Enantioselective C–H Insertion Reactions of Donor–Donor Carbenoids

**Significance:** Transition-metal carbenoids, which can be generated in situ from a variety of different precursors, demonstrate a diverse range of reactivity, such as the ability to perform allylic and benzylic C–H functionalizations (see Review below). While the use of acceptor–acceptor and donor–acceptor metal carbenoids is commonplace, the application of donor–donor metal carbenoids in a diastereo- and enantioselective C–H functionalization has not been previously demonstrated. Herein, Shaw and co-workers report the first Rh-catalyzed asymmetric insertion reactions of donor–donor carbenoids, which provide access to substituted dihydrobenzofurans.

**Comment:** The donor–donor rhodium carbenoid is generated in situ from the corresponding hydrazine in the presence of MnO₂. The methodology demonstrates a broad substrate scope, with a variety of functional groups tolerated on the benzylic or allylic ether as well as on the hydrazine motif. Allylic ethers containing a 1,2-disubstituted olefin do not undergo E/Z-isomerization under the reaction conditions. To demonstrate the utility of the method, an enantioselective total synthesis of E-[δ-viniferin was achieved.

Enantioselective Rhodium-Catalyzed Allylation of 2-Pyridones

Significance: Enantioenriched N-substituted 2-pyridones are an important class of biologically active molecules. Their synthesis has been described starting from chiral electrophiles (Y.-Q. Fang et al. J. Am. Chem. Soc. 2010, 132, 15525) and chiral amines (Y. Yu et al. J. Nat. Prod. 2013, 76, 2226). The authors report a chiral allylation strategy beginning from 2-pyridones and allenes.

Comment: Almost all substrates preferred N-allylation over O-allylation, except the 5-iodopyridone substrate. A 1:1 mixture of N/O-allylated products was observed in this case. Substitution on the allene component was also tolerated, including a tertiary alcohol. A decrease in N/O selectivity was observed for the substrate with a phthalamido group.
Palladium-Catalyzed Nucleophilic Allylation of Aldehydes or Aldimines

**Significance:** Ring-expansion reactions of vinylcyclopropanes are powerful tools for organic synthesis. The authors describe the palladium-catalyzed nucleophilic allylation of aldehyde and aldmines with vinylcyclopropane in the presence of dimethylzinc.

**Comment:** The allylation of aldehydes with vinylcyclopropane and diethylzinc proceeded to provide homoallyl alcohols with *anti* stereoselectivity. Aldimines prepared from aldehyde and primary amines in situ underwent a similar allylation to give homoallylamines with *syn* stereoselectivity. The products can be converted by reaction with a tetracnuclear zinc cluster into *γ*-vinyl-*δ*-valerolactons and *γ*-vinyl-*δ*-valerolactams. The transformation is useful for the efficient synthesis of bioactive molecules.
Enantioselective Rhodium-Catalyzed Synthesis of Axially Chiral Biaryls

**Significance:** Several bioactive molecules contain an axially chiral biaryl subunit. Although several methods exist for their synthesis, the use of direct C–H functionalization is less well studied. The authors present a rhodium-catalyzed dehydrogenative Heck coupling to produce axially chiral biaryls using the Cramer complex.

**Comment:** The substrate scope showed variability in the aza biaryl starting material and the olefin coupling partner. The products were shown to be competent in rhodium-catalyzed 1,4-additions to cyclohexenone with phenylboronic acid, producing the adduct in up to 77% yield and with 68% ee.
CuH-Catalyzed Enantioselective Anti-Markovnikov Hydroamination

**Significance:** β-Chiral amines are ubiquitous motifs in a range of biologically active molecules, including pharmaceuticals and natural products. The catalytic enantioselective hydroamination of alkenes provides an efficient route to such molecules using simple, and often commercially available, starting materials. Herein, Buchwald and co-workers present an enantioselective CuH-catalyzed anti-Markovnikov hydroamination of 1,1-disubstituted alkenes.

**Comment:** The report expands upon the authors’ previous work on the Cu-catalyzed enantioselective hydroamination of styrene derivatives (J. Am. Chem. Soc. 2013, 135, 15746). The proposed mechanism involves hydrocupration of the 1,1-disubstituted olefin in an anti-Markovnikov manner, which is intercepted by the hydroxylamine ester to give the final product and a Cu(I) alkoxide complex. The active CuH catalyst is regenerated by the addition of stoichiometric amounts of hydroxysilane.

**Selected examples:**

- [1] 88% yield; 95% ee
- [2] 91% yield; 99% ee
- [3] 96% yield; 90% ee
- [4] 90% yield; 96% ee
- [5] 91% yield; 99% ee
- [6] 96% yield; 90% ee
- [7] 90% yield; 96% ee

**Proposed mechanism:**

The reaction is catalyzed by CuH, which is generated from Cu(OAc)₂ and (R)-DTBM-SEGPHOS. The hydroamination reaction occurs with high enantioselectivity, and the products are obtained with up to 99% yield and 99% ee.
Zirconium/VANOL-Catalyzed Asymmetric α-Iminol Rearrangement

Significance: There has been no example of asymmetric α-iminol rearrangement so far. Herein, the authors developed an effective catalyst system, a zirconium/VANOL complex, which works well not only with α-iminols as starting material, but also with in situ generated α-iminols from an aldehyde and an aniline.

