B. Y. Park, K. D. Nguyen, M. R. Chaulagain, V. Komanduri, M. J. Krische*
(University of Texas at Austin, USA)
Alkynes as Allymetal Equivalents in Redox-Triggered C–C Couplings to Primary Alcohols: (Z)-Homoallylic Alcohols via Ruthenium-Catalyzed Propargyl C–H Oxidative Addition
J. Am. Chem. Soc. 2014, 136, 11902–11905.

Ruthenium-Catalyzed Synthesis of Z-Olefins from Alkynes and Primary Alcohols

Significance: Allylation of alcohols represents a useful method for introducing complexity into a molecule. Previous methods for their synthesis include the use of stoichiometric organometallic reductants (see Review below). The authors report a redox-triggered allylation of alcohols to provide Z-selective olefins.

Review: G. C. Hargaden, P. J. Guiry Adv. Synth. Catal. 2007, 349, 2407-2424.

Comment: The reaction was shown to be general with broad scope. Both aromatic and aliphatic aldehydes participated in the reaction, although the aliphatic substrates provided olefins with diminished selectivities. The starting alcohol acts as a reducing agent to reduce Ru(II) to Ru(0), before participating as an electrophile. The proposed catalytic cycle invokes either an allenylruthenium hydride or an alkylidene ruthenacyclop propane as intermediate in the catalytic cycle.
Asymmetric Arylation of β,γ-Unsaturated α-Keto Amides

**Significance:** Asymmetric arylation of α,β-unsaturated carbonyl compounds is now a well-established reaction, and the extension to more challenging substrate classes is an active area of research. In this report, Liao and co-workers describe the highly chemoselective and enantioselective arylation of β,γ-unsaturated α-keto amides.

**Comment:** The keto amide substrates possess a particularly electrophilic carbonyl group that could undergo 1,2-addition, but excellent chemoselectivity in favor of 1,4-addition is observed. While ortho-substituted arylboronic acids were not tolerated, ortho-substituted aryl groups could be introduced as Ar1 in the substrate. The reaction was applied to the formal synthesis of sertraline.
K. ENDO,* S. YAKEISHI, R. TAKAYAMA, T. SHIBATA* (KANAZAWA UNIVERSITY, PRESTO SCIENCE AND TECHNOLOGY AGENCY, KAWAGUCHI, AND WASEDA UNIVERSITY, TOKYO, JAPAN)
Highly Chemo-, Enantio-, and Regioselective Synthesis of α,α-Disubstituted Furanones by Cu-Catalyzed Conjugate Addition
Chem. Eur. J. 2014, 20, 8893–8897.

Asymmetric Synthesis of Furanones via Copper-Catalyzed Conjugate Addition

Significance: Enantioselective alkylation of the γ-position of butenolides has been extensively studied; however, the enantioselective and regioselective alkylation of the α-position of butenolides is undeveloped. The authors developed a highly chemo-, enantio-, and regioselective synthesis of butenolides bearing an α-chiral quaternary stereogenic center via copper-catalyzed asymmetric conjugate addition of organoaluminum reagents to unsaturated keto esters.

Comment: A wide variety of benzyl keto esters bearing both an electron-withdrawing group and an electron-donating group were compatible in the present reaction with high enantioselectivities. Furthermore, several synthetic transformations of furanones represent inexpensive facile approaches to various functionalization scaffolds bearing a quaternary stereogenic center.

SYNFACTS Contributors: Hisashi Yamamoto, Fengtao Zhou
Synfacts 2014, 10(10), 1043 Published online: 17.09.2014
DOI: 10.1055/s-0034-1379067; Reg-No.: H11714SF
Rhodium-Mediated Arylative 1,2-Addition Providing Chiral Thiadiazolines

General reaction:

\[
\begin{align*}
\text{ArB(OH)}_2 \text{(2 equiv)} & \quad [\text{Rh(coe)}_2\text{Cl}]_2 \text{(1.5 mol%)} \\
\text{L} \text{(3.3 mol%)} & \quad \text{KF (1.5 M), CH}_2\text{Cl}_2, 40 ^\circ\text{C}
\end{align*}
\]

0.25 mmol scale

Selected examples:

\[
\text{Ar} = 4-\text{MeOC}_6\text{H}_4, \quad \text{Ar} = 1-\text{Naph}, \quad \text{Ar} = 4-\text{FC}_6\text{H}_4
\]

Significance: The authors describe a rhodium-mediated asymmetric 1,2-addition of phenylboronic acids to 3,4-disubstituted 1,2,5-thiadiazol 1,1-dioxides under mild conditions employing a branched \(N\)-alkenylsulfonamide ligand. This process renders the installation of a chiral quaternary center possible, which represented a challenge in rhodium-catalyzed 1,2-additions. Noteworthy, no diarylation occurred in all shown cases.

