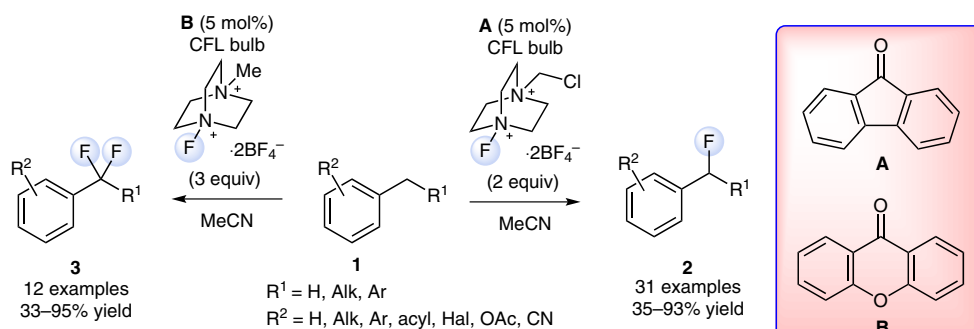


J.-B. XIA, C. ZHU, C. CHEN\* (THE UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER, DALLAS, USA)

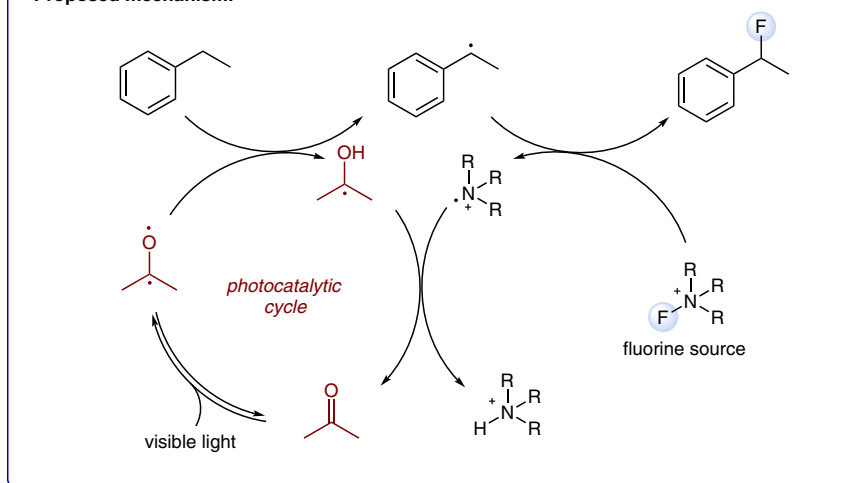
Visible Light-Promoted Metal-Free C–H Activation: Diarylketone-Catalyzed Selective Benzylic Mono- and Difluorination

*J. Am. Chem. Soc.* **2013**, *135*, 17494–17500.

## Photocatalytic Benzylic Fluorination



### Proposed mechanism:



**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.

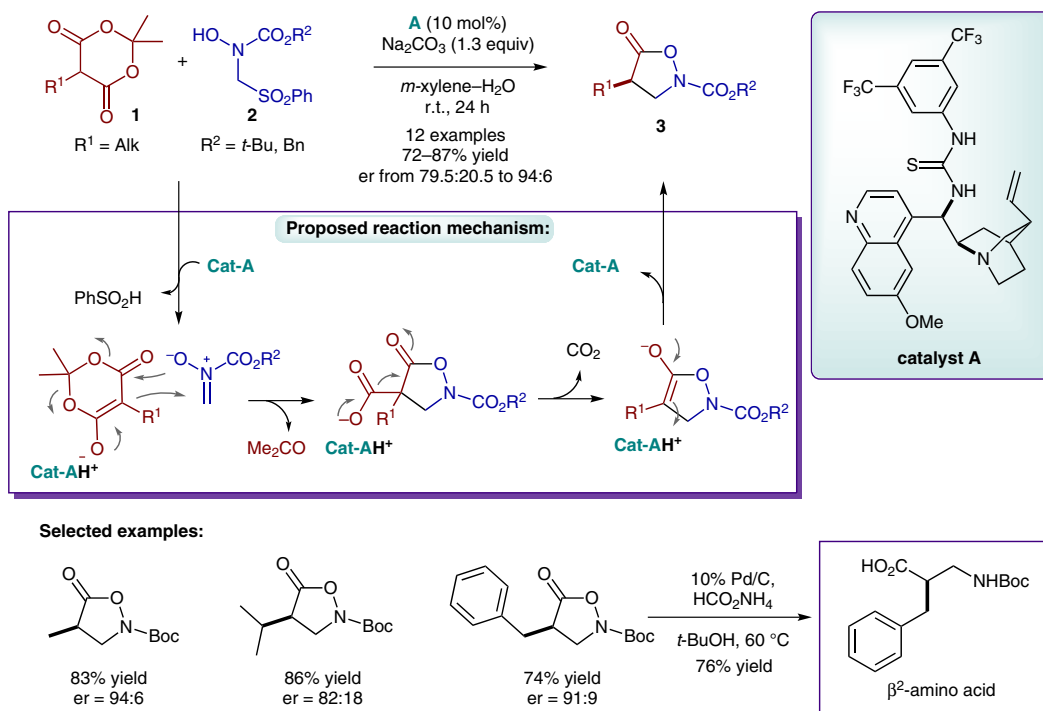
**SYNFACTS Contributors:** Benjamin List, Mattia Riccardo Monaco  
Synfacts 2014, 10(1), 0085 Published online: 13.12.2013  
**DOI:** 10.1055/s-0033-1340409; **Reg-No.:** B12213SF

