**Article:**
Mazuela, J, Antonsson, T, Knerr, L et al. (3 more authors) (2019) Iridium-Catalyzed Asymmetric Hydrogenation of N-Alkyl α-Aryl Furan-Containing Imines: an Efficient Route to Unnatural N-Alkyl Arylalanines and Related Derivatives. Advanced Synthesis and Catalysis, 361 (3). pp. 578-584. ISSN 1615-4150

https://doi.org/10.1002/adsc.201801143

Advanced Synthesis & Catalysis

## Accepted Article

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**To be cited as:** *Adv. Synth. Catal.* 10.1002/adsc.201801143

**Link to VoR:** http://dx.doi.org/10.1002/adsc.201801143

10.1002/adsc.201801143

UPDATE

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

# Iridium-Catalyzed Asymmetric Hydrogenation of N-Alkyl α-Aryl Furan-Containing Imines: an Efficient Route to Unnatural N-Alkyl Arylalanines and Related Derivatives.

Javier Mazuela[a,*], Thomas Antonsson[a], Laurent Knerr[a], Stephen P. Marsden[b], Rachel H. Munday[c] and Magnus J. Johansson[a,*]

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Received: ((will be filled in by the editorial staff))

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**Abstract.** High throughput experimentation (HTE) has enabled the rapid identification of ligand/precatalyst combinations that facilitate highly enantioselective hydrogenations of prochiral N-alkyl α-aryl ketimines containing a furyl moiety. The chiral amines obtained have proven to be modular precursors in the synthesis of unnatural mono N-alkylated arylalanines and related derivatives.

**Keywords:** asymmetric hydrogenation, iridium, high throughput experimentation, unnatural N-alkyl amino acids, arylalanines.

The pharmaceutical industry has an ever-growing interest in the synthesis of compounds containing asymmetric centers.[1,2] Today, most syntheses of α-chiral amines and alcohols rely on the asymmetric hydrogenation of prochiral substrates using transition metal mediated processes or on comparative organocatalytic methodologies.[2] In this context, chiral amines are available in the most straightforward manner from reduction of prochiral imines or enamines/amides.[2,3] While the reduction of activated imines (such as N-phosphinyl, N-sulfinyl or N-aryl imines) has a long history[3], there is still a need to develop methodologies for the efficient asymmetric reduction of N-alkyl imines due to their propensity to hydrolyze, the poisoning effect on the catalytic system of the resulting amines, and the belief that E/Z isomerisation would influence enantioselectivity in a negative way.[2f] Dealing with these compounds, we have had a program for several years focusing on the utilization of N-alkyl imines in synthesis, with the aim of producing enantioenriched amines with preinstalled aliphatic substituents on nitrogen.[4]

In recent years, D-arylalanines have attracted the attention of organic and medicinal chemists because of their presence in natural products as well as their potential use as building blocks in the design and optimization of bioactive peptides and peptidomimetics.[5,6] N-Alkylation of amino acids, highlighted by N-methylation, has become a powerful method to modulate the properties of acyclic and macrocyclic peptides, including proteolytic stability, conformational stability, selectivity and cellular permeability (Figure 1).[7] In addition, the introduction of N-alkylated residues into synthetic peptides changes the hydrogen bond patterns giving access to new conformational designs.[8] Therefore, direct modular approaches to both enantiomers of N-alkyl arylalanines are valuable but rare.