Comment: The derived thiadiazolines were obtained with very high yield (up to 99%) and enantioselectivity (up to 99%). The products may serve as valuable intermediates en route to chiral 1,2-diamines, \(\alpha\)-amino acids, or cyclic sulfonamides. In contrast to the high selectivity and yield, the low selectivity of unsymmetrically substituted 1,2,5-thiadiazol 1,1-dioxides remains an issue to be addressed in future work.
Y. LIU, P. DENG, X. LI, Y. XIONG, H. ZHOU* (CHONGQING MEDICAL UNIVERSITY AND CHONGQING UNIVERSITY, P. R. OF CHINA)

Asymmetric Henry Reaction Catalyzed by a Chiral Dinuclear Nickel Complex

*Synlett* 2014, 25, 1735–1738.

**Nickel-Catalyzed Enantioselective Henry Reaction**

**Synthesis of the ligand:**

![Ligand Synthesis](image)

**General reaction:**

![General Reaction](image)

**Selected examples:**

![Example Reactions](image)

**Significance:** The catalytic asymmetric Henry reaction is a useful carbon–carbon bond-forming process in organic chemistry. The resulting β-hydroxy nitroalkanes can be transformed into various biologically important building blocks. The authors report an enantioselective Henry reaction catalyzed by a chiral dinuclear nickel complex.

**Comment:** The authors developed the chiral polyfunctional ligand *L*₁, which was easily prepared from an L-amino acid and a commercial dialdehyde. A novel catalyst containing dinuclear nickel was applied to the asymmetric Henry reaction with good enantioselectivities (up to 91% ee) and moderate yields (up to 72%). The new ligand may be applicable to other dinuclear catalysts.
Silver-Catalyzed Asymmetric Aldol Reaction Using Alkenyl Trihaloacetates

**Significance:** The β-hydroxy carbonyl moiety is a key synthon for various natural products or bioactive compounds, and the aldol reaction is the most efficient way to synthesize that moiety. The authors reported a novel aldol reaction of an aldehyde with alkenyl trihaloacetate as source of an enolate equivalent.

**Comment:** The (S)-BINAP–AgOTf system affords the aldol product from alkenyl trihaloacetate in good to excellent yields with high enantioselectivity as well as good anti/syn selectivity. The reaction proceeds through the formation of chiral silver enolates from alkenyl trihaloacetates.
Copper–Lewis Acid Catalyzed Synthesis of Dihydroquinolones

Significance: The synthesis of the dihydroquinolone motif is an important subject due to its pharmaceutical relevance. The authors present a copper–Lewis acid catalyzed tandem synthesis of dihydroquinolones. Using BINOL-derived N-triflyl phosphoamide as ligand, the products were obtained in high yields.

Comment: Although the enantioselectivity of this reaction is modest, the authors have developed a one-step, convenient synthesis of dihydroquinolones. Their proposed reaction mechanism involves stepwise imine formation and subsequent intramolecular nucleophilic addition of the enolate.
Asymmetric Fluorination and Hydroxylation via Iron Catalysis

**Significance:** Iron-catalyzed C–H bond functionalizations are of profound interest, given the abundance and environmentally benign character of iron salts. In the present study, bipyrrrolidine backbones bearing iron(III)–salen complexes enable catalytic enantioselective α-fluorination and α-hydroxylation of β-keto esters and N-Boc oxindoles.

**Comment:** The rigid bipyrrrolidine backbone in the iron–salen complex enhances the stereoselectivities of the reactions. In both cases, the fluorination and the hydroxylation of β-keto esters, the enantioselectivity diminishes with the decrease in steric bulk of the alkoxy substituent of the ester group.

