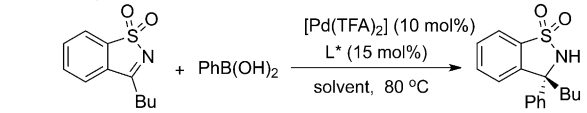
Table 1: Optimization of reaction conditions.[a]



1a **2aa**

Entry	Sol.	L*	*t* [h]	Yield [%][b]	*ee* [%][c]
1	MeOH	*i*Pr-Pyrox	48	96	70
2	MeOH	*i*Pr-Quinox	48	47	−9
3	MeOH	*i*Pr-Pyrim	48	56	69
4	MeOH	Bn-Pyrox	48	94	70
5	MeOH	*i*Bu-Pyrox	48	95	73
6	MeOH	Ph-Pyrox	48	89	76
7[d]	MeOH	*t*Bu-Pyrox	48	26	92
8[d]	MeOH	*t*Bu-Nicox	48	35	94
9[d,e]	MeOH	*t*Bu-Nicox	48	67	94
10[e]	TFE	*t*Bu-Nicox	1	99	92
11[e]	TFE	*t*Bu-Pyrox	24	78	89
12[e,f]	TFE	*t*Bu-Nicox	24	99	96
13[f,g]	TFE	*t*Bu-Nicox	24	99	95

[a] Reactions were carried out in air on a 0.20 mmol scale using 10 mol% $[Pd(TFA)_2]$, 15 mol% ligand in purified solvent (2.0 mL) and $PhB(OH)_2$ (0.40 mmol) at 80 °C in a sealed tube. [b] Yield of isolated product. [c] Determined by HPLC using a chiral Daicel column. [d] Palladium black was formed. [e] Charged with oxygen. [f] Using 5 mol% $Pd(TFA)_2$, 7.5 mol% ligand and 1.5 equiv of $PhB(OH)_2$ at 40 °C. [g] In a test tube which was opened to air. TFA = trifluoroacetic acetate, TFE = trifluoroethanol.

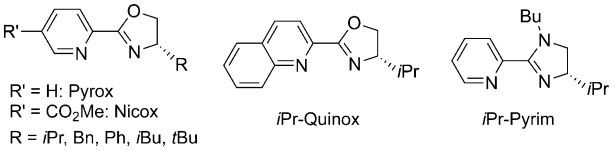
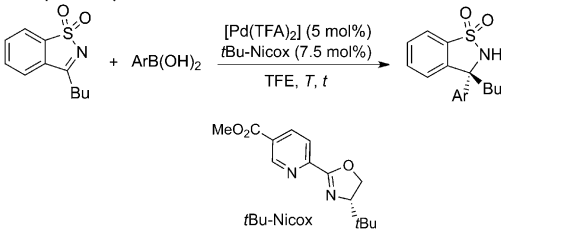


Table 2: Scope of arylboronic acids.[a]

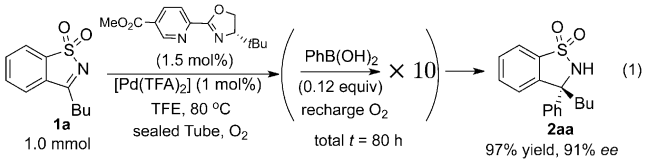


Entry	Ar	*T* [°C]	*t* []h	Yield [%][b]	*ee* [%][c]
1	Ph	40	24	99	95
2	4-MeC_6H_4	40	24	99	94
3[d]	4-$MeOC_6H_4$	40	12	98	90
4	4-PhC_6H_4	40	24	95	95
5	4-ClC_6H_4	60	26	99	94
6	4-FC_6H_4	60	16	99	94
7	4-$MeO_2CC_6H_4$	60	24	59 (78)[e]	94
8[e,f]	4-$CF_3C_6H_4$	80	48	95	93
9	3-MeC_6H_4	40	12	99	95
10[d]	3-$MeOC_6H_4$	40	18	99	95
11[e]	3-ClC_6H_4	60	48	87	92
12	3-$MeO_2CC_6H_4$	60	24	69 (84)[e]	95
13[e,f,g]	2-FC_6H_4	80	48	47	87
14[f,g]	2-$MeOC_6H_4$	80	48	ca. 15[h]	–
15	3,5-$Me_2C_6H_3$	40	12	99	95
16[d]	3,4-$(OCH_2O)C_6H_3$	40	12	99	93
17	2-naphthyl	40	24	74 (87)[e]	96
18[e]	3-thienyl	80	24	89	90

[a] Reactions were carried out in air on a 0.20 mmol scale using 5 mol% $Pd(TFA)_2$, 7.5 mol% ligand and $ArB(OH)_2$ (0.30 mmol) in unpurified TFE (2.0 mL) at a certain temperature in a test tube which was opened to air. [b] Yield of isolated product. [c] Determined by HPLC using a chiral Daicel column. [d] With 1.8 equiv of $ArB(OH)_2$. [e] Sealed tube charged with oxygen. [f] Using 10 mol% $Pd(TFA)_2$ and 15 mol% ligand. [g] With 2.0 equiv of $ArB(OH)_2$. [h] Determined by ^1H NMR spectroscopy.

improve the protonation step. Both of these improved the reaction outcome (entries 9 and 10). In TFE, the importance of the electron-deficient nature of *t*Bu-Nicox was observed (entry 10 versus 11). Furthermore, the effects of TFE and *t*Bu-Nicox were so strong that the catalysis could be carried out at 40 °C with lower catalyst and phenylboronic acid loading (5 mol% cat., 1.5 equiv of $PhB(OH)_2$) (entry 12). Notably, the reaction was insignificantly affected by performing the catalysis in unpurified TFE under "open to air" conditions (entry 13 versus 12).

