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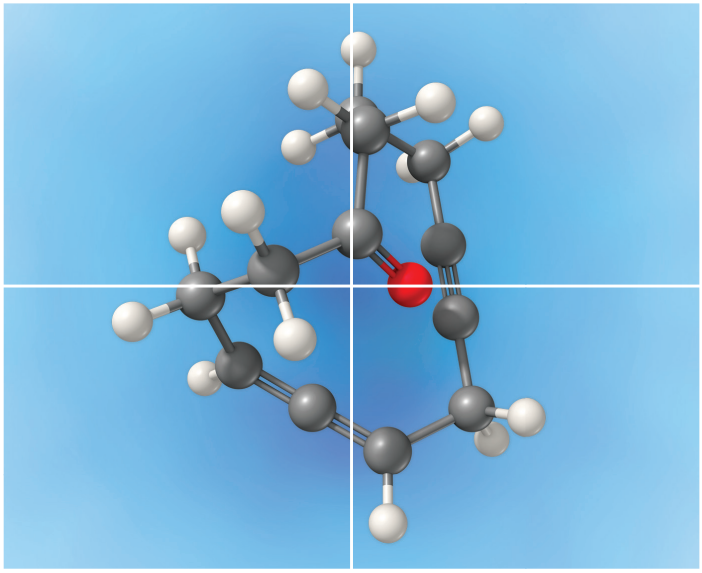

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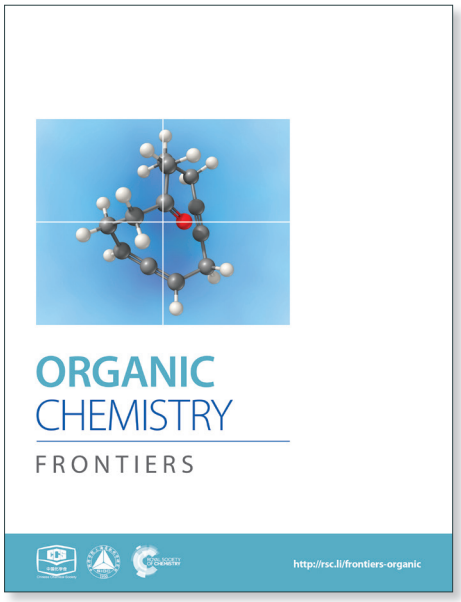

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ARTICLE TYPE

Pd(II)-catalyzed asymmetric addition of arylboronic acids to cyclic *N*-sulfonyl ketimine esters and a DFT study of its mechanism

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Dedicated to Professor Ei-ichi Negishi on the occasion of his 80th birthday

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A palladium-catalyzed asymmetric arylation of cyclic *N*-sulfonyl ketimine esters is described. The desired products could be prepared with excellent yields (up to 99%) and enantioselectivities (up to 99% ee) under mild reaction conditions. Furthermore, a possible reaction mechanism was determined using DFT calculations.

1. Introduction

The asymmetric formation of chiral tetrasubstituted carbon centers remains a challenge until now.[1] Chiral α-tertiary amines exist in numerous natural products and drugs,[2] thus many chemists are interested in their synthesis.[3] Among reactions involving the construction of chiral α-tertiary amines, the metal-catalyzed asymmetric addition to imines represents a powerful methodology for the synthesis of chiral α-tertiary amines.[4-9] Several groups have focused their research efforts towards the metal-catalyzed addition of arylboronic acids to ketimines.[5-9] The Hayashi group[6] has pioneered the rhodium-catalyzed asymmetric addition of arylboron reagents to ketimines which possess various functional groups. In addition, the groups of Lam,[7] Xu,[8] and Lin[9] have also reported the rhodium-catalyzed asymmetric addition of arylboron reagents to ketimines. Alternatively, using palladium catalysts in the same reaction is an attractive methodology because of their lower cost compared to rhodium catalysts.[10-13] The Lu group[11a-b] has pioneered the palladium-catalyzed asymmetric addition of arylboronic acids to aldimines. Besides, several other groups have also reported related studies.[11c-f] However, examples concerning the palladium-catalyzed asymmetric addition of arylboronic acids to ketimines are rare. Only recently, our group[12] and Lu/Hayashi[13] reported two different catalytic systems utilizing palladium catalysts for the arylation of cyclic *N*-sulfonyl ketimines. Therefore, more studies in this area are highly desired.

