NHC-Catalyzed Oxidative [4+2] Annulation of 2-Hydroxybenzaldehydes and Ketones

**Proposed mechanism:**

\[
\begin{align*}
\text{NHC} & \xrightarrow{[4+2]} \text{urea co-catalyst} \\
\text{o-QMs} & \quad \text{NHC}^+ \\
\text{H}^- & \xrightarrow{[4+2]} \text{NHC}^+ \\
\end{align*}
\]

**Selected examples:**

- 99% yield, er = 94:6
- 93% yield, er = 91:9
- 98% yield, er = 94:6
- 91% yield, er = 97:3
- 99% yield, er = 96:4
- 96% yield, er = 98:2
- 99% yield, er = 95:5
- 75% yield, er = 89:11

**Significance:** Chi and Hirao report an oxidative NHC-catalyzed [4+2] annulation of 2-hydroxybenzaldehydes with trifluoromethyl aryl ketones. This synthetic approach furnishes benzodioxinone derivatives in good to excellent yields and enantioselectivities. Several of these reported compounds show anti-fungal activities.

**Comment:** The azolium-bound ortho-quinone methide intermediate (o-QMs), obtained from the 2-hydroxybenzaldehyde by NHC catalysis in the presence of a weak oxidant (DQ), undergoes the oxidative [4+2] annulation with ketones. The enantioselectivities were increased by the addition of a urea co-catalyst (A). DFT calculations support the proposed mechanism.
Chiral Fullerene-Derived Thioureas as Recyclable Asymmetric Organocatalysts

Significance: Pedrosa and co-workers present the synthesis of fullerene-derived thioureas by using the Prato reaction of C_{60}, sarcosine, and an α-amino acid modified aldehyde as the key step. The synthesized fullerene-thioureas are used as organocatalysts for an asymmetric nitro-Michael reaction, providing the products in excellent yields and high stereoselectivities; the catalysts are also easily recyclable and active for at least five reaction cycles.

Comment: Chiral thioureas are a commonly found scaffold in the development of asymmetric organocatalysts. After bonding this moiety to the well-defined molecular structure of fullerene, the obtained organocatalysts are easily recyclable due to their low solubility. The use of fullerene as a more controllable catalyst support arises because of problems in employing polymer-supported organocatalysts, such as swelling or difficult access to the active site.

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Catalytic Stereoselective Synthesis of Pronucleotides

**Significance:** DiRocco and co-workers report a diastereoselective synthesis of pronucleotides from the corresponding nucleosides by a dynamic kinetic resolution of chlorophosphoramidate 1. Whereas the reaction with N-methylimidazole as catalyst proceeds with almost no stereoselectivity toward the newly formed stereogenic center on phosphorus, a dimeric, chiral, imidazole-based catalyst with additional hydrogen-bonding sites furnished a series of pronucleotides in good yields and good to excellent stereoselectivities.

**Comment:** Pronucleotides are important compounds for the treatment of viral diseases and cancer. The derivative MK-3682, for instance, is a hepatitis C viral RNA polymerase inhibitor, currently undergoing late-stage clinical trials. Because different absolute configurations of the P-based stereogenic center can significantly alter the drug’s potency and toxicity, stereoselective generation thereof is of great importance. Herein, the authors report the first catalytic, stereoselective access to compounds bearing P-based stereogenic centers.
A Shuttling Strategy for the Enantioselective β-Protonation of Enals

**Significance:** The Huang group reports an NHC-catalyzed enantioselective β-protonation of enals by a proton-shuttling strategy. Initial studies focused on the addition of a Lewis acid co-catalyst in order to guide the protonation by coordination to the formed enol. However, mechanistic studies revealed that the proton source is not the thiol but the organic base, which is protonated in situ.

**Comment:** An additional β-ester group, as used in previous reports on β-protonation of enals (K. A. Scheidt and co-workers *J. Am. Chem. Soc.* 2015, 137, 5891), was not required. β-Dialkyl enals failed under the reaction conditions due to unproductive homoenoate formation and, therefore, remain an unsolved challenge.