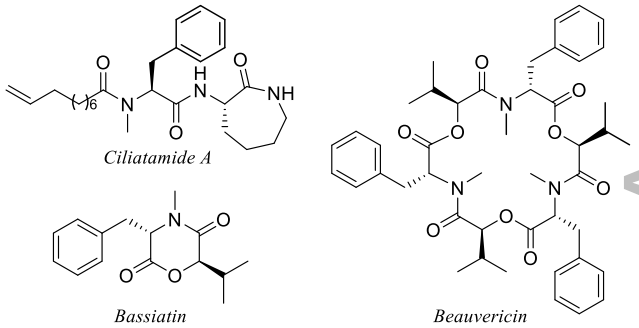


**Figure 1.** Examples of N-Me amino acid containing natural products/drugs

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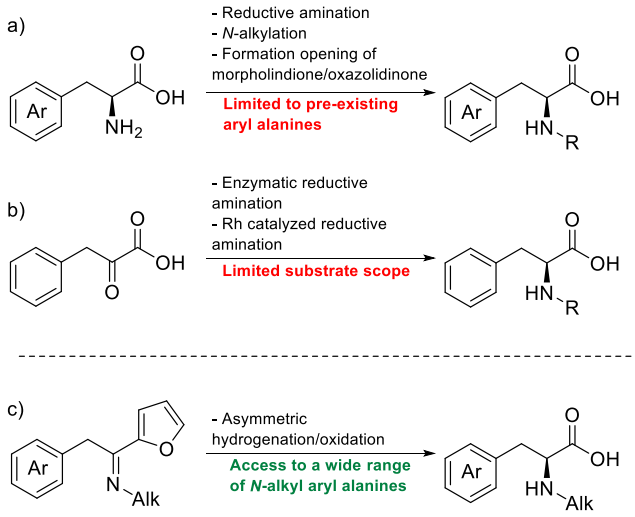
They are only available in a straightforward manner via alkylations of pre-existing amino acids[9] (Scheme 1a) or by recent elegant examples of enzymatic or Rh-catalyzed reductive amination[10] (Scheme 1b), which limits the range of N-alkyl amino acids that can be prepared. This is especially for the D-enantiomers of arylalanines considering their limited availability.




**Scheme 1.** Previous methodology vs current

The objective of the present work was to develop an asymmetric catalytic methodology for the preparation of N-alkyl arylalanines which would give access to the challenging unnatural N-alkyl D-enantiomer. Taking inspiration from nature, we initially set out to prepare N-alkyl arylalanine esters in an analogous way to our previous report on asymmetric Brønsted catalyzed transfer hydrogenation of N-alkyl aryl iminoesters,[4] but the protocol was not compatible with the preparation of these compounds because of the troublesome synthesis of the corresponding imines, which lead to the exclusive formation of 3-pyrrolin-2-ones.[11] As an alternative, we envisioned the use of a furyl moiety as a carboxylic acid surrogate in the reduction of N-alkyl imines derived from variously substituted arylmethyl (2-furyl) ketones. This motif would, in a modular fashion, provide access to heavily functionalized chiral non-natural amino acids after oxidative cleavage of the furyl group (Scheme 1c).[12]

With no precedence in the literature for the asymmetric hydrogenation of this class of imines we opted to take a HTE approach.[13] Selected catalysts capable of both asymmetric transfer and pressure hydrogenation were investigated and the best results are shown in Table 1.[14] A wide screen of asymmetric transfer hydrogenation catalysts was carried out investigating Ru, Rh and Ir catalyst precursors with a range of sulfonated diamine ligands as well as commercially available tethered catalysts. The best result was obtained with a Ru(Mes)$Cl_2$ dimer/R,R-TsDACH catalyst system, giving an er of 87:13.[15] We then moved on to investigating pressure hydrogenation conditions. Noyori-type Ru bisphosphine/diamine catalysts[16] have been used previously for hydrogenations of N-aryl/benzyl imines derived from acetophenone; however conversions with our substrate were very low both at 30 °C and 50 °C. Ir-based systems were then investigated with both chiral P,N ligands and bisphosphine ligands.[3] The Ir-P,N catalysts gave no improvement on the transfer hydrogenation conditions with the best er of 18:82 being obtained with an Ir-SpinPhox system.[17] A wide Ir-bisphosphine screen, however, yielded a single very promising result with an Ir-(S,S)-f-BINAPHANE catalyst giving an er of 91:9.[18] After this extensive catalyst screening it was clear that the optimal system capitalized on a cationic iridium(I) pre-catalyst ligated to the (S,S)-f-BINAPHANE ligand. Next, we wanted to see whether fine tuning of solvent, pressure and/or additives would improve the enantiomeric ratio or not (Table 2).

