The Principle of Vinylogy:
Potential and Applications in the Asymmetric Aldol/Mannich/Michael Reaction Domain

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The Principle of Vinylogy


Fuson, R.C., 1895-1979

THE PRINCIPLE OF VINYLOGY

REYNOLD C. FUSON

Department of Chemistry, University of Illinois, Urbana, Illinois

Received December 20, 1934

It has long been recognized that, in a molecule containing a system of conjugated double linkages, the influence of a functional group may sometimes be propagated along the chain and make itself apparent at a remote point in the molecule. For example, the methyl group in ethyl crotonate behaves in some respects as it does when it is attached directly to the ester group as in ethyl acetate.

$CH_3C{=}O$ (|) OC_2H_5 — Ethyl acetate

$CH_3{-}CH{=}CH{-}C{=}O$ (|) OC_2H_5 — Ethyl crotonate

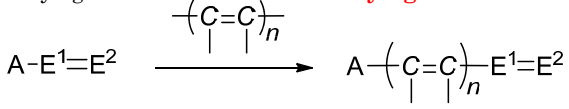
Fuson, R. C. *Chem. Rev.* **1935**, *16*, 1-27

1828 Whöler — **1838** Kane — **1872/1873** Wurtz/Borodin — **1887** Michael — **1917** Mannich — **1928** Diels-Alder — **1935** Fuson — **IASOC2012**

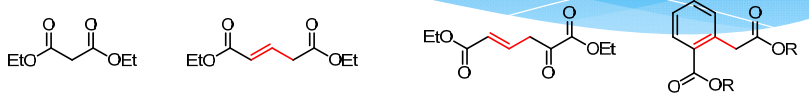
The Principle of Vinylogy

"It has long been recognized that, in a molecule containing a system of conjugated double linkages, the influence of a functional group may **sometimes** be **propagated** along the chain and make itself apparent at a **remote point** in the molecule…"

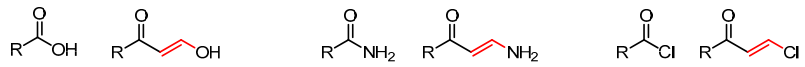
… the generalization takes the following form: *When in a compound of type A–E_1=E_2 or A–E_1≡E_2, a structural unit of type –(CH=CH)$_n$– is interposed between A and E_1 the function of E_2 remains qualitatively unchanged, but that of E_1 may be* ***usurped*** *by the carbon atom attached to A.* The resulting compound will have the form of A–(CH=CH)$_n$–E_1=E_2 … and in a any given series of this type the members will differ from each other by one or more vinylene residues. It is proposed to term such a group of compounds a **vinylogous series**. The members of a vinylogous series will then be **vinylogs** of one another."



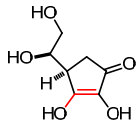
Vinylogous Series



Henrich (1899, 1902); Blaise (1903); Prager (1905); Dieckmann (1908, 1914)



Claisen, R.L. *Chem Ber.* **1926**, *59*, 144; Angeli, A. *Atti Acad. Lincei* **1926**, *3*, 371

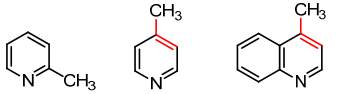



Claisen, R.L., 1851-1930

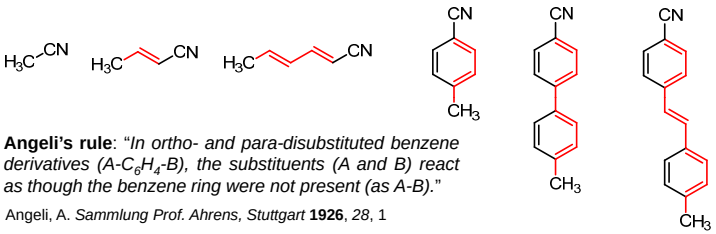

Angeli, A., 1864-1931

…anomalies cease to be anomalous…

Vinylogous Series

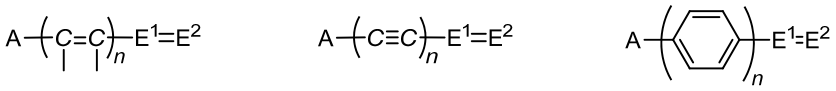


Koenigs, W. *Chem. Ber.* **1901**, *34*, 4326



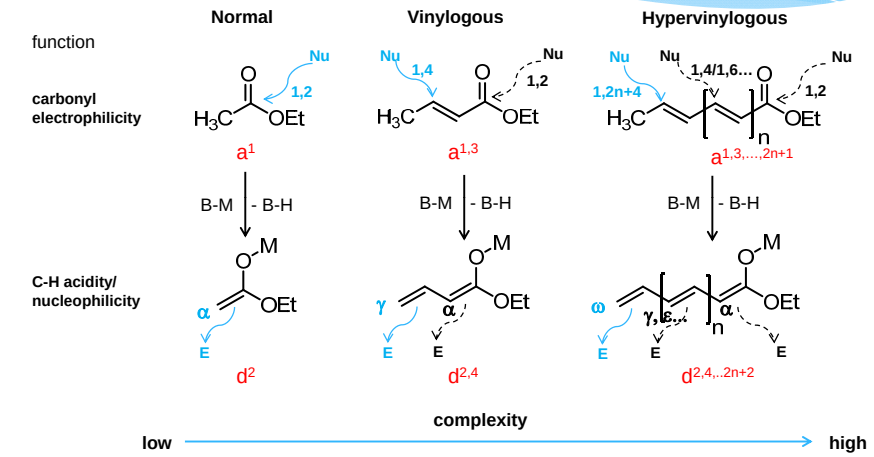
Angeli's rule: "*In ortho- and para-disubstituted benzene derivatives (A-C_6H_4-B), the substituents (A and B) react as though the benzene ring were not present (as A-B).*"

