

Asymmetric Vinylogous Mukaiyama–Michael Reaction via Iminium Catalysis

Category

Organo- and Biocatalysis

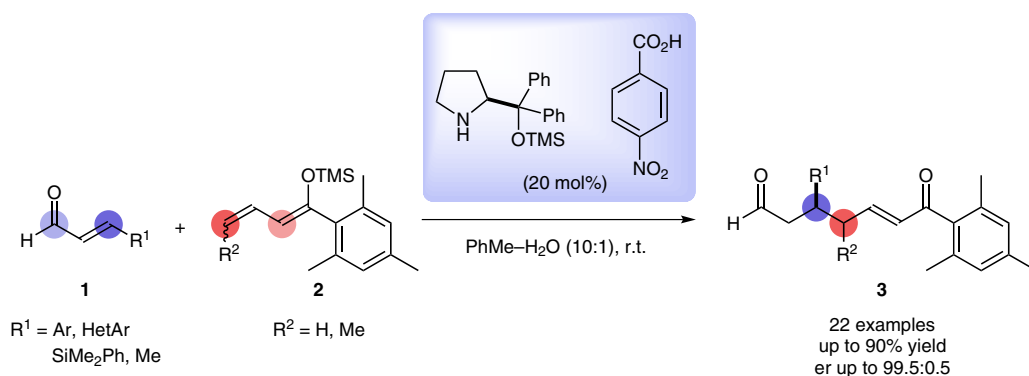
Key words

vinylogous Mukaiyama–Michael reaction

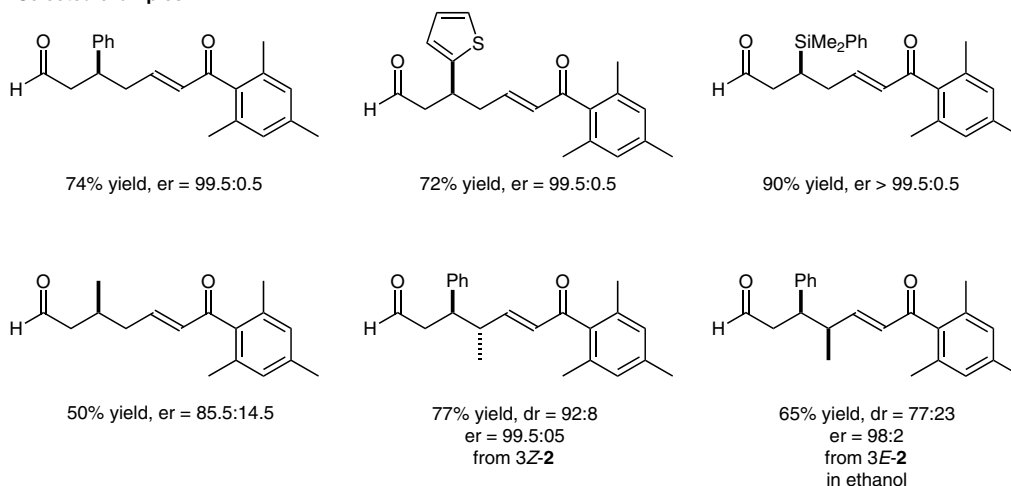
Jørgensen–Hayashi catalyst

enals

dienol silyl ethers



Selected examples:



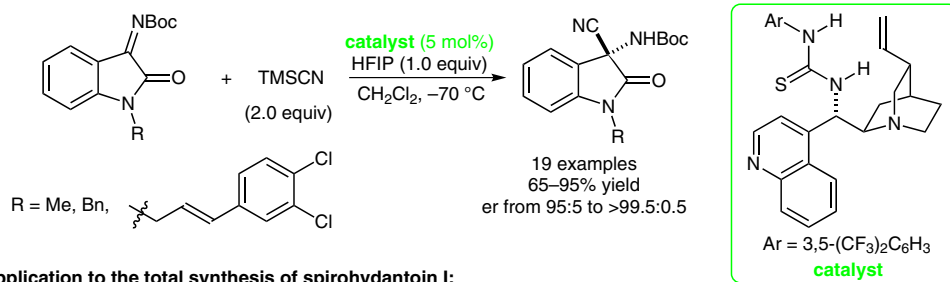
Significance: The authors report a highly enantio- and diastereoselective vinylogous Mukaiyama–Michael reaction of acyclic dienol silyl ethers **2** to various enals **1** by employing a Jørgensen–Hayashi catalyst. 1,7-Dicarbonyl compounds **3** are obtained under mild reaction conditions with good to excellent yield and remarkable regioselectivity. *Z/E*-Configured γ -methyl-substituted dienol silyl ethers are selectively converted into the *anti* and *syn* products **3** with excellent enantioselectivity.

Comment: Vinylogous Michael reactions of dienol derivatives can form a C–C bond with high regio- and stereoselectivity in the presence of a chiral catalyst. However, a catalytic enantioselective process of this reaction with acyclic nucleophiles and enals was elusive since the reaction can produce a number of regio- and stereoisomers. Herein, the catalyst nicely operates presumably by forming an iminium species with enal **1** to induce 1,4-addition of nucleophile **2** with high γ -selectivity.