T. TITE, M. SABBAH, V. LEVACHER, J.-F. BRIÈRE\* (NORMANDIE UNIVERSITÉ, UNIVERSITÉ DE ROUEN, AND CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE, MONT SAINT AIGNAN, FRANCE)

Organocatalysed Decarboxylative Protonation Process from Meldrum's Acid: Enantioselective Synthesis of Isoxazolidinones

*Chem. Commun.* **2013**, 49, 11569–11571.

## 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.

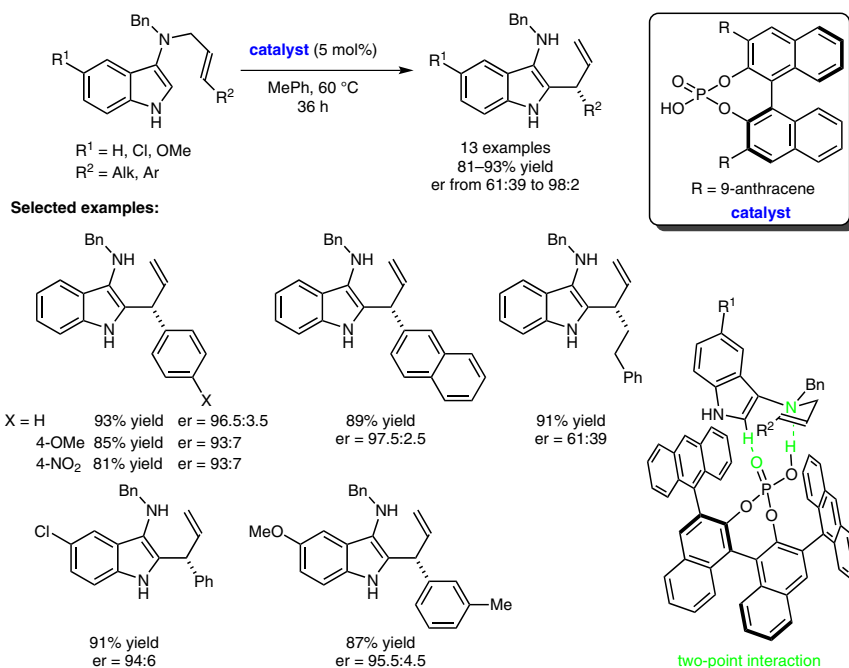
**Comment:** Asymmetric protonation reactions are a fascinating topic in organic chemistry. In this area, decarboxylative protonation processes have attracted the interest of the scientific community due to the elegant in situ generation of the reacting enolate upon release of carbon dioxide (see Review below). Based on this concept, the authors present a novel straightforward approach to the synthesis of isoxazolidinones, which are useful precursors for  $\beta^2$ -amino acids.

**Review:** J. Blanchet, J. Baudoux, M. Amere, M.-C. Lasne, J. Rouden *Eur. J. Org. Chem.* **2008**, 5493–5506.

**SYNFACTS Contributors:** Benjamin List, Mattia Riccardo Monaco  
Synfacts 2014, 10(1), 0086 Published online: 13.12.2013  
DOI: 10.1055/s-0033-1340410; Reg-No.: B12313SF

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# Brønsted Acid Catalyzed Enantioselective Indole Aza-Claisen Rearrangement

