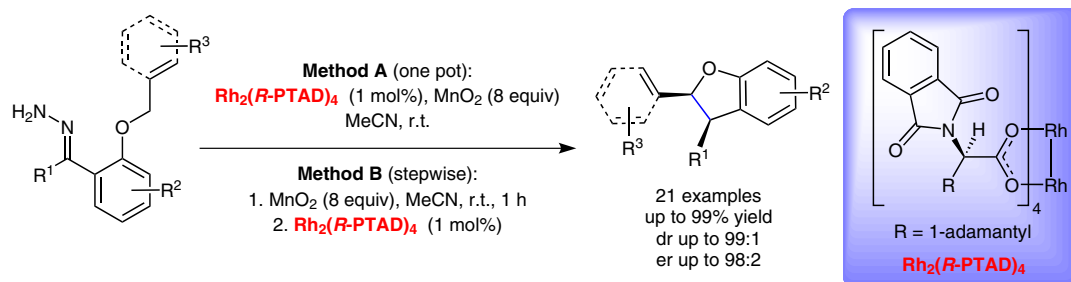
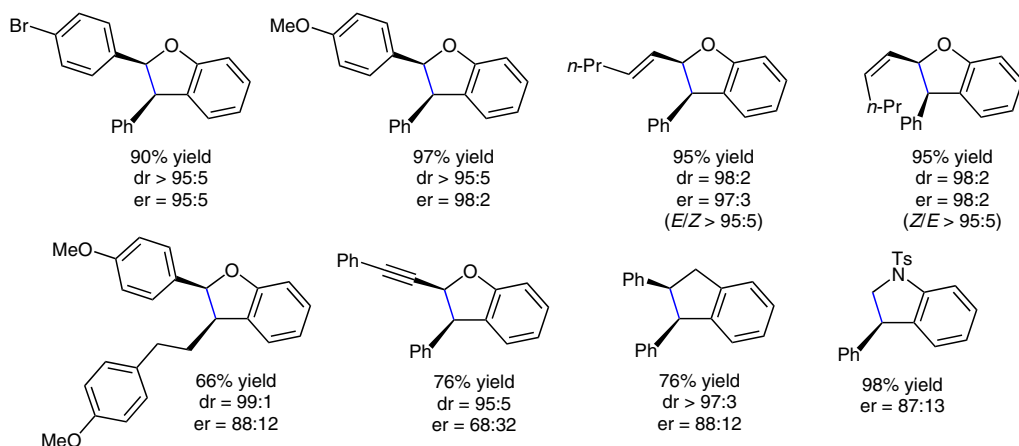


Enantioselective C–H Insertion Reactions of Donor–Donor Carbenoids



Selected examples:



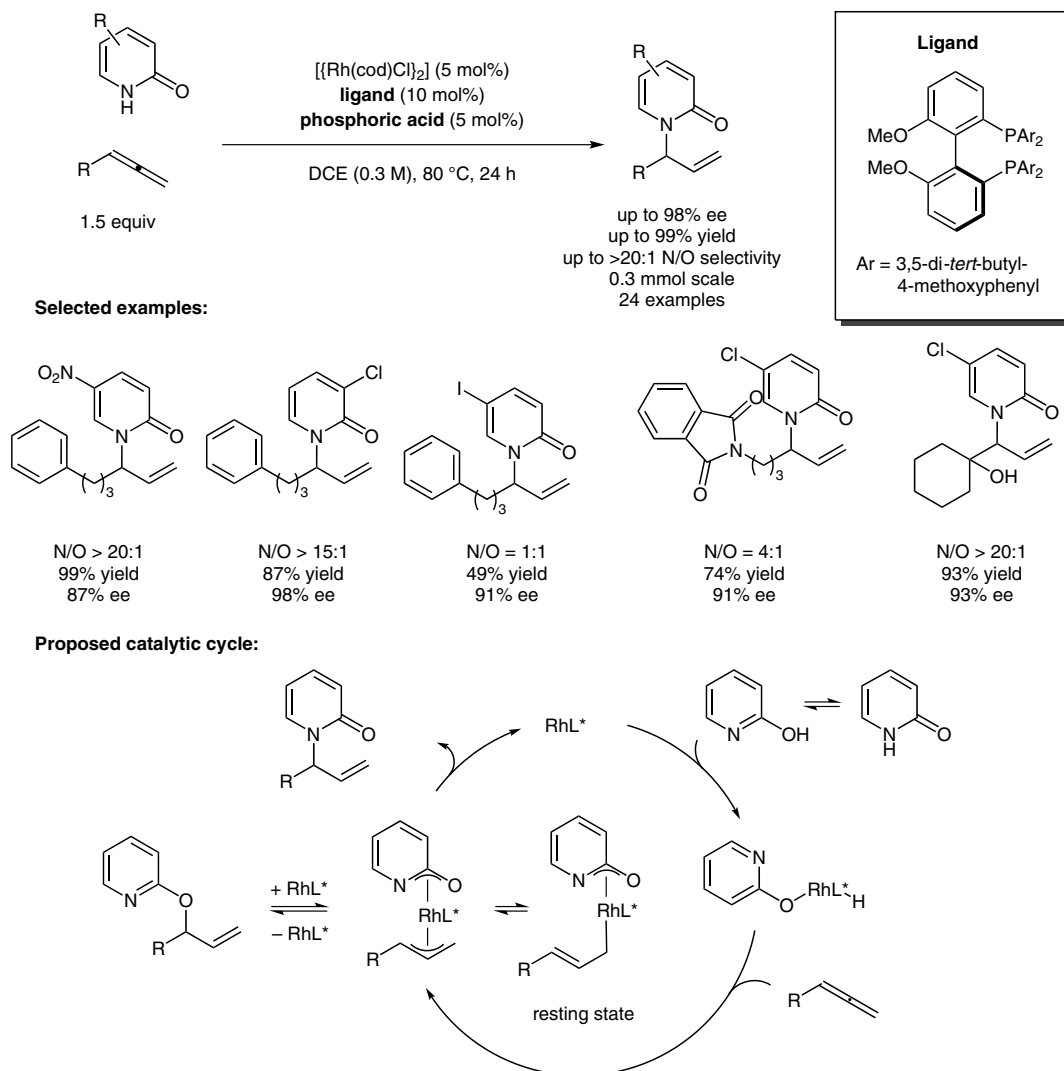
Significance: Transition-metal carbenoids, which can be generated in situ from a variety of different precursors, demonstrate a diverse range of reactivity, such as the ability to perform allylic and benzylic C–H functionalizations (see Review below). While the use of acceptor–acceptor and donor–acceptor 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 MnO_2 . 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.

Review: M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou *Chem. Rev.* **2010**, *110*, 704–724.

C. LI, M. KÄHNY, B. BREIT* (ALBERT-LUDWIGS-UNIVERSITÄT FREIBURG, GERMANY)
Rhodium-Catalyzed Chemo-, Regio-, and Enantioselective Addition of 2-Pyridones to Terminal Allenes
Angew. Chem. Int. Ed. **2014**, *53*, 13780–13784.

Enantioselective Rhodium-Catalyzed Allylation of 2-Pyridones

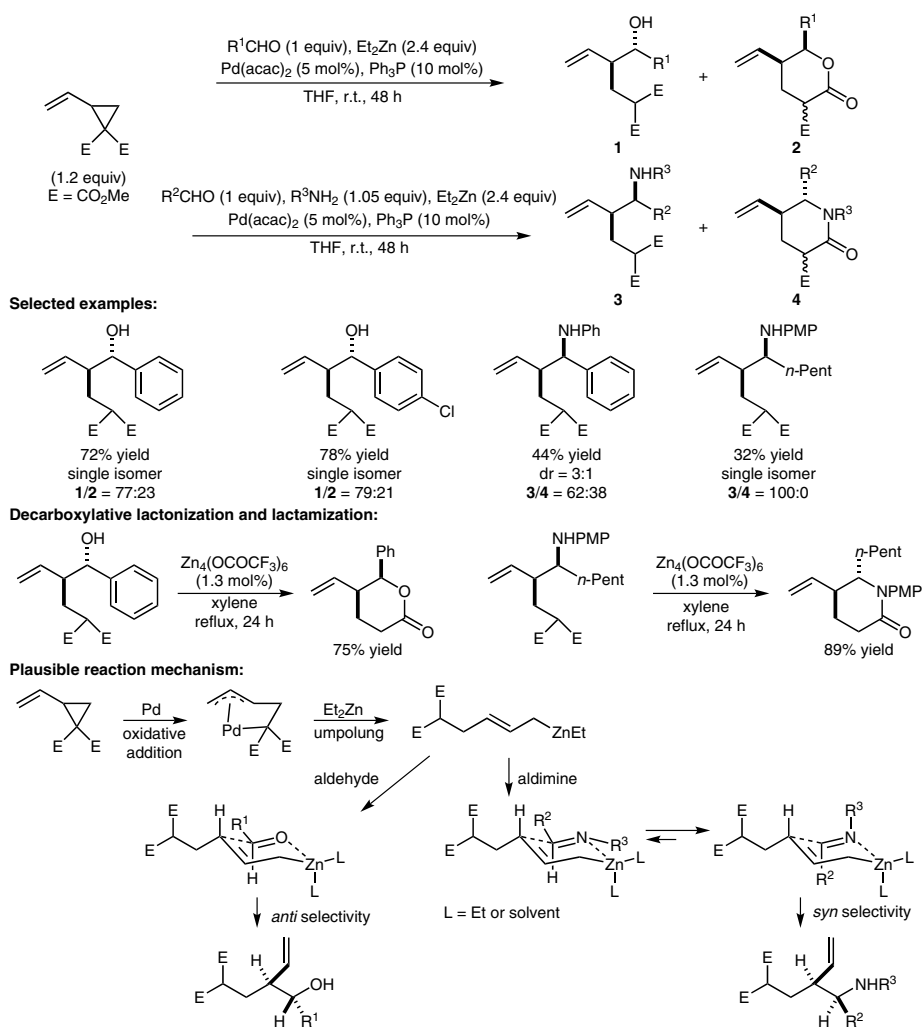


Significance: Enantioenriched N-substituted 2-pyridones are an important class of biologically active molecules. Their synthesis has been described starting from chiral electrophiles (Y.-Q. Fang et al. *J. Am. Chem. Soc.* **2010**, *132*, 15525) and chiral amines (Y. Yu et al. *J. Nat. Prod.* **2013**,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

SYNFACTS Contributors: Mark Lautens, Zafar Qureshi
 Synfacts 2015, 11(1), 0042 Published online: 15.12.2014
 DOI: 10.1055/s-0034-1379681; Reg-No.: L14714SF

Palladium-Catalyzed Nucleophilic Allylation of Aldehydes or Aldimines

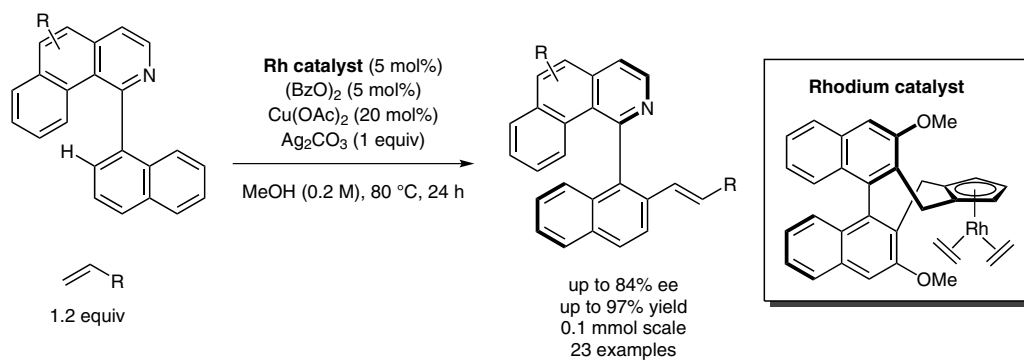


Significance: Ring-expansion reactions of vinylcyclopropanes are powerful tools for organic synthesis. The authors describe the palladium-catalyzed nucleophilic allylation of aldehyde and aldimines with vinylcyclopropane in the presence of dimethylzinc.

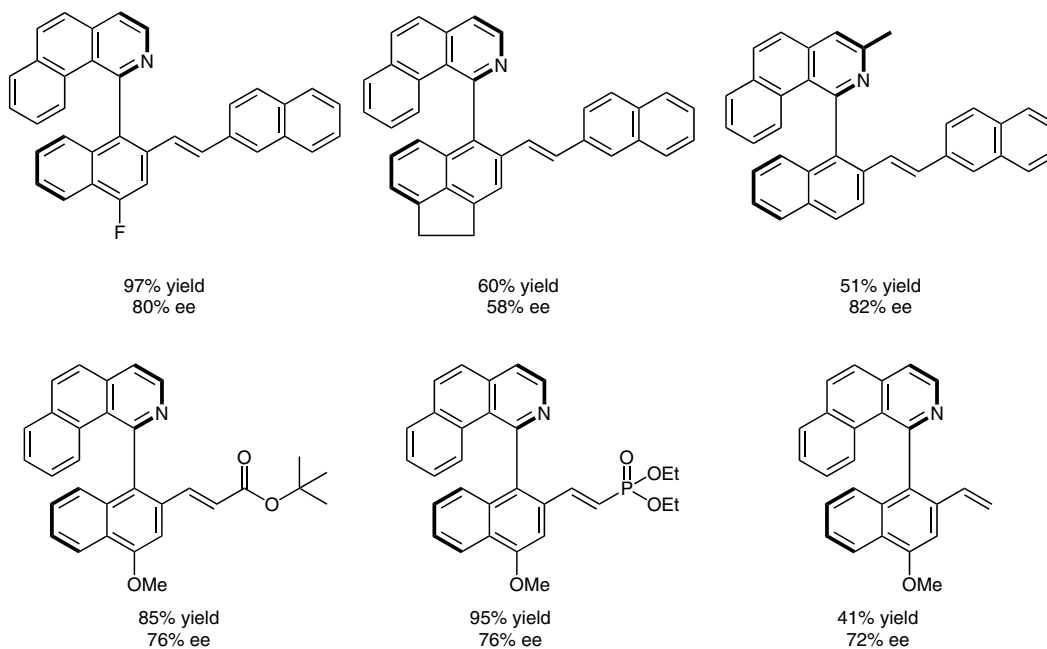
Comment: The allylation of aldehydes with vinylcyclopropane and diethylzinc proceeded to provide homoallyl alcohols with *anti* stereoselectivity. Aldimines prepared from aldehyde and primary amines in situ underwent a similar allylation to give homoallyl amines with *syn* stereoselectivity. The products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

J. ZHENG, S.-L. YOU* (SHANGHAI INSTITUTE OF ORGANIC CHEMISTRY, P. R. OF CHINA)
Construction of Axial Chirality by Rhodium-Catalyzed Asymmetric Dehydrogenative Heck Coupling of Biaryl
Compounds with Alkenes
Angew. Chem. Int. Ed. **2014**, *53*, 13244–13247.

