Doctoral Thesis

Iridium-catalyzed reactions
allylic amination using sulfamic acid and asymmetric transfer
hydrogenation using formic acid

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Publication Date:
2010

Permanent Link:
https://doi.org/10.3929/ethz-a-006300132

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Iridium-Catalyzed Reactions:
Allylic Amination using Sulfamic Acid and
Asymmetric Transfer Hydrogenation using Formic Acid

A dissertation submitted to

ETH ZÜRICH

For the degree of

Doctor of Sciences

Presented by

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Accepted on the recommendation of

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Prof. Dr. Ryan Gilmour, co-examiner

Zürich 2010
Acknowledgements

I am grateful to Professor Erick M. Carreira for giving me the opportunity to work in his group and for supervising my Ph. D. studies. I am thankful for the freedom I had in exploring science and for the trust and patience when things didn’t work as expected.

I would like to thank Professor Ryan Gilmour for being the co-examiner of my thesis.

I would like to thank Dr. Thomas Hoffman for carefully proofreading my thesis and therefore increasing the value of this work. Additionally I would like to thank Johannes Burkhard for checking the experimental part of this thesis.

Some of the projects described in this thesis were carried out as teamwork. I thank Dr. Henar Vázquez-Villa and Dr. Omid Soltani for their contribution, guidance and help in the asymmetric transfer hydrogenation projects. Additionally, I thank Dr. Christian Defieber for being my collaborator in the allylic amination project and for introducing me in the world of methodology projects.

Special thanks go to the H338 squad for a great working atmosphere. My labmates Stefan Reber, Shinji Fujimori, Philippe Kraaz, Florian Kleinbeck, Gary Chinigo, Johannes Burkhard, Bill Morandi, Fabienne Felder and Nick Deprez created a friendly and supporting environment. Along with many discussions about chemistry, there were always non-work related topics discussed and laughed about. They were always a backup when chemistry wouldn’t work out as wished. I also want to thank all other past and present members of the Carreira Group which are not mentioned in here by name.

The excellent infrastructure of the ETHZ with its technical staff simplifies the work of a chemist a lot. Therefore, I would like to thank the “Schalter”, the NMR team, the MS service and the ladies from the “Waschküche”. Special thanks go to Franziska Peyer for taking care of all the administrative work.
For the time I did not spend at the ETH, I would like to thank my friends from my hometown, from the UHCOG and the PUO, which gave me a pleasant time doing sports, organizing parties or just hanging out.

Ich möchte meiner Mutter und auch meiner Schwester für die Unterstützung während meiner Studien- und Doktorandenzeit danken. Dank gilt auch meinem Vater, der mein Interesse an der Wissenschaft geweckt hat.
**Publications**

Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M.

**Iridium-Catalyzed Synthesis of Primary Allylic Amines from Allylic Alcohols: Sulfamic Acid as Ammonia Equivalent**


Soltani, O.; Ariger, M. A.; Carreira, E. M.

**Transfer Hydrogenation in Water: Enantioselective, Catalytic Reduction of (E)-β,β-Disubstituted Nitroalkenes**


Soltani, O.; Ariger, M. A.; Vázquez-Villa, H.; Carreira, E. M.

**Transfer Hydrogenation in Water: Enantioselective, Catalytic Reduction of α-Cyano and α-Nitro Substituted Acetophenones**

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Abstract

The presented thesis summarizes the results of two independent projects. The common goal was to develop new catalytic methods for the introduction of stereogenic centers using small molecules such as sulfamic acid or formic acid.

Iridium-Catalyzed Allylic Amination

The synthesis of unprotected allylic amines remains of great importance since its structural element occurs in natural products and is a useful building block for further transformations. Furthermore, the use of unactivated precursors reduces the substitution by one step, which results in reducing waste, time and ultimately money. Sulfamic acid (H$_2$NSO$_3$H), which is a crystalline, inexpensive solid, does not only in situ activate the allylic alcohol, it also delivers the nucleophile unprotected. A commercially available iridium precursor together with a new phosphoramidite ligand is used as catalyst in this catalytic, racemic transformation (Scheme I).

![Scheme I](image)

Iridium-Catalyzed Asymmetric Transfer Hydrogenation

In the last two decades, catalytic, asymmetric transfer hydrogenation has emerged as a useful method for reducing carbonyls and imines as well as activated double bonds. The use of inexpensive formic acid (HCO$_2$H) makes this transformation especially useful since the only byproduct is gaseous CO$_2$. Additionally, reactions in water are advantageous with respect to safety, cost and environmental benign. The reductions reported herein use an iridium catalyst with a monosulfonylated diamine ligand. These
air- and moisture-stable catalysts are easily prepared by mixing an aqueous iridium precursor with an equimolar amount of a monosulfonylated diamine. It has been discovered that each substrate class favors its own characteristic catalyst (Scheme II).

**Scheme II**
Zusammenfassung

Die vorliegende Doktorarbeit fasst die Resultate von zwei unabhängigen Projekten zusammen. Das gemeinsame Ziel war es, neue katalytische Methoden für die Einführung neuer stereogenen Zentren mit kleinen Molekülen wie Sulfaminsäure oder Ameisensäure zu entwickeln.

**Iridium-katalysierte allylische Aminierung**


![Schema I](image)

**Iridium-katalysierte asymmetrischen Transferhydrierung**

In den letzten zwei Jahrznten hat sich die katalytische, asymmetrische Transferhydrierung zu einer nützlichen Methode zur Reduzierung von Karbonylen und Iminen sowie aktivierten Doppelbindungen entwickelt. Der Gebrauch der kostengünstigen Ameisensäure macht diese Transformation speziell wertvoll, da das

Schema II
### List of Abbreviations and Acronyms

- °C: degree celsius
- Ac: acetyl
- amyl: pentyl
- Anal.: elemental analysis
- Ar: aryl
- BINOL: 1,1′-bi-2,2′-naphthol
- Bn: benzyl
- Boc: tert-butoxycarbonyl
- bpy: bipyridine
- br: broad
- Bu: butyl
- Bz: benzoyl
- calc'd: calculated
- cat.: catalytically
- cm: centimeter
- cod: 1,5-cyclooctadiene
- coe: cyclooctene
- conc.: concentrated
- conv: conversion
- Cp*: pentamethyl cyclopentadienyl
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CsOH</td>
<td>camphor sulfonic acid</td>
</tr>
<tr>
<td>cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift in ppm</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethyl formamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>DPEN</td>
<td>diphenyl ethane diamine</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact ionization</td>
</tr>
<tr>
<td>eq</td>
<td>equivalent</td>
</tr>
<tr>
<td>ESI</td>
<td>electron spray ionization</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>ETHZ</td>
<td>Eidgenössische Technische Hochschule Zürich</td>
</tr>
<tr>
<td>Fmoc</td>
<td>9-fluorenylmethoxycarbonyl</td>
</tr>
<tr>
<td>g</td>
<td>gram</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
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<td>h</td>
<td>hour</td>
</tr>
<tr>
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<td>halogen</td>
</tr>
<tr>
<td>hex</td>
<td>hexyl</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>HPLC</td>
<td>high pressure liquid chromatography</td>
</tr>
<tr>
<td>HR, HRES</td>
<td>high resolution</td>
</tr>
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<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>i</td>
<td>iso</td>
</tr>
<tr>
<td>IR</td>
<td>infra-red</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant in Hz</td>
</tr>
<tr>
<td>l</td>
<td>liter</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium di-iso-propylamide</td>
</tr>
<tr>
<td>LG</td>
<td>leaving group</td>
</tr>
<tr>
<td>Lit.</td>
<td>literature</td>
</tr>
<tr>
<td>LOC</td>
<td>Laboratorium für Organische Chemie</td>
</tr>
<tr>
<td>μ</td>
<td>micro</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>M</td>
<td>molecule ion; molar</td>
</tr>
<tr>
<td>MALDI</td>
<td>matrix-assisted laser desorption ionization</td>
</tr>
<tr>
<td>mbar</td>
<td>millibar</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>Mes</td>
<td>mesityl</td>
</tr>
<tr>
<td>mg</td>
<td>milligram</td>
</tr>
<tr>
<td>min</td>
<td>minute</td>
</tr>
<tr>
<td>ml</td>
<td>milliliter</td>
</tr>
<tr>
<td>Symbol</td>
<td>Definition</td>
</tr>
<tr>
<td>--------</td>
<td>------------</td>
</tr>
<tr>
<td>mmol</td>
<td>millimol</td>
</tr>
<tr>
<td>Ms</td>
<td>mesyl, methane sulfonyl</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>n.d.</td>
<td>not determined</td>
</tr>
<tr>
<td>NADH</td>
<td>reduced form of nicotinamide adenine dinucleotide</td>
</tr>
<tr>
<td>NME</td>
<td>N-methyl ephedrine</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>Nu</td>
<td>nucleophile</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PHOX</td>
<td>phosphino oxazoline</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>quant</td>
<td>quantitative</td>
</tr>
<tr>
<td>Ra</td>
<td>Raney</td>
</tr>
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<td>reference</td>
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<td>room temperature</td>
</tr>
<tr>
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<td>singlet</td>
</tr>
<tr>
<td>t</td>
<td>tert</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>T</td>
<td>temperature</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Name</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethyl silyl</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoro acetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TIPS</td>
<td>tri-iso-propyl silyl</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Tol</td>
<td>toluene</td>
</tr>
<tr>
<td>Ts</td>
<td>tolyl, toluene sulfanyl</td>
</tr>
</tbody>
</table>
XVI
1 Iridium-Catalyzed Reaction of Unactivated Alcohols to Primary Allylic Amines using Sulfamic Acid as an Ammonia Surrogate

1.1 Background

The transition metal-catalyzed asymmetric allylation reaction is an important tool in synthetic organic chemistry. Its wide applicability in total synthesis of biologically active compounds has raised the importance of this transformation. The regio- and stereoselection is a function of several factors, for instance, the metal ion, ligand, nucleophile and substitution pattern on the allylic system (Figure 1).

![Figure 1: Transition metal catalyzed allylic substitution.](image)

In this asymmetric transformation, research was focused on finding catalytic systems which gave access to branched chiral products D derived from either linear achiral substrate A or branched racemic substrate B. Reports of Pd-catalyzed reactions favouring the branched product are scarce, whereas Mo-derived catalytic systems

---

1 The results discussed in this section were achieved in a collaboration with Dr. Christian Defiebe. Furthermore, Patricia Moriel contributed to the progress of the project with a two-month internship in the Carreira Group. Their work is gratefully acknowledged and appreciated.


favour the formation of product D with high degrees of regio- and enantioselectivities. It has been proposed that these reactions proceed through a \( \pi \)-allyl complex and therefore can isomerize through a \( \pi \)-\( \sigma \)-\( \pi \) rearrangement sequence where the stereogenic information in the branched substrate is lost.

Allylic substitution reactions using Rh,\(^6\) Fe,\(^7\) Ru\(^8\) and Ir-catalysts\(^9\) are slightly different from those mentioned above, since they generally react with a high degree of

---

enantiospecificity. In the case of the Rh-catalyzed system, it has been shown by Evans\textsuperscript{10} that the isomerization process (from E to ent-E via σ-enyl complex F) is slow compared to the attack of the nucleophile (Scheme 1). Additionally, in the case of Rh and Ir, $k_2$ is often faster than $k_3$, which explains why both linear substrate A and branched substrate B react to the branched product D. Later, it has been shown by Helmchen that iridium complexes can also be described as σ-enyl complexes.\textsuperscript{11} Furthermore, it has also been shown that this transformation proceeds through a double inversion process. Thus, substrates 1 and 3 have been investigated. Those substrates do not react in such a process, since oxidative addition of [Ir\textsuperscript{I}] to 1 and nucleophilic attack to 4 are prevented due to steric hindrance of either the substrate or the intermediate (Scheme 2).

![Scheme 2](image)

Scheme 2: Double inversion reaction pathway of Ir\textsuperscript{I}-catalyzed allylic substitution.

Another significant observation concerning the mechanism of the Ir-catalyzed allylic substitution with NaCH(CO\textsubscript{3}Me) as nucleophile was made when preparation of an (allyl)(P(OPh)\textsubscript{3})Ir-intermediate was attempted (Scheme 3). Mixing the catalyst precursor [Ir(cod)Cl]\textsubscript{2} (6) with two equivalents of P(OPh)\textsubscript{3} yields the coordinatively unsaturated d\textsuperscript{8}-Ir\textsuperscript{I} complex 7. This complex did not react with a typical allylic acetate; only when NaCH(CO\textsubscript{3}Me) was added, the reaction started. In this case, the nucleophile also reacts as a base, deprotonating at the ortho-position of the triphenylphosphite phenyl ring and

\textsuperscript{9} Helmchen, G.; Dahmz, A.; Bübon, P.; Schelwies, M.; Weihofen, R. Chem. Commun. 2007, 675.
\textsuperscript{10} Evans, P. A.; Nelson, J. D.; J. Am. Chem. Soc. 1998, 120, 5581. Enyl complexes are by definition those which contain discrete σ- and π-metal carbon interactions within a single ligand.
forming a cyclometallated complex which is coordinatively saturated (8). Therefore, in order for the reaction to proceed, the additional P(OPh)₃ must dissociate to generate a catalytically active species. A similar catalyst activation was found in phosphoramidite-Ir complexes (vide infra).

**Scheme 3: Catalyst activation through base induced deprotonation.**

### 1.2 Iridium-Catalyzed Allylic Amination

The first Ir-catalyzed allylation reactions were published by Takeuchi in 1997, the first asymmetric variant in the same year by Helmchen using a PHOX ligand. In 2002, Hartwig reported the first allylic amination using an iridium complex ligated with the phosphoramidite derived by Feringa as catalyst. These chiral phosphoramidites are popular ligands to study electronic and steric effects since their straightforward synthesis allows smooth fine tuning of either the BINOL- or amine-motifs. The most often used pathways to synthesize those ligands are shown in Scheme 4 and are conducted as followed:

---

A: Reaction of neat PCl$_3$ with a binaphthol or biphenol leads to the chlorophosphite which can be treated with a lithiated secondary amine to provide a phosphoramidite. The scope of this method is very broad.

B: An alternative route involves the reaction of PCl$_3$ with a secondary amine followed by treatment of the product with the binaphthol or biphenol to give the phosphoramidite. From a practical point of view, it is important to note that this procedure can also be carried out with the hydrochloride of a secondary amine.

In the first report about iridium-catalyzed allylic aminations, aliphatic amines were used as nucleophiles. These amines are sufficiently basic to induce cyclometallation and therefore activate the catalyst (Scheme 5).
Scheme 5: Catalyst activation through base induced deprotonation.

Some of the results obtained by the groups of Hartwig together with some obtained by the groups of Helmchen\textsuperscript{16} and Alexakis\textsuperscript{17} are collected in Table 1. In general, the monoallylated branched product is the major product, and the results were slightly better with ligand 10 than with ligand 9. With $R^1$ being Ph or alkenyl (Table 1, entries 1-6), enantiomeric excess and regioselectivity was high. Substrates possessing an electron withdrawing group (Table 1, entry 7) or a substituent at the aryl group ortho-position (Table 1, entry 8) proceeded with diminished selectivity. High enantio-, but poor regioselectivity was observed with substrates having an alkyl residue (Table 1, entries 9, 10).

---


In contrast to aliphatic amines, aromatic amines are not basic enough to induce cyclometallation. Therefore, the catalyst was activated by the addition of an external base (usually n-propylamine or DABCO). Some results are summarized in Table 2. Remarkably, high selectivities were obtained even with aliphatic allylic carbonates (Table 2, entries 7, 8).

\[ \text{Table 1: Ir-catalyzed aminations using aliphatic amines.} \]

<table>
<thead>
<tr>
<th>entry</th>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>( L^* )</th>
<th>time [h]</th>
<th>yield [%]</th>
<th>14:15:16</th>
<th>ee [%]</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Bn</td>
<td>9</td>
<td>10</td>
<td>84</td>
<td>98:1:1</td>
<td>95</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Bn</td>
<td>10</td>
<td>n.d.</td>
<td>88</td>
<td>98:2</td>
<td>97</td>
<td>17a</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>PMB</td>
<td>9</td>
<td>18</td>
<td>80</td>
<td>99:0:1</td>
<td>94</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>( \text{C}<em>6\text{H}</em>{11} )</td>
<td>9</td>
<td>9</td>
<td>88</td>
<td>98:2</td>
<td>96</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>( \text{C}<em>6\text{H}</em>{11} )</td>
<td>10</td>
<td>n.d.</td>
<td>89</td>
<td>98:2</td>
<td>98</td>
<td>17a</td>
</tr>
<tr>
<td>6</td>
<td>PhCH=CH</td>
<td>Bn</td>
<td>9</td>
<td>24</td>
<td>61</td>
<td>99:1</td>
<td>97</td>
<td>17a</td>
</tr>
<tr>
<td>7</td>
<td>( \rho-(\text{NO}_2)\text{C}_6\text{H}_4 )</td>
<td>Bn</td>
<td>9</td>
<td>12</td>
<td>67</td>
<td>83:13:4</td>
<td>86</td>
<td>14</td>
</tr>
<tr>
<td>8</td>
<td>( \alpha-(\text{MeO})\text{C}_6\text{H}_4 )</td>
<td>Bn</td>
<td>9</td>
<td>16</td>
<td>77</td>
<td>95:4:1</td>
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<td>9</td>
<td>( \text{o-Pr} )</td>
<td>Bn</td>
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<td>10</td>
<td>66</td>
<td>88:8:4</td>
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<td>3</td>
<td>63</td>
<td>84:16</td>
<td>96</td>
<td>9</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield of branched product.

---

<table>
<thead>
<tr>
<th>entry</th>
<th>R¹</th>
<th>R²</th>
<th>Activator</th>
<th>L*</th>
<th>time [h]</th>
<th>yield 18 [%]</th>
<th>18:19</th>
<th>ee [%]</th>
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<td>H</td>
<td>DABCO</td>
<td>9</td>
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<td>72</td>
<td>&gt;99 : 1</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>H</td>
<td>DABCO</td>
<td>11</td>
<td>6</td>
<td>80</td>
<td>&gt;99 : 1</td>
<td>96</td>
</tr>
<tr>
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<td>p-Me</td>
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<td>94</td>
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<td>4</td>
<td>Ph</td>
<td>p-OMe</td>
<td>DABCO</td>
<td>11</td>
<td>4</td>
<td>91</td>
<td>98 : 2</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>p-OMe</td>
<td>nPrNH₂</td>
<td>9</td>
<td>2</td>
<td>95</td>
<td>95 : 5</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>p-CF₃</td>
<td>DABCO</td>
<td>11</td>
<td>16</td>
<td>72</td>
<td>94 : 6</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>nPr</td>
<td>H</td>
<td>DABCO</td>
<td>11</td>
<td>3</td>
<td>87</td>
<td>98 : 2</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>tPr</td>
<td>H</td>
<td>DABCO</td>
<td>11</td>
<td>16</td>
<td>83</td>
<td>97 : 3</td>
<td>97</td>
</tr>
</tbody>
</table>

*1 mol% [IrCl(cod)]₂, 2 mol% L*, b 50 mol%, c 5 mol% DABCO.

Later, the enantiocontrol due to the stereochemical elements of the catalyst were elucidated. By screening a variety of unsymmetrically substituted secondary amines, it was determined by Hartwig that the stereogenic center in the distal phenethyl group does not affect the stereochemical outcome of the allylation reaction. Furthermore, by replacing BINOL with biphenol, which adopts only one atropisomer, the rates, yields and selectivities remained the same (Figure 2).

---

1.3 Sulfamic Acid as Ammonia Equivalent

Most of the methodologies described above use anilines and benzylamines as \( N \)-nucleophiles. This gives access to secondary and tertiary amines in good yields and selectivities. However, to arrive at primary amines, difficult deprotection steps are required. Some research groups already introduced different \( N \)-nucleophiles whose deprotection in the allylated product is more straightforward.

*Take moto* employed hydroxylamines as suitable nucleophiles, using phosphates instead of carbonates as the activated allylic precursor.\(^{20}\) To increase the selectivities, addition of CsOH-H\(_2\)O was required (Scheme 6).
Later on, Helmchen introduced sulfonylamines and acylated amines as nitrogen surrogates.\textsuperscript{21} No additional base was required since either the liberated methyl carbonate or the methoxide presumably act as base, only the doubly Boc-protected amine needs to be deprotonated prior to the addition (Scheme 7).

\textit{Scheme 7: Helmchen’s sulfonylated and acylated amines as N-nucleophiles.}

We were interested in finding an ammonia surrogate which would produce directly an unprotected primary amine, for practical and atom-economic\textsuperscript{22} reasons. We decided to explore the ability of sulfamic acid (H\textsubscript{2}NSO\textsubscript{3}H)\textsuperscript{23} to fulfill those criteria. This compound was used as acid catalyst in several processes\textsuperscript{24} as well as a scavenger for

\begin{itemize}
\item \textsuperscript{22} a) Trost, B. M. \textit{Science} \textbf{1991}, 254, 1471; b) Trost, B. M. \textit{Angew. Chem. Int. Ed.} \textbf{1995}, 34, 259.
\item \textsuperscript{23} Benson, G. A.; Spillane, W. J. \textit{Chem. Rev.} \textbf{1980}, 80, 151.
\item \textsuperscript{24} Wang, B. \textit{Synlett} \textbf{2005}, 1342.
\end{itemize}
hypochloric acid in the Lindgren oxidation. However, sulfamic acid was never used as a nitrogen source in a chemical process.

Our investigations started by examining tert-butyl cinnamyl carbonate 27 as activated allylic precursor together with Ir\(^1\) and phosphoramidite ligand 9. Presumably due to the insolubility of sulfamic acid in common organic solvents such as THF, CH\(_2\)Cl\(_2\), CH\(_3\)CN, EtOH, MeOH and acetone, no conversion was observed using these solvents for an allylic amination. Even in highly dipolar, aprotic solvents such as DMF, DMF or DMSO, which can solubilize sulfamic acid, no consumption of the carbonate was observed.

When branched carbonate 28 was used instead of linear carbonate 27, a modest conversion (15 %) in DMF was observed. Even more surprising and beneficial was the fact that unactivated branched alcohol 29 can be used under otherwise identical conditions to give the same result (15 % conversion). Since these metal-catalyzed allylic substitution reactions usually required pre-activation (halides, esters, carbonates etc.),

this was a big improvement on the process. Additionally, the ambivalent nature of the sulfamic acid simplifies the process, since it acts a nitrogen source as well as an in situ activator for the free alcohol.

![Figure 3: Employed substrates in the allylic amination.](image)

Further optimization studies focused on the influence of the ligand. The use of PyBOX-ligand 24 decreased the conversion of the process (5 %). The amination hardly proceeded when using either PPh\(_3\) or P(NMe\(_2\))\(_3\) (< 5 % conversion), however, an increase

in reactivity was observed using P(PhO)₃ (25 % conversion). Encouraged by this result, more P-ligands were examined to drive the reaction to completion.

![30][31][32]

*Figure 4: Phosphoramidites explored in the allylic amination reaction.*

A further modest improvement was achieved using 1.5 mol % [Ir(cod)Cl]₂ with 3 mol % of Ligand 30, as 30 % conversion was observed. Using the phosphoramidite derived from biphenol and the commercially available 5H-dibenzo[b,f]azepine (31), a very clean reaction converted the alcohol with more than 99 % conversion into the primary amine (DMF, 24 h, 23 °C). Repeating the reaction using the saturated analogue 32 under otherwise identical conditions caused the conversion to drop down to 20 %. Since the central 7-membered ring in 5H-dibenzo[b,f]azepine adopts a boat conformation, which isolates the double bond from conjugation with the annulated benzene rings,²⁷ it makes it more susceptible for coordination to a transition metal.²⁸ It’s worth mentioning that this allylation reaction proceeds with complete regioselectivity. Furthermore, neither di- nor triallylated products were detected.

With optimal reaction conditions, a series of allylic amines were synthesized. A convenient way of isolating the primary amines is to precipitate their hydrochloride salt (Table 3, entry 1). However, since a free amine is produced, it can subsequently be

protected with a protecting group of choice, e.g. by treating it with benzoyl chloride, Boc₂O or trifluoroacetic anhydride (Table 3, entries 2, 3 and 4 respectively). The reaction conditions also tolerate phenyl-, cyclohexyl and benzyloxysubstituents at the branched position (Table 3, entries 5, 6 and 7 respectively). In addition, the reaction of hexa-1,5-dien-3-ol proceeds without any double bond isomerization (Table 3, entry 8).

### Table 3: Investigation of the substrate scope.

<table>
<thead>
<tr>
<th>entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>substrate</th>
<th>product</th>
<th>yield [%]&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="Ph-CH=CH" alt="OH" />_OH</td>
<td><img src="Ph-CH=CH" alt="NH₂Cl" />_NH₂Cl</td>
<td>82&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td><img src="Ph-CH=CH" alt="OH" />_OH</td>
<td><img src="Ph-CH=CH" alt="NH₂Bz" />_NH₂Bz</td>
<td>73&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td><img src="Ph-CH=CH" alt="OH" />_OH</td>
<td><img src="Ph-CH=CH" alt="NH₂Boc" />_NH₂Boc</td>
<td>71&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td><img src="Ph-CH=CH" alt="OH" />_OH</td>
<td><img src="Ph-CH=CH" alt="NH₂COCF₃" />_NH₂COCF₃</td>
<td>71&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td><img src="Ph-CH=CH" alt="OH" />_OH</td>
<td><img src="Ph-CH=CH" alt="NH₂Cl" />_NH₂Cl</td>
<td>76&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td><img src="Cy-CH=CH" alt="OH" />_OH</td>
<td><img src="Cy-CH=CH" alt="NH₂Cl" />_NH₂Cl</td>
<td>75&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td><img src="BnO-CH=CH" alt="OH" />_OH</td>
<td><img src="BnO-CH=CH" alt="NH₂Cl" />_NH₂Cl</td>
<td>74&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td><img src="OH-CH=CH" alt="OH" />_OH</td>
<td><img src="OH-CH=CH" alt="NH₂Cl" />_NH₂Cl</td>
<td>76&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield after purification by chromatography. Regioselectivity was > 99:1 as determined by ¹H-NMR spectroscopy of the unpurified reaction mixtures by comparison of the vinyl protons.  
<sup>b</sup> Isolated as hydrochloride salt by treatment of the purified amine with 2 M HCl in Et₂O.  
<sup>c</sup> Treatment of the unpurified reaction mixture with Et₃N and BzCl.  
<sup>d</sup> Treatment of the unpurified reaction mixture with 0.5 M NaOH and Boc₂O.  
<sup>e</sup> Treatment of the unpurified reaction mixture with K₂CO₃ and (CF₃CO)₂O. For further experimental details, see experimental section.
1.4 Spectroscopic Investigations

To gain further insight in this transformation, the course of the reaction was screened using time dependent $^1$H-NMR spectroscopy, monitoring the allylic proton $H$-3 of test substrate 29 in DMF-d$_7$. With preparative scale experiments, NMR-studies revealed clean transformation of free alcohol 29 into free amine 33 within 3 h (Figure 5). The influence of excess sulfamic acid (2 eq) was examined in a distinct experiment. Initially, a free amine is formed within 2 h, as observed by the appearance of an allylic proton signal at $\delta$ 3.88 ppm. Upon exposure to the reaction conditions for another 8 h, the amine undergoes partial conversion into another product which has a characteristic allylic signal at $\delta$ 4.46 ppm. In order to assign a structure for this species, we conducted additional experiments in d$_7$-DMF: Treatment of alcohol 29 with two equivalents of sulfamic acid leads after 8 h to the quantitative formation of sulfate ester 34 with its signal at $\delta$ 4.72 ppm, which is consistent to what is known in the literature.

![Figure 5: Selected results from spectroscopic experiments.](image)

When using the more powerful sulfonylating agent sulfur trioxide $N,N$-dimethyl formamide on alcohol 29, sulfate 34 was obtained within 1 h. When free amine 33 was used under these conditions, sulfarmate 35 was obtained within 9 h along with side products. These spectroscopic observations allow us to draw the following conclusions: (1) When sulfamic acid is used in excess, the initially produced amine undergoes partial sulfamation with the second equivalent of sulfamic acid to form 35. This product is only formed after 29 has been entirely transformed into 33. (2) In the course of the iridium-catalyzed amination, no signals from 34 are observed during the reaction. Because of the long reaction time required for sulfation with sulfamic acid (8 h), it is unlikely that sulfate ester 34 serves as an activated intermediate in the iridium-catalyzed reaction. (3)
Moreover, the absence of 35 in the catalytic process leads us to suspect that sulfamic acid is not acting as nucleophile.

A working model has been proposed based on the observations made (Figure 6). It has been suggested in the literature that sulfamic acid undergoes a condensation with DMF\(^{29}\) to form a Vilsmeier-like intermediate 36,\(^{30}\) which is then attacked by the allylic alcohol to form 37.\(^{31}\) We assume that this reactive species allows the iridium to oxidatively insert into the C-O bond to form 38, which is sufficiently electrophilic to be attacked by NH\(_3\), liberating the free amine and the Ir\(^{1}\), which enters the catalytic cycle again.

\[ \text{Figure 6: Proposed working model.} \]


\(^{30}\) DMF-SO\(_2\) can be viewed as Vilsmeier adduct: Wolfson, M. L.; Shen Han, T. M. J. Am. Chem. Soc. 1959, 81, 1764.

1.5 Aiming at the Development of an Asymmetric, Catalytic Process

As we were interested in applying this allylic amination in an asymmetric process, it was investigated whether the reaction proceeds in an enantiospecific way. Thus, the enantiomerically enriched (R)-phenylprop-2-en-1-ol 39 was submitted to reaction conditions using achiral ligand 31. After 24 h at 23 °C, the amine was formed and isolated as its benzyolated derivative 40. However, during the course of the reaction, the enantioselectivity decreased from 88 % to 44 % (Scheme 8).

Scheme 8: Experiment to examine enantiospecificity.

Using (S)-BINOL instead of 2,2’-biphenol yields chiral ligand 43, which was used to catalyze the allylic amination of 1-cyclohexylprop-2-en-1-ol 41. The corresponding (S)-1-cyclohexylprop-2-en-1-amine hydrochloride 42 was obtained in 70 % yield and 70 % ee. The ee can be upgraded by trituration up to 93 % (Scheme 9).

Scheme 9: Experiment to examine enantioselectivity.
The straightforward procedure for synthesizing the phosphoramidites allows the incorporation of a wide range of diol-backbones as well as substituents at the 5H-dibenzob[\textit{b,f}]azepine site. Therefore, a series of substituted BINOL derived ligands were prepared and examined using standard substrate 29 (Table 4). To our displeasure, none of the newly synthesized ligands yielded an improved enantiomeric excess compared to ligand 43, the best being the monomethylated BINOL with 45 % ee (Table 4, entry 8).

**Table 4: Different ligands affecting the enantioselectivity.**

<table>
<thead>
<tr>
<th>entry\textsuperscript{a}</th>
<th>ligand</th>
<th>ee [%]\textsuperscript{b}</th>
<th>entry\textsuperscript{a}</th>
<th>ligand</th>
<th>ee [%]\textsuperscript{b}</th>
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<td>5</td>
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</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Image" /></td>
<td>25</td>
<td>6</td>
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<td>13</td>
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<td>3</td>
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<td>25</td>
<td>7</td>
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<tr>
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<td>20</td>
<td>8</td>
<td><img src="image8.png" alt="Image" /></td>
<td>45</td>
</tr>
</tbody>
</table>

\textsuperscript{a} 1 mol% \([\text{IrCl(cod)}]_2\), 2 mol % ligand. \textsuperscript{b} Analyzed by chiral HPLC (Chiralcel OD-H column) as their benzoylated derivatives.

### 1.6 Mechanistical Studies

It was in our interest to explore whether the low enantioselectivity is derived from poor stereoiinduction of the catalyst or from competing facial attacks (\textit{Re} or \textit{Si}) of the
nucleophile. Therefore, enantioenriched monodeuterated alcohol 48 was synthesized (Scheme 10).

![Chemical structure diagram](image)

(Scheme 10: Preparation of enantioenriched monodeuterated alcohol 48/49.

Cyclohexylcarboxaldehyde 44 was transformed into propargylic alcohol 45 using the acetylene addition methodology developed by Carreira in 98 % ee.\textsuperscript{32} After deprotection to terminal alkyne 46, a proton/deuterium exchange was conducted with ethyl magnesium bromide and DCl in D₂O. Hydrogenation with Lindlar’s catalyst produced diastereomeric alkenes 48 and 49 with a ratio of 4:1 favouring cis-alkene.

![Chemical structure diagram](image)

(Scheme 11: Deuterium labeled racemisation experiment.)

Iridium-catalyzed allylic substitutions are initiated by oxidative addition of iridium from the backside (Scheme 2). If we now assume the attack of “NH₃” also occurs through a S₂N₂ mechanism, the reaction of cis-alkene 48 with racemic ligand 31 would produce 50 and 51 with concomitant lowering of enantiomeric excess. The same consideration can be made for the reaction with trans-alkene 49, which would produce 52 and 53 (Scheme 11). A rationale for the isomerization of 48 is shown in Scheme 12. After oxidative addition of iridium, the allylic intermediate can now isomerize through σ-π-σ rearrangement. When “NH₃” attacked the intermediate prior to isomerization, compound 50 is produced. With σ-π-σ rearrangement, the iridium can change facial orientation with consequent rearrangement at the terminal alkene position to give 51. Diastereomer 49 can be converted into 52 and 53 via the same pathway.

Scheme 12: Rationale for isomerization of 48.
Therefore, the 4:1 mixture of 48 and 49 was submitted to reaction conditions and subsequently benzyolated. NMR of the isolated product revealed a cis:trans ratio of 59:41, where the cis-product was 50a+53a and trans-product 51a+52a (Scheme 13).

![Scheme 13: Result of deuterium labelled racemization experiment.](image)

If the assumption that the reaction proceeds through double inversion is correct, it should be possible to determine the enantiomeric excess of the products from the cis:trans ratio. For both isomers 48 and 49, we can define x as the percent mole fraction which did not isomerize at the terminal olefin (Scheme 14).

![Scheme 14: Determination of the enantiomeric excess.](image)

Since the NMR of the unpurified reaction mixture reveals that the amount of cis product (which is 50 + 53) is 59 %, and taking into account that initial ee of 48 and 49 was 98 %, the value of x can be determined as x = 0.677. Therefore, the enantiomeric excess can be calculated as \( \frac{[(50+52)-(51+53)]}{[(50+52)+(51+53)]} \), which gives a calculated value of ee = 33 %. Submitting the product mixture to HPLC conditions, an
enantiomeric excess of 33 % was measured, which is exactly what has been calculated. Therefore, it can be concluded that the low enantiomeric excess is due to poor stereoinduction of the catalyst, not because of competing facial attacks of “NH$_3$”.

