When Aminocatalysis Meets the Vinylogy Principle

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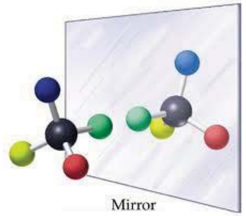
22-26 September 2012

ISCHIA ADVANCED SCHOOL OF ORGANIC CHEMISTRY

Stereochemistry is an Essential Dimension of our World



Nature's inherent chirality requires us to create chiral molecules in enantiomerically pure form in order to interact with or modify our world

Enantioselective Catalysis: rationally approaching stereochemistry in an economical, energy-saving, and environmentally benign way

METAL CATALYSIS

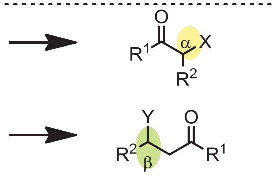
BIO CATALYSIS

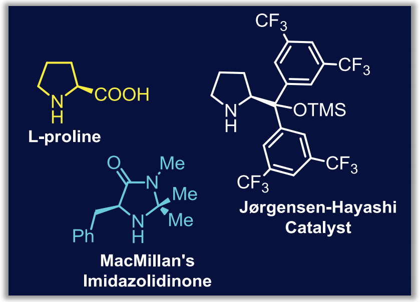
ORGANO CATALYSIS

Noyori, R. Synthesizing our future. *Nature Chemistry* **1**, 5–6 (2009)

Asymmetric Aminocatalysis

- enamine
- iminium-ion





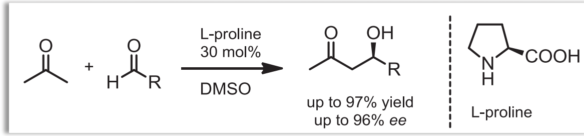
The *work-horses* of enantioselective organocatalysis

D. Seebach *et al.*, *Helvetica Chim. Acta* **2008**, *91*, 1999-2034

Revolutionizing the way to Asymmetrically Functionalize Carbonyl Compounds

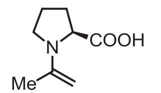
Activation Modes in Aminocatalysis

- Proline-catalyzed intermolecular aldol reaction



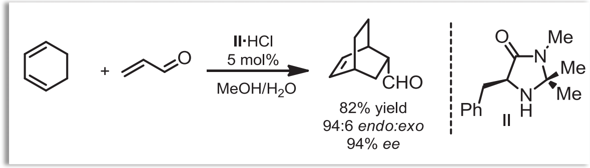
B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396

Enamine Catalysis



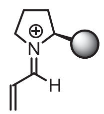
HOMO-Raising Activation

- Iminium ion catalyzed asymmetric Diels-Alder of enals



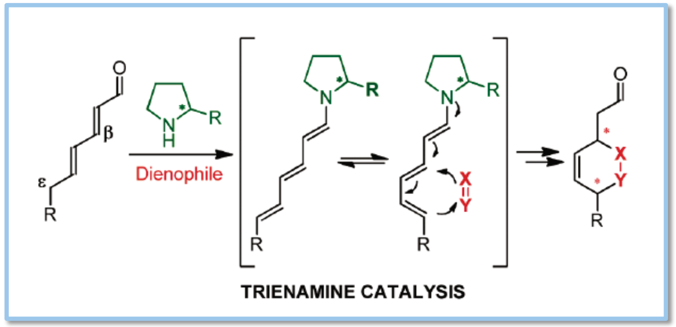
K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244

Iminium-Ion Catalysis



LUMO-Lowering Activation

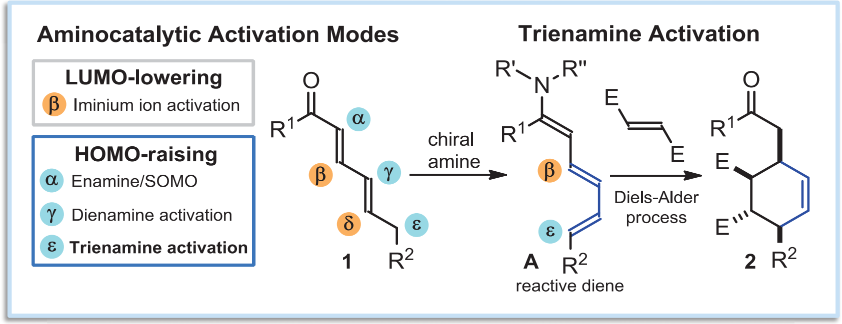
Activation Modes in Aminocatalysis



K.A. Jørgensen, Y.-C. Chen, et al.,
Trienamines in asymmetric organocatalysis: Diels-Alder and tandem reactions
JACS **2011**, *133*, 5053–35061

For a recent Highlight on Trienamines Activation:
E. Arceo, P. Melchiorre
"Extending the Aminocatalytic HOMO-Raising Activation Strategy: Where is the Limit?"
Angew. Chem. Int. Ed. **2012**, *51*, 5290–5292

Vinylogous Reactivity in Aminocatalysis

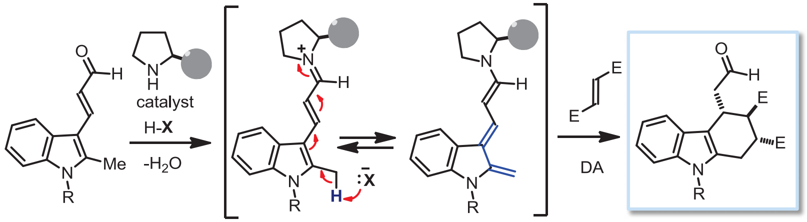


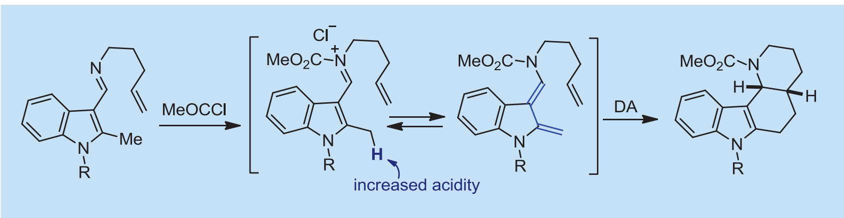
Fuson RC (1935) The Principle of Vinylogy *Chem. Rev.* 16: 1–27.

