Communication

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

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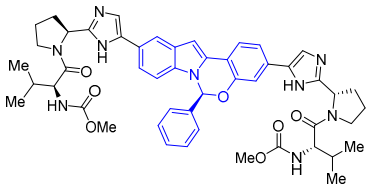
Supporting Information Placeholder

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 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 co-infected 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 co-infected 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 co-infection (Figure 1).[2]

Figure 1. Elbasvir Structure

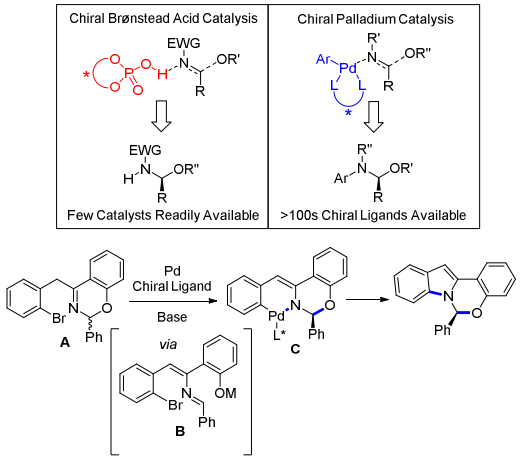


elbasvir

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 yielding the benzoazino indole present in elbasvir. In our design, a

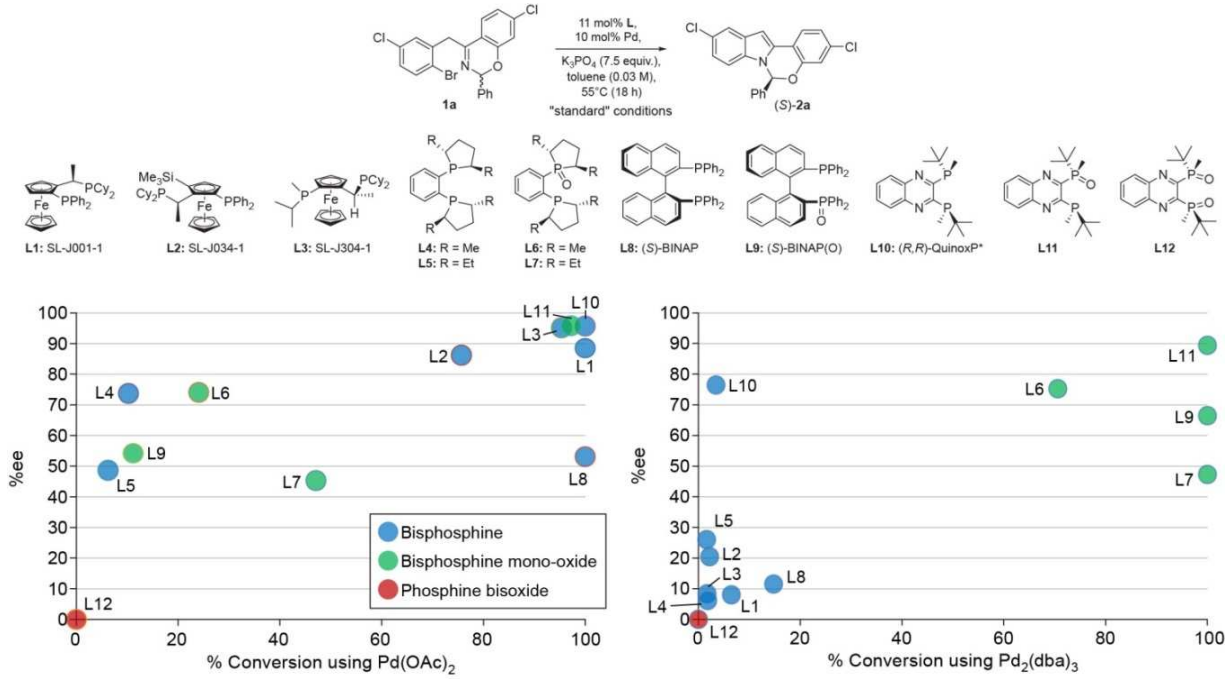
Figure 2. Design Plan



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 under basic conditions, 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 non-bis-phosphine mono-oxide (BPMO) ligands when switching from $Pd(OAc)_2$ to $Pd_2(dba)_3$. Josiphos[12] ligands **L1-L3** in combination with $Pd(OAc)_2$ provided some of