Enantioselective Rhodium-Catalyzed Synthesis of Axially Chiral Biaryls



Selected examples:



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.

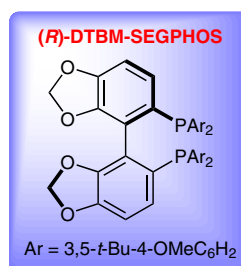
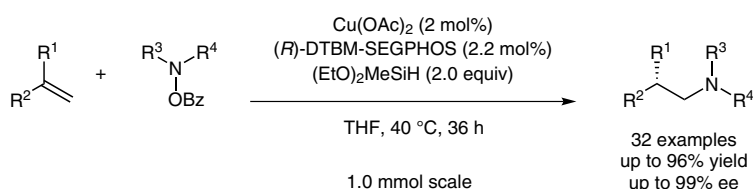
SYNFACTS Contributors: Mark Lautens, Zafar Qureshi
Synfacts 2015, 11(1), 0044 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379694; **Reg-No.:** L16014SF

S. ZHU, S. L. BUCHWALD* (MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE, USA)

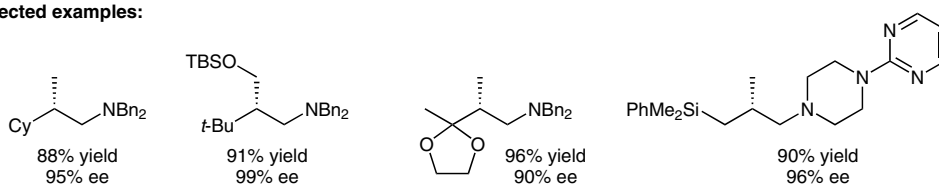
Enantioselective CuH-Catalyzed Anti-Markovnikov Hydroamination of 1,1-Disubstituted Alkenes

J. Am. Chem. Soc. **2014**, *136*, 15913–15916.

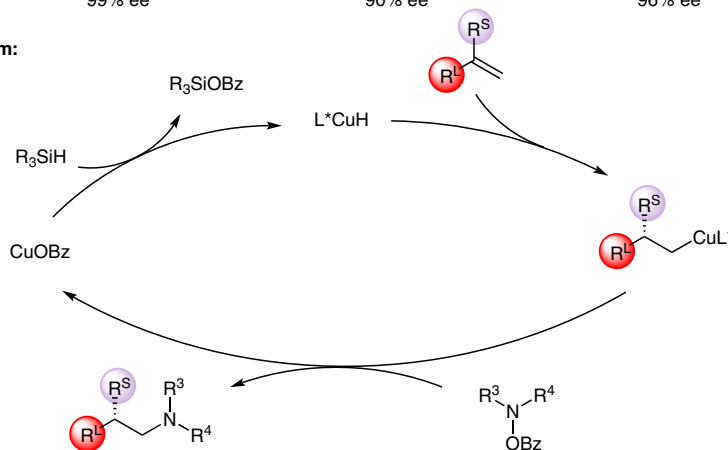
CuH-Catalyzed Enantioselective Anti-Markovnikov Hydroamination



Selected examples:



Proposed mechanism:



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.

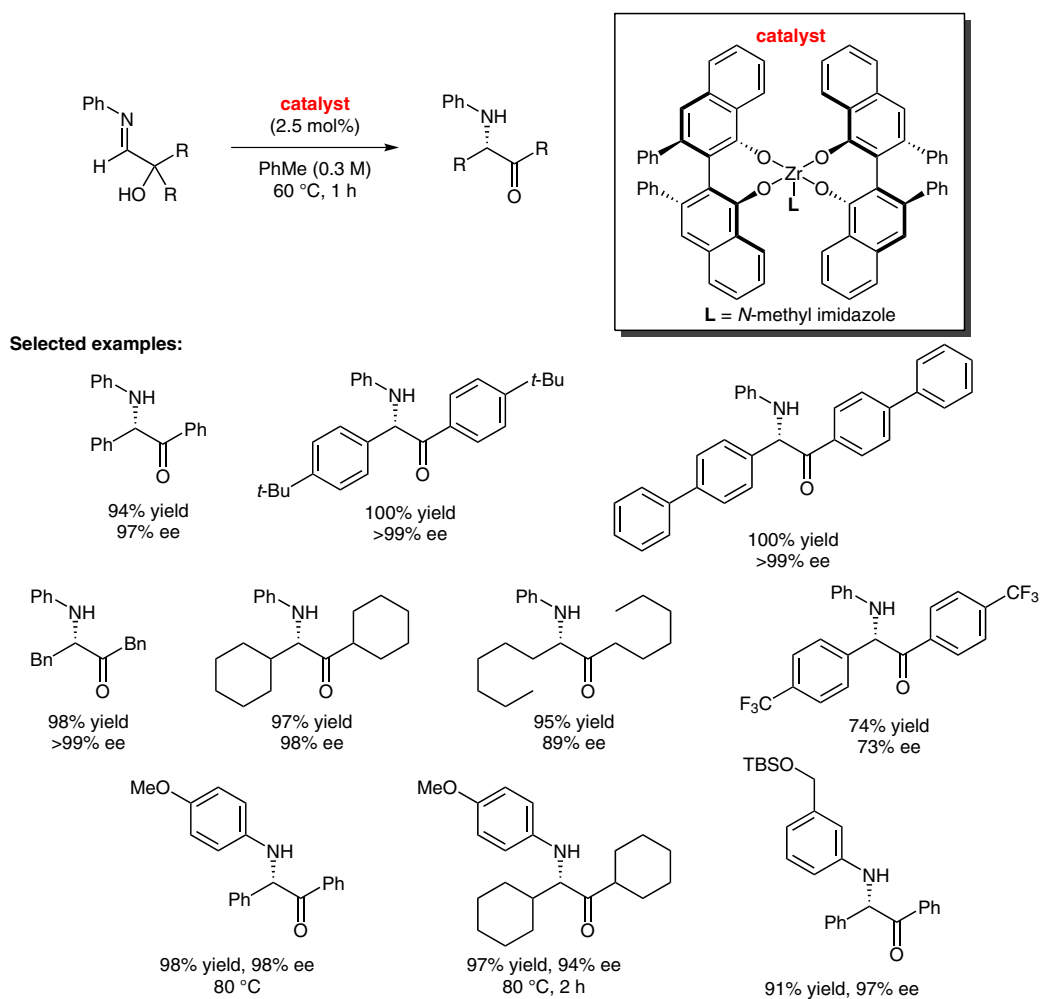
Comment: The report expands upon the authors' previous work on the Cu-catalyzed enantioselective hydroamination of styrene derivatives (*J. Am. Chem. Soc.* **2013**, *135*, 15746). The proposed mechanism involves hydrocupration of the 1,1-disubstituted olefin in an anti-Markovnikov manner, which is intercepted 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 hydrosilane.

SYNFACTS Contributors: Mark Lautens, Christine M. Le
Synfacts 2015, 11(1), 0045 Published online: 15.12.2014

DOI: 10.1055/s-0034-1379683; **Reg-No.:** L14914SF

X. ZHANG, R. J. STAPLES, A. L. RHEINGOLD,* W. D. WULFF* (MICHIGAN STATE UNIVERSITY AND UNIVERSITY OF CALIFORNIA, SAN DIEGO, USA)
Catalytic Asymmetric α -Iminol Rearrangement: New Chiral Platforms
J. Am. Chem. Soc. **2014**, *136*, 13971–13974.

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.

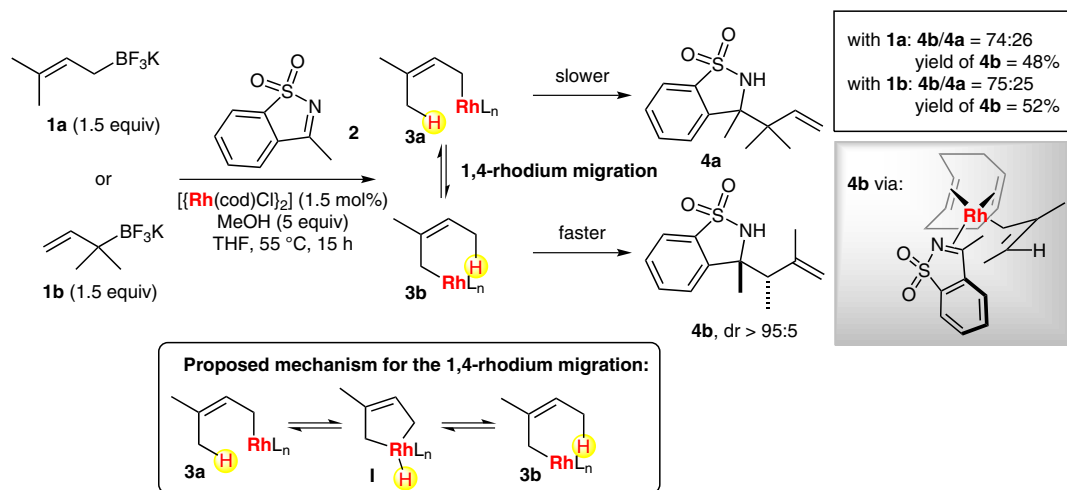
Comment: The zirconium/VANOL catalyst affords excellent yields and enantioselectivities for a broad range of substrates. Interestingly, *N*-methyl imidazole coordinated to zirconium dramatically influences the reaction. When there is a *para*-CF₃ substituent on the phenyl ring, more careful manipulations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

SYNFACTS Contributors: Hisashi Yamamoto, Takayuki Furukawa
Synfacts 2015, 11(1), 0046 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379745; Reg-No.: H15114SF

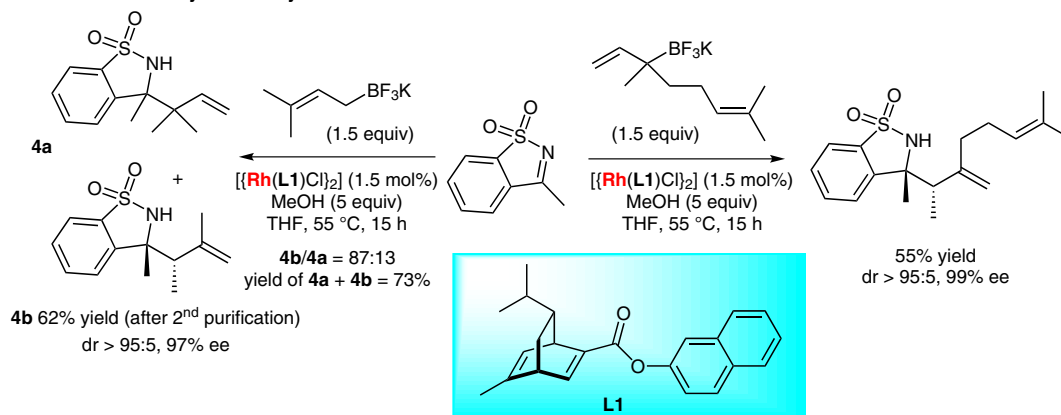
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Isomerization of Allylrhodium Intermediates During Allylations of Imines

Allylation of cyclic ketimines with allyltrifluoroborate via isomerization of prenylrhodium species:



Enantioselective allylation of cyclic ketimines:



Significance: The authors present a 1,4-rhodium(I) migration of allylrhodium intermediates 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.

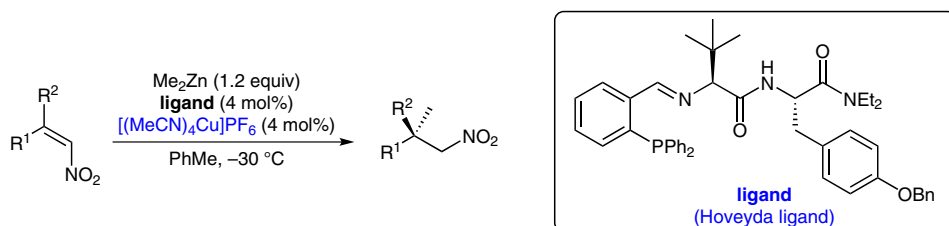
SYNFACTS Contributors: Hisashi Yamamoto, Biplab Maji
Synfacts 2015, 11(1), 0047 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379753; **Reg-No.:** H15914SF

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**.