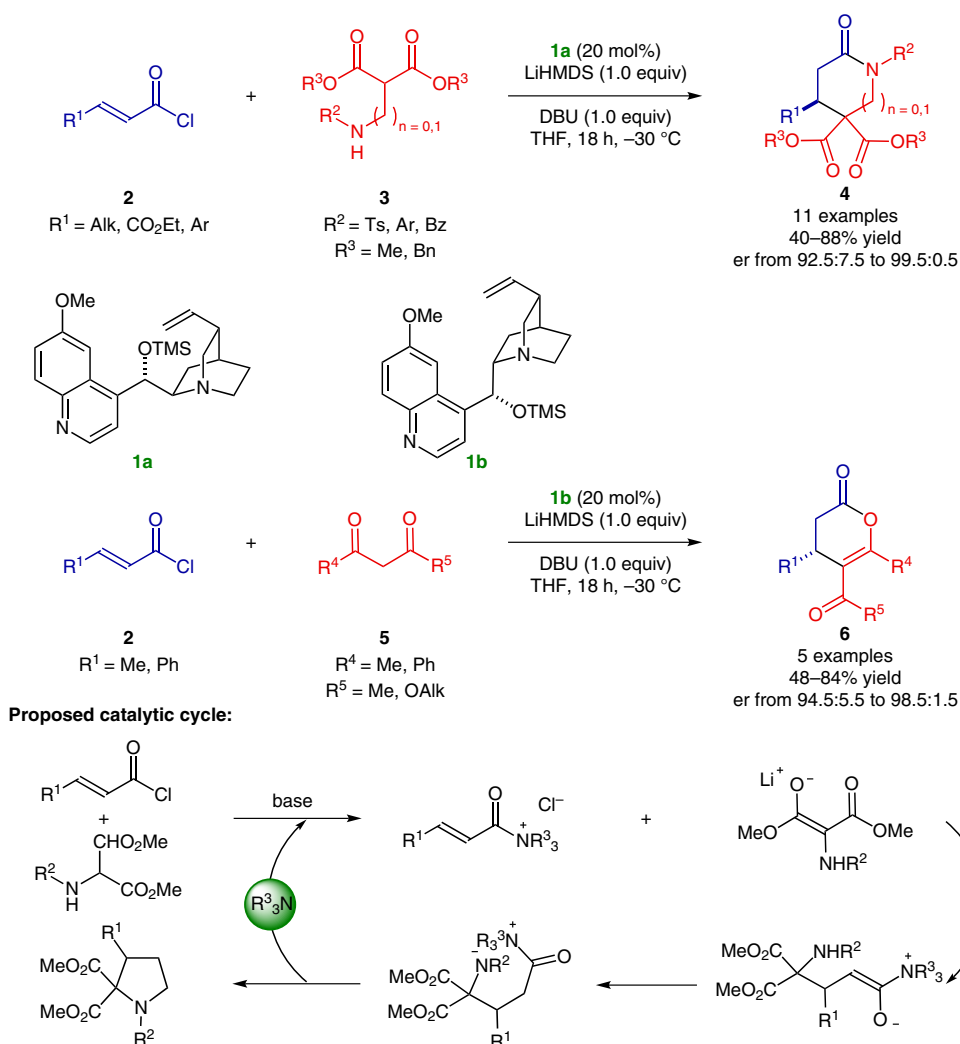


**Significance:** The first Brønsted acid catalyzed enantioselective indole aza-Claisen rearrangement for the generation of optically enriched 3-amino-2-substituted indoles is reported. An arene CH–O interaction is proposed to synergistically activate and stereo-induce as a second point of interaction (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– $\pi$  interaction between the R<sup>2</sup> group and the second 9-anthracene unit as well as CH–O interaction between the R<sup>2</sup> 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.

S. VELLALATH, K. N. VAN, D. ROMO\* (TEXAS A&M UNIVERSITY, COLLEGE STATION, USA)  
Direct Catalytic Asymmetric Synthesis of N-Heterocycles from Commodity Acid Chlorides by Employing  $\alpha,\beta$ -Unsaturated Acylammonium Salts  
*Angew. Chem. Int. Ed.* **2013**, DOI: 10.1002/anie.201306050.

## Synthesis of Pyrrolidinones via $\alpha,\beta$ -Unsaturated Acylammonium Ions

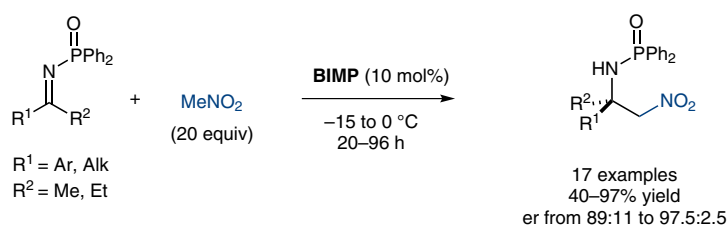


**Significance:** An asymmetric enantioselective Michael addition–proton transfer–lactamization or lactonization organocascade reaction is reported. The cinchona alkaloid derived catalysts **1** can generate chiral  $\alpha,\beta$ -unsaturated acylammonium salts with crotonyl chlorides **2**, giving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