α-Tertiary amino esters reside within a wide assortment of natural products and drugs[14] and can be easily converted to unnatural amino acids and amino alcohols, which possess greater potential value. In addition, to the best of our knowledge, there is no precedent for mechanistic studies concerning the palladium-catalyzed arylation of imines. Herein we report a synthesis of α-tertiary amino esters via the palladium-catalyzed asymmetric addition of arylboronic acids to cyclic *N*-sulfonyl ester imines. Furthermore, the mechanism of this reaction has been studied using DFT calculations.

2. Results and Discussion

We realized an efficient Pd-catalyzed arylation of substrate **1a** using (*S*)-methyl-6-(4-*tert*-butyl-4,5-dihydrooxazol-2-yl)nicotinate (**L1a**) as a chiral ligand, $Pd(TFA)_2$ as Pd source in TFE at 60 °C (98% ee; Table 1, entry 1). Table 1 provides information on the impact of various reaction parameters on the efficiency of this catalytic asymmetric synthesis of α-tertiary amino esters. When different chiral pyridine-oxazoline-type ligands were tested, product yields were all excellent and **L1a** gave the best ee (entries 1-6). The enantioselectivity decreased with smaller *R* groups at the chiral position of the ligand (entries 1-3 and entries 4-6). The COOMe group on the pyridine ring plays an important role in enantioselectivity (entries 1 vs 4, 2 vs 5, 3 vs 6, respectively). Different palladium salts were also investigated. When $Pd(OAc)_2$ was tested, both the enatioselectivity and yield decreased (entry 7). However, only a trace amount of product was obtained and most of the reactant was recovered when $PdCl_2$ was used, probably due to the strong coordinating ability of the chloride ion to palladium. In our previous work,[12] alcohols had a beneficial effect on the rate of the transmetalation and protonation steps of the catalytic cycle, thus MeOH and EtOH were also screened as solvents (entries 9-11). However, only trace amounts of the desired product were detected in these cases. When reaction was

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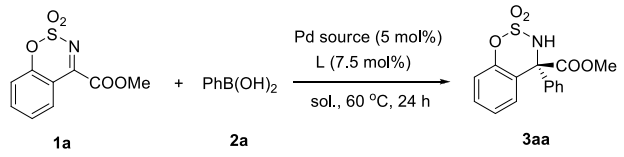
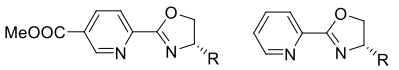
† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

Table 1 Conditions screening[a]



1a 2a 3aa



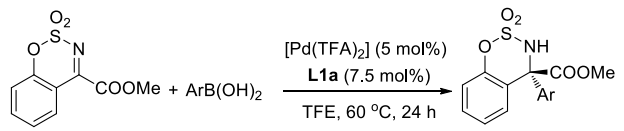
L1a: R = *t*Bu
L1b: R = *i*Pr
L1c: R = Bn

L2a: R = *t*Bu
L2b: R = *i*Pr
L2c: R = Bn

Entry	Ligand	Pd source	Solvent	Yield (%)[b]	ee (%)[c]
1	**L1a**	$Pd(TFA)_2$	TFE	99	98
2	**L1b**	$Pd(TFA)_2$	TFE	99	73
3	**L1c**	$Pd(TFA)_2$	TFE	99	50
4	**L2a**	$Pd(TFA)_2$	TFE	99	87
5	**L2b**	$Pd(TFA)_2$	TFE	92	62
6	**L2c**	$Pd(TFA)_2$	TFE	96	50
7	**L1a**	$Pd(OAc)_2$	TFE	82	93
8	**L1a**	$PdCl_2$	TFE	trace	--
9[d]	**L1a**	$Pd(TFA)_2$	MeOH	trace	--
10[d]	**L1a**	$Pd(TFA)_2$	EtOH	trace	--
11[e]	**L1a**	$Pd(TFA)_2$	EtOH	trace	--
12[f]	**L1a**	$Pd(TFA)_2$	TFE	90	98

[a] Reactions were carried out in air on a 0.20 mmol scale using 10 mol% PdX_2, 15 mol% ligand in unpurified solvent (2.0 mL) and $PhB(OH)_2$ (0.30 mmol) at 60 °C in a test tube for 24 h which was opened to air. [b] Yield of isolated product. [c] Determined by HPLC using a chiral Daicel column. [d] Palladium black was formed. [e] Charged with oxygen in a sealed tube. TFA= trifluoroacetic acetate, TFE= trifluoroethanol. [f] The reaction was carried out in N_2.