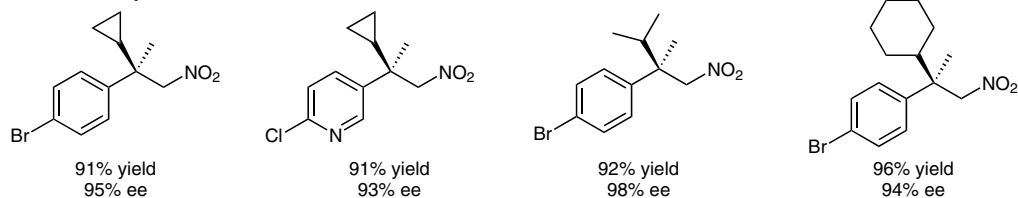
X. ZENG,* J. J. GAO, J. J. SONG, S. MA, J.-N. DESROSIERS, J. A. MULDER, S. RODRIGUEZ, M. A. HERBAGE, N. HADDAD, B. QU, K. R. FANDRICK, N. GRINBERG, H. LEE, X. WEI, N. K. YEE, C. H. SENANAYAKE (BOEHRINGER INGELHEIM PHARMACEUTICALS, RIDGEFIELD, USA)

Remarkable Enhancement of Enantioselectivity in the Asymmetric Conjugate Addition of Dimethylzinc to (*Z*)-Nitroalkenes with a Catalytic [(MeCN)₄Cu]PF₆-Hoveyda Ligand Complex
Angew. Chem. Int. Ed. **2014**, *53*, 12153–12157.

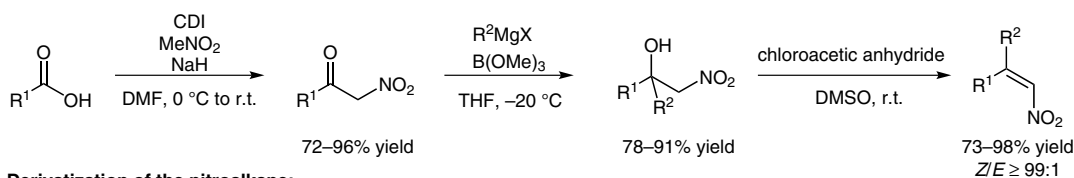
Asymmetric Conjugate Addition of Dimethylzinc to (*Z*)-Nitroalkenes



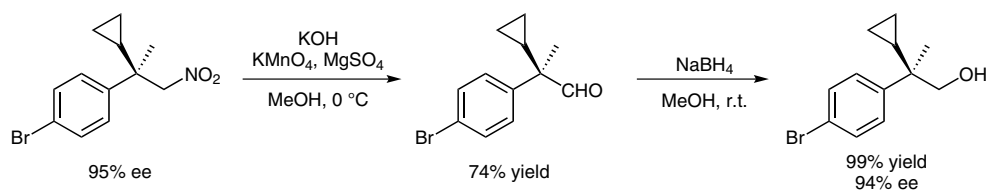
Selected examples:



Preparation of the (*Z*)-nitroalkenes:



Derivatization of the nitroalkane:



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).

SYNFACTS Contributors: Hisashi Yamamoto, Yasushi Shimoda
Synfacts 2015, 11(1), 0048 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379750; **Reg-No.:** H15614SF

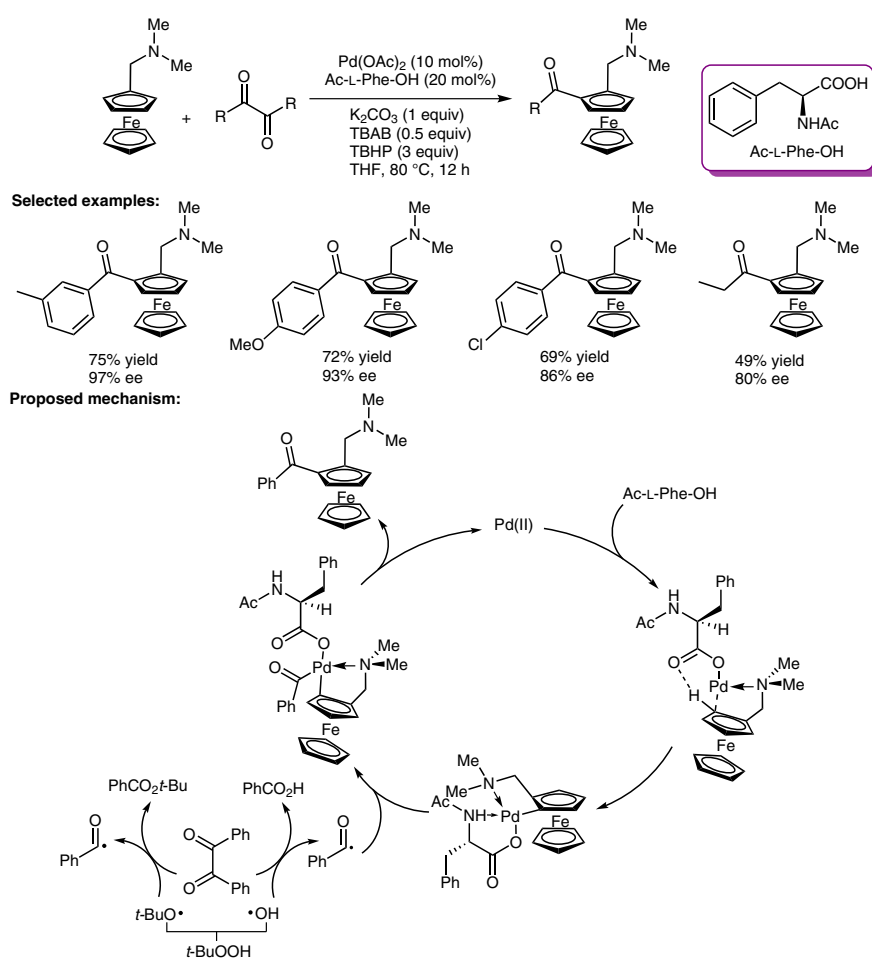
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C. PI, X. CUI,* X. LIU, M. GUO, H. ZHANG, Y. WU* (ZHENGZHOU UNIVERSITY AND XIAMEN KEY LABORATORY OF OCEAN AND GENE DRUGS, SCHOOL OF BIOMEDICAL SCIENCES AND INSTITUTE OF MOLECULAR MEDICINE OF HUAQIAO UNIVERSITY & ENGINEERING RESEARCH CENTER OF MOLECULAR MEDICINE OF CHINESE EDUCATION MINISTRY, XIAMEN, P. R. OF CHINA)

Synthesis of Ferrocene Derivatives with Planar Chirality via Palladium-Catalyzed Enantioselective C–H Bond Activation

Org. Lett. **2014**, *16*, 5164–5167.

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.

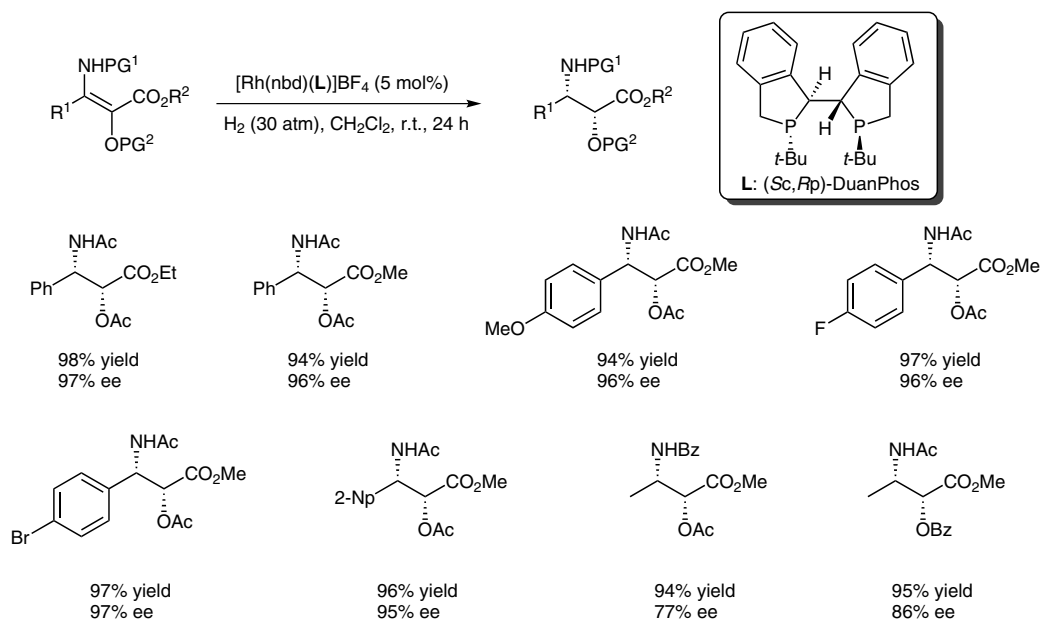
Comment: Due to their important role in promoting various asymmetric catalyzed reactions, 2-acyl-1-dimethylaminomethylferrocene derivatives with planar chirality were provided under one-pot reaction conditions in moderate to good yields and with excellent enantioselectivities via a palladium-catalyzed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

SYNFACTS Contributors: Hisashi Yamamoto, Wafa Gati
Synfacts 2015, 11(1), 0049 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379754; **Reg-No.:** H16014SF

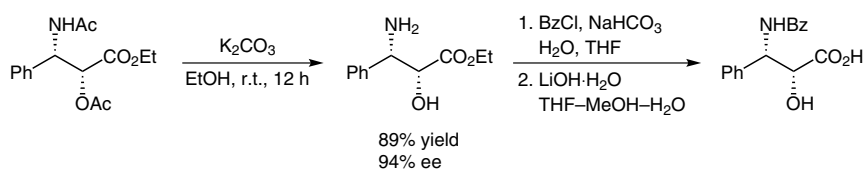
Q. WANG, W. HUANG, H. YUAN, Q. CAI, L. CHEN, H. LV,* X. ZHANG* (WUHAN UNIVERSITY, P. R. OF CHINA)

Rhodium-Catalyzed Enantioselective Hydrogenation of Tetrasubstituted α -Acetoxy β -Enamido Esters: A New Approach to Chiral α -Hydroxy- β -amino Acid Derivatives
J. Am. Chem. Soc. **2014**, *136*, 16120–16123.

Rhodium-Catalyzed Enantioselective Hydrogenation of Enamido Esters



Synthesis of the taxol C13 side chain:



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

Comment: $[\text{Rh}(\text{nbd})(\text{Sc},\text{Rp})\text{-DuanPhos}]\text{BF}_4$ 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.

SYNFACTS Contributors: Hisashi Yamamoto, Masahiro Sai
Synfacts 2015, 11(1), 0050 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379759; **Reg-No.:** H16514SF

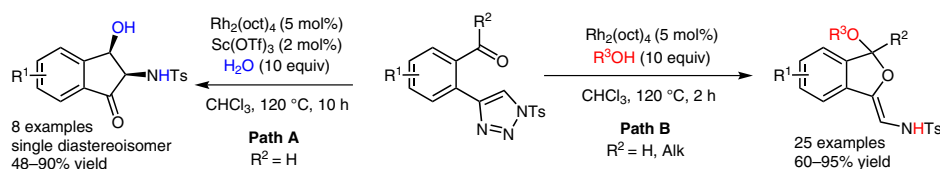
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H. SHEN, J. FU, J. GONG,* Z. YANG* (PEKING UNIVERSITY, BEIJING AND OCEAN UNIVERSITY OF CHINA, QINGDAO, P. R. OF CHINA)

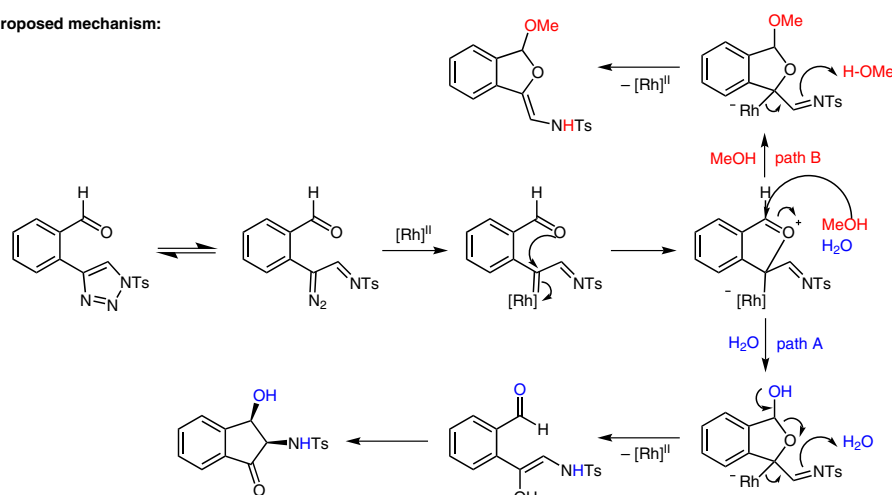
Tunable and Chemoselective Syntheses of Dihydroisobenzofurans and Indanones via Rhodium-Catalyzed Tandem Reactions of 2-Triazole-benzaldehydes and 2-Triazole-alkylaryl Ketones

Org. Lett. **2014**, *16*, 5588–5591.

Divergent Reactivity of 2-Triazole Benzaldehydes under Rhodium Catalysis



Proposed mechanism:



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-hydroxyindanones or dihydroisobenzofurans.

Comment: To support the existence of an oxonium intermediate, the starting triazole was reacted with the rhodium catalyst for two hours in the absence of nucleophiles. Upon addition of water, alcohol and $\text{Sc}(\text{OTf})_3$, products arising from paths A and B were formed in comparable yield, suggesting the presence of this common intermediate.