**Enantioselective fluorination of β-keto esters:**

**Enantioselective hydroxylation of β-keto esters:**

**Plausible mechanism:**

**SYNFACTS Contributors:** Hisashi Yamamoto, Sukalyan Bhadra

**SYNFACTS 2014, 10(10), 1048 Published online: 17.09.2014**

**DOI:** 10.1055/s-0034-1379064; **Reg-No.:** H11414SF
Catalytic Asymmetric Nitroaldol Reaction Using Continuous-Flow Technique

**Significance:** Recently, the use of continuous-flow techniques has emerged as an indispensable tool for the production of specialty chemicals. This technique allows performing reactions of extremely reactive and short-lived intermediates in a safer manner. The authors developed an anti-selective asymmetric nitroaldol reaction within a continuous-flow system by means of heterobimetallic catalysis.

**Comment:** The active Nd/Na-based heterobimetallic catalyst was confined on multiwalled carbon nanotubes (MWNT) via self-assembly of the chiral ligand and metal salts without covalent bond formation. The nitroaldol reaction was readily scaled-up to provide a practical synthesis of necessary chiral building blocks in high yield and enantioselectivity, towards the synthesis of AZD5423.

**SYNFACTS Contributors:** Hisashi Yamamoto, Sukalyan Bhadra

**Synfacts** 2014, 10(10), 1049 Published online: 17.09.2014

DOI: 10.1055/s-0034-1379063; Reg-No.: H11314SF
Copper-Catalyzed Asymmetric exo'-Selective [3+2] Cycloaddition

**Significance:** The authors present the copper-catalyzed asymmetric exo'-selective [3+2] cycloaddition of indoles with imino esters. A series of chiral pyrroindolines were prepared in good yields (up to 99%) with excellent enantioselectivities (up to 99% ee).

**Comment:** This reaction represents the first report of the asymmetric formal [3+2] cycloaddition using electrophilic indoles. The PyBidine/Cu complex is essential for the success. This protocol offers good opportunities to develop diverse and complex chiral pyrroindoline compounds.

**Selected examples:**

| Compound | Yield | Exo:Exo:Endo (or Endo') | Enantiomeric Excess |
|----------|-------|-------------------------|---------------------|
| NO2      | 97%   | 99:99:99 | 99.6% ee (exo) |
| NC       | 99%   | 99:99:99 | 99% ee (exo) |
| BzO      | 82%   | 99:99:99 | 99% ee (exo) |
| OMe      | 81%   | 99:99:99 | 99% ee (exo) |
| DS       | 82%   | 99:99:99 | 99% ee (exo) |

**Transformation of the product:**

- **Zn nanopowder (20 equiv) TMSCl**
  - MeOH, 70 °C, 30 min
- **Bu3SnH (2 equiv) AIBN (1.2 equiv)**
  - PhMe, 80 °C, 20 min

| Compound | Yield | Exo:Exo:Endo (or Endo') | Enantiomeric Excess |
|----------|-------|-------------------------|---------------------|
| NO2      | 84%   | 99:99:99 | 98% ee |
| NC       | 72%   | 99:99:99 | 98% ee |
Enantioselective Carbonyl Carboacylation Initiated by C–C Bond Activation

**Significance:** Catalytic reactions involving C–C bond activation as the key step have emerged in recent years. Asymmetric variants of such processes are relatively rare, and now include this highly enantioselective carbonyl carboacylation to give bicyclic lactones.

**Comment:** Very high enantiomeric ratios and good to high yields are obtained for a variety of cyclobutanone precursors. C=O extrusion was not observed, except with more hindered ketones \((R_3 = \text{Bu}, \text{not shown})\). The oxidative addition in the C–C bond in preference to the aldehydic C–H bond is notable.
Erratum

Enantioselective Carbonyl Carboacylation Initiated by C–C Bond Activation

L. Souillart, N. Cramer* Synfacts 2014, 10, 1051.

The starting materials are 3,3-disubstituted (not 2,3-disubstituted) cyclobutanones. The correct scheme is shown below. We apologize for this error.

Proposed mechanism:

Selected examples:
Six-Membered N-Heterocycles via Enantioselective Hydroacylation

**Significance:** Hydroacylation represents a well elaborated method for the functionalization of olefins. The synthesis of six- and seven-membered carbocycles became feasible in addition to the well-studied five-membered rings. However, nitrogen-containing heterocycles still remain rare or are realized under very sophisticated reaction conditions. The authors describe a simple rhodium-mediated asymmetric hydroacylation, providing six-membered N-heterocycles with excellent selectivity.

