Photocatalytic Benzylic Fluorination

Significance: A photocatalytic benzylic fluorination is reported by Chen and co-workers. Promoted by visible light, the photoexcitation of the ketone organocatalyst generates a short-lived diradical species, which abstracts a benzylic hydrogen from the starting material. Subsequently, the fluorine source delivers the F-atom and regenerates the catalyst. The methodology is operationally convenient and converts a large variety of substrates into the corresponding mono- and difluorinated products using a simple compact fluorescent light (CFL) bulb and commercially available Selectfluor (A) and Selectfluor II (B).

Comment: In the last few years, the interest of the scientific community in the synthesis of fluorinated compounds has risen impressively due to the importance of these substances in pharmaceutical and material sciences. Therefore, the development of selective and mild procedures for the introduction of fluorine atoms, even in a racemic fashion, is very attractive. Here, the authors present a solid protocol to achieve this target. A wide variety of substrates was reacted to give the fluorinated products in good to excellent yields, highlighting the efficiency of the disclosed photocatalytic system.
Organocatalysed Decarboxylative Protonation Process from Meldrum’s Acid: Enantioselective Synthesis of Isoxazolidinones


Isoxazolidinones via Asymmetric Decarboxylative Protonation

Significance: An organocatalytic approach for the synthesis of isoxazolidinones 3 is reported by the Brière group. The methodology is a tandem process promoted by the quinidine-derived catalyst A. An initial formal [3+2]-cycloaddition process couples 5-substituted Meldrum’s acids 1 and nitrones derived from sulfonamides 2. Then, an asymmetric decarboxylative protonation takes place via a putative stepwise mechanism. The desired products are generally obtained with good yields and with modest to good enantioselectivities.

Comment: Asymmetric protonation reactions are a fascinating topic in organic chemistry. In this area, decarboxylative protonation processes have attracted the interest of the scientific community due to the elegant in situ generation of the reacting enolate upon release of carbon dioxide (see Review below). Based on this concept, the authors present a novel straightforward approach to the synthesis of isoxazolidinones, which are useful precursors for β2-amino acids.

Brønsted Acid Catalyzed Enantioselective Indole Aza-Claisen Rearrangement Mediated by an Arene CH–O Interaction

**J. Am. Chem. Soc. 2013, 135, 16380–16383.**

**Significance:** The first Brønsted acid catalyzed enantioselective indole aza-Claisen rearrangement for the generation of optically enriched 3-amino-2-substituted indoles is reported. An arene CH–O interaction is proposed to synergistically activate and stereo-induce as a second point of interaction (two-point interaction). Several allylic moieties are compatible with the reaction conditions. Electron-donating and -withdrawing groups did not affect the efficiency. Yet, aliphatic substituents significantly lowered the stereoselectivity. The obtained products can be transformed into the corresponding 3-aminooxindoles, which are substrates for the synthesis of many biologically active small molecules.

**Comment:** The proposed two-point interaction was modeled on a B3LYP/6-31G(d) level. CH–O and NH–O interactions organize the adduct in a way that one 9-anthracene unit blocks the si face of the substrate inducing the allyl shift on the re face leading to the observed enantiomer. Other interactions such as edge-to-face CH–π interaction between the \( R^2 \) group and the second 9-anthracene unit as well as CH–O interaction between the \( R^2 \) group and the phosphate are also proposed. A synthetic derivative confirmed the absolute configuration by X-ray crystallography to be in accordance with the calculations. The aza-Claisen rearrangement to obtain chiral indole alkaloids is currently under investigation.

SYNFACTS Contributors: Benjamin List, Philip S. J. Kaib

**Category**
Organo- and Biocatalysis

**Key words**
indoles
aza-Claisen rearrangement
Brønsted acid catalysis
TRIP
Synthesis of Pyrrolidinones via \(\alpha,\beta\)-Unsaturated Acylammonium Ions

**Significance:** An asymmetric enantioselective Michael addition–proton transfer–lactamation or lactonization organocascade reaction is reported. The cinchona alkaloid derived catalysts 1 can generate chiral \(\alpha,\beta\)-unsaturated acylammonium salts with crotonyl chlorides 2, giving pyrrolidinones, piperid-2-ones, and dihydropyridinones in good yields and high enantioselectivities.

**Comment:** In the first step, the lithiated enolate is formed to participate in a conjugate addition to the acylammonium species, which derives from reaction of the chiral tertiary amine \(R_3N\) with the acid chloride. After an intra- or intermolecular proton transfer, the acylammonium species undergoes intramolecular lactamation to regenerate the tertiary amine catalyst \(R_3N\). The products could be transformed into known precursors of various biologically active compounds.
M. G. NÚÑEZ, A. J. M. FARLEY, D. J. DIXON* (UNIVERSITY OF OXFORD, UK)
Bifunctional Iminophosphorane Organocatalysts for Enantioselective Synthesis: Application to the Ketimine Nitro-Mannich Reaction

Iminophosphorane-Catalyzed Enantioselective Ketimine Nitro-Mannich Reaction

Significance: Dixon and co-workers report a new class of bifunctional Brønsted base/H-bond donor organocatalyst. The catalyst (bifunctional iminophosphorane, BIMP) can be applied to the ketimine nitro-Mannich reaction, generating β-nitroamines in good to excellent yields and enantioselectivities.