Comment: The zirconium/VANOL catalyst affords excellent yields and enantioselectivities for a broad range of substrates. Interestingly, N-methyl imidazole coordinated to zirconium dramatically influences the reaction. When there is a para-CF₃ substituent on the phenyl ring, more careful manipulations are required such as inert atmosphere and deoxygenation.
Isomerization of Allylrhodium Intermediates During Allylations of Imines

Significance: The authors present a 1,4-rhodium(I) migration of allylrhodium species which then react with cyclic imines to yield the allylation product with three stereochemical elements with high selectivity. Using a chiral diene–rhodium catalyst the reaction can be performed enantioselectively. The significance of this work is the generation of stereochemically more complex products from simple starting material through rhodium(I)-catalyzed isomerization processes.

Comment: The reaction is favored in combination of two factors: 1) the steric hindrance of the initially formed allylrhodium species, and 2) the reactivity of the imine such that normal allylation is disfavored. Through the deuterium-labeling experiments it is proposed that the 1,4-rhodium(I) migration (3a → 3b) occurs by a C–H oxidative addition–reductive elimination sequence via intermediate I.

SYNFACTS Contributors: Hisashi Yamamoto, Biglab Maji
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DOI: 10.1055/s-0034-1379753; Reg-No.: H15914SF
Asymmetric Conjugate Addition of Dimethylzinc to (Z)-Nitroalkenes

Significance: Asymmetric conjugate addition of organometallic species to nitroalkenes can be an efficient way to access all-carbon quaternary stereocenters. Herein, the authors demonstrate that the use of [(MeCN)₄Cu]PF₆ plays a crucial role in the asymmetric conjugate addition of dimethylzinc to (Z)-nitroalkenes with the Hoveyda ligand.

Comment: With the reported conditions, the undesired nitroalkene isomerization, resulting in low enantioselectivity, has been solved. The authors also developed a practical and highly controlled method for the synthesis of (Z)-nitroalkenes (Z/E ratio ≥ 99:1).

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Asymmetric Synthesis of Ferrocenes via Palladium-Catalyzed C–H Bond Activation

Significance: The authors report a highly enantioselective route to the synthesis of 2-acyl-1-dimethylaminomethylferrocene derivatives with planar chirality via a palladium-catalyzed asymmetric C–H bond activation using monoprotected amino acids as chiral ligands.

Comment: Due to their important role in promoting various asymmetric catalyzed reactions, 2-acyl-1-dimethylaminomethylferrocene derivatives with planar chirality were provided under one-pot reaction conditions in moderate to good yields and with excellent enantioselectivities via a palladium-catalyzed direct acylation of ferrocene.
Rhodium-Catalyzed Enantioselective Hydrogenation of Enamido Esters

**Significance:** Lv, Zhang and colleagues present a rhodium-catalyzed asymmetric hydrogenation of \( \alpha \)-acetoxy \( \beta \)-enamido esters. A series of chiral \( \alpha \)-hydroxy-\( \beta \)-amino acid derivatives were prepared in high yields (up to 98%) with excellent enantioselectivities (up to 97% ee).

**Comment:** \([\text{Rh(nbd)}(\text{L})]\text{BF}_4\) (5 mol%) is found to be an effective catalyst for the enantioselective hydrogenation of tetrasubstituted enamides. The synthetic utility of this method is demonstrated by the synthesis of biologically important molecules.
Divergent Reactivity of 2-Triazole Benzaldehydes under Rhodium Catalysis

**Significance:** *N*-Sulfonyl 1,2,3-triazoles can serve as convenient diazo compound precursors, when reacted with a suitable rhodium(II) catalyst. In the present report, the authors present the reaction of 2-triazole benzaldehydes and 2-triazole alkylaryl ketones with water and alcohols. The products generated are either valuable 2-amino-3-hydroxylindanones or dihydroisobenzofurans.

**Comment:** To support the existence of an oxoni-um intermediate, the starting triazole was reacted with the rhodium catalyst for two hours in the absence of nucleophiles. Upon addition of water, alcohol and Sc(OTf)₃, products arising from paths A and B were formed in comparable yield, suggesting the presence of this common intermediate.
Cobalt-Catalyzed Asymmetric Hydroboration of Alkenes

**Significance:** A cobalt-catalyzed asymmetric hydroboration of 1,1-disubstituted aryl alkenes is presented. A series of chiral α-alkyl-β-pinacolato-boranes were prepared with exclusive regioselectivities in high yields (up to 98%) with excellent enantoiselectivities (up to 99.5% ee).