1.7 Summary

In summary, we have demonstrated for the first time an iridium-catalyzed conversion from an allylic alcohol to a primary allylic amine with the use of sulfamic acid. A preactivation was not needed, and a protecting group for the nitrogen was not required. Further studies concerning this process are underway. Additionally, the use of sulfamic acid as an ammonia equivalent is interesting since it opens applications to similar substitution reactions.

2 Iridium-Catalyzed Asymmetric Transfer Hydrogenation using Formic Acid as Hydride Surrogate

2.1 Historical Background

2.1.1 Transfer Hydrogenation Reactions

Generally speaking, hydrogen transfer reactions are those where a hydrogen donor (DH$_2$) delivers hydrogen to an acceptor (A or A-X) via a metal catalyst, resulting in the net addition of H$_2$. This usually gives the hydrogenated product AH$_2$, or less often, hydrogenolysis of A-X affords A-H and H-X (Scheme 15).

\[
\begin{align*}
DH_2 + A & \xrightleftharpoons{\text{Metal}} D + AH_2 \\
DH_2 + A-X & \xrightleftharpoons{\text{Metal}} D + A-H + A-X
\end{align*}
\]

Scheme 15: Schematic representation of hydrogen transfer reactions.

Compared to hydrogenations using molecular H$_2$, transfer hydrogenation advantages feature avoidance of pressure vessels and minimizing risk concerning safety. A disadvantage is formation of by-product “D” in stoichiometric amounts, which can cause problems at several fronts, mainly because it can act as hydrogen acceptor and therefore compete with the substrate. This can be solved by correctly choosing the hydride donor by either making the reaction irreversible (by using formic acid or hydrazine, therefore “D” is a gas and instantly removed), or by making the reaction essentially irreversible (by using a secondary alcohol as reductant and solvent simultaneously).

---

The very first catalytic hydrogen transfer reaction was reported in 1903 by Knoevenagel. He observed that 1,4-dihyroterephthalate disproportionates in the presence of palladium to dimethyl terephthalate and hexahydrotarephthalate.\textsuperscript{35} In 1925, the first transfer hydrogenation of ketones and aldehydes was reported, which is known since then as the Meerwein-Ponndorf-Verley reduction (Scheme 16).\textsuperscript{36} The first asymmetric variant of this reaction was published in 1950 by Doering and Young, who used an enantioenriched secondary alcohol to induce chirality.\textsuperscript{37}

\textbf{Knoevenagel:}

\[
\begin{align*}
\text{MeO}_2\text{C} & \xrightarrow{\text{Pd}} \text{MeO}_2\text{C} + \text{MeO}_2\text{C}, \\
54 & \quad 55 \quad 56
\end{align*}
\]

\textbf{Meerwein-Ponndorf-Verley:}

\[
\begin{align*}
\text{MeOH} & \xrightarrow{\text{Pd}} \text{MeOH} + \text{MeOH}, \\
\text{57} & \quad \text{58} \quad \text{59}
\end{align*}
\]

\textbf{Scheme 16: First published transfer hydrogenation reactions.}

The use of homogeneous catalysis emerged in the 1960’s. Henbest and Mitchell discovered iridium complexes to be able to reduce cyclohexanones with iso-propanol.\textsuperscript{38a-c} A few years later Blum reported rhodium-catalyzed transfer hydrogenation with formic acid, albeit in low yield.\textsuperscript{38d-f} In the mid 1970’s, Sinou and Ohkubo disclosed ruthenium complexes to perform transfer hydrogenation, with asymmetric induction with a chiral carbohydrate.\textsuperscript{38g,h} Some examples are shown in Scheme 17.

\textsuperscript{35} Knoevenagel, E.; Bergdolt, B. \textit{Chem. Ber.} \textbf{1903}, 36, 2857.
Since the 1990’s, a number of catalytic systems have been developed. Worth mentioning are the reports by Pfaltz, Genêt, Lemaire and Evans. Reduction of acetophenone with iso-propanol as reductant works in good yields with moderate to good enantioselectivities (Figure 7).
However, for these systems the low stereoinduction or high catalyst loadings were significant drawbacks. A fundamental breakthrough was then made by Noyori, Ikariya and coworkers.\textsuperscript{40} An asymmetric transfer hydrogenation with a ruthenium catalyst having a monosulfonylated diamine or an amino alcohol as ligand and \textit{iso}-propanol or formic acid as reductant is reported. Ketones are reduced in high yields and excellent selectivities with a catalyst loading as low as 0.5 mol %.


\textit{Figure 7: Different catalytic systems for the asymmetric transfer hydrogenation.}
2.1.2 Mechanistic Considerations

Many advances in mechanistic insight have been made in the case of ruthenium catalyzed transfer hydrogenations, first published by Noyori.\textsuperscript{40a,41} Depending on the nature of the ligand, the reaction can either proceed through a ruthenium monohydride or a ruthenium dihydride as catalytically active species. If ruthenium is ligated with an amino alcohol or a monosulfonylated diamine, the hydrogen is delivered from a monohydridic species such as 68. The catalysts are formed by mixing ruthenium precursor 65 with 2 equivalents of ligand to give 66. Upon deprotonation, 16-electron complex 67 is formed which is then ready to react with the hydrogen donor to yield 18-electron complex 68. After hydride delivery, complex 67 is reformed and can enter the catalytic cycle again (Scheme 18).

Scheme 18: Catalytic cycle of Ru-monohydride promoted hydrogen transfer.

The reduction step takes place in six-membered pericyclic transition state 69. Both hydrogens (one from N and one from Ru) are transferred simultaneously to the ketone. Hydrogen bonding attracts the substrate to the reaction site on the metal (there is no coordination of the substrate to the metal), followed by insertion of the substrate into the metal-hydride bond (as observed in the classical hydridic route mechanism). The activation occurs via “metal-ligand bifunctionals catalysis”, which was already noted by Noyori.\textsuperscript{40a} This mechanism was later confirmed by related studies with different model systems.\textsuperscript{42} That the reaction takes place in an outer coordination sphere of the metal is the

main difference compared to the classical route. The other big difference is that this reaction pathway features anionic ligands rather than neutral ligands at the coordination site. Therefore, a bidentate chelating ligand having a protonated donor center X-H (where X=O or X=N_Y, with Y being electron withdrawing) vicinal to a nitrogen donor is crucial for this mechanistical pathway (e.g. aminoalcohols or monosulfonfylated diamines).

As shown in Scheme 18 in transition state 69, the reduction of an aryl alkyl ketone occurs preferentially from the more congested site. This asymmetric bias results from a favourable CH/π interaction in the transition state, which allows the reaction to proceed through the more encumbered face. Metal-ligand bifunctional catalysis also takes place in transfer hydrogenation reaction with Shvo catalyst 70 (Scheme 19), albeit with some differences to the case above, however this catalytic system does not require a base for initiation.

Scheme 19: Catalytic cycle of H-transfer promoted by Shvo catalyst.

---

Dimer 70 partially dimerizes in solution to fragments 71 and 72, with both species playing an active role in the catalytic cycle. The latter one, which is a 16-electron complex, gets reduced by taking up hydrogen from the donor substrate. After reduction of the substrate, complex 72 is regenerated and the catalytic cycle is closed. The hydroxycyclopentadienyl moiety acts as anionic ligand, therefore the proton from OH and the hydride from RuH are transferred simultaneously to the carbonyl.

If the ligand carrying the stereochemical information is not anionic, ruthenium-catalyzed transfer hydrogenation reaction proceeds through a distinct mechanistic pathway involving a ruthenium dihydride intermediate. The mechanism of tris(triphenylphosphine) dihydride 76 has been studied and elucidated by Bäckvall and is shown in Scheme 20.46

---

Scheme 20: Catalytic cycle of Ru-monohydride promoted hydrogen transfer.

When dichloro complex 74 is treated with base in iso-propanol, dihydrido complex 76 is formed, which is able to reduce ketones in contrast to intermediate 75 which is not an active species. Labelling studies with deuterium revealed that the hydrogens, which are delivered by the iso-propanol, do not retain their identity, but are scrambled between the two sites of the carbonyl moiety. In other words, the proton from
the hydroxyl group of iso-propanol does not forcefully become transferred to the oxygen of the hydroxyl group of the product, it can also be transferred to the α-position of the hydroxyl. Therefore, mixed hydride deuteride 81 has to be involved in the catalytic cycle.

Treating of precursor 74 with monodeuterated alcohol 78 and base leads to active catalyst 77. Addition of acetophenone leads to ruthenium complex 79, which reacts upon reductive elimination to the reactive 14-electron complex 80. After oxidative addition of 78 and β-hydride elimination, mixed hydride deuteride 82 is formed. In the next step, scrambling occurs since acetophenone can insert either in the Ru-D or in the Ru-H bond, which leads to isomers 81a and 81b respectively, and finally to phenylethanols 78a and 78b. In the monohydride mechanism, deuterium incorporation at the α-position is high, whereas the dihydridic pathway leads to equimolar incorporation of hydrogen and deuterium. It has later been shown that, with neutral ligands, rhodium and iridium catalysis occurs through monohydride pathway, while both mechanisms can operate with ruthenium, the choice being determined by the nature of the ancillary ligands.47

2.1.3 Hydrogen Donors

Iso-propanol and formic acid are by far the most frequently used sources of hydrogen in transfer hydrogenation processes. Iso-propanol can be used concomitantly as solvent, since it dissolves most substrates and doesn’t interfere with the catalyst during long reaction times, even at reflux. It usually requires a base such as hydroxide or an alkoxide for the reaction to occur.

Formic acid or sodium formate is the other main source for hydride delivery. It has the advantage that the dehydrogenation is irreversible, but the disadvantage lies in the formers acidity, since many complexes undergo decomposition in formic acid in water or in formic acid/triethylamine azeotrope (HCO₂H:NEt₃= 5:2).

---

Another hydrogen donor is the Hantzsch ester 83, discovered already in 1881.\textsuperscript{48} This reagent mimicks the natural NADH and is most often used in organocatalysis.\textsuperscript{49} Two representative examples of reduction of carbonyl groups are shown in Scheme 21.\textsuperscript{50}

\begin{align*}
\text{NADH} & \\
\text{Hantzsch ester 83} & \\
\text{List:} & \\

\begin{align*}
\text{CHO} & \\
\text{Me} & \\
\text{Me} & \\
\text{Me} & \\
\text{84} & \\
\rightarrow & \\
\text{CHO} & \\
\text{Me} & \\
\text{Me} & \\
\text{Me} & \\
\text{85} & \\
& \text{dioxane, 50 °C, 24 h} \\
& 87 \% \text{ yield} \\
& 96 \% \text{ ee} \\
& (\text{Ref 50a})
\end{align*}

\begin{align*}
\text{Me} & \\
\text{O} & \\
\text{86} & \\
\rightarrow & \\
\text{Me} & \\
\text{87} & \\
& \text{Et}_2\text{O, 0 °C, 7 h} \\
& 72 \% \text{ yield} \\
& 95 \% \text{ ee} \\
& (\text{Ref 50b})
\end{align*}

\textbf{Scheme 21: Transfer hydrogenation with Hantzsch ester as hydride donor.}

2.1.4 Catalysts

The most widely used and therefore most efficient catalysts are based on ruthenium, rhodium and iridium. These are the metals of choice, while other second or third row transition metals are less suited for this reaction.

A huge number of ligands have also been published in the last years. In general, aminoalcohols have higher reaction rates than the monosulfonylated diamines. In contrast, Noyori’s complex [Ru\{(S,S)-DPEN\}{\eta^6}\text{-cymene}] is the catalyst with the broadest scope. A list of some ligands with yields and enantiomeric excesses is shown in Figure 9.\textsuperscript{51}

![Figure 9: Yield/ee obtained in asymmetric transfer hydrogenation of acetophenone in iPrOH by different metal complexes (the relevant reference is reported in parantheses).]

Amongst these “classical” anionic and neutral ligands, Wills developed a catalyst class where the arene moiety is tethered to the chelating ligand. This additional element does not only stabilize the catalyst, it also adds another element of stereocontrol. The reactions rates with these catalysts are generally higher compared to their non-tethered analogues, with high yields and enantioselectivities (Figure 10).

![Catalyst Structures](image)

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield</th>
<th>Enantiomeric Excess (ee)</th>
</tr>
</thead>
<tbody>
<tr>
<td>88</td>
<td>iPrOH</td>
<td>99</td>
<td>96</td>
</tr>
<tr>
<td>89</td>
<td>HCO₂H/NEt₃</td>
<td>99</td>
<td>96</td>
</tr>
<tr>
<td>90</td>
<td>HCO₂H/NEt₃</td>
<td>99</td>
<td>98</td>
</tr>
</tbody>
</table>

Figure 10: Wills’ tethered ruthenium and rhodium catalysts.

### 2.1.5 Iridium-Catalyzed Transfer Hydrogenations in Water

In the last few decades, chemistry was investigated which is conducted in aqueous media. Water as solvent has several advantages, including costs, safety and...
environmental concerns.\textsuperscript{53} In 1969, \textit{Maitlis} and co-workers discovered that reaction of IrCl\(_3\) with hexamethyl \textit{Dewar} benzene \textit{91} to a dinuclear chloro bridged dimer \textit{92} in methanol.\textsuperscript{54} A few years later complex \textit{93} derived from \textit{92} was reported to perform a transfer hydrogenation with butadiene. However, this reaction was conducted in CH\(_2\)Cl\(_2\) and stochiometric in metal (Scheme 22).

\begin{equation*}
\text{Scheme 22: Synthesis of dinuclear iridium-Cp*-complex and transfer hydrogenation reaction.}
\end{equation*}

In 1999, \textit{Ogo} and \textit{Watanabe} reported an aqueous iridium catalyst derived from dinuclear complex \textit{92}, which is able to reduce aldehydes and ketones in water, using formate as hydride donor.\textsuperscript{55} The reaction is pH-dependent, showing a maximum turnover at pH 3.2. In \textit{\textsuperscript{1}H-NMR} titration experiments, the active catalyst has been elucidated as dinuclear complex \textit{95}. A proposed mechanism is shown in Figure 11.


\textsuperscript{55} Ogo, S.; Makihara, N.; Watanabe, Y. \textit{Organometallics} 1999, 18, 5470.
Asymmetric Transfer Hydrogenation

Figure 11: Proposed mechanism for the transfer hydrogenation of aqueous complex 96.

At pH 3.2, the aqueous complex 96 is in equilibrium with dinuclear complex 97. Addition of sodium formate to the equilibrium generates active catalyst 95 after β-hydride elimination and concomitant CO₂ evolution. It reacts with the substrate through transition state 98 to yield the reduced product, and, after replacement of the coordinating alcohol by formate and loss of CO₂, the active catalyst is regenerated.
Two years later, the same group reported a transfer reaction where two water molecules are replaced by a bipyridine. The resulting catalyst is active in reducing carbonyl compound as well as in reductive amination. This catalyst is easily prepared by mixing the parent aqueous complex 96 with an equimolar amount of bipyridine in water to give 100 (Scheme 23). The active catalytic species has been elucidated as structure 101, which is in contrast to 95 monomeric.

Scheme 23: Formation of catalyst precursor 100 and active catalyst 101.

2.2 Asymmetric Transfer Hydrogenation of $\alpha$-substituted Acetophenones$^{57}$

2.2.1 Background

Phenylethanols bearing functional groups in the $\beta$-position are useful building blocks. Depending on the nature of the functional group, these substrates give access to a broad range of transformations. For cyano- and nitro-substituted phenylethanols, a few possible transformations are shown in Figure 12. Furthermore, $\beta$-halogenated alcohols are viable precursors for terminal epoxides.

![Figure 12: Possible functional group transformations of $\beta$-substituted phenylethanols.](image)

$^{57}$ The results discussed in this section were achieved in collaboration with Dr. Omid Soltani. His work is gratefully acknowledged and appreciated.
Although acetophenones having substituents at the aryl site have been extensively studied, acetophenones bearing functional groups in the α-position have only been studied to a limited extent, namely catalytic reductions based on ruthenium$^{58a,b}$ and rhodium$^{58c}$ as well as enzymatic reductions$^{58d-g}$ with excellent yields and selectivities. Some representative examples are shown in Table 5.

**Table 5: Asymmetric transfer hydrogenation of α-substituted acetophenones.**

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>catalyst</th>
<th>reductant</th>
<th>yield $^b$ [%]</th>
<th>ee [%]</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>102</td>
<td>75</td>
<td>HCO$_2$H/NEt$_3$</td>
<td>99</td>
<td>98</td>
<td>57a</td>
</tr>
<tr>
<td>2</td>
<td>103</td>
<td>75</td>
<td>HCO$_2$H/NEt$_3$</td>
<td>90</td>
<td>98</td>
<td>57a</td>
</tr>
<tr>
<td>3</td>
<td>102</td>
<td>76</td>
<td>HCO$_2$H/NEt$_3$</td>
<td>98</td>
<td>97</td>
<td>57b</td>
</tr>
<tr>
<td>4</td>
<td>104</td>
<td>77</td>
<td>HCO$_2$H/NEt$_3$</td>
<td>99</td>
<td>97</td>
<td>57c</td>
</tr>
<tr>
<td>5</td>
<td>102</td>
<td>CMCR$^b$</td>
<td>NADPH</td>
<td>85</td>
<td>98</td>
<td>57d</td>
</tr>
<tr>
<td>6</td>
<td>102</td>
<td>Ymr226c$^c$</td>
<td>NADPH</td>
<td>83</td>
<td>99</td>
<td>57f</td>
</tr>
<tr>
<td>7</td>
<td>104</td>
<td>ADH-A$^d$</td>
<td>2-octanol</td>
<td>81</td>
<td>99</td>
<td>57g</td>
</tr>
</tbody>
</table>

$^a$Isolated yield. $^b$Carbonyl reductase from *candida magnoliae*. $^c$Alcohol dehydrogenase from *saccharomyces cerevisiae*. $^d$Alcohol dehydrogenase from *rhodococcus ruber*.

---

2.2.2 Optimization Studies and Substrate Scope

The preparation of \( \alpha \)-substituted acetophenones is shown in Scheme 24. For \( \alpha \)-cyano acetophenones, benzoic ester was added to a solution of KO\textsuperscript{amyl} in acetonitrile. For \( \alpha \)-nitro acetophenones, benzoic triazole was added to a solution of KO\textsuperscript{Bu} in nitromethane. The \( \alpha \)-chloro acetophenone is commercially available.

![Scheme 24: Preparation of \( \alpha \)-substituted acetophenones.](image)

Our strategy relied on using monosulfonylated diamines as chiral ligands, since Ikariya showed their ability to perform transfer hydrogenations reactions.\textsuperscript{59} The catalysts are easily prepared (similar to Scheme 23). To an aqueous solution of precursor 96 was added a solution of a monosulfonylated diamine of choice in methanol. After three hours at room temperature, the solvents were removed \textit{in vacuo} (Scheme 25). These catalysts can be stored without precaution, since they are stable to oxygen and moisture.

![Scheme 25: Catalyst preparation.](image)

For initial screening, 3-oxo-3-phenylpropanenitrile 108 was chosen as standard substrate, since it contains no additional functionalities. The conversion was determined

by integrating the methylene proton signals of $108$ and $109$. Using monotosylated cyclohexyl diamine discloses moderate reactivity with poor enantioselectivity (Table 6, entry 1). Replacing the tosyl group by the more electron withdrawing pentafluorophenyl sulfonyl group strongly diminishes reactivity (Table 6, entry 2). Mono-perfluorophenyl-sulfonylated dicyclohexyl ethane diamine as ligand is completely inactive (Table 6, entry 3). Changing to diphenyl ethane diamine based ligands dramatically improved reactivity and selectivity. Thus, tosylated diphenyl ethane diamine ligand increased the yield to 81% with 84% ee (Table 6, entry 4). Replacement of the tosyl group by a mesyl group further enhances reactivity and selectivity (Table 6, entry 5). Finally, small but significant improvement in selectivity was achieved using pentafluophenyl sulfonylated diphenyl ethane diamine as ligand, giving the product in 94% ee (Table 6, entry 6). The observation that more electron withdrawing sulfonyl groups are superior to their corresponding electron donating groups stands in sharp contrast to what has been observed with ruthenium-catalyzed asymmetric transfer hydrogenation, where more electron donating sulfonyl groups enhance reactivity.\cite{40a}
Table 6: Initial catalyst screening.

This protocol was now applied to a series of substituted α-cyano acetophenones (Table 7). Catalyst loadings as low as 0.25 mol % proved sufficient for full completion in many cases (Table 7, entries 1, 4-6, 8). It is necessary that for full completion of 2-naphthyl ketone (Table 7, entry 7), 10 mol % of hexafluoro-iso-propanol were added as cosolvent. We assume, since 2-naphthyl ketone is solid, the interaction of catalyst in water with the substrate is poor, but by addition of a cosolvent, the substrate behaves as oil.\(^{60}\)

---

\(^{60}\) Reaction of 2-naphthyl ketone without 10 mol % hexafluoro-iso-propanol for 24 h revealed only 19 % conversion.
The reaction protocol of reduction of α-nitroketones required some subtle changes. A modest general increase of catalyst loading was necessary to reach full conversion. Additionally, the pH was lowered to 2.0 (Table 8). Conducting the reaction with 2-nitro-1-phenylethanone at pH 3.5, 21 % benaldehyde was formed by retro-Henry reaction of the initially reduced product, the residual 79 % remained unreacted. It is

Table 7: Scope of α-cyano substituted acetophenones.

<table>
<thead>
<tr>
<th>entry&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>R</th>
<th>mol % cat.</th>
<th>yield [%]&lt;sup&gt;c&lt;/sup&gt;</th>
<th>ee [%]&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>0.25</td>
<td>96</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>p-F-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>0.5</td>
<td>95</td>
<td>91&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>p-CH&lt;sub&gt;3&lt;/sub&gt;-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>0.5</td>
<td>96</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>p-CN-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>0.25</td>
<td>97</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>m-Cl-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>0.25</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>m-MeO-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>0.25</td>
<td>96</td>
<td>95</td>
</tr>
<tr>
<td>7&lt;sup&gt;f&lt;/sup&gt;</td>
<td>2-naphthyl</td>
<td>0.5</td>
<td>95</td>
<td>96</td>
</tr>
<tr>
<td>8</td>
<td>2-furyl</td>
<td>0.25</td>
<td>83</td>
<td>96</td>
</tr>
<tr>
<td>9</td>
<td>2-thiophenyl</td>
<td>0.5</td>
<td>94</td>
<td>92</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions carried out with 0.5 mmol of ketone. <sup>b</sup> 1.0 M formic acid solutions were used. <sup>c</sup> Isolated yields. <sup>d</sup> Determined by chiral HPLC (Chiralcel OD-H column). <sup>e</sup> Chiralcel OD-H. <sup>f</sup> Addition of 10 mol % hexafluoro-isopropanol.
worth noting that substitution in the ortho position does not negatively affect selectivity, as seen in other cases (Table 8, entry 5).61

Table 8: Scope of α-nitro substituted acetophenones.

<table>
<thead>
<tr>
<th>entry&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>R</th>
<th>mol % cat.</th>
<th>yield [%]&lt;sup&gt;c&lt;/sup&gt;</th>
<th>ee [%]&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>0.5</td>
<td>94</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>p-&lt;sub&gt;Bu&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>0.5</td>
<td>92</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>m-Br-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>0.5</td>
<td>54</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>m-Cl-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>0.5</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>o-MeO-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>0.5</td>
<td>93</td>
<td>83</td>
</tr>
<tr>
<td>6&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2-naphthyl</td>
<td>0.5</td>
<td>53</td>
<td>93</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reactions carried out with 0.5 mmol of ketone. <sup>b</sup>1.0 M formic acid solutions were used. <sup>c</sup>Isolated yields. <sup>d</sup>Determined by chiral HPLC (Chiracel OD-H column). <sup>e</sup>Addition of 10 mol % hexafluoro-iso-propanol.

---

Additionally, 2-chloro-1-phenylethanone 111 was smoothly reduced with only 0.25 mol % catalyst in 24 h at room temperature (Scheme 26) to give the product 112 in 93 % yield and 91 % ee, which is close to what was published in the literature (compare to Table 5, entries 4 and 7). As mentioned above, this motif is a precursor for terminal epoxides.

Scheme 26: Reduction of α-chloro substituted acetophenone.
2.3 Asymmetric Transfer Hydrogenation of \(\beta,\beta\)-disubstituted Nitroalkenes\(^{62}\)

### 2.3.1 Background

Due to the straightforward conversion of the nitro group into other functional groups, nitroalkanes are important intermediates in organic synthesis.\(^{63}\) They are easily transformed into their corresponding amines, aldehydes, cyanides and other functional groups (Scheme 27).

![Scheme 27: Functional group transformations of the nitro group.](image)

The chiral nitroalkanes are obtained either by asymmetric conjugate reduction of \(\beta,\beta\)-disubstituted nitroalkenes,\(^{64}\) or by conjugate addition of a carbon nucleophile to \(\beta\)-monosubstituted nitroalkenes.\(^{65}\) Two representative examples are shown in Scheme 28.

---

\(^{62}\) The results discussed in this section were achieved in collaboration with Dr. Omid Soltani. His work is gratefully acknowledged and appreciated.


To explore whether the iridium-catalyzed transfer hydrogenation in water is able to reduce functional group motifs other than carbonyl and imine groups, we were interested in expanding the scope of this straightforward method to different substrate classes such as activated double bonds.

### 2.3.2 Optimization Studies and Substrate Scope

The nitroolefins explored were synthesized by a procedure from Stephens\(^{64c}\) (Scheme 29). Wittig reaction of corresponding acetophenone yielded a terminal olefin, which was nitrated with CAN, NaNO\(_2\) and acetic acid in chloroform to give the nitroolefin.

---

Asymmetric Transfer Hydrogenation

Scheme 29: Preparation of nitroalkenes.

We chose unsubstituted nitroolefin 118 as standard substrate to test the feasibility of the reaction (Table 9), conversion was determined by integrating the methyl proton signals of 118 and 119. The monosulfonylated 1,2-diphenylethane diamine proved to be a valuable ligand (Table 9, entry 1). Especially, when the diamine was monosulfonylated with the more electron withdrawing mesyl group, an enhancement in both reactivity and selectivity was observed (Table 9, entries 2 and 3). Another enhancement in reactivity was observed by using even more electron poor pentafluorophenyl sulfonyl group, although with a drop in selectivity (Table 9, entries 4 and 5). An increase in selectivity was achieved by using electron withdrawing groups in the diaryl ethane backbone of the diamine. Thus, employing pentafluorophenyl sulfonylated bis(3,5-difluorophenyl)ethane-1,2-diamine as ligand gives 119 in good yields and selectivities (Table 9, entries 6 and 7). A modest but significant improvement was achieved by using mesylated bis(3,5-diﬂuorophenyl)ethane-1,2-diamine as ligand at pH 2.0 (Table 9, entry 8). Unfortunately, this ligand is much more sensitive to pH changes, since the conversion substantially dropped to 72 % when conducting the reaction at pH 3.5 (Table 9, entry 9). The observation that more electron withdrawing sulfonyl groups enhance reactivity stands in contrast to what was observed with typical ruthenium based systems, where more electron donating sulfonyl groups enhance selectivity.40a
As shown in Table 10, a substrate scope was investigated using ligand 120. The procedure reduces nitroalkenes containing halides in the para- (Table 10, entries 2-4) as well as in the meta-position (Table 10, entry 5) in good yields and selectivities. Alkyl substituents still show good selectivities, although with reduced reactivity (Table 10, entries 6 and 9). Strongly electron donating as well as electron withdrawing groups are tolerated and deliver the products in good yields, although with higher catalyst loading for the ligands containing electron donating groups (Table 10, entries 7 and 8 respectively). Furthermore, substrates containing a naphthyl substituent required heating to 40 °C, since reaction at room temperature only yielded 33 % reduced product (Table 10, entry 10).
Table 10: Substrate Scope

![Chemical Structure](image)

5 eq HCO₂H, H₂O, 0.2 M, pH = 2.0, 24 h, rt

<table>
<thead>
<tr>
<th>entry(^{ab})</th>
<th>R</th>
<th>mol % cat</th>
<th>yield [%](^c)</th>
<th>ee [%](^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₅H₅</td>
<td>1.0</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>ρ-F-C₆H₄</td>
<td>1.0</td>
<td>82</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>ρ-Cl-C₆H₄</td>
<td>1.0</td>
<td>92</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>ρ-Br-C₆H₄</td>
<td>1.0</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>m-Cl-C₆H₄</td>
<td>1.0</td>
<td>94</td>
<td>91</td>
</tr>
<tr>
<td>6</td>
<td>ρ-Me-C₆H₄</td>
<td>1.0</td>
<td>78</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>ρ-MeO-C₆H₄</td>
<td>1.5</td>
<td>94</td>
<td>92</td>
</tr>
<tr>
<td>8</td>
<td>ρ-CN-C₆H₄</td>
<td>1.0</td>
<td>87</td>
<td>92(^e)</td>
</tr>
<tr>
<td>9</td>
<td>ρ-^Bu-C₆H₄</td>
<td>1.0</td>
<td>77</td>
<td>89</td>
</tr>
<tr>
<td>10(^f)</td>
<td>2-naphthyl</td>
<td>1.5</td>
<td>56</td>
<td>92</td>
</tr>
</tbody>
</table>

\(^a\) Reactions carried out with 0.5 mmol of nitroalkene. \(^b\) 1.0 M formic acid solutions were used. \(^c\) Isolated yields. \(^d\) Determined by chiral HPLC (Chiralcel OD-H column). \(^e\) Chiralcel IC column. \(^f\) 40 °C.
2.4 Asymmetric Transfer Hydrogenation of β-Nitro Acrylates

2.4.1 Background

After initial studies by the groups of Seebach and Gellman, β²-peptides (Figure 13) rose up as a new class of proteomimetics, with great potential in applications in medicine and biology. Because of the additional carbon atom in the backbone, β²-peptides form different secondary structures than α-peptides.

![Peptide Structures](image)

*Figure 13: Peptide nomenclature.*

The most widely used synthesis of β²-amino acids is application of Arndt-Eistert homologation of their corresponding α-amino acids, but Gellman recently described an organocatalytic Mannich reaction which yields β-amino aldehydes in good yields and selectivities (Scheme 30).

---

Asymmetric Transfer Hydrogenation

![Chemical structure](attachment:image.png)

Scheme 30: Arndt-Eistert- and Mannich-approach

The first protocol reducing nitroacrylates using transfer hydrogenation was published in 2006 by Stewart, where nitroacrylates were reduced with old yellow enzyme Saccharomyces Carlsbergensis using molecular hydrogen as reductant.\(^{71}\) In 2008, during our studies, List reported an organocatalytic approach, reducing nitroacrylates in the presence of a chiral thiourea catalyst and Hantzsch-ester as hydride donor.\(^{72}\)

### 2.4.2 Optimisation Studies and Substrate Scope

The preparation of the nitroacrylates is shown in Scheme 31. Grignard addition of the appropriate aryl magnesium bromide to dibenzyl oxalate provided the glyoxylic ester intermediate. After nucleophilic addition of nitromethane, the resulting alcohol was acetylated and eliminated to give the nitroacrylate.

![Chemical structure](attachment:image.png)

Scheme 31: Preparation of nitroacrylates.

Methyl- and benzylesters 122 and 123 were submitted to asymmetric transfer hydrogenation using perfluorosulfonylated ligand 110. Although the selectivity was

---

\(^{71}\) Swiderska, M. A.; Stewart, J. D. Org. Lett. 2006, 8, 6131.

good, with a higher regio- and enantioselectivity for the benzyl ester compared to the methyl ester, a significant amount of side product B was produced (Scheme 32). The reaction had to be heated to 60 °C, since reaction at room temperature revealed only 31% and 34% conversion for the methyl and the benzyl ester respectively.

\[
\text{Scheme 32 : Initial substrate screen.}
\]

Although Stewart and List did not observe any regioselectivity problems, there is a competition between conjugate addition with respect to the nitro group (a) followed by protonation, or with respect to the ester group (b), followed by concomitant loss of nitrite anion (Figure 14).

\[
\text{Figure 14: Competing reduction pathways.}
\]
The elimination of nitrous acid must occur subsequently after the conjugate reduction to the ester, since submission of substrate 124 to the reaction conditions for 48 h did not produce any side product. Additionally, labeling experiments with deuterated formic acid reveal both diverse reduction pathways occur under reaction conditions applied (Scheme 33). The mechanism is the same as in Figure 14.

Two conclusions can be drawn from these experiments. First, the initial reduction (pathway a or b) determines product distribution. Second, elimination of nitrous acid is faster than protonation, probably because the enolate is coordinated to the iridium, therefore favouring intramolecular elimination over intermolecular protonation.

We then proceeded to examine the effect of different substituents on the ligand to the reduction process. Conversion was determined by integrating alkene proton of 74, methylene protons of 75 and terminal alkene protons of 76. Therefore, a series of perfluorosulfonylated diamine based catalysts were synthesized and their effect on the
reaction was tested (Table 11). It turned out phenyl based ethylene diamines were superior to those with a difluoro-substitution concerning reactivity (e.g. compare Table 11, entries 1,2 with entries 7,8). Additionally, enantiomeric excess decreases along the series C₆F₅ > C₄F₉ > CF₃ (e.g. Table 11, entries 5, 3,1 and entries 6, 4, 2), reflecting their σ-acceptor ability. We therefore chose catalyst and conditions from entry 6 for a substrate investigation.