Comment: The authors developed a new catalyst motif consisting of a triarylaminophosphorane moiety as a Brønsted base and a thiourea moiety as an H-bond donor. The catalyst can be easily synthesized via Staudinger reaction of an organoazide and a triarylphosphine. The efficiency of the catalyst was demonstrated by the application to the first catalytic enantioselective addition of nitromethane to ketone-derived imines under metal-free conditions. The reaction can be scaled up to multigrams and gives access to enantiomerically pure quaternary α-amino acids.

Synthesis of new BIMP (bifunctional iminophosphorane) organocatalyst:

Selected examples:

86% yield er = 97.5:2.5
95% yield er = 96:4
62% yield er = 96.5:3.5
95% yield er = 95:5
71% yield er = 89:11
Cooperative Catalysis in Ionic [4+2] Cycloadditions

**Significance:** The Nagorny group reports an ionic [4+2] cycloaddition between $\alpha,\beta$-unsaturated acetal dienophiles 1 and dienes 2 to afford Diels–Alder adducts 3 in moderate to excellent yields. The reaction is promoted by a cooperative catalytic system involving a strong Brønsted acid [PTSA (p-toluenesulfonic acid)] and a triple hydrogen bond donor thiophosphoramide (A). NMR and computational studies suggest that the key feature of the catalytic system is the strong interaction between A and the sulfonate anion.

**Comment:** Ionic [4+2] cycloadditions (Gassman’s cycloadditions) have proven to be efficient complements to traditional Diels–Alder reactions when challenging unactivated substrates are involved. The authors report a variety of these reactions, which interestingly do neither require a Lewis acid nor a highly ionic medium for the generation of the reactive separated ion pair. The same objective is achieved by a cooperative catalytic system in which the sulfonic acid generates the oxocarbenium species and in which the thiophosphoramide co-catalyst ensures the formation of separated, highly reactive counterions via three hydrogen bonds to the sulfonate anion.

**Selected examples:**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Yield</th>
<th>Endo/Exo Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1 = Alk, Ar, R2 = H, Alk</td>
<td>92%</td>
<td>4:1</td>
<td></td>
</tr>
<tr>
<td>R1 = H, Alk, R2 = H, Alk</td>
<td>85%</td>
<td>4:1</td>
<td></td>
</tr>
<tr>
<td>R1 = Ph</td>
<td>63%</td>
<td>4:1</td>
<td></td>
</tr>
<tr>
<td>R1 = H, R2 = H, Ar</td>
<td>59%</td>
<td>4:1</td>
<td></td>
</tr>
</tbody>
</table>

**Proposed activation mode:**

The strong interaction between the thiophosphoramide and the sulfonate anion facilitates the formation of highly reactive oxocarbenium ions via three hydrogen bonds, leading to the observed endo/exo selectivity.

**SYNFACTS Contributors:** Benjamin List, Gabriele Pupo

SYNFACTS 2014, 10(1), 0090 Published online: 13.12.2013 DOI: 10.1055/s-0033-1340404; Reg-No.: B11613SF
Phosphoric Acid Mediated Glycosylation and Alcohol-Chirality Recognition

Selected examples:

- 1. HO<sub>2</sub>C<sub>6</sub>H<sub>5</sub>
  - (±) 75% yield (β, R)
  - (±) 67% yield (β, S)
  - (±) 75% yield (β, R)
  - (±) 0% yield (β, S)

- 2. HO<sub>2</sub>C<sub>6</sub>H<sub>5</sub> (±)
  - (±) 84% yield (β, R)
  - (±) 0% yield (β, S)

- 3. HO<sub>2</sub>C<sub>6</sub>H<sub>5</sub> OTBDPS
  - (±) 84% yield (β, R)
  - (±) 0% yield (β, S)

- 4. HO<sub>2</sub>C<sub>6</sub>H<sub>5</sub> OMe
  - (±) 84% yield (β, R)
  - (±) 0% yield (β, S)

- 5. HO<sub>2</sub>C<sub>6</sub>H<sub>5</sub> OTBDPS
  - (±) 84% yield (β, R)
  - (±) 0% yield (β, S)

- 6. HO<sub>2</sub>C<sub>6</sub>H<sub>5</sub> OTBDPS
  - (±) 84% yield (β, R)
  - (±) 0% yield (β, S)

- 7. HO<sub>2</sub>C<sub>6</sub>H<sub>5</sub> OMe
  - (±) 84% yield (β, R)
  - (±) 0% yield (β, S)

Reaction pathway:

Significance: Toshima and co-workers report a highly β-selective glycosylation of α-trichloroacetimidates 1α with various secondary alcohols. The diastereoselectivity is moderate to excellent, and the reaction is mediated by the phosphoric acid (S)-3. According to mechanistic studies, the exclusive β-selectivities are obtained through a (S)-3-mediated SN2 reaction pathway. The methodology was also applied to the total synthesis of a natural flavan glycoside using a racemic aglycone.