**Comment:** Novel iminopyridine-oxazoline (IPO) ligands are found to be highly efficient in the enantioselective hydroboration of alkenes under cobalt catalysis. The synthetic utility of this method is demonstrated by the synthesis of naproxen.

**Synthesis of naproxen:**

1. Hydroboration of 2-methylbut-2-ene with HBpin (1 equiv) and (R)-1 (0.5 mol%) in THF, r.t., 1.5 h. Products are isolated in 95% yield and 98% ee.

2. Oxidation of the obtained alcohols with 30% H₂O₂ and THF, r.t., 0.5 h. Products are isolated in 95% yield and 98% ee.

3. Cleavage of the pinacolato groups with NaClO₂ and NaH₂PO₄ in CH₂Cl₂, r.t., 1 h. Products are isolated in 91% yield and 98% ee.

4. Final steps involve condensation with 2-methylbut-2-ene, oxidation with NaClO₂ and NaH₂PO₄, and hydrolysis with t-BuOH, H₂O, r.t., 1 h. Products are isolated in 91% yield and 98% ee.
Asymmetric Reduction of α-Amino Ketones Catalyzed by Lewis Acids

**Significance:** The authors developed a metal-catalyzed asymmetric reduction of α-amino ketones using KBH$_4$ as hydride source. Under mild conditions, desired amino alcohols are obtained with high enantioselectivities.

**Comment:** β-Amino alcohols are important structural motif in natural or pharmaceutical compounds. The authors also presented a gram-scale version of this reaction and its possible transition state.

**R**$_1$H
\[\text{KBH}_4 \text{aq (0.6 equiv)} \quad \text{ligand (8 mol%)} \quad \text{Ni(OTf)}_2 \text{ (8 mol%)} \]
\[
\text{THF–CH}_2\text{Cl}_2 \quad \text{–20 to 0 °C, 24 h}
\]

**Selected examples:**

<table>
<thead>
<tr>
<th>R$_2$</th>
<th>OH</th>
<th>NH$_2$HCl</th>
<th>R$_1$H</th>
<th>OH</th>
<th>NH$_2$HCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>98% yield 92% ee</td>
<td>(with 12 mol% of catalyst)</td>
<td>Ph</td>
<td>95% yield 92% ee</td>
<td></td>
</tr>
<tr>
<td>MeO</td>
<td>80% yield 85% ee</td>
<td></td>
<td>MeO</td>
<td>65% yield 90% ee</td>
<td></td>
</tr>
<tr>
<td>MeO</td>
<td>98% yield 92% ee</td>
<td></td>
<td>MeO</td>
<td>90% yield 77% ee</td>
<td></td>
</tr>
<tr>
<td>Cl</td>
<td>90% yield 97% ee</td>
<td></td>
<td>Cl</td>
<td>90% yield 74% ee</td>
<td></td>
</tr>
</tbody>
</table>

**Possible transition state:**

**SYNFACTS Contributors:** Hisashi Yamamoto, Yasushi Shimoda

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**DOI:** 10.1055/s-0034-1379749; **Reg-No.:** H15514SF
Chiral Furans via Asymmetric [3+2] Cycloaddition

Significance: Tetrahydrofurans and 2,5-dihydrofurans containing a stereocenter are often found in natural products and medicinal compounds. Ni(ClO$_4$)$_2$·6H$_2$O in the presence of an N,N’-dioxide ligand promotes the asymmetric [3+2] cycloaddition of alicylic epoxides with alkynes to give 2,5-dihydrofurans. A catalytic amount of LiNTf$_2$ was necessary to increase the yield of the cycloaddition process.

Comment: Notably, the asymmetric [3+2] cycloaddition of an alkene and an epoxide under optimized conditions afforded an optically active tetrahydrofuran derivative. According to the proposed activation model, the chiral nickel complex activates the epoxide to form a carbonyl ylide intermediate, through which the alkene attacks from the re face, leading to the R-configured product.
Nickel-Catalyzed Asymmetric Claisen Rearrangement

**Significance:** The authors present an asymmetric propargyl and allyl Claisen rearrangement using a readily available chiral N,N'-dioxide–nickel(II) complex. Product allyl and allenyl compounds were obtained with good yield and excellent enantio- and diastereoselectivities.

**Comment:** This rearrangement works with relatively inexpensive metal (nickel) under mild reaction conditions. The produced β-keto esters with all-carbon quaternary stereogenic centers with allenyl and allyl substituents are highly useful chiral building blocks.