**Table 11: Catalyst screening.**

<table>
<thead>
<tr>
<th>entry</th>
<th>R¹</th>
<th>R²</th>
<th>pH</th>
<th>product [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>CF₃</td>
<td>2.0</td>
<td>81</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>CF₃</td>
<td>3.5</td>
<td>47</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>C₄F₉</td>
<td>2.0</td>
<td>39</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>C₄F₉</td>
<td>3.5</td>
<td>40</td>
<td>90</td>
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<tr>
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<td>Ph</td>
<td>C₆F₅</td>
<td>2.0</td>
<td>77</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>C₆F₅</td>
<td>3.5</td>
<td>63</td>
<td>93</td>
</tr>
<tr>
<td>7</td>
<td>3,5-di-F-C₆H₃</td>
<td>CF₃</td>
<td>2.0</td>
<td>42</td>
<td>84</td>
</tr>
<tr>
<td>8</td>
<td>3,5-di-F-C₆H₃</td>
<td>CF₃</td>
<td>3.5</td>
<td>30</td>
<td>86</td>
</tr>
<tr>
<td>9</td>
<td>3,5-di-F-C₆H₃</td>
<td>C₄H₉</td>
<td>2.0</td>
<td>32</td>
<td>82</td>
</tr>
<tr>
<td>10</td>
<td>3,5-di-F-C₆H₃</td>
<td>C₄H₉</td>
<td>3.5</td>
<td>31</td>
<td>82</td>
</tr>
</tbody>
</table>

*a Reactions carried out with 0.1 mmol of nitroacrylate. b Determined by ¹H-NMR of the unpurified product. c Determined by chiral SFC (Chiralpak IC column).*

A series of substrates were synthesized to examine the viability of this method (Table 12). Unfortunately, it turned out that the amount of side product formation
increased when the reaction was scaled up to 1 mmol of substrate (up to 50%). Nevertheless, good enantiomeric excesses were obtained for all substrates. Halogens are tolerated in the para- (Table 12, entries 2-4), meta- (Table 12, entry 5) and even in the ortho-position (Table 12, entry 6), which is in contrast to what was observed by Xiao.\textsuperscript{61} Strong (Table 12, entry 7) and moderate (Table 12, entries 9 and 10) electron donating groups react as well with good selectivities, but in poor yield.

**Table 12: Substrate scope.**

<table>
<thead>
<tr>
<th>entry\textsuperscript{a,b}</th>
<th>R</th>
<th>yield [%]\textsuperscript{c}</th>
<th>ee [%]\textsuperscript{d}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>57</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>(p)-F-C\textsubscript{6}H\textsubscript{4}</td>
<td>64</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>(p)-Cl-C\textsubscript{6}H\textsubscript{4}</td>
<td>48</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>(p)-Br-C\textsubscript{6}H\textsubscript{4}</td>
<td>45</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>(m)-Cl-C\textsubscript{6}H\textsubscript{4}</td>
<td>44</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>(o)-Cl-C\textsubscript{6}H\textsubscript{4}</td>
<td>44</td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td>(p)-MeO-C\textsubscript{6}H\textsubscript{4}</td>
<td>54</td>
<td>86</td>
</tr>
<tr>
<td>8</td>
<td>(p)-CF\textsubscript{3}-C\textsubscript{6}H\textsubscript{4}</td>
<td>43</td>
<td>82</td>
</tr>
<tr>
<td>9</td>
<td>(p)-Me-C\textsubscript{6}H\textsubscript{4}</td>
<td>44</td>
<td>86</td>
</tr>
<tr>
<td>10</td>
<td>(p)-\textsuperscript{t}Bu-C\textsubscript{6}H\textsubscript{4}</td>
<td>48</td>
<td>90</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reactions carried out with 1.0 mmol of nitroacrylate. \textsuperscript{b} 1.0 M formic acid solutions were used. \textsuperscript{c} Isolated yields. \textsuperscript{d} Determined by chiral SFC (Chiralpak IC column).
2.4.3 Mechanistical Studies

An interesting mechanistic study has been conducted by Xiao in 2005\(^\text{73}\), where the effect of pH-variation on both conversion and selectivity was studied in the reduction of acetophenone with Ru-TsDPEN catalyst, formic acid/triethylamine as reductant in water as solvent (Scheme 34). It has been suggested that at lower pH, the amido nitrogen is protonated, thus breaking the Ru-N bond. Therefore, two transition states are possible: One acting through bifunctional catalysis, but with a less well-organized transition state, the other one through convenient stepwise reduction of ketones (Scheme 34, left side). At higher pH, the monotosylated diamine is bidentate and the reduction follows bifunctional catalysis with a well organized transition state (Scheme 34, right side).

Therefore, at low pH, addition of the opposite enantiomer of the ligand should decrease the enantiomeric excess more effectively than at higher pH, since the ligand is only monodentate and therefore loosely bound, which has also been shown by Xiao. By adding \((S,S)\)-TsDPEN (1 eq) to an aqueous solution containing acetophenone, formic acid/triethylamine azeotrope and Ru-\((R,R)\)-TsDPEN lowered the value from 98 % ee at 5 % conversion to 5 % ee at full conversion at pH 4.6 (Figure 15, left diagram). In contrast, at pH 7.7, no significant decrease in enantioselectivity was observed (Figure 15, right diagram).

Asymmetric Transfer Hydrogenation

**Figure 15:** Ligand exchange studies by Xiao; diagrams copied from ref. 73.

This effect also takes place in the iridium-catalyzed reduction of nitroacrylates, as shown in Scheme 35. Addition of ligand with opposite absolute configuration produces *in situ* catalyst with opposite absolute configuration. Therefore, the longer the reaction proceeds, the more of **ent-124** is produced which lowers the overall enantiomeric excess.

**Scheme 35:** Ligand substitution effects.
To determine effects of the two distinct stereocenters on the ligand with respect to pH, a study similar to the one performed by Wills\textsuperscript{74} was performed. It analyzes the influence of the two distinct stereogenic centers of the monosulfonylated diamine, and it is concluded that stereochemical information at the carbon α to the amine is affecting the stereoinduction stronger than the stereochemical information at the carbon α to the sulfonyl amide (Scheme 35).

![Scheme 35](image)

<table>
<thead>
<tr>
<th>ligand</th>
<th>time</th>
<th>conv.</th>
<th>ee</th>
<th>R/S</th>
</tr>
</thead>
<tbody>
<tr>
<td>125</td>
<td>22 h</td>
<td>100</td>
<td>98</td>
<td>R</td>
</tr>
<tr>
<td>126</td>
<td>48 h</td>
<td>95</td>
<td>69</td>
<td>S</td>
</tr>
<tr>
<td>127</td>
<td>13 d</td>
<td>46</td>
<td>33</td>
<td>R</td>
</tr>
</tbody>
</table>

Figure 16: Ligand studies conducted by Wills.

The parent ligand 125 was compared to ligands 126 and 127 with respect to conversion and ee. It turns out influence of the chiral center at the β-position is bigger than the one at the α-position, which is also stronger at pH = 2.0 than pH = 3.5. At low pH, the amido group is protonated and therefore not or loosely bound to the iridium center. If the stereogenic center of ligand 127 is moved away from the reaction site, stereoinduction fails in this case (Figure 17).

\textsuperscript{74} Hayes, A.; Clarkson, G. L.; Wills, M. Tetrahedron Asymmetry, 2004, 15 2079.
Figure 17: Effect of the stereocenters on the ligand.
2.5 Asymmetric Transfer Hydrogenation of β-Keto Esters

2.5.1 Background

Optically active β-hydroxy carboxylic esters are important building blocks for natural product synthesis. Some ways to access these compounds are shown in Figure 18.

![Figure 18: Formal ways to access to β-hydroxy carboxylic esters.](image)

Historically, the aldol reaction developed by Evans is the method of choice to build a β-hydroxy ester. Due to poor diastereoselectivity of the Evans-aldol reaction with acetate enolates, a temporary methylsulfide was introduced to enhance stereoselectivity. The group is easily cleaved by Raney-Ni (Scheme 36).

![Scheme 36: Evans-aldol modification for acetate aldols.](image)

---


In the following years, many research groups started to explore catalytic methods for the aldol reaction. One of the most promising developments in catalytic aldol reaction started in the 1970’s, when Mukayama reported aldol reactions of silyl enol ethers with carbonyl compounds in the presence of TiCl₄. Based on this pioneering work, many asymmetric aldol reactions have been developed, most of them based on boron, tin, titanium and copper, which yields the aldol products in high yields and selectivities. Some representative reactions are shown in Scheme 37.

Scheme 37: Examples for catalytic aldol reactions

In the last decade, a huge number of methods for the asymmetric transfer hydrogenation of β-keto esters have been published, several using hydride sources such as formic acid or iso-propanol, giving access to secondary alcohols in high yields and selectivities. A few representative examples are shown in Table 13.

2.5.2 Optimization Studies and Substrate Scope

Our initial studies commenced with the use of parent TsDPEN ligated iridium. We chose ethyl 3-oxo-3-phenylpropanoate 136 as standard substrate for initial examinations since it lacks of additional functional groups (Table 14). Conversion was determined by integrating the methylene proton signals of 136 and 137.

Table 13: Asymmetric transfer hydrogenation of β-ketoesters.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>reductant</th>
<th>yield [%]</th>
<th>ee [%]</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>138</td>
<td>'PrOH</td>
<td>95</td>
<td>93</td>
<td>78a</td>
</tr>
<tr>
<td>2</td>
<td>139</td>
<td>'PrOH</td>
<td>99</td>
<td>94</td>
<td>78b</td>
</tr>
<tr>
<td>3</td>
<td>140</td>
<td>HCO₂H/NEt₃</td>
<td>99</td>
<td>86</td>
<td>78c</td>
</tr>
<tr>
<td>4</td>
<td>141</td>
<td>HCO₂Na</td>
<td>99</td>
<td>80</td>
<td>78f</td>
</tr>
</tbody>
</table>

*Isolated yield.
Table 14: Initial pH dependant screening.

<table>
<thead>
<tr>
<th>entry&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>pH</th>
<th>conversion [%]&lt;sup&gt;c&lt;/sup&gt;</th>
<th>ee [%]&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.0</td>
<td>100</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>3.5</td>
<td>100</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>5.0</td>
<td>100</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>8.0</td>
<td>100</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>10.5</td>
<td>100</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>12.5</td>
<td>78</td>
<td>nd</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions carried out with 0.1 mmol of ketoester.  
<sup>b</sup> 1.0 M formic acid solutions were used.  
<sup>c</sup> Determined by <sup>1</sup>H-NMR of the unpurified reaction mixture.  
<sup>d</sup> Determined by chiral SFC (Chiralpak I-A column).

To our delight, the reaction tolerates a broad range of pH, only under very basic conditions, the conversion is reduced (Table 14, entry 6). The enantiomeric excess is high under basic and under slightly acidic conditions (Table 14, entries 3-5), but only moderate under more acidic conditions (Table 14, entries 1,2). There is no retro-aldol observed, even under strongly basic conditions.

Although enantiomeric excesses are already high, the effect of substituents in the sulfonyl group was explored (Table 15). It turns out perfluorinated sulfonyl groups are worse compared to their nonfluorinated analogues (compare Table 15, entries 1-3 with
entries 4-6), which is in contrast to preceding projects. Additionally, more electron donating substituents are also unfavourable, which is again in contrast to what was observed by Noyori (Table 15, entries 2 and 3). The methyl substituted sulfonamide showed best selectivity amongst the catalysts examined (Table 15).

Table 15: Sulfonyl group dependent screening.

<table>
<thead>
<tr>
<th>entry&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>R</th>
<th>conversion [%]&lt;sup&gt;c&lt;/sup&gt;</th>
<th>ee [%]&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>100</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;Me</td>
<td>100</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;OMe</td>
<td>100</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>100</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>100</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;OCF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>100</td>
<td>86</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions carried out with 0.1 mmol of ketoester. <sup>b</sup> 1.0 M formic acid solutions were used. <sup>c</sup> Determined by <sup>1</sup>H-NMR of the unpurified reaction mixture. <sup>d</sup> Determined by chiral SFC (Chiralpak IA column).

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<sup>80</sup> See chapters 2.2 - 2.4.
With the optimal catalyst in hand, a substrate scope was explored to probe the
generality of the method. The reaction temperature could be lowered to 4 °C without any
loss of activity. The reaction tolerates electron withdrawing and electron donating
substituents in the *para-* and *meta-*position very well, but substitution in the *ortho-
position reduces selectivity significantly without affecting reactivity (Table 16, entries 2-
8). Arene groups bearing a π-acceptor significantly reduce selectivity (Table 16, entries 9,
13). Aliphatic substrates are inferior, either steric hindrance prevents reduction or
enantioselectivity is almost negligible (Table 16, entries 11, 12).
To investigate the pH independency of the method, the reduction of substrate 136 was conducted on a larger scale. As expected from the screening experiments (Table 14),
dramatic changes in pH do not affect the outcome of the reaction. From pH = 3.5 up to pH = 10.0, the reaction proceeds smoothly with full conversion and excellent enantiomeric excesses (Table 17).

Table 17: pH-independency of the reduction of β-keto esters.

<table>
<thead>
<tr>
<th>entry&lt;sup&gt;ab&lt;/sup&gt;</th>
<th>pH</th>
<th>yield [%]&lt;sup&gt;c&lt;/sup&gt;</th>
<th>ee [%]&lt;sup&gt;d,e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.5</td>
<td>98</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>5.0</td>
<td>98</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>8.0</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>10.0</td>
<td>97</td>
<td>96</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions carried out with 1 mmol of ketoester. <sup>b</sup> 1.0 M sodium formate solutions were used. <sup>c</sup> Isolated Yields. <sup>d</sup> Determined by chiral SFC (Chiralpak I-A column). <sup>e</sup> Absolute configuration established by correlation to known compounds.
2.6 Summary

The successful reductions of \( \alpha \)-substituted acetophenones, \( \beta,\beta \)-disubstituted nitroalkenes, nitroacrylates and \( \beta \)-ketoesters using catalysts 110, 120 or 143 have been described. Each substrate class favours a different catalyst (see 2.2 – 2.5). The stereoinduction in the reduction of these substrates can be described with a closed transition state similar to ruthenium catalyzed transfer hydrogenation (69, Scheme 18). Since these reactions are conducted at low pH, a closed transition state is in competition with an open transition state.

![Diagram of transition states](image)

**Figure 19: Proposed closed (top) and open (bottom) transition states.**

For the acetophenones, an open transition state is favoured since the reductions are at pH 2.0 or pH 3.5, but a closed transition state cannot be excluded. Ketoesters might be reduced through both transition states, since the reaction works in a broad pH range, albeit a closed transition state is favoured at higher pH. For nitroolefins and nitroacrylates, an open transition state seems more likely. First, the reductions are
conducted at pH 2.0, where the amido nitrogen is presumably protonated. Second, it opens a new coordination site at the iridium, allowing bidentated coordination for the substrate, which could explain the regioselectivity problems encountered for the reduction of nitroacrylates (Figure 20).

*Figure 20: Competing regioselectivity for the reduction of nitroacrylates.*
3 Conclusion and Outlook

In the first part of this thesis sulfamic acid was examined as a novel ammonia equivalent in the iridium-catalyzed allylic amination reaction. In addition to behave as a nucleophile, sulfamic acid also acts as an \textit{in situ} activator for the hydroxyl group, which significantly improved the practicability of the reaction.

Most obviously, the powerful substitution chemistry of sulfamic acid requires further investigation. Substitution reactions of unprotected alcohols at different activated positions (e.g. propargylic, benzylic or allenyllic) seem to be viable reactions to be investigated.

\textit{Scheme 38: Possible applications for sulfamic acid in substitution reactions.}

The second part of this thesis deals with iridium-catalyzed asymmetric transfer hydrogenation using formic acid or sodium formate as reductant. It has been shown that every substrate class prefers its specific ligand to reach high conversions and selectivities. One way to go is to find suitable catalysts for different substrate class, including activated double bonds as well as \(\alpha\)- or \(\beta\)-substituted ketones.
Scheme 39: Different substrate classes for the use in transfer hydrogenation reactions.

A different way to go is to alter the catalyst. This could include the placement of a tether between the Cp* and the diamine moiety, or induce chirality at the Cp*-site and explore its effect. One could also imagine to tether the catalyst on solid support, what would probably allow the catalyst to enter several cycles before being decomposed.

Figure 21: Possible catalyst derivatives.
4 Experimental Section

4.1 General Methods

All non-aqueous reactions were carried out under an atmosphere of dry argon or nitrogen unless otherwise stated. For the reactions, THF, Et₂O, CH₃CN, toluene and CH₂Cl₂ were purified by distillation and dried by passage over two 4 x 36 inch columns of anhydrous neutral A-2 alumina (8 x 14 mesh; Macherey und Nagel; activated under a flow of N₂ at 300°C over night; solvent drying system) under an argon atmosphere (H₂O content < 30 ppm, Karl-Fischer titration). 1,4-Dioxane (Acros, 99.5%, extra dry over molecular sieves) and N,N-Dimethylformamide (Fluka, > 99.5%, stored over molecular sieves) were employed. Et₃N and pyridine were distilled under nitrogen from KOH. All chemicals were purchased from Acros, Aldrich, Fluka, Merck or Lancaster and used as such unless otherwise stated. Sulfamic acid was received from Fluka (>99.3%, lot number: 1097230). [IrCl(cod)]₂ was bought from Strem Chemicals. [IrCl(coe)₂]₂ was prepared according to the following literature procedures from IrCl₃: R. H. Crabtree, J. M. Quirk, Synth. React. Inorg. Met.-Org. Chem. 1982, 12, 407. Deuterated solvents were obtained from Armar Chemicals, Döttingen, Switzerland in the indicated purity grade.

Chromatographic purification was performed as flash chromatography with 0.3-0.5 bar pressure using Brunschwig silica 32-63, 60 Å. Technical grade solvents were employed, which were distilled prior to use. Chromatographic purification of the allylic amines was performed using alumina Woelm N, Akt. 1 using CH₂Cl₂/Methanol as eluent.

TLC was performed on Merck silica gel 60 F₂₅₄ TLC glass plates and visualized with UV light or permanganate stain.

Melting points were measured on a Büchi B-540 melting point apparatus using open glass capillaries, the data is uncorrected.
\textsuperscript{1}H-NMR spectra were recorded on a VARIAN Mercury 300 MHz or a Gemini 300 MHz spectrometer in CDCl\textsubscript{3}, CD\textsubscript{3}OD and DMF-d\textsuperscript{7}. All signals are reported in ppm with the internal chloroform signal at 7.26 ppm, the internal methanol signal at 3.30 ppm, the internal DMF signal at 8.01 ppm as standard. The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet or unresolved, br = broad signal, coupling constant(s) in Hz, integration).

\textsuperscript{13}C-NMR spectra were recorded with \textsuperscript{1}H-decoupling on a VARIAN Mercury 75 MHz spectrometer in CDCl\textsubscript{3}, CD\textsubscript{3}OD and DMF-d\textsuperscript{7}. All signals are reported in ppm with the internal chloroform signal at 77.0 ppm, the internal methanol signal at 49.0 ppm.

\textsuperscript{19}F-NMR spectra were recorded with \textsuperscript{1}H-decoupling on a VARIAN Mercury 282 MHz spectrometer in the indicated deuterated solvent.

\textsuperscript{31}P-NMR spectra were recorded with \textsuperscript{1}H-decoupling on a VARIAN Mercury 121 MHz spectrometer in the indicated deuterated solvent.

Infrared spectra were recorded on a Perkin Elmer Spectrophotometer RX-I FT-IR as thin film or neat on a Varian 800 FT-IR Scimlar Series spectrophotometer.

Optical rotations were measured on a JASCO DIP-1000 digital polarimeter in 10 cm, 2 ml cells, the concentration in g/100 ml and the solvent is given in parentheses.

HPLC analyses were carried out on a Merck Hitachi D-7000 system with Daicel columns in Hexanes/iPrOH mixtures. Conditions, retention times and columns used are given in parentheses.

GC measurements were performed by Focus GC, AI/AS 3000 autosampler with Chrom-Card\textsuperscript{TM} software, from Thermo Electron Corporation (Brechbühler AG, Switzerland) and Capillary cyclodextrin column BGB 176 SE from BGB Analytics (Switzerland) (all 30m x 0.25 mm i.d., 0.25µm film thickness).

High resolution mass spectrometric measurements were performed by the mass spectrometry service of the Laboratorium für Organische Chemie at the ETH Zürich on a Finnigan TSQ 7000 ESI spectrometer for low resolution measurements. An IonSpec
Ultima HR FT-ICR MS MALDI was employed for high resolution measurements using the DHB-tl (2,5-Dihydroxybenzoic acid-two layers) method at 4.7 Tesla. Alternatively, an Ion Spec ESI-FT-ICR spectrometer at 4.7 Tesla or an EI-HIRES Micromass Autospel-Ultima spectrometer at 70 eV were employed.

Elemental analysis was performed by the Mikroelementaranalytisches Laboratorium der ETH Zürich.
4.2 Iridium-Catalyzed Allylic Amination

Synthesis of the Ligands

GP1: Synthesis of the Phosphoramidites

A Schlenk flask under argon was charged with the diol (1 eq), PCl$_3$ (15 eq) and a catalytic amount of N-methylpyrrolidone (0.03 eq) were added and the reaction mixture was heated at 50 °C for 30 min. The initially heterogeneous mixture turned into a brownish homogenous solution. After cooling to 23 °C, the excess PCl$_3$ was evaporated in vacuo, 1 ml toluene was added to azeotropically remove remaining PCl$_3$. The resulting phosphorchloridite (air-and moisture-sensitive!) was redissolved in 25 ml THF.

In a separate Schlenk flask under argon, the amine (1.2 eq) dissolved in 25 ml THF was deprotonated at -78 °C by the slow addition of $n$-BuLi (1.1 eq, 1.6 M solution in hexanes). The resulting deep blue solution was continued to stir at -78 °C for 1 hour before the phosphorchloridite solution was slowly transferred via cannula. The resulting mixture was stirred at -78 °C, then warmed to 23 °C and continued to stir during 8 h. After completion of the reaction, as determined by TLC, the solvents were evaporated in vacuo. Purification of the residue by flash chromatography on silica gel using hexanes/toluene as eluent afforded the desired product as a white foam.
Experimental Section

(3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a’]diphenyl-4-en)-dibenzo[b,f]azepine (31)

Prepared according to GP1 using 2.23 g (12.0 mmol) 2,2’-biphenol. Yield: 1.35 g (3.31 mmol, 28 %) (off-white powder). Keep under inert atmosphere for long-term storage.

mp 159 °C; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.35-7.38 (m, 2H), 7.22-7.27 (m, 4H), 7.10-7.20 (m, 8H), 6.98-7.08 (m, 2H), 6.96 (s, 2H); $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 150.6, 142.4, 135.8, 131.3, 130.4, 130.3, 129.4, 128.9, 128.8, 128.7, 126.4, 124.2, 121.9; $^{31}$P-NMR (121 MHz, CDCl$_3$) 137.9; IR (neat) 3062, 3025, 1486, 1434, 1196, 1095, 984, 890, 848, 759, 746; HR-MALDI-MS m/z calcd for C$_{26}$H$_{18}$NO$_2$P [M+H]$^+$ 408.1148, found 408.1149.

(3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a’]diphenyl-4-en)-10,11-dihydro-dibenzo-[b,f]azepine (32)

Prepared according to GP1 using 834 mg (4.48 mmol) 2,2’-biphenol. Yield: 568 mg (1.39 mmol, 31 %) (off-white powder). Keep under inert atmosphere for long-term storage.

mp 145 °C; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.43-7.6.94 (m, 16H), 3.77-3.61 (m, 2H), 3.01-2.93 (m, 2H); $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 150.5, 142.3, 136.8, 130.2, 130.0, 129.9, 128.8, 127.9, 126.5, 126.2, 124.2, 121.2, 31.6; $^{31}$P-NMR (121 MHz, CDCl$_3$)
136.4; **IR (neat)** 3061, 3029, 1486, 1436, 1184, 1094, 990, 880, 842, 699; **HR-MALDI-MS** m/z calcd for C_{26}H_{20}NO_{2}P [M+H]^+ 410.1304 found 410.1303.

(S)-(+)-(3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a’]dinaphthalen-4-yl)-dibenzo-[b,f]-azepine (43)

Prepared according to GP1 using 300 mg (1.05 mmol) (S)-BINOL. Yield: 239 mg (0.47 mmol, 45 %) (off-white powder). Keep under inert atmosphere for long-term storage.

**mp** 246 °C; **Optical rotation:** [α]_{D}^{25} +313.6 (c 1.07, CHCl₃); **¹H-NMR (500 MHz, CDCl₃)** δ 7.96 (d, J = 8.8 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 8.1 Hz, 1 H), 7.60 (dd, J = 8.8, 0.7 Hz, 1H), 7.41 (d, J = 8.7 Hz, 1 H), 7.38-7.31 (m, 2H), 7.23-7.13 (m, 2H), 7.19-7.13 (m, 6H), 7.11-7.07 (m, 1H), 6.96 (d, J = 11.6 Hz, 1H), 6.92-6.87 (m, 2H), 6.84 (dd, J = 8.8, 0.5 Hz, 1H), 6.53-6.49 (m, 2H); **¹³C-NMR (125 MHz, CDCl₃)** δ 149.9, 149.9, 148.7, 143.0, 142.8, 142.5, 135.4, 135.2, 132.8, 132.1, 131.5, 131.4, 131.3, 130.2, 130.1, 129.1, 129.0, 128.9, 128.8, 128.5, 128.4, 128.3, 127.8, 126.8, 126.7, 126.1, 126.0, 125.6, 124.8, 124.2, 122.1, 121.5, 121.1; **³¹P-NMR (121 MHz, CDCl₃)** 138.0; **IR (neat)** 3057, 3023, 1590, 1484, 1236, 1201, 1070, 979, 938, 800, 767; **HR-MALDI-MS** m/z calcd for C_{34}H_{22}NO_{2}P [M+H]^+ 508.1461, found 508.1463.
**GP2: Substrate, Solvent, Ligand Screening**

A Schlenk flask under argon was charged with \([\text{IrCl(cod)}]_2\) (10.1 mg, 15 µmol, 3 mol %) and the corresponding ligand (30 µmol, 6 mol %). 2 ml (0.25 M) solvent was added and the reaction mixture was stirred at 23 °C for 15 min. The allylic carbonate resp. alcohol (0.50 mmol, 1 eq) was added via syringe followed by the addition of solid sulfamic acid (49 mg, 0.50 mmol, 1 eq). The resulting mixture was stirred at 23 °C for 24 h. Conversion was checked by disappearance of the starting material on TLC and/or by measuring $^1\text{H-NMR}$ of an aliquot taken from the reaction mixture. In cases, in which the conversion was above 50%, triethylamine (202 mg, 2.00 mmol, 4 eq), and freshly distilled benzoylchloride (141 mg, 1.00 mmol, 2 eq) were added to the reaction mixture and stirring was continued during 4 hours at 23 °C. Subsequently, the reaction mixture was partitioned between 10 ml CH$_2$Cl$_2$ and 10 ml H$_2$O. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 15 ml). The combined organic layers were dried (Na$_2$SO$_4$) and concentrated under reduced pressure to afford the crude allylic benzamide. Purification of the residue by flash chromatography on silica gel using hexanes/EtOAc as eluent afforded the desired benzamide.

**GP3: Iridium-Catalyzed Allylic Amination with Sulfamic Acid**

A Schlenk flask under argon was charged with \([\text{IrCl(cod)}]_2\) (10 mg, 15 µmol, 1.5 mol %) and ligand \((3,5\text{-dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']diphenyl-4-en})\text{-dibenzo[b,f]azepine}\) 31 (12 mg, 30 µmol, 3 mol %). 2 ml N,N-dimethylformamide was added and the reaction mixture was stirred at 23 °C for 15 min. The allylic alcohol (1.00 mmol, 1 eq) was added via syringe followed by the addition of solid sulfamic acid (97 mg, 1.00 mmol, 1 eq). The resulting reaction mixture was heated to 50 °C. After completion of the reaction (usually 6-7 h), as determined by TLC, the solvent was evaporated at high vacuum. The resulting brown residue was dissolved in 10 ml CH$_2$Cl$_2$
and 10 ml sat. aqueous NaHCO₃ solution and stirred for 10 min. The aqueous layer was extracted with CH₂Cl₂ (3 x 15 ml). The combined organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure to afford the crude allylic amine. The ratio of regioisomers was determined by ¹H-NMR analysis of the unpurified sample. Purification of the residue by flash chromatography on basic or neutral alumina using CH₂Cl₂/MeOH as eluent afforded the desired amine. As some amines proved to be unstable and/or volatile, they were precipitated by addition of 2 M HCl in Et₂O and stored as their hydrochloride salts.

5-Phenylpent-1-en-3-amine hydrochloride (Table 3, entry 1)

\[
\begin{align*}
\text{Ph} & -\text{OH} + \text{H₂N} & \text{SO}_3^- \\
1 \text{eq} & 1 \text{eq} & \text{[IrCl(coatl)]₂} (1.5 \text{ mol%}) & \text{phosphoramide} 31 (3 \text{ mol%}) & \text{DMF}, 50 ^\circ \text{C}, 3 \text{ h} & \text{Ph} - \text{NH}_3 & \text{Cl}^- \\
\end{align*}
\]

Prepared according to GP3. Off-white solid. Yield: 162 mg (0.82 mmol, 82 %);

mp 168 °C; ¹H-NMR (300 MHz, CDCl₃) δ 8.67 (br. s, 3H), 7.31-7.19 (m, 5H), 5.93 (ddd, J = 17.3, 10.5, 7.7 Hz, 1H), 5.47 (d, J = 17.3 Hz, 1H), 5.36 (d, J = 10.5 Hz), 3.74 (br. s, 1H), 2.82-2.64 (m, 2H), 2.32-2.04 (m, 2H); ¹³C-NMR (75 MHz, CDCl₃) δ 139.8, 132.9, 128.4, 128.3, 126.2, 121.2, 54.1, 34.7, 31.4; IR (neat) 2882 (br), 2045, 1601, 1511, 1453, 988, 936, 765, 745; HR-ESI-MS m/z calcd for C₁₁H₁₆Cl⁺ [M-NH₃]+ 145.1012, found 145.1012; **Elemental analysis**: calculated for C₁₁H₁₆NCl: C, 66.83; H, 8.16; N, 7.08 found C, 66.54; H, 8.09; N, 6.81.
**N-(5-Phenylpent-1-en-3-yl)-benzamide (Table 3, entry 2)**

A Schlenk flask under argon was charged with [IrCl(cod)]₂ (10 mg, 15 μmol, 3 mol %) and ligand (3,5-dioxo-4-phospha-cyclohepta[2,1-a;3,4-a’]diphenyl-4-en)-dibenzo[b,f]azepine 31 (12 mg, 30 μmol, 6 mol %). 2 ml N,N-dimethylformamide were added and the reaction mixture was stirred at 23 °C for 15 min. 5-Phenylpent-1-en-3-ol 29 (81 mg, 0.50 mmol, 1 eq) was added via syringe followed by the addition of solid sulfamic acid (49 mg, 0.50 mmol, 1 eq). The resulting reaction mixture was heated to 50 °C. Conversion was checked by disappearance of the starting material on TLC and/or by measuring ¹H-NMR of an aliquot taken from the reaction mixture. After completion of the reaction (usually 3-4 h), triethylamine (202 mg, 2.00 mmol, 4 eq) and freshly distilled benzylic chloride (141 mg, 1.00 mmol, 2 eq) were added to the reaction mixture and stirring was continued for 4 hours at 23 °C. Subsequently, the reaction mixture was partitioned between 10 ml CH₂Cl₂ and 10 ml H₂O. The aqueous layer was extracted with CH₂Cl₂ (3 x 15 ml). The combined organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure to afford the crude allylic benzamide. Purification of the residue by flash chromatography on silica gel using hexanes/EtOAc as eluent afforded N-(5-phenylpent-1-en-3-yl)-benzamide (97 mg, 0.37 mmol, 73 %) as an off-white solid.

**mp** 131 °C; **¹H-NMR (300 MHz, CDCl₃)** δ 7.71-7.68 (m, 2H), 7.52-7.37 (m, 3H), 7.31-7.17 (m, 5H), 6.11 (d, J = 8.2 Hz, 1H), 5.90 (ddd, J = 17.2, 10.4, 5.6 Hz, 1H), 5.24 (dd, J = 17.2, 1.2 Hz, 1H), 5.18 (dd, J = 10.4, 1.2 Hz, 1H), 4.76 (br. quint, 1H), 2.75 (t, J = 2.9 Hz, 2H), 2.10-1.90 (m, 2H); **¹³C-NMR (75 MHz, CDCl₃)** δ 166.7, 141.5, 138.0, 134.5, 131.4, 128.5, 128.4, 128.4, 126.8, 126.0, 115.4, 51.6, 36.3, 32.1; **IR (neat)** 3326, 2946, 2979, 2862, 1633, 1526, 1487, 1334, 1292, 920, 748, 698; **HR-MALDI-MS** m/z calcd for C₁₈H₁₉NO [M+H]⁺ 266.1539, found 266.1538.
tert-Butyl 5-phenylpent-1-en-3-ylcarbamate (Table 3, entry 3)

A Schlenk flask under argon was charged with [IrCl(cod)]$_2$ (10 mg, 15 µmol, 3 mol %) and ligand (3,5-dioxo-4-phospha-cyclohepta[2,1-a;3,4-a']diphenyl-4-en)-dibenzo[b,f]azepine 31 (12 mg, 30 µmol, 6 mol %). 2 ml N,N-dimethylformamide was added and the reaction mixture was stirred at 23 °C for 15 min. 5-Phenylpent-1-en-3-ol 29 (81 mg, 0.50 mmol, 1 eq) was added via syringe followed by the addition of solid sulfamic acid (49 mg, 0.50 mmol, 1 eq). The resulting reaction mixture was heated to 50 °C. Conversion was checked by disappearance of the starting material on TLC and/or by measuring $^1$H-NMR of an aliquot taken from the reaction mixture. After completion of the reaction (usually 3-4 h), the reaction mixture was carefully concentrated and cooled to 23 °C. The resulting brownish oil was redissolved in 3 ml CH$_2$Cl$_2$ and at 0 °C, 202 mg (1.00 mmol, 2 eq) Boc$_3$O and a catalytic amount (ca. 10 mg) of the phase transfer reagent n-Bu$_4$NSO$_4$ was added. At 0 °C, the reaction mixture was treated with 3 ml of a 0.5 M aqueous NaOH solution and warmed to 23 °C within 6 hours. Subsequently, the reaction mixture was partitioned between 10 ml CH$_2$Cl$_2$ and 10 ml H$_2$O. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 15 ml). The combined organic layers were dried (Na$_2$SO$_4$) and concentrated under reduced pressure to afford the crude Boc-protected amine. Purification of the residue by flash chromatography on silica gel using hexanes/EtOAc as eluent afforded tert-Butyl 5-phenylpent-1-en-3-ylcarbamate (93 mg, 0.36 mmol, 71 %) as an off-white solid.

mp 53 °C; $^1$H-NMR (300 MHz, CDCl$_3$) δ 7.17-7.31 (m, 5H), 5.79 (ddd, J = 16.5, 10.3, 5.6 Hz, 1H), 5.10-5.21 (m, 2H), 4.49 (br. S, 1H), 4.16 (br. S, 1H), 2.62-2.96 (m, 2H), 1.78-1.89 (m, 2H), 1.46 (s, 9H); $^{13}$C-NMR (75 MHz, CDCl$_3$) δ 155.2, 141.5, 138.6, 128.3, 128.2, 125.8, 114.6, 79.3, 52.6, 37.0, 32.2, 28.6; IR (neat) 3364, 3028, 2979, 2945, 1681, 1517, 1330, 1243, 1172, 1045, 1030, 926, 752, 701; HR-ESI-MS m/z calcd for C$_{16}$H$_{23}$NO$_2$Na [MNa]$^+$ 284.1621, found 284.1623.
2,2,2-Trifluoro-N-(5-phenylpent-1-en-3-yl)-acetamide (Table 4, entry 4)

A Schlenk flask under argon was charged with [IrCl(cod)]$_2$ (10 mg, 15 μmol, 3 mol %) and ligand (3,5-dioxo-4-phospha-cyclohepta[2,1-a;3,4-a’]diphenyl-4-en)-dibenzo[b,f]azepine 31 (12 mg, 30 μmol, 6 mol %). 2 ml N,N-dimethylformamide was added and the reaction mixture was stirred at 23 °C for 15 min. 5-Phenylpent-1-en-3-ol 29 (81 mg, 0.50 mmol, 1 eq) was added via syringe followed by the addition of solid sulfamic acid (49 mg, 0.50 mmol, 1 eq). The resulting reaction mixture was heated to 50 °C. Conversion was checked by disappearance of the starting material on TLC and/or by measuring $^1$H-NMR of an aliquot taken from the reaction mixture. After completion of the reaction (usually 3-4 h), the reaction mixture was carefully concentrated and cooled to 23 °C. The resulting brownish oil was redissolved in 2 ml CH$_2$Cl$_2$ and at 0 °C, 315 mg trifluoroacetic anhydride (1.50 mmol, 3 eq) and 276 mg solid, anhydrous K$_2$CO$_3$ (2.00 mmol, 4 eq) were added. Stirring of the reaction mixture was continued for 8 hours at 23 °C. Subsequently, it was partitioned between 10 ml CH$_2$Cl$_2$ and 10 ml H$_2$O. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 15 ml). The combined organic layers were dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure to afford the crude trifluoroacetamide. Purification of the residue by flash chromatography on silica gel using hexanes/EtOAc as eluent afforded 2,2,2-trifluoro-N-(5-phenylpent-1-en-3-yl)-acetamide (91 mg, 0.36 mmol, 71 %) as a yellow oil.