The transmission of electronic effects through a conjugated π-system

For a recent Highlight on Trienamines Activation:
E. Arceo, P. Melchiorre
"Extending the Aminocatalytic HOMO-Raising Activation Strategy: Where is the Limit?"
Angew. Chem. Int. Ed. **2012**, *51*, 5290–5292

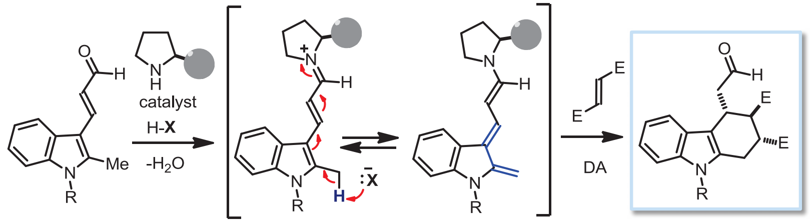
Revisiting the Indole-2,3-Quinodimethane Strategy

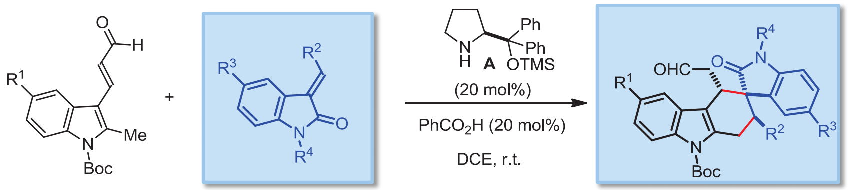




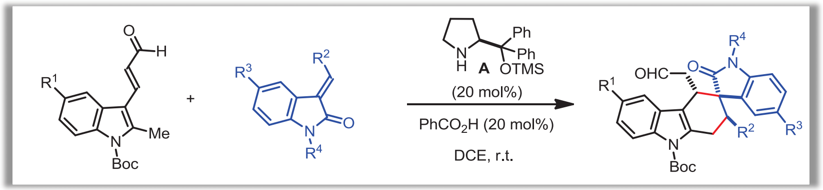
Magnus, P., *et al*
The indole-2,3-quinodimethane strategy for the synthesis of indole alkaloids.
Acc. Chem. Res. **17**, 35-41 (1984).

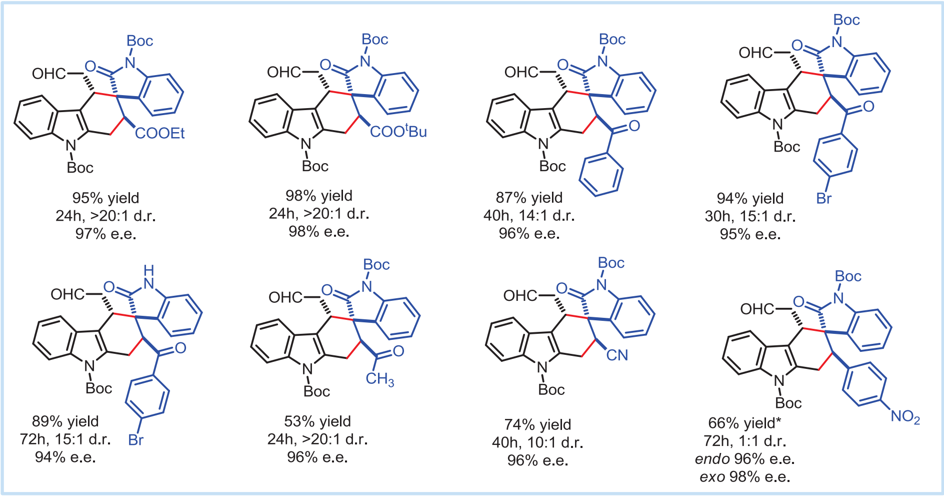
TetrahydroCarbazole Spirooxindoles



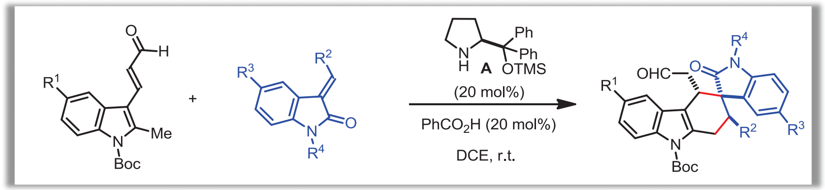


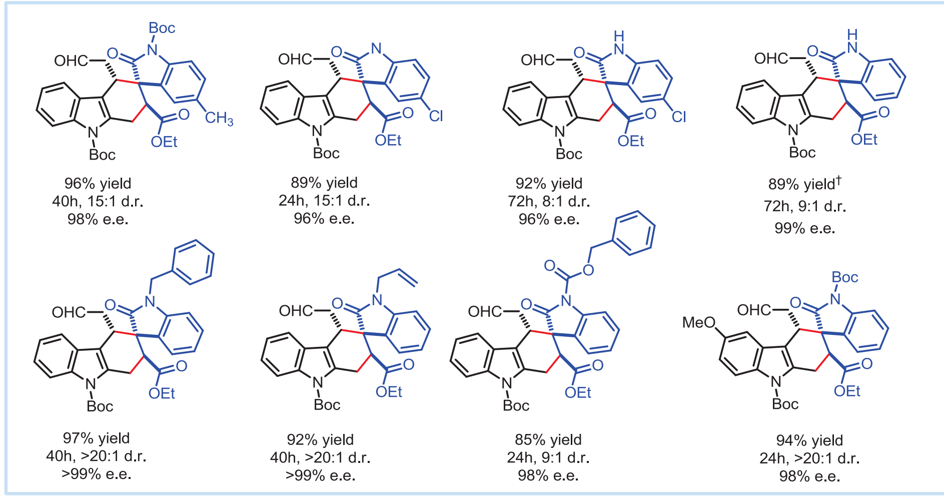
Meaningful Reference:
K.A. Jørgensen, Y.-C. Chen, et al., Trienamines in asymmetric organocatalysis: Diels-Alder and tandem reactions
JACS **2011**, *133*, 5053–35061





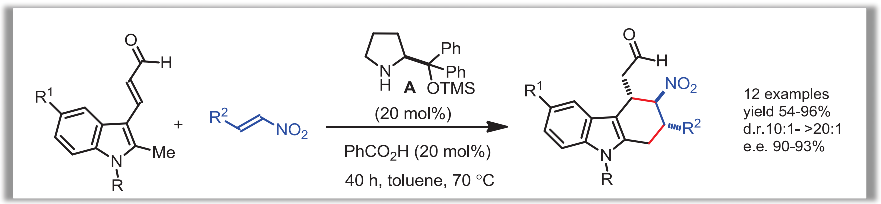
with Y. Liu, M. Nappi, E. Arceo & S. Vera
J. Am. Chem. Soc. **2011**, *133*, 15212-15218

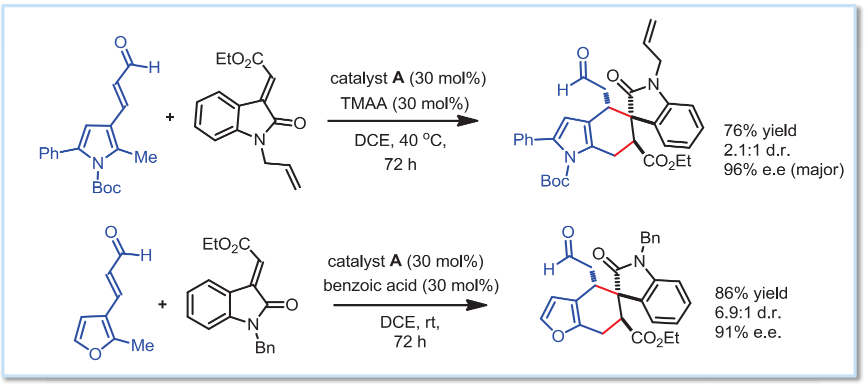




with Y. Liu, M. Nappi, E. Arceo & S. Vera
J. Am. Chem. Soc. **2011**, *133*, 15212-15218