Figure 3. Ligand Screening of Model Substrate with $Pd(OAc)_2$ and $Pd_2(dba)_3$

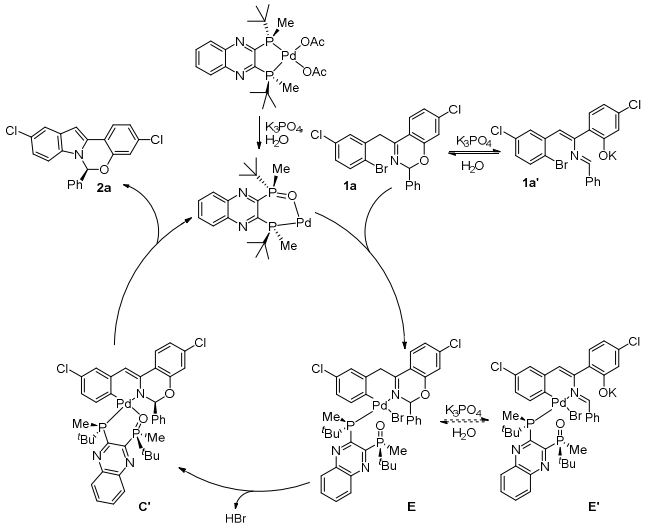


the highest selectivities with (*S*)-**2a** being formed in up to 95% *ee* with SL-304-1 (**L3**). In contrast, these same phosphines were found to be nearly inactive with $Pd_2(dba)_3$, resulting in the formation of only small amounts of **2a**. Duphos[13] ligands **L4** and **L5,** along with their respective 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 a signals that also match those observed when starting with **L11**/Pd(0). Based on these experimental results, we believe that many of the bis-phosphines surveyed may undergo *in-situ* oxidation to the corresponding BPMO by $Pd(OAc)_2$ to generate active and selective 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 its open form **E'**. Deprotonation leads to the stereodefined imido-Pd complex **C'** and then reductive elimination affords the benzoxazino-indole product and regenerates the Pd(0) catalyst. The exact nature of the enantiodetermining step in this process is currently under investigation.

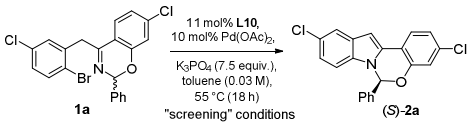
Figure 4. Plausible Catalytic Cycle



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 absence of ligand (Table 1, entries 1-2). Other bases were also found to cleanly facilitate indole formation (entries 3-5). 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 1.0 mol%

$Pd(OAc)_2$ (entry 6). Ligands **L1-L3** proved inferior at this lower Pd loading (entries 7-8).[19]

Table 1. Effect of Reaction Parameters

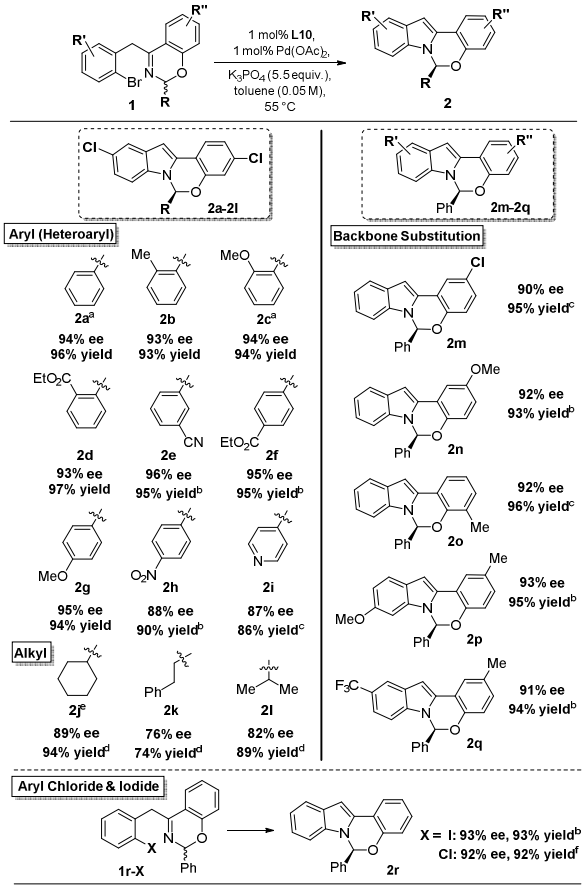


Entry	variation from the "screening" conditions[a]	conv.[b] (%)	ee[c] (%)
1	None	>99	96
2	No Ligand with $Pd(OAc)_2$ or $Pd_2(dba)_3$	<5	-
3	7.5 equiv. Cs_2CO_3, Rb_2CO_3, K_2CO_3, or $KHCO_3$	>99	96
4	1.1 equiv. KO*t*Bu or KHMDS	>99	96
5	2 equiv. BEMP, TMG, or *t*-Bu-TMG	>99	96
6[d]	1 mol% $Pd(OAc)_2$, 1 mol% **L10**	>99[f]	94
7[e]	1 mol% $Pd(OAc)_2$ and 1 mol% **L1** or **L3**	<10	69
8[e]	1 mol% $Pd(OAc)_2$ and 1 mol% **L2**	3	-79