**Comment:** The substrate scope is very general regarding the indole’s backbone substitution as well as the structure of the olefins employed for both the indole- and pyrrole-derived substrates, providing the desired products with high ee (92–99%). However, the yields vary widely, which was partly attributed to decarbonylation processes. The utility of the process was exemplified by the synthesis of the nonsteroidal aromatase inhibitor \((S,Z)\)-MR 20492.

**Selected examples:**

- 99% yield 97% ee
- 42% yield 96% ee
- 23% yield 96% ee
- 79% yield 97% ee
- 51% yield 94% ee
- 65% yield 95% ee
- 96% yield 97% ee
- 93% yield 93% ee
- 96% yield 97% ee
- 93% yield 97% ee
- 98% yield 98% ee

**Application within the synthesis of \((S,Z)\)-MR 20492**

- 85% yield 95% ee
- 57% yield

**General reaction:**

\[
\text{[Rh(coe)Cl]_2} \ (2.5 \text{ mol\%}) \\
\text{L} \ (5 \text{ mol\%}) \\
\text{AgBF}_4 \text{ or AgSbF}_6 \ (5 \text{ mol\%}) \\
1,4\text{-dioxane, 120 °C} \ (24 \text{ h}) \\
0.2 \text{ mmol scale}
\]

\[
\text{L: } \begin{array}{c}
\text{P(Tol)}_2 \\
\text{P(Tol)}_2
\end{array}
\]

\[
(R)\text{-Tol-BINAP}
\]
Rhodium-Catalyzed Enantioselective Synthesis of Allylic Sulfones

**Significance:** Chiral allylic sulfones are important biologically active motifs present in anticancer, antibacterial, and herbicidal agents. They can also serve as useful building blocks in organic synthesis. The authors report a palladium-catalyzed synthesis of allylic sulfones from chiral allylic alcohols through double inversion, leading to net stereo-retention.

**Comment:** Boric acid was used to facilitate the formation of the \( \pi \)-allyl palladium intermediate by making the hydroxyl group a better leaving group. The sulfinate nucleophile was shown to attack at the least hindered position. With symmetrical substrates, the chiral information is lost during the intermediate \( \pi \)-allyl palladium species, which leads to complete racemization of the substrate.

**Selected examples:**

- \( R^1 \): \( \text{NHAc} \), yield 88%, SM: 97% ee, PR: 97% ee
- \( R^1 \): \( \text{Cl}, \text{Cl} \), yield 51%, SM: 97% ee, PR: 97% ee
- \( R^1 \): \( \text{S} \), yield 58%, SM: 97% ee, PR: 97% ee
- \( R^1 \): \( \text{S} \), yield 72%, SM: 91% ee, PR: 91% ee
- \( R^1 \): \( \text{S} \), yield 51%, SM: 95% ee, PR: 95% ee

**Reactions of regioisomeric and symmetric starting materials:**

- \( \text{OH} \), yield 90%, ee 90%
- \( \text{OH} \), yield 90%, ee 90%
- \( \text{Ph} \), yield 77%, ee 90%
- \( \text{Ph} \), yield 67%, ee 0%

**Pd(OAc)\(_2\) (5 mol%)**
**rac-BINAP (5 mol%)**
**B(OH)\(_3\) (4 equiv)**

**dioxane (0.4 M), 100 °C, 5 h**

up to 97% ee
up to 97% yield
0.2 mmol scale
20 examples

**Key words**

- BINAP
- allylic sulfones
- palladium
**Synthesis of All-Carbon Quaternary Stereocenters via Copper-Catalyzed N-Arylation**

**Significance:** The authors report an enantioselective construction of cyano-bearing all-carbon quaternary stereogenic centers in high yields and excellent enantioselectivities by desymmetrization using a copper-catalyzed intramolecular N-arylation in the presence of a BINOL-derived ligand.