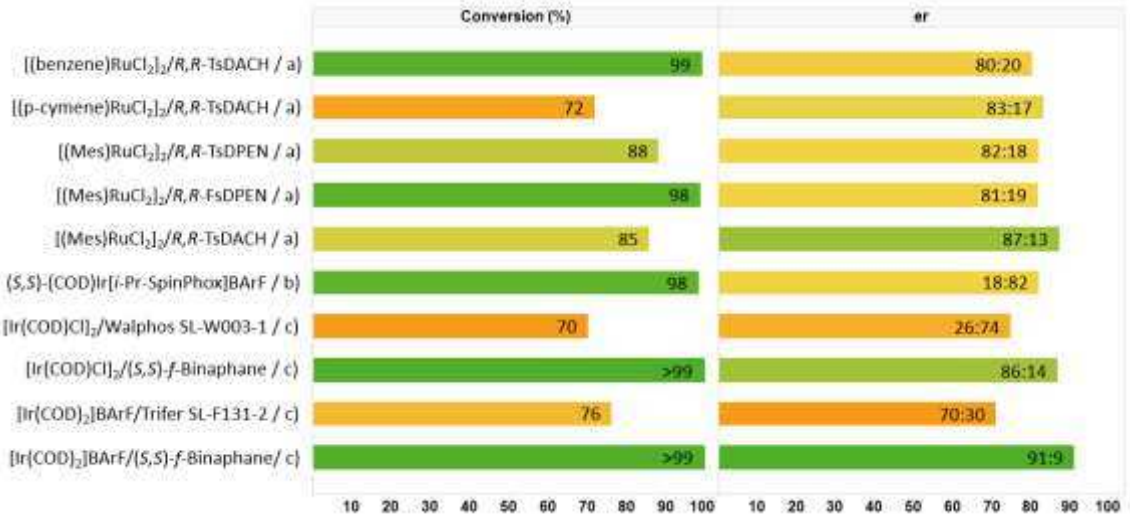
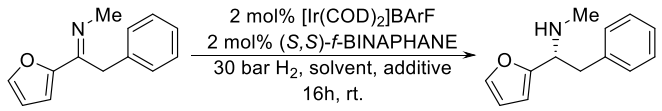



**Table 1.** Selected HTE results[a]

[a]Conditions: a) catalyst (4 mol%), $HCO_2H$:$Et_3N$ (5:2) (2 eq), DCM, 25 °C, 16 h; b) catalyst (2 mol%), DCM, 10 bar $H_2$, 25 °C, 16 h; c) catalyst (2 mol%), DCM, 50 bar $H_2$, 25 °C, 16 h.

**Table 2.** Screening of reaction conditions




| Entry | Solvent | Additive | Yield[b)] | er[c)] |
|---|---|---|---|---|
| 1 | MeOH | - | 68% | 87:13 |
| 2 | Dioxane | - | 100% | 82:18 |
| 3 | THF | - | 99% | 88:12 |
| 4 | DCM | - | 100% (92%) | 94:6 |
| 5 | $Et_2O$ | - | 80% | 85:15 |
| 6 | Toluene | - | 100% | 90:10 |
| 7[d)] | DCM | - | 97% | 87:12 |
| 8[e)] | DCM | - | 100% | 93:7 |
| 9[f)] | DCM | - | 88% | 92:8 |
| 10[g)] | DCM | - | 100% | 90:10 |
| 11[h)] | DCM | - | 75% | 94:6 |
| 12 | DCM | 10 mol% $I_2$ | 100% | 90:10 |
| 13 | DCM | 10 mol% (R)-TRIP | 99% | 87:13 |
| 14 | DCM | 10 mol% (S)-TRIP | 99% | 91:9 |

[a)] Reaction conditions: 0.1 mmol furyl-containing N-methyl imine, 2 mol % $[Ir(COD)_2]BAr_F$, 2 mol % (S,S)-f-BINAPHANE, 1.5 mL DCM, 30 bars $H_2$, 16h, room temperature. [b)] $^1$H NMR Yield using dibromomethane as internal standard. Isolated yield between brackets [c)] Determined by $^1$H NMR adding 4 mg (R)-TBPTA to 2 mg crude product. [d)] Using 5 bars $H_2$. [e)] Using 50 bars $H_2$. [f)] Using 1 mol % $[Ir(COD)Cl]_2$ as precatalyst. [g)] Using 1 mol % $[Ir(COD)OMe]_2$ as precatalyst. [h)] Using 1 mol % $[Ir(COD)_2]BAr_F$, 1 mol % (S,S)-f-BINAPHANE.