Angeli, A. *Sammlung Prof. Ahrens, Stuttgart* **1926**, *28*, 1

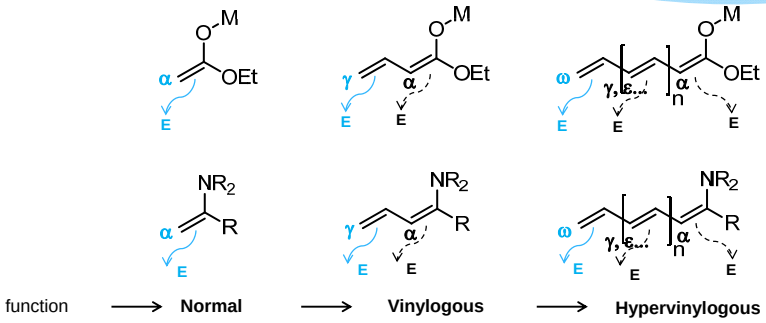


(Hyper)vinylogous | (Hyper)alkynilogous | (Hyper)phenylogous

Vinylogous Series in the Michael and Aldol Domains: the Acceptor-to-Donor Swap



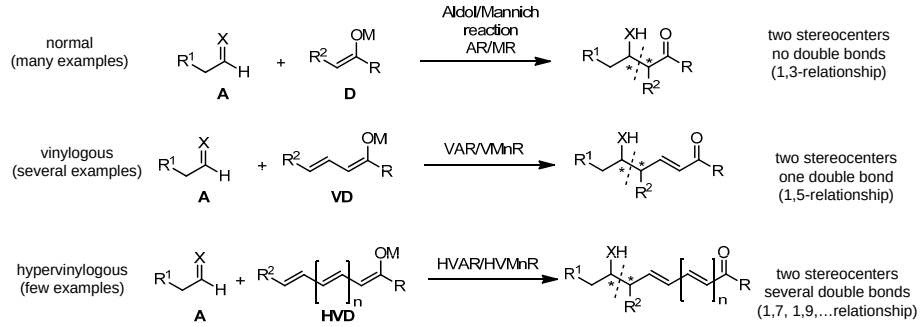
Vinylogy: a Domain as Wide as the Organic Synthesis



Focus

- alkylation
- amination
- aldol addition / condensation
- Mannich addition
- halogenation
- Claisen condensation
- Reformanski addition
- Michael addition

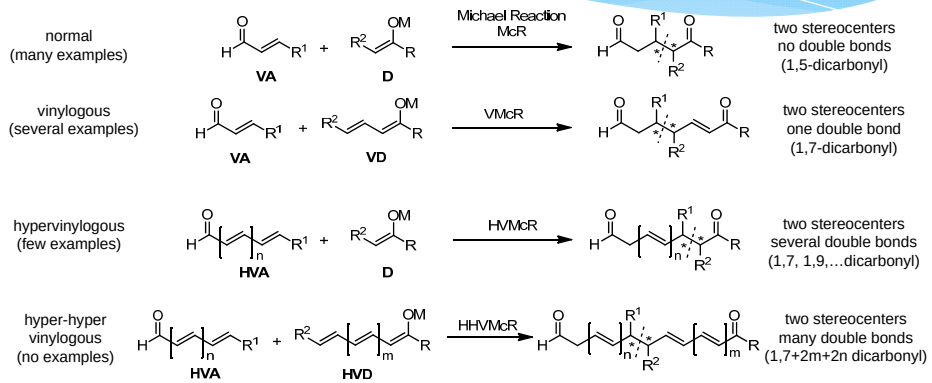
The Evolution of the Aldol-Mannich Chemistry: Increasing Product Complexity



Critical Issues:

- enolate production and geometry
- reactivity and chemoselectivity
- regio- and stereocontrol
- double-bond(s) positioning and geometry

The Evolution of the Michael Chemistry: Increasing Product Complexity



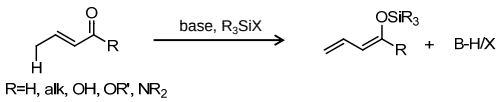
Critical Issues:
- enolate production and geometry
- reactivity and chemoselectivity
- regio- and stereocontrol
- double-bond(s) positioning and geometry

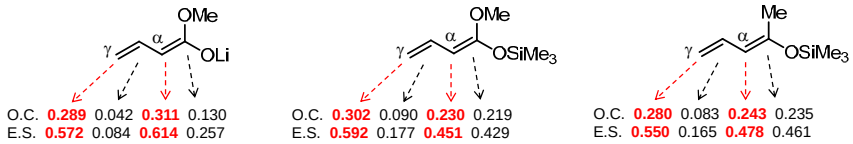
Full mastery of these issues gives the measure of the evolution of vinylogy in the aldol/Mannich/Michael domains

Routes to Preformed, Mukaiyama-Type Extended Carbon Nucleophiles for Use in Indirect Vinylogous and Hypervinylogous Methodologies

pro-nucleophile —(stoichiometric HOMO-raising activation; base, R_3SiX)→ nucleophile

