Organocatalytic Asymmetric Mannich Synthesis of α-Amino Esters

Significance: A novel asymmetric route to α-amino esters is reported by Roche, Jacobsen, and co-workers. The methodology, promoted by Takemoto’s aminothiourea catalyst A, delivers the desired product 3 upon coupling of N-protected α-chloroglycine ethyl ester 1 with β-dicarbonyl compounds 2. While two possible activation modes for the C–C bond formation can be hypothesized (anion-binding catalysis or hydrogen-bonding catalysis), the key feature of the catalytic cycle is the preceding chloride abstraction. Remarkably, a wide variety of amino esters can be obtained in good yield and enantioselectivity, albeit with low diastereoselectivity when two contiguous chiral centers are set at once.

Comment: The enantioselective synthesis of natural and unnatural amino acids is an evergreen target in organic chemistry. Here, the authors develop an organocatalytic strategy for the preparation of aspartic acid derivatives by means of an asymmetric Mannich reaction. Remarkably, the reported methodology proceeds under mild conditions and can be performed on a multi-gram scale in a one-pot protocol from simple and readily available starting materials. Further extension of this transformation to other classes of nucleophiles is highly desirable, because such developments would significantly broaden the variety of amino acids accessible.
Chiral Amine Synthesis Using ω-Transaminases: An Amine Donor that Displaces Equilibria and Enables High-Throughput Screening

*Angew. Chem. Int. Ed.* 2014, 53, 10714–10717.

**ω-Transaminase-Catalyzed Reductive Amination of Ketones**

Green, Turner, and O’Reilly report a general protocol for the enantioselective reductive amination of ketones catalyzed by ω-transaminases. The usage of commercially available *ortho*-xylylenediamine hydrochloride (1) as amine donor allowed the effective removal of the imine by-product 2 through spontaneous conversion into isoindole 3, which polymerizes to give intensely colored polymers. A remarkably high conversion was achieved with the challenging substrate 1-indanone.

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**Comment:** Catalytic methods for the synthesis of chiral amines are of high interest for industrial applications. Although enzymes are potent catalysts for these transformations, they suffer from certain drawbacks, such as by-product inhibition and an unfavorable equilibrium. Common strategies require a high excess of the amine donor, by-product removal by distillation, or the use of further cofactor-dependent enzymes. The presented protocol not only allows the transformation of challenging substrates by shifting the equilibrium, but, due to the colored side-product, it also enables high-throughput screenings and the use of colony-based assays.

**Selected examples:**

- >99% conversion (48 h) er > 99.5:0.5
- >99% conversion (48 h) er = 89:11
- 73% conversion (48 h) er > 99.5:0.5
- >99% conversion (48 h) er > 99.5:0.5

**Key words**

- ω-transaminases
- high-throughput screening
- enzyme catalysis

**Category**

- Organo- and Biocatalysis

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**Significance:** The Glorius group reports an enantioselective formal \([3+2]\) annulation of \(\alpha,\beta\)-unsaturated aldehydes and aurone derivatives. Using triazole salt 1 as a precursor for an N-heterocyclic carbene, the desired spiro-heterocyclic products can be obtained in moderate to good yields and with high enantio- and diastereoselectivity.

**Comment:** Spiro-heterocyclic molecules are core structures of various alkaloids as well as pharmaceuticals and show interesting bioactivities. The authors developed a new methodology to access these compounds enantioselectively using an N-heterocyclic carbene (NHC) as the catalyst. The enantioselective step in this transformation is the 1,4-addition from the back face of the NHC homo-enolate to the aurone derivative. After this Michael addition, the catalyst is regenerated by C-acylation, releasing the desired spiro-products.
Kinetic Resolution of Axially Chiral Diols and Amino Alcohols

Significance: Zhao and co-workers describe a highly efficient kinetic resolution of free biaryl diols and N-Boc-protected NOBINs via enantioselective acylation. By applying the known ability of NHCs to catalyze intramolecular redox transformations of α-oxy aldehydes, the chiral acyl azolium intermediate C is generated in situ. Under optimal conditions, high selectivity factors of 22 to 116 can be achieved. Non-acylated starting material was isolated in optically pure form (er ≥ 99.5:0.5), while the acylation products were obtained with moderate enantiomeric enrichment. However, the authors demonstrate that hydrolysis of the BINOL ester and a second kinetic resolution with ent-A, affords both enantiomers with er = 99.5:0.5 and a combined yield of 84%.

Comment: Given the high interest in biaryl diols and NOBIN derivatives as privileged chiral backbones for asymmetric catalysis, the reported kinetic resolution is highly important and represents a great advance in this field. The authors nicely circumvent the requirement for an additional oxidant with saturated aldehydes by using α-oxy aldehydes. The resulting protocol is operationally simple, scalable, and employs commercially available catalysts at ambient temperature. Nevertheless, further improvements are required because the kinetic resolution of SPINOL gives only low selectivity, and a second resolution step is required for high enantiomeric enrichment of both enantiomers.

