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Enantioselective Synthesis of Hemiaminals via Pd-Catalyzed C−N Coupling with Chiral Bisphosphine Mono-oxides

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Supporting Information

ABSTRACT: A novel approach to hemiaminal synthesis via palladium-catalyzed C−N coupling with chiral bisphosphine mono-oxides is described. This efficient new method exhibits a broad scope, provides a highly efficient synthesis of HCV drug candidate elbasvir, and has been applied to the synthesis of chiral *N,N*-acetals.

Recently, the World Health Organization reported that 150 million people are infected with the hepatitis C virus (HCV). It is estimated that as many as 5 million of these people are coinfected with the human immunodeficiency virus (HIV), which typically leads to higher viral loads and results in accelerated disease progression in these patients.[1] With limited treatment options for coinfected patients, HCV has become a leading cause of death for HIV patients. Elbasvir, an inhibitor of the HCV NS5A protein, administered in combination with grazoprevir, an HCV protease inhibitor, has been clinically studied as an oral, highly efficacious, and well tolerated regimen for the treatment of HCV infection, including patients with HIV coinfection (Figure 1).[2]

A defining structural feature of elbasvir is the benzoxazino-indole core containing a chiral hemiaminal juncture. Many other biologically active molecules contain the synthetically challenging chiral hemiaminal functionality, which is often critical to the biological activity.[3] Previous reports of catalytic asymmetric syntheses are rare and mostly rely on the chiral Brønsted acid catalyzed asymmetric addition of an oxygen nucleophile to an imine.[4,5] These methods require specific activating groups on nitrogen to effect reactivity, which limits their general application. Inspired by the synthetic challenge of assembling the benzoxazino-indole core of elbasvir to enable the manufacture of this important HCV therapy for patients, we developed a conceptually novel approach to this new class of important hemiaminals.[6]

We envisioned an enantioselective formation of the chiral hemiaminal with concomitant arylation of the nitrogen, directly

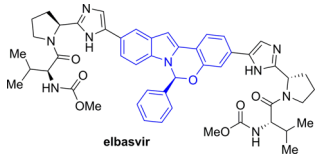

Figure 1. Elbasvir structure.

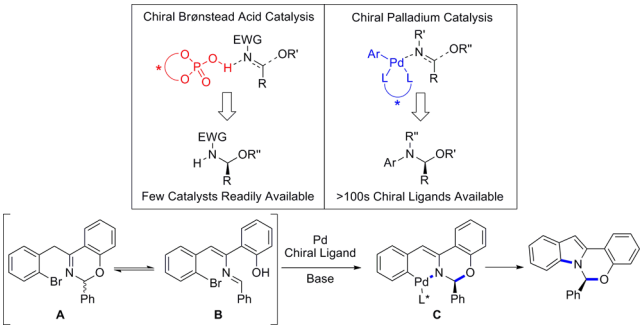

Figure 2. Design plan.

yielding the benzoazino indole present in elbasvir. In our design, a palladium/chiral phosphine complex capable of catalyzing the Buchwald−Hartwig C−N coupling would also control the formation of the stereogenic center at the hemiaminal (Figure 2).[7] This would allow us to leverage high-throughput experimentation[8] to rapidly evaluate the vast collection of existing chiral phosphine ligands available for asymmetric transition metal catalysis. We set out to test this hypothesis by preparing ene-imine **B** but discovered that it readily cyclized to the benzoxazine **A**. We then established that the stereogenic center in the hemiaminal **A** was stereochemically labile, presumably through the intermediacy of **B**.[9] This rapid equilibration of enantiomers provided the experimental foundation to test our desired reaction.