❖ From γ-enolizable α,β-unsaturated carbonyls (and higher homologues)

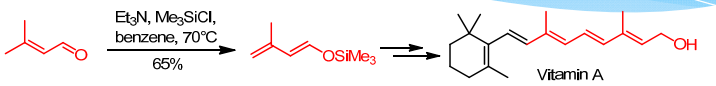




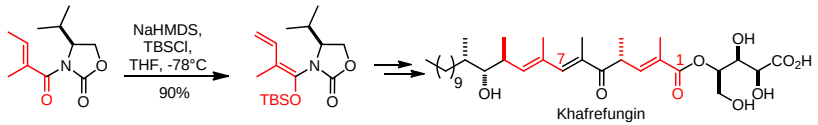
O.C.: HOMO orbital coefficients; E.S.: electrophilic susceptibility

Denmark, S.E. *et al. ACIE.* **2005**, *44*, 4682

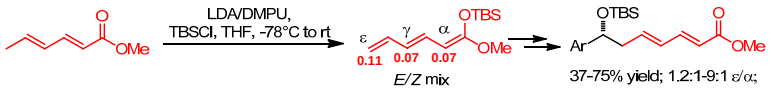
❖ From γ-enolizable α,β-unsaturated carbonyls (and higher homologues)



Mukaiyama, T. *et al. Chem. Lett.* **1975**, 1201

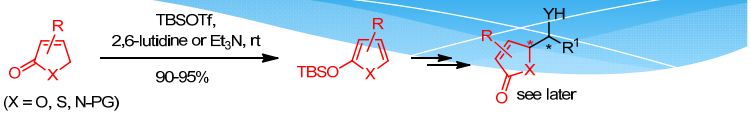


Kobayashi, S. *et al. JACS.* **2004**, *126*, 13604; *OL*. **2007**, *9*, 849

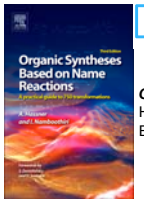


List, B. *et al. ACIE.* **2011**, *50*, 754

❖ From γ-enolizable α,β-unsaturated carbonyls (and higher homologues)

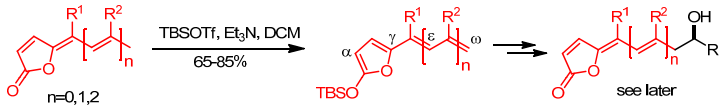


Yoshii, E. *et al. Heterocycles* **1976**, *4*, 1663; Takei, H. *et al. Bull. Chem. Soc. Jpn.* **1979**, *52*, 1953; Ricci, A.; Taddei, M. *et al. Heterocycles* **1982**, *19*, 2327; Boukouvalas, J. *et al. Tele* **1987**, *28*, 4037; Brown, D.W. *et al. Tele* **1987**, *28*, 985; Casiraghi, G.; Rassu, G. *et al. Tele* **1989**, *30*, 5325; *Synlett* **2009**, 1525



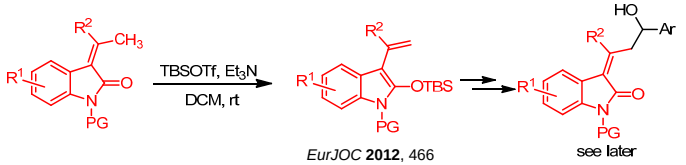
The TAKEI-CASIRAGHI reaction

Organic Syntheses Based on Named Reactions, A. Hassner and I. Namboothiri Eds., Third Edition, 2011, Elsevier

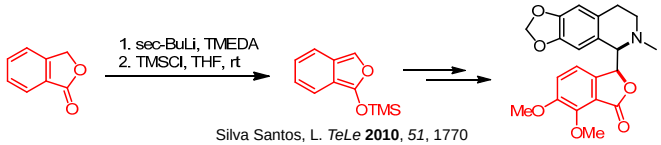


OL **2011**, *13*, 4738

❖ From γ-enolizable α,β-unsaturated carbonyls (and higher homologues)

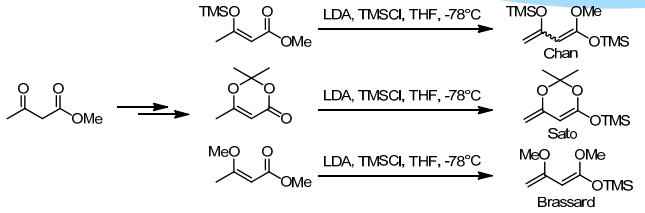


EurJOC **2012**, 466

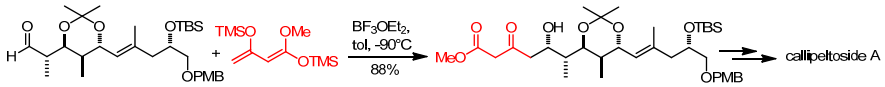


Silva Santos, L. *TeLe* **2010**, *51*, 1770

❖ From acetoacetates

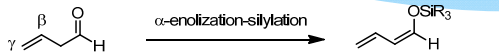


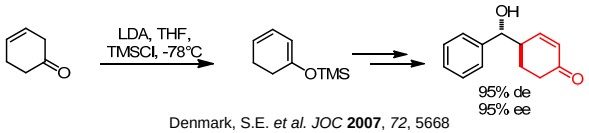
Reviews: Scettri, A. *et al. Curr. Org. Chem.* **2004**, *8*, 993; Denmark, S.E. *et al. ACIE* **2005**, *44*, 4682