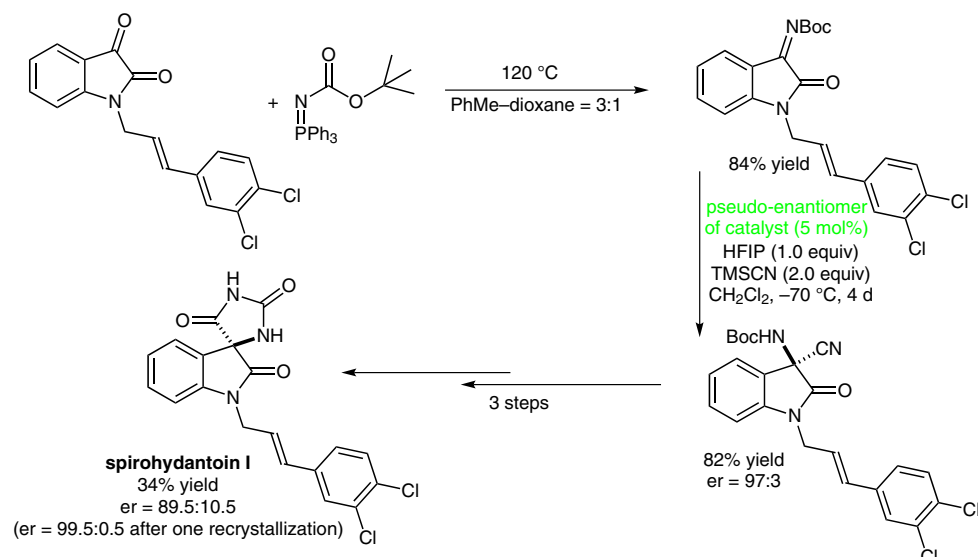
Y.-L. LIU, J. ZHOU* (EAST CHINA NORMAL UNIVERSITY, SHANGHAI, CHINA)

Organocatalytic Asymmetric Cyanation of Isatin Derived *N*-Boc Ketimines*Chem. Commun.* **2013**, DOI: 10.1039/c2cc36665g.

Thiourea-Catalyzed Asymmetric Cyanation of *N*-Boc Ketimines



Application to the total synthesis of spirohydantoin I:



Significance: The first catalytic asymmetric cyanation of isatin-derived *N*-Boc ketimines has been reported by Zhou and co-worker. Wide substrate scope and excellent enantioselectivities were obtained. A tandem aza-Wittig–Strecker reaction has also been reported, which was applied to the total synthesis of spirohydantoin I.

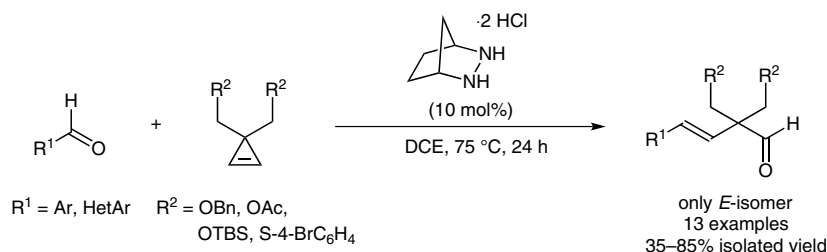
Comment: An aza-Wittig–Strecker reaction sequence has been reported, which offers a good methodology to develop a catalytic asymmetric reaction of *N*-Boc ketimines, generated in situ from the achiral ketones. The strategy has potential applications in other types of reactions, in which *N*-Boc imines are involved.

SYNFACTS Contributors: Benjamin List, Qinggang Wang
 Synfacts 2013, 9(1), 0096 Published online: 17.12.2012

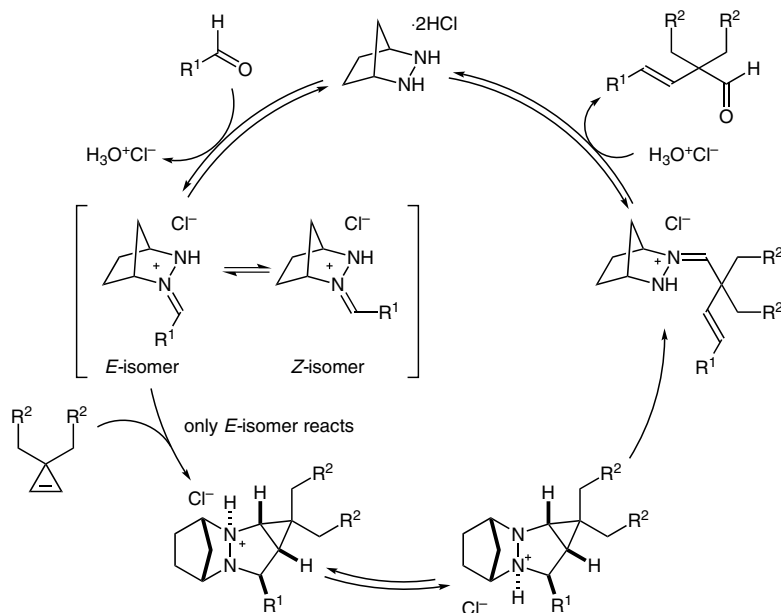
DOI: 10.1055/s-0032-1317897; **Reg-No.:** B11012SF

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Organocatalytic Carbonyl-Olefin Metathesis Using a Hydrazine Catalyst



Proposed catalytic cycle:



Significance: Lambert and co-workers have developed a carbonyl-olefin metathesis catalyzed by a bicyclic hydrazine. The reaction is based on the idea to replace the typically used [2+2]-cycloaddition–cycloreversion approach with a [3+2] analogue, which is thermochemically allowed. The reaction was found to require a bicyclic hydrazine as the bishydrochloride in order to proceed and is essentially restricted to aromatic aldehydes due to the many degradation pathways for aliphatic aldehydes in the presence of the hydrazine catalyst. The authors propose a catalytic cycle, in which the observed *E*-selectivity is explained.