Table 2 Scope of arylboronic acids[a]



1a 2a-2j 3aa-3aj

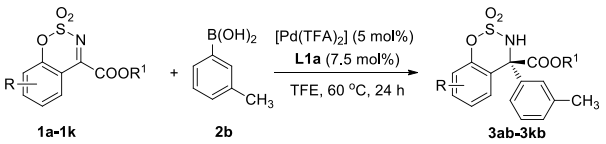
Entry	2	Ar	Yield (%)[b]	ee (%)[c]
1	**2a**	C_6H_5	99	98
2	**2b**	3-MeC_6H_4	99	99
3	**2c**	4-MeC_6H_4	99	98
4	**2d**	4-$MeOC_6H_4$	99	99
5	**2e**	4-PhC_6H_4	92	99
6[c]	**2f**	4-FC_6H_4	90	98
7[c]	**2g**	4-ClC_6H_4	94	98
8[c]	**2h**	4-BrC_6H_4	92	98
9[c, d]	**2i**	4-$MeO_2CC_6H_4$	52	97
10[c, d]	**2j**	2-naphthyl	74	99
11[c, d, e]	**2k**	3-thienyl	67	96

[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 60 °C in a test tube for 24 h which was opened to air. [b] Isolated yields. Ees were determined by chiral HPLC. [c] 80 °C. [d] Sealed tube charged with oxygen. [e] 36 h.

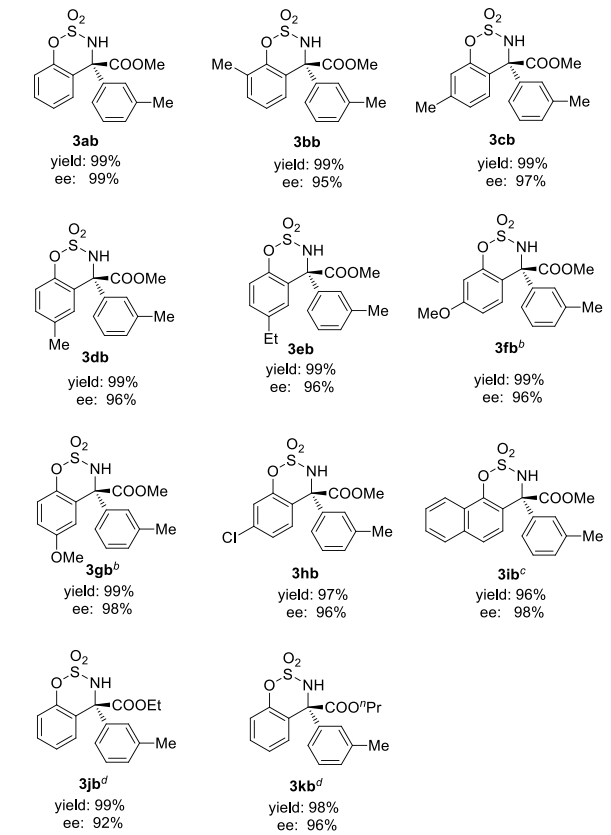
carried out under N_2 atmosphere, slightly lower yield was obtained with no change of ee (entry 12). Probably because some Pd (0) was formed by self-coupling of phenylboronic acid, which can't be oxidized to catalytic active Pd(II) by O_2 under N_2 atmosphere.

With the optimized conditions in hand, the arylboronic acid scope was examined, as shown in table 2. The results showed that arylboronic acids bearing electron-donating substituent groups on the benzene ring gave excellent yields and enantioselectivities (**3aa-3ae**). Slightly electronic-deficient arylboronic acids also have good results but the temperature needed to be increased to 80 °C (**3af-3ah**). However, a decrease in reaction rate was observed for arylboronic acids bearing a COOMe group (**3ai**). Fused-ring aryl or heteroaryl boronic acids also gave excellent ees but only moderate yields (**3aj-3ak**).

Table 3 Scope of substrates[a]



1a-1k 2b 3ab-3kb



[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 60 °C in a test tube for 24 h which was opened to air. The yields were isolated yields and ees were determined by chiral HPLC. [b] 36 h. [c] 48 h. [d] Charged with oxygen in a sealed tube.

The substrate scope was also investigated and the results are

summarized in table 3. They show that substrates possessing both electron-donating and electron-withdrawing substituents gave the corresponding products with excellent yields and enantioselectivities (**3bb-3hb**). Furthermore, the substitution position on the benzene ring has little influence on the results, and excellent yields and ees could be obtained in all cases (**3bb-3db**). Additionally, when the aryl group was changed to naphthyl, good ee was also observed but a prolonged reaction time was required (**3ib**). However, reactivity decreased sharply for substrates bearing COOEt or COO^{n}Pr ester groups. Thus, a sealed tube charged with oxygen was required to give the desired products with excellent yields and ees (**3jb-3kb**).