**Selected examples:**

<table>
<thead>
<tr>
<th>Reaction Conditions</th>
<th>Product Structure</th>
<th>Yield</th>
<th>ee (%)</th>
<th>Diastereoselectivity (dr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L/Ni(OTf)₂ (1:1, 5–10 mol%) CH₂Cl₂, 35 °C 24–96 h</td>
<td><img src="image" alt="Product 1" /></td>
<td>88%</td>
<td>98% ee</td>
<td></td>
</tr>
<tr>
<td>L/Ni(BF₄)₂·6H₂O (1:1, 0.5–2 mol%) CH₂Cl₂, 35 °C 1–48 h</td>
<td><img src="image" alt="Product 2" /></td>
<td>91%</td>
<td>98% ee</td>
<td></td>
</tr>
<tr>
<td>L/Ni(OTf)₂ (1:1, 5–10 mol%) CH₂Cl₂, 35 °C 24–96 h</td>
<td><img src="image" alt="Product 3" /></td>
<td>86%</td>
<td>97% ee</td>
<td></td>
</tr>
<tr>
<td>L/Ni(OTf)₂ (1:1, 5–10 mol%) CH₂Cl₂, 35 °C 24–96 h</td>
<td><img src="image" alt="Product 4" /></td>
<td>86%</td>
<td>97% ee</td>
<td></td>
</tr>
</tbody>
</table>
| L/Ni(OTf)₂ (1:1, 5–10 mol%) CH₂Cl₂, 35 °C 24–96 h | ![Product 5](image) | 95% | 97% ee | dr = 45:55
| L/Ni(OTf)₂ (1:1, 5–10 mol%) CH₂Cl₂, 35 °C 24–96 h | ![Product 6](image) | 95% | 97% ee | dr = 99:1
| L/Ni(OTf)₂ (1:1, 5–10 mol%) CH₂Cl₂, 35 °C 24–96 h | ![Product 7](image) | 90% | 97% ee | dr = 98:2
| L/Ni(OTf)₂ (1:1, 5–10 mol%) CH₂Cl₂, 35 °C 24–96 h | ![Product 8](image) | 90% | 97% ee | dr = 99:1

**Stereochemical model:**

![Stereochemical model](image)
Synthesis of trans-Cycloalkenes via Cyclopropanation and Rearrangement


**Comment:** The reaction is initiated by the in situ formation of an α-imino rhodium carbenoid from triazole. Cyclopropanation of the exocyclic methylene group of leads to the formation of spirocyclopentane, which can then undergo a thermal rearrangement under microwave irradiation to give trans-cycloalkene. The authors propose a concerted mechanism, which draws similarity to the retro-Claisen [3,3]-sigmatropic rearrangement.

**Method A:**

1. $\text{Rh}_2(S\text{-NTTL})_4$ (2.5 mol%) $\rightarrow$ CHCl$_3$, MS, 40 °C
2. CHCl$_3$, 120 °C (microwave)

Substrate scope: Method A

<table>
<thead>
<tr>
<th>R$_1$</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>88</td>
<td>97</td>
</tr>
<tr>
<td>4-MeOC$_6$H$_4$</td>
<td>82</td>
<td>98</td>
</tr>
<tr>
<td>4-CF$_3$C$_6$H$_4$</td>
<td>91</td>
<td>97</td>
</tr>
<tr>
<td>2-Naph</td>
<td>88</td>
<td>96</td>
</tr>
<tr>
<td>3-thienyl</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>1-cyclohexenyl</td>
<td>83</td>
<td>98</td>
</tr>
</tbody>
</table>

**Method B:**

$\text{CuTC}$ (10 mol%), $\text{Rh}_2(S\text{-NTTL})_4$ (2.5 mol%) $\rightarrow$ CHCl$_3$, MS, 0 °C to r.t.

2. CHCl$_3$–MeOH (1:1), 100 °C, MW

93% yield 97% ee
Enantioselective Zr-Catalyzed Carboalumination Plus Cu-Catalyzed Cross-Coupling

**Significance:** Deuterium-labeled chiral compounds can be excellent tools for probing reaction mechanisms. Commonly used strategies for their synthesis include the use of chiral auxiliaries in stoichiometric quantities (J. Haesler et al. *Nature* 2007, 446, 526). The authors present an asymmetric zirconium-catalyzed carboalumination. Following ee upgrades by lipase treatment, deuterium was incorporated to generate cryptochiral molecules (G. Zhang et al. *J. Am. Chem. Soc.* 2006, 128, 6026).

**Comment:** The products of the zirconium-catalyzed reaction were produced in modest ee’s (80–88%), which were then upgraded to >99% ee by lipase treatment. Introduction of deuterium was accomplished by treatment with LiAlD₄ or via copper-catalyzed cross-coupling. The enantiomeric ratios were determined via Mosher’s method (see recent Review below).