[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 uL, 0.03 molar in **1a**) at 55 °C (24 h). [b]Conversion is reported as the product of 100*[(area counts **2a**)/(area counts **1a** + area counts **2a**)] as determined by SFC analysis at a wavelength of 210 nm. [c]A negative ee value signifies (*R*)-**2a** was the major product. [d]Toluene*tert*-butyl methyl ether (6:1 v:v) was used as solvent. [e]Run at 0.05 M **1a** (0.35 mmole scale) using 5.5 equiv. K_3PO_4. [f]96% isolated yield of (*S*)-**2a**. BEMP = 2-tert-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine. TMG = 1,1,3,3-tetramethylguanidine.

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 lower product *ee* (~70%) with **L10**; however, ligand **L3**[20] afforded better enantioselectivities particularly with α-branched hemiaminals (**2j, 2l**). Modification of the dichlorobenzoxazine backbone demonstrated that high levels of stereoinduction were still attainable.

Table 2. Substrate Scope

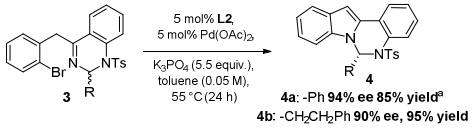


[a]*S* configuration determined by X-ray analysis; other products using **L10** assigned *S* configuration by analogy; [b]with 2 mol% **L10**/2 mol% $Pd(OAc)_2$; [c]5 mol% **L10**/5 mol%$Pd(OAc)_2$; [d]5 mol% **L3**/5 mol% $Pd(OAc)_2$; [e]*S* configuration determined by X-ray analysis; other products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

Benzoxazines **1m-1q** provided **2m-2q** in excellent enantioselectivities (90-93% *ee*). Varying the aryl halide coupling partner was also possible with aryliodide **1r-I** cleanly giving product **2r** in 93% *ee*. Arylchloride **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*.

Encouraged by these results, we envisioned that this approach might be applicable to the synthesis of chiral *N,N*-acetals which are also very valuable pharmacophores, with few reported catalytic asymmetric syntheses.[21] We found that substrate **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).

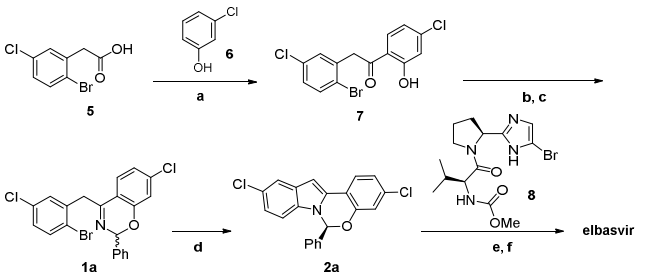
Scheme 1. Chiral *N,N*-acetal Synthesis



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

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 sidechain **8** in 42% overall yield.

Scheme 2. New Approach towards Synthesis of Elbasvir



a). TfOH, 55 °C; b). NH_3(7N in MeOH), 77% yield over 2 steps; c) benzaldehyde (1.1 eq.), (*E*)-*N*-(4-methoxyphenyl)-1-phenylmethanimine (0.2 eq.), TfOH (0.2 eq.), 4 A MS, 2-MeTHF, 82% yield; d) 1% QuinoxP/ 1% $Pd(OAc)_2$, K_3PO_4 (5.5 eq.), toluene, 55 °C, 94 %ee, 96% yield; e) 2% $Pd(OAc)_2$, 4% XPhos, B_2PIN_2 (2.2 equiv), 2-MeTHF, 75 °C, 85% yield; f) 1% $Pd_2(dba)_3$, 2.2% Amphos, K_2CO_3, **8** (2.1 eq.), DME-water, 85 °C, 82% 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 entioselective Pd-catalyzed C-N coupling. Furthermore, we discovered that an unexpected *in-situ* formation of a bisphosphine mono-oxide from the bisphosphine by $Pd(OAc)_2$ was a key step in the formation of the active catalyst necessary for C-N coupling. 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 of this novel reaction.

ASSOCIATED CONTENT

Supporting Information

Full characterization, analysis of enantioselectivities, copies of all spectral data, experimental procedures, and X-ray crystallographic data. 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 interests.