Starting with methanol (entry 1) a moderate er was observed and the reaction was also compromised by low conversion. Switching to ethereal solvents (entry 2,3 and 5) conversion was improved but the er still remained moderate. Toluene offered a slight improvement in er (entry 6). However, DCM (entry 4) rendered both a full conversion and a good er. Lowering $H_2$ pressure to 5 bar (entry 7) compromised the er while an increased pressure did not affect the ratio (entry 8). Changing the Ir precatalyst gave somewhat inferior results (entry 8 and 9) compared to the use of $[Ir(COD)_2]BAr_F$. Finally, reducing the catalyst loading to 1 mol% slowed the reaction down, however gratifyingly the er was unaffected (entry 11). The use of iodine (entry 12) as an additive to enter into a Ir(III) catalytic cycle, as proposed by Osborn, Zhang and others,[18b, 19] did not prove beneficial. Finally, we were intrigued to see if a chiral Brønsted acid would affect the ratio in a positive way by formation of a chiral immonium salt. However no increase in er was observed with either enantiomer of the acid. Having the optimal conditions in hand, we performed a hydrogenation on a 500 mg scale, maintaining the excellent selectivity and returning a good isolated yield (see Supp. Info.). It is noteworthy that although the N-alkyl imines were most commonly isolated as a mixture of E/Z isomers, we were pleased to see that the use of such mixtures never translated into a reduced er. A possible reason for this is that NOESY experiments revealed that the isomers were in a fast equilibrium (see SI).

We then set out to investigate the substrate scope, with an emphasis on designing useful and diverse non-natural phenylalanine precursors (Table 3). Substitution at the ortho, meta or para position with a methyl group was well tolerated (entries 2-4). Electron-donating groups were investigated (entries 5-7) again giving good er and excellent yields. Moving to an extended π-system (entry 8) a reduced enantioselectivity was observed. Next, we selected arenes set up for further functionalization. The para-TMS substituted compound (entry 9), a potential coupling partner in gold- catalyzed oxyarylations of ethylene,[20] gave a slightly lower enantioselectivity. Pleasingly moving to the bromo-substituted derivatives as potential partners in metal-catalyzed cross-couplings, both good ers and excellent yields were observed. Finally, different fluorinated analogues, interesting from a medicinal chemistry perspective, owing to their favorable metabolic properties and potential as reporter groups in NMR binding studies, were evaluated; again, good ers and excellent yields were seen (entries 12-14). Among the fluorinated derivatives prepared, the pentafluorosulfanyl($SF_5$)-containing building blocks are of interest as the effect of the introduction of this functional group in peptides has been scarcely studied.[21] The $SF_5$ group has emerged as a bioisostere of trifluoromethyl and tert-butyl functions. Indeed, it combines a large size and high lipophilicity with a strong negative inductive effect. All these traits make the $SF_5$ group an intriguing group for the optimization of peptides bioactivities and properties. [21a] In addition, amines **2** will give access to arylalanines where the "magic methyl effect" can be explored, by means of changing solubility, conformation, binding interaction and/or

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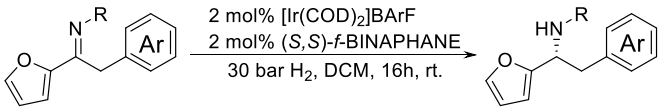
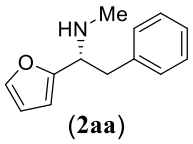
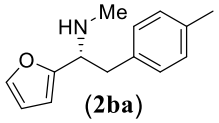
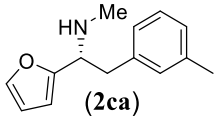
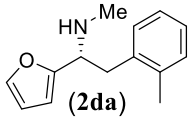
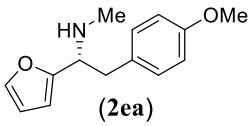
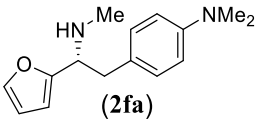
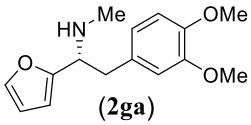
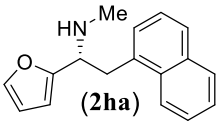
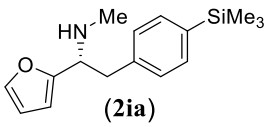
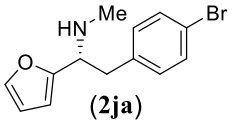
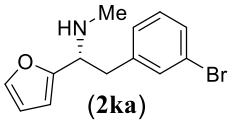
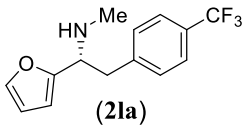
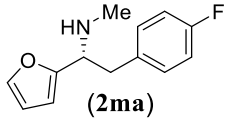
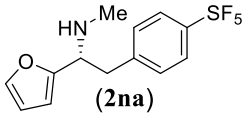
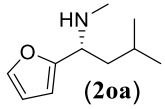
metabolism.[22] To our delight the precursor to N-Me leucine was also hydrogenated in good yield and high enantioselectivity (entry 15).