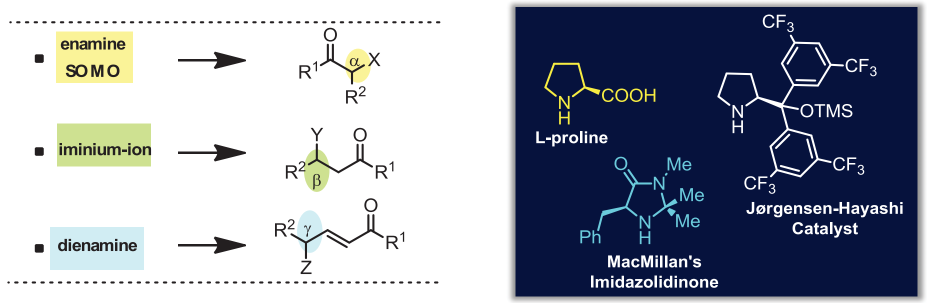
Scope





with Y. Liu, M. Nappi, E. Arceo & S. Vera
J. Am. Chem. Soc. **2011**, *133*, 15212-15218

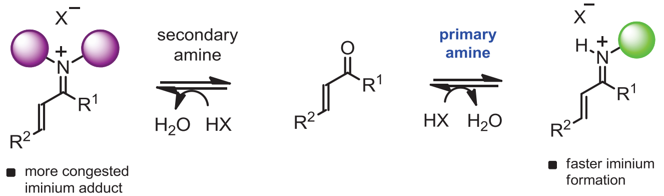
Asymmetric Aminocatalysis



P. Melchiorre, M. Marigo et al.
Angew. Chem. Int. Ed. **2008**, *47*, 6138-6171 (Review)

Developing General & Efficient Catalysts

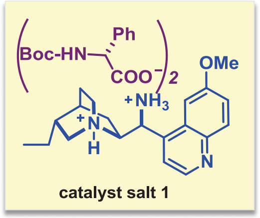
Activation of Challenging Compound Classes

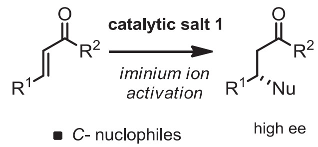


Functionalization of Hindered Carbonyls

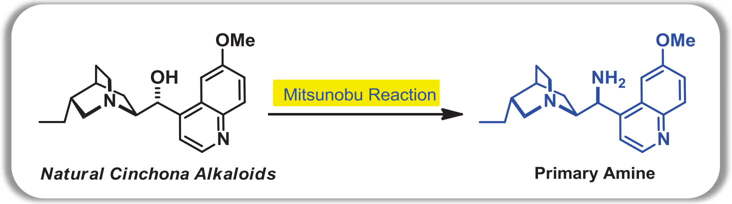
Expanding the potential of Aminocatalysis beyond Aldehyde Functionalization

Cinchona-based Primary Amines





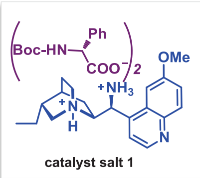
- *C*- nuclophiles
- *O*-nucleophiles
- *S*-nucleophiles



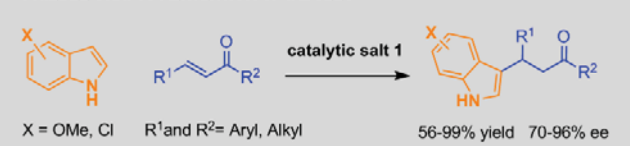
The first applications:
Y.-C. Chen et al., *ACIE* 2007, *119*, 393–396
P. Melchiorre, et al *OL* 2007, 1759–1771

Review:
Jiang, L.; Chen, Y.-C. *Catal. Sci. Technol.* 2011, 1, 354–365
Melchiorre, P. *Angew. Chem. Int. Ed. 2012, in press*

A Novel Iminium Activator of Enones

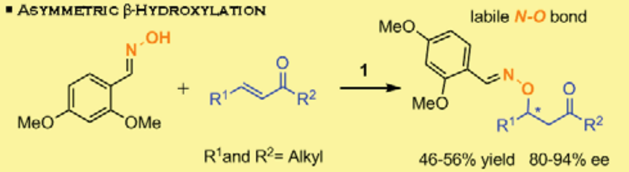


▪ Friedel-Crafts Alkylation of Indoles



Org. Lett. **2007**, *9*, 1403

▪ Asymmetric β-Hydroxylation

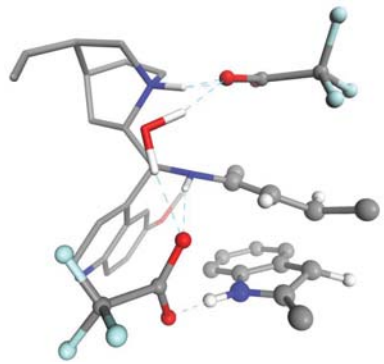


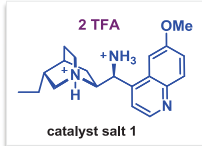
Eur. J.Org. Chem. **2007**, 5492

▪ Asymmetric Sulfa-Michael Addition

Adv. Synth. Catal. **2008**, *350*, 49

How does it work?

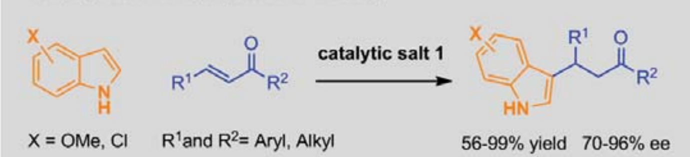




Major Enantiomer

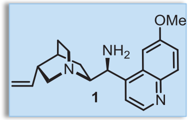
with A. Moran, A. Hamilton, & C. Bo
Unpublished results

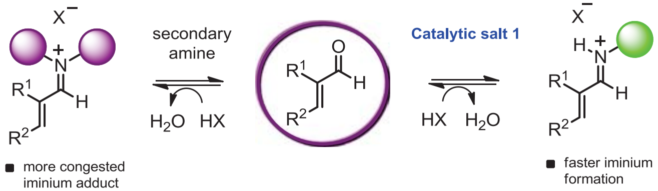
▪ Friedel-Crafts Alkylation of Indoles



Developing General & Efficient Catalysts

Activation of Challenging Compound Classes



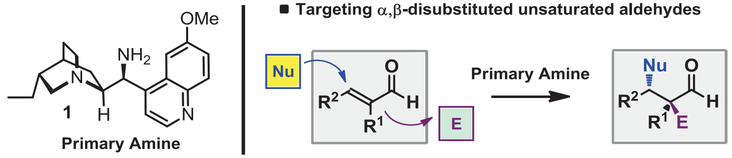


Functionalization of α-Branched Unsaturated Aldehydes

Previous aminocatalytic activations of α-substituted acroleyn derivatives:

K. Ishihara, K. Nakano, *J. Am. Chem. Soc.* **2005**, *127*, 10504.

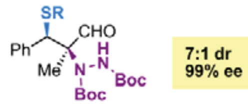
Organocascade with α-Branched Enals



One-step, Direct Creation of Adjacent Quaternary and Tertiary Stereocenters

Nu: Indole
E: Azodicarboxylate

Aryl-Amination



R = Bn, *t*-Bu

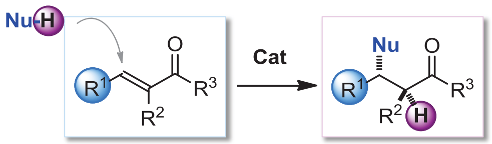
Nu: Thiol
E: Azodicarboxylate

Thio-Amination

with P. Galzerano & F. Pesciaioli *Angew. Chem. Int. Ed.* **2009**, *48*, 7892-7894

The next Target

α-branched enones

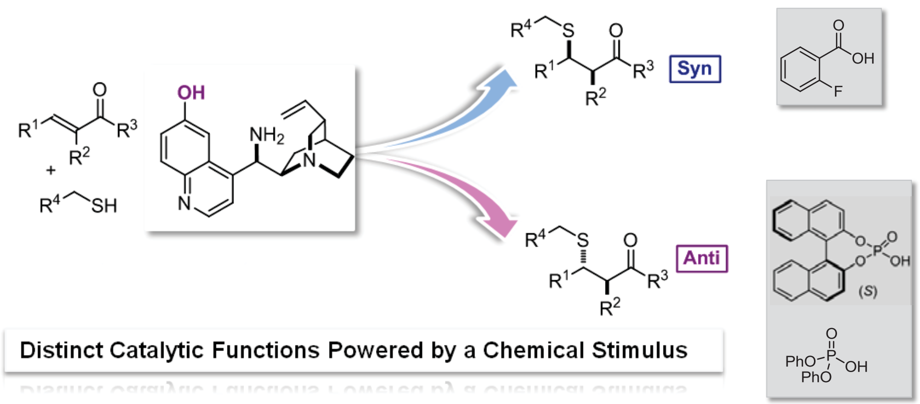


Nucleophilic Addition to α-Branched Enones generates 2 Stereocenters

Challenging Target in Asymmetric Synthesis:

access the full matrix of all possible stereoisomeric products

Toward a Programmable Chiral Organic Catalyst



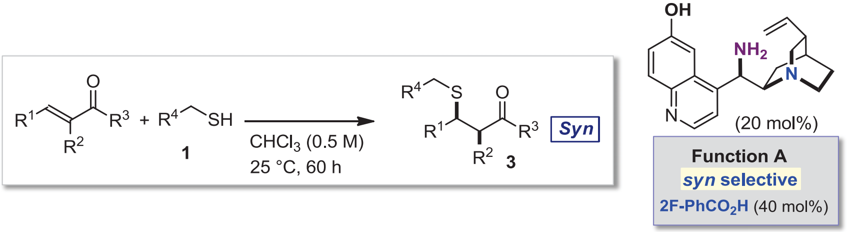
Distinct Catalytic Functions Powered by a Chemical Stimulus

A Programmable Chiral Organic Catalyst for Selecting Stereodivergent Chemical Pathways

with X. Tian, C. Cassani, Y. Liu, A. Moran, A. Urakawa, P. Galzerano, E. Arceo
J. Am. Chem. Soc., **2011**, *133*, 17934–17941

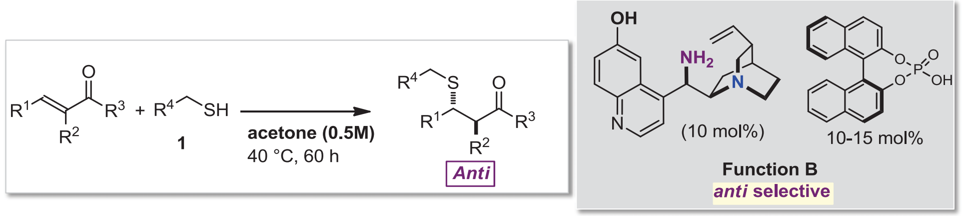
Selected for the Editors' Choice in *Science* 2011, *334*, 570

Syn-selective SMA of α-branched enones



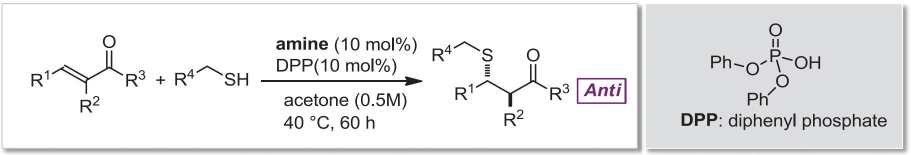
R^1	R^2	R^3	R^4	% yield	*syn*:*anti*	% ee_{syn}
Me	Me	Me	Ph	68	**5.1:1**	**86**
4NO$_2$-C$_6$H$_4$	Me	Me	Ph	79	**5.1:1**	**88**
Ph	Me	Me	Ph	54	**3.5:1**	**85**
4Br-C$_6$H$_4$	Me	Me	Ph	60	**3.8:1**	**89**
4NO$_2$-C$_6$H$_4$	Et	Me	Ph	68	**9.3:1**	**87**
4NO$_2$-C$_6$H$_4$	Me	Et	Ph	40	**5.0:1**	**81**
Et	Ph	Me	Ph	60	**2.8:1**	**73**
Me	Me	Me	**4MeO-C$_6$H$_4$**	56	**4.9:1**	**90**
Me	Me	Me	**4Cl-C$_6$H$_4$**	65	**5.0:1**	**89**
Me	Me	Me	**CH=CH$_2$**	60	**7.8:1**	**87**
Me	Me	Me	**CO$_2$Et**	68	**5.5:1**	**61**

