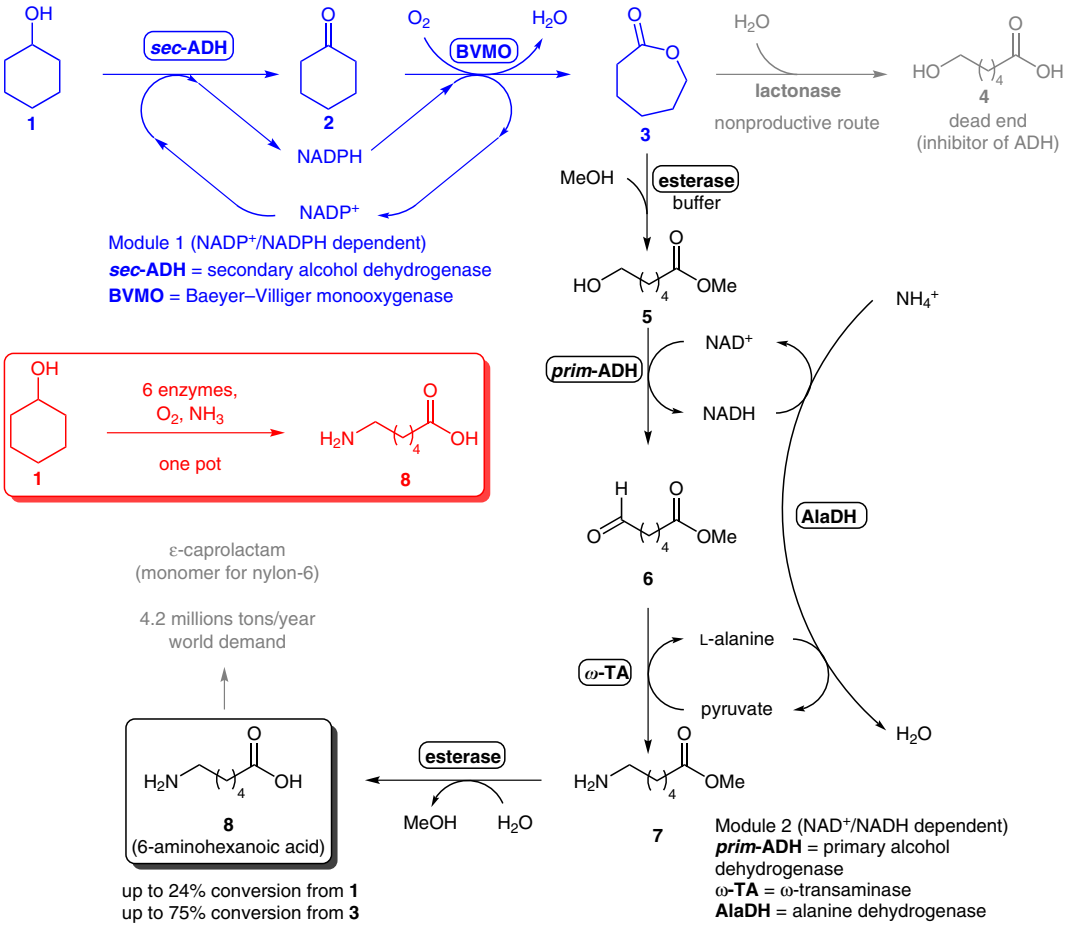
J. H. SATTLER, M. FUCHS, F. G. MUTTI, B. GRISCHEK, P. ENGEL, J. PFEFFER, J. M. WOODLEY, W. KROUTIL* (UNIVERSITY OF GRAZ AND AUSTRIAN CENTRE OF INDUSTRIAL BIOTECHNOLOGY, GRAZ, AUSTRIA; EVONIK INDUSTRIES, MARL, GERMANY; TECHNICAL UNIVERSITY OF DENMARK, LYNGBY, DENMARK)

Introducing an In Situ Capping Strategy in Systems Biocatalysis To Access 6-Aminohexanoic acid
Angew. Chem. Int. Ed. **2014**, *53*, 14153–14157.

A One-Pot Biocatalytic Sequence to 6-Aminohexanoic Acid



Significance: Kroutil and co-workers report two sequential biocatalytic self-sufficient redox modules (the co-factor required for a step is regenerated in successive step) for the synthesis of 6-aminohexanoic acid, the precursor of ε-caprolactam (the monomer of nylon-6). The process affords the desired product **8** from **1** (up to 24% conversion) or **3** (up to 75% conversion). The key of the system is to circumvent the formation of **4** via in situ capping (esterification).

Comment: The production of ε-caprolactam is one of the largest industrial processes in the world, and therefore, new environmentally friendly synthetic sequences are continuously required. The authors design an unprecedented sequence (two independent modules) in which **8** is obtained from cheap starting materials (**1** or **3**) via the methyl ester key intermediate **5**, at the sole expense of O_2 and NH_3.