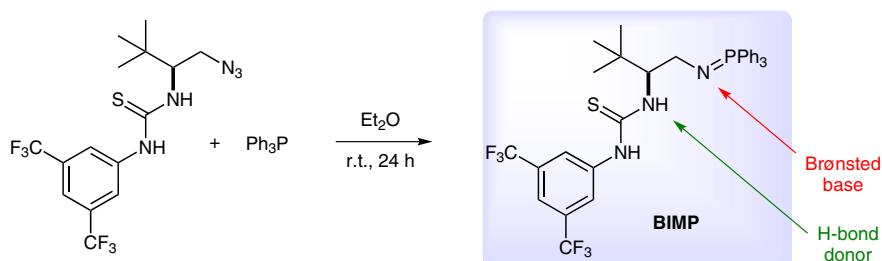
**SYNFACTS Contributors:** Benjamin List, Ji Hye Kim  
Synfacts 2014, 10(1), 0088 Published online: 13.12.2013  
DOI: 10.1055/s-0033-1340408; Reg-No.: B12113SF

**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 ( $R^3_3\text{N}$ ) with the acid chloride. After an intra- or intermolecular proton transfer, the acylammonium species undergoes intramolecular lactamization to regenerate the tertiary amine catalyst  $R^3_3\text{N}$ . The products could be transformed into known precursors of various biologically active compounds.

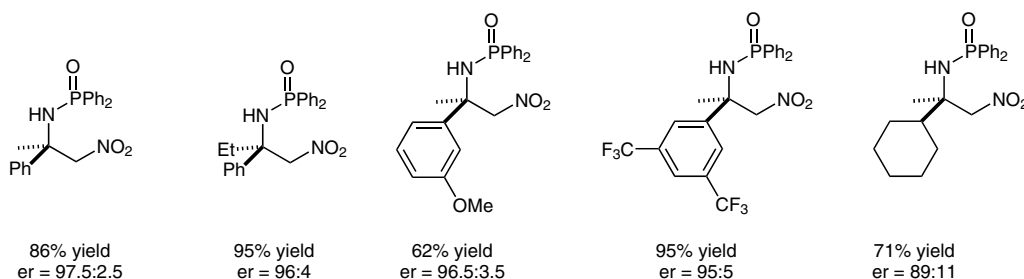
# Iminophosphorane-Catalyzed Enantioselective Ketimine Nitro-Mannich Reaction



## Synthesis of new BIMP (bifunctional iminophosphorane) organocatalyst:



## Selected examples:

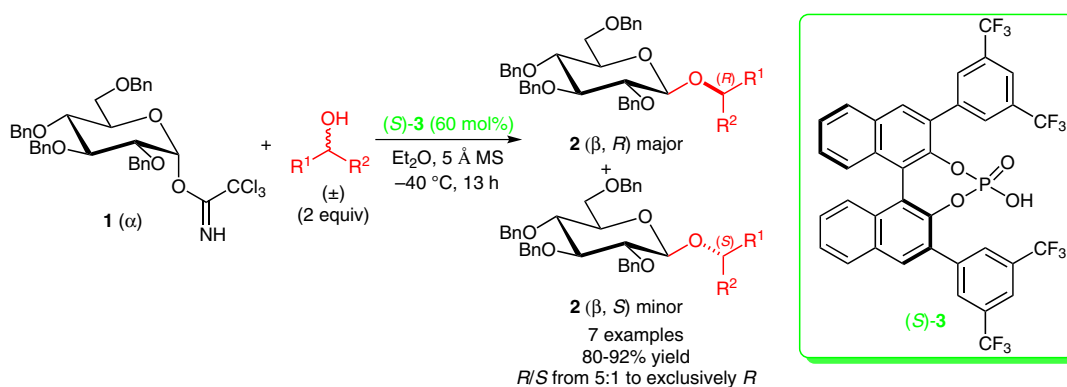


**Significance:** Dixon and co-workers report a new class of bifunctional Brønsted base/H-bond donor organocatalyst. The catalyst (bifunctional iminophosphorane, BIMP) can be applied to the ketimine nitro-Mannich reaction, generating β-nitroamines in good to excellent yields and enantioselectivities.

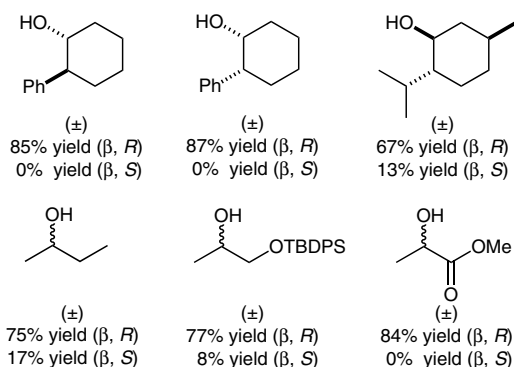
**Comment:** The authors developed a new catalyst motif consisting of a triaryliminophosphorane moiety as a Brønsted base and a thiourea moiety as an H-bond donor. The catalyst can be easily synthesized via Staudinger reaction of an organoazide and a triarylphosphine. The efficiency of the catalyst was 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.