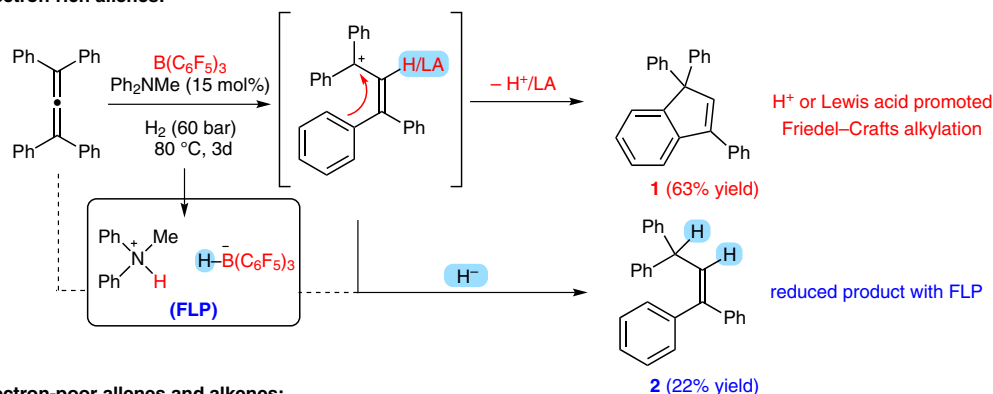
Comment: Metathesis reactions involving carbonyls are much less developed than reactions of olefins and alkynes with themselves. This work by Lambert and co-workers will hopefully encourage further developments in this field. Future challenges are the use of unactivated acyclic olefins, leading to a fragment coupling reaction, and the development of a desymmetrization of *meso*-cyclopropenes using an enantiomerically pure hydrazine catalyst or by replacing the chloride counteranion with one of the recently established chiral counteranions, such as BINOL-derived phosphates.

SYNFACTS Contributors: Benjamin List, Manuel Mahlau
Synfacts 2013, 9(1), 0097 Published online: 17.12.2012
DOI: 10.1055/s-0032-1317900; **Reg-No.:** B11312SF

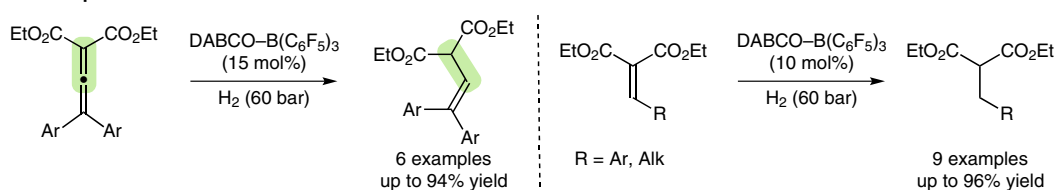
B. INÉS, D. PALOMAS, S. HOLLE, S. STEINBERG, J. A. NICASIO, M. ALCARAZO* (MAX-PLANCK-INSTITUT FÜR KOHLENFORSCHUNG, MÜLHEIM AN DER RUHR, GERMANY)
Metal-Free Hydrogenation of Electron-Poor Allenes and Alkenes
Angew. Chem. Int. Ed. **2012**, *51*, 12367–12369.

Frustrated Lewis Pairs for Catalytic Hydrogenation of Allenes and Alkenes

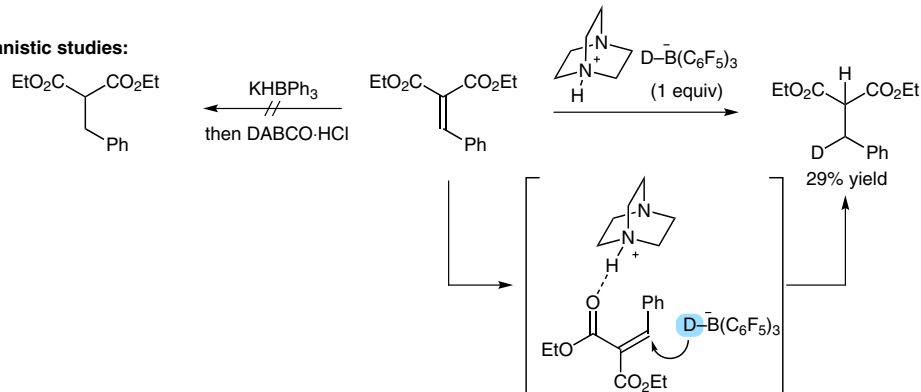
Electron-rich allenens:



Electron-poor allenens and alkenes:



Mechanistic studies:

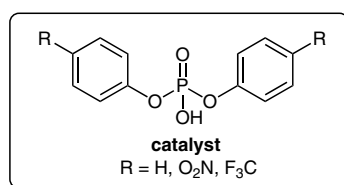
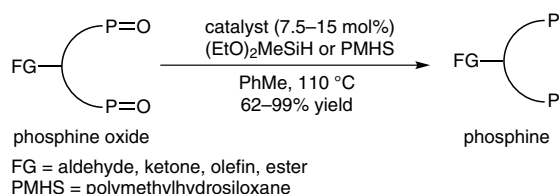


Significance: The Alcarazo group reports a frustrated Lewis pair (FLP)-catalyzed hydrogenation reaction of electron-poor allenens and alkenes. The reduced products were obtained with good to excellent yield and high chemoselectivity by employing DABCO-B(C₆F₅)₃ as a catalyst pair (10–15 mol%).

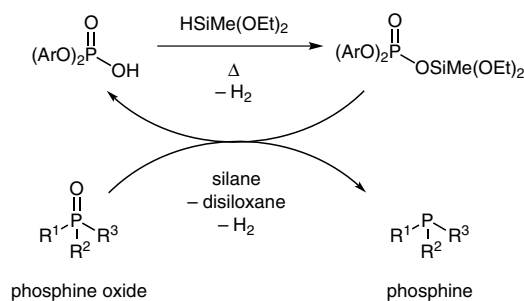
Comment: To overcome the inherent reactivity of electron-rich allenens to cyclize to Friedel-Crafts products **1** in the presence Brønsted acids and/or Lewis acids, the authors employ electron-poor substrates to facilitate FLP-catalyzed hydrogenation to the desired product **2**. According to the mechanistic studies, [DABCO-H]⁺ might act as a hydrogen-bond donor to activate the substrate. The hydride from the borohydride is transferred via 1,4-addition.