**Comment:** In addition to an excellent level of enantioselectivity, desymmetrization by copper-catalyzed N-arylation is an efficient entry to spirocyclic compounds. Interestingly, the presence of the cyano group at the prochiral center plays a key role in the title process. DFT studies are also reported, which account for the origin of the enantioselectivity.
Ruthenium-Catalyzed Asymmetric Addition of Malononitrile to α,β-Unsaturated Ketones

**Significance:** Asymmetric conjugate addition of carbanion nucleophiles to α,β-unsaturated carbonyl compounds represents one of the most powerful strategies for stereoselective formation of carbon–carbon bonds. However, using malononitrile as nucleophile for this reaction is relatively little explored. The authors report a ruthenium diamine complex catalyzed asymmetric Michael addition of malononitrile to chalcone and its analogues, giving adducts in good yields with moderate to good enantioselectivities.

**Comment:** Interestingly, reactivities and enantioselectivities can be greatly improved after adding the mixture of CsOAc with CsOH as bases. However, reactivities and enantioselectivities are highly dependent upon both the electronic properties and the hindrance of the substrates. Substrates with electron-withdrawing substituents on the aryl ring proceeded with higher enantioselectivities and reactivities than substrates with electron-donating substituents.
Stereoselective Synthesis of α-Amino Aldols from Terminal Alkynes

**Significance:** Few reactions have been more extensively studied than the aldol reaction. Nowadays, non-conventional protocols are being discovered to access aldol products from precursors other than aldehydes or ketones. The authors report such a procedure, in three steps, starting from terminal alkynes.

**Comment:** α-Amino aldol products could be obtained in moderate to good yields and with excellent syn selectivity in the three-step, two-pot process. In addition to the triazole scope, variation of the sulfonyl substituent was demonstrated (five examples, not shown). The authors mention that the formation of the lithium enolate of an α-amino ketone failed, affirming the superiority of their method over a traditional aldol reaction for this class of substrates.
Copper-Catalyzed Intramolecular Propargylic Amination

**Significance:** Nishibayashi and co-workers report an intramolecular amination of propargylic acetates catalyzed by chiral copper–pybox complexes. Using this method, biologically useful α-ethynyl isoindolines were synthesized in high yield with high enantioselectivities under mild conditions.

**Comment:** The authors previously reported intermolecular propargylic amination with secondary amines (*J. Am. Chem. Soc.* 2010, 132, 10592). In this report, they achieved intramolecular amination of propargylic acetate having the amine moiety at a suitable position. They suggested this intramolecular amination proceeded via a copper–alkylidene complex.
Enantioselective Hydrogenation of α,β-Disubstituted Nitroalkenes

Significance: Asymmetric hydrogenation is one of the most versatile methods for the synthesis of enantioenriched compounds, from laboratory to manufacturing scale. The authors report the hydrogenation of α-branched nitroalkenes (previously difficult substrates) using a Josiphos ligand to yield nitroalkanes, which can serve as precursors to chiral amphetamines.

Comment: The reaction tolerates various functional groups, including heterocycles, giving generally good to high yields of nitroalkanes. The enantiomeric excesses remain variable for this new entry to amphetamines, as exemplified by the synthesis of N-protected lisdexamfetamine (Vyvanse™) on gram scale.
Copper-Catalyzed Stereoselective Reactions of B₂(pin)₂, 1,3-Enynes, and Aldehydes

**Significance:** Optically active homopropargylic alcohols are an important class of molecules. Their synthesis usually requires the addition of alkenylmetal compounds to aldehydes (J. C. Antilla and co-workers *Angew. Chem. Int. Ed.* 2012, 51, 1391). The authors report the enantioselective copper-catalyzed borylation of an enyne followed by addition to an aldehyde to synthesize homopropargylic alcohols.

**Comment:** Although the reaction was followed by an oxidation step to give diols, the intermediate alkyl boron species was coupled with allyl phosphates or aryl bromides to elaborate the products. Transition states for both the borylation step and the addition to the aldehyde were modelled using DFT calculations to explain the stereochemical outcome.
Enantiospecific Ligand-Free Cross-Coupling of Ammonium Triflates and Boronic Acids

**Significance:** Watson and co-workers report a nickel-catalyzed ligand-free enantiospecific cross-coupling of benzylic ammonium triflates and heteroaromatic boronic acids.