SYNFACTS Contributors: Benjamin List, Gabriele Pupo
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DOI: 10.1055/s-0034-1379622; **Reg-No.:** B12514SF

Category
Organo- and Biocatalysis

Key words
aminohexanoic acid
nylon
capping strategy
enzyme catalysis

Category

Organo- and Biocatalysis

Key words

N-heterocyclic carbenes

hydroxylation

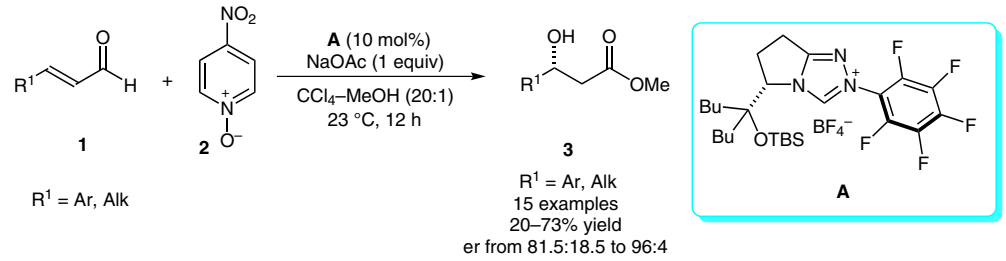
single electron transfer

N. A. WHITE, T. ROVIS* (COLORADO STATE UNIVERSITY, FORT COLLINS, USA)

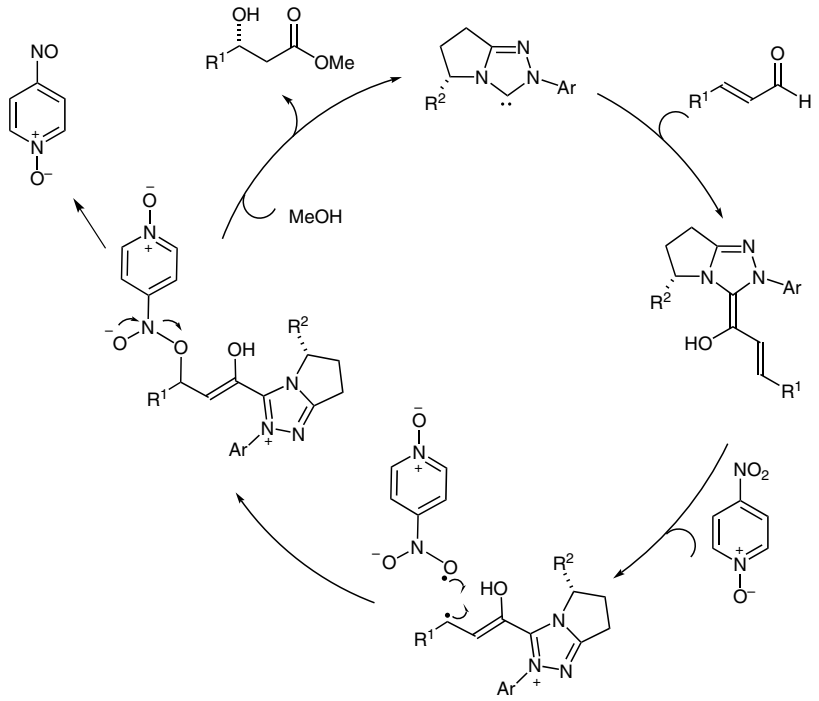
Enantioselective N-Heterocyclic Carbene-Catalyzed β-Hydroxylation of Enals Using Nitroarenes: An Atom Transfer Reaction That Proceeds via Single Electron Transfer

J. Am. Chem. Soc. **2014**, *136*, 14674–14677.

Asymmetric β-Hydroxylation of Enals Catalyzed by an N-Heterocyclic Carbene



Proposed catalytic cycle:



Significance: White and Rovis report an asymmetric β-hydroxylation of alkyl and aryl enals via oxygen transfer from electron-deficient nitroarenes. The reaction is catalyzed by an N-heterocyclic carbene to furnish the corresponding β-hydroxy esters in moderate to good yields (up to 73%) and with good to excellent enantioselectivities (er up to 96:4).

Comment: N-Heterocyclic carbenes are powerful catalysts in organic synthesis, with applications in various transformations. In this report, the authors present a novel NHC-catalyzed reaction that proceeds by a radical pathway. A significantly reduced yield of product was observed when the reaction was conducted in the presence of a radical inhibitor. Investigations of the stereoselectivities of the reaction when using *cis* and *trans* enals further support the proposed radical mechanism.

SYNFACTS Contributors: Benjamin List, Luping Liu
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C. ROMANO, M. JIA, M. MONARI, E. MANONI, M. BANDINI* (UNIVERSITY OF BOLOGNA, ITALY)

Metal-Free Enantioselective Electrophilic Activation of Allenamides: Stereoselective Dearomatization of Indoles
Angew. Chem. Int. Ed. **2014**, *53*, 13854–13857.

Category

Organo- and Biocatalysis

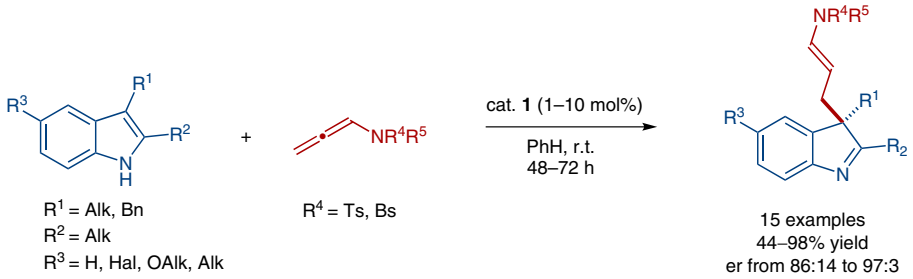
Key words

allenamides

dearomatization

quaternary carbon centers

Enantioselective Dearomatization of Indoles

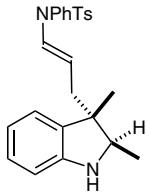


R^1 = Alk, Bn
R^2 = Alk
R^3 = H, Hal, OAlk, Alk

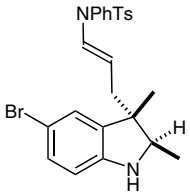
R^4 = Ts, Bs

15 examples
44–98% yield
er from 86:14 to 97:3

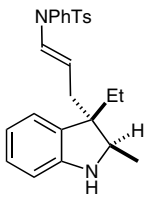
Selected examples of dearomatization–hydrogen transfer cascade:



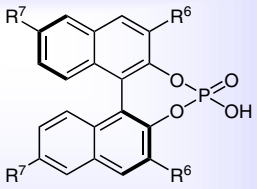
51% yield
er_{trans} = 99:1
er_{cis} = 91:9
dr = 19:1



60% yield
er_{trans} = 97.5:2.5
er_{cis} = 91:9
dr = 10:1

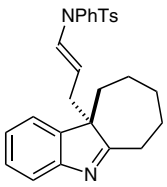


49% yield
er_{trans} = 99.5:0.5
er_{cis} = 66.5:33.5
dr = 15:1

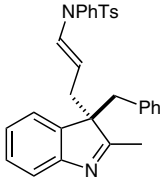


R^6 = 2,4,6-$Cy_3C_6H_2$ (*R*)-cat. **1**
R^7 = H, C_8H_{17}

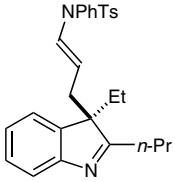
Selected examples:



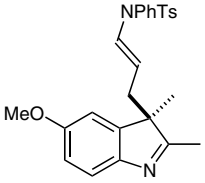
51% yield
er = 95.5:4.5



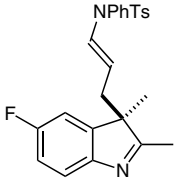
87% yield
er = 97:4



69% yield
er = 93.5:6.5
using (*S*)-cat. **1**



60% yield
er = 96:4
using (*S*)-cat. **1**



64% yield
er = 95.5:4.5
using (*S*)-cat. **1**

Significance: Bandini and co-workers report an enantioselective dearomatization of indoles. Using 1 to 10 mol% of chiral phosphoric acid catalyst **1**, the desired 3,3-disubstituted indolenines are obtained in moderate to high yields and good to excellent enantioselectivities.

Comment: The authors developed an enantioselective electrophilic activation of allenamides, generating enantioenriched dearomatized 3,3-disubstituted indolenines as products. Additionally, a dearomatization–hydrogen transfer cascade was conducted. Performing the reaction in the presence of molecular sieves and Hantzsch ester, the corresponding indolines are obtained in good yields and with high diastereo- and enantioselectivities.

SYNFACTS Contributors: Benjamin List, Lisa Kötzner
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DOI: 10.1055/s-0034-1379623; **Reg-No.:** B12614SF

Category

Organo- and Biocatalysis

Key words

enzyme catalysis

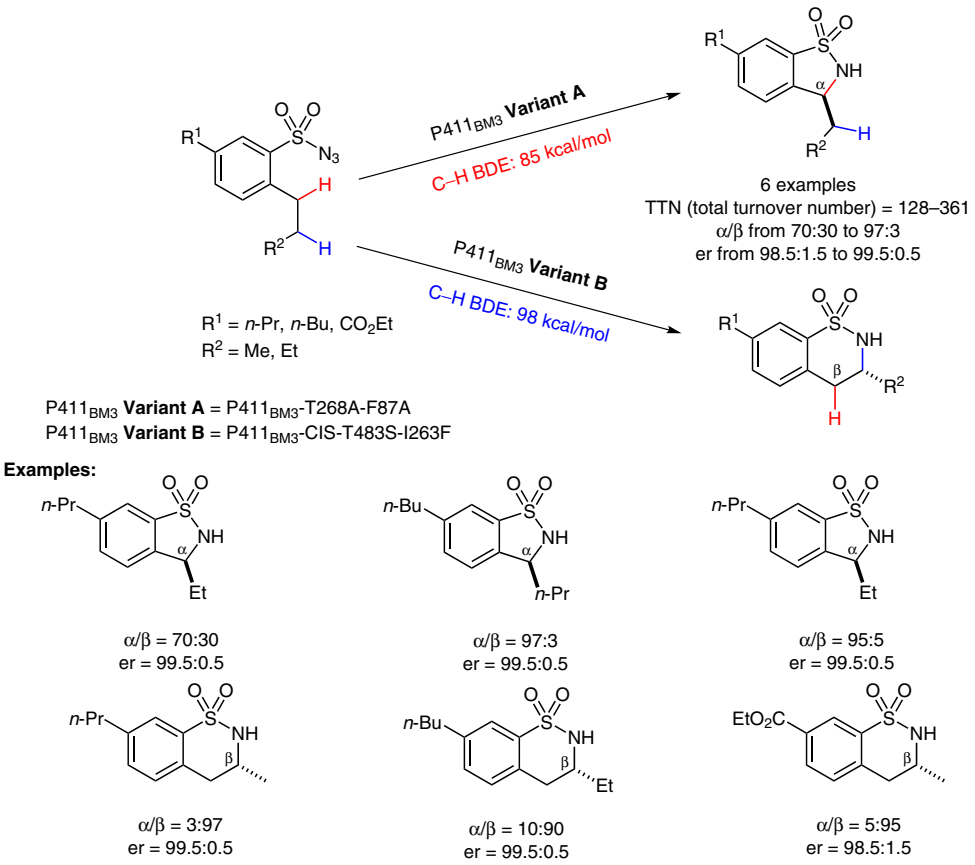
C–H amination

regiodivergency

T. K. HYSTER, C. C. FARWELL, A. R. BULLER, J. A. MCINTOSH, F. H. ARNOLD*
(CALIFORNIA INSTITUTE OF TECHNOLOGY, PASADENA, USA)

Enzyme-Controlled Nitrogen-Atom Transfer Enables Regiodivergent C–H Amination
J. Am. Chem. Soc. **2014**, *136*, 15505–15508.