The asymmetric arylation product **3cb** could be reduced to unnatural amino alcohol **4**, with the -SO_2- group deprotected at the same time. The yield was high and the ee value was increased to 99.9% (**Scheme 1**).[7a]

Scheme 1 Reduction of arylation product **3cb**.

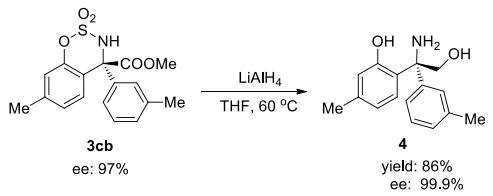
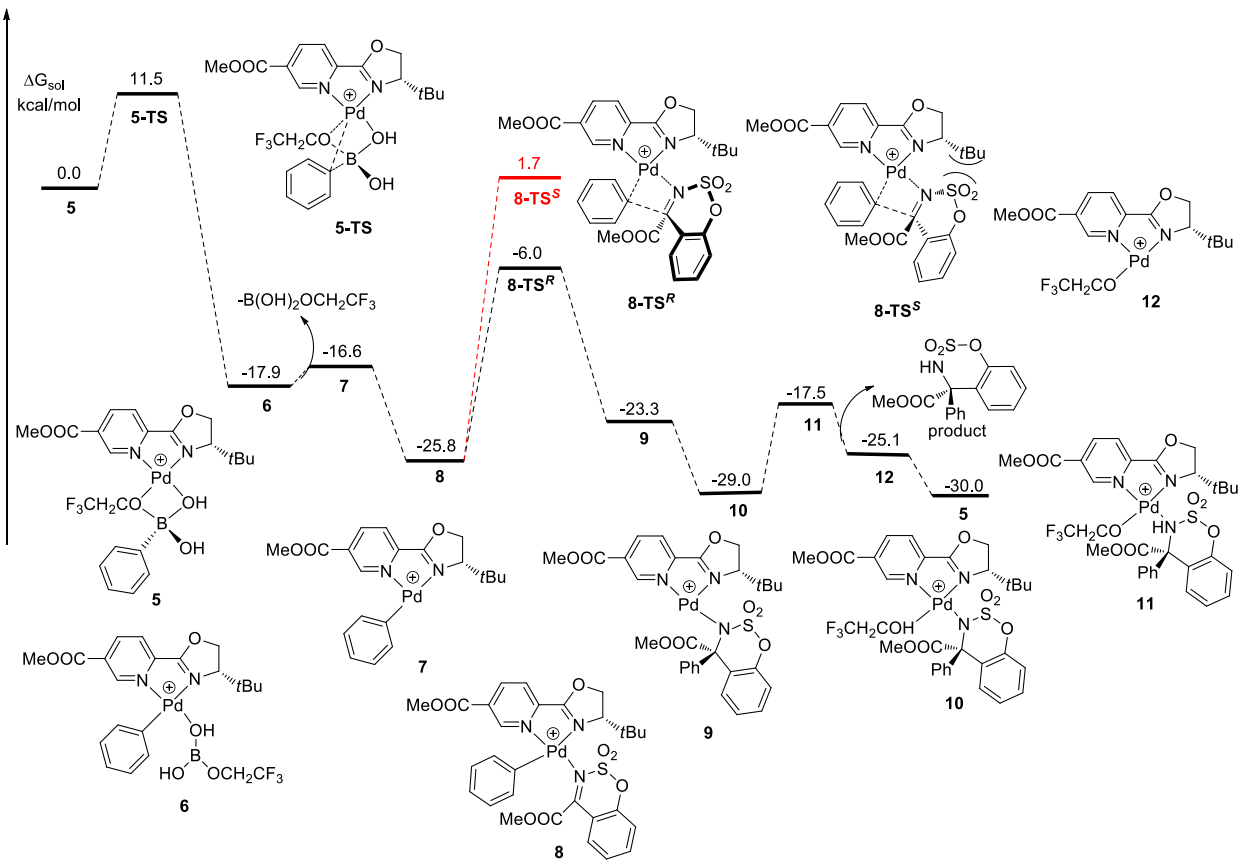


Figure 1 DFT-calculated catalytic circle.