Comment: Glycosylation is an important synthetic method to construct sugar moiety containing compounds. Here, the authors report a novel Bronsted acid mediated glycosylation, and a kinetic resolution of secondary alcohols occurs during the process at the same time. This methodology provides a straightforward way for the synthesis of sugar-derived products with high stereoselectivity.
**Significance:** The asymmetric enantioselective arylation of enecarbamates catalyzed by a chiral Brønsted acid is reported. An axially chiral dicarboxylic acid (1) catalyzes the reaction of quinone imine ketals 2 with enecarbamates 3 to give α-amino-β-aryl ethers 4 in good yields and enantioselectivities. The products could be transformed into various useful chiral building blocks.

**Comment:** It is notable that opposite enantiomers of the products are obtained by changing from Z- to E-enecarbamates. The authors propose that the isomeric enecarbamates approach the quinone imine ketals 2 from the same prochiral face, and that diastereomeric intermediates are generated that lead to the opposite enantiomers after aromatization.
Organocatalytic Total Syntheses of (+)- and (–)-Trigonoliimine A

**Significance:** The Zhu group reports an enantioselective Michael addition of methyl α-aryl-α-isocyanocetates to vinyl phenylselenone catalyzed by a cinchona-alkaloid derivative. The obtained enantioenriched α-aryl-α-(2′-phenylselenonyl-ethyl)-α-isocyanocetates are successfully transformed into linear and cyclic quaternary α-amino acids, oxindoles, and pyrrolidinones. A concise total synthesis of (+) and (–)-trigonoliimine A (9 steps, 7.5% and 6.8% overall yield) from the shown Michael adduct was completed via a modified Bischler–Napieralski cyclization.

**Comment:** α-Isocyanocetates are well-established glycine templates for the synthesis of racemic α,α-disubstituted α-amino acids. Yet, the catalytic enantioselective allylation of α-isocyanocetates remains underexploited. The reported Michael addition products are converted further without racemization into the corresponding amines and azides. The absolute configuration of the products obtained from the shown cinchona-alkaloid catalyst was determined after derivatization by X-ray analysis to be $R$. 
Organocatalytic Trifluoromethylthiolation of β-Keto Esters

Significance: A highly enantioselective trifluoromethylthiolation of β-keto esters is reported by Shen and co-workers. The reaction is catalyzed by quinine 1 or the quinine-derived phase-transfer catalyst 2. Good to excellent yields and enantioselectivities are obtained by utilizing different catalysts for different ring sizes of the β-keto esters. The free hydroxyl group of the catalyst is crucial for reactivity, and the SCF₃-substituted quaternary ammonium pathway was ruled out by control experiments. The proposed reaction pathway involves a dual activation, in which the catalyst activates both the β-keto ester and the SCF₃ reagent via a double hydrogen bonding.

Comment: The introduction of fluorine functional groups into different molecules is of great importance for the pharmaceutical and agrochemical industries. Here, the authors report a practical procedure for highly enantioselective trifluoromethylthiolation of β-keto esters. This methodology provides a straightforward way to build quaternary carbon centers with a SCF₃ group, which potentially could lead to useful drug candidates. At the same time, Rueping and co-workers report a very similar study, but utilizing different SCF₃ sources (T. Bootwicha, X. Liu, R. Pluta, I. Atodișei, M. Rueping Angew. Chem. Int. Ed. 2013, 52, 12856).
Novel Atropisomeric Chiral Dienes in Lewis Base Organocatalysis

Significance: The authors report a novel tetraline-based, atropisomeric, and configurationally stable chiral diene catalyst \(1\), which was successfully employed in the Lewis base catalyzed allylation of aldehydes \(2\) with trichlorosilanes \(3\) (see Review below). Products \(4\) were isolated in moderate to excellent yields and in good to excellent enantioselective ratios. Catalyst \(1\) also proved to be effective in a single example of enantioselective ring opening of a meso-epoxide to afford a 1,2-chlorohydrin.

Comment: Chiral atropisomeric biaryl scaffolds have been well studied and extensively applied in asymmetric catalysis. Yet, atropisomeric conjugated dienes have found limited application in asymmetric synthesis due to their low racemization-energy barrier. The authors avoid this major drawback by designing a catalyst bearing an extended conjugated system involving a diene and two phosphinoxide moieties, thus generating a stable conjugated helical system. Catalyst \(1\) proved to be configurationally stable even for prolonged periods (24 h) at high temperatures (135 °C). Its potential is well described by the reported allylation reaction as well as the promising results obtained in the ring opening of meso-epoxides with silicon tetrachloride.

Applications:

\[
\begin{align*}
R^1 & = \text{Ar, alkenyl} \\
R^2 & = \text{Ar, Alk} \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & + \text{SiCl}_3 \\
\text{OH} & + \text{Cl} \\
\end{align*}
\]