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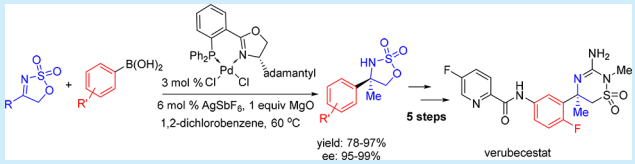
Palladium-Catalyzed Enantioselective Synthesis of Cyclic Sulfamidates and Application to a Synthesis of Verubecestat

Wenyong Chen,* Dongfang Meng, Blaise N'Zemba, and William J. Morris

Process Research & Development, Merck & Co., Inc., Rahway, New Jersey 07065, United States

Supporting Information

ABSTRACT: An enantioselective arylation reaction catalyzed by palladium complexed with substituted phosphinooxazoline (PHOX) ligands is described. Aza-quaternary stereocenters are readily accessible through the arylation reaction between cyclic iminosulfates and a wide variety of arylboronic acids, including electron-poor and *ortho*-substituted arylboronic acids. This reaction was applied to the preparation of verubecestat, which is currently undergoing clinical evaluation for the treatment of Alzheimer's disease.



Verubecestat (MK-8931) is a β-secretase inhibitor currently in phase III clinical trials for the treatment of Alzheimer's disease.[1] The current synthesis of verubecestat involves a diastereoselective addition of the necessary alkyllithium reagent to the appropriate Ellman ketimine to afford the aza-quaternary stereocenter.[2,3] This approach is in line with current literature for the state of the art in the formation of this chiral motif. Existing catalytic methods in the literature are effective for synthesizing aza-tertiary stereocenters, but the construction of aza-quaternary stereocenters remains a significant challenge.[4]

While the synthesis employing Ellman's auxiliary is robust and high-yielding, we sought to identify a catalytic approach that would obviate the need for this stoichiometric auxiliary to access verubecestat. We envisioned that a more efficient and elegant strategy to prepare verubecestat would instead involve direct asymmetric catalytic addition of an arylmetal reagent to a cyclic iminosulfate (Figure 1).[5] Several challenges exist in the

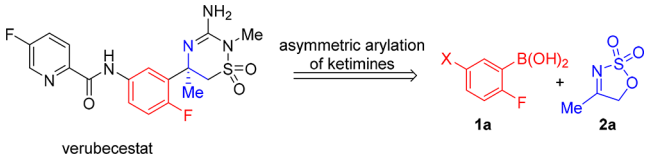


Figure 1. Proposed strategy for the synthesis of verubecestat.

construction of aza-quaternary stereocenters from arylmetal reagents and ketimines. In particular, the ketimine electrophile typically requires activation by incorporation of adjacent electron-withdrawing groups, such as carbonyl groups or a trifluoromethyl group.[5n,o] Furthermore, the scope of competent nucleophiles for metal-catalyzed arylation of ketimines has been limited to electron-rich arylboronic acids, as electron-deficient arylboronic acids and *ortho*-substituted arylboronic acids perform poorly or are even unreactive under previously described reaction conditions. Herein we report a general, enantioselective arylation reaction and its application to the synthesis of verubecestat. This enantioselective reaction, catalyzed by palladium complexed with substituted phosphinooxazoline (PHOX) ligands, provides access to aza-quaternary stereocenters from readily available arylboronic acids and cyclic iminosulfates.

Our initial efforts to develop a general arylation reaction focused on identifying a catalyst system that addressed this limited nucleophile scope. The reaction between arylboronic acid **1a** and cyclic iminosulfate **2a** was investigated to access the stereocenter in verubecestat in the presence of various metals and ligands (Table 1). Rh and Pd were first examined with various chiral ligands (entries 1−4). A rhodium−Josiphos catalyst and a palladium−PHOX catalyst were identified from this initial screen (entries 1 and 3). Ni and Co[6] were further investigated to identify a low-cost alternative metal catalyst, but the screen turned out to be fruitless (entries 5 and 6). The Pd−PHOX catalyst was selected for further development because it provided the product with superior enantioselectivity. Interestingly, this initial screen also revealed that a silver salt is a critical component of the reaction, presumably because the noncoordinative anion facilitates the addition of the arylpalladium intermediate into the C═N bond (entries 2, 3, and 7).[7]