**Examples:**

- 38% yield from alcohol 
  ≥99% ee  
  22% yield from alcohol ≥99% ee  
  22% yield from alcohol ≥99% ee  
  36% yield from silanol ≥99% ee  
  21% yield from silanol ≥99% ee  
  30% yield from silanol ≥99% ee  
  24% yield from silanol ≥99% ee  
  25% yield from silanol ≥99% ee

**Table:**

<table>
<thead>
<tr>
<th>Reaction Conditions</th>
<th>Yields</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zr catalyst (5 mol%), R₃Al (1 equiv), MAO or IBAO (1 equiv) in CH₂Cl₂ (0.67 M), 0 °C to r.t., overnight, then, I₂</td>
<td>≥99% ee</td>
<td>up to 75% yield</td>
</tr>
<tr>
<td>Zr catalyst (1–5 mol%), R₃Al (1 equiv), IBAO (1 equiv) in CH₂Cl₂ (0.4 M), 0 °C, 18 h then, O₂</td>
<td>80–88% ee</td>
<td>up to 78% yield</td>
</tr>
<tr>
<td>Amano lipase PS then LiAlD₄ or Li₂CuCl₄, CD₃Mgl</td>
<td>≥99% ee</td>
<td>up to 75% yield</td>
</tr>
<tr>
<td>Amano lipase PS then Ph₃P, imidazole, I₂ then CuCl₂, R₃MgX then TBAF</td>
<td>≥99% ee</td>
<td>5 examples</td>
</tr>
</tbody>
</table>
| Zr catalyst (5 mol%), R₃Al (1 equiv), MAO or IBAO (1 equiv) in CH₂Cl₂ (0.67 M), 0 °C to r.t., overnight, then, I₂ | 38% yield from alcohol | ≥99% ee  
  22% yield from alcohol ≥99% ee  
  22% yield from alcohol ≥99% ee  
  36% yield from silanol ≥99% ee  
  21% yield from silanol ≥99% ee  
  30% yield from silanol ≥99% ee  
  24% yield from silanol ≥99% ee  
  25% yield from silanol ≥99% ee |

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**Category:** Metal-Catalyzed Asymmetric Synthesis and Stereoselective Reactions

**Key words:** zirconium neomethylindenyl ligands cryptochirality
Nickel-Catalyzed Asymmetric Reductive Coupling of Vinyl and Benzyl Halides

Significance: The nickel-catalyzed reductive coupling of two organic electrophiles offers a unique synthetic approach to form C–C bonds (see Review below). Reisman and co-workers report an enantioselective Ni-catalyzed reductive coupling of vinyl bromides and racemic benzylic chlorides, giving rise to substituted alkenes bearing a chiral tertiary allylic center. Although transition-metal-catalyzed allylic alkylation methods using activated organometallic reagents can provide access to similar motifs, there are few regio- and enantioselective methods for the arylation of acyclic, unsymmetrical α,γ-disubstituted allylic electrophiles (for one recent example, see: S. Son, G. C. Fu J. Am. Chem. Soc. 2008, 130, 2756).

Comment: Using this method, a wide range of electron-rich and electron-deficient vinyl bromides and benzylic chlorides can be employed. Both meta and para substitution on the benzyl chloride component are well tolerated. However, ortho-substituted benzylic chloride derivatives demonstrate poor reactivity and lead to lower enantioselectivities. The coupled products are obtained in good to modest yields with generally high enantioselectivity. The use of β-substituted benzyl chlorides does not lead to any erosion in enantiomeric excess. Experiments using radical inhibitors or radical clocks are inconsistent with a radical chain mechanism.


A. H. CHERNEY, S. E. REISMAN* (CALIFORNIA INSTITUTE OF TECHNOLOGY, PASADENA, USA)
Nickel-Catalyzed Asymmetric Reductive Cross-Coupling Between Vinyl and Benzyl Electrophiles
Diastereo- and Enantioselective Iridium-Catalyzed Allylation of Ketone Enolates

**Significance:** The transition-metal-catalyzed asymmetric allylic alkylation (AAA) reaction is a versatile and powerful method for the construction of C–C bonds. Although palladium catalysts are routinely used in this reaction, iridium catalysts have been shown to have complementary and comparable reactivity to palladium (see Review below). Within this area of research, the diastereo- and enantioselective allylic alkylation of unstabilized ketone enolates remains a significant challenge. Herein, Hartwig and co-workers report a diastereo- and enantioselective iridium-catalyzed allylation of barium enolates derived from cyclic ketones.

**Comment:** The branched-selective allylic alkylation method developed by the authors provides access to products containing a vicinal quaternary and a tertiary stereogenic center—a difficult class of molecules to access using traditional Pd-catalyzed methods. The method is highly efficient and demonstrates a broad substrate scope. The authors show that good levels of diastereoselectivity can be achieved in this reaction simply through the facial selectivity of the prochiral barium enolate without necessitating coordination of the enolate directly to the metal center.