SYNFACTS Contributors: Benjamin List, Ji-Woong Lee
Synfacts 2013, 9(1), 0098 Published online: 17.12.2012
DOI: 10.1055/s-0032-1317905; **Reg-No.:** B11812SF

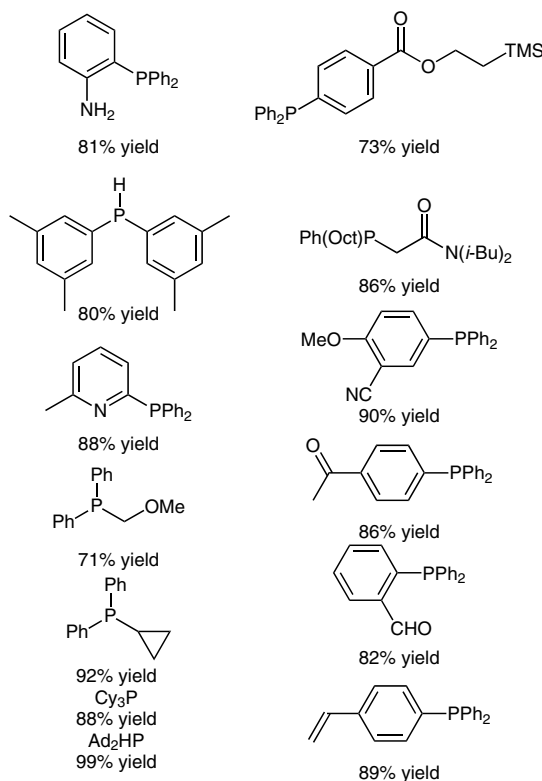
Organocatalytic Chemoselective Reduction of Phosphine Oxides to Phosphines



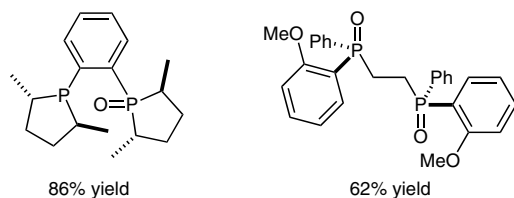
Proposed mechanism:



Some examples of phosphines:



Selected examples of converted phosphine oxides:



Significance: Organophosphines represent valuable intermediates, catalysts, and ligands for transition-metal catalysis. Here, the authors report the utilization of inexpensive silanes by Brønsted acid catalysis, which shows broad functional group tolerance towards aldehydes, ketones, olefins, nitriles, and esters. Chemoselectivities of 99:1 for P–O double bonds and retention of the configuration at the P-center were achieved.

SYNFACTS Contributors: Benjamin List, Philip S. J. Kaib
Synfacts 2013, 9(1), 0099 Published online: 17.12.2012
 DOI: 10.1055/s-0032-1317901; Reg-No.: B11412SF

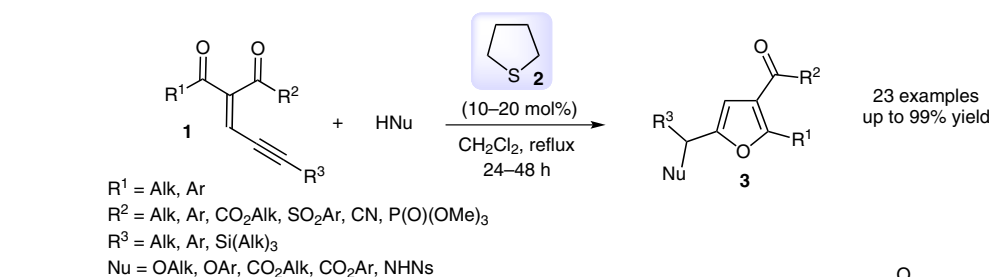
Comment: The catalytic chemoselective reduction of P–O double bonds (502 kJ/mol) is a formidable challenge in synthetic chemistry. This metal-free protocol under convenient, air-insensitive, and safe reaction conditions for aryl, alkyl, mono- and bidentate phosphine oxides with its high functional group tolerance indicates possible applications in catalytic Wittig, Appel, and Staudinger reactions.

J. S. CLARK,* A. BOYER, A. AIMON, P. E. GARCÍA, D. M. LINDSAY, A. D. F. SYMINGTON, Y. DANOY (UNIVERSITY OF GLASGOW, UK)

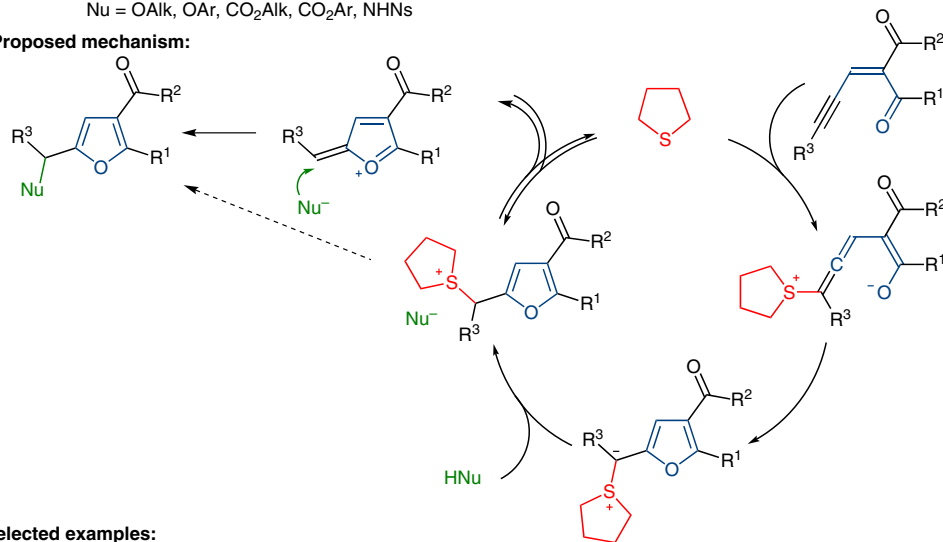
Organocatalytic Synthesis of Highly Substituted Furfuryl Alcohols and Amines

Angew. Chem. Int. Ed. **2012**, *51*, 12128–12131.