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REFERENCES

(1) (a) Kim, W. R. *Microbes Infect.* **2002**, *4*, 1219. (b) Shepard, C. W.; Finelli, L.; Alter, M. J. *Lancet Infect. Dis.* **2005**, *5*, 558. (c) Alter, M. J.; Kruszon-Moran, D.; Nainan, O. V.; McQuillan, G. M.; Gao, F.; Moyer, L. A.; Kaslow, R. A.; Margolis, H. S. *N. Engl. J. Med.* **1999**, *341*, 556.

(2) Coburn, C. A.; Meinke, P. T.; Chang, W.; Fandozzi, C. M.; Graham, D. J.; Hu, B.; Huang, Q.; Kargman, S.; Kozlowski, J.; Liu, R.; McCauley, J. A.; Nomeir, A. A.; Soll, R. M.; Vacca, J. P.; Wang, D.; Wu, H.; Zhong, B.; Olsen, D. B.; Ludmerer, S. W. *ChemMedChem* **2013**, *8*, 1930.

(3) (a) Warriner, S. Category 4: *Compounds with Two Carbon-Heteroatom Bonds*. In *Science of Synthesis*; Bellus, D., Ed.; Thieme: Stuttgart, **2007**, *30*, 7. (b) Heys, L.; Moore, C. G.; Murphy, P. *J. Chem. Soc. Rev.* **2000**, *29*, 57. (c) Coric, I.; Vellalath, S.; Muller, S.; Cheng, X.; List, B. *Top. Organomet. Chem.* **2013**, *44*, 165. (d) Richter, A.; Kocienski, P.; Raubo, P.; Davies, D. E. *Anti-Cancer Drug Des.* **1997**, *12*, 217.

(4) For chiral hemiaminal synthesis using using chiral phosphric acid catayst, see (a) Li, G.; Fronczek, F. R.; Antilla, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 12216. (b) Vellalath, S.; Coric, I.; List, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 9749. Other examples, see (c) Li, T-z; Wang, X-b; Sha, F.; Wu, X-y *Tetrahedron* **2013**, *69*, 7314. (d) Hashimoto, T.; Nakatsu, H.; Takiguchi, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2013**, *135*, 16010. (e) Honjo, T.; Phipps, R. J.; Rauniyar, V.; Toste, F. D. *Angew. Chem., Int. Ed.* **2012**, *51*, 9684.

(5) For Pd-catalyzed addition of sulfonyl-protected homopropargylic amines to alkoxyallene, see: (a) Kim, H.; Rhee, Y. H. *Synlett* **2012**, *23*, 2875. (b) Kim, H.; Rhee, Y. H. *J. Am. Chem. Soc.* **2012**, *134*, 4011.

(6) For a chiral relay strategy to elbasvir, see: (a) Mangion, I.; Chen, C-y; Li, H.; Maligres, P.; Chen, Y.; Christensen, M.; Cohen, R.; Jeon, I.; Klapars, A.; Krska, S.; Nguyen, H.; Reamer, R. A.; Sherry, B. D.; Zavialov, I. *Org. Lett.* **2014**, *16*, 2310. (b) Li, H.; Chen, C-y; Nguyen, H.; Cohen, R.; Maligres, P.; Yasuda, N.; Mangion, I.; Zavialov, I.; Reibarkh, M.; Chung, J. *J. Org. Chem.* **2014**, *79*, 8533.

(7) For recent reviews on the Buchwald-Hartwig reaction, see: (a) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534. (b) Surry, D. S.; Buchwald, S. L. *Chem. Sci*. **2011**, *2*, 27. (c) Bariwal, J.; Van der Eycken, E. *Chem. Soc. Rev.* **2013**, *42*, 9283. For kinetic resolution by enantioselective Buchwald-Hartwig reaction, see: (d) Rossen, K.; Pye, P.; Maliakal, A.; Volante, R. P. *J. Org. Chem.* **1997**, *62*, 6462. (e) Tagashira, J.; Imao, D.; Yamamoto, T.; Ohta, T.; Furukawa, I.; Ito, Y. *Tetrahedron: Asymmetry* **2005**, *16*, 2307. For enantioselective synthesis of atropisomeric lactams and anilides via Buchwald-Hartwig reaction, see: (f) Kitagawa, O.; Kurihara, D.; Tanabe, H.; Shibuya, T.; Taguchi, T. *Tet. Lett.* **2008**, *49*, 471 and references cited therein. For desymetrization using Buchwald-Hartwig conditions, see: (g) Porosa, L.; Viirre, R. *Tetrahedron Lett.* **2009**, *50*, 4170. For desymmetrization via copper-catalyzed enantioselective intramolecular aryl C−N coupling see: (h) He, N.; Huo, Y.; Lin, J.; Huang, Y.; Zhang, S.; Cai, Q. *Org. Lett.* **2015**, *17*, 374. (i) Shi, J.; Wang, T.; Huang, Y.; Zhang, X.; Wu, Y.; Cai. Q.; *Org. Lett.* **2015**, *17*, 840 and references cited therein.