Further reaction optimization, including ligand and solvent effects and the impact of additives, is summarized in Table 2.[8] Reactions that provided the desired product in low yield suffered from significant consumption of **1a** by protodeborylation. Additional screening of commercial PHOX ligands revealed that the substituent on the oxazoline had a significant effect on the extent of protodeborylation (entries 1−5). Among commercially available PHOX ligands, *t*Bu-PHOX was found to be superior to its less sterically hindered counterparts, and its palladium complex provided the arylation product in 30% yield (entry 1). Further exploring this trend, employment of adamantyl-PHOX led to an additional improvement in the yield of **3a** (entry 5). 1,2-Dichlorobenzene (DCB) proved to be

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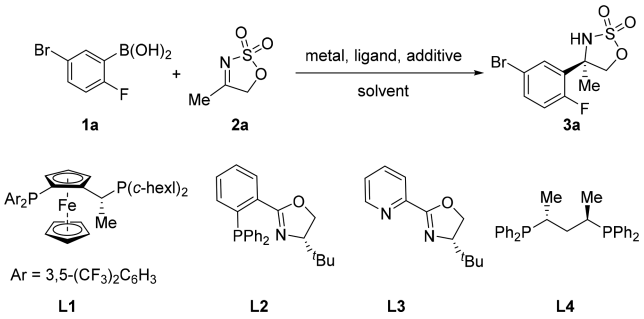
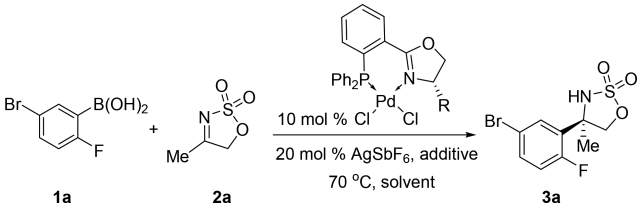
Table 1. Metal, Ligand, and Additive Screen for Enantioselective Arylation of Cyclic Iminosulfate 2a[a]



entry	metal	ligand	additive	yield/%[b]	ee/%[c]
1[d]	Rh	L1	K_3PO_4	12	77
2[e]	Pd	L2	none	0	–
3[e]	Pd	L2	$AgBF_4$	6	99
4[f]	Pd	L3	none	0	–
5[e]	Ni	L2	$AgBF_4$	0	–
6[e]	Co	L4	none	0	–
7[e]	Pd	L2	$AgSbF_6$	12	99

[a]3.0 equiv of **1a** and 1.0 equiv of **2a** were used in screening. See the Supporting Information (SI) for experimental details. The absolute configuration of the arylation product was determined by chemical correlation. [b]Determined by HPLC analysis with mesitylene as an internal standard. [c]Determined by chiral HPLC analysis of the reaction mixtures. [d]Dioxane was used as the solvent. [e]1,2-Dichloroethane was used as the solvent. [f]1,1,1-Trifluoroethanol was used as the solvent.

Table 2. Evaluation of Ligands, Additives, and Solvents in the Pd-Catalyzed Enantioselective Arylation of Cyclic Iminosulfate 2a[a]



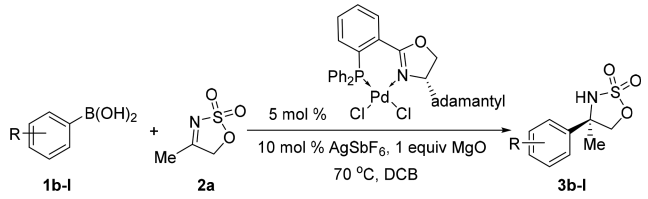
entry	R	additive[b]	solvent	yield/%[c]	ee/%[d]
1	*i*-Pr	none	DCE	11	97
2	Bn	none	DCE	0	–
3	Ph	none	DCE	0	–
4	*t*-Bu	none	DCE	30	99
5	adamantyl	none	DCE	45	99
6	adamantyl	none	DCB	72	99
7	adamantyl	K_2CO_3	DCB	16	99
8	adamantyl	MgO	DCB	94	99
9	adamantyl	CaO	DCB	94	99
10[e]	adamantyl	MgO	DCB	82	99
11[f]	adamantyl	MgO	DCB	92	99