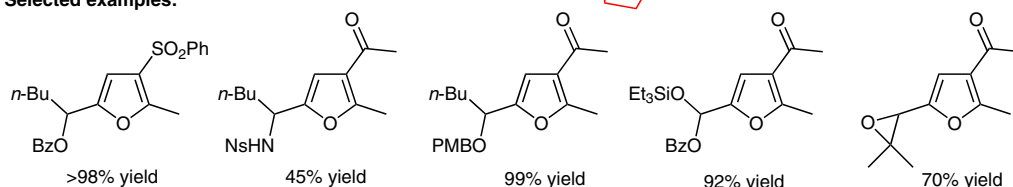
Organocatalytic Synthesis of Substituted Furfuryl Alcohols and Amines



Proposed mechanism:



Selected examples:



Significance: The authors present an organocatalytic approach for the synthesis of highly substituted furfuryl alcohols and amines in good to excellent yield. The reaction is catalyzed by tetrahydrothiophene (**2**), using a Lewis base for the activation of the alkynylcarbonyl derivatives **1**. In contrast to **2**, other Lewis bases such as DABCO or Bu_3P led to decomposition.

Comment: While electrophilic metal-catalyzed furan syntheses are common, organocatalytic approaches are rare. Inspired by the work of Krische (*J. Am. Soc. Chem.* **2004**, 4118) and Kuroda (*Tetrahedron* **2004**, 1913), Clark and co-workers applied a Lewis base activation concept for their reaction. By using tetrahydrothiophene (**2**) as a catalyst, an enolate is formed that cyclizes to a sulfur ylide containing furan which can react with different nucleophiles. This method can also be used for a multi-component domino synthesis of substituted furans.

SYNFACTS Contributors: Benjamin List, Lisa Kötzner
 Synfacts 2013, 9(1), 0100 Published online: 17.12.2012
 DOI: 10.1055/s-0032-1317898; Reg-No.: B11112SF

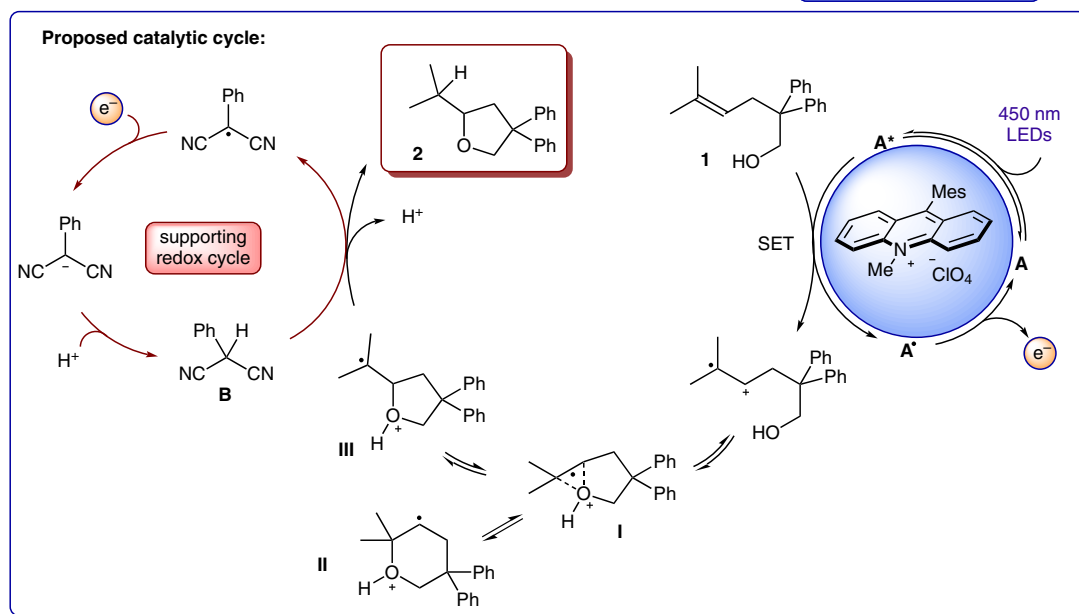
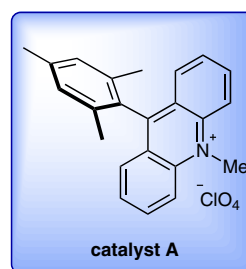
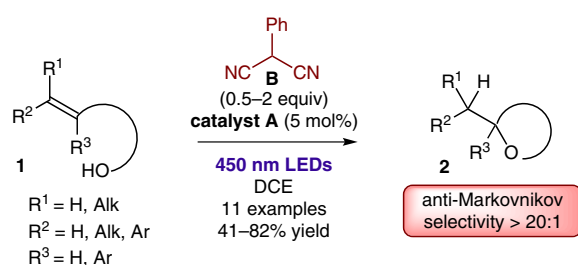
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D. S. HAMILTON, D. A. NICEWICZ* (UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL, USA)

Direct Catalytic Anti-Markovnikov Hydroetherification of Alkenols

J. Am. Chem. Soc. **2012**, *134*, 18577–18580.

Photocatalytic Anti-Markovnikov Hydroetherification



Significance: A direct photocatalytic anti-Markovnikov hydroetherification has been described by the Nicewicz group. The reported procedure is promoted by the commercially available sensitizer 9-mesityl-10-methylacridinium perchlorate (**A**) and the H-atom donor 2-phenylmalonitrile (**B**). The authors suggest that the methodology is based on two different redox cycles. A primary one, which initiates the reaction by a single-electron transfer (SET) and a supporting one, which simultaneously facilitates the hydrogen exchange and serves as an electron-redox mediator.