Enzyme-Controlled Regiodivergent C–H Amination



Significance: Arnold and co-workers report an enzyme-catalyzed asymmetric and regiodivergent C–H amination. By modifying the active site of $P411_{BM3}$, a cytochrome $P450_{BM3}$ variant in which the axial position of the iron-heme prosthetic group is ligated by serine instead of cysteine, two variants enabling different regioselectivity were obtained. One allowed the selective amination of the energetically more favored benzylic position, while the other was selective for the homobenzylic position of 2,5-disubstituted benzenesulfonyl azides.

Comment: Due to the availability of a weaker benzylic C–H bond, direct C–H amination of homobenzylic positions are a challenge in small-molecule catalysis. Breaking the C–H bond is kinetically controlled, and therefore, this can in some cases be overcome by variation of the steric properties of the used ligands. However, genetically engineered enzymes are an attractive alternative for regiodivergent C–H amination, enabling access to the desired products in good to excellent regio- and enantioselectivities.

SYNFACTS Contributors: Benjamin List, Grigory A. Shevchenko
Synfacts 2015, 11(1), 0090 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379624; **Reg-No.:** B12714SF

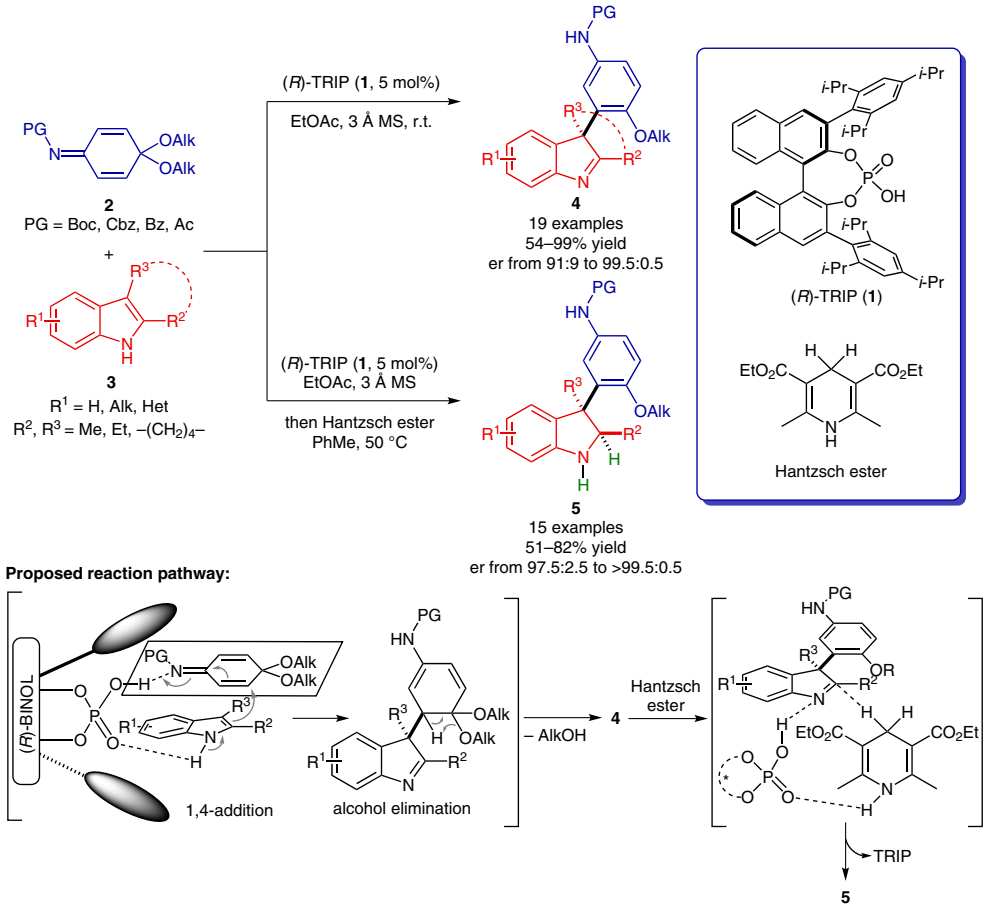
Y.-C. ZHANG, J.-J. ZHAO, F. JIANG, S.-B. SUN, F. SHI* (JIANGSU NORMAL UNIVERSITY, XUZHOU, P. R. OF CHINA)

Organocatalytic Asymmetric Arylative Dearomatization of 2,3-Disubstituted Indoles Enabled by Tandem Reactions
Angew. Chem. Int. Ed. **2014**, *53*, 13912–13915.

Category
Organo- and Biocatalysis

Key words
dearomatization
tandem reaction
indoles
indolines

Asymmetric Arylative Dearomatization of 2,3-Disubstituted Indoles



Significance: A chiral phosphoric acid catalyzed asymmetric arylative dearomatization of indoles is reported. The chiral phosphoric acid (*R*)-TRIP (**1**) promotes the cascade 1,4-addition–alcohol elimination of quinone imine ketals **2** and disubstituted indoles **3** to give arylation products **4**. If the reaction is followed by the addition of a Hantzsch ester, a one-pot tandem arylative dearomatization–transfer hydrogenation can be promoted to give indolines **5** possessing two consecutive stereocenters in high yields and excellent enantioselectivities.