Anti-selective SMA of α-branched enones

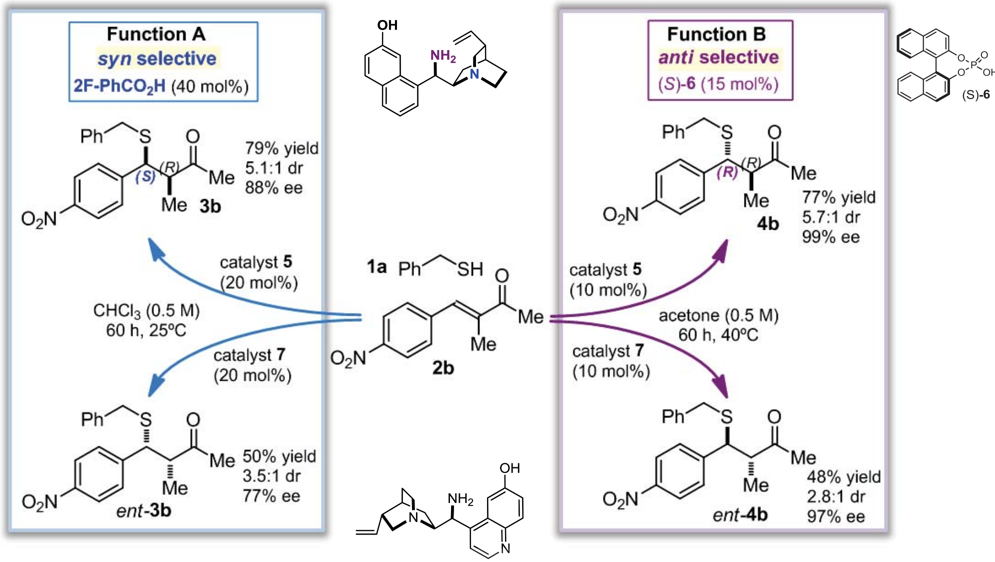


R^1	R^2	R^3	R^4	% yield	*anti*:*syn*	% ee_{anti}
Me	Me	Me	Ph	80	**6.2:1**	**98**
4NO$_2$-C$_6$H$_4$	Me	Me	Ph	77	**5.7:1**	**99**
CH$_2$Bn	Me	Me	Ph	69	**8.2:1**	**97**
Ph	Me	Me	Ph	41	**5.2:1**	**99**
4NO$_2$-C$_6$H$_4$	Et	Me	Ph	35	**1.8:1**	**98**
4MeO-C$_6$H$_4$	Me	Me	Ph	42	**4.2:1**	**96**
4Br-C$_6$H$_4$	Me	Me	Ph	59	**6.5:1**	**99**
4Cl-C$_6$H$_4$	Me	Me	Ph	58	**5.3:1**	**99**
2-thiophenyl	Me	Me	Ph	44	**4.2:1**	**98**
CO$_2$Et	Me	Me	Ph	56	**5.2:1**	**96**
Me	Me	Me	**4MeO-C$_6$H$_4$**	42	**7.2:1**	**98**
Me	Me	Me	**4Cl-C$_6$H$_4$**	58	**7.1:1**	**94**
Me	Me	Me	**CH=CH$_2$**	73	**4.5:1**	**98**
Me	Me	Me	**CO$_2$Et**	50	**2.4:1**	**92**

Anti-selective SMA of α-branched enones

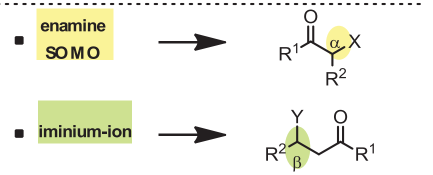


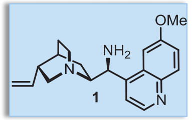
R^1	R^2	R^3	R^4	% yield	*anti*:*syn*	% ee_{anti}
Me	Me	Me	Ph	68 (80)	6.1:1 (6.2:1)	98 (98)
4NO$_2$-C$_6$H$_4$	Me	Me	Ph	56 (77)	4.7:1 (5.7:1)	96 (99)
Ph	Me	Me	Ph	44 (41)	5.1:1 (5.2:1)	95 (99)
4Br-C$_6$H$_4$	Me	Me	Ph	38 (59)	6.3:1 (6.5:1)	96 (99)
4Cl-C$_6$H$_4$	Me	Me	Ph	59 (58)	5.3:1 (5.3:1)	98 (99)
Me	Me	Me	4MeO-C$_6$H$_4$	42 (68)	7.0:1 (7.2:1)	98 (98)
Me	Me	Me	4Cl-C$_6$H$_4$	71 (58)	4.2:1 (7.1:1)	97 (94)
Me	Me	Me	CO$_2$Et	65 (50)	2.0:1 (2.4 :1)	83 (92)



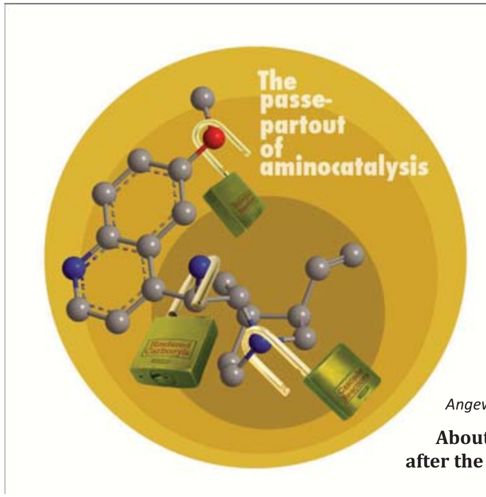
A Single Catalyst able to fully control the stereochemical outcome of the SMA reaction

Aminocatalytic Activations





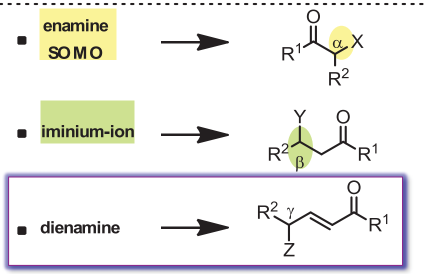
Suitable Catalyst for:
Enones & α-Branched Enals/Enones Activation
Design Novel Organocascade Reactions

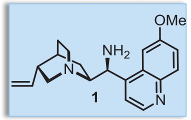


Angew. Chem. Int. Ed. **2012**, DOI: 10.1002/anie.201109036

About the Asymmetric Functionalisation of Carbonyls after the Advent of Cinchona-based Primary Amine Catalysis

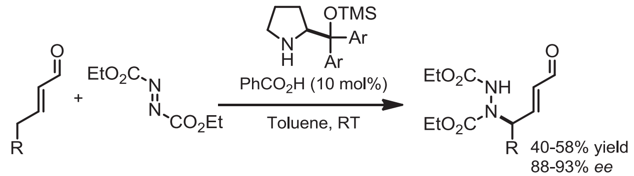
Aminocatalytic Activations





Suitable Catalyst for:
Enones & α-Branched Enals/Enones Activation
Design Novel Organocascade Reactions

- Dienamine catalyzed γ-amination of α,β-unsaturated aldehydes.