The mechanism of the palladium-catalyzed conjugate addition of arylboronic acids to α,β-unsaturated compounds has been studied via DFT calculations.[15] Although several groups have reported the Pd-catalyzed addition of arylboronic acids to imines, there are no reports concerning mechanistic studies for this reaction.[11-13] Herein, a DFT study was carried out and the results are shown in figure 1. Firstly, phenylboronic acid coordinates with the Pd(II) catalyst to form intermediate **5**. The benzene ring then transfers to palladium to generate a phenyl-palladium-boronic acid complex with a free energy barrier of 11.5 kcal/mol (**5-TS** and **6**). Following this, trifluoroethoxylboronic acid leaves from intermediate **6** and a relatively unstable phenyl-palladium species **7** is formed. The nitrogen atom of substrate **1a** coordinates with palladium to lower the positive charge so that the intermediate **8** is more stable. The phenyl group then transfers to the carbon atom which is adjacent to the nitrogen atom of the substrate with a free energy barrier of 19.8 kcal/mol (**8** and **8-TS^R**). This step is the rate-determining step and also the stereoselectivity-determining step. The absolute configuration of the product was determined to be *R* by X-ray crystallographic analysis (**Figure 2**),[16] consistent with the calculation result. The enantiomeric imine insertion transition state **8-TS^S** requires 7.7 kcal/mol higher activation free energy than **8-TS^R**, indicating that the formation of the *S*-configuration is unfavorable due to the strong steric interaction between the coordinated substrate and the Bu^t group of the catalyst Finally, a TFE solvent molecule combines with the product-palladium species **9**. A proton from the combined solvent transfers to the nitrogen atom to form the product following the release of the catalyst.

Figure 2 Single-crystal X-ray structure of **3aa** and hydrogen atoms are omitted for clarity.

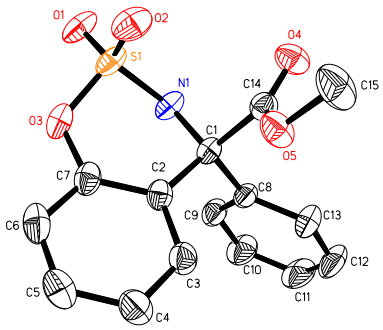
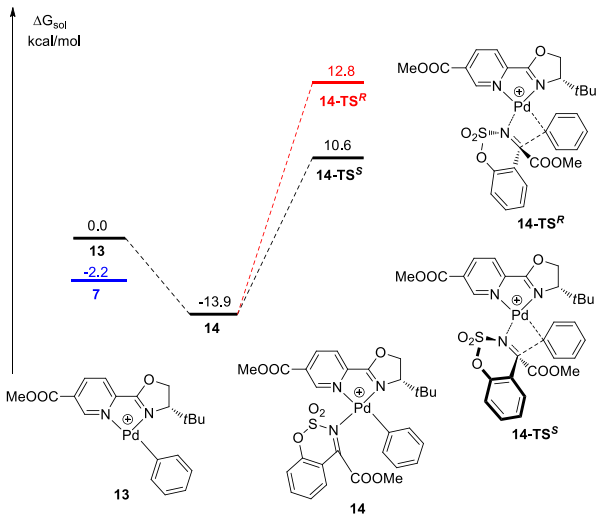


Figure 3 Alternative pathways of arylation.



It is worth mentioning that phenylpalladium(II) complexes **7** could isomerize to **13** by the counterion CF_3COO^- with an energy barrier of 2.2 kcal/mol (**Figure 3**).[17] Similarly, **1a** coordinates with **13** to form a stable intermediate **14**. Then the phenyl group transfers to the substrate to form the product. The free energy barriers are 24.5 kcal/mol and 26.7 kal/mol when the absolute configurations of the products are *S* (**14-TS^S**) and *R* (**14-TS^R**), respectively. Both of them are higher than the free energy barrier of **8-TS^R** but lower than **8-TS^S**. It means that the enantioselectivity probably influenced by the transition state of **14-TS^S**.

3. Conclusions

To summarize, we have synthesized a series of α-tertiary amino esters via a palladium-catalyzed asymmetric addition of arylboronic acids to cyclic *N*-sulfonyl imine esters. All the substrates gave excellent yields (up to 99%) and enantioselectivities (up to 99% ee value) under mild reaction conditions. The DFT study revealed the mechanism of enantioselection. Computations indicated that the imine insertion step (**8 – 8TS^R**) is the rate and stereoselectivity-determining step.

Acknowledgments

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16. CCDC 1047798 (**3aa**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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