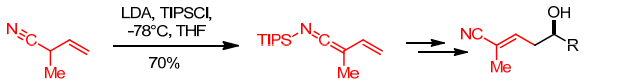
Evans, D.A. *et al. Tetrahedron* **2008**, *64*, 4671

❖ From deconjugated (allylic) carbonyls/nitriles





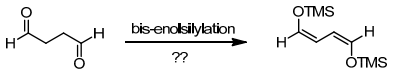
Denmark, S.E. *et al. JOC* **2007**, *72*, 5668

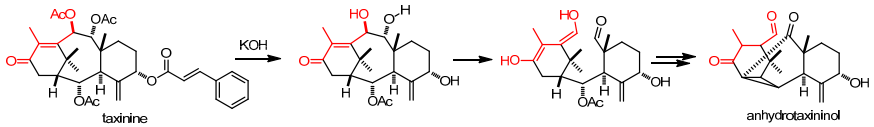


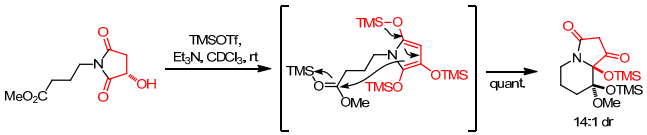
Denmark, S.E. *et al. JACS* **2012**, *51*, 3236

❖ Other modalities?

❖ From 1,4-dicarbonyl equivalents…lessons from Natural Products



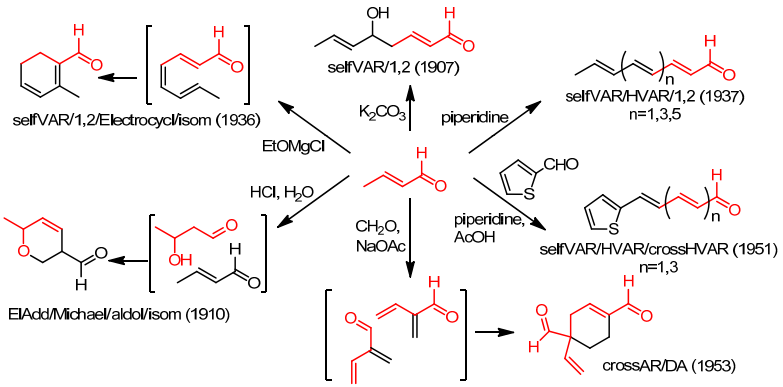




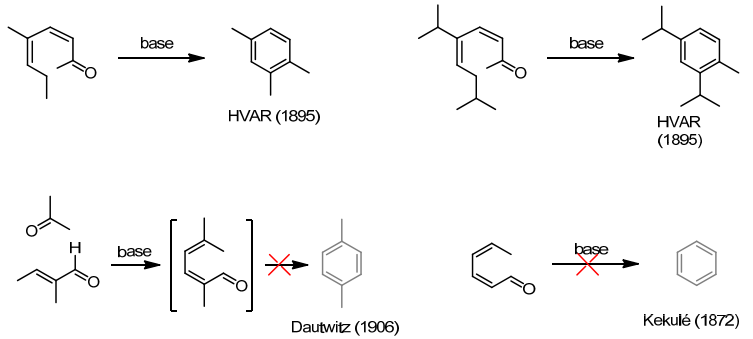
Hoye, T.R. *et al. OL* **2006**, *8*, 5191

Routes to *in Situ*-Generated Substoichiometric Extended Carbon Nucleophiles for Use in Direct Vinylogous/Hypervinylogous Methodologies

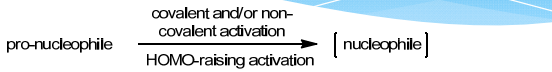
•Lessons from the past centuries



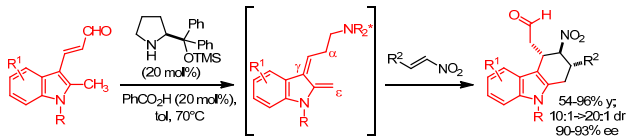
•Lessons from the past centuries



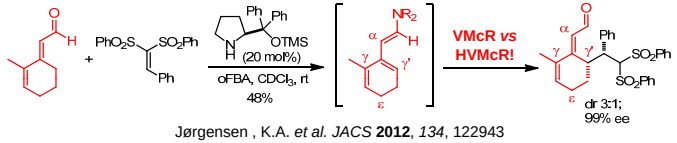
Routes to *in Situ*-Generated Substoichiometric Extended Carbon Nucleophiles for Use in Direct Vinylogous/Hypervinylogous Methodologies



Review: Ramachary, D.B. *et al. EurJOC* **2012**, 865

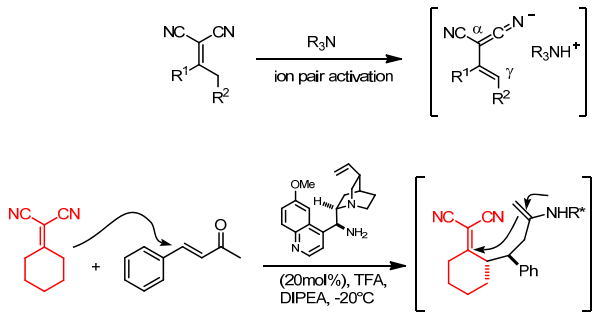


Melchiorre, P. *et al. JACS* **2011**, *133*, 15212



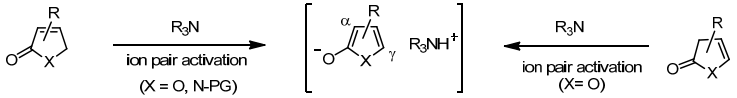
Jørgensen , K.A. *et al. JACS* **2012**, *134*, 122943