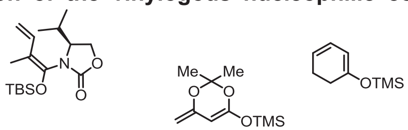


K. A. Jørgensen et.al. *J. Am. Chem. Soc.* **2006**, *128*, 12973–12980

Functionalizing γ-Position

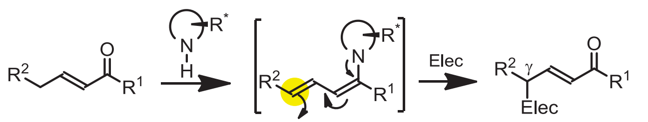
Challenges connected with the γ-Functionalization

- **Site-selectivity**
- **Stoichiometric pre-activation of the vinylogous nucleophilic components (dienolate equivalents)**



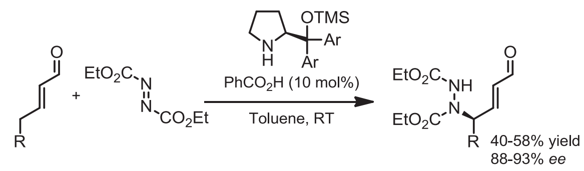
Solution: Dienamine Catalysis

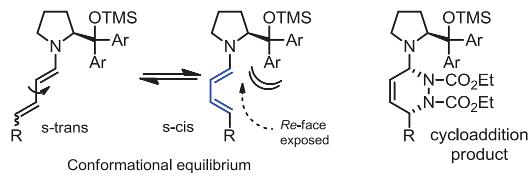
Dienamine Catalysis-induced Vinylogous Nucleophilicity



Fuson RC, The Principle of Vinylogy, *Chem. Rev.* 1935, *16*, 1–27.
The transmission of electronic effects through a conjugated π-system

- Dienamine catalyzed γ-amination of α,β-unsaturated aldehydes.





S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973–12980

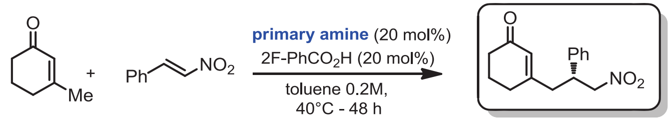
why Dienamine Catalysis is not considered a generic mode of activation?

- **follow a [4+2] cycloaddition path instead of a more generalizable nucleophilic addition manifold**
- **α-site selective alkylation step via enamine catalysis**

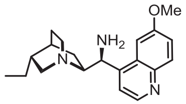
MacMillan, D. W. C. The advent and development of asymmetric organocatalysis. *Nature* **455**, 304-308 (2008)

Expanding the potential of Dienamine Catalysis

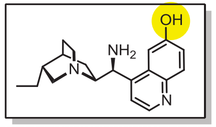
Direct Vinylogous Michael Addition



γ-site selective pathway



90% yield, 82% ee

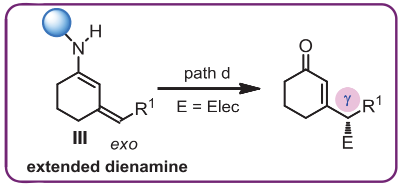


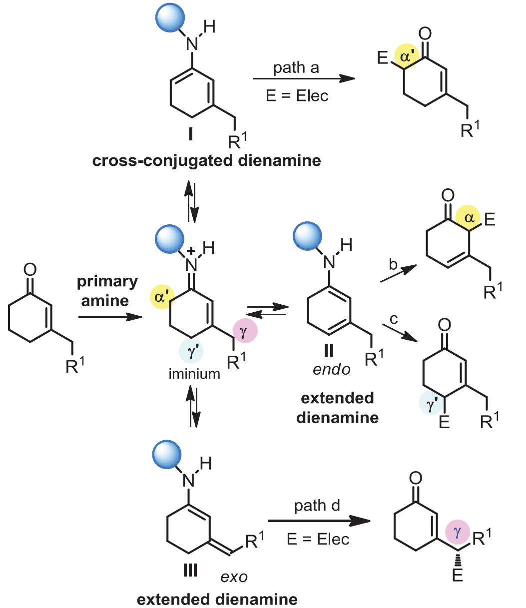
77% yield, 98% ee

Bifunctional Catalysis

Y.-C. Chen *et al.*

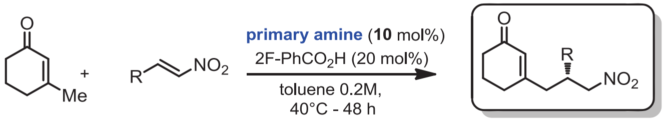
Angew. Chem. Int. Ed. **2007**, 46: 7667



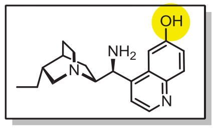


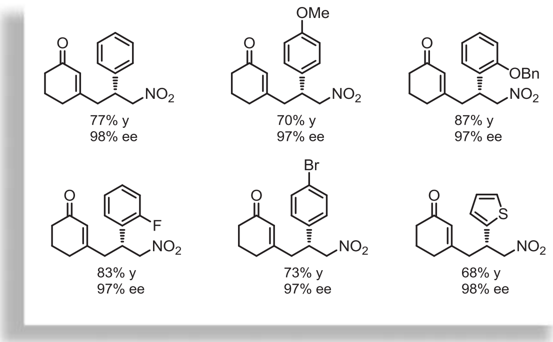
Regioselective Issue: 4 possible sites of Alkylation!!

Direct Vinylogous Michael Addition

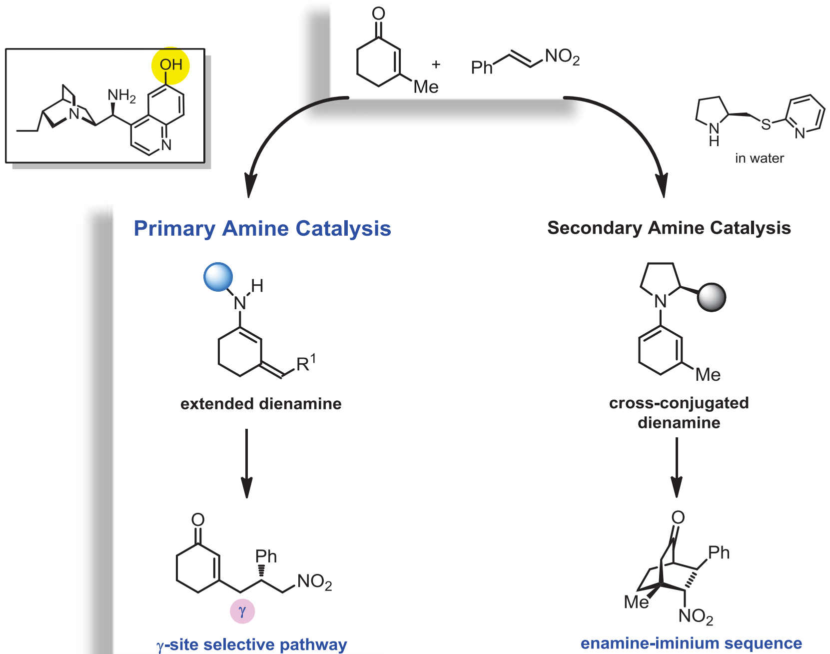


γ-site selective pathway





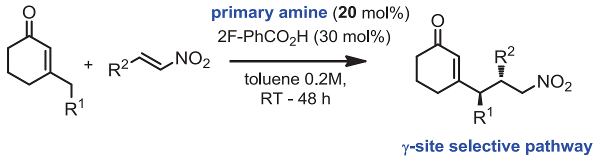
with G. Bencivenni & P. Galzerano *PNAS* **2010**, *107*, 20642