The catalyst loading could be lowered to 1 mol% by the sequential addition of phenylboronic acid [Eq. (1)]. A one-portion addition of 1.2 equivalents of phenylboronic acid resulted in the formation of palladium black on trace amounts of product.

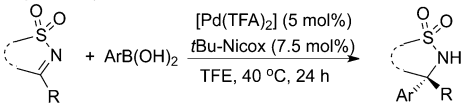


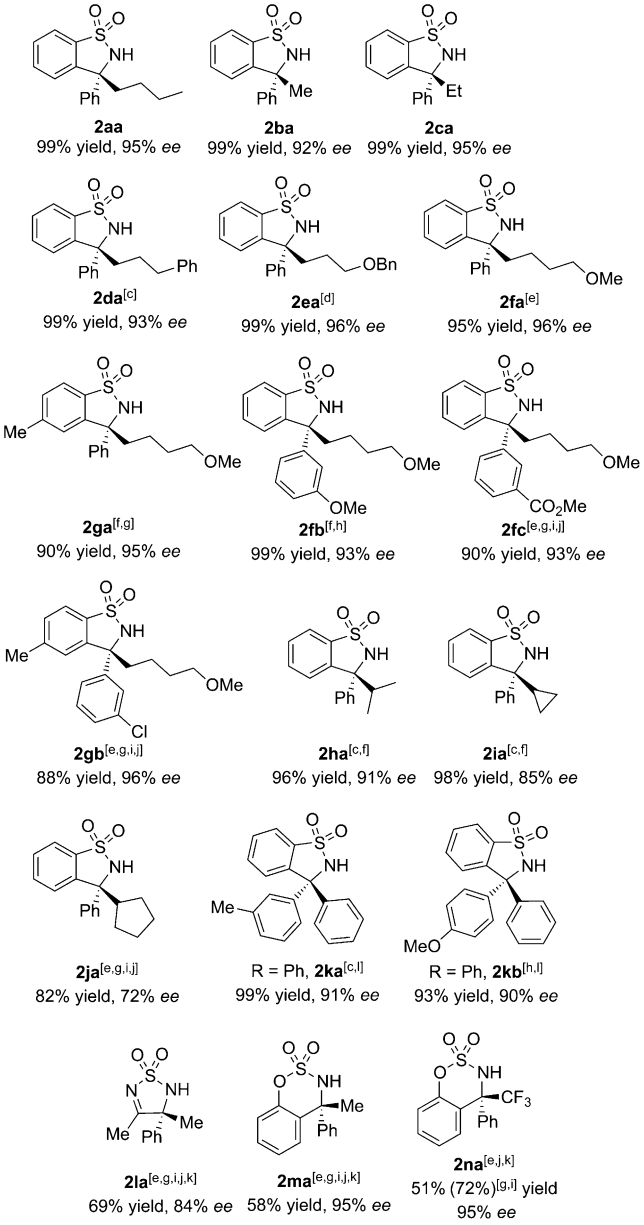
(1)

Having identified the catalytic system, a variety of arylboronic acids were examined for addition to substrate **1a** (Table 2). Electron-rich and electron-deficient arylboronic acids had little influence on enantioselectivity (entries 1–12). Excellent yields were obtained for most of the reactions using electron-rich and electron-deficient arylboronic acids (entries 1–12). However, a decrease in reaction rate was observed when electron-deficient arylboronic acids were used (entries 5, 7, 8, 11, and 12). *ortho*-Substituents on the arylboronic acids dramatically decreased the enantioselectivity and catalytic activity (entries 13 and 14), and arylboronic acids possessing two substituents gave good results (entries 15 and 16). Fused-ring aryl or heteroaryl boronic acids could also be used as the nucleophiles, thus providing the α-tertiary amines in high *ee* values, albeit with slightly lower yields (entries 17 and 18).