We began our investigation using racemic **1a**. A variety of commercially available chiral phosphines (**L1**−**L10**) were surveyed utilizing high-throughput experimentation tools and techniques.[10] These ligands, in combination with either 10 mol % $Pd(OAc)_2$ or 5 mol % $Pd_2(dba)_3$, were found to cleanly catalyze formation of indole **2a** under mild conditions utilizing toluene as solvent and K_3PO_4 as base at 55 °C (see Figure 3). Several of these ligands provided **2a** with good to excellent enantioselectivity; however, the Pd-source was found to have a very profound effect on the overall performance of each class of ligands investigated. This difference was readily identified by comparing the graphs in Figure 3 which show enantiomeric excess (%) vs % conversion of **1a** to **2a** under the standard conditions for both Pd-precursors.[11] Overall, a significant decrease in indole formation was observed with all bis-phosphine ligands when switching from $Pd(OAc)_2$ to $Pd_2(dba)_3$. Josiphos[12]

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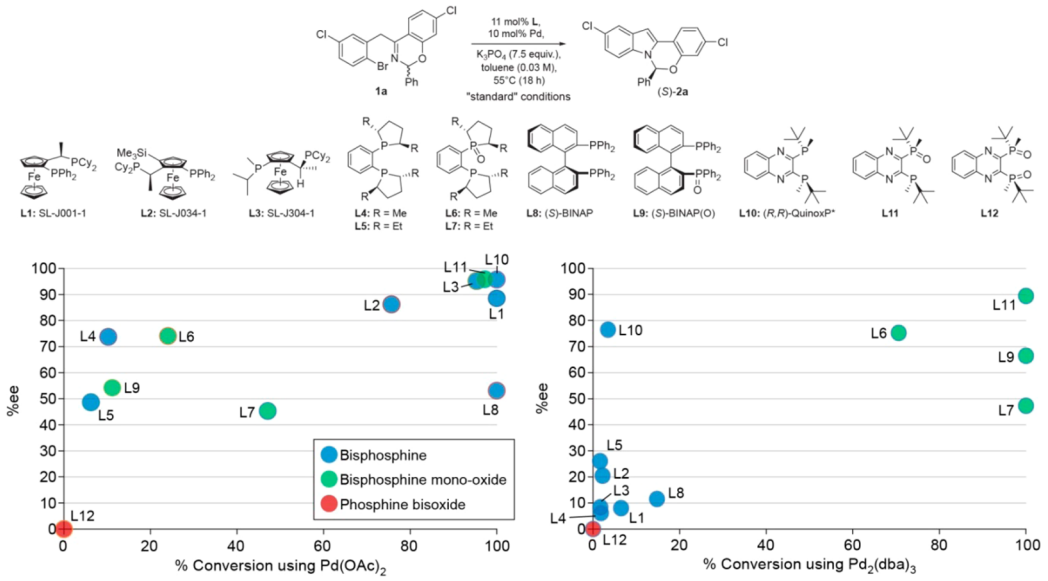

Figure 3. Ligand screening of model substrate with $Pd(OAc)_2$ and $Pd_2(dba)_3$.

ligands **L1**–**L3** in combination with $Pd(OAc)_2$ provided some of the highest selectivities with (*S*)-**2a** being formed in up to 95% *ee* with SL-304-1 (**L3**). In contrast, these same phosphines were found to be nearly inactive with $Pd_2(dba)_3$, resulting in the formation of only small amounts of **2a**. Duphos[13] ligands **L4** and **L5**, along with their respective bis-phosphine mono-oxide (BPMO) derivatives[14] **L6** and **L7**, gave poor to modest reactivities and selectivities with $Pd(OAc)_2$. In the presence of $Pd_2(dba)_3$ the BPMO ligands **L6** and **L7** showed excellent reactivity while **L4** and **L5** gave almost no conversion to **2a**. Indole formation was also significantly depressed when (*R*,*R*)-QuinoxP* (**L10**)[15] was used with $Pd_2(dba)_3$; however, the same ligand produced the best performing catalyst with $Pd(OAc)_2$. The (*S*)-**2a** indole was cleanly obtained in 96% *ee* with **L10** under the standard conditions. The substantial reactivity difference between the BPMOs and parent bis-phosphines shown in Figure 3 suggested that the bis-phosphines surveyed may undergo *in situ* oxidation to the corresponding BPMO.