**Comment:** The authors describe a nickel-catalyzed enantiospecific conversion of a wide range of amine derivatives into highly enanto-enriched di- and triarylalkanes and 1,3-diaryl allylic products without any ancillary phosphine or NHC ligand. Amazingly, these reaction conditions gave inversion of the absolute stereochemistry of the benzylic stereocenter with a high level of stereochemical fidelity, high yields, and high enantioselectivities.
Asymmetric Construction of Quaternary Stereocenters by Magnesium Catalyzed Direct Amination of β-Ketoesters Using In Situ Generated Nitrosocarbonyl Compounds as Nitrogen Sources

Chem. Sci. 2014, 5, 3941–3945.

Direct Amination of β-Keto Esters Employing Nitrosocarbonyl Compounds

Significance: The authors report a new Lewis acid catalyzed hydroxyamination process of β-keto esters under very mild conditions. The nitrosocarbonyl compounds PG-N=O (NH₂⁺ source) are generated in situ from the respective acceptor-substituted hydroxylamines and MnO₂ to overcome their pronounced instability. The substrate scope is remarkable, especially because the yields (up to 97%) and enantioselectivities (up to 96%) are consistently very high.

Comment: In contrast to the usually employed nitrosobenzene derivatives or azodicarboxylates, the protecting group on the nitrosocarbonyl compounds can be deprotected readily. In addition to the activation of the dicarbonyl compound, the magnesium-based Lewis acid causes the excellent N selectivity due to its oxophilicity (O complexation). Chemoselectivities are excellent throughout the substrate scope (>20:1); tert-butyl esters were shown to give the best results.
Erratum

Direct Amination of β-Keto Esters Employing Nitrosocarbonyl Compounds

B. Maji,* M. Baidya, H. Yamamoto* Synfacts 2014, 10, 1061.

The stereochemistry of the ligand was drawn incorrectly. The correct structure is shown below. We apologize for this error.
Scandium-Catalyzed Enantioselective Carboannulation with Allylsilanes

Significance: The authors report the first example of catalytic asymmetric carboannulation of α,β-unsaturated carbonyl compounds with allylsilanes. The ScCl₃/(R,S)-indapybox catalyst delivered the annulation products in very high chemical yield with excellent enantio- and diastereoselectivity. A Tamao–Fleming oxidation converted the products into the corresponding hydroxyl compounds with good yield and without erosion of enantioselectivity.

Comment: The catalytic activity was enhanced by the use of NaBArF and strongly depends on its amount. Particularly, ester-substituted alkylidines showed an enhanced rate compared to phenyl substitution, which is likely due to stabilization of the β-silyl cation by the ester group. Bulky substituents in allylsilanes are necessary to suppress the β-allylation (Hosomi–Sakurai) reaction. Poor selectivity was observed for malonate and coumarine derivatives.

SYNFACTS Contributors: Hisashi Yamamoto, Ramesh C. Samanta

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DOI: 10.1055/s-0034-1379059; Reg-No.: H10914SF
Diastereoselective Rhodium-Catalyzed Hydroamination of N-Allyl Imines

**Significance:** Hydroamination represents an effective and atom-economic strategy for the incorporation of nitrogen into molecular scaffolds. In particular, transition-metal-catalyzed processes can be extremely selective in dictating how the nitrogen-containing subunit is integrated. The authors report a rhodium-catalyzed diastereoselective hydroamination of N-allyl imines to produce 1,2-diamines.

**Comment:** Following an acidic cleavage of the resulting hydronaminated imine, the diamine products are obtained with good to excellent diastereoselectivities. Deuterium labelling studies with an N-deutero amine nucleophile revealed the incorporation of the deuterium exclusively at the terminal position of what was the allyl group.
Enantioselective Palladium-Catalyzed Decarboxylative Protonation of Carbazolones

Significance: The C3-monosubstituted chiral carbazolones are important structural motifs in medicinal chemistry. The authors report palladium-catalyzed decarboxylative enantioselective protonation of carbazolones as a method for their synthesis. The use of methyl 2-cyclopentanonecarboxylate over Meldrum’s acid as proton donor leads to significant increase in enantioselectivity.

Comment: As an application of this method, a formal total synthesis of (+)-aspidofractinine was accomplished. Thus, the key pentacyclic intermediate was synthesized in a total of ten steps in catalytic asymmetric manner. For a previous synthesis of (+)-aspidofractinine, see: D. Gagnon, C. Spino J. Org. Chem. 2009, 74, 6035. Enantioselective decarboxylative protonation of cyclic ketones has previously been reported (J. T. Mohr et al. J. Am. Chem. Soc. 2006, 128, 11348).