[a]3.0 equiv of **1a** and 1.0 equiv of **2a** were used in the reactions. See the SI for experimental details. [b]1.0 equiv of additive. [c]Determined by HPLC analysis with mesitylene as an internal standard. [d]Determined by chiral HPLC analysis of the isolated products. [e]1.2 equiv of **1a**, 3 mol % Pd–adamantyl-PHOX catalyst, 6 mol % $AgSbF_6$. [f]2.0 equiv of **1a**, 3 mol % Pd–adamantyl-PHOX catalyst, 6 mol % $AgSbF_6$.

the optimal solvent for this reaction, providing the arylation product in 72% yield (entry 6). In order to reduce the amount of **1a** required in the reaction, various additives were investigated in the reaction to further suppress the undesired protodeborylation pathway. MgO and CaO were found to be particularly effective in this respect, leading to the arylation product in 94% yield with 99% ee (entries 8 and 9).[9] Under the optimized conditions, cyclic iminosulfate **2a** reacted with 2.0 equiv of boronic acid **1a** to deliver the arylation product **3a** in 92% yield with 99% ee (entries 10 and 11).

We explored the substrate scope of this reaction by evaluating a series of arylboronic acids with imine **2a** under the optimized conditions (Table 3). Arylboronic acids

Table 3. Scope of the Arylboronic Acid Component in the Pd-Catalyzed Enantioselective Arylation of Cyclic Iminosulfate 2a[a]



entry	R	product	yield/%[b]	ee/%[c]
1	4-Me	**3b**	95	96
2	4-F	**3c**	97	98
3	4-Cl	**3d**	83	99
4	4-Br	**3e**	94	99
5	4-I	**3f**	78	99
6[d]	4-OPh	**3g**	98	98 (0[e])
7	4-CF_3	**3h**	93	98
8	3-acetyl	**3i**	95	99
9	3-Cl	**3j**	77	97
10	2-F	**3k**	94	98
11[d]	2-MeO	**3l**	94	99 (2[e])

[a]2.0 equiv of **1b–l** and 1.0 equiv of **2a** were used in the reactions. See the SI for experimental details. The absolute configurations of the arylation products were assigned by analogy. [b]Isolated yields. [c]Determined by chiral HPLC analysis of the isolated products. [d]The reaction was run in the presence of 5 mol % DTBMP. [e]The value in parentheses is the ee value of the product in the absence of DTBMP.

containing either methyl or halo substitution reacted with **2a** to provide the corresponding products in good to excellent yields with 97–99% ee (entries 1–5). Unexpectedly, 4-phenoxyphenylboronic acid reacted with **2a** to yield racemic **3g**. We hypothesized that this product might racemize through an intramolecular S_N1 process due to the presence of an electron-donating group on the aryl rings. To test this hypothesis, we evaluated a series of tertiary amines to suppress the racemization. Gratifyingly, we found that 5 mol % 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) successfully suppressed the racemization and provided the product in 98% yield with 98% ee.[10] The reaction with electron-poor 4-trifluoromethylphenylboronic acid likewise provided the arylation product **3h** in 93% yield with 97% ee. It is worth noting that electron-poor arylboronic acids have rarely functioned as competent nucleophiles under previously disclosed conditions for transition-metal-catalyzed arylation of cyclic iminosulfates. Arylboronic acids containing electron-withdrawing substituents at the *meta* position also reacted with **2a** to form the corresponding arylation products in high yields with high enantioselectivities (entries 8 and 9). Although *ortho*-substituted arylboronic acids were problematic in previous reports, our reaction conditions provided these arylation

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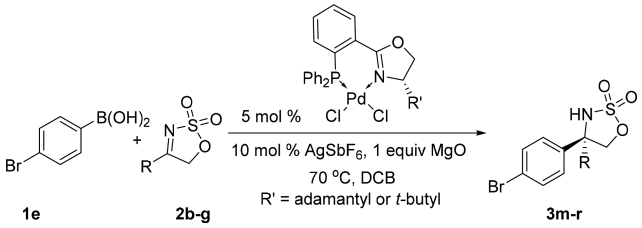
products in 94% yield with 99% ee (entries 10 and 11). The current catalyst system is the first reported in which both electron-poor and *ortho*-substituted arylboronic acids are competent partners in this reaction motif.