The ketimine substrate scope was also investigated (Table 3). A range of ketimines possessing alkyl substituents were tolerable to the enantioselective palladium-catalyzed addition reaction (**2aa–ga**, **2fb**, **2fc**, **2gb**, **2ha–ja**). All of the substrates with linear alkyl groups, including alkoxy-functionalized substituents, gave excellent yields and good *ee* values (**2aa–ga**, **2fb**, **2fc**, **2gb**). The catalytic additions involving 5-methyl-substituted ketimine gave the corresponding products in high *ee* values (**2ga** and **2gb**). The *ee* values and yields of the catalysis involving substrates with branched and cyclic alkyl substituents decreased (**2ha–ja**). Interestingly, the reaction of phenyl-substituted substrates provided products in good results (**2ka** and **2kb**). Finally, the more electron-rich

Table 3: Scope of arylboronic acids.[a]





[a] Reactions were carried out in air on a 0.20 mmol scale using 5 mol% $Pd(TFA)_2$, 7.5 mol% ligand and $ArB(OH)_2$ (0.30 mmol) in unpurified TFE (2.0 mL) at 40 °C in a test tube for 24 h which was opened to air. [b] Yield of isolated product. The *ee* values were determined by HPLC using a chiral Daicel column. [c] 36 h. [d] 18 h. [e] 80 °C. [f] 60 °C. [g] Sealed tube charged with oxygen. [h] With 1.8 equiv of $ArB(OH)_2$ for 12 h. [i] Using 10 mol% $Pd(TFA)_2$ and 15 mol% ligand. [j] 48 h. [k] Another 1.5 equiv of $PhB(OH)_2$ was added after 24 h. [l] The absolute configurations of **2ka** and **2kb** were determined to be *R* by comparison of its optical rotation and HPLC retention time with the literature value.[8c,d] The others were proposed according to this result.

ketimine substrates, the products of which also may be synthetically useful, showed lower reactivity but provided high enantioselectivities (**2la** and **2ma**). These kinds of substrates remain a challenge for our catalytic system. The electron-withdrawing alkyl group CF_3 could improve the reactivity of the substrate, thus giving the product in better yield (72% under O_2, 51% open to air), but has no effect on the enantioselectivity (**2na** versus **2ma**).

The stereochemical outcome can be explained using a model shown in Figure 1. The nucleophilic aryl group

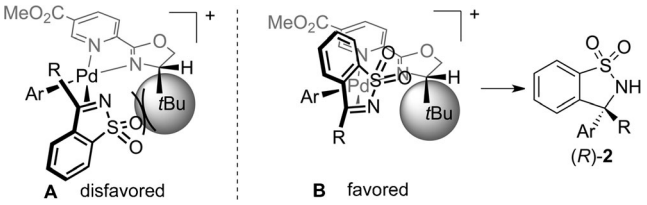
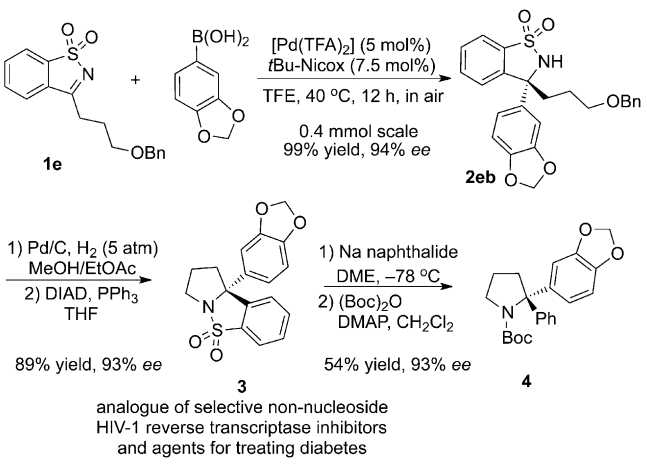


Figure 1. Stereochemical model.

bound to the Pd center is *cis* to the pyridine of Nicox, and the imine is *trans* to the pyridine. The sterically favored intermediate **B**, wherein the substrate coordinates to the palladium with the -SO_2- group oriented upward, (*re*-face) away from the *tert*-butyl group of Nicox, leads to the optically major product being the one we obtained.

A short synthesis of the chiral pyrrolidine compound **4** was also conducted (Scheme 1). The enantioselective cata-



Scheme 1. Transformations of chiral product. Boc = *tert*-butoxycarbonyl, DIAD = diisopropylazodicarboxylate, DMAP = 4-(dimethylamino)pyridine, DME = 1,2-dimethoxyethane, THF = tetrahydrofuran.

lytic addition of piperonylboronic acid to substrate **1e** provided the product **2eb** with good *ee* value and in 99% yield. The chiral polycyclic compound **3**, an analogue of selective non-nucleoside HIV-1 reverse transcriptase inhibitors[12a] and agents for treating diabetes,[12b] was obtained by benzyl removal from **2eb** and subsequent Mitsunobu reaction. No loss of enatiomeric purity was observed. This product could be further transformed in moderate overall yield to the pyrrolidine structure **4**, thus bearing a chiral α-tertiary amine motif (93% *ee*) through removal of the SO_2 group and installation of the Boc group.

In summary, we have developed the first catalytic system of the palladium-catalyzed addition of arylboronic acids to ketimines. The catalysis is highly efficient with good enantioseletivities and yields (up to 96% *ee* and 99% yield). Additionally, the majority of the reactions could be performed in open air and with unpurified TFE solvent. A wide range of cyclic N-sufonyl ketimines and arylboronic acids are tolerated under the reaction conditions.

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