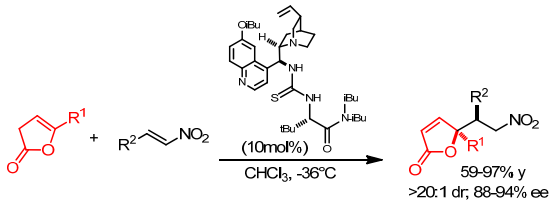
Routes to *in Situ*-Generated Substoichiometric Extended Carbon Nucleophiles for Use in Direct Vinylogous/Hypervinylogous Methodologies



Chen, Y.-C.; Deng, J.-G. *et al. ACIE* **2007**, *46*, 389

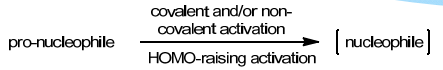
Routes to *in Situ*-Generated Substoichiometric Extended Carbon Nucleophiles for Use in Direct Vinylogous/Hypervinylogous Methodologies

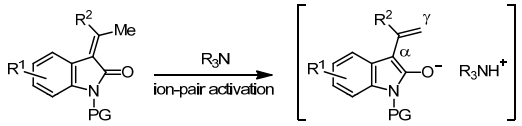


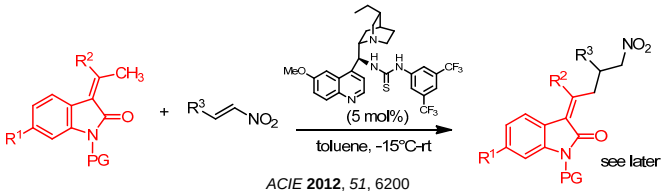


Mukherjee, S. *et al. Chem. Commun.* **2012**, 5193

Routes to *in Situ*-Generated Substoichiometric Extended Carbon Nucleophiles for Use in Direct Vinylogous/Hypervinylogous Methodologies

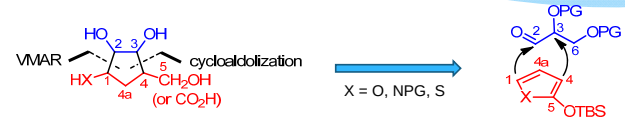


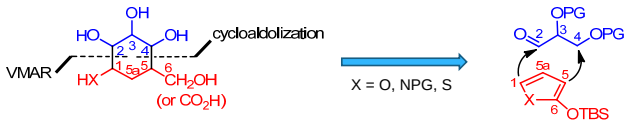




ACIE **2012**, *51*, 6200

Five- and Six-Membered Carbasugars: Retrosynthesis



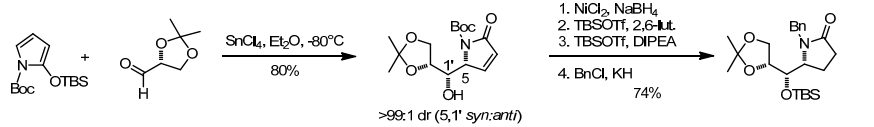


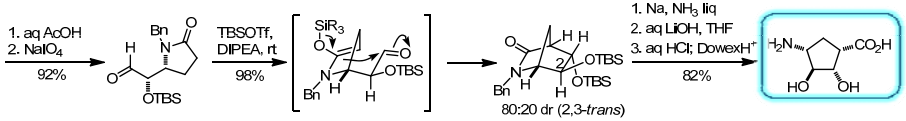
Key-steps sequence

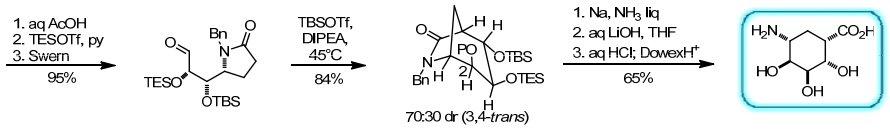
1. vinylogous Mukaiyama-aldol reaction, C1-C2 bonding
2. silylative cycloaldolization, C3-C4 or C4-C5 bonding
3. reductive or hydrolytic C5-X or C6-X bond fission

JOC. **2000**, *65*, 6307; *JOC* **2001**, *66*, 8070; *EurJOC* **2002**, 1956; *JOC.* **2002**, *67*, 5338; *JOC* **2003**, *68*, 5881; *JOC* **2004**, *69*, 1625

Variable Synthesis of Hydroxylated Aminocyclopentane and Aminocyclohexane Carboxylic Acids