The scope of the cyclic iminosulfate electrophile under our optimized conditions is shown in Table 4. 4-Bromophenylboronic acid (**1e**) reacted smoothly with ethyl- and phenethyl-substituted cyclic iminosulfates (**2b** and **2c**) under the reaction conditions and furnished the products in high yields with excellent enantioselectivities (entries 1 and 2). Iminosulfates containing bulky alkyl groups provided the corresponding products in modest yields with high enantioselectivities under our optimized conditions: for example, the product from isopropyl-substituted substrate **2d** was isolated in only 42% yield. We hypothesized that the bulky adamantyl group in the ligand clashed with the *i*-Pr group and lowered the rate of the arylation process. Consistent with this hypothesis, when *t*-Bu-PHOX was employed as the ligand instead, the product was generated in 89% yield while maintaining the same 99% ee (entry 3). Cyclic iminosulfates containing other bulky groups, such as *c*-hexyl, *c*-pentyl, and *i*-Bu, all underwent the arylation smoothly when *t*-BuPHOX was employed as the ligand (entries 4–6).

Table 4. Scope of Cyclic Iminosulfates[a]



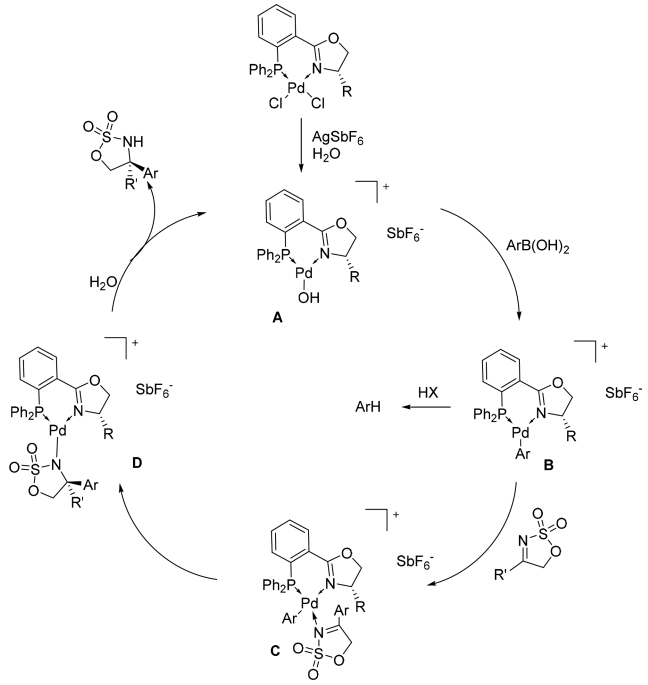
entry	R	product	yield/%[b]	ee/%[c]
1[d]	Et	**3m**	93	99
2[d]	$PhCH_2CH_2$	**3n**	96	99
3[e]	*i*-Pr	**3o**	89 (42[f])	98
4[e]	*c*-hexyl	**3p**	90	96
5[e]	*c*-pentyl	**3q**	90	95
6[e]	*i*-Bu	**3r**	83	95

[a]2.0 equiv of **1e** and 1.0 equiv of **2b–g** were used in the reactions. See the SI for experimental details. The absolute configurations of the arylation products were assigned by analogy. [b]Isolated yields. [c]Determined by chiral HPLC analysis of the isolated products. [d]Adamantyl-PHOX was used. [e]*t*-Bu-PHOX was used. [f]The value in parentheses is the yield of the product with adamantyl-PHOX as the ligand.

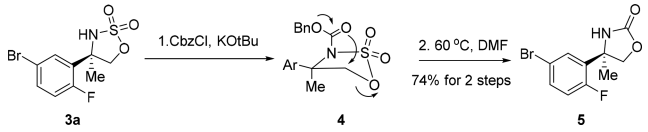
A proposed mechanism is shown in Scheme 1. The Pd–PHOX complex is converted to the cationic palladium complex **A** in the presence of $AgSbF_6$ and water. The hydroxide group in **A** assists the transmetalation of $ArB(OH)_2$ to form Ar–Pd complex **B**. Coordination of cyclic iminosulfates with **B** leads to intermediate **C**, which allows insertion of the C=N bond into the Pd–C bond to form **D**. Protonation releases the arylation product and turns over the palladium catalyst to complex **A**. In the catalytic cycle, protonation of intermediate **B** leads to the undesired protodeborylation product ArH.