$^1$H-NMR (300 MHz, CDCl$_3$) δ 7.13-7.99 (m, 5H), 6.14 (br. s, 1H), 5.79 (ddd, J = 17.0, 10.7, 6.0 Hz, 1H), 5.19-5.25 (m, 2H), 4.46-4.55 (br. quint, 1H), 2.67 (t, J = 7.8 Hz, 2H), 1.89-2.01 (m, 2H); $^{13}$C-NMR (75 MHz, CDCl$_3$) δ 156.5 (q, J = 36.9 Hz), 140.6, 135.9, 128.6, 128.3, 126.3, 117.0, 115.8 (q, J = 288.3 Hz), 52.1, 35.7, 31.9; $^{19}$F-NMR (282 MHz, CDCl$_3$) δ -75.7; IR (neat) 3293, 3088, 2928, 1698, 1554, 1206, 1181, 1154, 747, 724, 698; HR-ESI-MS m/z calcd for C$_{13}$H$_{14}$NOF$_3$Na [MNa]$^+$ 280.0919, found 280.0919.
1-Phenylprop-2-en-1-amine hydrochloride (Table 3, entry 5)

\[
\begin{array}{c}
\text{Ph} \quad \text{OH} \\
\text{1 equiv}
\end{array}
\quad \xrightarrow{\text{[IrCl(cod)]_2 (1.5 mol\%), phosphoramidite 31 (3 mol\%)}}
\begin{array}{c}
\text{Ph} \quad \text{NH}_2 \quad \text{Cl} \\
\text{1 equiv}
\end{array}
\]

Prepared according to GP3. Off-white solid. Yield: 132 mg (0.78 mmol, 78 %);

\(^1\text{H-NMR (300 MHz, CD}_3\text{OD)} \delta 7.43-7.57 \text{ (m, 5H), 6.19 (ddd, } J = 17.3, 10.6, 6.5 \text{ Hz, 1H), 5.51 (dd, } J = 10.6, 1.0 \text{ Hz, 1H), 5.44 (dd, } J = 17.3, 1.3 \text{ Hz, 1H), 5.04 (d, } J = 6.5, 1\text{H), 4.55 (br. s, 3H). All other spectroscopic data were in agreement with the literature.}^{81}\]

1-Cyclohexylprop-2-en-1-amine hydrochloride (Table 3, entry 6)

\[
\begin{array}{c}
\text{CH} \quad \text{OH} \\
\text{1 equiv}
\end{array}
\quad \xrightarrow{\text{[IrCl(cod)]_2 (1.5 mol\%), phosphoramidite 31 (3 mol\%)}}
\begin{array}{c}
\text{CH} \quad \text{NH}_2 \quad \text{Cl} \\
\text{1 equiv}
\end{array}
\]

Prepared according to GP3. White flakes. Yield: 132 mg (0.75 mmol, 75 %);

\text{mp 231 °C; } ^1\text{H-NMR (300 MHz, CDCl}_3\text{)} \delta 8.54 \text{ (br. s, 3H), 5.91-5.79 (ddd, } J = 17.3, 9.6, 6.9 \text{ Hz, 1H), 5.42 (d, } J = 17.3 \text{ Hz, 1H), 5.37 (d, } J = 9.6 \text{ Hz, 1H); 3.51-3.46 \text{ (m, 1H), 1.89-1.61 \text{ (m, 6H), 1.45-1.03 \text{ (m, 5H)}; } ^13\text{C-NMR (75 MHz, CDCl}_3\text{)} \delta 131.9, 121.0, 59.5, 40.3, 29.1, 28.1, 25.6; } \text{IR (neat) 3274, 2921, 2851, 1629, 1600, 1510, 1447, 993, 933, 918, 687; } \text{HR-ESI-MS } m/z \text{ calcd for C}_{11}\text{H}_{13} [\text{MH-NH}_3]^+ 145.1012, \text{ found 145.1012.}

^{81}\text{Zwierzak, A.; Napieraj, A. Synthesis, 1999, 930.}
1-(Benzyloxy)but-3-en-2-amine hydrochloride (Table 3, entry 7)

\[
\text{BnO-} \quad \begin{array}{c}
\text{OH} \\
\text{1 equiv}
\end{array} + \quad \begin{array}{c}
\text{H3N+SO3}^- \\
\text{1 equiv}
\end{array} \xrightarrow{\text{[IrCl(cod)]2(1.5 mol%)}} \text{phosphoramidite 31 (3 mol%)} \quad \xrightarrow{\text{DMF, 50 °C, 3 h}} \quad \text{BnO-} \quad \begin{array}{c}
\text{NH3}^+ \\
\text{Cl-}
\end{array}
\]

Prepared according to GP3. White powder. Yield: 152 mg (0.71 mmol, 71 %);

\(^1\text{H-NMR (300 MHz, CD}_{3}\text{OD}) \ \delta \ 7.39-7.26 \ (m, 5H), \ 5.88 \ (m, 1H), \ 5.41 \ (d, J = 17.4 \ Hz, 1H), \ 5.37 \ (d, J = 11.2 \ Hz, 1H), \ 4.59 \ (s, 2H), \ 3.87 \ (m, 1H), \ 3.64 \ (dd, J = 10.1, 3.9 \ Hz, 1H), \ 3.49 \ (dd, J = 10.1, 7.8 \ Hz, 1H). \ All \ other \ spectroscopic \ data \ are \ in \ agreement \ with \ the \ literature.\textsuperscript{82}\)

Hexa-1,5-dien-3-amine hydrochloride (Table 3, entry 8)

\[
\begin{array}{c}
\text{OH} \\
\text{1 equiv}
\end{array} + \quad \begin{array}{c}
\text{H3N+SO3}^- \\
\text{1 equiv}
\end{array} \xrightarrow{\text{[IrCl(cod)]2(1.5 mol%)}} \text{phosphoramidite 31 (3 mol%)} \quad \xrightarrow{\text{DMF, 50 °C, 3 h}} \quad \begin{array}{c}
\text{NH3}^+ \\
\text{Cl-}
\end{array}
\]

Prepared according to GP3. Off-white solid. Yield: 101 mg (0.75 mmol, 75 %);

\(^1\text{H-NMR (300 MHz, D}_2\text{O}) \ \delta \ 5.64-5.86 \ (m, 2H), \ 5.14-5.34 \ (m, 4H), \ 3.81 \ (q, J = 6.7 \ Hz, 1H), \ 2.31-2.46 \ (m, 2H). \ All \ other \ spectroscopic \ data \ are \ in \ agreement \ with \ the \ literature.\textsuperscript{83}\)


Test for Enantiospecificity: (R)-N-Benzoyl-1-phenyl-2-propenylamine (40)

A Schlenk flask under argon was charged with [IrCl(coe)$_2$]$_2$ (13.1 mg, 15 μmol, 3 mol %) and ligand (3,5-dioxo-4-phospha-cyclohepta[2,1-a;3,4-a’]diphenyl-4-en)-dibenzo[b,f]azepine 31 (12 mg, 30 μmol, 6 mol %). 2 ml N,N-dimethylformamide was added and the reaction mixture was stirred at 23 °C for 15 min. Optically active (R)-1-phenylprop-2-en-1-ol (67 mg, 0.50 mmol, 1 eq, 88% ee) was added via syringe followed by the addition of solid sulfamic acid (49 mg, 0.50 mmol, 1 eq). The resulting reaction mixture was stirred at 23°C for 24 hours. After completion of the reaction (checked by TLC), triethylamine (202 mg, 2.00 mmol, 4 eq) and freshly distilled benzoyl chloride (141 mg, 1.00 mmol, 2 eq) were added to the reaction mixture and stirring was continued for 4 hours at 23 °C. Subsequently, the reaction mixture was partitioned between 10 ml CH$_2$Cl$_2$ and 10 ml H$_2$O. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 15 ml). The combined organic layers were dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure to afford the crude allylic benzamide. Purification of the residue by flash chromatography on silica gel using hexanes/EtOAc as eluent afforded (R)-N-benzoyl-1-phenyl-2-propenylamine (84 mg, 0.36 mmol, 71 %) as an off-white solid. The enantioselectivity was 44% ee (Chiralpak AD-H, 220 nm, hexanes/iPrOH = 95:5, flow rate 1.0 ml/min, $t_r$ (minor) = 23.9 min, $t_r$ (major) = 40.9 min).

$^1$H-NMR (300 MHz, CDCl$_3$) δ 7.79-7.28 (m, 10H), 6.74 (d, $J$ = 7.5 Hz, 1H), 6.08 (ddd, $J$ = 15.7, 10.0, 5.5 Hz, 1H), 5.85-5.78 (m, 1H), 5.30 (m, 1H), 5.25 (d, $J$ = 11.5 Hz, 1H).

All other spectroscopic data are in agreement with the literature.$^{84}$

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(S)-1-Cyclohexylprop-2-en-1-amine hydrochloride (42)

A Schlenk flask under argon was charged with [IrCl(coe)₂]₂ (13.1 mg, 15 µmol, 3 mol %) and ligand (S)-(−)-(3,5-dioxo-4-phospha-cyclohepta[2,1-a;3,4-a′]dinaphthalen-4-yl)-dibenzo-[b,f]-azepine 43 (16.2 mg, 30 µmol, 6 mol %). 2 ml N,N-dimethylformamide was added and the reaction mixture was stirred at 23 °C for 15 min. Racemic 1-cyclohexylprop-2-en-1-ol 41 (70 mg, 0.50 mmol, 1 eq) was added via syringe followed by the addition of solid sulfamic acid (49 mg, 0.50 mmol, 1 eq). The resulting reaction mixture was stirred at 23 °C for 24 hours. After completion of the reaction, as determined by TLC, the solvent was carefully evaporated at high vacuum. The resulting brown residue was dissolved in 10 ml CH₂Cl₂ and 10 ml saturated aqueous NaHCO₃ solution and stirred for 10 min. The aqueous layer was extracted with CH₂Cl₂ (3 x 15 ml). The combined organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure to afford the crude allylic amine. The ratio of regioisomers was determined by ¹H-NMR analysis of the unpurified sample. Purification of the residue by flash chromatography on neutral alumina using CH₂Cl₂/MeOH as eluent afforded the desired amine which was immediately treated with 2 M HCl in diethylether. The corresponding hydrochloride salt 42 precipitated as a white solid in 70 % yield (61 mg, 0.35 mmol).

**Determination of the absolute configuration**

To determine the absolute configuration, 50 mg (0.28 mmol, 1 eq) of the amine hydrochloride 42 was suspended in 1 ml Et₂O and treated with 0.5 ml (10 eq) 6 M KOH. After stirring at 23 °C for 30 min, the mixture was partitioned between Et₂O and H₂O.
The aqueous phase was extracted three times with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄ and filtered. The mixture was carefully concentrated under reduced pressure to obtain a brownish oil that was immediately dissolved in 2 ml CH₂Cl₂ and treated with 115 mg (1.14 mmol, 4 eq) triethylamine and 103 mg (0.57 mmol, 2 eq) freshly distilled trichloroacetyl chloride. After 3 h stirring at 23 °C, the reaction mixture was partitioned between CH₂Cl₂ and H₂O. The aqueous phase was extracted three times with CH₂Cl₂. The combined organic layers were washed with brine, dried over MgSO₄ and filtered. Concentration of the filtrate under reduced pressure yielded in a brownish residue that was subjected to chromatography on silica gel (30:1 hexanes/EtOAc) to obtain 36 mg (0.13 mmol, 45 %) 2,2,2-trichloro-N-(1-cyclohexylallyl)-acetamide as a colorless solid. The optical rotation was measured: [α]D²⁵ -26.5 (c = 0.45, CHCl₃); Comparison to the literature [α]D²⁵ +30.7, c = 0.42, CHCl₃ allowed to establish the absolute configuration for the product as: (S)-2,2,2-Trichloro-N-(1-cyclohexylallyl)acetamide.

**¹H-NMR (300 MHz, CDCl₃)** δ 6.58 (br s, 1H), 5.79 (ddd, J = 17.1, 10.5, 6.0 Hz, 1H), 5.19-5.25 (m, 2H), 4.27 (dd, J = 14.8, 6.2 Hz, 1H), 1.65-1.81 (m, 5H), 1.51-1.60 (m, 1H), 0.95-1.30 (m, 5H). All other spectroscopic data are in agreement with the literature.

**Determination of enantioselectivity**

![Chemical structure](image)

For determination of the enantioselectivity, the allylic amination procedure described above was repeated but it differed in the workup: Thus, the resulting amine was directly protected by the addition of triethylamine (202 mg, 2.00 mmol, 4 eq) and freshly distilled benzoylchloride (141 mg, 1.00 mmol, 2 eq). The mixture was stirred at 23 °C for 3 hours,

---

Experimental Section

When the hydrochloride salt obtained from the allylic amination was triturated with Et₂O, enantiomeric enrichment could be improved to 93% ee. Enantioselectivity was determined after derivatisation to the corresponding benzamide in an analogous way.


Detailed description of the spectroscopic experiments.

A) Iridium-catalyzed allylic amination using 1 equivalent sulfamic acid

\[
\begin{align*}
\text{H₂N}^{+}H_{3}^{}\text{SO}_3^{-} & \quad \text{H₂N}^{+}H_{3}^{}\text{SO}_3^{-} \\
(3 \text{ mol\%}) & \quad (1.5 \text{ mol\%}) \\
{\text{H2O}} & \quad {\text{H2O}} \\
1 \text{ equiv} & \quad 1 \text{ equiv} \\
\delta (\text{H-3}) 4.04 \text{ ppm} & \quad \delta (\text{H-3}) 3.88 \text{ ppm} \\
& \quad 100\% \text{ conversion} \\
& \quad \text{33}
\end{align*}
\]

A Schlenk flask under argon was charged with [[Ir(cod)Cl]₂] (10 mg, 15 µmol, 1.5 mol %) and ligand (3,5-dioxa-4-phospha-cyclohepta[2,1-a;3,4-a′]diphenyl-4-en)-dibenzo[b,f]azepine 31 (12 mg, 30 µmol, 3 mol %). 1.5 ml N,N-dimethylformamide-d⁷ were added and the reaction mixture was stirred at 23 °C for 15 min. 5-Phenylpent-1-en-3-ol 29 (81 mg, 0.50 mmol, 1 eq) was added via syringe followed by the addition of solid sulfamic acid (49 mg, 0.50 mmol, 1 eq). The resulting reaction mixture was heated...
to 50 °C. At regular intervals, aliquots of 100 µl were taken from the reaction mixture and $^1$H-NMR spectra were measured. In the spectra the relevant range (δ 6.49-3.21 ppm) is depicted.

5-Phenylpent-1-en-3-ol (29):

$^1$H-NMR (CDCl$_3$, 300 MHz) δ 7.32-7.17 (m, 5H), 5.92 (ddd, $J = 17.4$, 10.4, 6.1 Hz, 1H), 5.26 (d, $J = 17.4$ Hz, 1H), 5.15 (d, $J = 10.4$ Hz, 1H), 4.14 (br quintet, $J = 5.9$ Hz, 1H), 2.81-2.64 (m, 2H), 1.86 (q, $J = 7.5$ Hz, 2H), 1.49 (d, $J = 4.0$ Hz, 1H). All other spectroscopic data are in agreement with the literature.$^{86}$

1H-NMR (DMF-d$_7$, 300 MHz) δ 7.31-7.14 (m, 5H), 5.91 (ddd, $J = 17.4$, 10.4, 5.6 Hz, 1H), 5.20 (d, $J = 17.4$ Hz, 1H), 5.02 (d, $J = 10.4$ Hz), 4.83 (d, $J = 4.7$ Hz), 4.04 (br. quint, $J = 5.6$ Hz, 1H), 2.78-2.60 (m, 2H), 1.78-1.71 (m, 2H).

Experimental Section

spectrum measured after 22 min

spectrum measured after 1 h 30 min

spectrum measured after 2 h 30 min
B) Iridium-catalyzed allylic amination using 2 equivalents sulfamic acid
A Schlenk flask under argon was charged with \([\text{IrCl(cod)}]_2\) (10 mg, 15 µmol, 1.5 mol %) and ligand (3,5-dioxa-4-phospha-cyclohepta[2,1-a;3,4-a’]diphenyl-4-en)-dibenzo[b,f]azepine 31 (12 mg, 30 µmol, 3 mol %). 1.5 ml \(N,N\)-dimethylformamide-d\(^7\) were added and the reaction mixture was stirred at 23 °C for 15 min. 5-Phenylpent-1-en-3-ol 29 (81 mg, 0.50 mmol, 1 eq) was added via syringe followed by the addition of solid sulfamic acid (97 mg, 1.00 mmol, 2 eq). The resulting reaction mixture was heated to 50 °C. At regular intervals, aliquots of 100 µL were taken from the reaction mixture and \(^1\)H-NMR spectra were measured. In the spectra the relevant range (δ 6.49-3.21 ppm) is depicted.
Iridium-Catalyzed Reactions

spectrum measured after 2 hours 30 min

spectrum measured after 4 hours

spectrum measured after 9 hours
C) Sulfation of alcohol 29 using 2 equivalents sulfamic acid

\[
\begin{align*}
\text{C} = & \text{Sulfation of alcohol 29 using 2 equivalents sulfamic acid} \\
\text{\hspace{1cm}} & \text{Experimental Section} \\
\text{A Schlenk flask under argon was charged with 5-phenylpent-1-en-3-ol 29 (81 mg, 0.50 mmol, 1 eq). 0.7 ml N,N-dimethylformamide-d7 were added followed by the addition of} \\
\end{align*}
\]
solid sulfamic acid (97 mg, 1.00 mmol, 2 eq). The resulting homogenous reaction mixture was heated to 50 °C. At regular intervals, aliquots of 100 µl were taken from the reaction mixture and $^1$H-NMR spectra were measured. In the spectra the relevant range ($\delta$ 6.49-3.21 ppm) is depicted.
Experimental Section

spectrum measured after 5 hours

spectrum measured after 6 hours

spectrum measured after 8 hours
D) Sulfation of alcohol 29 using 2 equivalents SO$_3$-DMF

\[
\begin{align*}
\text{H-OH} & \quad \text{SO}_3 \cdot \text{DMF} \quad \text{DMF-d$_7$, 50°C} \quad \text{1h} \\
\text{1 eq} & \quad \text{δ (H-3) 4.04 ppm} \\
\text{2 eq} & \quad \text{100% conversion} \\
\text{δ (H-3) 4.72 ppm} \\
\end{align*}
\]

A Schlenk flask under argon was charged with 5-phenylpent-1-en-3-ol 29 (81 mg, 0.50 mmol, 1 eq). 0.7 ml N,N-dimethylformamide-d$_7$ were added followed by the addition of solid SO$_3$-DMF (153 mg, 1.00 mmol, 1 eq). The resulting homogenous reaction mixture was heated to 50 °C. After one hour reaction time, an aliquot of 100 μl was taken from the reaction mixture and a $^1$H-NMR spectrum was measured.

E) Sulfamation of the amine 33 with 2 equivalents SO$_3$-DMF

\[
\begin{align*}
\text{H-NH}_2 & \quad \text{SO}_3 \cdot \text{DMF} \quad \text{DMF-d$_7$, 50°C} \quad \text{9h} \\
\text{1 eq} & \quad \text{δ (H-3) 3.88 ppm} \\
\text{2 eq} & \quad \text{δ (H-3) 4.46 ppm} \\
\text{3 eq} & \quad \text{δ (H-3) 4.72 ppm} \\
\end{align*}
\]

A Schlenk flask under argon was charged with 5-phenylpent-1-en-3-amine (81 mg, 1.00 mmol, 1 eq). 0.7 ml N,N-dimethylformamide-d$_7$ were added followed by the addition of
solid SO$_3$-DMF (153 mg, 0.50 mmol, 1 eq). The resulting homogenous reaction mixture was heated to 50 °C. At regular intervals, aliquots of 100 µl were taken from the reaction mixture and $^1$H-NMR spectra were measured. In the spectra the relevant range ($\delta$ 6.49-3.21 ppm) is depicted. The analysis was complicated due to the formation of various side products.
Mechanistical Studies

(R)-1-Cyclohexyl-3-(triethylsilyl)prop-2-yn-1-ol

A 25 ml flask was charged with Zn(OTf)$_2$ (400 mg, 11 mmol, 1.1 eq) and (+)-N-Methylephedrine (215 mg, 12 mmol, 1.2 eq) and purged with nitrogen for 15 min. To the flask was added toluene (30 ml) and triethylamine (1.67 ml, 12 mmol, 1.2 eq). The resulting mixture was stirred at 23 °C for 2 hours before TMS-acetylene (1.70 ml, 12 mmol, 1.2 eq) was added in one portion. After 15 min, cyclohexylcarboxaldehyde (1.21 ml, 10 mmol, 1 eq) was added in one portion. After 2 h, the reaction was quenched by the addition of saturated aqueous NH$_4$Cl solution (30 ml). The reaction mixture was poured into a separatory funnel, the layers were separated and the aqueous phase was extracted with Et$_2$O (3 x 30 ml). The combined organic layers were washed with brine (30 ml), dried over anhydrous MgSO$_4$, filtered and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel using pentane/Et$_2$O as eluent afforded (R)-1-cyclohexyl-3-(triethylsilyl)prop-2-yn-1-ol 45 (1.751 g, 8.32 mmol, 83 %). The enantioselectivity was 98 % ee (Chiralpak OD-H, 254 nm, hexanes, flow rate 1.0 ml/min, $t_c$ (minor) = 6.2 min, $t_c$ (major) = 7.0 min).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 4.12 (t, $J$ = 5.9 Hz, 1H), 1.95 – 1.61 (m, 6H), 1.59 – 1.47 (m, 1H), 1.33 – 0.97 (m, 5H), 0.17 (s, 9H).
Experimental Section

**(R)-1-Cyclohexylprop-2-yn-1-ol**

\[
\begin{align*}
\text{Cyclohexylprop-2-yn-1-ol} & \quad \xrightarrow{\text{K}_2\text{CO}_3} \quad \text{MeOH, rt, 5 h} \\
45 & \quad \xrightarrow{} \quad 46
\end{align*}
\]

A 25 ml flask was charged with (R)-1-cyclohexyl-3-(triethylsilyl)prop-2-yn-1-ol (1.68 g, 8 mmol) and MeOH (16 ml). K\textsubscript{2}CO\textsubscript{3} (2.54 g, 18.4 mmol, 2.3 eq) was added and the reaction was stirred for 5 h. To the reaction mixture was added Et\textsubscript{2}O (20 ml) and H\textsubscript{2}O (20 ml) and the layers were separated. The aqueous layer was extracted with Et\textsubscript{2}O (3 x 20 ml), the combined organic layers were washed with brine (30 ml), dried over anhydrous MgSO\textsubscript{4} and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel using pentane/Et\textsubscript{2}O afforded (R)-1-cyclohexylprop-2-yn-1-ol 46 (865 mg, 6.26 mmol, 78%).

\(^1\text{H-NMR (300 MHz, CDCl}_3\text{) } \delta 4.16 (\text{td, } J = 5.9, 2.2 \text{ Hz, 1H}), 2.46 (\text{d, } J = 2.2 \text{ Hz, 1H}), 1.94 – 1.64 (\text{m, 6H}), 1.64 – 1.50 (\text{m, 1H}), 1.34 – 0.98 (\text{m, 5H}).

**(R)-1-Cyclohexylprop-3-deutero-2-yn-1-ol**

\[
\begin{align*}
\text{EtMgBr, Et}_2\text{O} & \quad \xrightarrow{\text{then DCl/D}_2\text{O}} \\
46 & \quad \xrightarrow{} \quad 47
\end{align*}
\]

A solution of (R)-1-cyclohexylprop-2-yn-1-ol (138 mg, 1 mmol, 1 eq) in Et\textsubscript{2}O (1 ml) was slowly added to a solution of EtMgBr (3 mmol, 3 eq) in Et\textsubscript{2}O (3 M, 1 ml) at rt, then refluxed for 1 h. The reaction was cooled to rt, then quenched with DCl in D\textsubscript{2}O (20 % wt, 0.5 ml) and stirred for further 15 min. Water (1 ml) was added and the layers were separated, the aqueous layer was extracted with Et\textsubscript{2}O (3 x 1 ml). The combined organic phases were washed with brine, dried over anhydrous MgSO\textsubscript{4}, filtered and concentrated. Purification of the residue by flash chromatography on silica gel using pentane/Et\textsubscript{2}O...
afforded (R)-1-cyclohexylprop-3-deutero-2-yn-1-ol 47 (103 mg, 0.740 mmol, 74 %) with 95 % D-incorporation.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 4.16 (t, $J = 5.9$ Hz, 1H), 1.91 – 1.64 (m, 6H), 1.63 – 1.49 (m, 1H), 1.34 – 0.99 (m, 5H).

(R)-1-cyclohexyl-3-deutero-prop-2-en-1-ol (48/49)

To a solution of (R)-1-cyclohexylprop-3-deutero-2-yn-1-ol (103 mg, 0.740 mmol) in EtOAc (8 ml) was added Pd/CaCO$_3$ (30 mg) and quinoline (18 µl). The flask was flushed with H$_2$ (3 x) and the reaction was vigorously stirred for 15 min. H$_2$ was removed in vacuo and the resulting mixture was filtered over a short plug of celite and concentrated. Purification of the residu by flash chromatography on silica gel using pentane/Et$_2$O afforded (R)-1-cyclohexyl-3-deutero-prop-2-en-1-ol 48/49 (74 mg, 0.524 mmol, 70 %) with a cis:trans ratio of 4:1

(R,Z)-1-Cyclohexyl-3-deutero-prop-2-en-1-ol (48)

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 5.91 – 5.78 (m, 1H), 5.11 (dd, $J = 10.5$, 1.1 Hz, 1H), 1.89 – 1.56 (m, 6H), 1.46 – 0.85 (m, 5H).

(R,E)-1-Cyclohexyl-3-deutero-prop-2-en-1-ol (49)

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 5.91 – 5.78 (m, 1H), 5.17 (dd, $J = 17.4$, 1.3 Hz, 1H), 5.14 (d, $J = 1.1$ Hz, 1H), 1.89 – 1.56 (m, 6H), 1.46 – 0.85 (m, 5H).
Experimental Section

N-Benzoyl-1-cyclohexyl-3-deutero-prop-2-en-1-ol

A Schlenk flask under argon was charged with [IrCl(cod)]₂ (6.7 mg, 7.5 µmol, 3 mol %) and ligand (3,5-dioxo-4-phospha-cyclohepta[2,1-a;3,4-a’]diphenyl-4-en)-dibenzo[b,f]azepine 31 (6.1 mg, 30 µmol, 6 mol %). 2 ml N,N-dimethylformamide were added and the reaction mixture was stirred at 23 °C for 15 min. (R)-1-Cyclohexyl-3-deutero-prop-2-en-1-ol 48/49 (35 mg, 0.25 mmol, 1 eq) was added via syringe followed by the addition of solid sulfamic acid (24 mg, 0.25 mmol, 1 eq). The resulting reaction mixture was heated to 50 °C. Conversion was checked by disappearance of the starting
material on TLC. After completion of the reaction (6 h), triethylamine (0.28 ml, 1 mmol, 4 eq) and freshly distilled benzoylchloride (0.06 ml, 0.5 mmol, 2 eq) were added to the reaction mixture and stirring was continued for 4 hours at 23 °C. Subsequently, the reaction mixture was partitioned between 5 ml CH₂Cl₂ and 10 ml H₂O. The aqueous layer was extracted with CH₂Cl₂ (3 x 5 ml). The combined organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure to afford the crude allylic benzamide. Purification of the residue by flash chromatography on silica gel using hexanes/EtOAc as eluent afforded N-benzoyl-1-cyclohexyl-3-deutero-prop-2-en-1-ol (23 mg, 0.094 mmol, 38 %) with a cis:trans ratio of 59:41

*(Z)-N-Benzoyl-1-cyclohexyl-3-deutero-prop-2-en-1-ol (50a+53a)*

\(^1\)H-NMR (300 MHz, CDCl₃) \(\delta\) 7.80 – 7.77 (m, 2H), 7.51 – 7.42 (m, 3 H), 6.03 (d, J = 6.9 Hz, 1H), 5.16 (dd, J = 9, 1.2 Hz, 1H), 4.60 – 4.52 (m, 1 H), 1.79 – 1.55 (m, 7 H), 1.34 – 0.98 (m, 5 H).

*(E)-N-Benzoyl-1-cyclohexyl-3-deutero-prop-2-en-1-ol (51a+52a)*

\(^1\)H-NMR (300 MHz, CDCl₃) \(\delta\) 7.80 – 7.77 (m, 2H), 7.51 – 7.42 (m, 3 H), 6.03 (d, J = 6.9 Hz, 1H), 5.21 (dd, J = 12.3, 1.4 Hz, 1H), 4.60 – 4.52 (m, 1 H), 1.79 – 1.55 (m, 7 H), 1.34 – 0.98 (m, 5 H).

*N-Benzoyl-1-cyclohexyl-3-deutero-prop-2-en-1-ol*

\(^13\)C-NMR (300 MHz, CDCl₃) \(\delta\) 166.6, 136.6, 134.8, 131.3, 128.5, 126.7, 56.5, 42.3, 29.5, 28.9, 26.4, 26.2.

**Elemental analysis:** calculated for C₁₆H₂₀DNO: C 78.65, H 8.25, N 5.73; found C 78.4, H 8.52, N 5.70.
4.3 Iridium-Catalyzed Asymmetric Transfer Hydrogenation

GP4: Synthesis of the Catalysts

To a solution of \( [\text{Cp}^{\ast}\text{Ir(H}_2\text{O)}_3](\text{SO}_4) \) (1 eq) in \( \text{H}_2\text{O} \) (1 M) was added a solution of the monosulfonylated diamine (1 eq) in methanol (1 M) and it was stirred for 1 h at room temperature. Removal of the solvents \textit{in vacuo} provided the catalyst complex as a powder in quantitative yield.

4.3.1 Asymmetric Transfer Hydrogenation of \( \alpha \)-Substituted Acetophenones

Synthesis of the Ligands:

Synthesis of ligands required for the catalysts described below were prepared as outlined in the literature,\(^{87,88,89}\) otherwise commercially available ligands were utilized.

\( \text{N-}((1R,2R)-2\text{-Amino-1,2-dicyclohexylethyl})\text{-2,3,4,5,6-pentafluorobenzenesulfonamide (Ligand Table 6, Entry 2)} \)

\[
\text{H}_2\text{N} \quad \text{NH}_2 \quad \text{SO}_2\text{C}_6\text{F}_5
\]

To a stirred solution of the free diamine\(^{90}\) (83 mg, 0.37 mmol) and DIPEA (0.13 ml, 0.74 mmol) in anhydrous \( \text{CH}_2\text{Cl}_2 \) (10 ml) at 0 °C was added pentafluorophenyl sulfonyl chloride (dropwise) and the resulting mixture was stirred over night. The reaction was then quenched by addition of saturated \( \text{NH}_4\text{Cl} \) (10 ml). After extraction with \( \text{CH}_2\text{Cl}_2 \)


from H$_2$O, and drying with Na$_2$SO$_4$, the crude was purified by FC (MeOH/CH$_2$Cl$_2$ = 5/95) to afford pure product 51 mg (30%) as a white powder.

$^1$H-NMR (300 MHz, CDCl$_3$) δ 6.62 (br s, 3H, NH’s), 3.42 (d, $J = 4.2$, 1H), 2.66 (d, $J = 3.9$, 1H), 1.59-1.72 (m, 12H), 1.42 (m, 1H), 0.83-1.19 (m, 9H); $^{13}$C-NMR (75 MHz, CDCl$_3$) δ 144.1 (m, 2C), 143.2 (m, 1C), 137.7 (m, 2C), 118.8 (m, 2C), 29.8, 29.8, 29.1, 26.2, 26.2, 26.1, 26.1, 25.9; IR (thin film, cm$^{-1}$) 3377, 3089, 2922, 2852, 1646, 1589, 144.1 (m, 2C), 143.2 (m, 1C), 137.7 (m, 2C), 118.8 (m, 2C), 29.8, 29.8, 29.1, 26.2, 26.2, 26.1, 26.1, 25.9; HR-MALDI calcd for C$_{20}$H$_{10}$F$_{9}$N$_2$O$_2$S $[M-H]^+$ 455.1792, found 455.1779; Optical rotation: $[\alpha]_D^{26}$ -66.6 ($c$ = 1.0, CH$_3$OH).