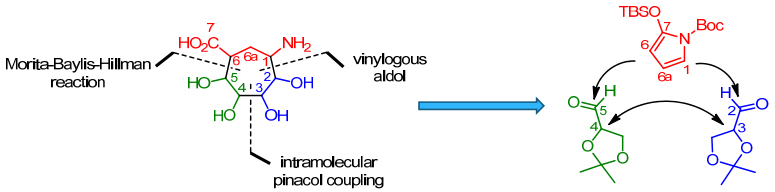






JOC. **2002**, *67*, 5338

Medium-Sized Aminocyclitols

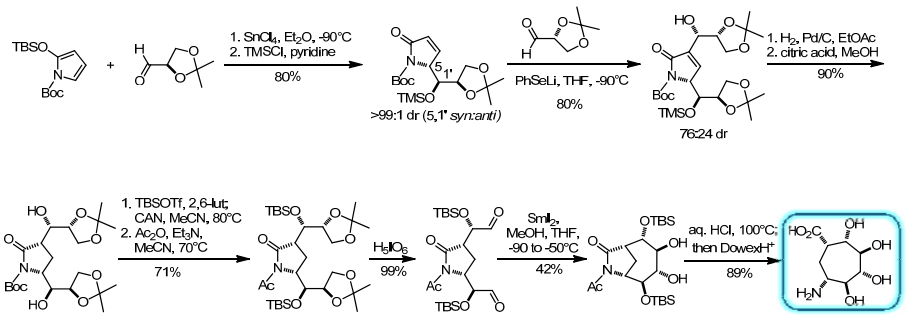


Key-steps sequence

1. vinylogous Mukaiyama-aldol reaction, C1-C2 diastereoselective bonding
2. Morita-Baylis-Hillman reaction, C5-C6 diastereoselective bonding
3. bilateral oxidative diol fragmentation
4. intramolecular pinacol coupling
5. N1-C7 hydrolytic fission

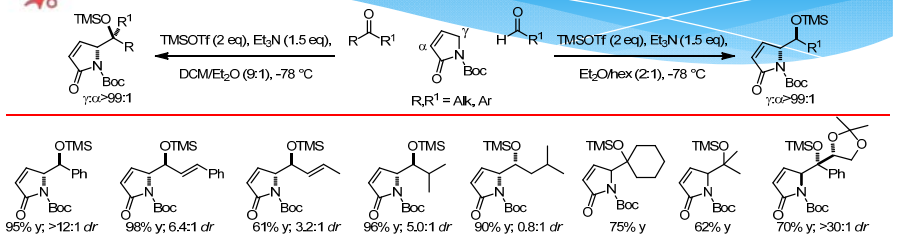
JOC **2006**, *71*, 225

Synthesis of Aminocyclitols

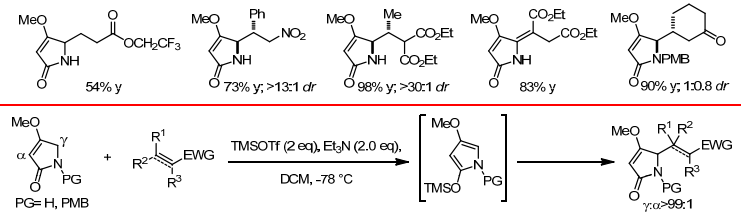


JOC **2006**, *71*, 225

Direct VMAR/VMMcR Modalities of Pyrrolinone Donors

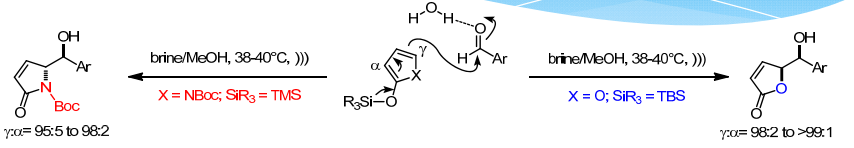


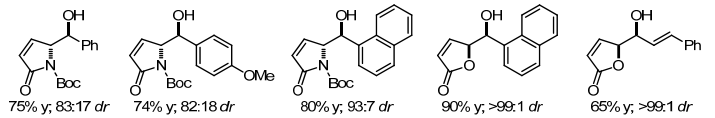
JOC **2008**, *73*, 5446

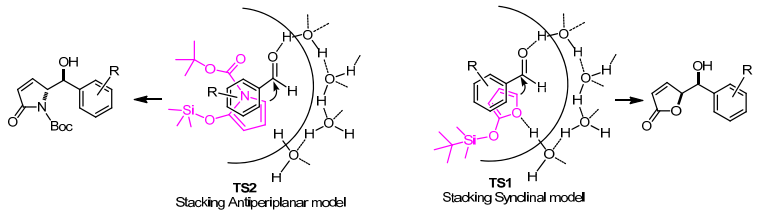


Tetrahedron **2008**, *64*, 11697

Pyrrole-/Furan-Based Silyl Dienolates and Water: A Fruitful Relationship in VMAR/VMMcR Processes

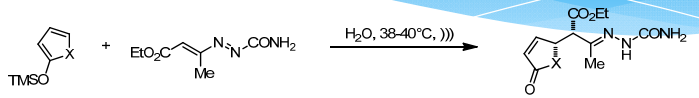






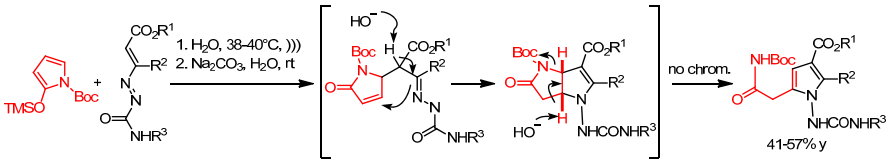
JOC **2010**, *75*, 8681

Pyrrole-/Furan-Based Silyl Dienolates and Water: A Fruitful Relationship in VMAR/VMMcR Processes



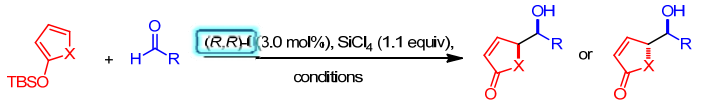
X= NBoc: 96% y; 80:20 *dr*
X= O: 53% y; >99:1 *dr*
X= S: 87% y; 63:37 *dr*