SYNFACTS Contributors: Mark Lautens, Thomas Johnson
Synfacts 2015, 11(1), 0051 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379688; **Reg-No.:** L15414SF

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Category

Metal-Catalyzed
Asymmetric
Synthesis and
Stereoselective
Reactions

Key words

triazoles

rhodium

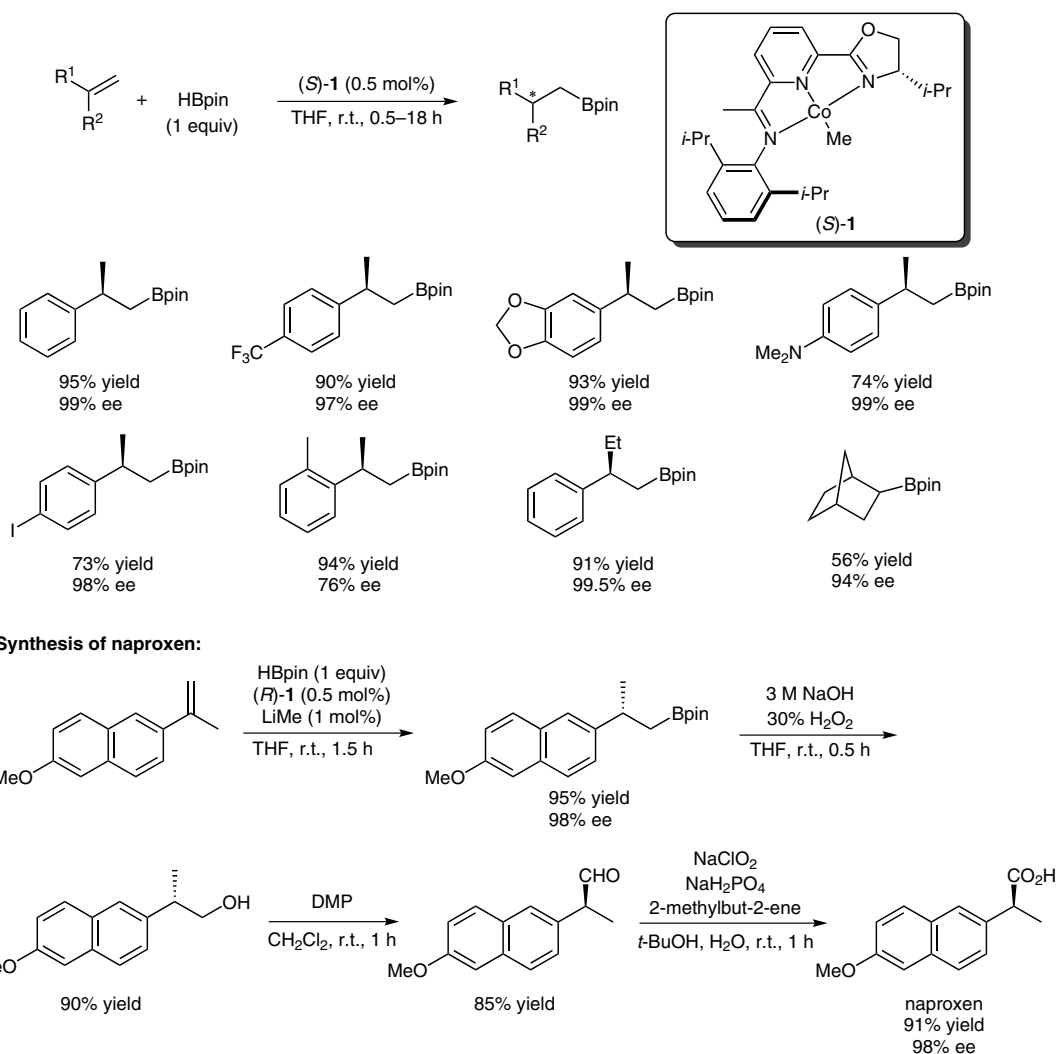
carbenoids

indanones

L. ZHANG, Z. ZUO, X. WAN, Z. HUANG* (SHANGHAI INSTITUTE OF ORGANIC CHEMISTRY, P. R. OF CHINA)

Cobalt-Catalyzed Enantioselective Hydroboration of 1,1-Disubstituted Aryl Alkenes
J. Am. Chem. Soc. **2014**, *136*, 15501–15504.

Cobalt-Catalyzed Asymmetric Hydroboration of Alkenes of Alkenes



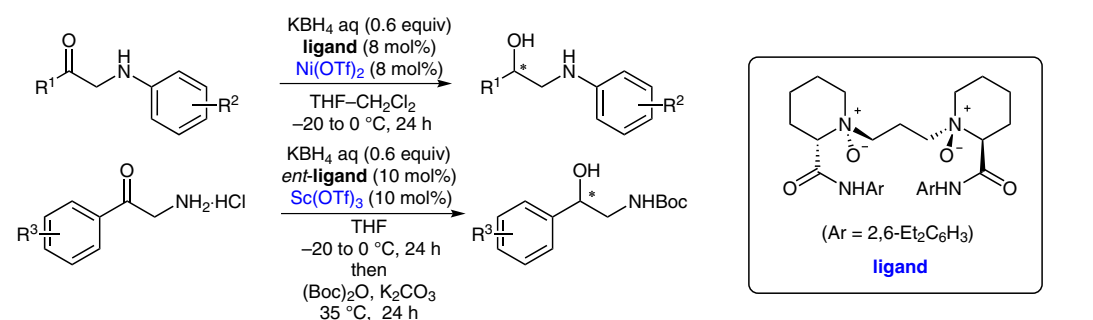
Significance: A cobalt-catalyzed asymmetric hydroboration of 1,1-disubstituted aryl alkenes is presented. A series of chiral α -alkyl- β -pinacolboranes were prepared with exclusive regioselectivities in high yields (up to 98%) with excellent enantioselectivities (up to 99.5% ee).

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.

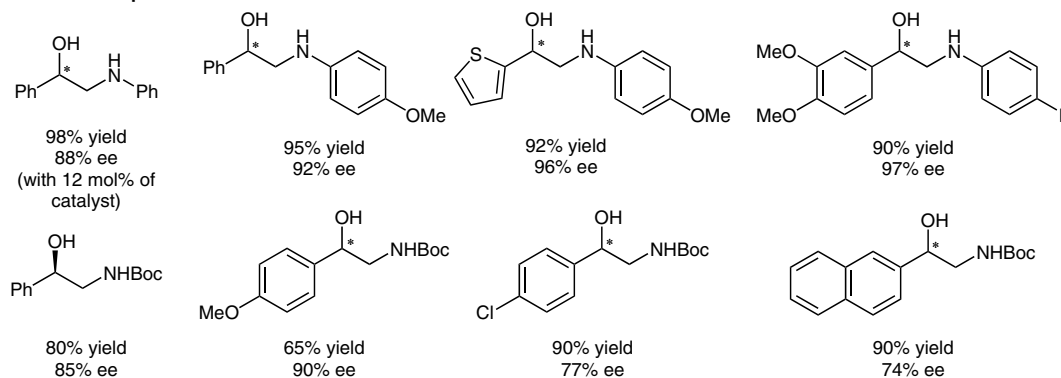
SYNFACTS Contributors: Hisashi Yamamoto, Masahiro Sai
Synfacts 2015, 11(1), 0052 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379758; Reg-No.: H16414SF

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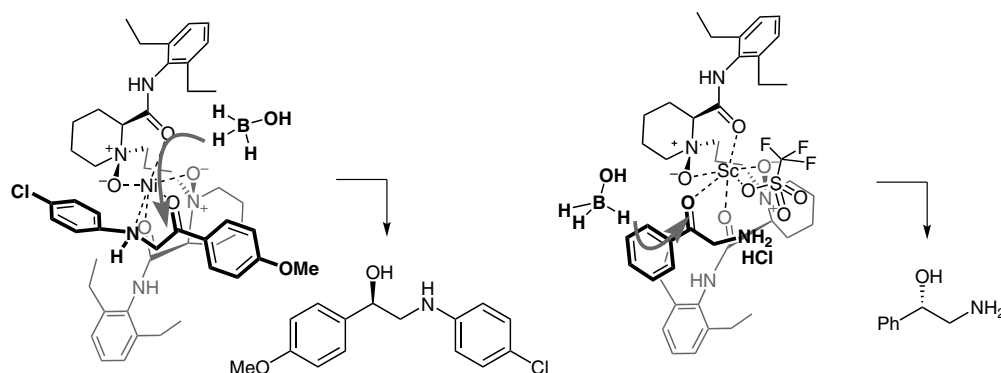
Asymmetric Reduction of α -Amino Ketones Catalyzed by Lewis Acids



Selected examples:



Possible transition state:



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.

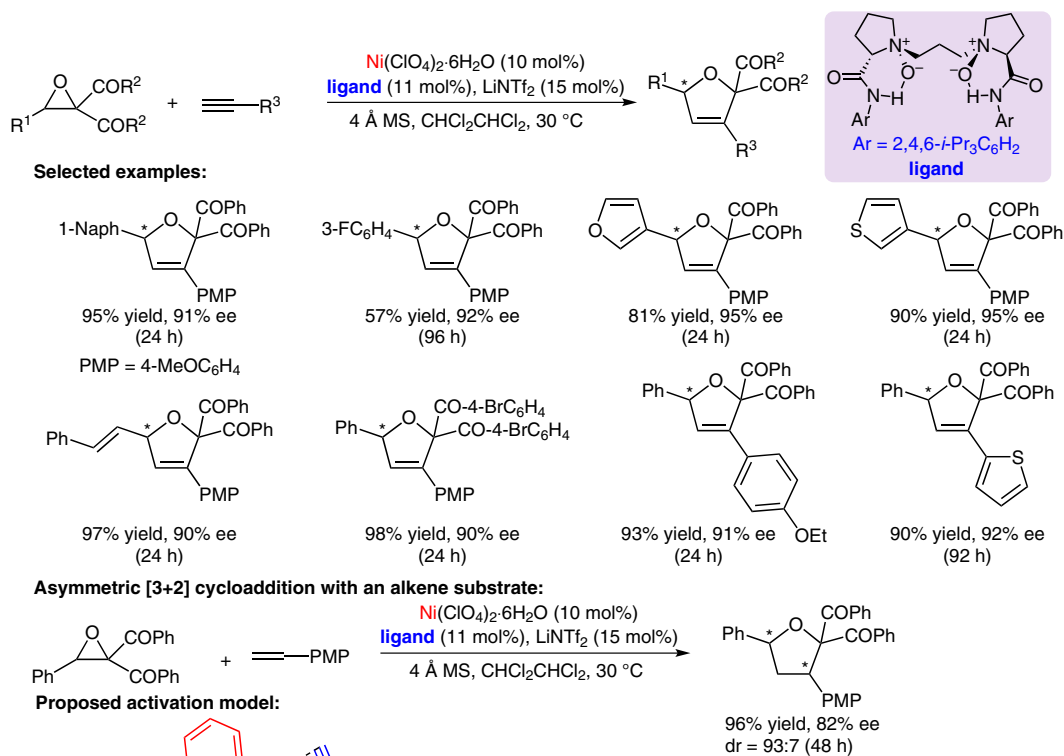
SYNFACTS Contributors: Hisashi Yamamoto, Yasushi Shimoda
Synfacts 2015, 11(1), 0053 Published online: 15.12.2014

DOI: 10.1055/s-0034-1379749; **Reg-No.:** H15514SF

W. CHEN, X. FU, L. LIN, X. YUAN, W. LUO, J. FENG, X. LIU, X. FENG* (SICHUAN UNIVERSITY, CHENGDU, P. R. OF CHINA)

An Asymmetric [3+2] Cycloaddition of Alkynes with Oxiranes by Selective C–C Bond Cleavage of Epoxides: Highly Efficient Synthesis of Chiral Furan Derivatives
Chem. Commun. **2014**, 50, 11480–11483.

Chiral Furans via Asymmetric [3+2] Cycloaddition



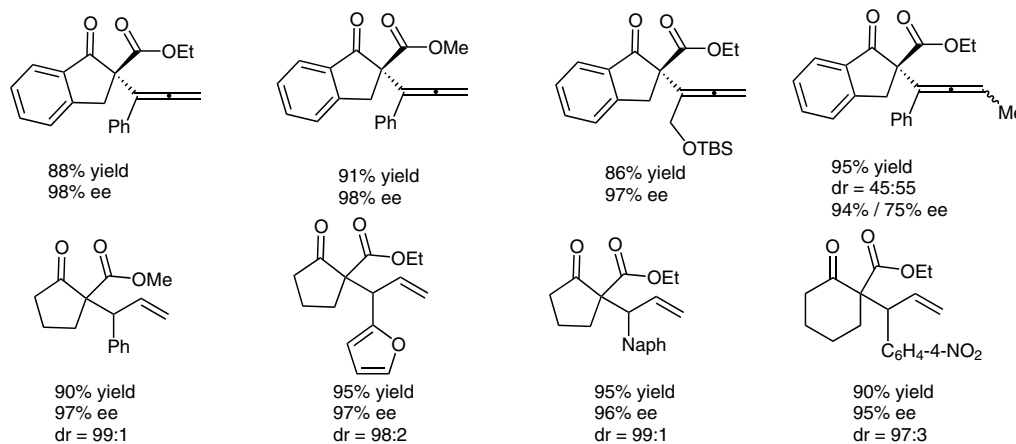
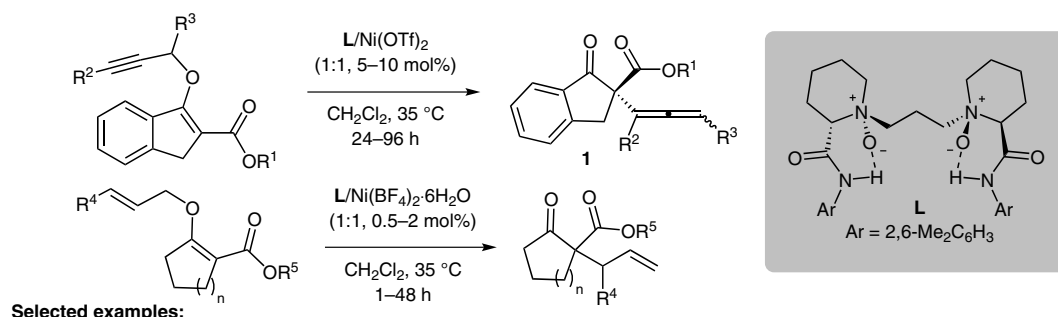
Significance: Tetrahydrofurans and 2,5-dihydrofurans containing a stereocenter are often found in natural products and medicinal compounds. Ni(ClO₄)₂·6H₂O in the presence of an *N,N'*-dioxide ligand promotes the asymmetric [3+2] cycloaddition of alkynes with epoxides via a regioselective C–C bond cleavage to give 2,5-dihydrofurans. A catalytic amount of LiNTf₂ was necessary to increase the yield of the cycloaddition process.