Comment: The study of catalytic anti-Markovnikov additions of nucleophiles to olefins has gained great interest in the last decades since it had been described as one of the 'top ten challenges for catalysis' [J. Haggin *Chem. Eng. News* **1993**, *71* (22), 23]. In this work, the authors describe the addition of alcohols to alkenes via a newly developed two-component organic photoredox catalytic system. The reaction affords a wide range of cyclic ethers with complete selectivity, which reflects the thermodynamic equilibrium between the three radical intermediates **I**, **II** and **III**.

SYNFACTS Contributors: Benjamin List, Mattia Riccardo Monaco
Synfacts 2013, 9(1), 0101 Published online: 17.12.2012

DOI: 10.1055/s-0032-1317903; **Reg-No.:** B11612SF

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Category

Organo- and Biocatalysis

Key words

photoredox catalysis

hydroetherification

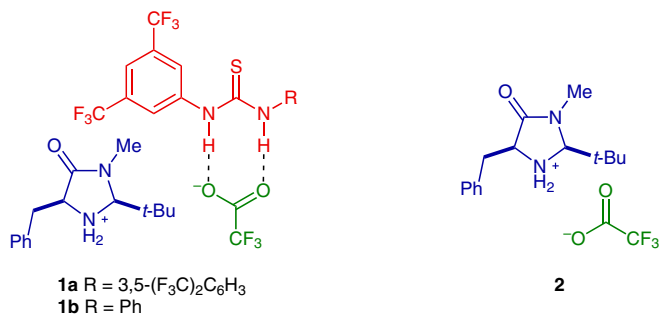
anti-Markovnikov selectivity

Y. WANG, T.-Y. YU, H.-B. ZHANG, Y.-C. LUO, P.-F. XU* (LANZHOU UNIVERSITY, P. R. OF CHINA)

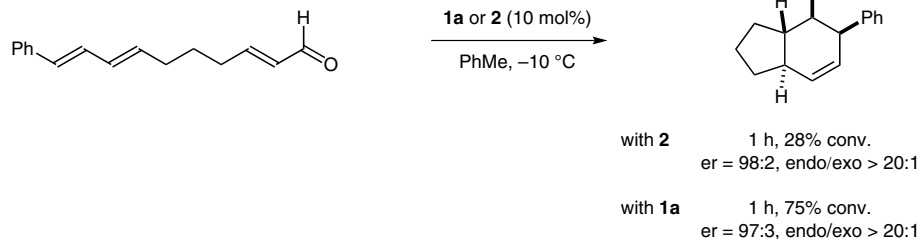
Hydrogen-Bond-Mediated Supramolecular Iminium Ion Catalysis

Angew. Chem. Int. Ed. **2012**, *51*, 12339–12342.

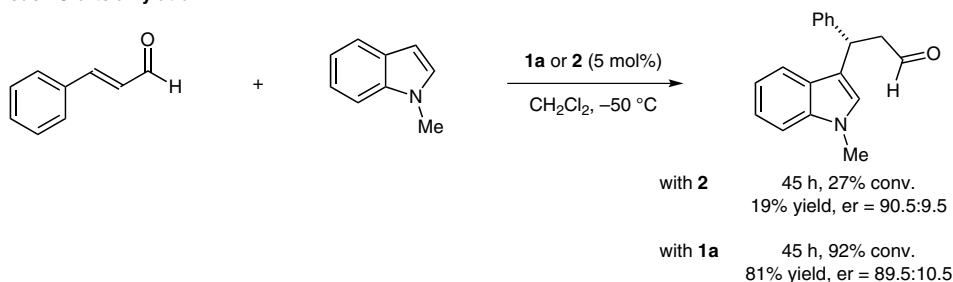
Thiourea-Assisted Iminium Catalysis



An intramolecular Diels–Alder reaction:



A Friedel–Crafts alkylation:



Significance: A thiourea-assisted iminium catalysis has been described. It was found that simple thioureas accelerate previously established reactions of α,β -unsaturated aldehydes with MacMillan's organocatalyst, presumably by binding to the counteranion of the iminium intermediate. The use of chiral thioureas did not have a significant effect on the enantioselectivity.

Comment: The profound influence of anions on reactivity and selectivity in asymmetric iminium catalysis is well established (S. Mayer, B. List *Angew. Chem. Int. Ed.* **2006**, *45*, 4193). Therefore, thioureas could be expected to influence the activity and selectivity by anion binding during the catalysis (see Review below). In the current report, a mild positive influence of thioureas on reactivity is demonstrated. Development of a chiral thiourea as the only source of asymmetric information remains as the true challenge of this approach.

Review: Z. Zhang, P. R. Schreiner *Chem. Soc. Rev.* **2009**, *38*, 1187–1198.

SYNFACTS Contributors: Benjamin List, Ji Hye Kim
 Synfacts 2013, 9(1), 0102 Published online: 17.12.2012
 DOI: 10.1055/s-0032-1317904; Reg-No.: B11712SF

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Asymmetric Protonation in Dienamine-Catalysis