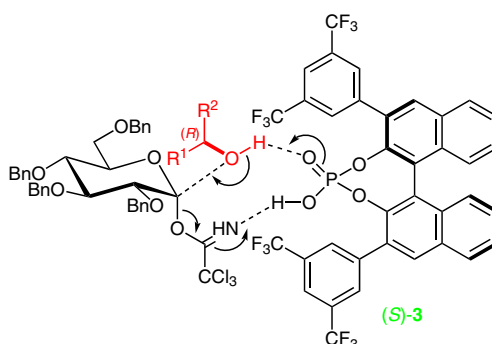
# Phosphoric Acid Mediated Glycosylation and Alcohol-Chirality Recognition



## Selected examples:



## Reaction pathway:



**Significance:** Toshima and co-workers report a highly  $\beta$ -selective glycosylation of  $\alpha$ -trichloroacetimidates **1a** 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  $\beta$ -selectivities are obtained through a (*S*)-**3**-mediated  $\text{S}_{\text{N}}2$  reaction pathway. The methodology was also applied to the total synthesis of a natural flavan glycoside using a racemic aglycone.

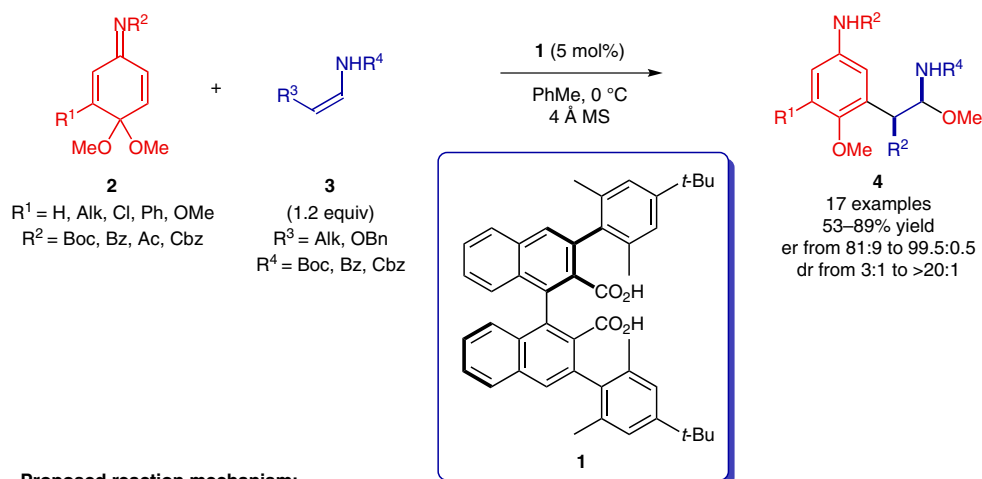
**Comment:** Glycosylation is an important synthetic method to construct sugar moiety containing compounds. Here, the authors report a novel Brønsted acid mediated glycosylation, and a kinetic resolution of secondary alcohols occurs during the process at the same time. This methodology provides a straightforward way for the synthesis of sugar-derived products with high stereoselectivity.

T. HASHIMOTO, H. NAKATSU, Y. TAKIGUCHI, K. MARUOKA\* (KYOTO UNIVERSITY, JAPAN)

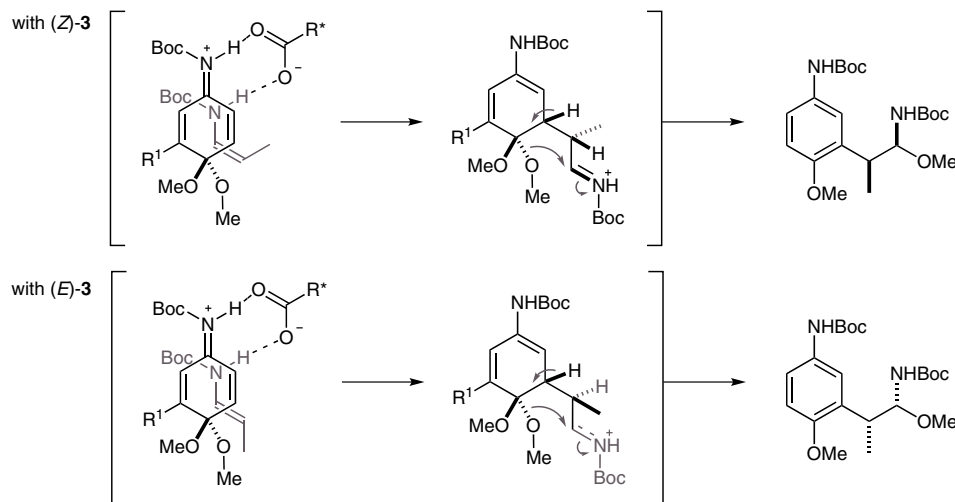
Axially Chiral Dicarboxylic Acid Catalyzed Activation of Quinone Imine Ketals: Enantioselective Arylation of Enecarbamates

*J. Am. Chem. Soc.* **2013**, *135*, 16010–16013.