Based on the experimental results and literature precedent,[16] we hypothesized that BPMO **L11** was formed from **L10** under the standard conditions with $Pd(OAc)_2$. We separately prepared BPMO **L11** to test this hypothesis.[17] In contrast to **L10**, **L11** provided a very active catalyst with $Pd_2(dba)_3$ cleanly giving (*S*)-**2a** in 89% *ee* and almost complete conversion of **1a** as shown in Figure 3. Conversely, bis-phospine oxide **L12** results in an inactive catalyst for the cyclization with either $Pd(OAc)_2$ or $Pd_2(dba)_3$. To further support our hypothesis, a series of ^{31}P NMR spectroscopy experiments[18] following the catalyst formation and reaction with either iodobenzene or model substrate **1a** provides evidence supporting *in situ* formation of a BPMO–Pd complex. A mixture of **L10** and $Pd(OAc)_2$ in the presence of base, water, and dba in toluene-d_8 produces ^{31}P NMR signals at ~20 and ~60 ppm. These signals compare favorably to those observed when **L11** is mixed with $Pd_2(dba)_3$. Alternatively, substitution of dba with iodobenzene in simlar experiments produces ^{31}P NMR signals matching those formed starting from either **L10**/$Pd(OAc)_2$ or **L11**/Pd(0). Finally, ^{31}P NMR monitoring of the standard reaction conditions with $Pd(OAc)_2$ using **1a** shows the formation of signals that also match those observed when starting with **L11**/Pd(0). Based on these

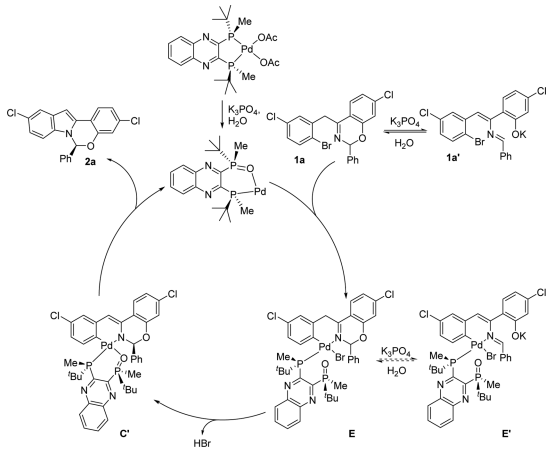

Figure 4. Plausible catalytic cycle.

experimental results, we believe that many of the bis-phosphine/$Pd(OAc)_2$ combinations surveyed may undergo disproportionation to generate the corresponding active and selective BPMO/Pd(0) catalysts.

A plausible catalytic cycle for this transformation is shown in Figure 4. In the presence of K_3PO_4 and water, **L10**/$Pd(OAc)_2$ undergoes intramolecular redox reaction to generate the active BPMO–Pd(0) catalyst. Starting material **1a** can isomerize via its open form **1a**′, and oxidative addition gives Pd(II) complex **E** which may also isomerize via **E**′. Deprotonation leads to the stereodefined imido–Pd complex **C**′, and then reductive elimination affords **2a** and regenerates the Pd(0) catalyst. The exact nature of the enantiodetermining step in this process is currently under investigation.

Additional reaction parameter screening to reduce catalyst loading established that ligand **L10** and $Pd(OAc)_2$ provided the most robust catalyst system. There was almost no detectable background reaction observed with $Pd(OAc)_2$ or $Pd_2(dba)_3$ in the absence of ligand (Table 1, entry 2). Other bases were also found to cleanly facilitate indole formation (entries 3–4). However, optimization of the reaction with **L10** using K_3PO_4 was found to cleanly provide (*S*)-**2a** in 96% isolated yield (94% *ee*) at