Category

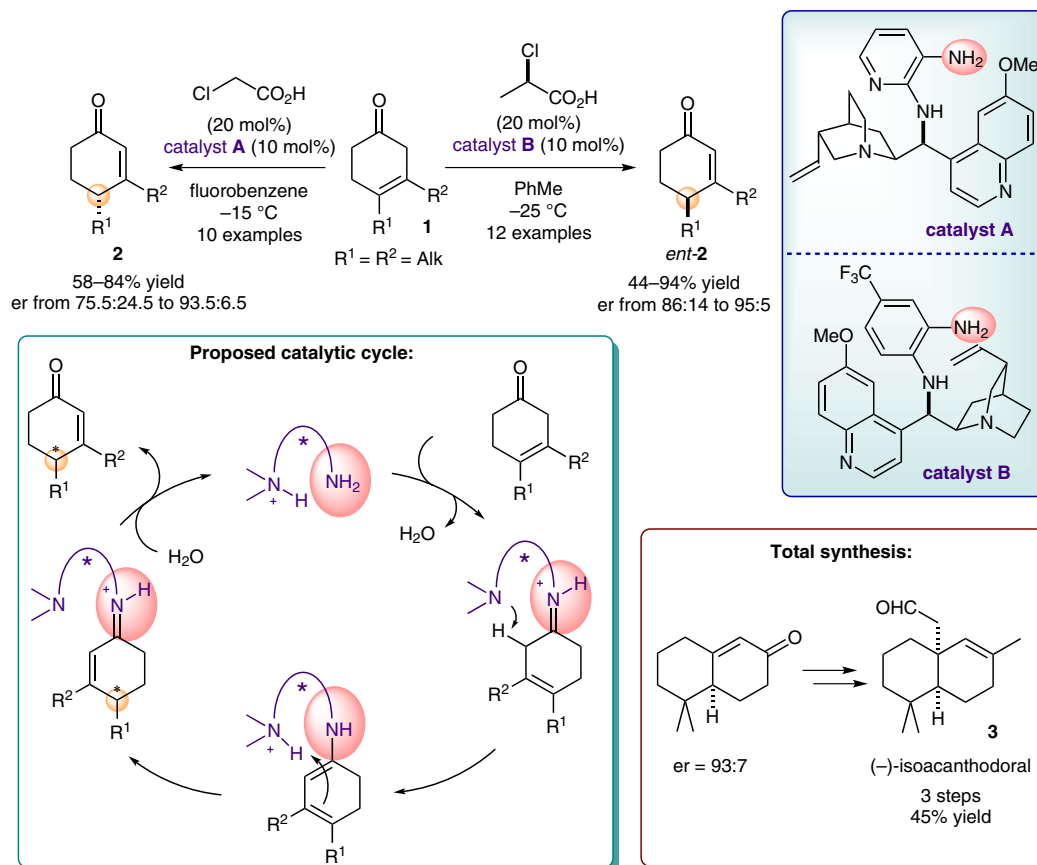
Organo- and Biocatalysis

Key words

double bond isomerization

bifunctional catalysts

total synthesis



Significance: The Deng group reports the catalytic enantioselective isomerization of β,γ -unsaturated cyclohex-3-en-1-ones **1** to the corresponding chiral α,β -unsaturated cyclic enones **2**. The authors designed a new class of cinchona alkaloid-derived catalysts bearing substituted anilines as tunable handles. In particular, combining the newly synthesized catalysts **A** and **B** with carboxylic acid co-catalysts, they developed two different systems to achieve the synthesis of the two enantiomers of the desired products.

Comment: During the last few years interest has grown towards asymmetric primary amine catalyzed γ -functionalization of enones via dienamine intermediates. These methodologies mainly rely on the remote control of the stereochemistry achievable with the cinchona-alkaloid skeletons. Herein, the authors tackle the challenge of asymmetric γ -protonation and report the development of new bifunctional catalysts, which allow such transformations. Moreover, the usefulness of the process is highlighted by the first asymmetric total synthesis of the marine sesquiterpenoid isoacanthodoral (**3**).

SYNFACTS Contributors: Benjamin List, Mattia Riccardo Monaco

Synfacts 2013, 9(1), 0103 Published online: 17.12.2012

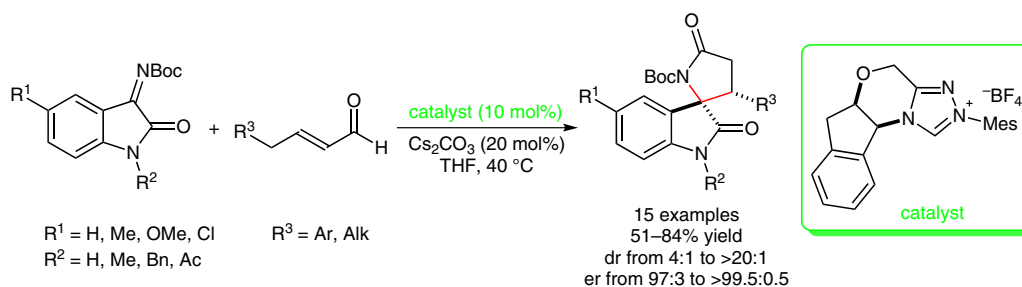
DOI: 10.1055/s-0032-1317896; Reg-No.: B10912SF

H. LV, B. TIWARI, J. MO, C. XING, Y. R. CHI* (NANYANG TECHNOLOGICAL UNIVERSITY, SINGAPORE)

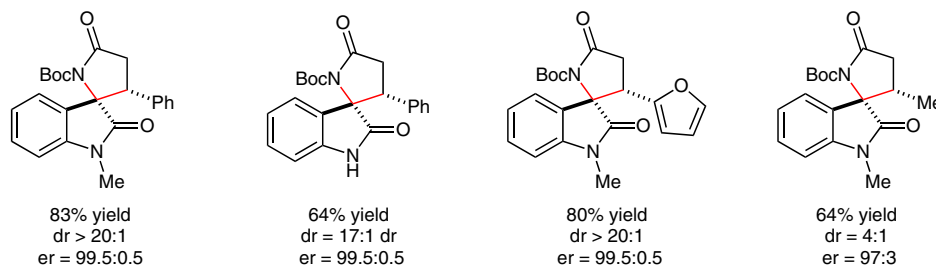
Highly Enantioselective Addition of Enals to Isatin-Derived Ketimines Catalyzed by N-Heterocyclic Carbenes: Synthesis of Spirocyclic γ -Lactams

Org. Lett. **2012**, *14*, 5412–5415.