Selected examples:

- SM: 44% yield; er = 99.5:0.5
  P: 53% yield; er = 91:9
  s = 52 (with A)

- SM: 37% yield; er = 99.75:0.25
  P: 61% yield; er = 80:20
  s = 22 (with A)

- SM: 43% yield; er = 99.5:0.5
  P: 55% yield; er = 86:14
  s = 37 (with A)

- SM: 47% yield; er = 99.5:0.5
  P: 50% yield; er = 96:4
  s = 116 (with A)

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Significance: Sibi and co-workers report a novel chiral 4-dimethylaminopyridine catalyzed acylative kinetic resolution of secondary alcohols and axially chiral biaryl derivatives. Both, the recovered axially chiral biaryl alcohols and the acylated products are obtained in good to excellent enantioselectivities. The addition of 2,6-di-tert-butylpyridine (as a base to remove the side-product isobutyric acid) accelerates the acylation rate.

Comment: Chiral biaryl compounds, especially axially chiral BINOL derivatives, are useful structural frameworks of various catalysts. In this paper, the authors synthesize and employ a new chiral DMAP-type catalyst that includes the 4-(dimethylamino)pyridine, a chiral pyrazolidinone, and a sterically demanding naphthyl group. The reported method provides the first effective chiral DMAP catalyzed catalytic asymmetric kinetic resolution of 1,1′-binaphthyl derivatives.
Enantioselective Formation of All-Carbon Quaternary Stereocenters

**Significance:** The Sun group reports a highly enantioselective intermolecular C–C bond-forming reaction to give acyclic all-carbon quaternary stereocenters. This chiral phosphoric acid mediated transformation converts racemic tertiary alcohols with excellent stereocontrol into highly enantioenriched (er ≥ 98.5:1.5) indole products containing a quarternary stereocenter with good yields (up to 99% yield). A competitive elimination (E1) of the reactive centers was overcome, and preliminary control experiments provide insight into the reaction mechanism.

**Comment:** The efficient formation of quaternary stereocenters is a longstanding challenge in organic synthesis. The described asymmetric nucleophilic substitution between a racemic tertiary alkyl electrophile and a carbon nucleophile represents an S_N1 transformation. The reported method is limited to electron-rich phenol derivatives bearing methyl groups at their benzylic positions. Methyl protection of the phenol o-hydroxy group or the indole leads exclusively to the E1 product. A mesomeric structure between the tertiary carbocation and the o-quinone methide was proposed to be essential for this Michael-type reaction.

**Selected examples:**
- 98% yield er = 95.5:4.5
- 90% yield er = 96:4
- 47% yield er = 95.5:4.5
- 99% yield er = 96:4

**Proposed intermediate:**
- tertiarly carboxation
- o-quinone methide

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Biocatalytic Oxidative Desymmetrization of Piperidine Carboxylates

**Significance:** Schofield and co-workers desymmetrize N,N-dimethyl-piperidine-4-carboxylic acid 1 with γ-butyrobetaine hydroxylase (BBOX), a 2-oxoglutarate-dependent oxygenase, to afford hydroxylated product 2. A crystal structure of BBOX in complex with 1, N-oxalylglycine (mimics 3) and NiII (FeII surrogate) was obtained, thus giving insight into the active site and providing a rationale for the stereochemical outcome.

**Comment:** BBOX is a monooxygenase catalyzing the final hydroxylation in the biosynthesis of carnitine, a key molecule for the transport of fatty acids into cells. Based on a mass-spectrometry assay, the authors show as a proof-of-principle that BBOX can also catalyze the oxidative desymmetrization of 1 in perfect enantioselectivity as well as a kinetic resolution of an analogue of 1 (N-stereo-center bearing a methyl and ethyl substituent). Broadening the scope of the transformation is envisioned via enzyme engineering.
Significance: The List group reports the development of a catalytic asymmetric Torgov cyclization. For this purpose, the novel, backbone-nitrated disulfonimide B was developed, which enabled lower reaction temperatures compared to the parent catalyst A, and thus gave higher enantioselectivities. The methodology was implemented in the shortest total synthesis of (+)-estrone reported to date. Additionally, a number of analogues were also synthesized with modest to good results, depending on the substitution pattern. Different temperature programs were found to be optimal for substrates with varying steric and electronic properties.

Comment: It is noteworthy that temperature programs were employed in this methodology. In accompanying mechanistic studies, List and co-workers showed that such temperature programs ideally suit the stepwise nature of the Torgov cyclization. While the enantiodetermining step is best catalyzed at the lowest possible temperature, the subsequent steps require higher temperatures to occur within a reasonable amount of time. However, if temperatures are raised too much, the preceding steps become reversible, leading to a deterioration of the previously achieved enantioselection.
Catalytic Asymmetric Synthesis of 4-Nitropyrazolidines

Significance: Jørgensen and co-workers report a catalytic asymmetric synthesis of 4-nitropyrazolidines. The title compounds are synthesized by highly enantio- and diastereoselective thiourea-catalyzed 1,3-dipolar cycloadditions (er up to 99.5:0.5, dr up to >20:1) of aromatic or aliphatic nitroalkenes and ketone-derived hydrazones in moderate to excellent yields (55–97%). A further derivatization to the corresponding 1,2,3-triamines was realized via step-wise reduction of the nitro group and the N–N bond, providing the triamine in a 23% yield from one particular 4-nitropyrazolidine.