**Selected examples:**

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Yield</th>
<th>dr</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCH₂Me</td>
<td>OCO₂Me</td>
<td>92%</td>
<td>8:1</td>
<td>95%</td>
</tr>
<tr>
<td>OCH₂Me</td>
<td>OCO₂Me</td>
<td>92%</td>
<td>9:1</td>
<td>95%</td>
</tr>
<tr>
<td>OCH₂Me</td>
<td>OCO₂Me</td>
<td>81%</td>
<td>5:5:1</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>OCH₂Me</td>
<td>OCO₂Me</td>
<td>95%</td>
<td>12:1</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>OCH₂Me</td>
<td>OCO₂Me</td>
<td>95%</td>
<td>15:1</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>OCH₂Me</td>
<td>OCO₂Me</td>
<td>79%</td>
<td>6:1</td>
<td>98%</td>
</tr>
<tr>
<td>OCH₂Me</td>
<td>OCO₂Me</td>
<td>90%</td>
<td>6:1</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>OCH₂Me</td>
<td>OCO₂Me</td>
<td>80%</td>
<td>7:1</td>
<td>99%</td>
</tr>
<tr>
<td>OCH₂Me</td>
<td>OCO₂Me</td>
<td>79%</td>
<td>6:1</td>
<td>98%</td>
</tr>
<tr>
<td>OCH₂Me</td>
<td>OCO₂Me</td>
<td>90%</td>
<td>6:1</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>OCH₂Me</td>
<td>OCO₂Me</td>
<td>80%</td>
<td>7:1</td>
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</tr>
<tr>
<td>OCH₂Me</td>
<td>OCO₂Me</td>
<td>90%</td>
<td>6:1</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>OCH₂Me</td>
<td>OCO₂Me</td>
<td>80%</td>
<td>7:1</td>
<td>99%</td>
</tr>
</tbody>
</table>

**SYNFACTS Contributors:** Mark Lautens, Christine M. Le

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**Category:** Metal-Catalyzed Asymmetric Synthesis and Stereoselective Reactions

**Key words:** iridium phosphoramidites asymmetric allylic alkylation barium enolates
Enantioselective Allylation of Diphenylphosphine Oxide

**Significance:** Enantioselective reactions for the formation of C–P bonds have received less attention than other carbon-heteroatom bond-forming reactions. The phosphorus-containing products or their derivatives can be used as chiral ligands, for example. Zhao and co-workers describe here the enantioselective allylation of diphenylphosphine oxide and the racemic allylation of diisopropyl phosphonate. Related work by Togni and co-workers has been reported with diarylphosphines (Angew. Chem. Int. Ed. 2008, 47, 4878).

**Comment:** In the reaction with diphenylphosphine oxide, the products are formed in moderate to high yields, with enantiomeric excesses showing similar variation. Electron-poor substrates were superior partners, probably compensating for the low nucleophilicity of the phosphine oxide. The second reaction, which uses a different catalyst, shows a somewhat broader substrate scope.

**Reaction with diphenylphosphine oxide**

Selected examples:

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO(Ph)₂</td>
<td>95</td>
<td>97</td>
</tr>
<tr>
<td>PO(Ph)₂</td>
<td>92</td>
<td>90</td>
</tr>
<tr>
<td>PO(Ph)₂</td>
<td>92</td>
<td>90</td>
</tr>
<tr>
<td>PO(Ph)₂</td>
<td>60</td>
<td>95 ee</td>
</tr>
<tr>
<td>PO(Ph)₂</td>
<td>93</td>
<td>86</td>
</tr>
<tr>
<td>PO(Ph)₂</td>
<td>45</td>
<td>70</td>
</tr>
</tbody>
</table>

**Reaction with diisopropyl phosphonate**

Selected examples:

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO(O-i-Pr)₂</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>PO(O-i-Pr)₂</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>PO(O-i-Pr)₂</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>PO(O-i-Pr)₂</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>PO(O-i-Pr)₂</td>
<td>65</td>
<td></td>
</tr>
</tbody>
</table>
Tandem α-Alkylation–Asymmetric Transfer Hydrogenation of Acetophenones

Significance: The authors present the first example of a direct formation of enantiomerically enriched secondary alcohols from ketones and primary alcohols by a tandem α-alkylation–asymmetric transfer hydrogenation process using [Ru(p-cymene)Cl₂]₂ as catalyst in the presence of an amino acid hydroxy amide as ligand.

Comment: Diversely substituted acetophenones were successfully converted into chiral secondary alcohols via the borrowing hydrogen methodology in moderate yields and in moderate to good enantiomeric excess. In this process, primary alcohols served as both alkylating and reducing agents.
D. ZHANG, T. CHENG,* Q. ZHAO, J. XU, G. LIU* (SHANGHAI NORMAL UNIVERSITY, P. R. OF CHINA)
Highly Enantioselective One-Pot Synthesis of Chiral β-Hydroxy Sulfones via Asymmetric Transfer Hydrogenation in an Aqueous Medium

Enantioselective Synthesis of β-Hydroxy Sulfones via Transfer Hydrogenation

Significance: Chiral β-hydroxy sulfones are useful building blocks in organic synthesis, as the α-position can easily be functionalized and the sulfonyl group easily be removed or transformed. In the present report, the authors describe a one-pot approach to chiral β-hydroxy sulfones, starting from α-bromo ketones and involving transfer hydrogenation.