The utility of the arylation products is shown in Scheme 2. Cyclic sulfamidate **3a** was protected with CbzCl to form **4**, which underwent rearrangement in DMF at 60 °C to form cyclic carbamate **5**. We speculated that cyclic carbamate **5** was formed through intramolecular nucleophilic substitution of the carbonyl oxygen in the Cbz group followed by desulfonylation. This observation inspired the synthetic strategy to forge the C–S bond found in verubecestat (Scheme 3). After acylation of **3a** with *O*-phenyl chlorothionoformate, the thiocarbamate underwent rearrangement–desulfonylation to yield dihydrothiazole **6**. Exposure to NCS in HCl led directly to the formation of an intermediate sulfonyl chloride, which was quenched with *p*-methoxybenzylmethylamine. After addition of TBAF, amine **7** was isolated in 64% yield from **6**. Copper-catalyzed amidation[11] with 5-fluoropicolinamide followed by PMB deprotection and guanidinylation provided verubecestat in 41% overall yield from iminosulfate **2a**. The catalytic route provided enantiopure verubecestat in yield and efficiency comparable to those of the

Scheme 1. Proposed Mechanism of Pd-Catalyzed Asymmetric Arylation

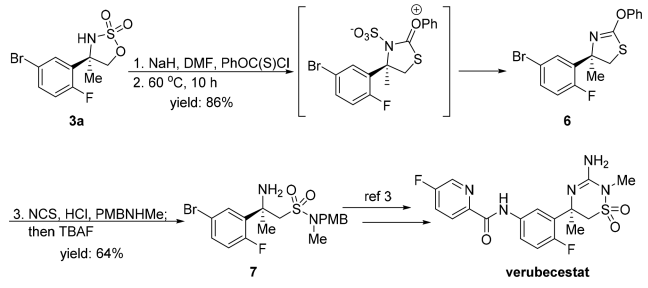


Scheme 2. Utility of the Cyclic Sulfamidate Products[a]



[a]See the SI for experimental details.

Scheme 3. Synthesis of Verubecestat from 3a



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recently developed commercial process, which produced verubecestat in 61% overall yield by employing a chiral Ellman sulfinyl ketimine as the starting material and a recrystallization to upgrade the enantiopurity.[3b]

In summary, we have described a general Pd-catalyzed enantioselective arylation reaction between cyclic iminosulfates and a wide variety of arylboronic acids. The reaction tolerates electron-rich, electron-poor, and *ortho*-substituted arylboronic acids and provides cyclic sulfamidates in high yields with excellent enantioselectivities. This palladium catalyst system significantly expands the scope for the asymmetric arylation of ketimines. The cyclic sulfamidates formed in the reaction can be funtionalized to generate the corresponding amino alcohols and cyclic carbamates. A novel desulfonyl rearrangement of thiocarbamate led to the formation of the desired C−S bond found in verubecestat. A sequential oxidation−amination reaction followed by C−N coupling, PMB deprotection, and guanidine formation led to verubecestat in six total steps from cyclic iminosulfate **2a** (41% overall yield).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03639.

Experimental procedures, compound characterization data, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wenyong.chen@merck.com.

ORCID

Wenyong Chen: 0000-0002-7337-0876
William J. Morris: 0000-0003-4322-4509

Notes

The authors declare no competing financial interest.

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(8) Preformed Pd−PHOX complex was used in further development because of improved reproducibility.

(9) The protodeborylation appeared to occur through the Ar−Pd intermediate because **1a** was stable under the conditions without metal catalyst. MgO/CaO suppressed the protodeborylation, presumably by tuning the pH of the system and the water concentration.

(10) Isolated **3l** (99% ee) underwent complete racemization after stirring with 5 mol % Pd−Phox complex and $AgSbF_6$ in the presence of MgO at 70 °C for 4 h.

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