One-Pot Three-Step Entry to Functionality-Rich Pyrroles



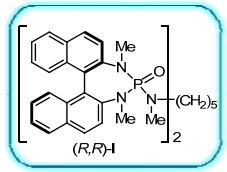
Adv. Synth. Catal. **2011**, *353*, 1966

Catalytic, Asymmetric VMAR of Pyrrole- and Furan-Based Silyl Dienolates



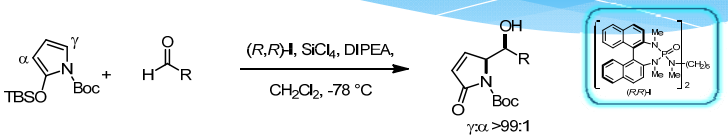
X = NBoc or O

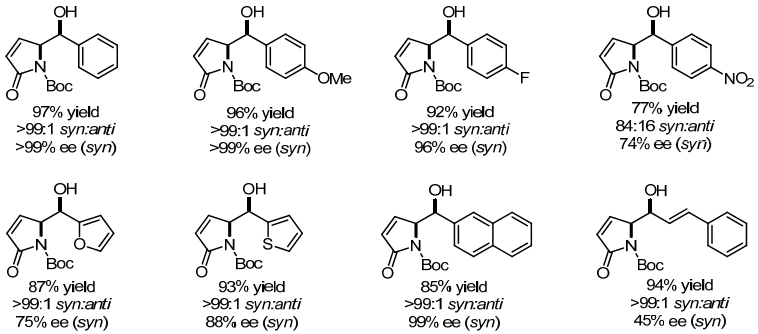
Optimized conditions: aldehyde (1.0 equiv); diene substrate (2.0 equiv); DIPEA (10.0 mol%); 0.25 M in CH_2Cl_2 at -78 °C; reaction time 20 h



Tele **2009**, *50*, 3428; *Adv. Synth. Catal.* **2010**, *352*, 2011

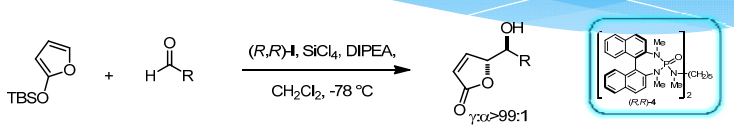
Substrate Scope for the Asymmetric VMAR of Pyrrole-Based Silyl Dienolates

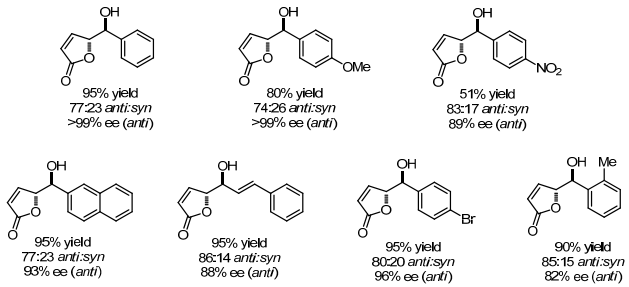




Tele **2009**, *50*, 3428; *Adv. Synth. Catal.* **2010**, *352*, 2011

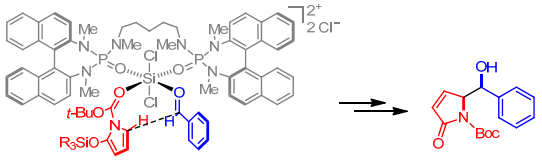
Substrate Scope for the Asymmetric VMAR of Furan-Based Silyl Dienolates



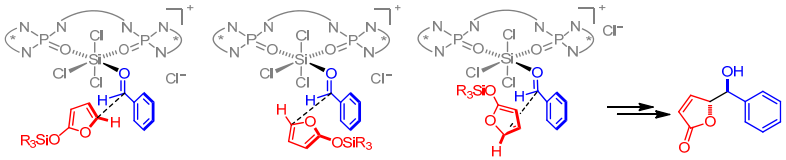


Tele **2009**, *50*, 3428; *Adv. Synth. Catal.* **2010**, *352*, 2011

Proposed Transition State Models for the Asymmetric VMAR of Pyrrole/Furan Silyl Dienolates



TS-*syn*
(*Re-Re* face trajectory)

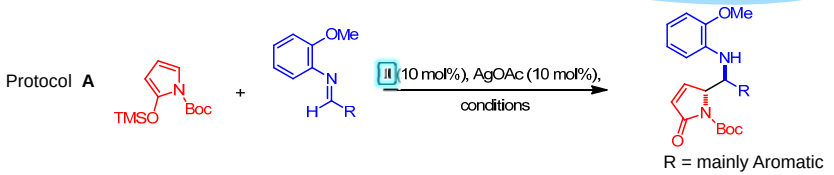


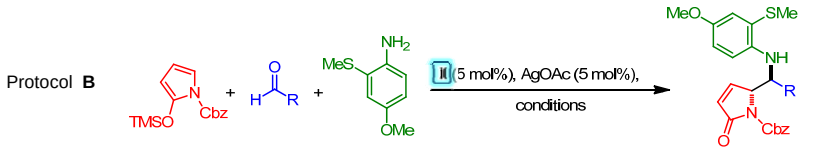
TS-*anti*-A **TS-*anti*-B** **TS-*anti*-C**

(*Si-Re* face trajectory)