Comment: A variety of products could be formed in high yield and high to excellent enantioselectivity. Interestingly, both alkyl and aryl substituents can be tolerated at the R1 and R2 positions, with aryl groups giving superior results. Through kinetic studies, the authors demonstrate that nucleophilic substitution followed by transfer hydrogenation is the dominant sequence.
**Intramolecular Asymmetric Desymmetrization via Copper Catalysis**

**Significance:** Hydroxy- and amino-functionalized C3-fragments play a pivotal role as synthetic intermediates. Whereas enantioselective desymmetrization of diols and glycerol were developed to provide hydroxyl-containing C3-fragments, the corresponding preparation of amino-containing C3-fragments has been rarely documented. Herein, Gu and co-workers present the asymmetric desymmetrization of 1,3-diazido-2-propanols catalyzed by copper–PhBox.

**Comment:** The title transformation is enabled in an enantioselective fashion by CuPF₆(MeCN)₄ in the presence of (S,S)-PhBox and NaBARF with the larger and non-coordinating BARF− anion. The new method provides reliable access to enanti-enriched azido-substituted 5,6-dihydro-1,4-oxazin-2-ones, which can be further converted into useful N-containing scaffolds.

**Selected examples:**

1. **N**<sub>R</sub> **O**<sub>2</sub> **N₃**
   - 96% yield, 89% ee (41 h)

2. **N**<sub>Cl</sub> **O**<sub>2</sub> **N₃**
   - 97% yield, 93% ee (72 h)

3. **N**<sub>Br</sub> **O**<sub>2</sub> **N₃**
   - 99% yield, 91% ee (53 h)

4. **N**<sub>MeO</sub> **O**<sub>2</sub> **N₃**
   - 99% yield, 89% ee (43 h)

5. **N**<sub>Br</sub> **O**<sub>2</sub> **N₃**
   - 98% yield, 91% ee (43 h)

**CuPF₆(MeCN)₄ (5 mol%), ligand (6 mol%), NaBARF (6 mol%)**

**CHCl₃, -5 °C**

**NaBARF = sodium tetrakis[3,5-bis-(trifluoromethyl)phenyl]borate**

**Key words**
- asymmetric desymmetrization
- alkyl azides
- bisoxazolines
- copper
P-Chiral P,π-Dihydrobenzooxaphosphole Ligands in Asymmetric Catalysis

**Significance:** A new family of P-chiral P,π-hybrid ligands has been synthesized from a chiral dihydrobenzooxaphosphole core (Z. S. Han et al. *J. Am. Chem. Soc.* 2013, 135, 2474). These newly developed ligands show a very high level of enantiocontrol in the rhodium-catalyzed addition of aryl boronic acids to tosyl imines.

**Comment:** The synthesis of the ligands with strong electron-withdrawing substituents (like CF₃) failed by the alkylation with cinnamyl derivatives, alternatively an allylation and subsequent metathesis strategy was employed. Steric and electronic properties were controlled easily by varying the substituents on the phosphorus atom and on the π-system.

**Selected examples:**

- **L1:** R₁ = 2,6-(MeO)₂C₆H₃, R₂ = t-Bu, Ar₁ = Ph; 45% yield
- **L2:** R₁ = H, R₂ = t-Bu, Ar₁ = Ph; 42% yield
- **L3:** Ar² = 4-F₃CC₆H₄; 36% yield
- **L4:** Ar² = 3,5-(F₃C)₂C₆H₃; 31% yield

**Application:** 98% yield, 96% ee; 78% yield, 92% ee; 92% yield, 98% ee; 92% yield, 98% ee; 78% yield, 92% ee
Axially Chiral Biaryl Compounds via Dynamic Kinetic Resolution

**Significance:** Axially chiral biaryl motifs are privileged structures as ligands for transition-metal catalysis. The authors present a dynamic kinetic resolution of racemic biaryls with a palladium catalyst using point chirality of a sulfoxide directing group.

**Comment:** Although some substrates were slow to react (up to 7 days), good yields and stereoselectivities were observed. Treatment of the products with t-BuLi at −90 °C led to an axially stable aryllithium species, which was trapped with CO₂.
Enantioselective Palladium/Organo-Catalyzed Additions to Unsaturated Aldehydes

**Significance:** Synergistic catalysis has recently been gaining attention because the two separate catalysts can be optimized independently (see Review below). The authors present a palladium/chiral secondary amine catalyzed reaction between azaarenes and unsaturated aldehydes.

**Comment:** Although diastereoselectivity was poor (highest ratio 2.7:1), good enantioselectivities were observed for both major and minor isomers. The palladium acts as a Lewis acid to activate the azaarene, whereas the proline-derived organocatalyst activates the aldehyde towards 1,4-addition.