SYNFACTS Contributors: Hisashi Yamamoto, Sukalyan Bhadra
Synfacts 2015, 11(1), 0054 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379747; **Reg-No.:** H15314SF

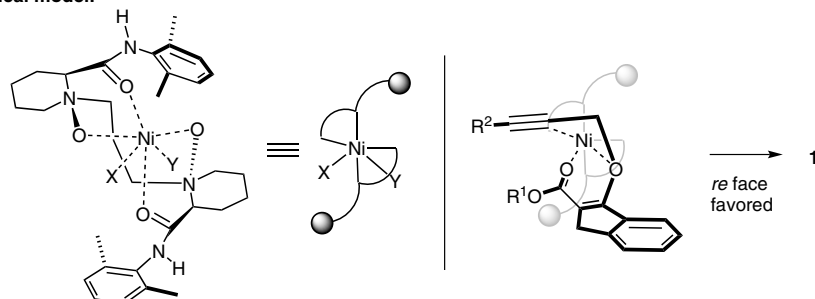
Comment: Notably, the asymmetric [3+2] cycloaddition of an alkene and an epoxide under optimized conditions afforded an optically active tetrahydrofuran derivative. According to the proposed activation model, the chiral nickel complex activates the epoxide to form a carbonyl ylide intermediate, through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

Y. LIU, H. HU, H. ZHENG, Y. XIA, X. LIU, L. LIN, X. FENG* (SICHUAN UNIVERSITY, CHENGDU AND LANZHOU UNIVERSITY, P. R. OF CHINA)
 Nickel(II)-Catalyzed Asymmetric Propargyl and Allyl Claisen Rearrangements to Allenyl- and Allyl-Substituted β -Ketoesters
Angew. Chem. Int. Ed. **2014**, *53*, 11579–11582.

Nickel-Catalyzed Asymmetric Claisen Rearrangement



Stereochemical model:



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.

SYNFACTS Contributors: Hisashi Yamamoto, Ramesh C. Samanta
Synfacts 2015, 11(1), 0055 Published online: 15.12.2014

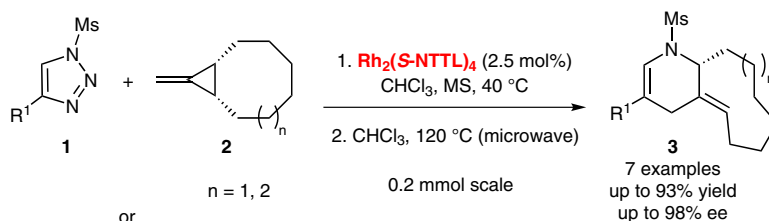
DOI: 10.1055/s-0034-1379752; **Reg-No.:** H15814SF

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.

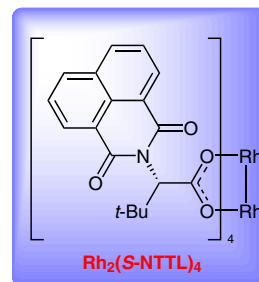
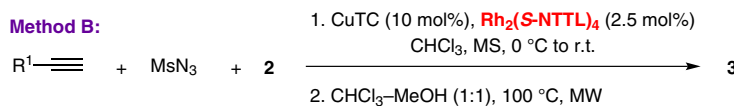
T. MIURA,* T. NAKAMURO, C.-J. LIANG, M. MURAKAMI* (KYOTO UNIVERSITY, JAPAN)
Synthesis of *trans*-Cycloalkenes via Enantioselective Cyclopropanation and Skeletal Rearrangement
J. Am. Chem. Soc. **2014**, *136*, 15905–15908.

Synthesis of *trans*-Cycloalkenes via Cyclopropanation and Rearrangement

Method A:



Method B:

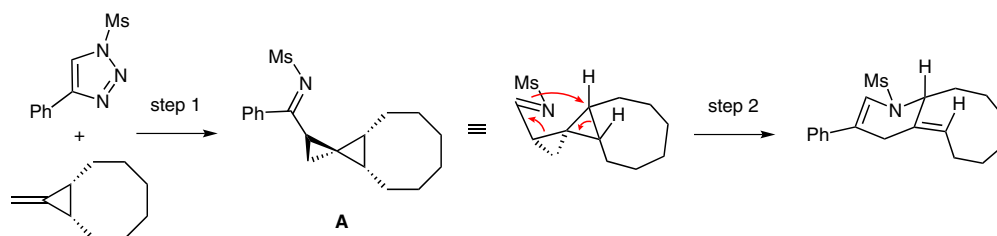


Substrate scope: Method A

R^1	Yield (%)	ee (%)
Ph	88	97
4-MeOC ₆ H ₄	82	98
4-CF ₃ C ₆ H ₄	91	97
2-Naph	88	96
3-thienyl	93	93
1-cyclohexenyl	83	98

93% yield
97% ee

Proposed mechanism:



Significance: There are few ways to access chiral medium-sized rings possessing a *trans* double bond (for selected examples, see: A. Deiters et al. *Chem. Eur. J.* **2002**, *8*, 1833; X.-N. Wang et al. *J. Am. Chem. Soc.* **2014**, *136*, 9802). Such motifs often exhibit planar chirality and may find application in the synthesis of complex polycyclic frameworks. The authors report an efficient procedure for the asymmetric synthesis of piperidine-fused *trans*-cycloalkenes **3** from triazoles **1** and methylenecyclopropanes **2**.

Comment: The reaction is initiated by the in situ formation of an α -imino rhodium carbenoid from triazole **1**. Cyclopropanation of the exocyclic methylene group of **2** leads to the formation of spirocyclic intermediate **A**, which can then undergo a thermal rearrangement under microwave irradiation to give *trans*-cycloalkene **3**. The authors propose a concerted mechanism, which draws similarity to the retro-Claisen [3,3]-sigmatropic rearrangement.

SYNFACTS Contributors: Mark Lautens, Christine M. Le
Synfacts 2015, 11(1), 0056 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379684; **Reg-No.:** L15014SF

Enantioselective Zr-Catalyzed Carboalumination Plus Cu-Catalyzed Cross-Coupling

Category

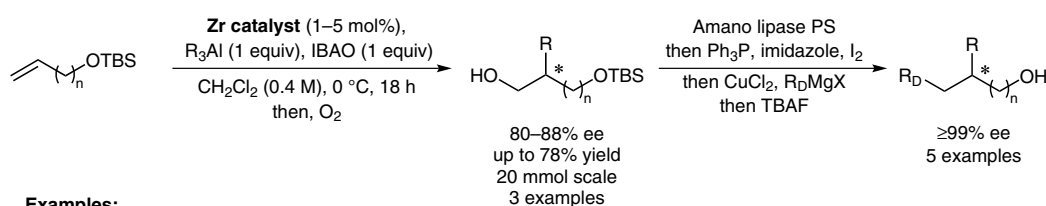
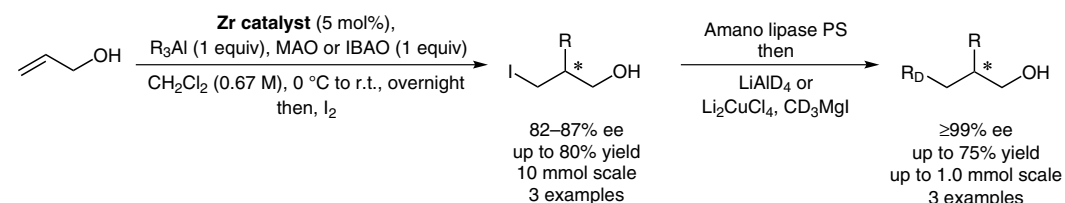
**Metal-Catalyzed
Asymmetric
Synthesis and
Stereoselective
Reactions**

Key words

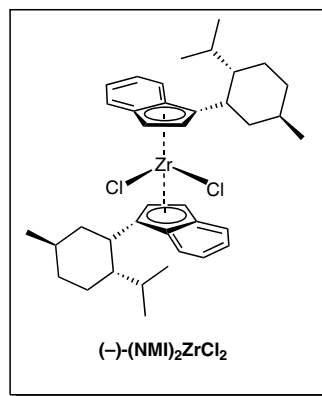
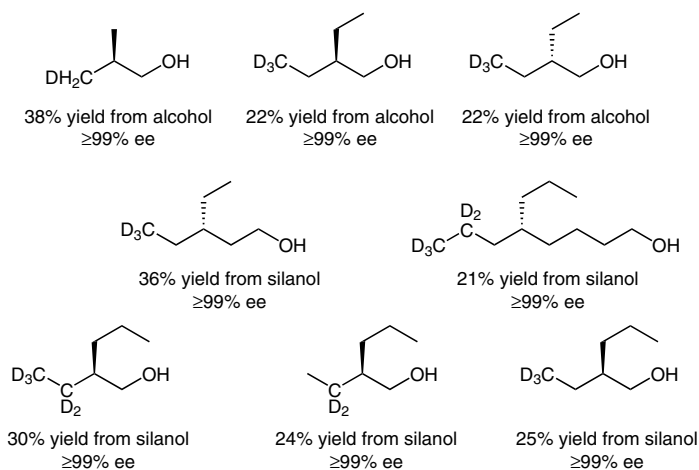
zirconium

neomenthylindanyl
ligands

cryptochirality



Examples:



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).

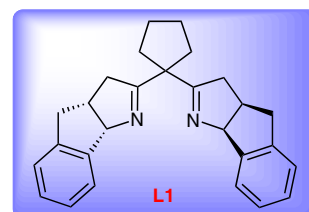
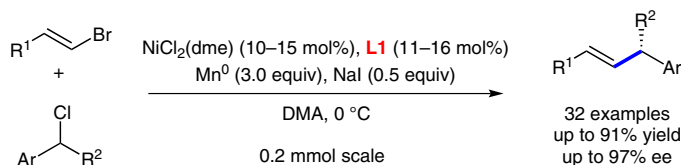
Comment: The products of the zirconium-catalyzed reaction were produced in modest ee's (80–88%), which were then upgraded to $\geq 99\%$ ee by lipase treatment. Introduction of deuterium was accomplished by treatment with LiAlD₄ or via copper-catalyzed cross-coupling. The enantiomeric ratios were determined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

Review: J. M. Seco, E. Quiñoá, R. Riguera *Chem. Rev.* **2004**, *104*, 17–118.

A. H. CHERNEY, S. E. REISMAN* (CALIFORNIA INSTITUTE OF TECHNOLOGY, PASADENA, USA)

Nickel-Catalyzed Asymmetric Reductive Cross-Coupling Between Vinyl and Benzyl Electrophiles
J. Am. Chem. Soc. **2014**, *136*, 14365–14368.

Nickel-Catalyzed Asymmetric Reductive Coupling of Vinyl and Benzyl Halides

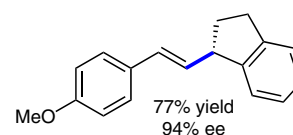
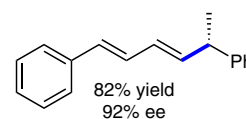
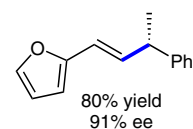


Selected examples:

R ²	R ³	Yield (%)	ee (%)
Me	H	91	93
Me	2-Me	44	85
Me	4-OMe	64	93
Et	H	80	97
Bn	H	82	93

R¹ = 4-MeOC₆H₄

R ¹	Yield (%)	ee (%)
4-MeC ₆ H ₄	83	96
4-FC ₆ H ₄	74	94
4-ClC ₆ H ₄	66	95
4-BPinC ₆ H ₄	59	94
4-OHC ₆ H ₄	86	93



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).

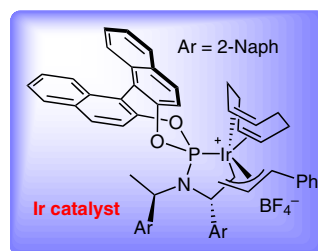
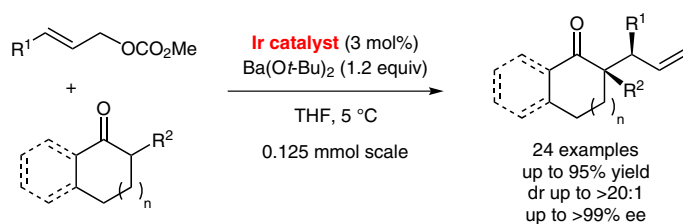
Comment: Using this method, a wide range of electron-rich and electron-deficient vinyl bromides and benzylic chlorides can be employed. Both *meta* and *para* substitution on the benzyl chloride component are well tolerated. However, *ortho*-substituted benzyl chloride derivatives demonstrate poor reactivity 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.