Comment: The authors propose that TRIP activates the indole nucleophile and the α,β-unsaturated imine electrophile through dual hydrogen bonding, promoting the enantioselective 1,4-addition, which is followed by alcohol elimination. The transfer hydrogenation step occurs with excellent diastereoselectivity, controlled by the first stereocenter. However, the enhanced enantiomeric excess of products **5** compared to products **4** is due to a kinetic resolution effect facilitated by the catalyst.

SYNFACTS Contributors: Benjamin List, Ji Hye Kim
Synfacts 2015, 11(1), 0091 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379619; **Reg-No.:** B12114SF

Category

Organo- and Biocatalysis

Key words

supramolecular catalysis

iminium catalysis

vinylogous Michael addition

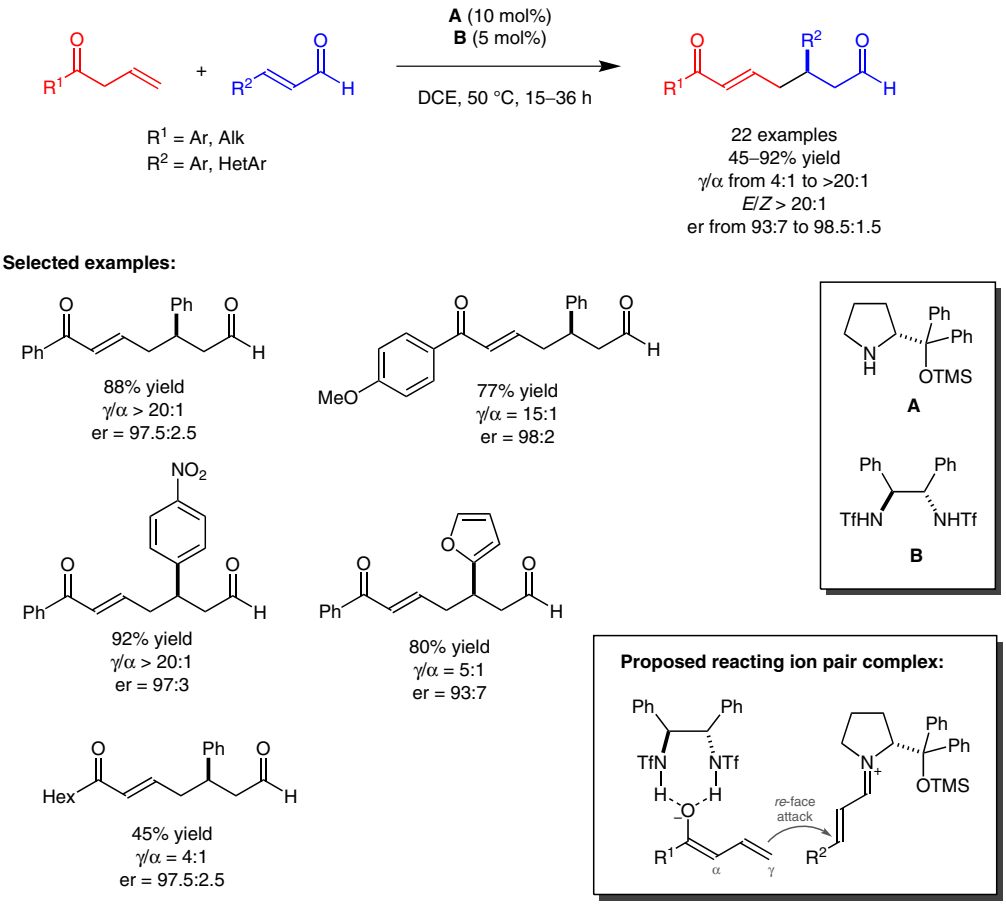
anion binding

Y. GU, Y. WANG, T.-Y. YU, Y.-M. LIANG, P.-F. XU* (LANZHOU UNIVERSITY, P. R. OF CHINA)

Rationally Designed Multifunctional Supramolecular Iminium Catalysis: Direct Vinylogous Michael Addition of Unmodified Linear Dienol Substrates

Angew. Chem. Int. Ed. **2014**, *53*, 14128–14131.

Amine-Catalyzed Direct Vinylogous Michael Addition of Dienols to Enals



Significance: Xu and co-workers report a vinylogous Michael addition of acyclic alkyl and aryl allyl ketones to enals. The reaction is catalyzed by a chiral secondary amine (**A**) and a chiral hydrogen bond donor (**B**), which in combination enable the formation of the desired enones in moderate to excellent yields and regioselectivities, and with excellent enantioselectivities. The scalability of the reaction was proven in one experiment starting with 1.46 gram of phenyl allyl ketone.

Comment: While the application of catalyst **A** in combination with a 'regular' Brønsted acid or base (e.g., benzoic acid or DABCO) already furnished small amounts of desired product with excellent enantioselectivity, it required a second, anion-binding catalyst (**B**) to enhance the reactivity of the proposed α,β-unsaturated iminium ion intermediate by ion pair separation and to shield the α-position of the nucleophile, effecting the desired γ-selectivity. The concept of *supramolecular iminium ion catalysis* was previously reported by the same group (*Angew. Chem. Int. Ed.* **2012**, *51*, 12339).