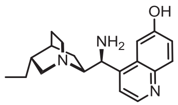


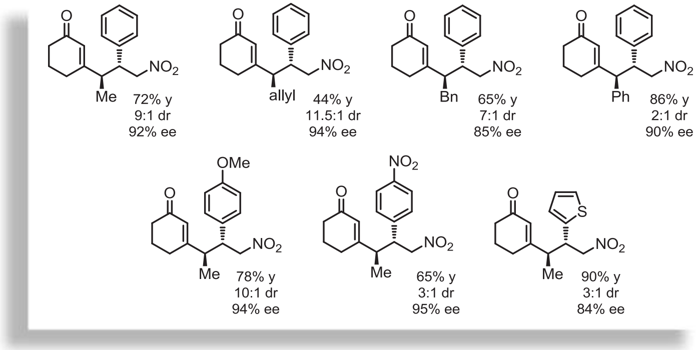
Dienamine-induced Vinylogous Nuclophilicity

Z.-Y. Xu *et al. Angew. Chem. Int. Ed.* **2009**, 48: 3821-3824

Direct Vinylogous Michael Addition







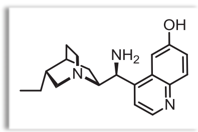
with G. Bencivenni & P. Galzerano *PNAS* **2010**, *107*, 20642

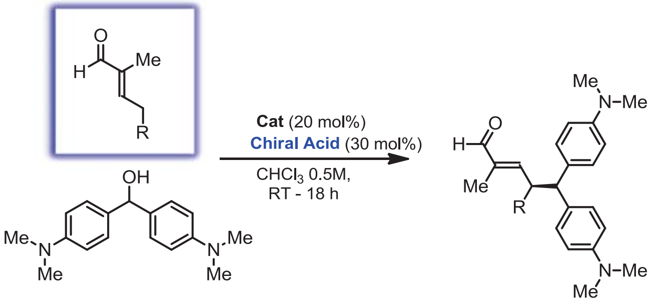
Target:

Expanding the Scope of Dienamine Catalysis

➢ **to Nucleophilic Substitution Reactions**

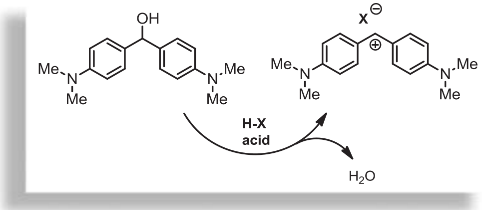
The γ-Alkylation of Unsaturated Aldehydes





TFA as the acid: ee in the range of the **60's**

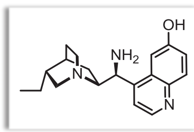
Can we use a Chiral Acid?

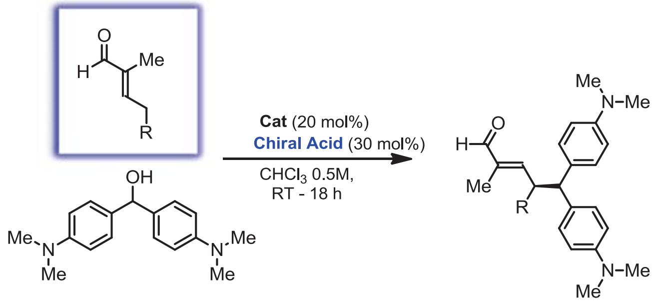


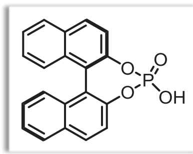
P.G. Cozzi *et al., Angew. Chem. Int. Ed.* **2009**, *48*, 1313-1316

H. Mayr *et al. JACS* **2001**, *123*, 9500-9512

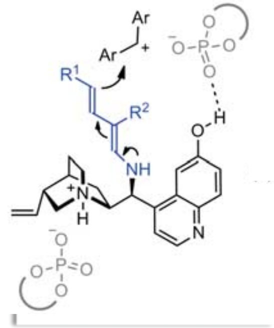
The γ-Alkylation of Unsaturated Aldehydes