## Enantioselective Arylation of Enecarbamates with Quinone Imine Ketals



### Proposed reaction mechanism:



**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.

**SYNFACTS Contributors:** Benjamin List, Ji Hye Kim  
Synfacts 2014, 10(1), 0092 Published online: 13.12.2013  
DOI: 10.1055/s-0033-1340403; Reg-No.: B11513SF

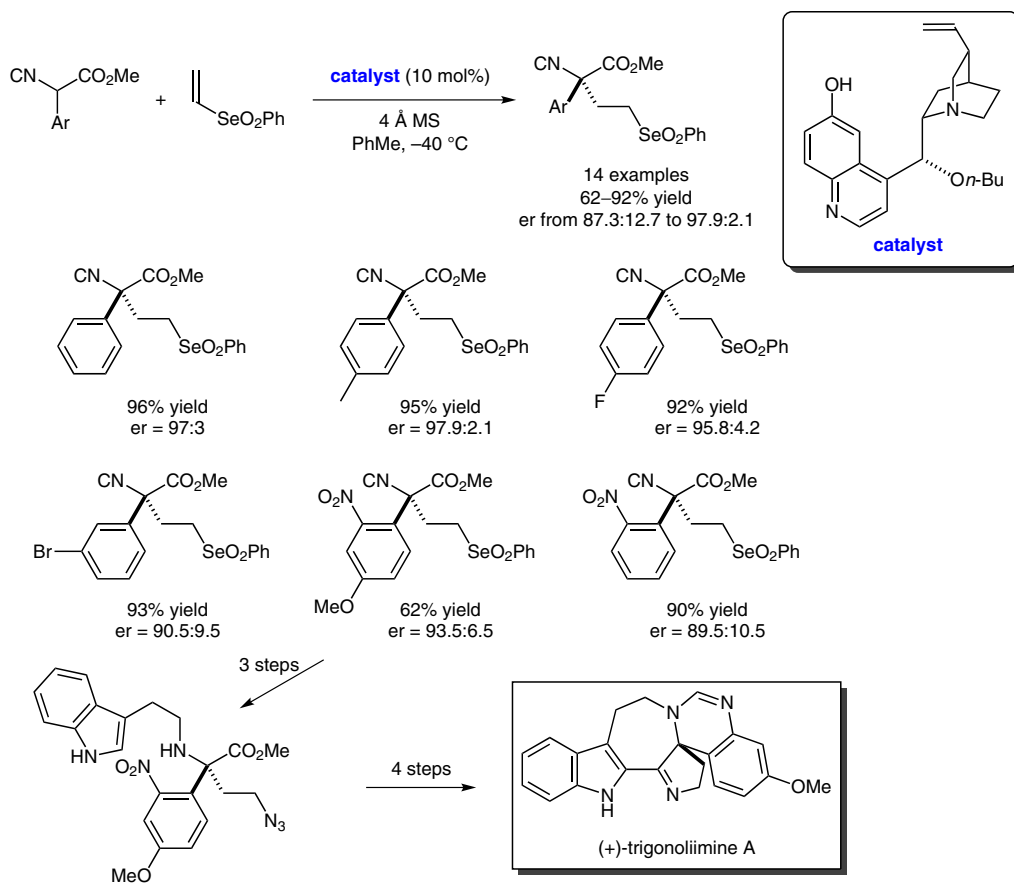
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T. BUYCK, Q. WANG, J. ZHU\* (ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE, SWITZERLAND)

Catalytic Enantioselective Michael Addition of  $\alpha$ -Aryl- $\alpha$ -Isocyanoacetates to Vinyl Selenone: Synthesis of  $\alpha,\alpha$ -Disubstituted  $\alpha$ -Amino Acids and (+)- and (–)-Trigonoliimine A  
*Angew. Chem. Int. Ed.* **2013**, 52, 12714–12718.