Application: Catalytic asymmetric formal synthesis of (+)-aspidofractinine

Selected examples:

| Structure | Yield | Enantiomeric Excess |
|-----------|-------|---------------------|
| ![Structure](image1.png) | 92% | 92% ee |
| ![Structure](image2.png) | 93% | 83% ee |
| ![Structure](image3.png) | 94% | 88% ee |
| ![Structure](image4.png) | 94% | 81% ee |

LiAlH₄, Et₂O reflux
1. Na/NH₃, THF, –78 °C
2. ICH₂COCl, Et₃N, r.t.
3. AgOTf, CH₂Cl₂ four steps key intermediate total ten-step synthesis catalytic and asymmetric

(+)-aspidofractinine

SYNFACTS Contributors: Hisashi Yamamoto, Biplab Maji
Synthesis of 3,4-Disubstituted Hexahydro-1H-furo[3,4-c]pyran Derivatives

Significance: The authors report an InBr₃-catalyzed tandem Prins cyclization of a γ,δ-unsaturated alcohol tethered with a hydroxy group with aldehydes. Thus, 3,4-disubstituted hexahydro-1H-furo[3,4-c]pyran derivatives were synthesized in high yields (up to 90% yield) with good diastereoselectivity (dr up to 98:2).

Comment: The highlight of this work is the construction of two fused heterocyclic rings with four stereogenic centers in a one-pot operation. As an application of this methodology, a 6-7-6 carbocyclic framework, a core structure of allocolchicines, was synthesized.
Cobalt-Mediated Darzens Reaction Providing Spiro-epoxyoxindoles

**General reaction:**

Co(acac)₂/L (1:1.1) (10 mol%) [K₃PO₄]/[K₂HPO₄] (10:1 or 6:1) THF–acetone (3:1) 5 Å MS, –30 °C

**0.1 mmol scale**

35 examples up to 99% yield up to 95% ee
dr = 99:1

**Selected examples:**

- R² = Me
  - R³ = H
  - 60% yield
  - 95% ee
- R³
  - 72% yield
  - 85% ee
- R⁴
  - 71% yield
  - 85% ee
- R⁵
  - 35% yield
  - 81% ee
- R⁶
  - 35% yield
  - 78% ee

**Comment:** The results are very variable depending on the respective substrates. Control experiments have shown that the starting material is in equilibrium with the bromohydrin intermediate, which was found to be a critical factor for the diminished yields and enantioselectivities. The diastereoselectivity is excellent throughout all substrates (99:1). This work represents a valuable starting point for further investigations regarding an in-depth understanding of the mechanism with the aim to create a more universal and efficient process.

**Significance:** The catalytic asymmetric Darzens reaction employing α-halo-substituted ketones is a synthetically challenging transformation. In particular, metal-mediated processes are extremely rare. The cobalt-catalyzed asymmetric variant described by the authors renders this transformation by using bidentate N,N-dioxide ligands, providing the desired benzoyl-substituted spiro-epoxyoxindole products in moderate to excellent yield and enantioselectivities.

**SYNFACTS Contributors:** Mark Lautens, Steffen Kress

**SYNFACTS 01102014, 10(10), 1066 Published online: 17.09.2014**

**DOI:** 10.1055/s-0034-1379158; **Reg-No.** L10614SF ©Georg Thieme Verlag Stuttgart · New York

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

**Key words:** Darzens reaction epoxyoxindoles isatins cobalt
Copper-Catalyzed Asymmetric Formal [3+2] Cycloaddition to Dihydrofurans

**Significance:** The authors reported a copper-catalyzed asymmetric [3+2] cycloaddition of β-keto esters with propargylic esters. The use of Cu(OTf)₂ and a chiral tridentate P,N,N-ligand delivered the product dihydrofurans in good yield and with very high enantioselectivity. The reduction of the exomethylic double bond gives access to unusual cis-2,3-dihydrofuran derivatives.

**Comment:** This work highlights the formal [3+2] cycloaddition of β-keto esters to propargyl esters. Under these reaction conditions internal alkynes are not tolerated; this is due to the lack of formation of the copper–acetylide complex, which is the key intermediate for this reaction. The stereodetermination occurs in the propargyl alkylation step.