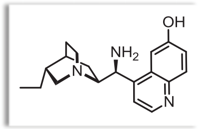


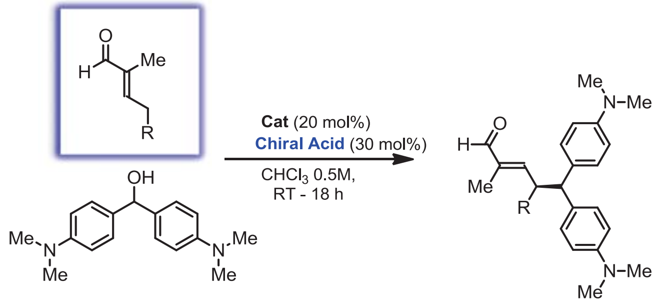
Ee in the range of the **90's**

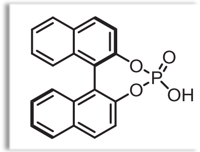


Cooperative Dual Catalysis:
Dienamine & Brønsted Acid Catalysis

The γ-Alkylation of Unsaturated Aldehydes



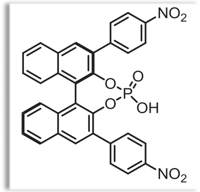




R = Bn
82%y, 90% ee

R = Allyl
91%y, 87% ee

R = Ph
63%y, 90% ee

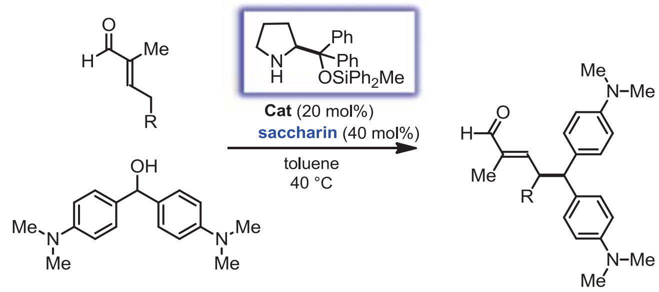


R = Bn
84%y, 95% ee

R = Allyl
65%y, 94% ee

with G. Bergonzini & S. Vera,
Angew. Chem. Int. Ed. **2010**, **49**, 9685–9688

The γ-Alkylation of Unsaturated Aldehydes

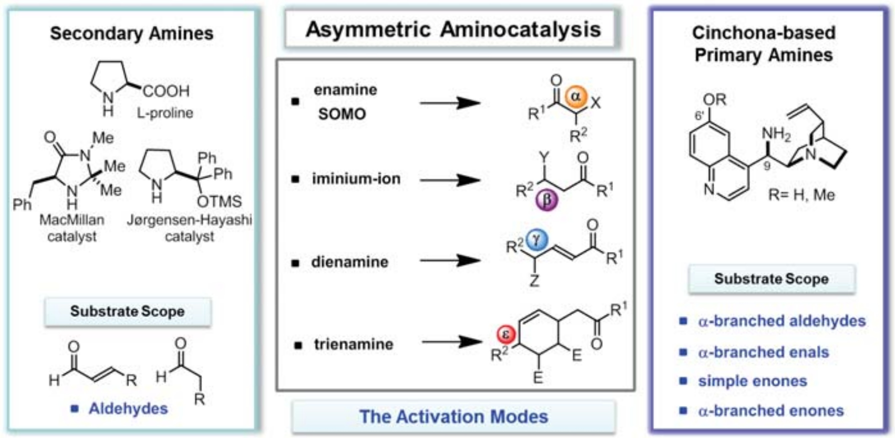


with M. Silvi & C. Cassani,
Unpublished results

9 examples: 40-84% yield; 87-96% ee

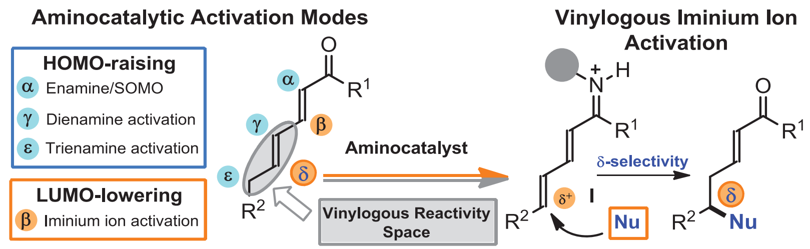
Pertinent precedent:
Córdova, A. *et al. Chem. Eur. J.* **2011**, 17, 7904–7917

State of the Art of Aminocatalysis

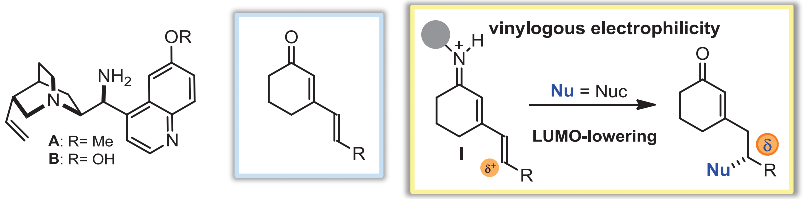


TRIENAMINE WITH ENONES:
Chen, Y.-C. *et al., Angew. Chem. Int. Ed.* **2012**, *51*, 4401-4404

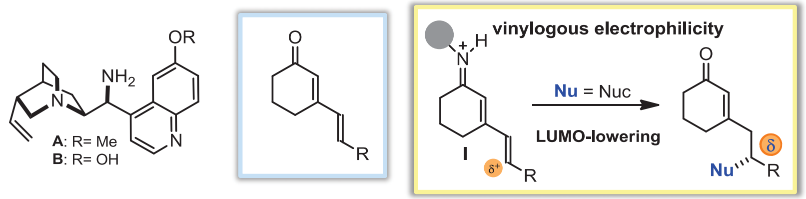
About Vinylogous Reactivity

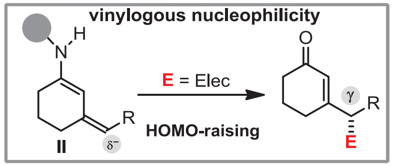


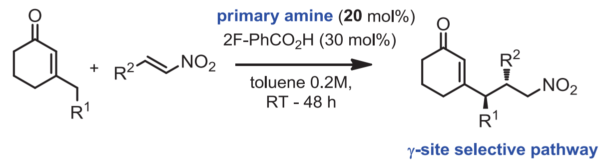
About Vinylogous Reactivity



About Vinylogous Reactivity

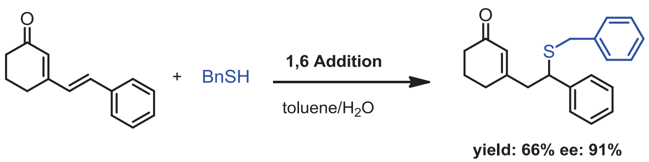


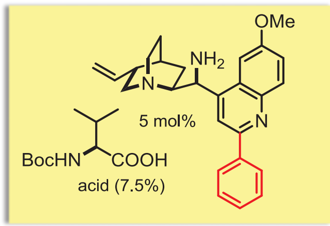




PNAS **2010**, *107*, 20642

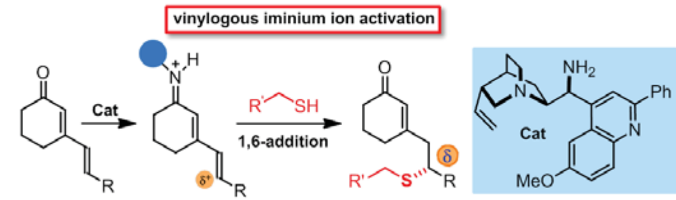
A Step Further… the δ-Functionalization via 1,6 Addition





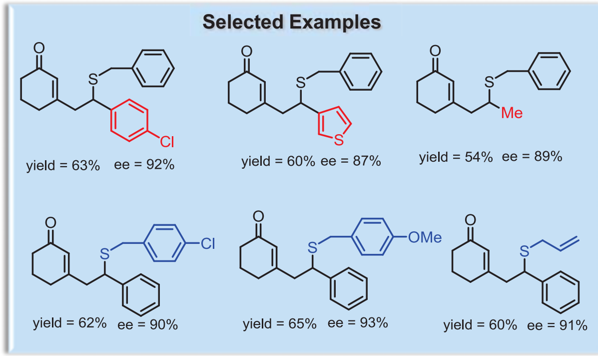
1,6-Additions
precedents based on the selective activation of the nucleophiles:
Jørgensen, K. A. et al. *J. Am. Chem. Soc.* **2007**, *129*, 5772–5778.
Alexakis, A., Stephens, J. C. et al. *Angew. Chem., Int. Ed.* **2011**, *50*, 5095

First use of the 2'-modified cinchona amine:
List, B. et al. *Angew. Chem., Int. Ed.* **2011**, *50*, 1707

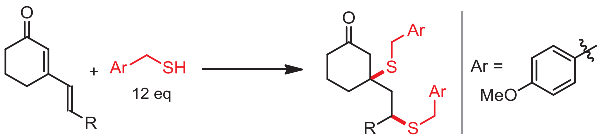


14 examples: 51-70% yield; 87-93% ee

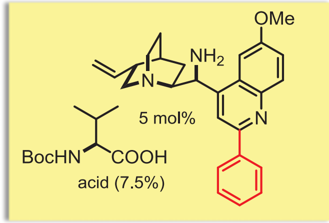
with X. Tian & Y. Liu
Angew. Chem. Int. Ed. **2012**, *51*, 6439–6442



Cascade Reactions by Sequential Iminium Ion Activation



5 examples: 4:1 dr; 95-97% ee



with X. Tian & Y. Liu
Angew. Chem. Int. Ed. **2012**, *51*, 6439–6442

Acknowledgments

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MARIE CURIE ACTIONS

GOBIERNO DE ESPAÑA MINISTERIO DE CIENCIA E INNOVACIÓN

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