S. J. CANIPA, A. STUTE, P. O’BRIEN* (UNIVERSITY OF YORK, HESLINGTON, UK)
Use of Copper(II)/Diamine Catalysts in the Desymmetrisation of \textit{meso}-Diols and Asymmetric Henry Reactions: Comparison of (–)-Sparteine and (+)-Sparteine Surrogates

(–)-Sparteine versus (+)-Sparteine Surrogates in Copper(II)–Diamine-Catalyzed Reactions

\textbf{Significance:} O’Brien and co-workers present an evaluation of copper(II)–diamine complexes comprising (–)-sparteine, (+)-sparteine surrogates, and Alexakis diamine in the desymmetrization of \textit{meso}-diols and asymmetric Henry reaction. One of the nitro alcohol products was utilized in a concise synthesis of a chiral morpholine.

\textbf{Comment:} In order to compare the reactivity in asymmetric induction, the copper(II)–diamine catalysts, containing diamine 1 and 2, were investigated in the enantioselective monobenzoylation of \textit{meso}-1,2-diols and in the asymmetric Henry reaction. In both reactions the products were obtained in good to high enantioselectivities with the opposite sense of induction depending on the used diamine. As expected, (+)-sparteine surrogate 2 generated the antipodal products of those obtained using (–)-sparteine.

\textbf{SYNFACTS Contributors:} Hisashi Yamamoto, Wafa Gati
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DOI: 10.1055/s-0034-1379755; Reg-No.: H16114SF
Enantioselective Reaction of Tertiary Enamides with Salicylaldehydes

Significance: Tertiary enamides are related to enamines by replacement of an N-alkyl substituent with an electron-withdrawing group. Despite this change, they remain nucleophilic. Taking advantage of this characteristic and of the electrophilicity of the transient iminium, the authors developed a modular titanium(IV)-catalyzed synthesis of 4-chromanol derivatives, by reaction with salicylaldehydes.

Comment: The use of a titanium–(R)-BINOL complex enabled the synthesis of diverse 4-chromanol products with good to excellent enantio- and diastereoselectivity. Water was found to have a marked effect on enantioselectivity: under anhydrous conditions, the ee decreased to 50.8%, whereas it was measured at 96.5% in the presence of 20 mol% water, in the model reaction. The exact mechanism remains to be elucidated.

SYNFACTS Contributors: Mark Lautens, Thomas Johnson
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DOI: 10.1055/s-0034-1379692; Reg-No.: L15814SF
Enantioselective Synthesis of Chiral 1,2-Amino Alcohols via Asymmetric Hydrogenation of α-Amino Ketones with Chiral Spiro Iridium Catalysts


Synthesis of 1,2-Amino Alcohols via Asymmetric Hydrogenation

Significance: Chiral 1,2-amino alcohols are very commonly found in pharmaceuticals and natural products. Although many methods exist for their synthesis, the present one, based on asymmetric hydrogenation, is notable for its efficiency in terms of enantioselectivity and turnover number (up to 100 000).

Comment: Excellent yields and enantioselectivities were obtained on a range of aromatic α-amino ketones with a low catalyst loading (0.02 mol%). When an alkyl α-amino ketone was employed, the product was formed in 98% yield, but was nearly racemic. The authors demonstrate the utility and scalability of their method with the synthesis of (R)-phenylephrine hydrochloride, using only 0.001 mol% catalyst (TON = 100 000).
Asymmetric Reductive Amination of Ketones

**Significance:** Enantiomerically pure chiral amines are very important building blocks to synthesize numerous pharmaceutical drugs as well as bioactive compounds. The authors report the first iron-catalyzed asymmetric reductive amination of ketones with anilines in the presence of hydrogen, leading to chiral amines in moderate to good yields and good to excellent enantioselectivities.

**Comment:** The protocol represents a more convenient, simple and practical method for the synthesis of chiral amines. Interestingly, the combination of the chiral Brønsted acid (TRIP) catalyst and the non-chiral Knölker complex enabled the reductive amination of ketones with anilines in a cooperative manner.

**Selected examples:**

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>Catalyst</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeO</td>
<td>H</td>
<td>catalyst 1 (3 mol%)</td>
<td>60%</td>
<td>84% ee</td>
</tr>
<tr>
<td></td>
<td></td>
<td>catalyst 2 (5 mol%)</td>
<td>64%</td>
<td>94% ee</td>
</tr>
<tr>
<td>H</td>
<td></td>
<td></td>
<td>70%</td>
<td>94% ee</td>
</tr>
<tr>
<td>Ph</td>
<td>H</td>
<td></td>
<td>80%</td>
<td>73% ee</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>60%</td>
<td>94% ee</td>
</tr>
<tr>
<td>H</td>
<td>Et</td>
<td></td>
<td>68%</td>
<td>93% ee</td>
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<td></td>
<td></td>
<td>74%</td>
<td>93% ee</td>
</tr>
<tr>
<td>Ph</td>
<td></td>
<td></td>
<td>62%</td>
<td>95% ee</td>
</tr>
</tbody>
</table>

**SYNFACTS Contributors:** Hisashi Yamamoto, Fengtao Zhou
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DOI: 10.1055/s-0034-1379757; Reg-No.: H16314SF