## Organocatalytic Total Syntheses of (+)- and (–)-Trigonoliimine A



**Significance:** The Zhu group reports an enantioselective Michael addition of methyl  $\alpha$ -aryl- $\alpha$ -isocyanoacetates to vinyl phenylselenone catalyzed by a cinchona-alkaloid derivative. The obtained enantioenriched  $\alpha$ -aryl- $\alpha$ -(2'-phenylselenonyl-ethyl)- $\alpha$ -isocyanoacetates are successfully transformed into linear and cyclic quaternary  $\alpha$ -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.

**SYNFACTS Contributors:** Benjamin List, Philip S. J. Kaib  
Synfacts 2014, 10(1), 0093 Published online: 13.12.2013  
DOI: 10.1055/s-0033-1340402; Reg-No.: B11413SF

**Comment:**  $\alpha$ -Isocyanoacetates are well-established glycine templates for the synthesis of racemic  $\alpha,\alpha$ -disubstituted  $\alpha$ -amino acids. Yet, the catalytic enantioselective allylation of  $\alpha$ -isocyanoacetates 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*.

Category

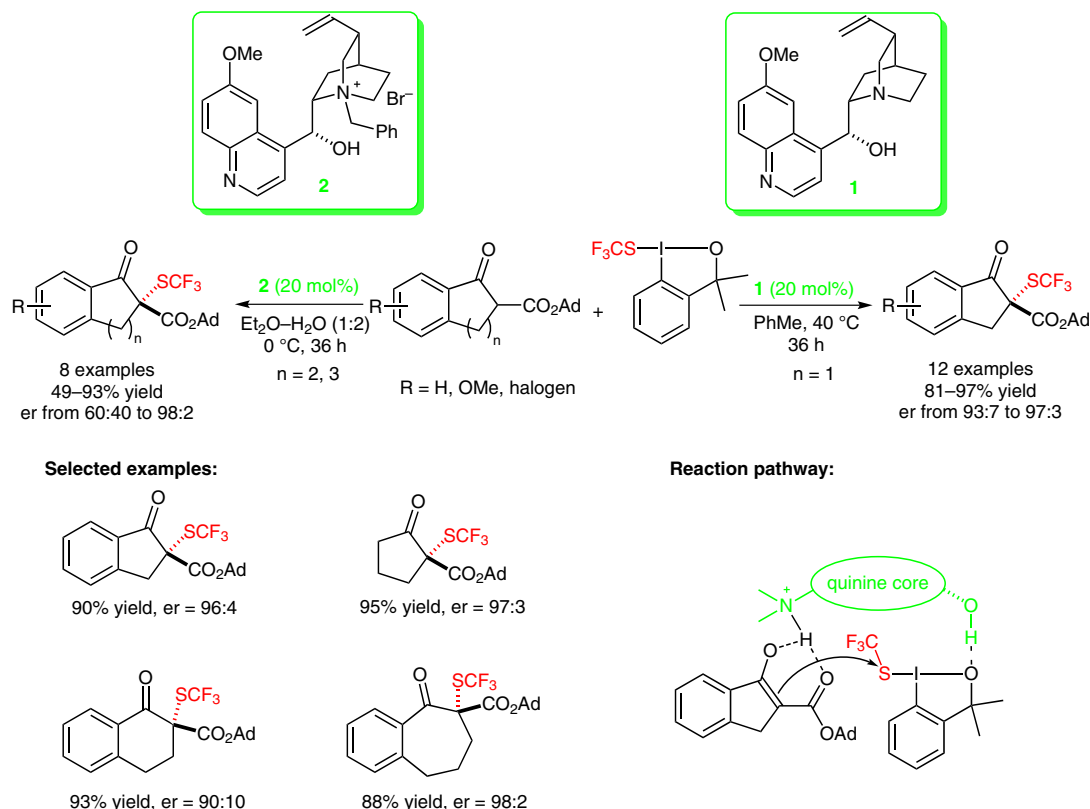
Organo- and  
Biocatalysis

Key words

Michael addition  
cinchona alkaloid  
trigonoliimine A

X. WANG, T. YANG, X. CHENG, Q. SHEN\* (SHANGHAI INSTITUTE OF ORGANIC CHEMISTRY, P. R. OF CHINA AND OAK RIDGE NATIONAL LABORATORY, USA)  
Enantioselective Electrophilic Trifluoromethylthiolation of  $\beta$ -Ketoesters: A Case of Reactivity and Selectivity Bias for Organocatalysis  
*Angew. Chem. Int. Ed.* **2013**, 52, 12860–12864.

## Organocatalytic Trifluoromethylthiolation of $\beta$ -Keto Esters



**Significance:** A highly enantioselective trifluoromethylthiolation of  $\beta$ -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  $\beta$ -keto esters. The free hydroxyl group of the catalyst is crucial for reactivity, and the SCF<sub>3</sub>-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  $\beta$ -keto ester and the SCF<sub>3</sub> reagent via a double hydrogen bonding.