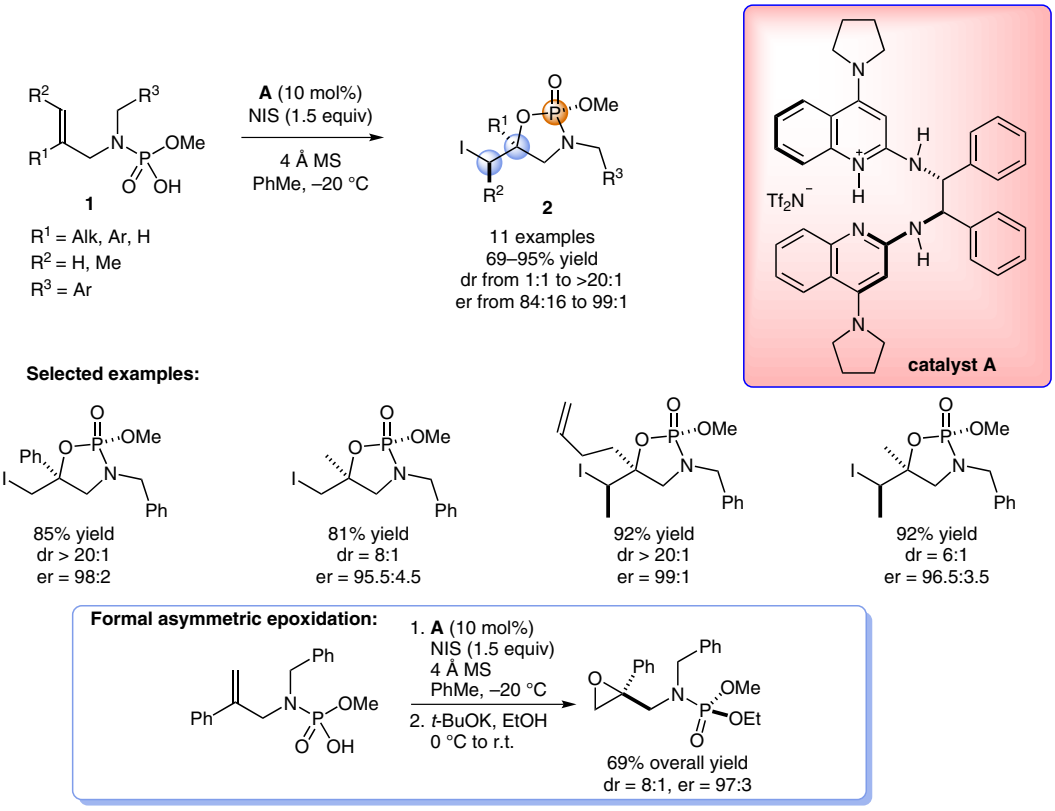
SYNFACTS Contributors: Benjamin List, Lucas Schreyer
Synfacts 2015, 11(1), 0092 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379627; **Reg-No.:** B13114SF

Y. TODA, M. PINK, J. N. JOHNSTON* (VANDERBILT UNIVERSITY, NASHVILLE AND INDIANA UNIVERSITY MOLECULAR STRUCTURE CENTER, BLOOMINGTON, USA)

Brønsted Acid Catalyzed Phosphoramidic Acid Additions to Alkenes: Diastereo- and Enantioselective Halogenative Cyclizations for the Synthesis of *C*- and *P*-Chiral Phosphoramidates

J. Am. Chem. Soc. **2014**, *136*, 14734–14737.

P-Chiral Phosphoramidates from a Catalytic Asymmetric Halocyclization



Significance: The Johnston group reports an organocatalytic asymmetric iodocyclization for the synthesis of cyclic phosphoramidates bearing C- and P-chiral centers. The methodology relies on the previously reported catalytic system based on the combination of an achiral Brønsted acid and a chiral enantiopure Brønsted base **A**. Using *N*-iodosuccinimide (NIS) as an electrophilic source of iodine, the desired products **2** are obtained under very mild conditions in good yields and in good to excellent enantioselectivities. Notably, if coupled with a simple basic treatment, the transformation is an interesting alternative to asymmetric epoxidations of allylamine derivatives.

Comment: Phosphorous-containing compounds largely occur as pharmaceuticals and agrochemicals; thus, significant interest is focused on the development of procedures for their preparation. Interestingly however, despite chirality often being a crucial issue for marketed substances, there is a general lack of catalytic methodologies for the enantioselective synthesis of P-chiral compounds. Here, the authors tackle the challenge disclosing the first organocatalytic protocol for this goal. The synthetic value of the methodology is highlighted by the conversion of the cyclic products into acyclic compounds in a stereospecific process.

SYNFACTS Contributors: Benjamin List, Mattia Riccardo Monaco
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DOI: 10.1055/s-0034-1379621; **Reg-No.:** B12314SF

Category

Organo- and Biocatalysis

Key words

halocyclization

phosphoramidates

P-chiral compounds

Category

Organo- and Biocatalysis

Key words

keto esters

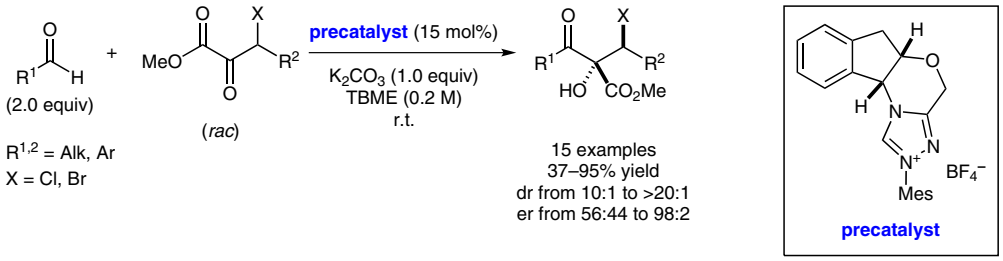
cross-benzoin addition

N-heterocyclic carbenes

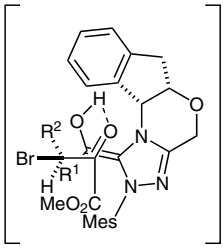
C. G. GOODMAN, J. S. JOHNSON* (UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL, USA)

Dynamic Kinetic Asymmetric Cross-Benzoin Additions of β-Stereogenic α-Keto Esters
J. Am. Chem. Soc. **2014**, *136*, 14698–14701.