**Table 3.** Scope of furan-containing N-alkyl imines:



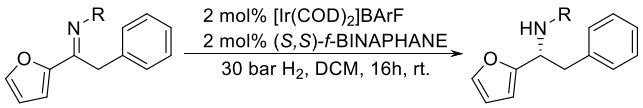

Substituents in the aryl ring.[a)]

| Entry | Product | Yield[b)] | er[c)] |
|---|---|---|---|
| 1 |  (**2aa**) | 92% | 94:6 |
| 2 |  (**2ba**) | 93% | 94:6 |
| 3 |  (**2ca**) | 92% | 94:6 |
| 4 |  (**2da**) | 91% | 92:8 |
| 5 |  (**2ea**) | 98% | 92:8 |
| 6 |  (**2fa**) | 92% | 93:7 |
| 7 |  (**2ga**) | 84% | 95:5 |
| 8 |  (**2ha**) | 95% | 91:9 |
| |  (**2ia**) | 88% | 90:10 |
| 10 |  (**2ja**) | 96% | 93:7 |
| 11 |  (**2ka**) | 94% | 94:6 |
| 12 |  (**2la**) | 89% | 94:6 |
| 13 |  (**2ma**) | 84% | 93:7 |
| 14 |  (**2na**) | 98% | 93:7 |
| 15 |  (**2oa**) | 89% | 91:9 |

a) Reaction conditions: 0.2 mmols furan-containing N-methyl imine, 2 mol % $[Ir(COD)_2]BAr_F$, 2 mol % (S,S)-f-BINAPHANE, 3 mL DCM, 30 bars $H_2$, 16h, room temperature. b) Isolated Yield. c) Determined by 1H NMR adding 4 mg (R)-TBPTA to 2 mg pure amine.

To take advantage of the modularity of this approach we then studied the effect of incorporation of various N-alkyl groups (Table 4). Pleasingly an ethyl group (entry 2) was well tolerated, while the introduction of a n-propyl group gave a small decrease in the enantioselectivity (entry 3). Upon evaluation of different branched substituents, it was observed that distal branching (entry 5) was preferred in comparison with proximal branching (entry 4) which unfortunately gave only a moderate 67:33 er. The introduction of bulky aryl substituents in the terminal position of the N-alkyl chain also led to a significant decrease in the enantioselectivity (entry 6). In addition, a silyl ether moiety was tolerated in terms of reactivity maintaining the excellent yield but giving a somewhat lower enantioselectivity (entry 7). It should be noted that the silyl ether protecting group can be easily removed, giving access to a terminal alcohol group that could be used for further transformations.

**Table 4.** Scope of furan-containing N-alkyl imines:



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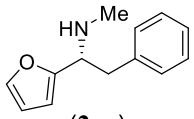
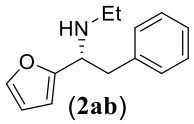
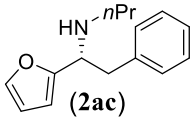
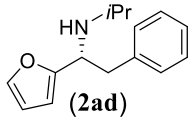
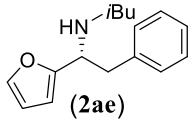
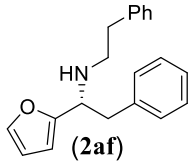
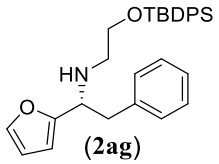
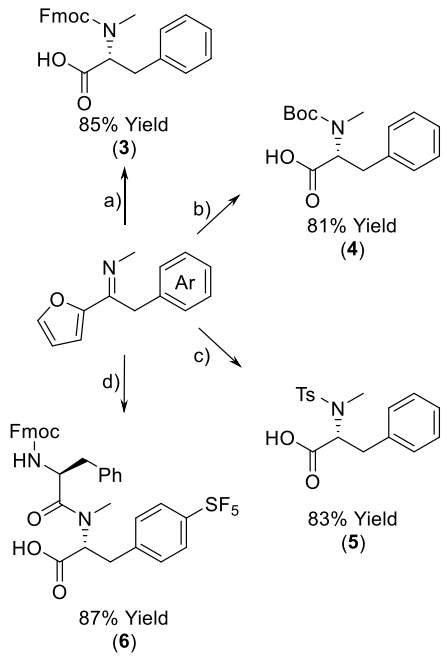
Substituents on the Nitrogen.[a)]