Comment: Within the presented methodology, the authors offer a new asymmetric way of accessing pyrazolidines and 1,2,3-triamines, moieties found in many biologically active natural products. On the basis of previously reported pyrazole syntheses from nitroalkenes and aldehyde-derived hydrazones (e.g., X. Deng, N. S. Mani Org. Lett. 2006, 8, 3505), the authors utilized hydrogen-bonding activation of the nitroalkene by a chiral thiourea derivative, allowing the reaction to proceed at temperatures at which no background reactions were observed.
C. E. HENRY, Q. Xu, Y. C. FAN, T. J. MARTIN, L. BELDING, T. DUDDING, O. KWON* (UNIVERSITY OF CALIFORNIA, LOS ANGELES, USA AND BROCK UNIVERSITY, ST. CATHARINES, CANADA)

Hydroxyproline-Derived Pseudoenantiomeric [2.2.1] Bicyclic Phosphines: Asymmetric Synthesis of (+)- and (−)-Pyrrolines

*J. Am. Chem. Soc. 2014, 136, 11890–11893.

Asymmetric Synthesis of Pyrrolines Using Bicyclic Phosphine Catalysts

Significance: A phosphine-catalyzed asymmetric [3+2] annulation is reported by the Kwon group. The novel 2-aza-5-phosphabicyclo[2.2.1]heptanes 1, which were synthesized from commercially available trans-4-hydroxy-L-proline, were found to be suitable catalysts for the [3+2] annulation of γ-substituted allenoates 2 with imines 3. A variety of 1,2,3,5-substituted pyrrolines 4 were prepared in good yields and enantioselectivities. It was found that the opposite absolute configurations of the pyrrolines can be obtained using the two diastereoisomeric phosphines 1a and 1b, although 1b performed significantly better than 1a.

Comment: According to DFT calculations, a hydrogen bond between the imine N-sulfonyl oxygen atom and a hydrogen atom of the catalyst, as well as a favorable Coulombic interaction between the oxygen atom of allenoate and the phosphorus atom stabilize the transition states. The opposite absolute configurations of the products are due to the two diastereoisomeric spatial arrangements. In particular, catalyst 1a effectively shields the si face of the phosphonium dienolate (TS1a), whereas the re face of the phosphonium dienolate is significantly hindered when 1b is employed (TS1b).

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Enantioselective Route to Piperidines via Covalent Phosphoric Acid Catalysis

**Significance:** Zimmerman, Nagorny, and co-workers report an enantioselective synthesis of piperidines. The transformation is promoted by the BINOL-derived phosphoric acid catalyst and converts α,β-unsaturated acetals into heterocycles via a formal enantioselective SN2′ displacement. The reaction proceeds under mild conditions and gives the products in good yield and with good to excellent stereoselectivity. Interestingly, theoretical investigations undertaken to elucidate the reaction mechanism suggest the transformation to proceed via the formation of a mixed phosphoric acid acetal intermediate rather than the initially hypothesized oxocarbenium ion.

**Comment:** Asymmetric Bronsted acid catalysis is believed to proceed through ion-pairing between the chiral anion of the acidic catalyst and the activated electrophile. Recently, the Toste group has proposed a different type of mechanism based on covalent catalysis for an intramolecular hydroamination reaction on diene substrates (Nature 2011, 470, 245). Here, the authors report a related transformation which in silico was found to involve a similar catalytic cycle. The isolation and study of such reactive intermediates is of high interest for future developments in this research area.
Chiral Phosphoric Acid Catalyzed Highly Enantioselective Desymmetrization of 2-Substituted and 2,2-Disubstituted 1,3-Diols via Oxidative Cleavage of Benzylidene Acetals

**Desymmetrization of 1,3-Diols via Oxidative Cleavage of Benzylidene Acetals**

**Significance:** An enantioselective desymmetrization of 1,3-diols through oxidative cleavage of benzylidene acetals is reported. Employing chiral phosphoric acid catalyst (S)-TRIP (1), oxidative desymmetrization of various 2-substituted and 2,2-disubstituted 1,3-diols 2 proceeded with high enantioselectivity to afford mono-protected diols 3 in high yield.

**Comment:** DFT calculations indicate that the oxidation of the acetal by DMDO (TS1) is the rate-determining step. The formation of ortho-ester intermediate A is followed by a proton-transfer process which is accelerated by the phosphoric acid via TS2. A significantly lower free energy of activation is required than for the transition state in the absence of the catalyst. The key for achieving high enantioselectivity are attractive interactions between the PMP group of the substrate and the 2,4,6-trisopropyl group of the catalyst.

**Selected examples:**
- 99% yield er = 97.5:2.5
- 95% yield er = 87:13
- 95% yield er = 95.5:4.5
- 90% yield er = 96.5:3.5