**N-((1R,2R)-2-Aminocyclohexyl)-2,3,4,5,6-pentafluorobenzenesulfonamide**  (Ligand Table 6, Entry 3)

![Structural formula](image)

To a stirred solution of the free diamine (300 mg, 2.63 mmol) and DIPEA (0.90 ml, 5.26 mmol) in anhydrous CH$_2$Cl$_2$ (30 ml) at 0 °C was added pentafluorophenyl sulfonyl chloride (dropwise) and the resulting mixture was stirred over night. The reaction was then quenched by addition of saturated NH$_4$Cl (10 ml). After extraction with CH$_2$Cl$_2$ from H$_2$O, and drying with Na$_2$SO$_4$, the crude was purified by FC (MeOH/CH$_2$Cl$_2$ = 5/95) to afford pure product 383 mg (42%) as a white powder.

$^1$H-NMR (300 MHz, CDCl$_3$) δ 6.62 (br s, 3H, NH’s), 3.50 (m, 1H), 3.34 (m, 1H), 2.32 (d, $J = 8.1$ Hz, 1H), 1.25-1.70 (m, 9H); $^{13}$C-NMR (75 MHz, CDCl$_3$) δ 144.3 (m, 2C) 143.6 (m, 1C), 137.8 (m, 2C), 118.5 (m, 1C), 33.1, 31.8, 31.5, 31.0, 24.3, 23.7; IR (thin film, cm$^{-1}$) 2940, 2866, 1645, 1520, 1495, 1453, 1355, 1299, 1266, 1169, 1098, 988, 932, 909, 889; HR-MALDI calcd for C$_{20}$H$_{10}$F$_{9}$N$_2$O$_2$S $[M-H]^+$ 345.0691, found 345.0690. Optical rotation: $[\alpha]_D^{26}$ -46.7 ($c$ = 1.0, CH$_3$OH).
**Synthesis of the Catalysts:**

\[
\text{[Cp}^*\text{Ir[(R,R)-Ts-DACH](H}_2\text{O)})(\text{SO}_4) \text{]} \quad \text{(Catalyst Table 6, entry 1)}
\]

Prepared according to GP4.

\[\text{^1H-NMR (300 MHz, CD}_2\text{OD) } \delta 7.79 \text{ (d, } J = 6.3 \text{ Hz, 2H, Diastereomer A), 7.74 \text{ (d, } J = 6.3 \text{ Hz, 2H, Diastereomer B), 7.41 \text{ (d, } J = 6.0 \text{ Hz, 2H, Diastereomer A), 7.38 \text{ (d, } J = 6.0 \text{ Hz, 2H, Diastereomer B), 2.77-2.92 \text{ (m, 1H, Diastereomer A), 2.96-3.03 \text{ (m, 1H, Diastereomer B), 2.45 \text{ (s, 3H, Diastereomer A), 2.43 \text{ (s, 3H, Diastereomer B), 1.99-2.16 \text{ (m, 2H, Diastereomer A+B), 1.76 \text{ (s, 15H, Diastereomer B), 1.63 \text{ (s, 15H, Diastereomer A), 0.70-1.66 \text{ (m, 9H, Diastereomer A+B); } ^{13}\text{C-NMR (75 MHz, CD}_2\text{OD) } \delta 131.0, 130.7, 128.1, 127.8, 91.4, 90.8, 85.1, 82.8, 56.5, 56.1, 34.0, 33.6, 32.0, 30.8, 26.0, 25.8, 25.6, 24.7, 21.5, 21.4, 10.3, 9.4, 9.4, 8.9; HR-MALDI calcd for C}_{31}\text{H}_{36}\text{IrN}_2\text{O}_2\text{S [M-SO}_4\text{-H}_2\text{O]}^+ 693.2121, found 693.2109; Optical rotation: } [\alpha]_D^{25} = -273.92^\circ \text{ (c = 1.0, CHCl}_3).\]

\[
\text{[Cp}^*\text{Ir[(R,R)-C}_8\text{F}_5\text{SO}_2\text{-DACH](H}_2\text{O)})(\text{SO}_4) \text{]} \quad \text{(Catalyst Table 6, entry 2)}
\]

Prepared according to GP4.
Experimental Section

$^1$H-NMR (300 MHz, CD$_3$OD) $\delta$ 3.48 (d, $J = 3.3$ Hz, 1H) 2.86 (d, $J = 5.1$ Hz, 1H), 1.02-1.21, 1.81 (s, 15H), 0.73-0.61 (m, 5H), 0.43-0.51 (m, 1H); $^{13}$C-NMR (75 MHz, CD$_3$OD) $\delta$ 93.1, 73.9, 62.0, 43.0, 41.0, 32.3, 31.1, 30.7, 29.4, 27.8, 27.6, 27.4, 27.0, 27.0, 10.4; $^{19}$F-NMR (282 MHz, CD$_3$OD) $\delta$ 160.4 (m, 2F), 147.8 (m, 1F), 134.9 (m, 2F); HR-MALDI calcld for C$_{30}$H$_{29}$Ir$_{2}$O$_{3}$S [M-SO$_4$-H$_2$O]$^+$ 769.1494, found 769.1479; Optical rotation: $[\alpha]_D^{20}$ -242.22° ($c = 1.0$, CHCl$_3$).

$\{\text{Cp}^*\text{Ir}[(R,R)-\text{C}_6\text{F}_5\text{SO}_2\text{-Dicyclohexyl}](\text{H}_2\text{O})]\}(\text{SO}_4)$ (Catalyst Table 6, entry 3)

Prepared according to GP4.

$^1$H-NMR (300 MHz, CD$_3$OD) $\delta$ 2.86-2.97 (s, 15H), 1.04-2.22 (m, 37H); $^{13}$C-NMR (75 MHz, CD$_3$OD) $\delta$ 89.4 85.1, 66.0, 56.9, 55.7, 35.2, 33.2, 32.2, 30.2, 26.1, 25.9, 25.4, 24.6, 9.6; $^{19}$F-NMR (282 MHz, CD$_3$OD) $\delta$ 160.1 (m, 2F), 147.6 (m, 1F), 134.9 (m, 2F); HR-MALDI calcld for C$_{23}$H$_{29}$Ir$_{2}$O$_{3}$S [M-SO$_4$-H$_2$O]$^+$ 671.1525, found 671.1514; Optical rotation: $[\alpha]_D^{28}$ -293.16° ($c = 0.25$, CH$_3$OH).
**Synthesis of Substrates:**

**Synthesis of β-Ketonitriles:**

A solution of KOt-Amyl (1.33 ml, 2.61 mmol, 3.00 eq, 1.7 M in toluene, Fluka) was added dropwise at room temperature to a stirred solution of acetonitrile (0.87 mmol, 1.00 eq) in THF (3.0 ml) followed by dropwise addition of the ester (3.48 mmol, 4.00 eq). After 20 min at room temperature, the reaction mixture was diluted with HCl (0.25 M, 100 ml) and EtOAc (100 ml). The layers were separated and the organic layer was washed sequentially with H₂O (2 x 50 ml) and brine (2 x 50 ml), dried over Na₂SO₄, filtered, concentrated, and chromatographed (silica gel, EtOAc/Hex) to provide the corresponding β-ketonitrile.

**Synthesis of α-Nitroketones:**

A mixture of nitromethane (0.11 ml, 2.0 mmol, 1 eq) and KOt-buty (0.5 g, 4.4 mmol, 2.2 eq) in DMSO (10 ml) was stirred for 10 min while the temperature was maintained at 10 °C. The corresponding N-acetylbenzotriazole (2.0 mmol, 1 eq) in DMSO (10 ml) was added dropwise to the resulting solution, and the mixture was stirred for 2 h at 10 °C, and then for additional 6 h at room temperature. The mixture was poured into water (40 ml), acidified with acetic acid (10 % in water), and then extracted with ethyl acetate (3 x 30 ml). The combined extracts were washed with water, dried over Na₂SO₄, filtered

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concentrated, and chromatographed (silica gel, EtOAc/Hex) to provide the corresponding α-nitroketone.

**GP5: Transfer Hydrogenation Reaction of β-Ketonitriles**

The β-ketonitrile (1.0 eq), catalyst 110 (0.25 - 0.5 mol %) and aqueous solution of formic acid (1.0 M formate soln., pH = 3.5, 5.0 eq, 0.2 M overall concentration) were combined in a glass vial and sealed with a punctured plastic cap. The reaction mixture was then stirred at ambient temperature for 24 h. The reaction mixture was then extracted with dichloromethane (3 x). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography to provide the corresponding β-hydroxynitrile.

**(R)-3-Hydroxy-3-phenylpropanenitrile (Table 7, entry 1)**

\[
\text{\begin{center}
\begin{align*}
\text{CH₂CN} & \quad \text{OH} \\
\text{\includegraphics[width=1cm]{image.png}} & \\
\end{align*}
\end{center}}
\]

Prepared according to GP5 using 80 mg (0.55 mmol) ketone and 0.25 mol % catalyst. Yield: 78 mg (0.54 mmol, 96 %); ee = 94% (HPLC: OJ-H, 215 nm, hexane:2-propanol = 90:10, flow rate 1 ml/min, \( t_{(\text{major})} = 26.9 \) min, \( t_{(\text{minor})} = 22.0 \) min).

\(^1\text{H-NMR (300 MHz, CDCl}_3\) δ 2.43 (br s, 1H, OH), 2.78 (d, \( J = 6.3 \) Hz, 2H), 5.03-5.08 (m, 1H), 7.33-7.42 (m, 5H); \(^13\text{C-NMR (75 MHz, CDCl}_3\) δ 28.1, 70.2, 117.6, 125.5, 128.8, 128.9, 139.1; \textbf{Optical rotation: } [\alpha]_D^{24} +56.93^\circ (c = 1.0, \text{CHCl}_3), \text{Lit.} [\alpha]_D^{20} = +56.1^\circ (c 0.9, \text{EtOH}) for (R) enantiomer (99% ee). All other spectroscopic data were in agreement with the literature.\(^93\)

(R)-3-(4-Fluorophenyl)-3-hydroxypropanenitrile (Table 7, entry 2)

Prepared according to GP5 using 100 mg (0.61 mmol) ketone and 0.5 mol % catalyst. Yield: 95 mg (0.58 mmol, 95 %); ee = 91% (HPLC: OD-H, 215 nm, hexane:2-propanol = 95:5, flow rate 0.5 ml/min, t\textsubscript{r(major)} = 93.6 min, t\textsubscript{r(minor)} = 77.7 min).

$^1$H-NMR (300 MHz, CDCl\textsubscript{3}) $\delta$ 7.31-7.42 (m, 2H), 7.06-7.13 (m, 2H), 5.05 (t, $J$ = 6.3 Hz, 1H), 2.77 (d, $J$ = 6.3 Hz, 2H), 2.44 (br s, 1H, OH); $^{13}$C-NMR (75 MHz, CDCl\textsubscript{3}) $\delta$ 160.8 (d, $J$ = 245.2 Hz), 136.7 (d, $J$ = 3.0 Hz), 127.1 (d, $J$ = 8.5 Hz), 117.2, 115.4 (d, $J$ = 21.2 Hz), 69.1, 28.0; Optical rotation: [$\alpha$]$_D$$^{29}$ +43.58$^\circ$ (c = 1.0, CHCl\textsubscript{3}), Lit.$^5$ [$\alpha$]$_D$$^{29}$ = +53.7$^\circ$ (c = 0.86, EtOH) for (R) enantiomer (99% ee); All other spectroscopic data were in agreement with the literature.$^{94}$

(R)-3-Hydroxy-3-p-tolylpropanenitrile (Table 7, entry 3)

Prepared according to GP5 using 103 mg (0.64 mmol) ketone and 0.5 mol % catalyst. Yield: 99 mg (0.62 mmol, 96 %); ee = 93% (HPLC: OJ-H, 215 nm, hexane:2-propanol = 90:10, flow rate 1 ml/min, t\textsubscript{r(major)} = 21.3 min, t\textsubscript{r(minor)} = 18.6 min).

$^1$H-NMR (300 MHz, CDCl\textsubscript{3}) $\delta$ 7.29 (d, $J$ = 8.4 Hz, 2H), 7.21 (d, $J$ = 8.4 Hz, 2H), 4.99-5.05 (ddd, $J$ = 3.9, 6.3, 12.3 Hz, 1H), 2.82 (d, $J$ = 6.9 Hz, 1H), 2.76 (d, $J$ = 5.7 Hz, 1H), 2.36 (s, 3H), 2.28 (d, $J$ = 3.6 Hz, 1H, OH); $^{13}$C-NMR (75 MHz, CDCl\textsubscript{3}) $\delta$ 138.9, 138.3, 129.7, 125.7, 117.7, 70.1, 28.1, 21.4; Optical rotation: [$\alpha$]$_D$$^{29}$ +29.68$^\circ$ (c = 1.0, CHCl\textsubscript{3}).

---

Lit. $^{5} [\alpha]_{D}^{20} = +65.8^\circ$ (c 1.09, CHCl$_3$) for (R) enantiomer (99% ee). All other spectroscopic data were in agreement with the literature.$^{95}$

**(R)-4-(2-Cyano-1-hydroxyethyl)benzonitrile (Table 7, entry 4)**

![Chemical Structure](image)

Prepared according to GP5 using 100 mg (0.59 mmol) ketone and 0.25 mol % catalyst. Yield: 98 mg (0.58 mmol, 97 %); ee = 86% (HPLC: OJ-H, 215 nm, hexane:2-propanol = 90:10, flow rate 1 ml/min, $t_{\text{r(major)}} = 62.4$ min, $t_{\text{r(minor)}} = 51.9$ min).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.70 (d, $J = 8.1$, 2H), 7.56 (d, $J = 8.1$, 2H), 5.11-5.17 (m, 1H), 2.79 (d, $J = 5.7$ Hz, 2H), 2.52-2.78 (br s, 1H, OH); $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 146.0, 132.6, 126.3, 118.3, 116.6, 112.3, 69.1, 28.1; IR (thin film, cm$^{-1}$) 3448, 2230, 1610, 1150, 1413, 1071, 842, 567; HR-EI calcd for C$_{10}$H$_8$N$_2$O $[^{172.0637}$, found 172.0630; **Optical rotation**: $[\alpha]_{D}^{25} +48.16^\circ$ (c 1.0, CHCl$_3$).

**(R)-3-(3-Chlorophenyl)-3-hydroxypropanenitrile (Table 7, entry 5)**

![Chemical Structure](image)

Prepared according to GP5 using 200 mg (1.11 mmol) ketone and 0.25 mol % catalyst. Yield: 182 mg (1.00 mmol, 90 %); ee = 90% (HPLC: OJ-H, 215 nm, hexane:2-propanol = 90:10, flow rate 1 ml/min, $t_{\text{r(major)}} = 15.4$ min, $t_{\text{r(minor)}} = 13.6$ min).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.41 (m, 1H), 7.26-7.35 (m, 3H), 5.04 (ddd, $J = 3.3$, 6.0, 12.0 Hz, 1H), 2.76 (d, $J = 6.3$ Hz, 2H), 2.56 (br s, 1H, OH); $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 146.0, 132.6, 126.3, 118.3, 116.6, 112.3, 69.1, 28.1; IR (thin film, cm$^{-1}$) 3448, 2230, 1610, 1150, 1413, 1071, 842, 567; HR-EI calcd for C$_{10}$H$_8$N$_2$O $[^{172.0637}$, found 172.0630; **Optical rotation**: $[\alpha]_{D}^{25} +48.16^\circ$ (c 1.0, CHCl$_3$).

Iridium-Catalyzed Reactions

δ 143.1, 134.5, 130.1, 128.6, 125.7, 123.8, 117.4, 68.8, 27.8; IR (thin film, cm\(^{-1}\)) 3436, 2256, 1576, 1478, 1434, 1303, 1193, 1063, 883, 790; HR-EI calcd for C\(_9\)H\(_8\)ClNO [M]\(^+\) 181.0294, found 181.0289; Optical rotation: \([\alpha]_D^{25}\) +41.76° (c = 1.0, CHCl\(_3\)).

(R)-3-Hydroxy-3-(3-methoxyphenyl)propanenitrile (Table 7, entry 6)

\[
\begin{align*}
\text{Prepared according to GP5 using 100 mg (0.57 mmol) ketone and 0.25 mol % catalyst.}
\text{Yield: 97 mg (0.55 mmol, 96 %); ee = 95% (HPLC: OJ-H, 215 nm, hexane:2-propanol = 95:5, flow rate 0.5 ml/min, t}_{(\text{major})} = 152.0 \text{ min, t}_{(\text{minor})} = 137.7 \text{ min).}
\end{align*}
\]

^1H-NMR (300 MHz, CDCl\(_3\)) δ 7.27-7.34 (m, 1H), 6.86-6.97 (m, 3H), 4.98-5.03 (m, 1H), 3.82 (s, 3H), 2.77 (d, J = 3.0 Hz, 1H), 2.75 (d, J = 2.4 Hz, 1H), 2.35 (br s, 1H, OH); \(^13\)C-NMR (75 MHz, CDCl\(_3\)) δ 159.9, 142.5, 130.0, 117.6, 117.2, 114.2, 111.0, 70.1, 55.4, 28.0; IR (thin film, cm\(^{-1}\)) 3448, 2940, 2838, 2253, 1603, 1490, 1457, 1436, 1267, 1155, 1043, 771; HR-EI calcd for C\(_{10}\)H\(_{11}\)NO\(_2\) [M]\(^+\) 177.0789, found 177.0783; Optical rotation: \([\alpha]_D^{25}\) +44.08° (c = 1.0, CHCl\(_3\)).

(R)-3-Hydroxy-3-(naphthalen-2-yl)propanenitrile (Table 7, entry 7)

\[
\begin{align*}
\text{Prepared according to GP5 using 117 mg (0.60 mmol) ketone and 0.5 mol % catalyst.}
\text{Yield: 111 mg (0.57 mmol, 95 %); ee = 96% (HPLC: OJ-H, 254 nm, hexane:2-propanol = 90:10, flow rate 1 ml/min, t}_{(\text{major})} = 65.9 \text{ min, t}_{(\text{minor})} = 60.6 \text{ min). For this substrate 10% hexafluoroisopropanol was added.}
\end{align*}
\]
1H-NMR (300 MHz, CDCl₃) δ 7.85-7.91 (m, 4H), 5.63-5.68 (m, 1H), 7.47-7.55 (m, 3H), 4.4.71 (dd, J = 9.3, 13.5 Hz, 2H), 4.61 (dd, J = 3.3, 13.5 Hz, 2H), 2.90 (d, J = 3.6 Hz, 2H); 13C-NMR (75 MHz, CDCl₃) δ 138.2, 133.3, 133.0, 128.8, 128.0, 128.8, 127.7, 126.5, 126.4, 124.7, 122.9, 117.3, 70.2, 28.0; Optical rotation: [α]D²⁵ +43.85° (c = 1.0, CHCl₃), Lit. [α]D²⁰ = +59.5° (c 0.5, EtOH) for (R) enantiomer (99% ee). All other spectroscopic data were in agreement with the literature.⁹⁶

(R)-3-(Furan-2-yl)-3-hydroxypropanenitrile (Table 7, entry 8)

![Structure of (R)-3-(Furan-2-yl)-3-hydroxypropanenitrile]

Prepared according to GP5 using 75 mg (0.55 mmol) ketone and 0.25 mol % catalyst. Yield: 63 mg (0.46 mmol, 83 %); ee = 96% (HPLC: OJ-H, 220 nm, hexane:2-propanol = 90:10, flow rate 1 ml/min, t_r(major) = 22.6 min, t_r(minor) = 19.9 min).

1H-NMR (300 MHz, CDCl₃) δ 2.57 (br s, 1H, OH), 2.91 (d, J = 6.0 Hz, 2H), 5.06 (t, J = 6.3 Hz, 1H), 6.37-6.42 (m, 2H), 7.41-7.42 (m, 1H); 13C-NMR (75 MHz, CDCl₃) δ 152.8, 142.8, 117.0, 110.5, 107.4, 63.6, 24.8. IR (thin film, cm⁻¹) 3426, 2931, 2255, 1504, 1416, 1233, 1057, 1013, 748, 598, 348; HR-EI calcd for C₇H₇NO₂ [M]⁺ 137.0477, found 137.0472; Optical rotation: [α]D²⁷ +37.16° (c = 1.0, CHCl₃).

(R)-3-Hydroxy-3-(thiophen-2-yl)propanenitrile (Table 7, entry 9)

![Structure of (R)-3-Hydroxy-3-(thiophen-2-yl)propanenitrile]

Prepared according to GP5 using 76 mg (0.50 mmol) ketone and 0.5 mol % catalyst. Yield: 73 mg (0.48 mmol, 94 %); ee = 94% (HPLC: OJ-H, 215 nm, hexane:2-propanol = 90:10, flow rate 1 ml/min, t_r(major) = 26.9 min, t_r(minor) = 22.0 min).

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**1H-NMR (300 MHz, CDCl$_3$)** $\delta$ 5.28-5.34 (m, 1H), 7.33 (dd, $J = 1.2$, 4.8 Hz, 1H), 7.10 (td, $J = 0.9$, 3.9 Hz, 1H), 7.01 (dd, $J = 3.6$, 5.1 Hz, 1H), 2.90 (d, $J = 1.2$ Hz, 1H), 2.88 (d, $J = 0.9$ Hz, 1H), 2.62 (d, $J = 3.9$ Hz, 1H, OH); **13C-NMR (75 MHz, CDCl$_3$)** $\delta$ 144.3, 127.1, 125.8, 124.7, 116.8, 66.4, 28.3; **Optical rotation:** $[\alpha]_D^{26}$ +33.23° ($c = 1.0$, CHCl$_3$).

All other spectroscopic data were in agreement with the literature.  

**GP6: Transfer Hydrogenation Reaction of α-Nitroketones**

The β-ketonitrile (1.0 eq), catalyst 110 (0.5 mol %) and aqueous solution of formic acid (1.0 M formate soln., pH = 2.0, 5.0 eq, 0.2 M overall concentration) were combined in a glass vial and sealed with a punctured plastic cap. The reaction mixture was then stirred at ambient temperature for 24 h. The reaction mixture was then extracted with CH$_2$Cl$_2$ (3 x). The combined organic layer was washed, dried over Na$_2$SO$_4$, filtered, and concentrated. The residue was purified by flash chromatography to give the corresponding β-nitroalcohol.

**{(S)-2-Nitro-1-phenylethanol (Table 8, entry 1)}**

Prepared according to GP6 using 85 mg (0.51 mmol) ketone and 0.5 mol % catalyst. Yield: 84 mg (0.48 mmol, 94 %); ee = 93% (HPLC: OD-H, 215 nm, hexane:2-propanol = 97:3, flow rate 1 ml/min, $t_{r(major)} = 42.6$ min, $t_{r(minor)} = 36.5$ min).

**1H-NMR: (300 MHz, CDCl$_3$)** $\delta$ 7.34-7.45 (m, 5H), 5.47 (dt, $J = 3.3$, 9.6 Hz 1H), 4.62 (dd, $J = 9.3$, 13.5 Hz, 1H), 4.52 (dd, $J = 3.3$, 13.5 Hz, 1H), 2.82 (d, $J = 3.9$ Hz, 1H, OH); **13C-NMR (75 MHz, CDCl$_3$)** $\delta$ 138.4, 129.3, 129.3, 126.2, 81.6, 71.4; **Optical rotation:** $[\alpha]_D^{26}$ +33.23° ($c = 1.0$, CHCl$_3$).

---

Experimental Section

\[ \alpha_D^{24} = 42.99^\circ \ (c = 1.0, \text{CHCl}_3) \], Lit.\(^{11} \) \[\alpha_D^{20} = -20.2^\circ \ (c = 1.00, \text{EtOH}) \] for \((R)\) enantiomer (98% ee). All other spectroscopic data were in agreement with the literature.\(^9\)

(S)-1-(4-tert-Butylphenyl)-2-nitroethanol (Table 8, entry 2)

Prepared according to GP6 using 109 mg (0.50 mmol) ketone and 0.5 mol % catalyst. Yield: 103 mg (0.47 mmol, 92 %); ee = 99% (HPLC: OD-H, 215 nm, hexane:2-propanol = 90:10, flow rate 1 ml/min, \(t_{(\text{major})} = 16.0 \text{ min}, t_{(\text{minor})} = 11.6 \text{ min}\)).

\(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta 7.41-7.45 \ (m, 2H), 7.32-7.36 \ (m, 2H), 5.42-5.48 \ (m, 1H), 4.63 \ (dd, J = 9.6, 13.5 \text{ Hz, } 1H), 4.51 \ (dd, J = 3.3, 13.5 \text{ Hz, } 1H), 2.71 \ (d, J = 3.6 \text{ Hz, } 1H), 1.32 \ (s, 9H); \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \(\delta 152.0, 134.9, 125.9, 125.6, 81.2, 70.8, 34.7, 31.3; \) IR (thin film, cm\(^{-1}\)) 3546, 2963, 2360, 1555, 1378, 1219, 1078, 836, 772; HR-EI calcd for C\(_{12}\)H\(_{17}\)NO\(_3\) [M]+ 223.1208, found 223.1204; Optical rotation: \([\alpha]_D^{28} +38.32 \ (c = 1.0, \text{CHCl}_3)\).

(S)-1-(3-Bromophenyl)-2-nitroethanol (Table 8, entry 3)

Prepared according to GP6 using 122 mg (0.50 mmol) ketone and 0.5 mol % catalyst. Yield: 66 mg (0.27 mmol, 54 %); ee = 91% (HPLC: OD-H, 215 nm, hexane:2-propanol = 90:10, flow rate 1 ml/min, \(t_{(\text{major})} = 21.4 \text{ min}, t_{(\text{minor})} = 15.9 \text{ min}\)).

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$^1$H-NMR: (300 MHz, CDCl$_3$) $\delta$ 7.59-7.60 (m, 1H), 7.48-7.52 (m, 1H), 7.25-7.35 (m, 2H), 5.43-5.48 (m, 1H), 4.59 (dd, $J$ = 9.0, 13.5 Hz, 1H), 4.51 (dd, $J$ = 3.3, 13.5 Hz, 1H), 2.90 (d, $J$ = 3.9 Hz, 1H, OH); $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 140.1, 132.0, 130.5, 129.0, 124.5, 123.1, 80.9, 70.3; Optical rotation: $[\alpha]_D^{26}$ +25.76° ($c$ = 1.0, CHCl$_3$). All other spectroscopic data were in agreement with the literature.$^{99}$

(S)-1-(3-Chlorophenyl)-2-nitroethanol (Table 8, entry 4)

![Structure of (S)-1-(3-Chlorophenyl)-2-nitroethanol]

Prepared according to GP6 using 100 mg (0.50 mmol) ketone and 0.5 mol % catalyst. Yield: 96 mg (0.48 mmol, 95 %); ee = 95% (HPLC: OD-H, 215 nm, hexane:2-propanol = 90:10, flow rate 1 ml/min, $t_{(major)}$ = 17.8 min, $t_{(minor)}$ = 14.1 min).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.43-7.45 (m, 1H), 7.26-7.36 (m, 3H), 5.43-5.49 (m, 1H), 4.59 (dd, $J$ = 9.0, 13.5 Hz, 1H), 4.51 (dd, $J$ = 3.6, 13.5 Hz, 1H), 2.91 (d, $J$ = 3.9, 1H); $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 139.9, 135.0, 130.2, 129.1, 126.1, 124.0, 109.9, 80.9, 70.3; Optical rotation: $[\alpha]_D^{27}$ +31.17° ($c$ = 1.0, CHCl$_3$). All other spectroscopic data were in agreement with the literature.$^{100}$


(S)-1-(2-Methoxyphenyl)-2-nitroethanol (Table 8, entry 5)

\[
\begin{align*}
\text{OMeOH} & \quad \text{NO}_2 \\
\end{align*}
\]

Prepared according to GP6 using 90 mg (0.50 mmol) ketone and 0.5 mol % catalyst. Yield: 85 mg (0.47 mmol, 93 %); ee = 83% (HPLC: OD-H, 215 nm, hexane:2-propanol = 90:10, flow rate 1 ml/min, \( t_{\text{major}} = 12.4 \text{ min}, t_{\text{minor}} = 10.6 \text{ min} \)).

\[ ^1H\text{-NMR (300 MHz, CDCl}_3 \delta 7.45 \text{ (dd, } J = 1.8, 7.5 \text{ Hz, 1H}), 7.34 \text{ (dt, } J = 1.2, 7.8 \text{ Hz, 1H}), 7.02 \text{ (dt, } J = 0.9, 7.5 \text{ Hz, 1H}), 6.92 \text{ (dd, } J = 0.9, 8.4 \text{ Hz, 1H}), 4.66 \text{ (dd, } J = 3.6, 13.2 \text{ Hz, 1H}), 4.58 \text{ (dd, } J = 9.0, 13.2 \text{ Hz, 1H}), 3.89 \text{ (s, 3H), 2.80 \text{ (d, } J = 6.3 \text{ Hz, 1H, OH)}; ^{13}\text{C-NMR (75 MHz, CDCl}_3 \delta 136.1, 134.3, 130.7, 128.6, 126.7, 125.5, 80.2, 67.9, 19.0; \text{ Optical rotation: } [\alpha]_D^{28} +40.62^\circ \text{ (c = 1.0, CHCl}_3), \text{ Lit.}^{12} [\alpha]_D^{21} -50.1^\circ \text{ (c = 1.01, CH}_2\text{Cl}_2) \text{ for } (R) \text{ enantiomer (93% ee). All other spectroscopic data were in agreement with the literature.}^{98}
\]

(S)-1-(Naphthalen-2-yl)-2-nitroethanol (Table 8, entry 6)

\[
\begin{align*}
\text{OH} & \quad \text{NO}_2 \\
\end{align*}
\]

Prepared according to GP6 using 113 mg (0.53 mmol) ketone and 0.5 mol % catalyst. Yield: 66 mg (0.31 mmol, 58 %); ee = 93% (HPLC: OD-H, 215 nm, hexane:2-propanol = 90:10, flow rate 1 ml/min, \( t_{\text{major}} = 59.2 \text{ min}, t_{\text{minor}} = 43.0 \text{ min} \)).

\[ ^1H\text{-NMR (300 MHz, CDCl}_3 \delta 7.85\text{-}7.91 \text{ (m, 4H), 7.47\text{-}7.56 \text{ (m, 3H), 5.65 \text{ (td, } J = 3.6, 9.0 \text{ Hz, 1H), 4.71 \text{ (dd, } J = 9.3, 13.5 \text{ Hz, 1H}), 4.61 \text{ (dd, } J = 3.3, 13.5 \text{ Hz, 1H}), 2.91 \text{ (d, } J = 3.6 \text{ Hz, 1H, OH)}; ^{13}\text{C-NMR (75 MHz, CDCl}_3 \delta 135.3, 133.3, 133.1, 128.9, 128.0,}
\]
127.7, 126.7, 126.3, 125.3, 123.1, 81.2, 71.2; **Optical rotation:** $[\alpha]_D^{28} +37.52^\circ$ (c = 1.0, CHCl$_3$). All other spectroscopic data were in agreement with the literature.$^{101}$

(S)-2-Chloro-1-phenylethanol (Scheme 26)

![Schematic](image)

Prepared according to GP6 using 84 mg (0.54 mmol) ketone and 0.5 mol % catalyst. Yield: 79 mg (0.51 mmol, 93 %); ee = 91% (HPLC: OD-H, 215 nm, hexane:2-propanol = 95:5, flow rate 1 ml/min, $t_{R(major)} = 10.3$ min, $t_{R(minor)} = 12.2$ min).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.30-7.40 (m, 3H), 4.91 (dd, $J = 3.6$, 8.7 Hz, 1H), 3.76 (dd, $J = 3.3$, 11.1 Hz, 1H), 3.65 (dd, $J = 8.7$, 11.1 Hz, 1H), 2.62 (br s, 1H, OH); **Optical rotation:** $[\alpha]_D^{28} +37.52^\circ$ (c = 1.0, CHCl$_3$) Lit.$^{16}$ $[\alpha]_D^{25} -48.10^\circ$ (c = 1.73, C$_6$H$_{12}$) for (R) enantiomer (>99% ee). All other spectroscopic data were in agreement with the literature.$^{102}$

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4.3.2 Asymmetric Transfer Hydrogenation of $\beta,\beta$-disubstituted nitroalkenes

Synthesis of the Ligands:

Synthesis of ligands required for the catalysts described below were prepared as outlined in the literature, otherwise commercially available ligands were utilized.

$(S,S)$-C$_6$F$_5$SO$_2$-3,5-F-DPEN (Ligand Table 9, Entries 6,7)

To a stirred solution of diamine105 (121 mg, 0.43 mmol) and DIPEA (0.18 ml, 1.03 mmol) in anhydrous CH$_2$Cl$_2$ (4 ml) at -50 °C was added a solution of pentafluorophenylsulfonyl chloride (136 mg, 0.51 mmol, in 0.5 ml CH$_2$Cl$_2$). The reaction was allowed to warm to room temperature and stirred overnight (18 h) at room temperature. The reaction was then quenched by addition of saturated NH$_4$Cl (5 ml). After extraction with CH$_2$Cl$_2$ from H$_2$O, and drying with Na$_2$SO$_4$, the crude was purified by FC (MeOH/CH$_2$Cl$_2$ = 5/95) to afford pure product 42.8 mg (19%) as a white powder.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 6.87-6.93 (m, 2H), 6.73-6.81 (m, 4H), 4.61 (d, $J$ = 7.4 Hz), 4.20 (d, $J$ = 7.4 Hz, 1H); $^{13}$C-NMR (150 MHz, CDCl$_3$) $\delta$ 164.3 (dd, $J$ = 70.4, 246.0 Hz), 145.4 (dt, $J$ = 8.6, 251.6 Hz), 144.5 (d, $J$ = 256.7 Hz), 138.9 (dm, $J$ = 252.5 Hz),

131.6 (J = 378 Hz), 125.6 (d, J = 101.9, 2H), 118.7 (t, J = 14.1 Hz), 111.5 (ddd, J = 5.1, 20.8, 26.3 Hz, 2C), 103.8 (t, J = 25.6 Hz, 2C), 65.5, 60.7; IR (thin film, cm⁻¹) 3435, 2540, 1624, 1599, 1495, 1172, 1100, 989, 856. HR-MALDI calcd for C₂₄H₁₀F₃N₂O₂S [M-H]⁺ 513.0325, found 513.0317. Optical rotation: [α]D²⁶ -29.1 (c = 2.0, CH₃OH).

\[N-(15,2S)-2-Amino-1,2-bis(3,5-difluorophenyl)ethyl)-1,1,1-trifluoromethanesulfonamide\] (Ligand Table 9, Entries 8,9)

![Chemical structure]

To a stirred solution of the free diamine105 (185 mg, 0.65 mmol) in anhydrous THF (6 ml) at -78 °C was added n-BuLi (0.81ml, 1.3 mmol, 1.6 M in hexane) dropwise. Upon addition of the base the reaction turned pale brown and was aged for 20 min. At this stage a solution of PhN(Tf)₂ (255 mg, 0.72 mmol) in THF (1 ml) was added dropwise and allowed to stir at -78 °C for 1 h. The reaction was then quenched by addition of saturated NH₄Cl (5 ml). After extraction with CH₂Cl₂ from H₂O, and drying with Na₂SO₄, the crude was purified by FC (MeOH/CH₂Cl₂ = 5/95) to afford pure product 137 mg (51%) as a white powder.