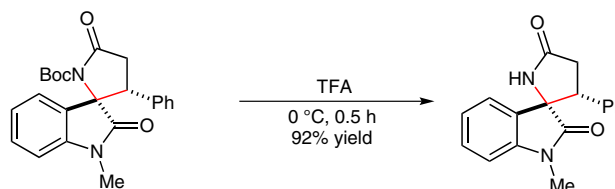
NHC-Catalyzed Annulation of Isatin *N*-Boc Ketimines and Enals



Selected examples:



Removal of the Boc protecting group:



Significance: Chi and co-workers report an N-heterocyclic carbene (NHC)-catalyzed annulation of isatin *N*-Boc imines with enals, which affords spirocyclic oxindole- γ -lactams bearing one quaternary chiral center in good diastereo- and excellent stereoselectivities (dr up to >20:1 and er > 99.5:0.5). Ketimines and γ -aryl enals with electron-donating substituents lead to better yield and selectivity compared to electron-withdrawing substituents. The presence of a trace of water is beneficial for the conversion of the reaction. The resulting products can be easily deprotected to free γ -lactams in high yield.

SYNFACTS Contributors: Benjamin List, Qinggang Wang
 Synfacts 2013, 9(1), 0104 Published online: 17.12.2012

DOI: 10.1055/s-0032-1317902; **Reg-No.:** B11512SF

Comment: γ -Lactams are privileged scaffolds found in naturally occurring and synthetic biologically active compounds. Herein, the authors have developed a novel NHC-catalyzed annulation methodology, which allows for a rapid construction of spirocyclic oxindole- γ -lactams with high diastereoselectivity and enantioselectivity. More efficient catalysts and the application to more challenging substrates are expected.

NMR Characterization of Breslow Intermediates

Category

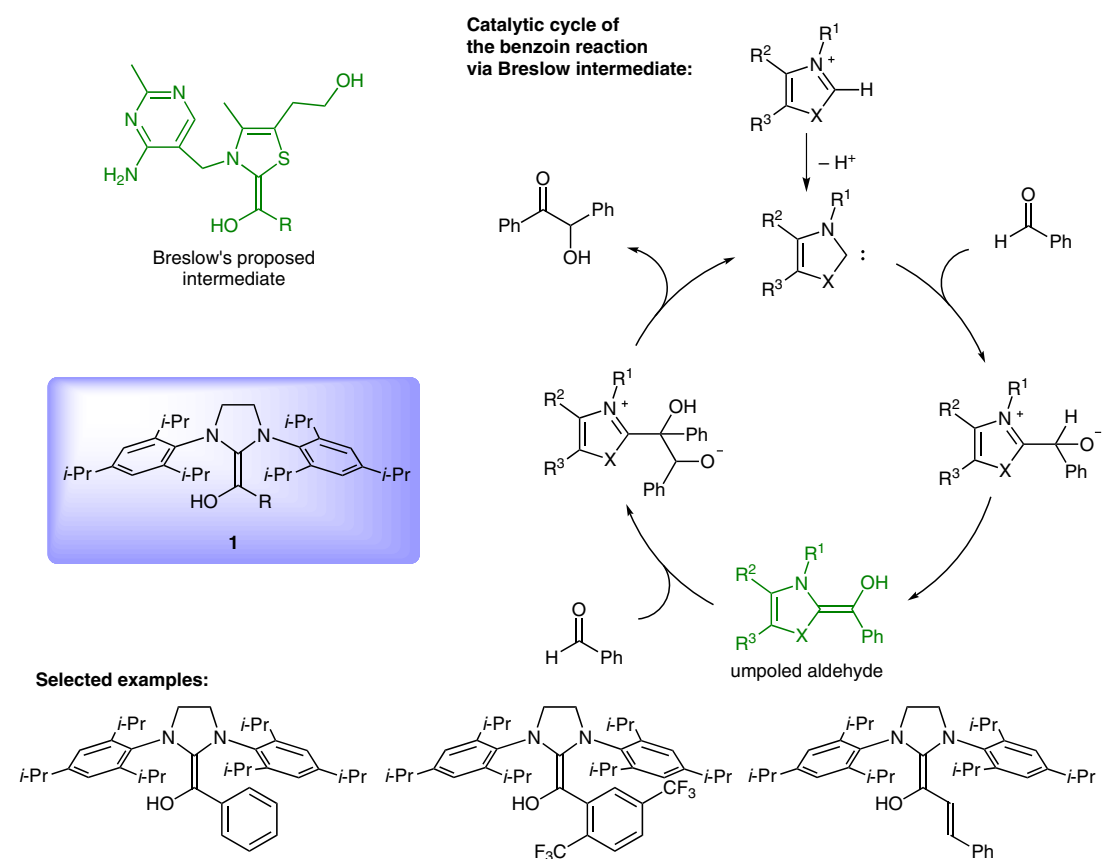
Organo- and Biocatalysis

Key words

carbenes

umpolung

Breslow intermediates



Significance: The generation of 2,2-diamino enols **1** from the corresponding N-heterocyclic carbenes and aldehydes has been reported. Species like **1** are commonly invoked as intermediates in aldehyde-umpolung reactions such as the benzoin reaction, and are known as Breslow intermediates. Different Breslow intermediates were characterized by NMR methods for the first time, and are shown to possess the expected benzoin reactivity.

Comment: In 1958, Breslow proposed that thiamine-mediated reactions in biochemistry rely on carbene reactivity and invoked the intermediates that today bear his name (*J. Am. Chem. Soc.* **1958**, *80*, 3719). In the current report the identification of relatively unreactive Breslow intermediates such as **1** by combination of aromatic aldehydes with a saturated carbene was crucial for making the intermediates detectable. More common Breslow intermediates with unsaturated N-heterocyclic carbenes remain to be characterized. For a previous characterization of aza analogues of Breslow intermediates, see: *J. Am. Chem. Soc.* **2012**, *134*, 6143.