Dynamic Kinetic Asymmetric Cross-Benzoin Additions

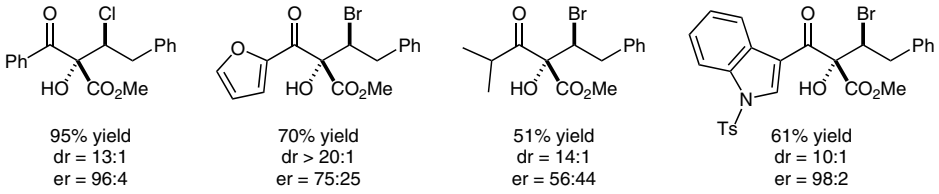


Proposed stereochemical model:



- Felkin–Ahn control
- catalyst control

Selected examples:



Significance: The Johnson group reports a dynamic kinetic resolution of β-halo α-keto esters via asymmetric cross-benzoin reaction catalyzed by a chiral N-heterocyclic carbene. This umpolung reaction adds aldehydes to racemic α-keto esters to provide products in good yields (up to 95% yield), good diastereoselectivities (dr > 20:1), and excellent enantioselectivities (er up to 98:2). Furthermore, the obtained products undergo diastereoselective substrate-controlled reductions to generate highly functionalized stereotriads.

Comment: *ortho*-Tolualdehyde and other sterically encumbered aldehydes gave no desired transformation. Another limitation of this methodology at the current level is its requirement for aromatic aldehydes in order to obtain high enantioselectivity. Control experiments indicate irreversible benzoin formation under the applied reaction conditions. The high chemoselectivity observed is suggested to be based on the greater electrophilicity of these α-keto esters toward the Breslow intermediate.

SYNFACTS Contributors: Benjamin List, Philip S. J. Kaib
Synfacts 2015, 11(1), 0094 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379618; **Reg-No.:** B12014SF

K. S. YANG, V. H. RAWAL* (THE UNIVERSITY OF CHICAGO, USA)

Synthesis of α-Amino Acid Derivatives and Peptides via Enantioselective Addition of Masked Acyl Cyanides to Imines

J. Am. Chem. Soc. **2014**, *136*, 16148–16151.

Category

Organo- and Biocatalysis

Key words

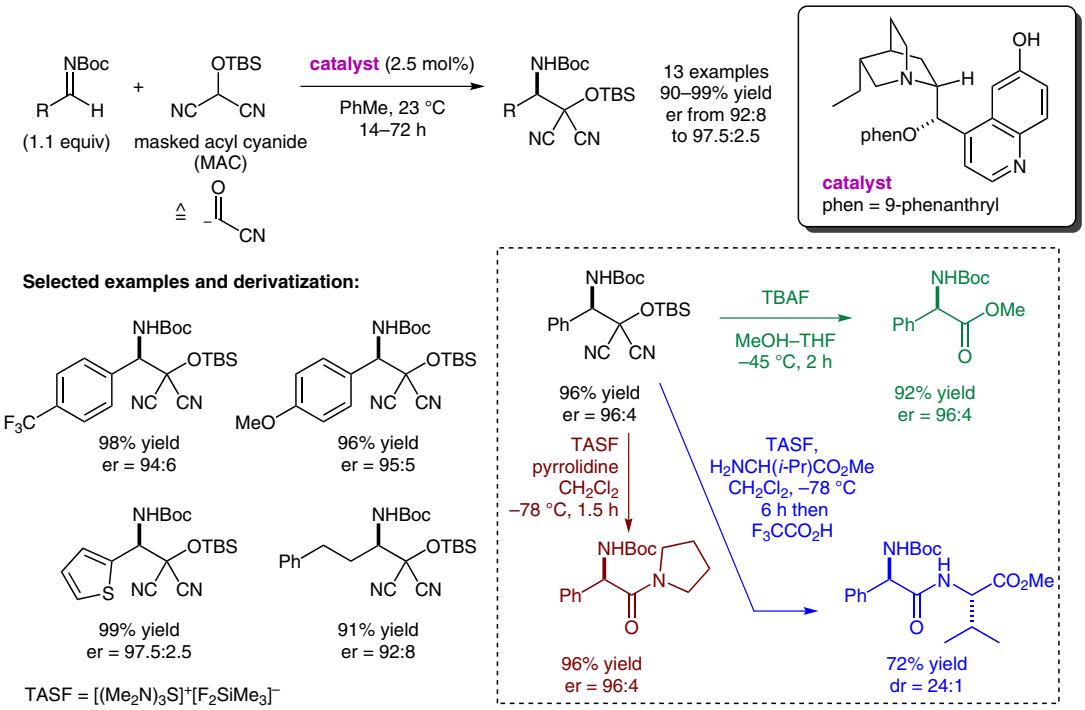
masked acyl cyanides

amino acids

imines

peptides

Enantioselective Addition of Masked Acyl Cyanides to *N*-Boc Imines



Significance: Yang and Rawal report the enantioselective synthesis of α-amino acid derivatives and peptides starting from *N*-Boc imines and TBS-protected hydroxyl malononitriles as masked acyl cyanides (MACs). The reaction is catalyzed by an easily accessible quinidine-derived catalyst which generates the desired addition products with good to excellent yields and enantioselectivities under mild reaction conditions. Further derivatization of the primary products to the corresponding esters, amides, and peptides was demonstrated without loss of enantioenrichment.