\(^1\)H-NMR (300 MHz, CDCl₃) δ 6.89-6.99 (m, 4H), 6.79-6.86 (m, 2H), 4.63 (d, J = 2.7 Hz, 1H), 4.38 (d, J = 2.7 Hz, 1H); \(^1^3\)C-NMR (75 MHz, CDCl₃) δ 161.5 (d, J = 12.7 Hz), 164.8 (d, J = 12.7 Hz), 142.3, 109.6 (dd, J = 17.6, 25.5 Hz, 4C), 104.0 (dd, J = 24.9, 49.8 Hz, 2C), 64.0, 59.8; IR (thin film, cm⁻¹) 3098, 2927, 1626, 1603, 1466, 1326, 1278, 1198, 1124, 993, 925, 856, 694, 604; HR-MALDI calcd for C₁₅H₁₁F₇N₂O₂S [M-CF₃]⁺ 347.0472, found 347.0470; Optical rotation: [α]D²⁶ +3.3° (c = 0.35, CHCl₃).
**Experimental Section**

*Synthesis of the Catalysts:*

\[ \text{Cp}^*\text{Ir}[(R,R)-\text{Ts-DPEN}](\text{H}_2\text{O})\text{(SO}_4\text{)} \text{(Catalyst Table 9, Entry 1)} \]

Prepared according to GP4.

\(^1\text{H-NMR (300 MHz, CD}_3\text{OD}) \delta 7.10-7.38 \text{ (m, 12H), 6.92-6.95 (m, 2H), 4.65 (s, 1H), 4.26 (s, 1H), 2.30 (s, 3H), 1.95 (s, 15H); } ^{13}\text{C-NMR (75 MHz, CD}_3\text{OD}) \delta 10.3, 21.2, 68.5, 78.5, 92.2, 127.0, 127.6, 127.8, 128.5, 128.6, 129.0, 129.1, 135.8, 137.9, 141.5, 143.8; \text{HR-MALDI calc for C}_{31}\text{H}_{36}\text{IrN}_2\text{O}_2\text{S [M-SO}_4\text{-H}_2\text{O}]^{+} 693.2121, found 693.2109. \]

**Optical rotation:** \([\alpha]_D^{25} -273.92^\circ (c = 1.0, \text{CHCl}_3).\)

\[ \text{Cp}^*\text{Ir}[(R,R)-\text{Tf-DPEN}](\text{H}_2\text{O})\text{(SO}_4\text{)} \text{(Catalyst Table 9, Entries 2,3)} \]

Prepared according to GP4.

\(^1\text{H-NMR (300 MHz, CD}_3\text{OD}) \delta 7.06-7.27 \text{ (m, 10H), 4.74 (d, J = 7.2 Hz, 1H), 4.15 (d, J = 6.9 Hz, 1H), 1.80 (s, 15H); } ^{13}\text{C-NMR (75 MHz, CD}_3\text{OD}) \delta 129.8, 129.2, 129.4, 129.0, 128.5, 89.6, 73.2, 72.6, 9.9; \text{HR-MALDI calc for C}_{25}\text{H}_{29}\text{IrN}_2\text{O}_2\text{S [M-SO}_4\text{-H}_2\text{O}]^{+} 671.1525, found 671.1514; \text{Optical rotation: } [\alpha]_D^{28} -293.16^\circ (c = 0.25, \text{CH}_3\text{OH}).\)
{Cp*Ir[(R,R)-C₆F₅SO₂-DPEN](H₂O)}(SO₄) (Catalyst Table 9, Entries 4,5)

Prepared according to GP4.

¹H-NMR (300 MHz, CD₃OD) δ 7.18-7.36 (m, 10H), 4.67 (d, J = 3.1 Hz, 1H), 4.30 (d, J = 3.1 Hz, 1H), 1.91 (s, 15H); ¹³C-NMR (75 MHz, CD₃OD) δ 145.0, 144.0, 142.9, 142.0, 138.9, 138.1, 136.8, 136.0, 127.9, 127.8, 127.7, 126.8, 126.0, 103.4, 91.2, 75.3, 67.2, 8.8; HR-MALDI calcd for C₃₀H₂₉IrN₂O₂S [M-SO₄-H₂O]⁺ 769.1494, found 769.1479. Optical rotation: [α]D²⁶ -242.22° (c = 1.0, CHCl₃).

{Cp*Ir[(S,S)-C₆F₅SO₂-3,5-F-DPEN](H₂O)}(SO₄) (Catalyst Table 9, Entries 6,7)

Prepared according to GP4.

¹H-NMR (300 MHz, CD₃OD) δ 6.87-6.98 (m, 6H), 4.64-4.66 (m, 1H), 4.27-4.31 (m, 1H), 1.87 (s, 15H); ¹³C-NMR (75 MHz, CD₃OD) δ 165.4, 162.0, 147.1, 144.6, 141.6, 111.3, 110.7, 104.2, 93.0, 89.1, 75.4, 66.9, 10.2; HR-MALDI calcd for C₃₀H₂₅IrN₂O₂S [M-SO₄-H₂O]⁺ 841.1117, found 841.1102; Optical rotation: [α]D²⁶ -206.25° (c = 0.50, CHCl₃).
\{ \text{Cp}^* \text{Ir}[(S,S)-\text{Tf}-3,5-\text{F-DPEN}](\text{H}_2\text{O})]\text{(SO}_4\text{)} \} \text{(Catalyst Table 9, Entries 8,9)}

Prepared according to GP4.

\textbf{1H-NMR (300 MHz, CD}_2\text{OD) } \delta 6.99-7.03 \text{ (m, 2H), 6.89-6.98 \text{ (m, 5H), 4.86 \text{ (d, J = 4.8 Hz), 4.38 \text{ (d, J = 4.8 Hz), 1.82 \text{ (s, 15H); 13C-NMR (150 MHz, CD}_2\text{OD) } \delta 167.8, J = 13.3, 282.8 \text{ Hz), 164.9 \text{ (dd, J = 15.2, 295.4 Hz), 164.6 \text{ (dd, J = 15.5, 269.6 Hz), 120.8 \text{ (q, J = 387.1 Hz, CF}_3\text{), 110.6 \text{ (d, J = 31.5 Hz), 101.9 \text{ (d, J = 28.4 Hz), 101.7 \text{ (d, J = 28.5 Hz), 89.1, 72.5, 64.2, 10.3; HR-MALDI calcd for C}_25\text{H}_25\text{IrN}_2\text{O}_2\text{S [M-SO}_4\text{-H}_2\text{O]}^+ 743.1148, found 743.1147; Optical rotation: } [\alpha]_D^{26} +18.8^\circ \text{ (c = 0.25, CH}_3\text{OH).}}}

\textit{Synthesis of Substrates:}

The substrates were synthesized according to a known procedure.\textsuperscript{106}

\textit{(E)-1-tert-Butyl-4-(1-nitroprop-1-en-2-yl)benzene}

\textbf{1H-NMR: (300 MHz, CDCl}_3\text{) } \delta 7.39 - 7.47 \text{ (m, 4H), 7.34 \text{ (q, J = 1.5 Hz, 1H), 2.65 \text{ (d, J = 1.5 Hz, 3H), 1.34 \text{ (s, 9H); 13C-NMR (75 MHz, CDCl}_3\text{) } \delta 154.1, 149.9, 135.9, 135.3, 126.7, 126.0, 34.8, 31.1, 18.4; IR (thin film, cm}^{-1}\text{) 2964, 2869, 1619, 1513, 1402, 1339,}

GP7: Transfer Hydrogenation of β,β-Nitroalkenes

The β,β-nitroalkene (0.50 mmol, 1.0 eq) and \{Cp*Ir[(S,S)-Tf-3,5-F-DPEN](H_2O)}(SO_4) (0.005 mmol, 1.0 mol%) were combined in a glass vial, followed by addition of an aqueous formic acid solution (1.0 M formate soln., pH = 2.0, 0.2 M overall concentration). The reaction mixture was stirred at ambient temperature for 24 h. The reaction mixture was then extracted with CH_2Cl_2 (3 x) from H_2O and dried over Na_2SO_4. The organic phase was then filtered, concentrated and purified by FC (EtOAc/Hex). The nitroalkane products were analyzed by standard spectroscopic methods and found to be in agreement with the previously reported values for all known compounds. Enantiomeric excess was determined by chiral HPLC.

\textbf{(R)-(1-Nitropropan-2-yl)benzene (Table 9, Entry 1)}

\begin{center}
\includegraphics[width=0.2\textwidth]{image}
\end{center}

Prepared according to GP7.

90% Yield, ee = 90% (HPLC: OD-H, 215 nm, hexane:2-propanol = 99:1, flow rate 0.5 ml/min, t_{(major)} = 28.4 min, t_{(minor)} = 36.9 min).

\textbf{^1H-NMR: (300 MHz, CDCl_3)} δ 7.22-7.38 (m, 5H), 4.45-4.59 (m, 2H), 3.60-3.68 (m, 1H), 1.39 (d, J = 6.9 Hz, 3H); \textbf{Optical rotation}: [\alpha]_D^{22} +44.2° (c = 1.0, CHCl_3) Lit.\textsuperscript{107} [\alpha]_D^{25} = +44.3° (c = 3.4, CHCl_3) 98% ee. All other spectroscopic data were in agreement with the literature.\textsuperscript{107}

(R)-1-Fluoro-4-(1-nitropropan-2-yl)benzene (Table 9, Entry 2)

\[
\begin{align*}
\text{Prepared according to GP7.} \\
82\% \text{ Yield, } ee = 94\% \ (\text{HPLC: OD-H, 215 nm, hexane, flow rate 0.2 ml/min, } t_{(major)} = 89.0 \text{ min, } t_{(minor)} = 108.2 \text{ min}). \\
^{1}\text{H-NMR: } (300 \text{ MHz, CDCl}_3) \delta 7.17-7.23 \ (m, 2H), 6.99-7.07 \ (m, 2H), 4.44-4.55 \ (m, 2H), 3.57-3.70 \ (m, 1H), 1.37 \ (d, J = 6.9 \text{ Hz, 3H};) \text{ Optical rotation: } [\alpha]_D^{22} +44.0^\circ \ (c = 1.0, \text{CHCl}_3) \text{ Lit.106 } [\alpha]_D^{30} +48.4^\circ \ (c = 0.52, \text{CHCl}_3) 99\% \text{ ee. All other spectroscopic data were in agreement with the literature.106}
\end{align*}
\]

(R)-1-Chloro-4-(1-nitropropan-2-yl)benzene (Table 9, Entry3)

\[
\begin{align*}
\text{Prepared according to GP7.} \\
92\% \text{ Yield, } ee = 90\% \ (\text{HPLC: OD-H, 215 nm, hexane:2-propanol = 99:1, flow rate 0.5 ml/min, } t_{(major)} = 30.2 \text{ min, } t_{(minor)} = 43.0 \text{ min}). \\
^{1}\text{H-NMR: } (300 \text{ MHz, CDCl}_3) \delta 7.29-7.34 \ (m, 2H), 7.14-7.19 \ (m, 2H), 4.44-4.56 \ (m, 2H), 3.56-3.69 \ (m, 1H), 1.37 \ (d, J = 6.6 \text{ Hz, 3H};) \text{ Optical rotation: } [\alpha]_D^{25} +42.0^\circ \ (c = 1.0, \text{CHCl}_3) \text{ Lit.106 } [\alpha]_D^{30} +51.3 \ (c = 0.60, \text{CHCl}_3) 99\% \text{ ee. All other spectroscopic data were in agreement with the literature.106}
\end{align*}
\]
(R)-1-Bromo-4-(1-nitropropan-2-yl)benzene (Table 9, Entry 4)

Prepared according to GP7.

92% Yield, ee = 92% (HPLC: OD-H, 215 nm, hexane:2-propanol = 99:1, flow rate 0.5 ml/min, $t_{\text{r(major)}}$ = 35.7 min, $t_{\text{r(minor)}}$ = 59.1 min).

$^{1}$H-NMR: (300 MHz, CDCl$_3$) $\delta$ 7.45-7.49 (m, 2H), 7.09-7.13 (m, 2H), 4.43-4.55 (m, 2H), 3.55-3.67 (m, 1H), 1.45 (d, $J$ = 7.2 Hz, 3H); Optical rotation: $\left[\alpha\right]_{D}^{24}$ +39.4° ($c$ = 1.0, CHCl$_3$) Lit.$^{106}$ $\left[\alpha\right]_{D}^{30}$ +43.2° ($c$ = 0.58, CHCl$_3$) 99% ee. All other spectroscopic data were in agreement with the literature.$^{106}$

(R)-1-Chloro-3-(1-nitropropan-2-yl)benzene (Table 9, Entry 5)

Prepared according to GP7.

94% Yield, ee = 91% (HPLC: OD-H, 215 nm, hexane:2-propanol = 99:1, flow rate 0.5 ml/min, $t_{\text{r(major)}}$ = 30.5 min, $t_{\text{r(minor)}}$ = 45.6 min).

$^{1}$H-NMR: (300 MHz, CDCl$_3$) $\delta$ 7.22-7.28 (m, 3H), 7.10-7.13 (m, 1H), 4.45-4.58 (m, 2H), 3.56-3.68 (m, 1H), 1.38 (d, $J$ = 7.2 Hz, 3H); Optical rotation: $\left[\alpha\right]_{D}^{26}$ +37.3° ($c$ = 1.0, CHCl$_3$). All other spectroscopic data were in agreement with the literature.$^{108}$

(R)-1-Methyl-4-(1-nitropropan-2-yl)benzene (Table 9, Entry 6)

Prepared according to GP7.

78% Yield, ee = 90% (HPLC: OD-H, 215 nm, hexane:2-propanol = 99:1, flow rate 0.5 ml/min, t_{major} = 23.7 min, t_{minor} = 38.0 min).

^1H-NMR: (300 MHz, CDCl₃) δ 7.10-7.17 (m, 4H), 4.43-4.57 (m, 2H), 3.54-3.66 (m, 1H), 2.33 (s, 3H), 1.37 (d, J = 6.6 Hz, 3H); Optical rotation: [α]_D^{25} +34.5° (c = 0.5, CHCl₃). All other spectroscopic data were in agreement with the literature.108

(R)-1-Methoxy-4-(1-nitropropan-2-yl)benzene (Table 9, Entry 7)

Prepared according to GP7.

Reaction with 1.5 mol% catalyst gives 94% Yield, ee = 92% (HPLC: OD-H, 215 nm, hexane:2-propanol = 99:1, flow rate 0.5 ml/min, t_{major} = 33.7 min, t_{minor} = 58.3 min).

^1H-NMR: (300 MHz, CDCl₃) δ 7.12-7.17 (m, 4H), 6.85-6.90 (m, 2H), 4.41-4.54 (m, 2H), 3.80 (s, 3H), 3.53-3.65 (m, 1H), 1.36 (d, J = 7.2 Hz, 3H); Optical rotation: [α]_D^{27} +50.2° (c = 0.5, CHCl₃) Lit.106 [α]_D^{30} +66.2° (c = 0.99, CHCl₃) 97% ee. All other spectroscopic data were in agreement with the literature.106

(R)-1-Cyano-4-(1-nitropropan-2-yl)benzene (Table 9, Entry 8)
Iridium-Catalyzed Reactions

Prepared according to GP7.

87% Yield, ee = 92% (HPLC: IC, 215 nm, hexane:2-propanol = 9:1, flow rate 1.0 ml/min, t\text{r(major)} = 36.1 min, t\text{r(minor)} = 44.0 min).

\textbf{\textsuperscript{1}H-NMR: (300 MHz, CDCl\textsubscript{3})} \(\delta 7.63-7.66 \text{ (m, 2H)}, 7.34-7.37 \text{ (m, 2H)}, 4.49-4.60 \text{ (m, 2H)}, 3.65-3.77 \text{ (m, 1H)}, 1.40 \text{ (d, } J = 6.9 \text{ Hz, 3H)}. \textbf{Optical rotation:} [\alpha]\textsubscript{D}\textsuperscript{30} +53.8° (c = 0.5, CHCl\textsubscript{3}). All other spectroscopic data were in agreement with the literature.

(R)-1-tert-Butyl-4-(1-nitropropan-2-yl)benzene (Table 9, Entry 9)

Prepared according to GP7.

77% Yield, ee = 89% (HPLC: OD-H, 215 nm, hexane:2-propanol = 99:1, flow rate 0.5 ml/min, t\text{r(major)} = 14.9 min, t\text{r(minor)} = 29.4 min).

\textbf{\textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3})} \(\delta 7.36 \text{ (d, } J = 8.4 \text{ Hz, 2H}), 7.16 \text{ (d, } J = 8.5 \text{ Hz, 2H}), 4.43-4.58 \text{ (m, 2H)}, 3.55-3.68 \text{ (m, 1H)}, 1.37 \text{ (d, } J = 7.2 \text{ Hz, 3H)}, 1.31 \text{ (s, 9H);} \textbf{\textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{3})} \delta 137.7, 126.5, 125.8, 150.4, 81.9, 38.0, 34.4, 31.2, 18.6; \textbf{IR (thin film, cm}\textsuperscript{-1}) \text{ 2965, 1553, 1382, 1270, 1130, 1016, 833, 653, 575; HR-EI} \text{ calcd for C}_{13}\text{H}_{19}\text{NO}_2 [M]^+ 221.1416, \text{ found 221.1412.} \textbf{Optical rotation:} [\alpha]\textsubscript{D}\textsuperscript{24} +40.5° (c = 0.5, CHCl\textsubscript{3}).
(R)-2-(1-Nitropropan-2-yl)naphthalene (Table 9, Entry 10)

Prepared according to GP7.

Reaction with 1.5 mol% catalyst at 40 °C gives 56% Yield, ee = 92% (HPLC: OD-H, 215 nm, hexane:2-propanol = 99:1, flow rate 1.0 ml/min, \( t_{r(major)} = 53.9 \) min, \( t_{r(minor)} = 79.2 \) min).

\( ^1\text{H-NMR (300 MHz, CDCl}_3 \) \( \delta \) 1.48 (d, \( J = 7.2 \) Hz, 3H), 3.78-3.85 (m, 1H), 4.54-7.70 (m, 2H), 7.36 (dd, \( J = 1.8, 8.4 \) Hz, 1H), 7.45-7.52 (m, 2H), 7.68 (m, 1H) 7.79-7.85 (m, 2H). Optical rotation: \( [\alpha]_{D}^{28} \) +46.4 (\( c = 0.5, \) CHCl\(_3\)). All other spectroscopic data were in agreement with the literature.108
4.3.3  Asymmetric Transfer Hydrogenation of β-Nitro Acrylates

GP8: Synthesis of α-Ketoesters\textsuperscript{109}

To a suspension of dibenzyl oxalate\textsuperscript{110} (1 eq) in Et\textsubscript{2}O/THF (10:1, 0.25 M) at -78 °C was added the appropriate Grignard reagent (1 eq) in Et\textsubscript{2}O (0.4 M) dropwise and the resulting suspension was stirred overnight to reach room temperature. After quenching with saturated ammonium chloride solution, the mixture was extracted with ethyl acetate. The organic phases were combined, dried over MgSO\textsubscript{4}, filtered and concentrated \textit{in vacuo} to give crude products, which were purified by FC (Hex:EtOAc).

Benzyl 2-(4-fluorophenyl)-2-oxoacetate (Precursor Table 12, Entry 2)

![chemical structure]

Synthesized according to GP8.

\textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 8.09 – 7.98 (m, 2H), 7.51 – 7.32 (m, 5H), 7.23 – 7.10 (m, 2H), 5.41 (s, 2H); \textsuperscript{13}C-NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) 184.2, 168.1, 165.5, 134.5, 133.0, 132.9, 128.9, 128.8, 128.6, 116.4, 116.2, 67.9; IR (thin film, cm\textsuperscript{-1}) 3440, 2084, 1731, 1644, 1600, 1506, 1456, 1414, 1300, 1190, 154, 995, 913, 800; HR-ESI calcd for C\textsubscript{15}H\textsubscript{11}FNaO\textsubscript{3} [M + Na]\textsuperscript{+} 281.0584, found 281.0591.


Benzyl 2-(4-chlorophenyl)-2-oxoacetate (Precursor Table 12, Entry 3)

\[
\begin{align*}
\text{Synthesized according to GP8.} \\
^{1}H-\text{NMR (400 MHz, CDCl}_3\text{)} & \delta 7.96 - 7.89 (m, 2H), 7.53 - 7.34 (m, 7H), 5.41 (s, 2H); \\
^{13}C-\text{NMR (101 MHz, CDCl}_3\text{)} & \delta 184.5, 163.1, 141.7, 134.4, 131.4, 130.9, 129.3, 128.9, 128.8, 128.6, 68.0; \text{IR (thin film, cm}^{-1}\text{)} 3452, 1733, 1688, 1587, 1489, 1456, 1403, 1283, 1194, 1170, 1086, 995, 913, 847; \text{HR-ESI calcd for C}_{15}\text{H}_{11}\text{ClNaO}_3 [M + Na]^+ 297.0289, found 297.0300.
\end{align*}
\]

Benzyl 2-(4-bromophenyl)-2-oxoacetate (Precursor Table 12, Entry 4)

\[
\begin{align*}
\text{Synthesized according to GP8.} \\
^{1}H-\text{NMR (400 MHz, CDCl}_3\text{)} & \delta 7.88 - 7.82 (m, 2H), 7.67 - 7.61 (m, 2H), 7.47 - 7.35 (m, 5H), 5.41 (s, 2H); \\
^{13}C-\text{NMR (101 MHz, CDCl}_3\text{)} & \delta 184.7, 163.0, 134.4, 132.3, 131.4, 131.3, 130.6, 128.9, 128.8, 128.6, 68.0; \text{IR (thin film, cm}^{-1}\text{)} 3435, 1732, 1648, 1587, 1484, 1455, 1400, 1312, 1194, 1170, 1070, 994, 913, 799, 743; \text{HR-ESI calcd for C}_{15}\text{H}_{11}\text{BrNaO}_3 [M + Na]^+ 340.9784, found 340.9790.
\end{align*}
\]
Benzyl 2-(3-chlorophenyl)-2-oxoacetate (Precursor Table 12, Entry 5)

\[
\begin{array}{c}
\text{C} \\
\text{O} \\
\text{O} \\
\text{C} \\
\text{H} \\
\end{array}
\]

Synthesized according to GP8.

\[^{1}H\text{-NMR (400 MHz, CDCl}_3\text{)}\ \delta\ 7.97\ (t, J = 2.0\ Hz, 1H),\ 7.91 - 7.82\ (m, 1H),\ 7.61\ (ddd, J \ =\ 8.0, 2.0, 1.0\ Hz, 1H),\ 7.49 - 7.34\ (m, 6H),\ 5.42\ (s, 2H);\ \[^{13}C\text{-NMR (101 MHz, CDCl}_3\text{)}\ \delta\ 184.5,\ 162.8,\ 135.3,\ 134.8,\ 134.4,\ 134.1,\ 130.2,\ 129.9,\ 128.9,\ 128.8,\ 128.7,\ 128.2,\ 68.0;\ \text{IR (thin film, cm}^{-1}\text{)}\ 3068,\ 3035,\ 2962,\ 2957,\ 1958,\ 1738,\ 1694,\ 1591,\ 1573,\ 1498,\ 1471,\ 1420,\ 1378,\ 1276,\ 1187,\ 1110,\ 1077,\ 1003,\ 941,\ 903,\ 810;\ \text{HR-ESI calcd for C}_{15}\text{H}_{11}\text{ClNaO}_3 [M + Na]^+ 297.0289, found 297.0295.\]

Benzyl 2-(2-chlorophenyl)-2-oxoacetate (Precursor Table 12, Entry 6)

\[
\begin{array}{c}
\text{Cl} \\
\text{O} \\
\text{O} \\
\text{C} \\
\text{H} \\
\end{array}
\]

Synthesized according to GP8.

\[^{1}H\text{-NMR (400 MHz, CDCl}_3\text{)}\ \delta\ 7.76\ (dd, J = 7.7, 1.7\ Hz, 1H),\ 7.55 - 7.48\ (m, 1H),\ 7.45 - 7.33\ (m, 7H),\ 5.38\ (s, 2H);\ \[^{13}C\text{-NMR (101 MHz, CDCl}_3\text{)}\ \delta\ 186.2,\ 162.9,\ 134.4,\ 134.2,\ 134.0,\ 133.2,\ 131.7,\ 130.6,\ 128.8,\ 128.7,\ 127.2,\ 68.3;\ \text{IR (thin film, cm}^{-1}\text{)}\ 3431,\ 3035,\ 1736,\ 1698,\ 1589,\ 1568,\ 1499,\ 1378,\ 1294,\ 1255,\ 1192,\ 1136,\ 1064,\ 1038,\ 995;\ \text{HR-ESI calcd for C}_{15}\text{H}_{11}\text{ClNaO}_3 [M + Na]^+ 297.0289, found 297.0286.\]
Experimental Section

Benzyl 2-(4-methoxyphenyl)-2-oxoacetate (Precursor Table 12, Entry 7)

\[
\text{MeO} \quad \text{O} \quad \text{O}
\]

Synthesized according to GP8.

\(^1\text{H-NMR (400 MHz, CDCl}_3\) \(\delta 8.00 - 7.91 \text{ (m, 2H)}, 7.51 - 7.30 \text{ (m, 5H)}, 6.99 - 6.90 \text{ (m, 2H)}, 5.40 \text{ (s, 2H)}, 3.88 \text{ (s, 3H)}; \)^\(^{13}\text{C-NMR (101 MHz, CDCl}_3\) \(\delta 184.5, 165.1, 164.0, 134.7, 132.6, 128.7 (2C), 128.5, 125.6, 114.2, 67.6, 55.6; \)^\(\text{IR (thin film, cm}^{-1}\) 3436, 2842, 2063, 1733, 1599, 1573, 1512, 1456, 1426, 1378, 1310, 1268, 1203, 1162, 1118, 1026, 1011, 991, 905, 847; \)^\(\text{HR-ESI calcd for C}_{16}\text{H}_{14}\text{NaO}_4 [M + Na]^+ 293.0784, found 293.0787.}\)

Benzyl 2-oxo-2-(4-(trifluoromethyl)phenyl)acetate (Precursor Table 12, Entry 8)

\[
\text{F}_3\text{C} \quad \text{O} \quad \text{O}
\]

Synthesized according to GP8.

\(^1\text{H-NMR (400 MHz, CDCl}_3\) \(\delta 8.03 \text{ (d, } J = 8.4 \text{ Hz, 2H}), 7.68 \text{ (d, } J = 8.4 \text{ Hz, 2H}), 7.39 - 7.30 \text{ (m, 5H)}, 5.36 \text{ (s, 2H)}; \)^\(^{13}\text{C-NMR (101 MHz, CDCl}_3\) \(\delta 184.6, 162.6, 136.1, 135.3, 134.3, 130.4, 129.0, 128.8, 128.7, 125.9 (q, } J = 3.7 \text{ Hz, CF}_3\), 68.1; \)^\(^{19}\text{F-NMR (376 MHz, CDCl}_3\) \(\delta -63.44 \text{ (s, 3F)}; \)^\(\text{IR (thin film, cm}^{-1}\) 3037, 1736, 1698, 1511, 1456, 1412, 1326, 1176, 1130, 1066, 996, 906, 857; \)^\(\text{HR-ESI calcd for C}_{16}\text{H}_{14}\text{F}_3\text{NaO}_3 [M + Na]^+ 331.0552, found 331.0559.\)
Benzyl 2-oxo-2-p-tolylacetate (Precursor Table 12, Entry 9)

\[
\begin{array}{c}
\text{Synthesized according to GP8.} \\
\text{H-NMR (400 MHz, CDCl}_3\text{)} \delta 7.89 – 7.83 (m, 2H), 7.47 – 7.34 (m, 5H), 7.29 – 7.27 (m, 2H), 5.41 (s, 1H), 2.43 (s, 2H); \text{C-NMR (101 MHz, CDCl}_3\text{)} \delta 185.7, 163.84, 146.3, 134.7, 130.2, 130.0, 129.7, 129.6, 128.7, 128.6, 67.6, 21.9; \text{IR (thin film, cm}^{-1}\text{)} 3066, 3035, 2959, 2923, 1738, 1682, 1605, 1573, 1499, 1456, 1412, 1378, 1304, 1256, 1199, 1171, 1121, 1082, 1000, 905, 841; \text{HR-ESI calcd for C}_{16}\text{H}_{14}\text{NaO}_3 [M + Na]^+ 277.0835, found 277.0827. \\
\end{array}
\]

Benzyl 2-(4-tert-butylphenyl)-2-oxoacetate (Precursor Table 12, Entry 10)

\[
\begin{array}{c}
\text{Synthesized according to GP8.} \\
\text{H-NMR (400 MHz, CDCl}_3\text{)} \delta 7.93 – 7.88 (m, 2H), 7.54 – 7.48 (m, 2H), 7.47 – 7.33 (m, 5H), 5.41 (s, 2H), 1.34 (s, 9H); \text{C-NMR (101 MHz, CDCl}_3\text{)} \delta 185.7, 163.9, 159.1, 134.7, 130.0, 129.9, 128.8, 128.7, 128.6, 67.6, 35.4, 31.0; \text{IR (thin film, cm}^{-1}\text{)} 3067, 3036, 2964, 2906, 2871, 1952, 1732, 1682, 1603, 1567, 1499, 1456, 1411, 1396, 1366, 1321, 1306, 1269, 1212, 1175, 1125, 1109, 1019, 995, 905, 853; \text{HR-ESI calcd for C}_{19}\text{H}_{20}\text{NaO}_3 [M + Na]^+ 319.1305, found 319.1309. \\
\end{array}
\]
**GP9: Synthesis of Nitroacrylates**

To a solution of α-ketoester (1 eq) in CH$_3$NO$_2$ (0.25 M) was added NEt$_3$ (0.2 eq) and the resulting solution was stirred 24 h. CH$_3$NO$_2$ and NEt$_3$ were removed in vacuo. The reddish residue was redissolved in DMSO (0.25 M), Ac$_2$O (1 eq) was added, and the resulting solution was stirred for 48 h at rt. The reaction mixture was then poured in water, extracted with CH$_2$Cl$_2$ (3x), washed with saturated aq. NaHCO$_3$, dried, concentrated and purified by FC (Hex:EtOAc).

*(Z)-Benzyl 2-(4-fluoroophenyl)-3-nitroacrylate (Substrate Table 12, Entry 2)*

![Chemical structure](image)

Synthesized according to GP9.

$^1$H-NMR (400 MHz, CDCl$_3$) δ 7.50 – 7.35 (m, 7H), 7.31 (s, 1H), 7.16 – 7.08 (m, 2H), 5.43 (s, 2H); $^{13}$C-NMR (101 MHz, CDCl$_3$) δ 164.9 (d, $^1$J$_{C,F}$ = 256.1 Hz), 164.5, 141.8, 134.5, 134.3, 129.8 (d, $^3$J$_{C,F}$ = 9.0 Hz), 128.9, 128.9, 128.7, 125.6 (d, $^4$J$_{C,F}$ = 3.4 Hz), 116.9 (d, $^2$J$_{C,F}$ = 22.4 Hz), 68.7; $^{19}$F-NMR (376 MHz, CDCl$_3$) δ -105.9; IR (thin film, cm$^{-1}$) 3454, 3110, 3036, 2957, 2359, 1898, 1738, 1625, 1601, 1561, 1513, 1456, 1414, 1348, 1333, 1283, 1241, 1195, 1166, 1110, 1082, 1024, 1014, 941, 908, 833; HR-ESI calcd for C$_{16}$H$_{12}$FNNaO$_4$ [M + Na]$^+$ 324.0643, found 324.0652.

*(Z)-Benzyl 2-(4-chlorophenyl)-3-nitroacrylate (Substrate Table 12, Entry 3)*

![Chemical structure](image)

Synthesized according to GP9.
**Iridium-Catalyzed Reactions**

\[^1\text{H-NMR} \ (400 \text{ MHz, CDCl}_3) \: \delta \ 7.44 - 7.34 \ (m, 9H), \ 7.32 \ (s, \ 1H), \ 5.42 \ (s, \ 2H);\]^13\text{C-NMR} \ (101 \text{ MHz, CDCl}_3) \: \delta \ 164.3, \ 141.7, \ 138.6, \ 134.8, \ 134.3, \ 129.9, \ 129.0, \ 128.9, \ 128.8, \ 128.7, \ 127.9, \ 68.8; \ \text{IR (thin film, cm}^{-1} \) \ 3451, \ 1737, \ 1626, \ 1524, \ 1494, \ 1345, \ 1252, \ 1197, \ 1094, \ 1012, \ 913, \ 827; \ \text{HR-ESI calcd for C}_{16}H_{12}ClNNaO_4 [M + Na]^+ 340.0347, found 340.0346.

\textbf{(Z)-Benzyl 2-(4-bromophenyl)-3-nitroacrylate (Substrate Table 12, Entry 4)}

\[
\begin{align*}
\text{Br} & \quad \text{NO}_2 \\
\text{O} & \quad \text{C} \\
\text{C} & \quad \text{C}
\end{align*}
\]

Synthesized according to GP9.

\[^1\text{H-NMR} \ (300 \text{ MHz, CDCl}_3) \: \delta \ 7.59 - 7.53 \ (m, \ 2H), \ 7.44 - 7.35 \ (m, \ 5H), \ 7.34 \ (s, \ 1H), \ 7.33 - 7.27 \ (m, \ 2H), \ 5.42 \ (s, \ 2H);\]^13\text{C-NMR} \ (75 \text{ MHz, CDCl}_3) \: \delta \ 164.1, \ 141.7, \ 134.6, \ 134.1, \ 132.7, \ 128.9, \ 128.8, \ 128.7, \ 128.6, \ 128.1, \ 126.9, \ 68.8; \ \text{IR (thin film, cm}^{-1} \) \ 3105, \ 1737, \ 1624, \ 1584, \ 1523, \ 1491, \ 1456, \ 1402, \ 1345, \ 1251, \ 1197, \ 1076, \ 1008, \ 942, \ 824; \ \text{HR-ESI calcd for C}_{16}H_{12}BrNNaO_4 [M + Na]^+ 379.9842, found 379.9841.