**SYNFACTS Contributors:** Benjamin List, Qinggang Wang  
Synfacts 2014, 10(1), 0094 Published online: 13.12.2013  
**DOI:** 10.1055/s-0033-1340412; **Reg-No.:** B12513SF

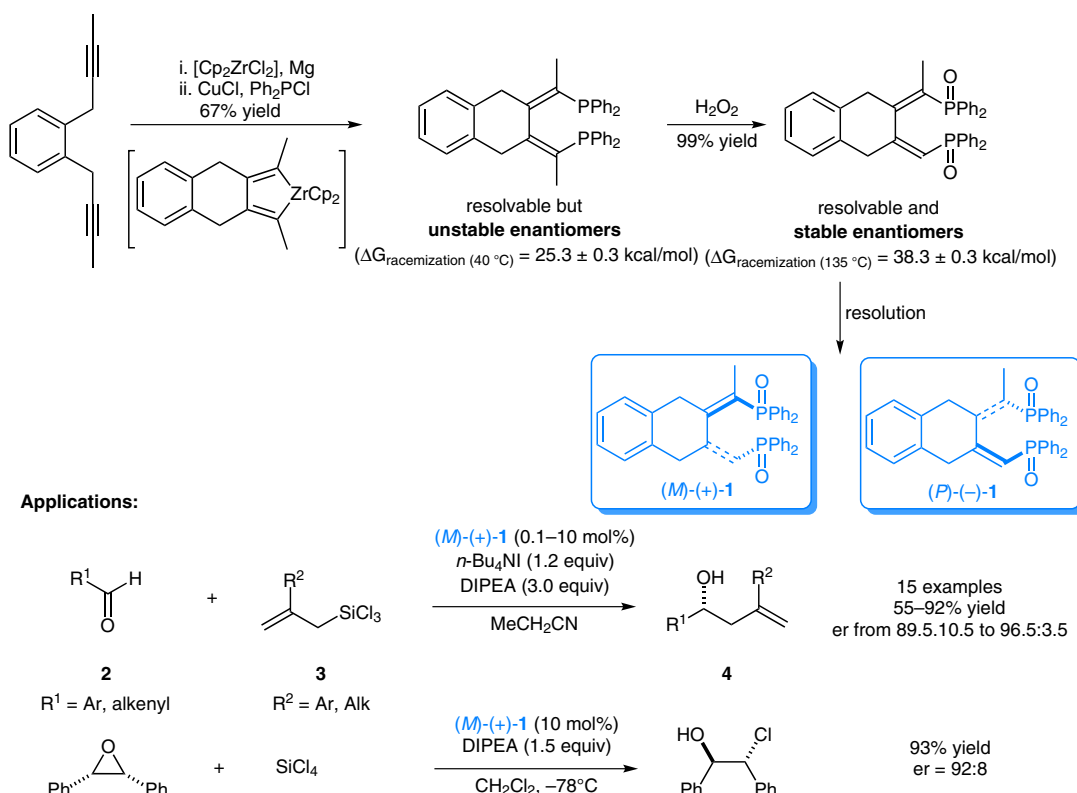
**Comment:** The introduction of fluorine functional groups into different molecules is of great importance for the pharmaceutical and agrochemical industries. Here, the authors report a practical procedure for highly enantioselective trifluoromethylthiolation of  $\beta$ -keto esters. This methodology provides a straightforward way to build quaternary carbon centers with a SCF<sub>3</sub> 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 SCF<sub>3</sub> sources (T. Bootwicha, X. Liu, R. Pluta, I. Atodiresei, M. Rueping *Angew. Chem. Int. Ed.* **2013**, 52, 12856).

M. OGASAWARA,\* S. KOTANI, H. NAKAJIMA, H. FURUSHO, M. MIYASAKA, Y. SHIMODA, W.-Y. WU, M. SUGIURA, T. TAKAHASHI, M. NAKAJIMA\* (HOKKAIDO UNIVERSITY, SAPPORO, AND KUMAMOTO UNIVERSITY, JAPAN)

Atropisomeric Chiral Dienes in Asymmetric Catalysis:  $C_2$ -Symmetric (Z,Z)-2,3-Bis[1-(diphenylphosphynyl)-ethylidene]tetralin as a Highly Active Lewis Base Organocatalyst

Angew. Chem. Int. Ed. 2013, DOI: 10.1002/anie.201308112.

# 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 enantiomeric 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.

**Review:** S. E. Denmark, J. Fu *Chem. Rev.* 2003, 103, 2763–2794.

**SYNFACTS Contributors:** Benjamin List, Gabriele Pupo  
Synfacts 2014, 10(1), 0095 Published online: 13.12.2013  
DOI: 10.1055/s-0033-1340406; Reg-No.: B11913SF

**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.