| Entry | Product | Yield[b] | er[c)] |
|---|---|---|---|
| 1 |  (**2aa**) | 92% | 94:6 |
| 2 |  (**2ab**) | 88% | 93:7 |
| 3 |  (**2ac**) | 87% | 91:9 |
| 4 |  (**2ad**) | 91%[d] | 67:33 |
| 5 |  (**2ae**) | 90% | 88:12 |
| 6 |  (**2af**) | 86%[d] | 78:22 |
| 7 |  (**2ag**) | 96% | 81:19 |

a) Reaction conditions: 0.2 mmols furan-containing N-methyl imine, 2 mol % [Ir(COD)2]$BAr_F$, 2 mol % (S,S)-f-BINAPHANE, 3 mL DCM, 30 bars $H_2$, 16h, room temperature. b) Isolated Yield. c) Determined by 1H NMR adding 4 mg (R)-TBPTA to 2 mg pure amine. d) In 2d.

Finally, we demonstrated conversion of the reaction products to the desired amino acids. The chiral furyl substituted phenethylamines were subjected to oxidative cleavage using ruthenium trichloride and sodium periodate, having first been N-protected or functionalized as the corresponding Fmoc- or Boc- carbamate **3** or **4** or tolylsulfonamide **5** (Scheme 2). Pleasingly these transformations occurred with high levels of conserved stereochemistry. Additionally, the Fmoc protected dipeptide **6** could be obtained in a similar fashion thus allowing the modular preparation of synthetically useful building blocks for solid phase peptide synthesis.

In summary, this report describes a modular and highly enantioselective synthesis of furan-containing




N-alkyl amines which can be easily transformed into unnatural N-alkylated phenylalanine analogues without loss of the stereochemistry. This constitutes a novel and valuable source of synthetically useful chiral building blocks for peptidic and peptidomimetic medicinal chemistry as well as the total synthesis of peptide based natural products and analogues.

**Scheme 2.** Preparation of N-methyl arylalanines analogues: a) 1. Hydrogenation, then FmocCl, $NEt_3$. 2. $RuCl_3$, $NaIO_4$, $H_2O$, ACN, $CCl_4$. b) 1. Hydrogenation + $Boc_2O$. 2. $RuCl_3$, $NaIO_4$, $H_2O$, ACN, $CCl_4$. c) 1. Hydrogenation + TsCl, $NEt_3$. 2. $RuCl_3$, $NaIO_4$, $H_2O$, ACN, $CCl_4$. d) 1. Hydrogenation + Fmoc-Phe, HATU, DIPEA. 2. $RuCl_3$, $NaIO_4$, $H_2O$, ACN, $CCl_4$

## Experimental Section

For detailed experimental information and the characterization of compounds, see the supporting information.

**General procedure for the asymmetric Iridium catalyzed hydrogenation**: In a nitrogen-filled glovebox and to a oven-dried microwave vial, [Ir(COD)$_2$]$BAr_F$ (5.09 mg, 0.004 mmol), (S,S)-f-Binaphane (3.23 mg, 0.004 mmol) and DCM (1 mL) were added and stirred at room temperature for 30 min. The solution was transferred to a solution of the corresponding imine (0.2 mmol) in 3 mL DCM. The resulting vial was transferred to an autoclave, which was charged with 30 bars $H_2$ and stirred at room temperature for 16 h or 2 d. The hydrogen gas was released

slowly and the solution was concentrated. The crude was transferred to a 5g SCX cation exchanger which was washed with 20 mL DCM and 20 mL MeOH. A final wash with 20 mL of 2M $NH_3$ in methanol and after solvent removal in vacuo afforded the pure chiral amine. The enatiomeric ratio was determined adding 4 mg (R)-TBPTA to a solution of 2 mg chiral amine in 0.7 mL CDCl3.

## Acknowledgements

We would like to acknowledge the AZ postdoctoral program for funding of JMA. Dr Malin Lemurell for generous support of the project.

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UPDATE

# Iridium-Catalyzed Asymmetric Hydrogenation of N-Alkyl α-Aryl Furan-Containing Imines: an Efficient Route to Unnatural N-Alkyl Arylalanines and Related Derivatives.

Adv. Synth. Catal. **Year**, Volume, Page – Page

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