**Selected examples:**

- **Cu(OTf)$_2$ DABCO**
  - PhO=S=S=Ph
  - 96% yield er = 97.5:2.5
  - PhO=S=S=Ph
  - 70% yield er = 96.5:3.5

- **Cu(OTf)$_2$ quinuclidine**
  - CF$_3$O=S=S=Ph
  - 95% yield er = 95:5

- **PA quinuclidine**
  - PhO=S=S=Ph
  - 99% yield er = 90.5:9.5

- **TfOH quinuclidine**
  - PhO=S=S=Ph
  - 99% yield er = 94.5:5.5

- **Cu(OTf)$_2$ quinuclidine**
  - PhO=S=S=Ph
  - 97% yield er = 99.5:0.5

- **PA quinuclidine**
  - PhO=S=S=Ph
  - 80% yield er = 98.2

- **TfOH quinuclidine**
  - PhO=S=S=Ph
  - 99% yield dr = 97:3
Enantioselective Formal $\alpha$-Methylation and $\alpha$-Benzylation of Aldehydes by Means of Photo-organocatalysis

Angew. Chem. Int. Ed. 2017, 56, 4447–4451.

**Significance:** Melchiorre and co-workers report an enantioselective formal $\alpha$-alkylation of aldehydes, which proceeds through photoexcitation of catalytically generated enamine B. The excited enamine $\text{Ia}^*$ transfers an electron to iodosulfone $\text{2}$ to generate radical $\text{Ila}$, which is trapped by enamine B to ultimately furnish product $\text{3}$.

**Comment:** The direct (organo)catalytic enantioselective $\alpha$-alkylation of carbonyl compounds with alkyl halides remains a challenge. The reported strategy offers an attractive path to the enantio-enriched product $\text{4}$ through reduction and mild desulfonylation of intermediate $\text{3}$.

**Proposed reaction mechanism:**

1. **Excited state**

2. **SET**

3. **Photochemical initiation**

**Selected examples:**

- **1** (3 equiv) $\text{R}^1 = \text{Alk, CH}_2\text{SMe}$
- **2** (1 equiv) $\text{R}^2 = \text{H, Ar}$
- **3** 17 examples 35–95% yield $\text{er}$ from 87.5:12.5 to 98.5:1.5 $\text{dr} = 3.2:1$
- **4**

**Key words**

- alkylation
- redox auxiliary groups
- photoorganocatalysis
- methylation
- benzylation
- aldehydes
Total Synthesis of (+)-Rishirilide B through Oxidative Kinetic Resolution

**Significance:** The groups of Odagi and Nagasawa report a concise asymmetric total synthesis of (+)-rishirilide B by applying an oxidative kinetic resolution catalyzed by chiral guanidine–bisurea \(A\) as a key step. This bifunctional hydrogen-bonding catalyst enables the \(\alpha\)-hydroxylation of a racemic \(\beta\)-keto ester by cumene hydroperoxide (CHP) with high enantioselectivity \((s = 53)\).

**Comment:** The application of asymmetric organocatalytic methodologies in total synthesis highlights their robustness and applicability in a complex molecular environment. The recent work is a good example how a nontrivial stereochemistry of a tetralone system with two adjacent tertiary alcohol stereocenters can be installed elegantly by such a method. The completed synthesis allowed revision of the previously reported absolute configuration of (+)-rishirilide B to 2\(S\), 3\(S\), 4\(S\).
Chemoenzymatic Route to Chiral Gamma Secretase Inhibitor Intermediates

**Significance:** Research groups from Pfizer and Euticals present a chemoenzymatic route to amino acid derivative 5, a key intermediate in the synthesis of the gamma secretase inhibitor 6. The route includes (1) a transaminase-catalyzed asymmetric reductive amination of tetralone 1 to furnish aminotetralin 2 in excellent yield and excellent enantioselectivity, and (2) an alcohol dehydrogenase-catalyzed asymmetric reduction of 3 to give hydroxy ester 4, again, in good yield and with excellent enantioselectivity.