Review: D. A. Everson, D. J. Weix *J. Org. Chem.* **2014**, *79*, 4793–4798.

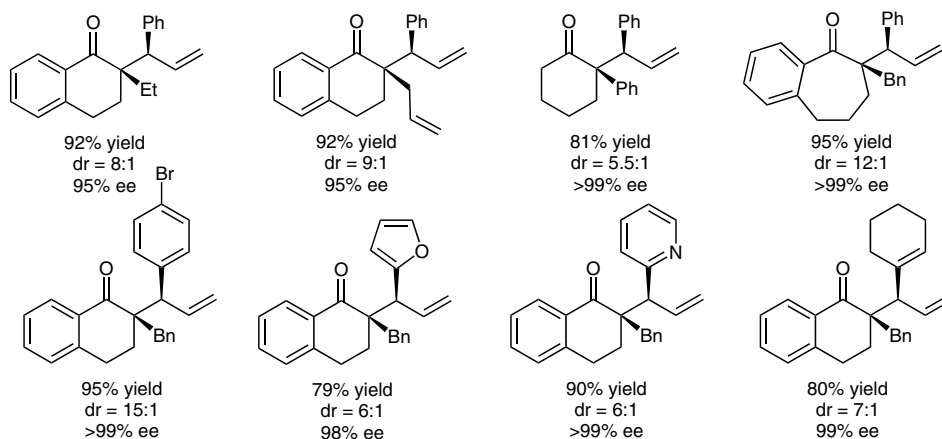
SYNFACTS Contributors: Mark Lautens, Christine M. Le
Synfacts 2015, 11(1), 0058 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379687; Reg-No.: L15314SF

W. CHEN, M. CHEN, J. F. HARTWIG* (UNIVERSITY OF CALIFORNIA, BERKELEY, USA)
Diastereo- and Enantioselective Iridium-Catalyzed Allylation of Cyclic Ketone Enolates: Synergistic Effect of Ligands and Barium Enolates
J. Am. Chem. Soc. **2014**, *136*, 15825–15828.

Diastereo- and Enantioselective Iridium-Catalyzed Allylation of Ketone Enolates



Selected examples:



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.

Review: J. F. Hartwig, L. M. Stanley *Acc. Chem. Res.* **2010**, *43*, 1461–1475.

SYNFACTS Contributors: Mark Lautens, Christine M. Le
Synfacts 2015, 11(1), 0059 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379686; **Reg-No.:** L15214SF

L. ZHANG, W. LIU, X. ZHAO* (TONGJI UNIVERSITY, SHANGHAI, P. R. OF CHINA)

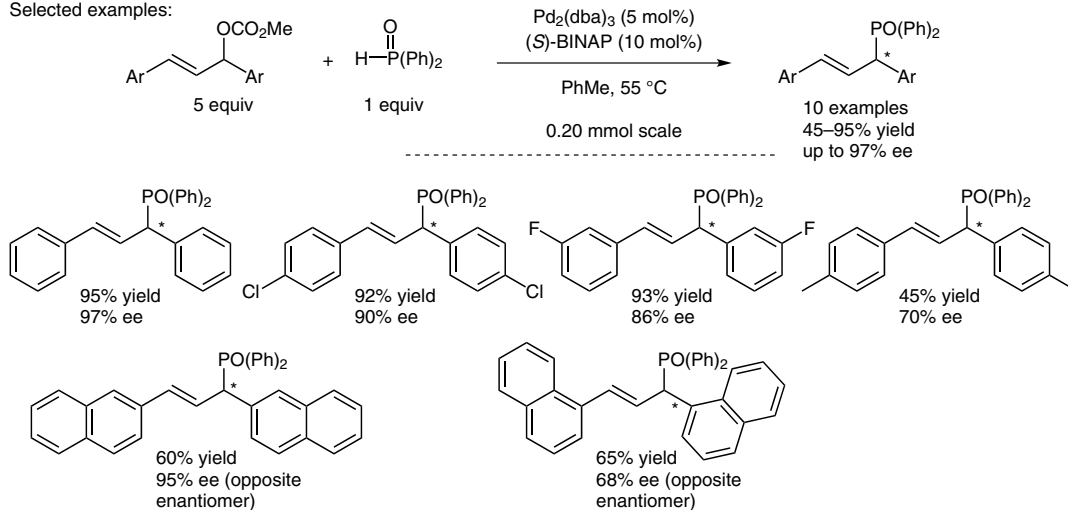
Carbon–Phosphorus Bond Formation by Enantioselective Palladium-Catalyzed Allylation of Diphenylphosphine Oxide

Eur. J. Org. Chem. **2014**, 6846–6849.

Enantioselective Allylation of Diphenylphosphine Oxide

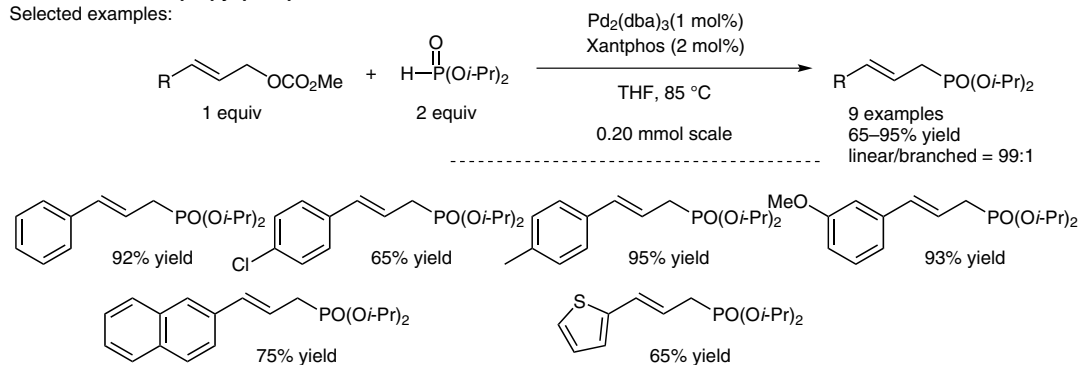
Reaction with diphenylphosphine oxide

Selected examples:



Reaction with diisopropyl phosphonate

Selected examples:

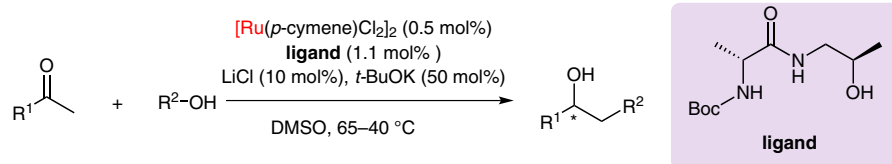


Significance: Enantioselective reactions for the formation of C–P bonds have received less attention than other carbon-heteroatom bond-forming reactions. The phosphorus-containing products or their derivatives can be used as chiral ligands, for example. Zhao and co-workers describe here the enantioselective 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).

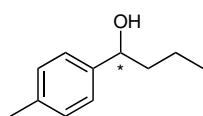
SYNFACTS Contributors: Mark Lautens, Thomas Johnson
Synfacts 2015, 11(1), 0060 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379695; **Reg-No.:** L16114SF

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.

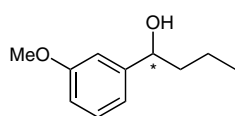
Tandem α -Alkylation–Asymmetric Transfer Hydrogenation of Acetophenones



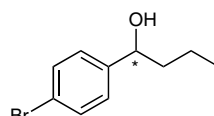
Selected examples:



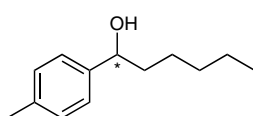
35% yield, 84% ee



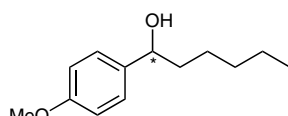
43% yield, 86% ee



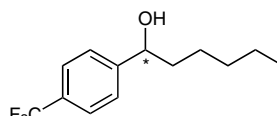
9% yield, 79% ee



34% yield, 88% ee

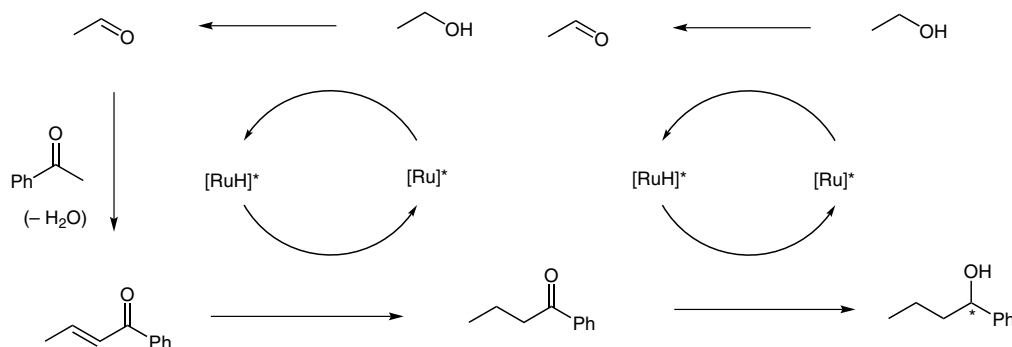


28% yield, 83% ee



19% yield, 57% ee

Proposed mechanism:



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 $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ as catalyst in the presence of an amino acid hydroxy amide as ligand.

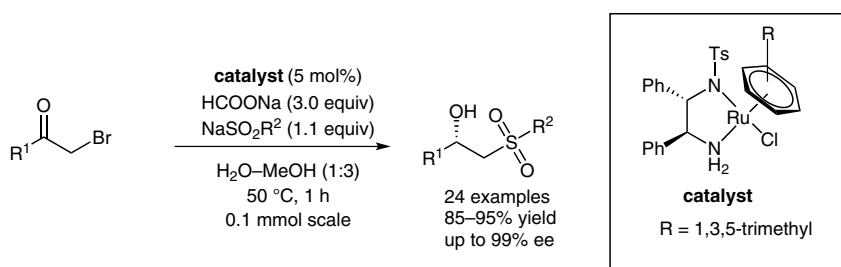
Comment: Diversely substituted acetophenones were successfully converted into chiral secondary alcohols via the borrowing hydrogen methodology in moderate yields and in moderate to good enantiomeric excess. In this process, primary alcohols served as both alkylating and reducing agents.

D. ZHANG, T. CHENG,* Q. ZHAO, J. XU, G. LIU* (SHANGHAI NORMAL UNIVERSITY, P. R. OF CHINA)

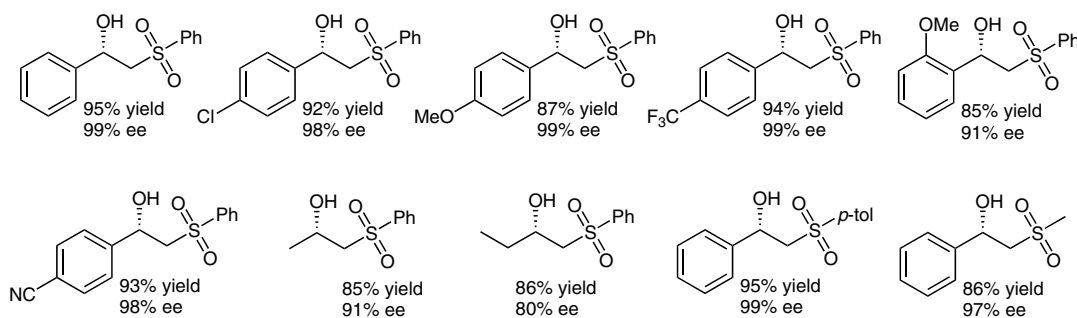
Highly Enantioselective One-Pot Synthesis of Chiral β -Hydroxy Sulfones via Asymmetric Transfer Hydrogenation in an Aqueous Medium

Org. Lett. **2014**, *16*, 5764–5767.

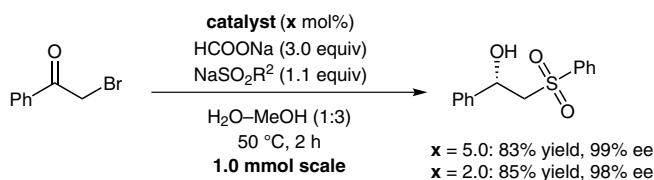
Enantioselective Synthesis of β -Hydroxy Sulfones via Transfer Hydrogenation



Selected examples:



Scale-up of the reaction:



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.