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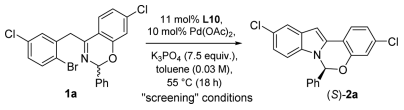
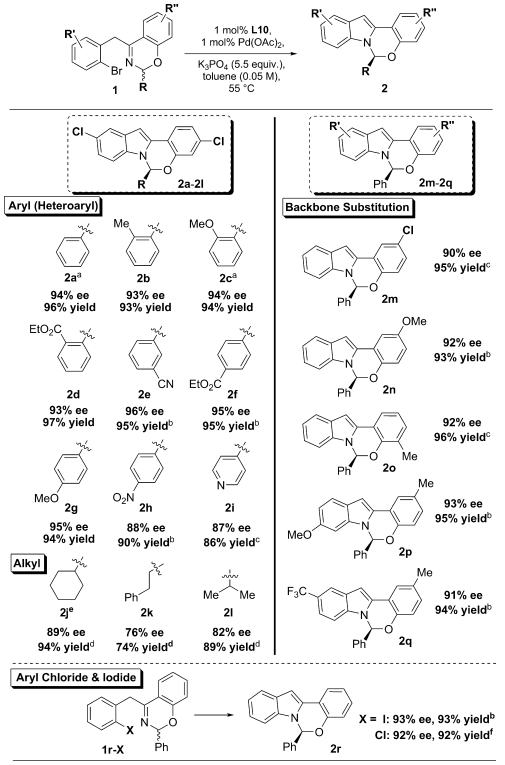
Table 1. Effect of Reaction Parameters



entry	variation from the "screening" conditions[a]	conv[b] (%)	ee (%)
1	none	>99	96
2	no ligand with $Pd(OAc)_2$ or $Pd_2(dba)_3$	<5	–
3	7.5 equiv, Cs_2CO_3, K_2CO_3, or $KHCO_3$	>99	96
4	1.1 equiv KO*t*Bu or KHMDS	>99	96
5[c]	1 mol % $Pd(OAc)_2$, 1 mol % **L10**	>99[d]	94
6[c]	1 mol % $Pd(OAc)_2$ and 1 mol % **L1** or **L3**	<10	69

[a]Reaction conditions: **1a** (4.0 μmol), $Pd(OAc)_2$ (0.4 μmol, 10 mol %), **L10** (0.42 μmol, 11 mol %), K_3PO_4 (30 μmol, 7.5 equiv) toluene (130 μL, 0.03 molar in **1a**) at 55 °C (24 h). [b]Conversion is reported as described in reference 11. [c]Run at 0.05 M **1a** (0.35 mmol scale) using 5.5 equiv of K_3PO_4. [d]96% isolated yield of (*S*)-**2a**.

Table 2. Substrate Scope

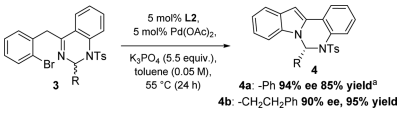


[a]*S* configuration determined by X-ray analysis; other products using **L10** assigned *S* configuration by analogy. [b]With 2 mol % **L10**/2 mol % $Pd(OAc)_2$. [c]5 mol % **L10**/5 mol %$Pd(OAc)_2$. [d]5 mol % **L3**/5 mol % $Pd(OAc)_2$. [e]*S* configuration determined by X-ray analysis; other products using **L3** assigned *S* configuration by analogy. [f]10 mol % **L3**/5 mol % $Pd(OAc)_2$.

1.0 mol % $Pd(OAc)_2$ (entry 5). Ligands **L1**–**L3** proved inferior at this lower Pd loading (entry 6).[19]

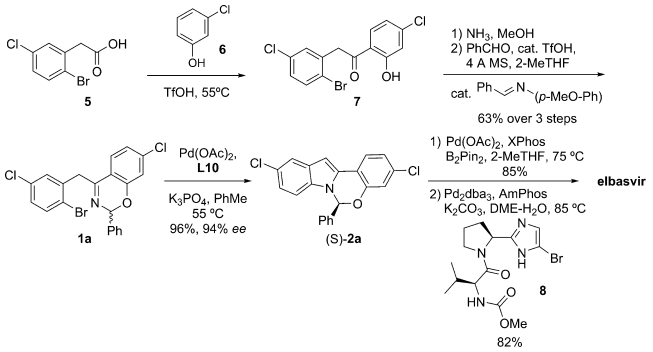
Using these optimized reaction conditions, we explored the substrate scope, which proved to be quite general (Table 2). Excellent yields and enantioselectivities (up to 96% *ee*) were obtained with substrates containing various aryl and heteroaryl substituents (**2a**–**2i**). Alkyl substituted hemiaminals (**1j**–**l**) gave a lower product *ee* (~70%) with **L10**; however, ligand **L3**[20] afforded better enantioselectivities particularly with α-branched hemiaminals (**2j**, **2l**). Modification of the backbone demonstrated that high levels of stereoinduction were still attainable. Benzoxazines **1m**–**1q** provided **2m**–**2q** in excellent enantioselectivities (90–93% *ee*). Varying the aryl halide coupling partner was also possible with aryl iodide **1r-I** cleanly giving **2r** in 93% *ee*. Aryl chloride **1r-Cl** only gave trace amounts of product with **L10** as ligand; however, the more electron-rich ligand **L3** provided a suitable catalyst giving **2r** in 92% *ee*.