\textbf{(Z)-Benzyl 2-(3-chlorophenyl)-3-nitroacrylate (Substrate Table 12, Entry 5)}

\[
\begin{align*}
\text{Cl} & \quad \text{NO}_2 \\
\text{O} & \quad \text{C} \\
\text{C} & \quad \text{C}
\end{align*}
\]

Synthesized according to GP9.

\[^1\text{H-NMR} \ (400 \text{ MHz, CDCl}_3) \: \delta \ 7.52 - 7.29 \ (m, \ 10H), \ 5.42 \ (s, \ 2H);\]^13\text{C-NMR} \ (101 \text{ MHz, CDCl}_3) \: \delta \ 164.1, \ 141.5, \ 135.7, \ 135.5, \ 134.3, \ 132.0, \ 131.2, \ 130.7, \ 129.0, \ 128.9, \ 128.7, \ 127.5, \ 125.6, \ 68.9; \ \text{IR (thin film, cm}^{-1} \) \ 3436, \ 1732, \ 1627, \ 1566, \ 1521, \ 1476, \ 1456, \ 1347,
Experimental Section

1248, 1191, 1082, 1026, 948, 908; **HR-ESI** calcd for C$_{16}$H$_{12}$ClNNaO$_{4}$ [M + Na]$^+$ 340.0347, found 340.0344.

(Z)-Benzyl 2-(2-chlorophenyl)-3-nitroacrylate (Substrate Table 12, Entry 6)

![Structure](image)

Synthesized according to GP9.

$^1$H-NMR (400 MHz, CDCl$_3$) δ 7.52 – 7.46 (m, 1H), 7.37 – 7.28 (m, 2H), 7.25 – 7.21 (m, 1H), 7.19 (s, 1H), 5.34 (s, 2H); $^{13}$C-NMR (101 MHz, CDCl$_3$) δ 164.3, 141.9, 134.8, 134.3, 132.8, 129.0, 128.9, 128.7, 128.3, 127.0, 68.8; IR (thin film, cm$^{-1}$) 3429, 1747, 1632, 1598, 1566, 1498, 1398, 1301, 1287, 1187, 1083, 1011, 947, 897; **HR-ESI** calcd for C$_{16}$H$_{12}$ClNNaO$_{4}$ [M + Na]$^+$ 340.0347, found 340.0340.

(Z)-Benzyl 2-(4-methoxyphenyl)-3-nitroacrylate (Substrate Table 12, Entry 7)

![Structure](image)

Synthesized according to GP9.

$^1$H-NMR (400 MHz, CDCl$_3$) δ 7.46 – 7.33 (m, 1H), 6.96 – 6.89 (m, 1H), 5.43 (s, 1H), 3.85 (s, 1H); $^{13}$C-NMR (101 MHz, CDCl$_3$) δ 165.1, 163.0, 142.9, 134.5, 132.5, 129.5, 128.9, 128.7, 121.4, 115.1, 68.6, 55.6; IR (thin film, cm$^{-1}$) 3108, 3012, 3018, 2991, 2899, 1927, 1901, 1737, 1613, 1578, 1561, 1515, 1502, 1489, 1455, 1422, 1349, 1340, 1312, 1279, 1195, 1101, 1079, 1022, 989, 95; **HR-ESI** calcd for C$_{17}$H$_{15}$NNaO$_{5}$ [M + Na]$^+$ 336.0852, found 336.0841.
(Z)-Benzyl 3-nitro-2-(4-(trifluoromethyl)phenyl)acrylate (Substrate Table 12, Entry 8)

![Chemical structure of (Z)-Benzyl 3-nitro-2-(4-(trifluoromethyl)phenyl)acrylate](image)

Synthesized according to GP9.

**¹H-NMR (400 MHz, CDCl₃)** δ 7.45 – 7.40 (m, 1H), 7.39 – 7.26 (m, 8H), 7.20 (s, 1H), 5.37 (s, 2H); **¹³C-NMR (101 MHz, CDCl₃)** δ 164.09, 141.5, 135.7, 135.5, 134.2, 132.0, 131.2, 130.7, 129.0, 128.7, 127.5, 125.6, 68.9; **IR (thin film, cm⁻¹)** 3108, 3068, 3034, 2953, 1739, 1622, 1605, 1562, 1518, 1456, 1378, 1346, 1331, 1280, 1256, 1202, 1186, 1167, 1026, 1016, 942, 908, 816; **HR-ESI** calcd for C₁₉H₂₀NaO₃ [M + Na]⁺ 374.0611, found 374.0608.

(Z)-Benzyl 3-nitro-2-p-tolylacrylate (Substrate Table 12, Entry 9)

![Chemical structure of (Z)-Benzyl 3-nitro-2-p-tolylacrylate](image)

Synthesized according to GP9.

**¹H-NMR (400 MHz, CDCl₃)** δ 7.45 – 7.31 (m, 8H), 7.23 (dd, J = 8.6, 0.6 Hz, 2H), 5.43 (s, 2H), 2.39 (s, 3H); **¹³C-NMR (101 MHz, CDCl₃)** δ 164.9, 143.2, 143.1, 134.5, 133.7, 130.3, 128.9, 128.8, 128.7, 127.5, 126.5, 68.6, 21.5; **IR (thin film, cm⁻¹)** 3108, 3034, 2953, 1739, 1622, 1605, 1562, 1518, 1456, 1378, 1346, 1331, 1280, 1256, 1202, 1186, 1167, 1026, 1016, 942, 908, 816; **HR-ESI** calcd for C₁₇H₁₅NNaO₄ [M + Na]⁺ 320.0893, found 320.0885.
(Z)-Benzy1 2-(4-tert-butylphenyl)-3-nitroacrylate (Substrate Table 12, Entry 10)

Synthesized according to GP9.

\[ ^1H-\text{NMR} \ (400 \text{ MHz, CDCl}_3) \delta \ 7.44 – 7.25 \ (m, \ 10H), \ 5.36 \ (s, \ 2H), \ 1.25 \ (m, \ 9H); \ ^{13}C-\text{NMR} \ (101 \text{ MHz, CDCl}_3) \delta \ 164.9, \ 156.3, \ 143.0, \ 134.5, \ 133.8, \ 128.9, \ 128.8, \ 128.7, \ 127.4, \ 126.6, \ 126.4, \ 68.6, \ 35.1, \ 31.0; \ \text{IR (thin film, cm}^{-1}\text{)} \ 3112, \ 3029, \ 2961, \ 1744, \ 1620, \ 1607, \ 1544, \ 1509, \ 1466, \ 1379, \ 1345, \ 1319, \ 1278, \ 1242, \ 1191, \ 1178, \ 1166, \ 1013, \ 1009, \ 955, \ 912, \ 832; \ \text{HR-ESI calcd for C}_{20}H_{21}NNaO_4 \ [M + Na]^+ 362.1363, \ \text{found 362.1367.} \]

GP10: Reduction of Nitroacrylates

To the nitroacrylate (1 mmol) in a 10 ml round bottom flask was added formic acid solution (5 ml, 1 M HCO\textsubscript{2}H) and catalyst (1 mol %, 0.01 mmol), and the resulting solution was heated to 60 °C for 24 h. The solution was then extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x), dried, concentrated and purified by FC (Hex:EtOAc).

(S)-Benzy1 3-nitro-2-phenylpropanoate (Product Table 12, Entry 1)

Synthesized according to GP10.

57% Yield, ee = 80% (SFC: I-C, 200 nm, CO\textsubscript{2}:MeOH = 95:5, flow rate 2 ml/min, \textit{t}_{(\text{minor})} = 5.9 \text{ min}, \textit{t}_{(\text{major})} = 6.7 \text{ min}).
**Iridium-Catalyzed Reactions**

$^1$H-NMR (400 MHz, CDCl$_3$) δ 7.39 – 7.29 (m, 6H), 7.26 – 7.20 (m, 3H), 5.18 (dd, $J = 31.1$, 8.3 Hz, 2H), 5.11 (dd, $J = 8.3$, 6.3 Hz, 1H), 4.57 (dd, $J = 14.6$, 5.2 Hz, 1H), 4.49 (dd, $J = 9.8$, 5.2 Hz, 1H); $^{13}$C-NMR (101 MHz, CDCl$_3$) δ 170.4, 135.1, 133.1, 129.3, 128.7, 128.5, 128.4, 128.0, 127.9, 75.7, 67.5, 48.8.

IR (thin film, cm$^{-1}$) 3461, 3038, 2318, 1732, 1538, 1373, 1191, 969; HR-ESI calcd for C$_{16}$H$_{20}$N$_2$O$_4$ [M + NH$_4$]$^+$ 303.1339, found 303.1334.

(S)-Benzyl 2-(4-fluorophenyl)-3-nitropropanoate (Product Table 12, Entry 2)

![Chemical Structure](image)

Synthesized according to GP10.

64% Yield, ee = 83% (SFC: I-C, 200 nm, CO$_2$:MeOH = 95:5, flow rate 2 ml/min, $t_{(\text{minor})}$ = 4.8 min, $t_{(\text{major})}$ = 5.5 min).

$^1$H-NMR (400 MHz, CDCl$_3$) δ 7.36 – 7.30 (m, 3H), 7.25 – 7.19 (m, 4H), 7.09 – 7.00 (m, 2H), 5.24 – 5.00 (m, 3H), 4.56 (dd, $J = 14.5$, 5.5 Hz, 1H), 4.47 (dd, $J = 9.5$, 5.5 Hz, 1H); $^{13}$C-NMR (101 MHz, CDCl$_3$) δ 170.2, 164.0, 161.5, 134.9, 129.7, 129.7, 128.9, 128.6, 128.5, 128.1, 116.5, 116.3, 75.6, 67.6, 48.0; IR (thin film, cm$^{-1}$) 3461, 3037, 2639, 2459, 2325, 2065, 1733, 1518, 1374, 1200, 968; HR-ESI calcd for C$_{16}$H$_{19}$FN$_2$O$_4$ [M + NH$_4$]$^+$ 321.1245, found 321.1237.

(S)-Benzyl 2-(4-chlorophenyl)-3-nitropropanoate (Product Table 12, Entry 3)

![Chemical Structure](image)

Synthesized according to GP10.
Experimental Section

48% Yield, ee = 81% (SFC: I-C, 200 nm, CO₂:MeOH = 95:5, flow rate 2 ml/min, \( t_{\text{r(minor)}} = 6.9 \text{ min} \), \( t_{\text{r(major)}} = 8.3 \text{ min} \)).

\(^1\text{H-NMR (400 MHz, CDCl}_3\) δ 7.36 – 7.30 (m, 5H), 7.25 – 7.20 (m, 2H), 7.20 – 7.16 (m, 2H), 5.28 – 4.98 (m, 31H), 4.54 (dd, \( J = 10.4, 4.5 \text{ Hz} \), 1H), 4.46 (dd, \( J = 9.5, 5.5 \text{ Hz} \), 1H);

\(^{13}\text{C-NMR (101 MHz, CDCl}_3\) δ 170.0, 134.9, 131.6, 129.6, 129.3, 128.6, 128.5, 128.1, 123.0, 75.4, 67.7, 48.2;

IR (thin film, cm\(^{-1}\)) 3436, 2842, 2063, 1733, 1674, 1599, 1573, 1512, 1456, 1426, 1378, 1310, 1268, 1203, 1162, 1118, 1026, 1011, 991, 905, 847; HR-ESI calcd for C\(_{16}\)H\(_{18}\)ClN\(_2\)O\(_4\) [M + NH\(_4^+\)] 337.0950, found 337.0952.

(S)-Benzyl 2-(4-bromophenyl)-3-nitropropanoate (Product Table 12, Entry 4)

![Structure](image)

Synthesized according to GP10.

45% Yield, ee = 82% (SFC: I-C, 200 nm, CO₂:MeOH = 95:5, flow rate 2 ml/min, \( t_{\text{r(minor)}} = 8.6 \text{ min} \), \( t_{\text{r(major)}} = 10.7 \text{ min} \)). \(^1\text{H-NMR (400 MHz, CDCl}_3\) δ 7.48 (d, \( J = 8.5 \text{ Hz} \), 2H), 7.37 – 7.30 (m, 3H), 7.22 (dd, \( J = 6.6, 2.9 \text{ Hz} \), 2H), 7.12 (d, \( J = 8.4 \text{ Hz} \), 2H), 5.25 – 5.03 (m, 3H), 4.55 (dd, \( J = 14.6, 5.5 \text{ Hz} \), 1H), 4.45 (dd, \( J = 9.5, 5.5 \text{ Hz} \), 1H);

\(^{13}\text{C-NMR (101 MHz, CDCl}_3\) δ 169.9, 134.9, 132.5, 132.1, 129.6, 128.6, 128.6, 128.1, 123.0, 75.4, 67.7, 48.2;

IR (thin film, cm\(^{-1}\)) 2960, 2646, 2344, 2063, 1732, 1554, 1374, 1175, 1007; HR-ESI calcd for C\(_{16}\)H\(_{18}\)BrN\(_2\)O\(_4\) [M + NH\(_4^+\)] 381.0444, found 381.454.
(S)-Benzyl 2-(3-chlorophenyl)-3-nitropropanoate (Product Table 12, Entry 5)

\[
\text{Cl} \quad \text{NO}_2 \\
\text{CO}_2\text{Bn}
\]

Synthesized according to GP10.

43% Yield, ee = 82% (SFC: I-C, 200 nm, CO\(_2\):MeOH = 95:5, flow rate 2 ml/min, \(t_{(\text{minor})}\) = 6.4 min, \(t_{(\text{major})}\) = 7.3 min).

\(^1\text{H-NMR (400 MHz, CDCl}_3\) \(\delta 7.37 - 7.27\) (m, 5H), 7.25 - 7.21 (m, 3H), 7.13 (dt, \(J = 7.3, 1.5\) Hz, 1H), 5.28 - 5.02 (m, 3H), 4.56 (dd, \(J = 14.7, 5.4\) Hz, 1H), 4.46 (dd, \(J = 9.6, 5.4\) Hz, 1H); \(^{13}\text{C-NMR (101 MHz, CDCl}_3\) \(\delta 169.8, 135.2, 134.9, 134.9, 130.6, 129.0, 128.6, 128.6, 128.2, 128.1, 126.2, 75.4, 67.8, 48.4; IR (thin film, cm\(^{-1}\)) 2963, 2347, 2062, 1734, 1555, 1373, 1179, 1012, 899; HR-ESI calcd for C\(_{16}\)H\(_{18}\)ClN\(_2\)O\(_4\) [M + NH\(_4\)]\(^+\) 337.0950, found 337.0944.

(S)-Benzyl 2-(2-chlorophenyl)-3-nitropropanoate (Product Table 12, Entry 6)

\[
\text{Cl} \quad \text{NO}_2 \\
\text{CO}_2\text{Bn}
\]

Synthesized according to GP10.

44% Yield, ee = 82% (SFC: I-C, 200 nm, CO\(_2\):MeOH = 95:5, flow rate 2 ml/min, \(t_{(\text{minor})}\) = 8.3 min, \(t_{(\text{major})}\) = 10.4 min).

\(^1\text{H-NMR (400 MHz, CDCl}_3\) \(\delta 7.53 - 7.44\) (m, 2H), 7.36 - 7.29 (m, 3H), 7.25 - 7.19 (m, 2H), 7.16 - 7.09 (m, 2H), 5.26 - 4.99 (m, 3H), 4.55 (dd, \(J = 14.6, 5.5\) Hz, 1H), 4.45 (dd, \(J = 9.5, 5.5\) Hz, 1H); \(^{13}\text{C-NMR (101 MHz, CDCl}_3\) \(\delta 169.92, 134.86, 132.52, 132.09, 129.60, 128.60, 128.55, 128.12, 122.96, 75.37, 67.72, 48.21; IR (thin film, cm\(^{-1}\)) 3456,}
(S)-Benzyl 2-(4-methoxyphenyl)-3-nitropropanoate (Product Table 12, Entry 7)

\[
\begin{align*}
&\text{Synthesized according to GP10.} \\
&54\% \text{ Yield, ee = } 86\% \text{ (SFC: I-C, 200 nm, CO}_2\text{:MeOH = 95:5, flow rate 2 ml/min, } t_{(\text{minor})} = 9.0 \text{ min, } t_{(\text{major})} = 10.4 \text{ min).} \\
&{^1}\text{H-NMR (400 MHz, CDCl}_3\text{) } \delta \text{ 7.35 – 7.28 (m, 3H), 7.25 – 7.20 (m, 2H), 7.19 – 7.14 (m, 2H), 6.91 – 6.82 (m, 2H), 5.12 (ddd, } J = 28.6, 18.6, 11.1 \text{ Hz, 3H), 4.53 (dd, } J = 14.6, 5.3 \text{ Hz, 1H), 4.43 (dd, } J = 9.8, 5.3 \text{ Hz, 1H), 3.80 (s, 1H); } {^{13}}\text{C-NMR (101 MHz, CDCl}_3\text{) } \delta \text{ 170.7, 159.8, 135.2, 129.1, 128.5, 128.4, 128.0, 125.0, 114.7, 75.8, 67.4, 55.3, 48.0; } \text{IR (thin film, cm}^{-1}\text{)} \text{ 3668, 2965, 2348, 2203, 2055, 1989, 1906, 1883, 1798, 1731, 1603, 1552, 1375, 1248, 1174, 1030, 831; } \text{HR-ESI calcd for } C_{17}H_{21}N_2O_5 [M + NH}_4^+ \text{ 333.1445, found 333.1452.}
\end{align*}
\]

(S)-Benzyl 3-nitro-2-(4-(trifluoromethyl)phenyl)propanoate (Product Table 12, Entry 8)

\[
\begin{align*}
&\text{Synthesized according to GP10.}
\end{align*}
\]
Iridium-Catalyzed Reactions

43% Yield, ee = 82% (SFC: I-C, 200 nm, CO2:MeOH = 95:5, flow rate 2 ml/min, t_{(minor)} = 6.6 min, t_{(major)} = 7.5 min).

\(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.34 – 7.28 (m, 1H), 7.26 – 7.21 (m, 1H), 7.13 (dt, \(J = 7.3, 1.5\) Hz, 1H), 5.28 – 5.02 (m, 1H), 4.56 (dd, \(J = 14.7, 5.4\) Hz, 1H), 4.46 (dd, \(J = 9.6, 5.4\) Hz, 1H); \(^{13}\)C-NMR (101 MHz, CDCl\(_3\)) \(\delta\) 169.8, 135.2, 134.9, 130.6, 129.0, 128.6, 128.2, 126.2, 75.4, 67.8, 48.4; IR (thin film, \(cm^{-1}\)) 3460, 2970, 2348, 2062, 1733, 1555, 1374, 1178, 1086, 1015, 899; HR-ESI calcd for C\(_{16}\)H\(_{14}\)NaO\(_4\) [M + Na]\(^+\) 293.0784, found 293.0787.

(S)-Benzyl 3-nitro-2-\(p\)-tolylpropanoate (Product Table 12, Entry 9)

\[
\begin{align*}
\text{NO}_2 & \quad \text{CO}_2\text{Bn} \\
\text{Me} & \quad \text{CO}_2\text{Bn}
\end{align*}
\]

Synthesized according to GP10.

44% Yield, ee = 86% (SFC: I-C, 200 nm, CO2:MeOH = 95:5, flow rate 2 ml/min, t_{(minor)} = 6.6 min, t_{(major)} = 7.4 min).

\(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.35 – 7.28 (m, 3H), 7.25 – 7.20 (m, 2H), 7.18 – 7.09 (m, 4H), 5.13 (dd, \(J = 28.3, 14.6, 10.6\) Hz, 3H), 4.54 (dd, \(J = 14.6, 5.2\) Hz, 1H), 4.45 (dd, \(J = 9.9, 5.2\) Hz, 1H), 2.34 (s, 1H); \(^{13}\)C-NMR (101 MHz, CDCl\(_3\)) \(\delta\) 170.6, 138.6, 135.2, 130.1, 130.0, 128.5, 128.4, 128.0, 127.8, 75.8, 67.4, 48.4, 21.1; IR (thin film, \(cm^{-1}\)) 3671, 2971, 2348, 1990, 1909, 1885, 1733, 1553, 1375, 1175, 1045, 963; HR-ESI calcd for C\(_{17}\)H\(_{21}\)N\(_2\)O\(_4\) [M + NH\(_4\)]\(^+\) 317.1496, found 317.1497.
(S)-Benzyl 2-(4-tert-butylphenyl)-3-nitropropanoate (Product Table 12, Entry 10)

\[
\text{Synthesized according to GP10.}
\]

48% Yield, ee = 90% (SFC: I-C, 200 nm, CO₂:MeOH = 95:5, flow rate 2 ml/min, \( t_{\text{r(minor)}} = 6.4 \) min, \( t_{\text{r(major)}} = 7.4 \) min).

\(^1\)H-NMR (400 MHz, CDCl₃) \( \delta \) 7.39 – 7.33 (m, 2H), 7.33 – 7.28 (m, 3H), 7.22 (td, \( J = 6.2, 2.0 \) Hz, 2H), 7.19 – 7.14 (m, 2H), 5.16 (tt, \( J = 16.2, 10.0 \) Hz, 3H), 4.55 (dd, \( J = 14.6, 5.0 \) Hz, 1H), 4.46 (dd, \( J = 10.1, 5.0 \) Hz, 1H), 1.30 (s, 9H); \(^{13}\)C-NMR (101 MHz, CDCl₃) \( \delta \) 170.6, 151.8, 128.5, 128.3, 127.9, 127.6, 126.3, 75.7, 67.3, 48.3, 34.6, 31.2; IR (thin film, cm\(^{-1}\)) 3675, 2347, 1729, 1549, 1457, 1376, 1235, 1161, 1097, 1023, 936; HR-ESI calcd for C₂₀H₂₇N₂O₄ [M + NH₄]\(^+\) 359.1965, found 359.1959.
4.3.4 Asymmetric Transfer Hydrogenation of β-Keto Esters

GP11: Synthesis of the Ligands

To a solution of the free diamine (425 mg, 2.0 mmol, 1 eq) and triethylamine (0.56 ml, 4.0 mmol, 2.0 eq) in CH$_2$Cl$_2$ (10 ml) at 0 °C was added dropwise a solution of the corresponding sulfonyl chloride (2.0 mmol, 1 eq) in CH$_2$Cl$_2$ (1 ml) dropwise and the resulting solution was stirred over night (12 h) at room temperature.

$N$-((1$R$,2$R$)-2-Amino-1,2-diphenylethyl)methanesulfonamide (Ligand Table 15, Entry 1)

![Structure](image)

Synthesized according to GP11.

$^1$H-NMR (400 MHz, MeOD) δ 7.30 – 7.07 (m, 5H), 4.49 (d, $J$ = 8.6 Hz, 1H), 4.07 (d, $J$ = 8.6 Hz, 1H), 2.41 (s, 3H); $^{13}$C-NMR (101 MHz, MeOD) δ 142.4, 141.1, 129.5, 129.3, 128.7, 128.7, 128.6, 128.5, 66.6, 62.1, 41.5. All other spectroscopic data were in agreement with the literature.$^{111}$

**Experimental Section**

**N-((1R,2R)-2-Amino-1,2-diphenylethyl)-4-methoxybenzenesulfonamide (Ligand Table 15, Entry 3)**

![Chemical structure][1]

Synthesized according to GP11.

**^1H-NMR (400 MHz, MeOD)** δ 7.45 – 7.36 (m, 1H), 7.17 – 7.02 (m, 3H), 6.98 – 6.86 (m, 2H), 6.77 (dt, \(J = 3.7, 2.2\) Hz, 1H), 6.73 – 6.66 (m, 1H), 4.35 (d, \(J = 8.9\) Hz, 1H), 3.97 (d, \(J = 8.9\) Hz, 1H), 3.74 (s, 2H); **^13C-NMR (101 MHz, MeOD)** δ 162.5, 140.7, 138.5, 132.5, 128.6, 127.7, 127.4, 127.3, 127.2, 126.9, 126.6, 113.4, 65.2, 60.91, 54.6. All other spectroscopic data were in agreement with the literature.\(^{111}\)

**N-((1R,2R)-2-Amino-1,2-diphenylethyl)-4-(trifluoromethyl)benzenesulfonamide (Ligand Table 15, Entry 5)**

![Chemical structure][2]

Synthesized according to GP11.

**^1H-NMR (400 MHz, MeOD)** δ 7.61 (d, \(J = 8.2\) Hz, 1H), 7.45 (d, \(J = 8.3\) Hz, 1H), 7.14 – 7.04 (m, 2H), 6.98 – 6.83 (m, 2H), 6.76 (dd, \(J = 8.0, 1.4\) Hz, 1H), 4.45 (d, \(J = 8.7\) Hz, 1H), 4.02 (d, \(J = 8.7\) Hz, 1H); **^13C-NMR (101 MHz, MeOD)** δ 176.8, 146.2, 142.0, 139.5, 129.2, 128.9, 128.6, 128.6, 128.6, 128.5, 128.1, 126.7, 126.7, 66.8, 62.1; **^19F-NMR (376 MHz, MeOD)** δ - 64.76. All other spectroscopic data were in agreement with the literature.\(^{111}\)
N-((1R,2R)-2-Amino-1,2-diphenylethyl)-4-(trifluoromethoxy)benzenesulfonamide
(Ligand Table 15, Entry 6)

Synthesized according to GP11.

\[ \text{1H-NMR (300 MHz, CD}_3\text{OD)} \delta 7.57 \text{–} 7.50 (m, 2H), 7.13 \text{–} 7.00 (m, 7H), 6.96 \text{–} 6.83 (m, 3H), 6.79 \text{–} 6.72 (m, 2H), 4.43 \text{ (d, } J = 8.9 \text{ Hz, 1H)}, 4.00 \text{ (d, } J = 8.9 \text{ Hz, 1H}); \text{13C-NMR (75 MHz, CD}_3\text{OD)} \delta 152.5, 142.0, 141.3, 139.5, 130.2, 129.2, 128.9, 128.7, 128.6, 128.4, 128.1, 121.8, 66.8, 62.2; \text{19F-NMR (282 MHz, CD}_3\text{OD)} \delta 59.3 \text{ (s, 3F); IR (thin film, cm}^{-1} \text{) 338, 3291, 3161, 2880, 2853, 2734, 2341, 1592, 1491, 1454, 1408, 1375, 1298, 1281, 1211, 1147, 1096, 1054, 1018, 1000, 949, 919; HR-MALDI calcd for C_{31}H_{38}IrN_{2}O_{5}S [M+H]^+ 437.1141, found 437.1140; Optical rotation: } [\alpha]_{D}^{\text{29}} -7.90^\circ (c = 1.0, \text{CHCl}_3). \]

\[ \text{Synthesis of the Catalysts:} \]

\[ \{\text{Cp}^*\text{Ir}[(R,R)-\text{Ms-DPEN}(\text{H}_2\text{O})](\text{SO}_4) \text{ (Catalyst Table 15, Entry 1)} \]

Synthesized according to GP4.

\[ \text{1H-NMR (400 MHz, MeOD)} \delta 7.48 \text{–} 7.27 (m, 1H), 5.01 \text{ (d, } J = 2.4 \text{ Hz, 1H)}, 4.33 \text{ (d, } J = 2.5 \text{ Hz, 1H)}, 2.29 \text{ (s, 1H)}, 1.88 \text{ (s, 1H); 13C-NMR (101 MHz, MeOD)} \delta 141.9, 139.5, 129.8, 129.8, 129.7, 129.4, 128.3, 128.3, 92.1, 78.8, 69.2, 40.8, 10.3; \text{ IR (thin film, cm}^{-1} \text{)}\]
3676, 3662, 2989, 2972, 2901, 2360, 2342, 1772, 1700, 1603, 1559, 1540, 1507, 1496, 1473, 1454, 1406, 1394, 1381, 1313, 1250, 1229, 1187, 138, 1103, 1176, 958; HR-MALDI calcd for C$_{25}$H$_{32}$IrN$_2$O$_2$S [M-HSO$_4$-H$_2$O]$^+$ 617.1814, found 617.1808; **Optical rotation:** $[\alpha]_D^{25}$ -592.34° ($c = 1.0$, CHCl$_3$).

{Cp*Ir[(R,R)-p-OMe-C$_6$H$_4$-DPEN](H$_2$O)}(SO$_4$) (Catalyst Table 15, Entry 3)

```
\begin{center}
\begin{tikzpicture}
\node (ir) at (0,0) {\text{Ir}};
\node (cp) at (-1,0) {\text{Cp}};
\node (water) at (1,0) {\text{H}_2\text{O}};
\node (nso) at (-0.5,-0.5) {\text{NSO}_2};
\node (om) at (0.5,-0.5) {\text{OMe}};
\node (phen) at (0,-1) {\text{Ph}};
\node (phen2) at (1,-1) {\text{Ph}};
\draw[black, thick] (ir) -- (cp) -- (water) -- (nso) -- (om) -- (phen) -- (phen2);\end{tikzpicture}
\end{center}
```

Synthesized according to GP4.

$^1$H-NMR (400 MHz, MeOD) $\delta$ 7.44 – 7.10 (m, 1H), 6.68 – 6.60 (m, 1H), 4.63 (s, 1H), 4.25 (s, 1H), 3.79 (s, 1H), 1.95 (s, 1H); $^{13}$C-NMR (101 MHz, MeOD) $\delta$ 164.1, 142.0, 138.5, 130.4, 130.3, 129.6, 129.5, 129.3, 129.0, 128.0, 127.6, 115.1, 92.6, 79.0, 68.9, 56.1, 10.5; IR (thin film, cm$^{-1}$) 3684, 3676, 2989, 2972, 2901, 2363, 2342, 1772, 1700, 1617, 1595, 1577, 1559, 1540, 1497, 1454, 1406, 1394, 1381, 1313, 1298, 1250, 1229, 1185, 1143, 1076, 1028, 944; HR-MALDI calcd for C$_{31}$H$_{36}$IrN$_2$O$_5$S [M-HSO$_4$-H$_2$O]$^+$ 709.2076, found 709.2235; **Optical rotation:** $[\alpha]_D^{29}$ -594.39° ($c = 1.0$, CHCl$_3$).

{Cp*Ir[(R,R)-p-CF$_3$-C$_6$H$_4$-DPEN](H$_2$O)}(SO$_4$) (Catalyst Table 15, Entry 5)

```
\begin{center}
\begin{tikzpicture}
\node (ir) at (0,0) {\text{Ir}};
\node (cp) at (-1,0) {\text{Cp}};
\node (water) at (1,0) {\text{H}_2\text{O}};
\node (nso) at (-0.5,-0.5) {\text{NSO}_2};
\node (cf3) at (0.5,-0.5) {\text{CF}_3};
\node (phen) at (0,-1) {\text{Ph}};
\node (phen2) at (1,-1) {\text{Ph}};
\draw[black, thick] (ir) -- (cp) -- (water) -- (nso) -- (cf3) -- (phen) -- (phen2);\end{tikzpicture}\end{center}
```

Synthesized according to GP4.

$^1$H-NMR (400 MHz, MeOD) $\delta$ 7.49 – 7.40 (m, 4H), 7.39 – 7.23 (m, 5H), 7.20 – 7.04 (m, 5H), 4.70 – 4.62 (m, 1H), 4.33 – 4.26 (m, 1H), 1.97 (s, 15H); $^{13}$C-NMR (101 MHz,
Iridium-Catalyzed Reactions

MeOD) $\delta$ 143.3, 141.5, 138.2, 134.5, 134.2, 129.6, 129.5, 129.3, 129.2, 128.9, 128.2, 127.5, 127.0, 127.0, 92.9, 78.3, 68.8, 10.5. $^{19}$F-NMR (282 MHz, CD$_3$OD) $\delta$ -64.6; IR (thin film, cm$^{-1}$) 3684, 3676, 3210, 2989, 2972, 2901, 2360, 2341, 1772, 1700, 1604, 1559, 1540, 1447, 1454, 1405, 1394, 1382, 1321, 1212, 1181, 1158, 1120, 1076, 946; HR-MALDI calcd for C$_{31}$H$_{33}$F$_3$IrN$_2$O$_2$S [M-HSO$_4$-H$_2$O]$^+$ 747.1844, found 747.1846; Optical rotation: $[\alpha]_D^{29}$ -370.94° ($c$ = 1.0, CHCl$_3$).

$^{1}$H-NMR (400 MHz, MeOD) $\delta$ 7.41 – 7.10 (m, 12H), 7.04 (d, $J$ = 8.0 Hz, 2H), 4.67 (s, 1H), 4.28 (s, 1H), 1.95 (s, 15H); $^{13}$C-NMR (101 MHz, MeOD) $\delta$ 152.7, 141.5, 138.4, 130.6, 129.6, 129.3, 129.1, 128.2, 127.6, 121.8, 92.8, 78.5, 68.9, 10.5; $^{19}$F-NMR (282 MHz, CD$_3$OD) $\delta$ -59.1 (s, 3F); IR (thin film, cm$^{-1}$) 3684, 3676, 2989, 2972, 2901, 2360, 2342, 1701, 1647, 1603, 1588, 1540, 1491, 1477, 1454, 1406, 1394, 1383, 1310, 1250, 1230, 1187, 1159, 1141, 1072, 946; HR-MALDI calcd for C$_{31}$H$_{33}$F$_3$IrN$_2$O$_2$S [M-HSO$_4$-H$_2$O]$^+$ 763.1793, found 763.1799; Optical rotation: $[\alpha]_D^{25}$ -649.04° ($c$ = 1.0, CHCl$_3$).
Synthesis of Substrates:

The substrates which are not commercially available were synthesized according to a known procedure.