**Comment:** Enzymatic transformations ideally offer the great advantages of high performance and high selectivity, mild reaction conditions, low catalyst loadings, and large scale. All of these were impressively demonstrated in the presented transformations, which were performed on multikilogram scales using <1 mass% catalyst loadings.
Chiral Phosphoric Acid Catalyzed Kinetic Resolution of 2-Pyridyl Esters

**Significance:** Shimoda and Yamamoto report a kinetic resolution of 2-pyridyl esters via amide bond formation for the stereoselective synthesis of α-substituted carboxylic acid derivatives. A variety of α-branched amides, including substrates bearing an α-quaternary center, were obtained in good conversions with high s-factors. The synthetically useful 2-pyridyl esters can be recovered in moderate yield and excellent enantiopurity and functionally derivatized with high enantiospecificity.

**Comment:** The authors utilize a phosphoric acid catalyst bearing 2,4,6-trimethyl-3,5-dinitrophenyl groups at the 3- and 3′-positions, which was reported previously by Zhou and Yamamoto (*Angew. Chem. Int. Ed.* 2016, 55, 8970). They suggest that the pyridyl ester interacts with a proton from the chiral Brønsted acid to form a chiral ion pair that is activated toward nucleophilic substitution.

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**Category:** Organo- and Biocatalysis

**Key words**

kinetic resolution
chiral phosphoric acid catalysis
pyridyl esters
amide bond formation
Construction of a Quaternary Carbon by a Mannich Reaction

**Significance:** The Maruoka group reports the in situ generation of relatively inaccessible N-Boc-protected imines from ynals, and their application in the direct Mannich reaction with \( \beta \)-dicarbonyls. Their method leads to the construction of a quaternary carbon atom under acid-catalyzed conditions in moderate to excellent yields. Additionally, they report the aldol reaction between ynals and \( \beta \)-dicarbonyls under neat conditions in moderate to excellent yields.

**Comment:** In a previous work (Angew. Chem. Int. Ed. 2013, 52, 5532), the authors showed that with preformed Boc-aminals, Mannich-type products could be obtained under acid catalysis. Here, Maruoka and co-workers developed a methodology that does not require precursor formation, thus operationally simplifying the method for obtaining the Mannich products.
Direct Hydroxylation of Benzene to Phenol by Cytochrome P450BM3

**Significance:** The Watanabe and Shoji groups report an oxidation of benzene to phenol. The reaction is catalyzed by cytochrome P450BM3 using dipeptide, which can be encapsulated into the enzyme with a substrate and is inert toward the oxidation. The methodology is also applicable to toluene and anisole, and the oxidized products are obtained with excellent regioselectivities.

**Comment:** The authors have previously developed the oxidation of aliphatic C–H bonds by a similar strategy (Angew. Chem. Int. Ed. 2011, 50, 5315), which is further extended to the oxidation of arenes. The use of unreactive decoy molecule with arenes enables the desired transformation. Although a stoichiometric amount of NADPH is required, the presented methodology can be a nice alternative approach to access phenol derivatives.

**General reaction mechanism of P450BM3:**

**Plausible reaction mechanism:**

**Other substrates:**

- **R = Me**
  - turnover rate = 641 ± 22
  - coupling efficiency = 62%
  - ortho selectivity = 96%
- **R = OMe**
  - turnover rate = 623 ± 27
  - coupling efficiency = 58%
  - ortho selectivity = 92%

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**Significance:** The Studer group reports an asymmetric, oxidative intramolecular spirocyclization of indoles catalyzed by chiral N-heterocyclic carbenes (NHCs). An acyl azolium intermediate, generated by oxidation of the Breslow intermediate by the bisquinone (BQ), effects indole acylation to give spirocyclic indolenine products.

**Comment:** Spirocyclic indol(en)ines with a C3-all-carbon quaternary stereocenter are interesting scaffolds found in natural products and in compounds with various biological activities. The oxidative dearomatization strategy with NHC catalysis is fairly successful in providing a wide range of spirocyclic indol(en)ines in moderate to excellent yields and enantioselectivities.