Scheme 1. Chiral *N,N*-Acetal Synthesis



[a]*R* configuration for **4a** was determined by X-ray analysis; **4b** assigned by analogy.

Scheme 2. New Approach towards Synthesis of Elbasvir



We envisioned that this approach might be applicable to the synthesis of chiral *N,N*-acetals which are also valuable pharmacophores, with few reported catalytic asymmetric syntheses.[21] Both substrates **3a** and **3b** underwent the Pd-catalyzed asymmetric C–N coupling using **L2** as ligand, to provide **4a** and **4b** in 94% *ee* and 90% *ee* respectively (Scheme 1).

Based on this novel reaction methodology, we developed a new 6-step synthesis of elbasvir (Scheme 2).[6] Racemic hemiaminal **1a** was assembled via Fries rearrangement, imine formation, and condensation with benzaldehyde. After establishing the key hemiaminal center in 96% yield (94% *ee*), elbasvir could be accessed via Pd-catalyzed borylation and then Suzuki coupling with side chain **8** in 42% overall yield.

In conclusion, we have developed an unprecedented approach to the enantioselective synthesis of hemiaminals via a Pd-catalyzed C–N coupling using chiral bisphosphine mono-oxides. Essential to this discovery was the observation that benzoxazine derivatives such as **1a** readily undergo racemization via the open form **1a**′, and this equilibration process could be terminated via enantioselective Pd-catalyzed C–N coupling. Furthermore, we discovered that an unexpected *in situ* formation of a bisphosphine mono-oxide/Pd(0) complex was a key step in the formation of the active catalyst. This new approach was successfully applied to the highly efficient synthesis of the HCV drug candidate, elbasvir, and the methodology has been successfully applied to the enantioselective synthesis of *N,N*-acetals. Further applications of this methodology are being investigated as well as mechanistic studies to identify the enantio- and rate-determining steps.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b05934.

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Full characterization, analysis of enantioselectivities, spectral data, experimental procedures (PDF)
X-ray crystallographic data for **2c** (CIF)
X-ray crystallographic data for **2a** (CIF)
X-ray crystallographic data for **2j** (CIF)
X-ray crystallographic data for **4a** (CIF)

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Notes

The authors declare no competing financial interest.

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(9) Treatment of **1a** with KOBu^t afforded the corresponding K-salt of open form **1a′**. The ee of optically enriched **1a** decreased from 96% to 2% within 30 min in THF with K_3PO_4 at 50 °C. Alternatively, the ee of optically enriched **1a** decreased from 96% to 0% within 5 h in toluene with K_3PO_4 at 50 °C. In the absence of added base, the ee of optically enriched **1a** (96% ee) decreased to 11% and 0% ee respectively in THF and toluene within 23 h at 50 °C.

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(17) The procedure described in ref 16a was nonselective while the procedure described in ref 14 cleanly provided **L11**.

(18) See Supporting Information for experimental details and results.

(19) The poor reactivity and diminished selectivity observed for **L1**–**L3** could be the result of nonselective mono-oxidation.

(20) Josiphos ligand SL-J304-1 (**L3**) is commercially available from Solvias and has not received absolute stereochemical assignment.

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(22) This work will be the subject of a future publication.

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