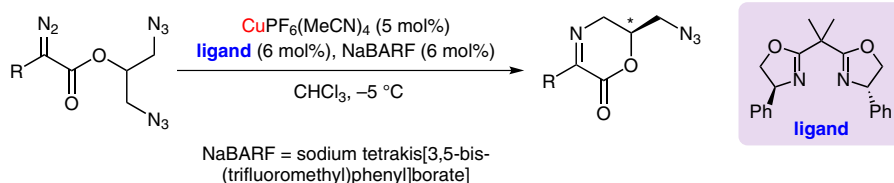
Comment: A variety of products could be formed in high yield and high to excellent enantioselectivity. Interestingly, both alkyl and aryl substituents can be tolerated at the R¹ and R² positions, with aryl groups giving superior results. Through kinetic studies, the authors demonstrate that nucleophilic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

SYNFACTS Contributors: Mark Lautens, Thomas Johnson
Synfacts 2015, 11(1), 0062 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379682; **Reg-No.:** L14814SF

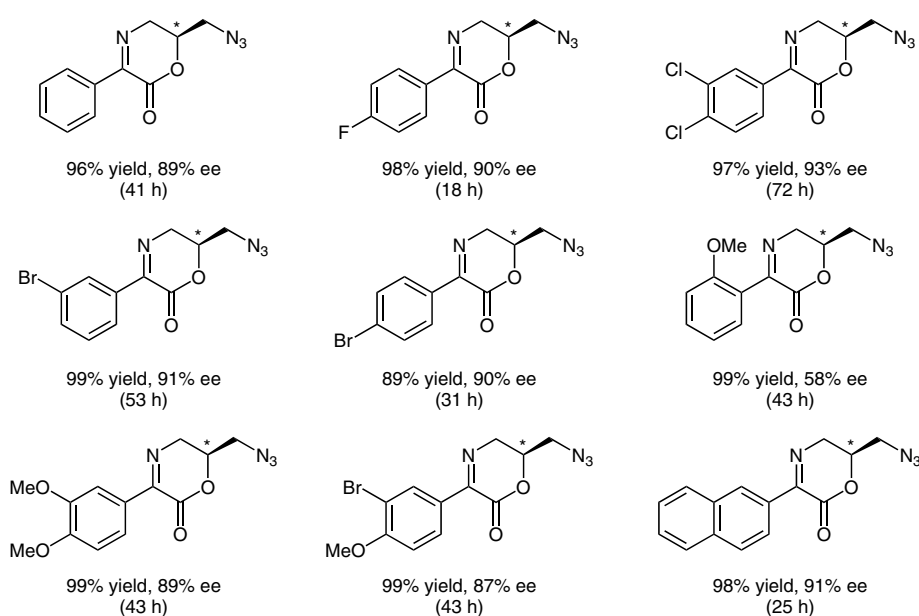
X.-P. WU, Y. SU, P. GU* (NINGXIA UNIVERSITY, YINCHUAN AND LANZHOU UNIVERSITY, P. R. OF CHINA)

Catalytic Enantioselective Desymmetrization of 1,3-Diazido-2-propanol via Intramolecular Interception of Alkyl Azides with Diazo(aryl)acetates
Org. Lett. **2014**, *16*, 5339–5341.

Intramolecular Asymmetric Desymmetrization via Copper Catalysis



Selected examples:



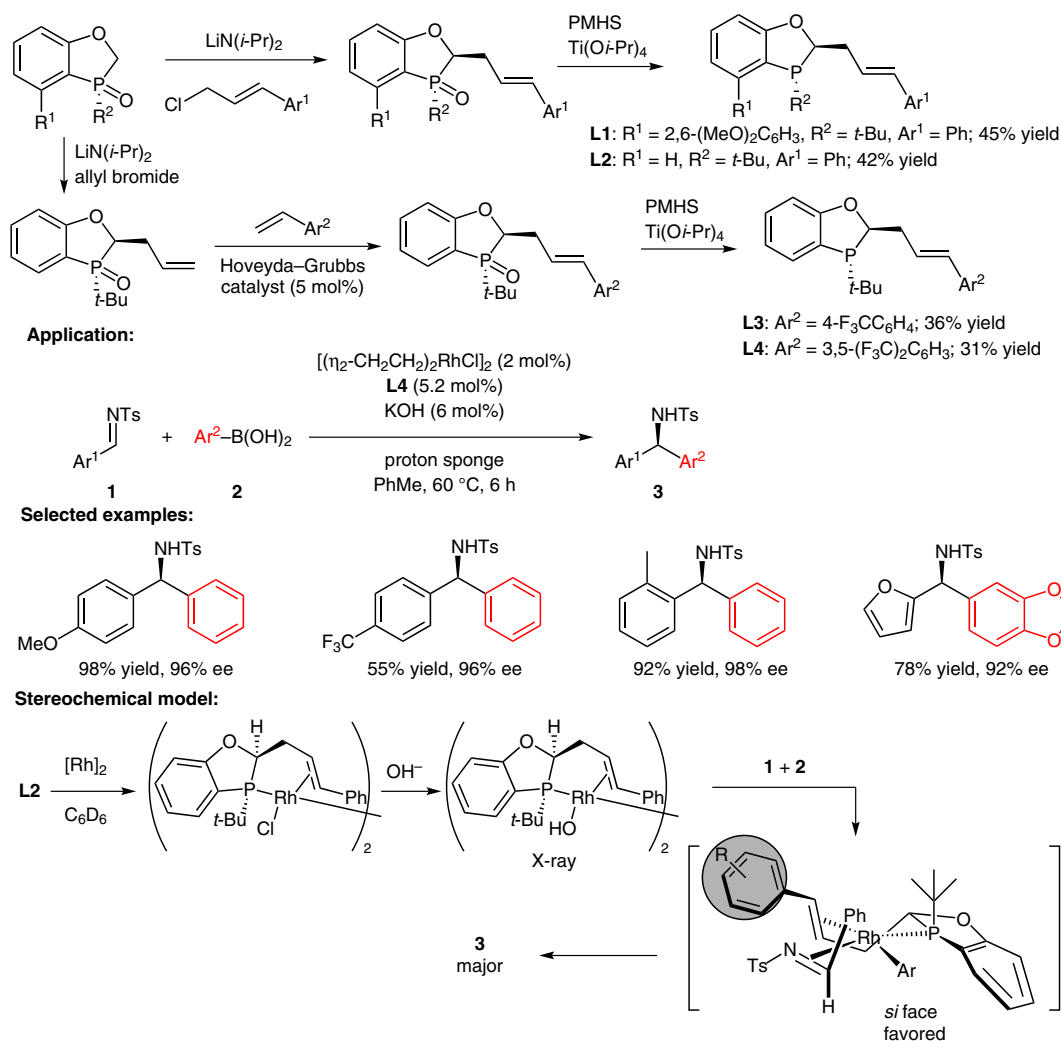
Significance: Hydroxy- and amino-functionalized C3-fragments play a pivotal role as synthetic intermediates. Whereas enantioselective desymmetrization of diols and glycerol were developed to provide hydroxyl-containing C3-fragments, the corresponding preparation of amino-containing C3-fragments has been 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 $\text{CuPF}_6(\text{MeCN})_4$ in the presence of (*S,S*)-PhBox and NaBARF with the larger and non-coordinating BARF⁻ anion. The new method provides reliable access to enantio-enriched azido-substituted 5,6-dihydro-1,4-oxazin-2-ones, which can be further converted into useful N-containing scaffolds.

SYNFACTS Contributors: Hisashi Yamamoto, Sukalyan Bhadra
Synfacts 2015, 11(1), 0063 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379746; **Reg-No.:** H15214SF

J. D. SIEBER,* D. CHENNAMADHAVUNI, K. R. FANDRICK, B. QU, Z. S. HAN, J. SAVOIE, S. MA, L. P. SAMANKUMARA, N. GRINBERG, H. LEE, J. J. SONG, C. H. SENANAYAKE (BOEHRINGER INGELHEIM PHARMACEUTICALS, RIDGEFIELD, USA)
Development of New P-Chiral P, π -Dihydrobenzooxaphosphole Hybrid Ligands for Asymmetric Catalysis
Org. Lett. **2014**, *16*, 5494–5497.

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.

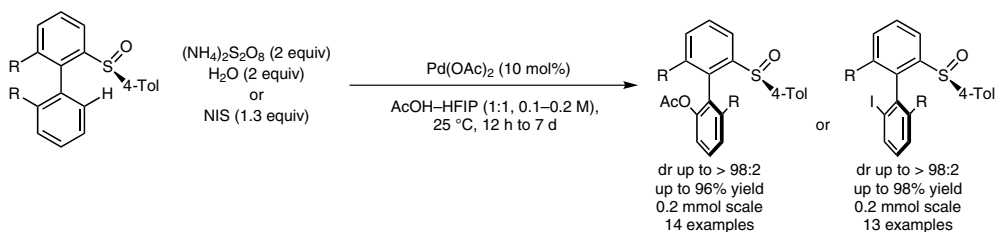
SYNFACTS Contributors: Hisashi Yamamoto, Ramesh C. Samanta
Synfacts 2015, 11(1), 0064 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379751; Reg-No.: H15714SF

C. K. HAZRA, Q. DHERBASSY, J. WENCEL-DELORD,* F. COLOBERT* (UNIVERSITÉ DE STRASBOURG, FRANCE)

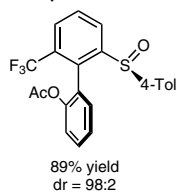
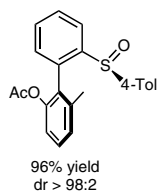
Synthesis of Axially Chiral Biaryls through Sulfoxide-Directed Asymmetric Mild C–H Activation and Dynamic Kinetic Resolution

Angew. Chem. Int. Ed. **2014**, *53*, 13871–13875.

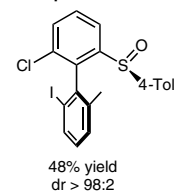
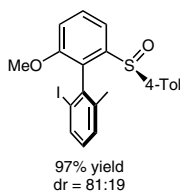
Axially Chiral Biaryl Compounds via Dynamic Kinetic Resolution



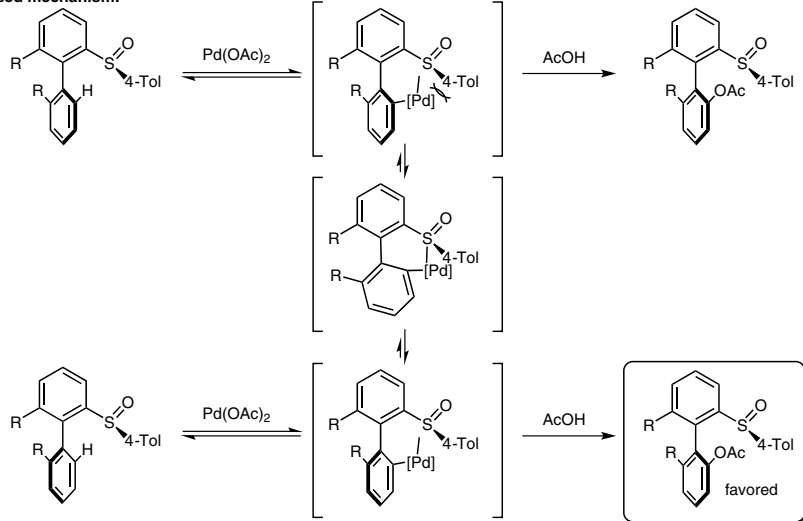
Selected acetoxyated examples:



Selected iodinated examples:



Proposed mechanism:



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 CO_2 .

SYNFACTS Contributors: Mark Lautens, Zafar Qureshi
Synfacts 2015, 11(1), 0065 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379689; Reg-No.: L15514SF

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Category

Metal-Catalyzed
Asymmetric
Synthesis and
Stereoselective
Reactions

Key words

palladium

chiral sulfoxides

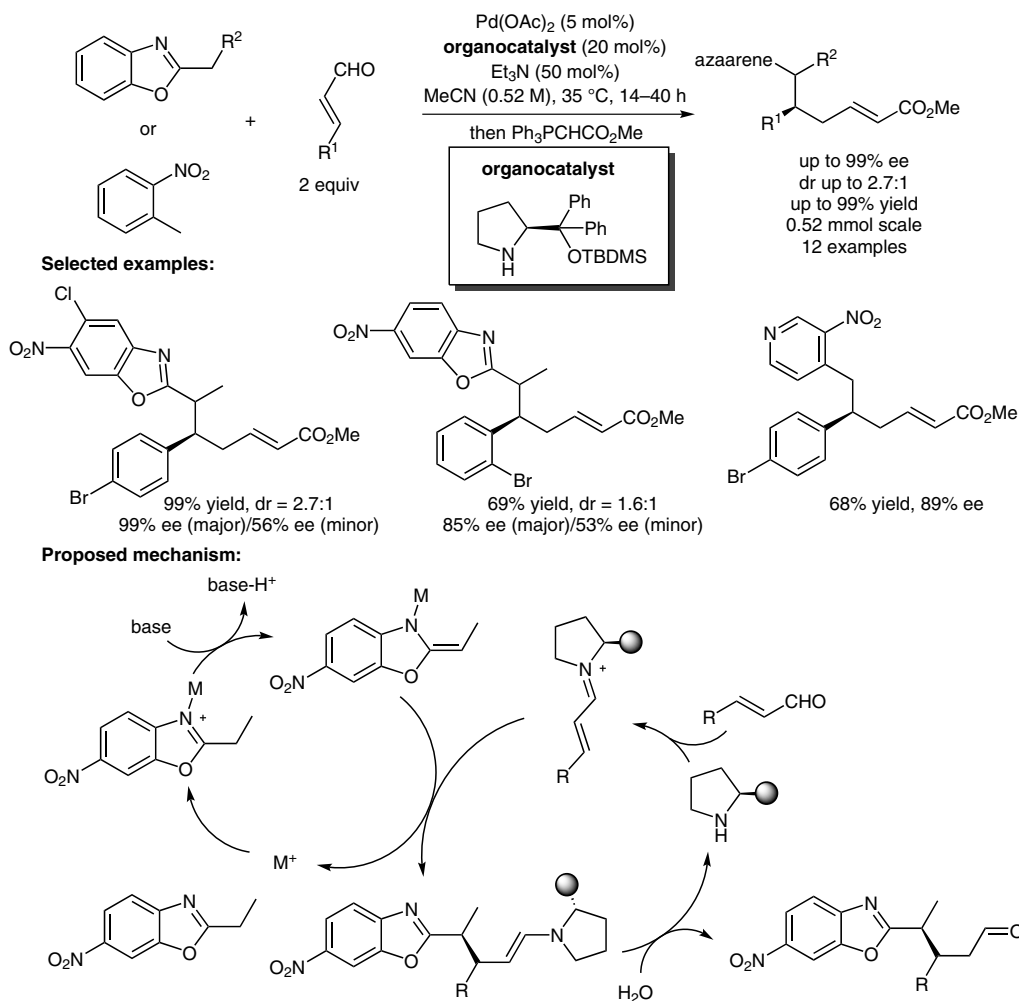
atropisomers

M. MEAZZA, V. CEBAN, M. B. PITAK, S. J. COLES, R. RIOS* (UNIVERSITY OF SOUTHAMPTON, UK)

Synergistic Catalysis: Enantioselective Addition of Alkylbenzoxazoles to Enals

Chem. Eur. J. **2014**, *20*, 16853–16857.