(8) For recent reviews highlighting the utility of high-throughput experimentation in academia and industry, see: (a) Schmink, J. R.; Bellomo, A; Berritt, S. *Aldrichim. Acta* **2013**, *46*, 71-80. (b) Collins, K. D.; Gensch, T.; Glorius, F. *Nat. Chem.* **2014**, *6*, 859.

(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 mins 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.

(10) For recent applications of high-throughput experimentation see: (a) Belyk, K. M.; Xiang, B.; Bulger, P. G.; Leonard, W. R., Jr.; Balsells, J.; Yin, J.; Chen, C. *Org. Process Res. Dev.* **2010**, *14*, 692. (b) Robbins, D. W.; Hartwig, J. F. *Science* **2011**, *333*, 1423. (c) Friedfeld, M. R.; Shevlin, M.; Hoyt, J. M.; Krska, S. W.; Tudge, M. T.; Chirik, P. J. *Science* **2013,** *342*, 1076. (d) Chung, C. K.; Bulger, P. G.; Kosjek, B.; Belyk, K. M.; Rivera, N.; Scott, M. E.; Humphrey, G.; Limanto, J.; Bachert, D. C.; Emerson, K. M. *Org. Process Res. Dev.* **2014**, *18*, 215. (e) DiRocco, D. A.; Dykstra, K.; Krska, S.; Vachal, P.; Conway, D. V.; Tudge, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 4802.

(11) Conversion is reported as the product of 100*[(area counts **2a**)/(area counts **1a** + area counts **2a**)] as determined by SFC analysis at a wavelength of 210 nm.

(12) (a) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. J. Am. Chem. Soc. **1994**, *116*, 4062. (b) Blaser, H.-U.; Pugin, B.; Spindler, F.; Mejia, E.; Togni, A. *Privileged Chiral Ligands and Catalysts*; Zhou, Q.-L., Ed.; Wiley-VCH: Weinheim, Germany, **2011**; pp 93.
(13) (a) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518. (b) Crépy, K. V. L.; Imamoto, T. *Adv. Synth. Catal.* **2003**, *345*, 79. (c) Zhang, W.; Zhang, X. *Privileged Chiral Ligands and Catalysts*; Zhou, Q.-L., Ed.; Wiley-VCH: Weinheim, Germany, **2011**; pp 55.
(14) (a) Boezio, A. A.; Pytkowicz, J.; Côté, A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 14260. (b) Côté, A.; Desrosiers, J.-N.; Alessandro, B. A.; Charette, A. B. *Org. Synth.* **2006**, *83*, 1.
(15) Imamoto, T.; Sugita, K.; Yoshida, K. *J. Am. Chem. Soc.* **2005**, *127*, 11934.
(16) (a) Grushin, V. V. *J. Am. Chem. Soc*. **1999**, *121*, 5831. (b) Marshall, W. J.; Grushin, V. V. *Organometallics* **2003**, *22*, 555. (c) Grushin, V. V. *Chem. Rev*. **2004**, *104*, 1629.
(17) The procedure described in ref. 16(a) was non-selective while the procedure described in ref. 14(b) 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 non-selective mono-oxidation.
(20) Josiphos ligand SL-J304-1 (**L3**) is commercially available from Solvias and has not received absolute stereochemical assignment.
(21) (a) Agranat, I.; Caner, H.; Caldwell, *J. Nat. Rev. Drug Discovery* **2002**, *1*, 753. (b) Agranat, I.; Wainschtein, S. R. *Drug Discovery Today* **2010**, *15*, 163. (c) Kasprzyk-Hordern, B. *Chem. Soc. Rev.* **2010**, *39*, 4466. For recent examples of chiral *N*,*N*-aetal synthesis, see: He, Y.; Cheng, C.; Chen, R.; Duan, K.; Zhuang, Y.; Yuan, B.; Zhang, M.; Zhou, Y.; Zhou, Z.; Su, Y.-J.; Cao, R.; Qiu, L. *Org. Lett.* **2014**, *16*, 6366 and references cited therein.
(22) This work will be the subject of a future publication.

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