Comment: In light of the high academic and industrial interest in the synthesis of (protected) amino acids and peptides, the development of new enantioselective approaches to such scaffolds is an attractive research goal. The Rawal group contributes nicely to this area by exploiting the nucleophilic character of the MAC reagent, which enables an umpolung-type bond-forming event (see also: *J. Am. Chem. Soc.* **2013**, *135*, 16050; *Synfacts* **2013**, *9*, 1348). It is remarkable that even highly sensitive aliphatic *N*-Boc imines are employed in this methodology.

SYNFACTS Contributors: Benjamin List, Manuel van Gemmeren
Synfacts 2015, 11(1), 0095 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379625; **Reg-No.:** B12914SF

Category

Organo- and Biocatalysis

Key words

anhydrides

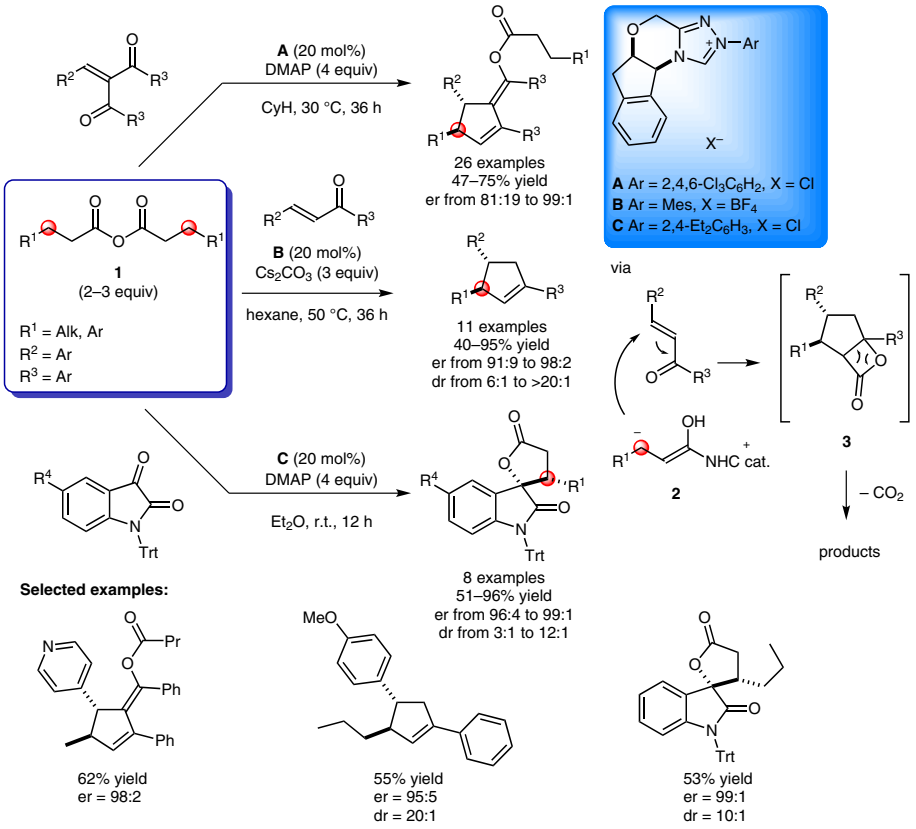
N-heterocyclic carbenes

β-functionalization

Z. JIN, S. CHEN, Y. WANG, P. ZHENG, S. YANG,* Y. R. CHI* (NANYANG TECHNOLOGICAL UNIVERSITY, SINGAPORE, SINGAPORE AND GUIZHOU UNIVERSITY, GUIYANG, P. R. OF CHINA)

β-Functionalization of Carboxylic Anhydrides with β-Alkyl Substituents through Carbene Organocatalysis
Angew. Chem. Int. Ed. **2014**, *53*, 13506–13509.

β-Functionalization of Carboxylic Anhydrides with N-Heterocyclic Carbenes



Significance: Chi, Yang, and co-workers report the asymmetric β-functionalization of symmetrical aliphatic anhydrides **1**. Nucleophilic attack of the N-heterocyclic carbene catalyst to the anhydride generates the NHC-bound ester intermediate, which upon deprotonation forms nucleophile **2**. This adds to various electrophiles, such as alkylidene diketones, chalcones, and isatins, in a highly selective manner. Decarboxylation of the β-lactone intermediates **3** yields the final products. For almost all substrates tested, consistently very high enantioselectivities accompanied with good diastereoselectivities were achieved.

Comment: In continuation of the work by the Chi group on the activation of esters with NHC catalysts for the functionalization of the β-position (*Nature Chem.* **2013**, *5*, 835), overcoming the limitation of β-aryl substrates is the main objective of the current work. Under the previous reaction conditions, only low yields (8–40%) were obtained. The presented solution for these challenging substrates utilizes anhydride substrates instead, affording the desired products in moderate to very good yields under the optimized conditions.

SYNFACTS Contributors: Benjamin List, Tim Gatzenmeier
Synfacts 2015, 11(1), 0096 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379626; **Reg-No.:** B13014SF