Ethyl 3-(4-fluorophenyl)-3-oxopropanoate (Substrate Table 16, Entry 2)

\[ \text{H-NMR (5:1 mixture of keto- and enol-tautomer, asterisk denotes enol-tautomer, 400 MHz, CDCl}_3 \delta 12.61^* (s, 1H), 8.02 – 7.94 (m, 2H), 7.81 – 7.75^* (m, 2H), 7.20 – 7.06 (m, 2H), 7.20 – 7.06^* (m, 2H), 5.60^* (s, 1H), 4.27^* (q, } J = 7.2 \text{ Hz, 2H), 4.21 (q, } J = 7.2 \text{ Hz, 2H) 3.96 (s, 2H), 1.33^* (t, } J = 7.2 \text{ Hz, 3H), 1.26 (t, } J = 7.2 \text{ Hz, 15H); } ^{13}\text{C-NMR (101 MHz, CDCl}_3 \delta 190.9, 173.1^*, 170.4^* 167.4, 167.3, 164.8^*, 132.5 (d, } J = 1.5 \text{ Hz), 131.3 (d, } J = 4.8 \text{ Hz), 129.9^* (d, } J = 1.5 \text{ Hz), 128.2^* (d, } J = 4.4 \text{ Hz), 116.0 (d, } J = 22.1 \text{ Hz), 115.6^* (d, } J = 24.0 \text{ Hz), 87.2^*, 61.6, 60.4^*, 46.0, 14.3^*, 14.1. All other spectroscopic data were in agreement with the literature.}

Ethyl 3-(4-chlorophenyl)-3-oxopropanoate (Substrate Table 16, Entry 3)

\[ \text{H-NMR (3.5:1 mixture of keto- and enol-tautomer, asterisk denotes enol-tautomer, 400 MHz, CDCl}_3 \delta 12.57^* (s, 1H), 7.92 – 7.86 (m, 2H), 7.74 – 7.69^* (m, 2H), 7.49 – 7.43 (m, 2H), 7.42 – 7.36^* (m, 2H), 5.63^* (s, 1H), 4.27^* (q, } J = 3.6 \text{ Hz, 2H), 4.21 (q, } J = 3.6 \text{ Hz, 2H).}

3.6, Hz, 2H), 3.96 (s, 2H), 1.33 (t, $J = 7.1$ Hz, 3H), 1.25 (t, $J = 7.1$ Hz, 12H); $^{13}$C-NMR (101 MHz, CDCl$_3$) δ 191.3, 173.0*, 170.2*, 167.2, 140.3, 137.3*, 134.4, 131.9*, 129.9, 129.1, 128.8*, 127.4*, 87.7*, 61.6, 60.5*, 46.0, 14.3*, 14.1. All other spectroscopic data were in agreement with the literature.$^{113}$

Ethyl 3-(4-bromophenyl)-3-oxopropanoate (Substrate Table 16, Entry 4)

$^1$H-NMR (2.5:1 mixture of keto- and enol-tautomer, asterisk denotes enol-tautomer, 400 MHz, CDCl$_3$) δ 12.56* (s, 1H), 7.84 – 7.78 (m, 2H), 7.67 – 7.60 (m, 2H), 7.67 – 7.60* (m, 2H), 7.59 – 7.52* (m, 2H), 5.64* (s, 1H), 4.27* (q, $J = 7.2$ Hz, 2H), 4.21, 3.94 (s, 2H), (q, $J = 7.2$ Hz, 2H), 1.33* (t, $J = 7.1$ Hz, 3H), 1.25 (t, $J = 7.1$ Hz, 3H); $^{13}$C-NMR (101 MHz, CDCl$_3$) δ 191.5, 173.0*, 170.2*, 167.2, 134.8*, 132.1*, 131.8, 130.0, 129.1, 127.5*, 125.7*, 87.7*, 61.6, 60.5*, 45.9, 14.3*, 14.1. All other spectroscopic data were in agreement with the literature.$^{113}$

Ethyl 3-(4-iodophenyl)-3-oxopropanoate (Substrate Table 16, Entry 5)

$^1$H-NMR (2.5:1 mixture of keto- and enol-tautomer, asterisk denotes enol-tautomer, 400 MHz, CDCl$_3$) δ 12.54* (s, 1H), 7.89 – 7.82 (m, 2H), 7.80 – 7.74* (m, 2H), 7.69 – 7.62 (m, 2H), 7.54 – 7.46* (m, 2H), 5.65* (s, 1H), 4.27* (q, $J = 3.6$ Hz, 2H), 4.21 (q, $J = 3.6$, Hz, 2H), 3.94 (s, 2H), 1.33* (t, $J = 7.1$ Hz, 3H), 1.25 (t, $J = 7.1$ Hz, 3H); $^{13}$C-NMR (101 MHz, CDCl$_3$) δ 191.8, 173.0*, 170.3*, 167.2, 138.1, 137.8*, 135.3, 133.0*, 129.8, 127.6*, 101.9, 97.9*, 87.7*, 61.6, 60.5*, 45.9, 14.3*, 14.1; IR (thin film, cm$^{-1}$) 2981,
2936, 1920, 1732, 1700, 1674, 1658, 1634, 1622, 1580, 1564, 1486, 1424, 1393, 1262, 1200, 1150, 1112, 1096, 1061, 1030, 1005, 944, 897, 838; **HR-ESI** calcld for C_{11}H_{12}IO_{3} [M-H]^+ 318.9826, found 318.9818.

### Ethyl 3-(3-chlorophenyl)-3-oxopropanoate (Substrate Table 16, Entry 6)

![Structure Image](#)

**1H-NMR (3:1 mixture of keto- and enol-tautomer, asterisk denotes enol-tautomer, 400 MHz, CDCl₃)** δ 12.54* (s, 1H), 7.92 (t, ḳ = 1.9 Hz, 1H), 7.82 (ddd, ḳ = 7.8, 1.6, 1.1 Hz, 1H), 7.76* (t, ḳ = 1.9 Hz, 1H), 7.67 – 7.62* (m, 1H), 7.47 – 7.28 (m, 9H), 7.47 – 7.28* (m, 9H), 5.65* (s, 1H), 4.27 (q, ḳ = 3.6 Hz, 2H), 4.22 (q, ḳ = 3.4 Hz, 9H), 3.96 (s, 7H), 1.34 (t, ḳ = 7.1 Hz, 3H), 1.26 (t, ḳ = 7.1 Hz, 3H); **13C-NMR (101 MHz, CDCl₃)** δ 191.3, 173.0*, 169.7*, 167.1, 137.6, 135.3*, 135.2, 134.7*, 133.6, 131.1*, 130.1, 129.8*, 128.6, 126.6, 126.2*, 124.1*, 88.3*, 61.6, 60.5*, 46.0, 14.2*, 14.0. All other spectroscopic data were in agreement with the literature.¹¹³

### Ethyl 3-(2-chlorophenyl)-3-oxopropanoate (Substrate Table 16, Entry 7)

![Structure Image](#)

**1H-NMR (2:1 mixture of keto- and enol-tautomer, asterisk denotes enol-tautomer, 400 MHz, CDCl₃)** δ 12.48* (s, 1H), 7.64 – 7.59 (m, 1H), 7.59 – 7.55* (m, 1H), 7.47 – 7.28 (m, 9H), 7.47 – 7.28* (m, 9H), 5.55* (s, 1H), 4.28* (q, ḳ = 7.1 Hz, 2H), 4.19 (q, ḳ = 7.1 Hz, 4H), 1.34* (t, ḳ = 7.1 Hz, 3H), 1.24 (t, ḳ = 7.1 Hz, 7H); **13C-NMR (101 MHz, CDCl₃)** δ 194.7, 172.7*, 170.4*, 166.9, 137.7, 133.6*, 132.6, 132.2*, 131.5*, 131.0*,
130.7, 130.6*, 130.1*, 130.0, 127.0, 126.8*, 93.3*, 61.5, 60.5*, 49.2, 14.2*, 14.0. All other spectroscopic data were in agreement with the literature.\textsuperscript{114}

**Ethyl 3-(naphthalen-2-yl)-3-oxopropanoate (Substrate Table 16, Entry 10)**

\begin{center}
\includegraphics[width=0.3\textwidth]{ethylnaphthaleneno.png}
\end{center}

\textsuperscript{1}H-NMR (4:1 mixture of keto- and enol-tautomer, asterisk denotes enol-tautomer, 400 MHz, CDCl\textsubscript{3}) \(\delta\) 12.67* (s, 1H), 8.46 (d, \(J = 1.3\) Hz, 1H), 8.36* (d, \(J = 0.7\) Hz, 1H), 8.02 (dd, \(J = 8.6, 1.8\) Hz, 1H), 7.98 (dd, \(J = 8.0, 0.7\) Hz, 1H), 7.94 – 7.83 (m, 2H), 7.94 – 7.83* (m, 3H), 7.78* (dd, \(J = 8.7, 1.8\) Hz, 1H), 7.67 – 7.49 (m, 2H), 7.67 – 7.49* (m, 2H), 5.81* (s, 1H), 4.30* (q, \(J = 7.1\) Hz, 2H), 4.24 (q, \(J = 7.1\) Hz, 2H), 4.12 (s, 2H), 1.36* (t, \(J = 7.1\) Hz, 3H), 1.26 (t, \(J = 7.1\) Hz, 11H); \textsuperscript{13}C-NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) 192.4, 173.2*, 171.3*, 167.6, 135.8, 134.7*, 133.4, 132.4, 130.6*, 130.6, 129.7, 129.1*, 128.9, 128.7, 128.3*, 127.8, 127.7*, 127.5*, 127.0, 126.7*, 126.7*, 123.8, 122.6*, 87.9*, 61.5, 60.4*, 46.1, 14.3*, 14.1. All other spectroscopic data were in agreement with the literature.\textsuperscript{115}

**Ethyl 3-(adamantoyl)-3-oxopropanoate (Substrate Table 16, Entry 11)**

\begin{center}
\includegraphics[width=0.3\textwidth]{ethyladamanteno.png}
\end{center}

\textsuperscript{1}H-NMR (4:1 mixture of keto- and enol-tautomer, asterisk denotes enol-tautomer, 400 MHz, CDCl\textsubscript{3}) \(\delta\) 12.28* (s, 1H), 4.96* (s, 1H), 4.18* (q, \(J = 5.4\) Hz, 2H), 4.18 (q, \(J = 5.4\) Hz, 3H), 2.09 - 1.95* (m, 3H), 2.09 - 1.95 (m, 3H), 1.82 – 1.67* (m, 12H), 1.82 – 1.67 (m, 12H), 1.27* (t, \(J = 5.4\) Hz, 3H), 1.27 (t, \(J = 5.4\) Hz, 11H); \textsuperscript{13}C-NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) 207.8, 173.5* 168.0*, 85.3*, 61.2, 59.9*, 47.0, 43.5, 39.1, 37.9, 36.6, 36.4,

\textsuperscript{114} Wierenga, W.; Skulnick, H. I. J. Org. Chem. 1979, 44, 310.
Experimental Section

Ethyl 3-oxododecanoate (Substrate Table 16, Entry 12)

\[
\text{C}_9\text{H}_{19} \text{C(}=\text{O})\text{OEt}
\]

\(^1\text{H-NMR (4:1 mixture of keto- and enol-tautomer, asterisk denotes enol-tautomer, 400 MHz, CDCl}_3\) \(\delta\) 12.10* (s, 1H), 4.97* (s, 1H), 4.19 (q, \(J = 5.4\) Hz, 2H), 4.18* (q, \(J = 5.1\) Hz, 2H), 3.42 (s, 2H), 2.53 (m, 2H), 2.18* (m, 2H), 1.69 – 1.51* (m, 4H), 1.69 – 1.51 (m, 4H), 1.40 – 1.21* (m, 13H), 1.40 – 1.21 (m, 13H), 0.87* (t, \(J = 5.1\) Hz, 3H); 0.87 (t, \(J = 5.4\) Hz, 3H); \(^{13}\text{C-NMR (101 MHz, CDCl}_3\) \(\delta\) 203.0, 179.1* 173.2*, 171.3*, 88.9*, 61.3, 59.9*, 49.3, 43.1, 35.1, 31.8, 29.4, 29.3, 29.2, 29.0, 26.2, 23.5, 22.7, 14.1; \text{IR (thin film, cm}^{-1}\) 3477, 2041, 1789, 1688, 1612, 1498, 1398, 1378, 1270, 1155, 1103, 1098, 1001, 857; \text{HR-ESI calcd for C}_{14}H_{27}O_3 [M-H]^+ 243.1955, found 243.1949.

Ethyl 3-oxo-3-(pyridin-3-yl)propanoate (Substrate Table 16, Entry 13)

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{O} & \quad \text{Et}
\end{align*}
\]

\(^1\text{H-NMR (2:1 mixture of keto- and enol-tautomer, asterisk denotes enol-tautomer, 400 MHz, CDCl}_3\) \(\delta\) 12.55* (s, 1H), 9.15 (dd, \(J = 2.3\), 0.7 Hz, 2H), 9.01 – 8.97* (m, 1H), 8.81 (dt, \(J = 5.7\), 2.8 Hz, 1H), 8.68* (dd, \(J = 4.8\), 1.6 Hz, 1H), 8.24 (ddd, \(J = 8.0\), 2.2, 1.8 Hz, 2H), 8.08 – 8.03* (m, 1H), 7.48 – 7.42 (m, 1H), 7.39 – 7.33* (m, 1H), 5.70* (s, 1H), 4.28* (q, \(J = 7.1\) Hz, 2H), 4.22 (q, \(J = 7.1\) Hz, 2H), 4.00 (s, 4H), 1.34* (t, \(J = 7.1\) Hz, 3H), 1.26 (t, \(J = 7.1\) Hz, 3H); \(^{13}\text{C-NMR (101 MHz, CDCl}_3\) \(\delta\) 191.4, 172.8*, 168.8*, 166.8, 154.1, 151.8*, 150.0, 147.5*, 135.8, 133.4*, 131.4, 129.4*, 123.7, 123.4*, 88.7*, 61.8,
60.6*, 46.0, 14.2*, 14.0; **IR (thin film, cm\(^{-1}\))** 3430, 2088, 1734, 1652, 1586, 1475, 1420, 1326, 1271, 1148, 1095, 1081, 1021, 802; **HR-ESI** calcd for C\(_{10}\)H\(_{12}\)NO\(_3\) [M-H]\(^+\) 194.0812, found 194.0803.

**Ethyl 3-(furan-2-yl)-3-oxopropanoate (Substrate Table 16, Entry 14)**

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\end{align*}
\]

\(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta 7.61\) (dd, \(J = 1.7, 0.7\) Hz, 1H), \(7.27\) (dd, \(J = 3.6, 0.7\) Hz, 1H), \(6.57\) (dd, \(J = 3.6, 1.7\) Hz, 1H), \(4.21\) (q, \(J = 7.1\) Hz, 2H), \(3.85\) (s, 2H), \(1.26\) (t, \(J = 7.1\) Hz, 3H); \(^13\)C-NMR (101 MHz, CDCl\(_3\)) \(\delta 181.1, 167.0, 152.0, 147.0, 118.3, 112.7, 61.5, 45.5, 14.1\). All other spectroscopic data were in agreement with the literature.\(^{115}\)

**GP12: Transfer hydrogenation of β-Ketoesters**

The α-ketoester (1 mmol, 1.0 eq) and \(\{\text{Cp}^*\text{Ir}(\text{R,R})-\text{Ms-DPEN})(\text{H}_2\text{O})\}(\text{SO}_4)\) (0.02 mmol, 2.0 mol %) were combined in a glass vial, followed by addition of an aqueous formic acid solution (1.0 M formate soln., pH = 8.0, 0.2 M overall concentration). The reaction mixture was stirred at ambient temperature for 24 h. The reaction mixture was then extracted with CH\(_2\)Cl\(_2\) (3x) from H\(_2\)O and dried over MgSO\(_4\). The organic phase was then filtered, concentrated and purified over a short plug of silica (Et\(_2\)O). The β-hydroxyester products were analyzed by standard spectroscopic methods and found to be in agreement with the literature reported values for all known compounds. Enantiomeric excess was determined by chiral SFC.
**Experimental Section**

(R)-Ethyl 3-hydroxy-3-phenylpropanoate (Product Table 16, Entry 1)

![Chemical structure](image)

Synthesized according to GP12.

96% Yield, ee = 96% (SFC: I-A, 200 nm, CO$_2$:MeOH = 95:5, flow rate 2 ml/min, $t_{(major)}$ = 6.7 min, $t_{(minor)}$ = 7.9 min).

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.42 – 7.33 (m, 4H), 7.32 – 7.26 (m, 1H), 5.19 – 5.09 (m, 1H), 4.19 (q, $J$ = 7.1 Hz, 3H), 3.30 – 3.21 (m, 1H), 2.84 – 2.64 (m, 2H), 1.27 (t, $J$ = 7.1 Hz, 3H); $^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 172.4, 142.5, 128.6, 127.8, 125.7, 70.3, 60.9, 43.3, 14.1. **Optical rotation:** $[\alpha]_D^{25} = +53.6^\circ$ (c = 1.2, CHCl$_3$) Lit.$^{116}$ $[\alpha]_D^{25} = -51^\circ$ (c = 1.5, CHCl$_3$), ($S$)-enantiomer). All other spectroscopic data were in agreement with the literature.$^{116}$

(R)-Ethyl 3-(4-fluorophenyl)-3-hydroxypropanoate (Product Table 16, Entry 2)

![Chemical structure](image)

Synthesized according to GP12.

95% Yield, ee = 94% (SFC: I-A, 200 nm, CO$_2$:MeOH = 95:5, flow rate 2 ml/min, $t_{(major)}$ = 5.7 min, $t_{(minor)}$ = 6.3 min).

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.46 – 7.31 (m, 2H), 7.11 – 6.98 (m, 2H), 5.21 – 5.05 (m, 1H), 4.19 (q, $J$ = 7.2 Hz, 2H), 3.33 (d, $J$ = 3.4 Hz, 1H), 2.79 – 2.62 (m, 2H), 1.26 (t, $J$ = 7.2 Hz, 2H); $^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 172.3, 163.4 (d, $J$ = 242.1 Hz), 138.2 (d, $J$

---

3.0 Hz), 127.4 (d, J = 8.2 Hz), 115.4 (d, J = 21.6), 69.7, 61.0, 43.3, 14.1. All other spectroscopic data were in agreement with the literature.\(^{117}\)

(R)-Ethyl 3-(4-chlorophenyl)-3-hydroxypropanoate (Product Table 16, Entry 3)

```
\begin{center}
\includegraphics[width=0.2\textwidth]{chlorophenyl.png}
\end{center}
```

Synthesized according to GP12.

94% Yield, ee = 92% (SFC: I-A, 200 nm, CO\(_2\):MeOH = 95:5, flow rate 2 ml/min, \(t_{(\text{major})} = 9.6\) min, \(t_{(\text{minor})} = 11.6\) min).

\(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.32 (s, 1H), 5.15 – 5.05 (m, 1H), 4.18 (q, \(J = 7.1\) Hz, 1H), 3.36 (d, \(J = 3.5\) Hz, 1H), 2.80 – 2.60 (m, 1H), 1.27 (t, \(J = 7.1\) Hz, 1H); \(^{13}\)C-NMR (101 MHz, CDCl\(_3\)) \(\delta\) 172.3, 141.0, 133.5, 128.7, 127.1, 69.6, 61.0, 43.2, 14.1. All other spectroscopic data were in agreement with the literature.\(^{117}\)

(R)-Ethyl 3-(4-bromophenyl)-3-hydroxypropanoate (Product Table 16, Entry 4)

```
\begin{center}
\includegraphics[width=0.2\textwidth]{bromophenyl.png}
\end{center}
```

Synthesized according to GP12.

91% Yield, ee = 78% (SFC: I-A, 200 nm, CO\(_2\):MeOH = 95:5, flow rate 2 ml/min, \(t_{(\text{major})} = 13.4\) min, \(t_{(\text{minor})} = 16.7\) min).

Experimental Section

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.51 – 7.45 (m, 2H), 7.30 – 7.22 (m, 2H), 5.14 – 5.04 (m, 1H), 4.19 (q, $J = 7.2$ Hz, 2H), 3.37 (d, $J = 3.5$ Hz, 1H), 2.78 – 2.63 (m, 2H), 1.26 (t, $J = 7.2$ Hz, 3H); $^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 172.3, 141.5, 131.6, 127.4, 121.6, 69.7, 61.0, 43.1, 14.1. All other spectroscopic data were in agreement with the literature.$^{117}$

**(R)-Ethyl 3-(4-iodophenyl)-3-hydroxypropanoate (Product Table 16, Entry 5)**

![Structure](image)

Synthesized according to GP12.

96% Yield, ee = 96% (SFC: I-A, 200 nm, CO$_2$:MeOH = 95:5, flow rate 2 ml/min, $t_{(major)} = 6.7$ min, $t_{(minor)} = 7.9$ min);

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.41 – 7.33 (m, 3H), 7.32 – 7.26 (m, 1H), 5.20 – 5.10 (m, 1H), 4.19 (q, $J = 7.1$ Hz, 2H), 3.29 – 3.22 (m, 1H), 2.82 – 2.66 (m, 2H), 1.27 (t, $J = 7.1$ Hz, 3H); $^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 172.4, 142.5, 128.6, 127.8, 125.7, 70.3, 60.9, 43.3, 14.1; IR (thin film, cm$^{-1}$) 3566, 2978, 2360, 2340, 1907, 1732, 1733, 1716, 1700, 1682, 1652, 1634, 1558, 1538, 1520, 1506, 1486, 1436, 1220, 1006, 772; HR-MALDI calcd for C$_{11}$H$_{13}$INaO$_3$ [M-Na]$^+$ 342.9802, found 342.9790; Optical rotation: $[\alpha]$$_D^{24}$ +31.0° ($c = 1.1$, CHCl$_3$);

**(R)-Ethyl 3-(3-chlorophenyl)-3-hydroxypropanoate (Product Table 16, Entry 6)**

![Structure](image)

Synthesized according to GP12.
92% Yield, ee = 94% (SFC: I-A, 200 nm, CO$_2$:MeOH = 95:5, flow rate 2 ml/min, $t_{(major)}$ = 7.7 min, $t_{(minor)}$ = 9.2 min).

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.41 – 7.38 (m, 1H), 7.34 – 7.22 (m, 4H), 5.17 – 5.06 (m, 1H), 4.19 (q, $J$ = 7.1 Hz, 2H), 3.39 (dd, $J$ = 3.5, 2.1 Hz, 1H), 2.77 – 2.66 (m, 2H), 1.27 (t, $J$ = 7.1 Hz, 3H); $^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 172.2, 144.5, 134.5, 129.8, 127.9, 125.9, 123.8, 69.7, 61.0, 43.1, 14.1. All other spectroscopic data were in agreement with the literature.

$(R)$-Ethyl 3-(2-chlorophenyl)-3-hydroxypropanoate (Product Table 16, Entry 7)

![Structure of $(R)$-Ethyl 3-(2-chlorophenyl)-3-hydroxypropanoate]

Synthesized according to GP12.

97% Yield, ee = 70% (SFC: I-A, 200 nm, CO$_2$:MeOH = 95:5, flow rate 2 ml/min, $t_{(major)}$ = 5.7 min, $t_{(minor)}$ = 6.4 min).

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.63 (dd, $J$ = 7.7, 1.7 Hz, 1H), 7.36 – 7.28 (m, 2H), 7.22 (td, $J$ = 7.6, 1.7 Hz, 1H), 5.49 (dt, $J$ = 9.6, 3.1 Hz, 1H), 4.21 (q, $J$ = 7.1 Hz, 2H), 3.55 (d, $J$ = 3.6 Hz, 1H), 2.86 (dd, $J$ = 16.6, 2.7 Hz, 1H), 2.59 (dd, $J$ = 16.6, 9.6 Hz, 1H), 1.28 (t, $J$ = 7.1 Hz, 3H); $^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 172.6, 139.8, 131.4, 129.4, 128.7, 127.2, 127.1, 67.1, 61.0, 41.3, 14.1. All other spectroscopic data were in agreement with the literature.

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Experimental Section

(R)-Ethyl 3-(4-methoxyphenyl)-3-hydroxypropanoate (Product Table 16, Entry 8)

\[
\text{MeO} \quad \text{OH} \quad \text{OEt}
\]

Synthesized according to GP12.

95% Yield, ee = 97% (SFC: I-A, 200 nm, CO\textsubscript{2}:MeOH = 95:5, flow rate 2 ml/min, t\textsubscript{major} = 6.8 min, t\textsubscript{minor} = 8.5 min).

\textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.35 – 7.28 (m, 2H), 6.94 – 6.84 (m, 2H), 5.09 (dt, \(J\) = 9.1, 3.6 Hz, 1H), 4.18 (q, \(J\) = 7.2 Hz, 2H), 3.80 (s, 2H), 3.15 (d, \(J\) = 3.4 Hz, 1H), 2.76 (dd, \(J\) = 16.3, 9.1 Hz, 1H), 2.68 (dd, \(J\) = 16.3, 3.8 Hz, 1H), 1.27 (t, \(J\) = 7.2 Hz, 2H); \textsuperscript{13}C-NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) 172.5, 159.2, 134.7, 127.0, 113.9, 70.0, 60.8, 55.3, 43.3, 14.2. All other spectroscopic data were in agreement with the literature.\textsuperscript{117}

(R)-Ethyl 3-(4-nitrophenyl)-3-hydroxypropanoate (Product Table 16, Entry 9)

\[
\text{O}_2\text{N} \quad \text{OH} \quad \text{OEt}
\]

Synthesized according to GP12.

99% Yield, ee = 87% (SFC: I-A, 200 nm, CO\textsubscript{2}:MeOH = 95:5, flow rate 2 ml/min, t\textsubscript{major} = 3.7 min, t\textsubscript{minor} = 4.4 min).

\textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 8.26 – 8.20 (m, 2H), 7.61 – 7.52 (m, 2H), 5.23 (dt, \(J\) = 8.1, 3.8 Hz, 1H), 4.20 (q, \(J\) = 7.1 Hz, 2H), 3.63 (d, \(J\) = 3.6 Hz, 1H), 2.82 – 2.63 (m, 1H), 1.28 (t, \(J\) = 7.1 Hz, 3H); \textsuperscript{13}C-NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) 172.0, 149.6, 147.5, 126.5,
123.8, 69.4, 61.3, 42.9, 14.1. All other spectroscopic data were in agreement with the literature.\textsuperscript{119}

\textbf{(R)-Ethyl 3-hydroxy-3-(naphthalen-2-yl)propanoate (Product Table 16, Entry 10)}

\begin{center}
\includegraphics[width=1in]{figure1}
\end{center}

Synthesized according to GP12.

96% Yield, ee = 94 % (SFC: I-A, 200 nm, CO\textsubscript{2}:MeOH = 95:5, flow rate 3 ml/min, \(t_{(\text{major})}\) = 12.7 min, \(t_{(\text{minor})}\) = 15.2 min);

\textbf{\textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3})} \(\delta\) 7.90 – 7.77 (m, 1H), 7.58 – 7.42 (m, 1H), 5.31 (dt, \(J = 8.1, 4.0\) Hz, 1H), 4.20 (q, \(J = 7.1\) Hz, 1H), 3.39 (d, \(J = 3.5\) Hz, 1H), 2.97 – 2.71 (m, 1H), 1.27 (t, \(J = 7.1\) Hz, 1H); \textbf{\textsuperscript{13}C-NMR (101 MHz, CDCl\textsubscript{3})} \(\delta\) 172.4, 139.9, 133.3, 133.0, 128.4, 128.0, 127.7, 126.2, 126.0, 124.5, 123.7, 70.4, 60.9, 43.3, 14.2. All other spectroscopic data were in agreement with the literature.\textsuperscript{120}

\textbf{(R)-Ethyl 3-hydroxydodecanoate (Substrate Table 16, Entry 12)}

\begin{center}
\includegraphics[width=1in]{figure2}
\end{center}

97 % yield, ee = 7 % (GC: BGB 176/SE, (70 °C, 1.0 °C/min until 210 °C), \(t_{(\text{major})}\) = 85.7 min, \(t_{(\text{minor})}\) = 86.4 min);

\textbf{\textsuperscript{1}H-NMR (4:1 mixture of keto- and enol-tautomer, asterisk denotes enol-tautomer, 400 MHz, CDCl\textsubscript{3})} \(\delta\) 12.10\textsuperscript{*} (s, 1H), 4.97\textsuperscript{*} (s, 1H), 4.19 (q, \(J = 5.4\) Hz, 2 H), 4.18\textsuperscript{*} (q, \(J =


5.1 Hz, 2 H), 3.42 (s, 2H), 2.53 (m, 2H), 2.18* (m, 2H), 1.69 – 1.51* (m, 4H), 1.69 – 1.51 (m, 4H), 1.40 – 1.21* (m, 15H), 1.40 – 1.21 (m, 15H), 0.87* (t, J = 5.1 Hz, 24H); 0.87 (t, J = 5.4 Hz, 24H); 13C-NMR (101 MHz, CDCl3) δ 173.2, 68.0, 60.7, 41.3, 36.5, 31.9, 29.6, 29.5, 29.3, 25.5, 22.7, 14.2, 14.1; IR (thin film, cm⁻¹) 3399, 2102, 1768, 1655, 1499, 1447, 1401, 1378, 1251, 1121, 1103, 1081, 1019, 804; HR-ESI calcd for C14H28NaO3 [M-Na]⁺ 267.1931, found 267.1928.

(R)-Ethyl 3-hydroxy-3-(pyridin-3-yl)propanoate (Product Table 16, Entry 13)

Synthesized according to GP12.

77% Yield, ee = 73% (SFC: I-B, 200 nm, CO2:MeOH = 95:5, flow rate 2 ml/min, tₘᵣᵢₙᵢₙ = 8.7 min, tₘᵢₐᵢᵢᵢᵢᵢᵢᵢₙ = 9.2 min);

1H-NMR (400 MHz, CDCl₃) δ 8.60 (d, J = 2.2 Hz, 1H), 8.53 (dd, J = 4.8, 1.6 Hz, 1H), 7.79 – 7.72 (m, 1H), 7.29 (ddd, J = 7.9, 4.8, 0.6 Hz, 1H), 5.18 (dd, J = 8.1, 4.6 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.70 (s, 1H), 2.84 – 2.67 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H); 13C-NMR (101 MHz, CDCl₃) δ 172.1, 149.2, 147.6, 137.9, 133.5, 123.5, 68.1, 61.1, 42.9, 14.1; IR (thin film, cm⁻¹) 3628, 2986, 1738, 1700, 1682, 1668, 1634, 1580, 1558, 1538, 1506, 1480, 1456, 1418, 1374, 1220, 1038, 949; HR-MALDI calcd for C10H13NNaO3 [M-Na]⁺ 218.0788, found 218.0791; Optical rotation: [α]D²⁴ +31.9° (c = 1.0, CHCl₃).
(R)-Ethyl 3-(furan-2-yl)-3-hydroxypropanoate (Product Table 16, Entry 14)

Synthesized according to GP12.

77% Yield, ee = 96% (SFC: I-A, 200 nm, CO₂:MeOH = 95:5, flow rate 2 ml/min, t<sub>(major)</sub> = 5.7 min, t<sub>(minor)</sub> = 6.4 min);

<sup>1</sup>H-NMR (400 MHz, CDCl₃) δ 7.38 (dd, J = 1.8, 0.8 Hz, 1H), 6.34 (dd, J = 3.2, 1.8 Hz, 1H), 6.30 – 6.27 (m, J = 3.3 Hz, 1H), 5.14 (dt, J = 8.8, 4.5 Hz, 1H), 4.20 (q, J = 7.2 Hz, 3H), 3.21 (dd, J = 5.0, 3.3 Hz, 1H), 2.91 (dd, J = 16.5, 8.5 Hz, 1H), 2.83 (dd, J = 16.5, 4.1 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H); <sup>13</sup>C-NMR (101 MHz, CDCl₃) δ 172.0, 154.7, 142.2, 110.2, 106.3, 64.2, 61.0, 39.8, 14.1. All other spectroscopic data were in agreement with the literature.<sup>121</sup>

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Curriculum Vitae

Born February 26, 1983 in Kilchberg, Switzerland.

              Title: Asymmetric Transfer Hydrogenation Reactions of Carbonyl
              Compounds using Ir(III) Catalysts and Formic Acid as Hydrogen
              Source
9/2006 – 11/2010 Ph.D. in the group of Prof. E.M. Carreira, ETH Zürich
              Title: Iridium Catalyzed Reactions: Allylic Amination using
              Sulfamic Acid and Asymmetric Transfer Hydrogenation using
              Formic Acid

During my Ph.D. studies I was teaching assistant for three organic chemistry laboratory
courses and teaching assistant for two organic chemistry lectures.

Zürich, October 2010                                           Martin Ariger
5 Appendix: NMR Spectra of New Compounds
Iridium-Catalyzed Reactions
Iridium-Catalyzed Reactions

[Chemical structure image]

[Chemical structure image]

[Chemical structure image]
Appendix

Sample AM-975.1
Group name:
PRO CDCl3 /opt/earige 36

Sample AM-975.1-13C
Group name:
CARS CDCl3 29/40 range 36
Iridium-Catalyzed Reactions

Sample AM-977.1
group name
Pro MeOD (top) vs. time 51

Sample AM-977.1-13C
group name
Catalyst MeOD (top) vs. time 51
[Sample AM-975.1

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PRO METHOD /opt/earige 52

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(SO₄)²⁻
Appendix

SAMPLE: DEC & VT
solvent: CDCl3
dec. temp.: 293 K
NMR: 600 MHz
spectra: 1H NMR
shifts: 6.0 6.5 7.0 7.5 8.0
f1 (ppm): 0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5

M. Aigner/Carreira AH-88310010-02
ISO PED 2.1 NMR
Iridium-Catalyzed Reactions
Iridium-Catalyzed Reactions
Iridium-Catalyzed Reactions
Iridium-Catalyzed Reactions
Iridium-Catalyzed Reactions
Iridium-Catalyzed Reactions
Iridium-Catalyzed Reactions
Appendix
Iridium-Catalyzed Reactions
Iridium-Catalyzed Reactions
Iridium-Catalyzed Reactions
Iridium-Catalyzed Reactions
Iridium-Catalyzed Reactions

[Chemical Structures]

[1H-NMR Spectra]

[19-12-DB-ename]
Sample AM-357-1H
group.carnes
PRO CDCl3 (pa/pa enzime 19)
Iridium-Catalyzed Reactions
Appendix

25-12-06-9912
Sample: AM-981-1H
group carre
PRO COCO (ppm) range 25

25-12-06-9912
Sample: AM-981-1H
group carre
CAK COCO (ppm) range 25
Iridium-Catalyzed Reactions
Appendix
Iridium-Catalyzed Reactions
Appendix

$^\text{1}H$ NMR spectra
Sample: AM-13a-1H
group carriage
Pro-NHCl (top) / enrage 7

$^\text{13}C$ NMR spectra
Sample: AM-13b-13C
group carriage
CaH-NHCl (top) / enrage 7
54-06-26-estige
Sample AM-1350-1H
group.carre
PRO CDCl3 /op/c estige 54

54-06-26-estige
Sample AM-1350-13C
group.carre
CAR CDCl3 /op/c estige 54
Iridium-Catalyzed Reactions
Iridium-Catalyzed Reactions