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.

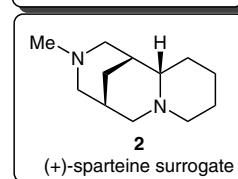
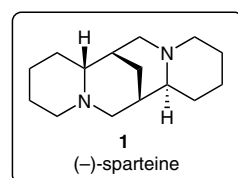
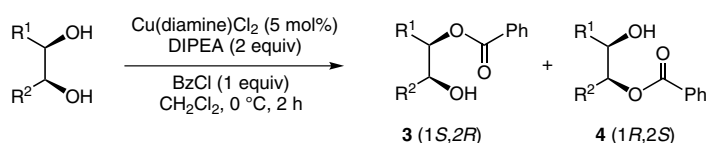
Comment: Although diastereoselectivity was poor (highest ratio 2.7:1), good enantioselectivities were observed for both major and minor isomers. The palladium acts as a Lewis acid to activate the azaarene, whereas the proline-derived organocatalyst activates the aldehyde towards 1,4-addition.

Review: A. E. Allen, D. W. C. MacMillan *Chem. Sci.* **2012**, *3*, 633–658.

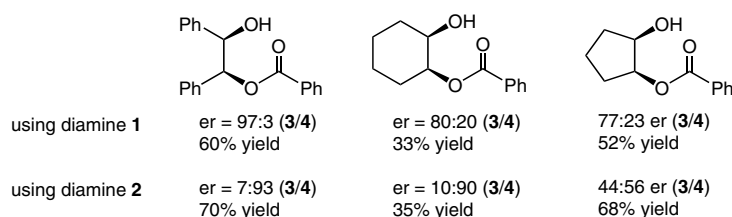
SYNFACTS Contributors: Mark Lautens, Zafar Qureshi
Synfacts 2015, 11(1), 0066 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379691; Reg-No.: L15714SF

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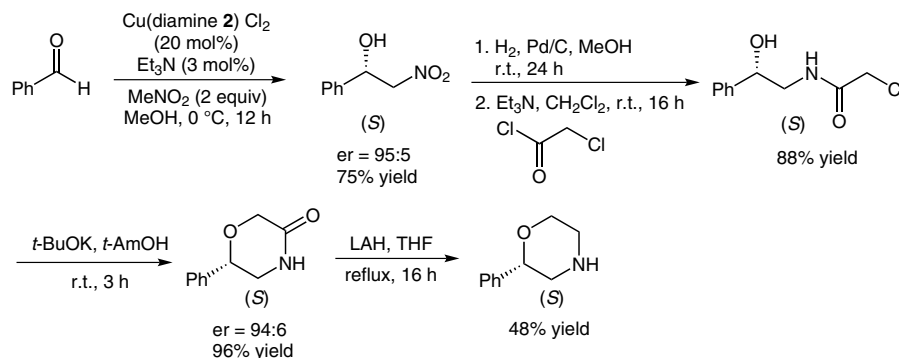
(–)-Sparteine versus (+)-Sparteine Surrogates in Copper(II)–Diamine-Catalyzed Reactions



Selected examples:



Application in the asymmetric Henry reaction, preparation of a chiral morpholine:

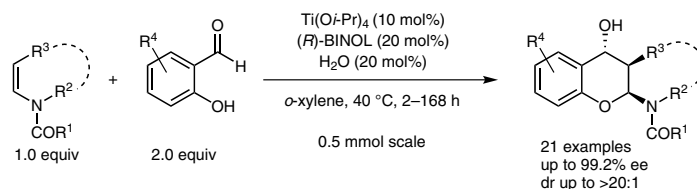


Significance: O'Brien and co-workers present an evaluation of copper(II)–diamine complexes comprising (–)-sparteine, (+)-sparteine surrogates, and Alexakis diamine in the desymmetrization of *meso*-diols and asymmetric Henry reaction. One of the nitro alcohol products was utilized in a concise synthesis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

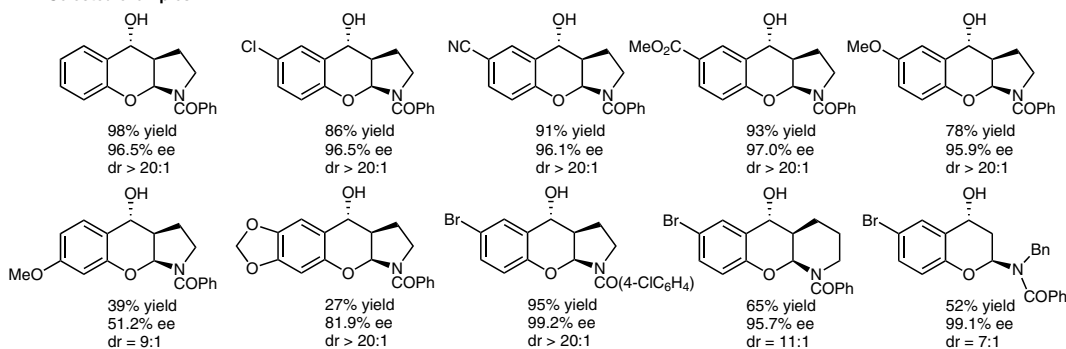
Comment: In order to compare the reactivity in asymmetric induction, the copper(II)–diamine catalysts, containing diamine **1** and **2**, were investigated in the enantioselective monobenzoylation of *meso*-1,2-diols and in the asymmetric Henry reaction. In both reactions the products were obtained 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.

L. HE, L. ZHAO, D.-X. WANG, M.-X. WANG* (INSTITUTE OF CHEMISTRY, CHINESE ACADEMY OF SCIENCES AND TSINGHUA UNIVERSITY, BEIJING, P. R. OF CHINA)
Catalytic Asymmetric Difunctionalization of Stable Tertiary Enamides with Salicylaldehydes: Highly Efficient, Enantioselective, and Diastereoselective Synthesis of Diverse 4-Chromanol Derivatives
Org. Lett. **2014**, *16*, 5972–5975.

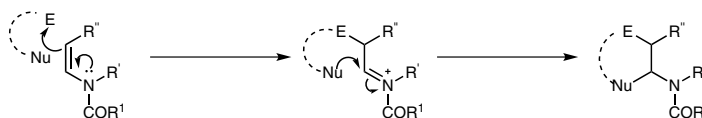
Enantioselective Reaction of Tertiary Enamides with Salicylaldehydes



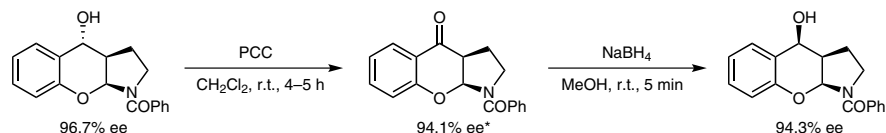
Selected examples:



Mode of reactivity:



Product derivatization:



*Slight loss in ee is explained by the presence of a minor amount of the opposite diastereomer of lower ee in starting material.

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.

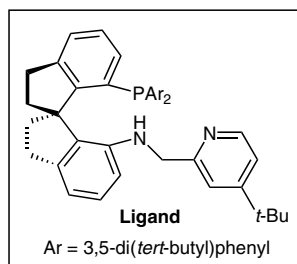
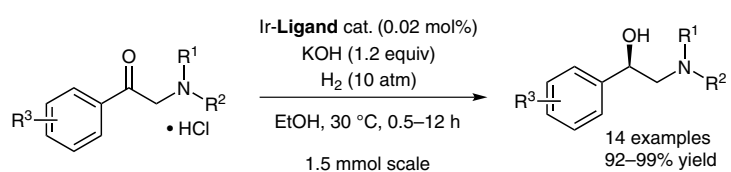
Comment: The use of a titanium–(*R*)-BINOL complex enabled the synthesis of diverse 4-chromanol products with good to excellent enantio- and diastereoselectivity. Water was found to have a marked effect on enantioselectivity: under anhydrous conditions, the ee decreased to 50.8%, whereas it was measured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

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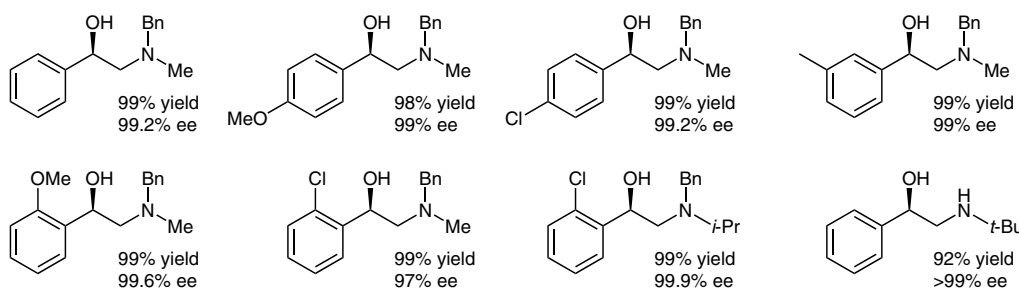
M.-L. YUAN, J.-H. XIE,* X.-H. YANG, Q.-L. ZHOU* (NANKAI UNIVERSITY, TIANJIN, P. R. OF CHINA)

Enantioselective Synthesis of Chiral 1,2-Amino Alcohols via Asymmetric Hydrogenation of α -Amino Ketones with Chiral Spiro Iridium Catalysts
Synthesis 2014, 46, 2910–2916.

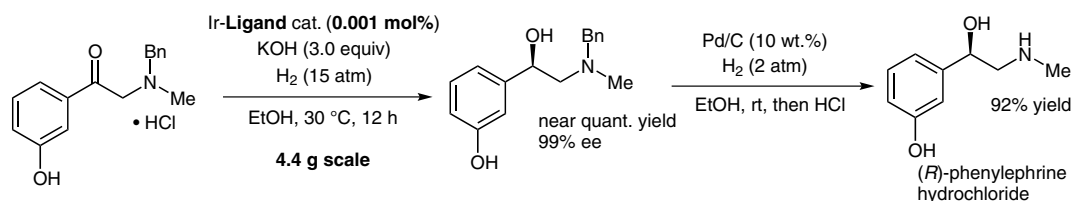
Synthesis of 1,2-Amino Alcohols via Asymmetric Hydrogenation



Selected examples:



Gram-scale synthesis of (*R*)-phenylephrine hydrochloride:



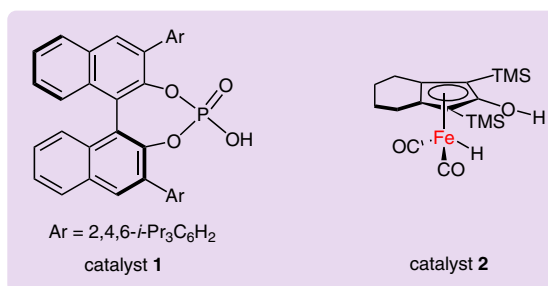
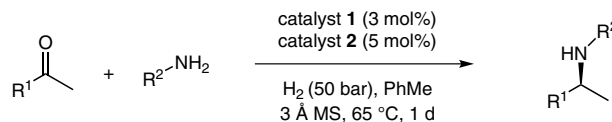
Significance: Chiral 1,2-amino alcohols are very commonly found in pharmaceuticals and natural products. Although many methods exist for their synthesis, the present one, based on asymmetric hydrogenation, is notable for its efficiency in terms of enantioselectivity and turnover number (up to 100 000).

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).

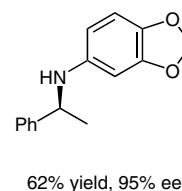
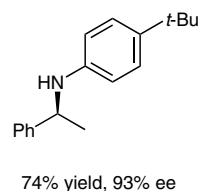
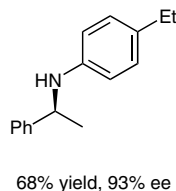
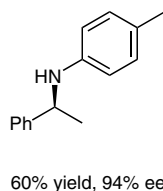
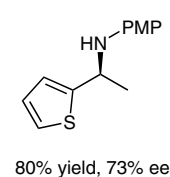
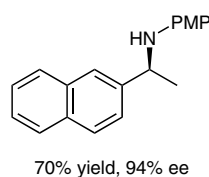
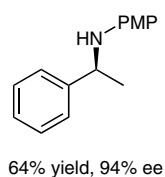
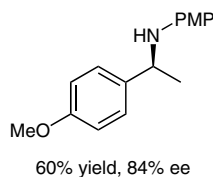
SYNFACTS Contributors: Mark Lautens, Thomas Johnson
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DOI: 10.1055/s-0034-1379693; Reg-No.: L15914SF

S. ZHOU, S. FLEISCHER, H. JIAO, K. JUNGE, M. BELLER* (LEIBNIZ-INSTITUT FÜR KATALYSE E.V. AN DER UNIVERSITÄT ROSTOCK, GERMANY AND CENTRAL CHINA NORMAL UNIVERSITY, WUHAN, P. R. OF CHINA)
Cooperative Catalysis with Iron and a Chiral Brønsted Acid for Asymmetric Reductive Amination of Ketones
Adv. Synth. Catal. **2014**, 356, 3451–3455.

Asymmetric Reductive Amination of Ketones



Selected examples:



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.