Tele **2009**, *50*, 3428; *Adv. Synth. Catal.* **2010**, *352*, 2011

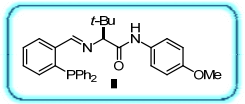
Catalytic, Asymmetric Vinylogous Mannich Reactions of Pyrrole-Based Silyl Dienolates with *N*-Aryl Imines





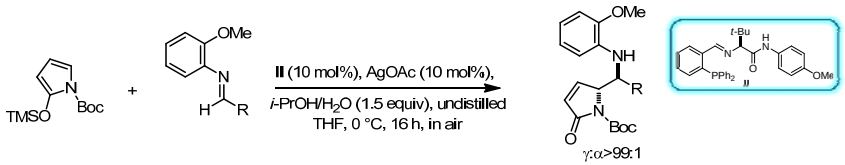
*Conditions **A***:
i-PrOH/H_2O (1.5 equiv), undistilled THF, 0 °C, 16 h, in air

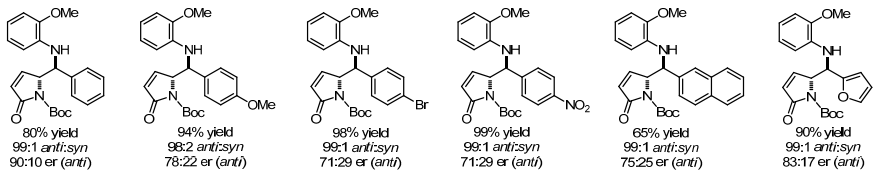
*Conditions **B***:
$MgSO_4$, *i*-PrOH/H_2O, THF, -30 °C



JOC **2011**, *76*, 2248; *JOC* **2011**, *76*, 10291

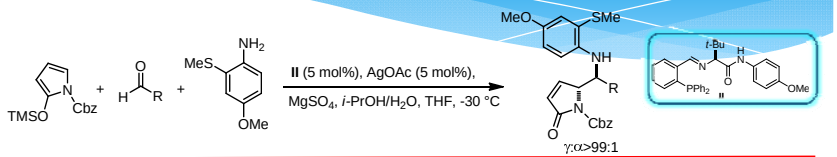
Substrate Scope for the Asymmetric Two-Component VMMnR of Pyrrole Silyl Dienolates (Protocol A)

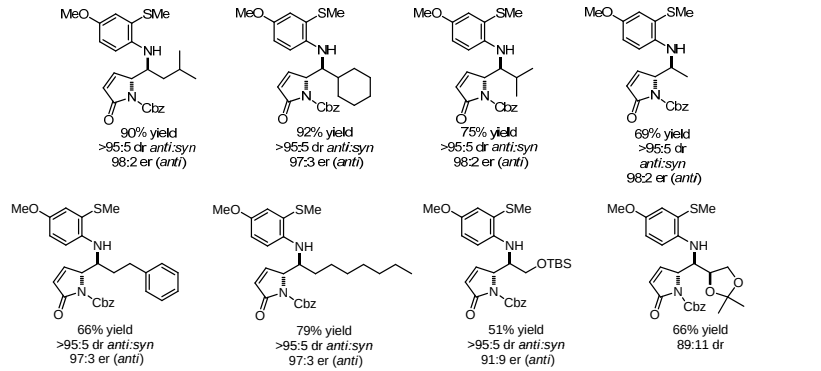




JOC **2011**, *76*, 2248

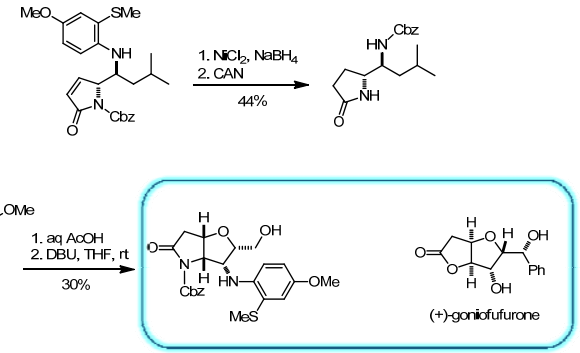
Substrate Scope for the Asymmetric Three-Component VMMnR of Pyrrole Silyl Dienolates (Protocol B)





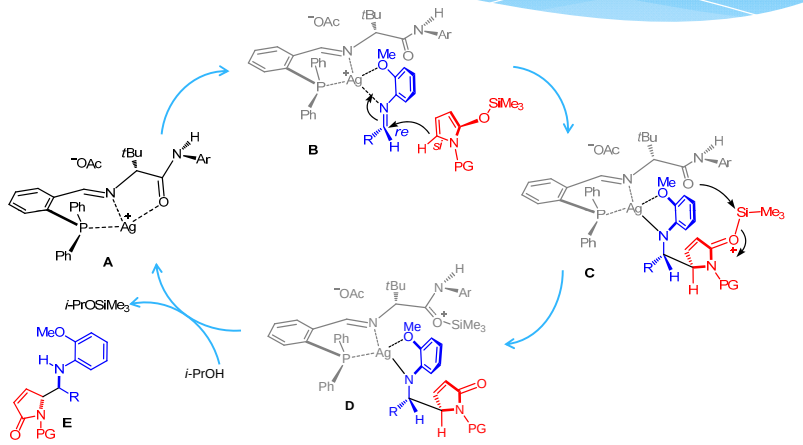
JOC **2011**, *76*, 10291

Asymmetric Three-Component VMMnR of Pyrrole Silyl Dienolates: Skeletal Elaboration



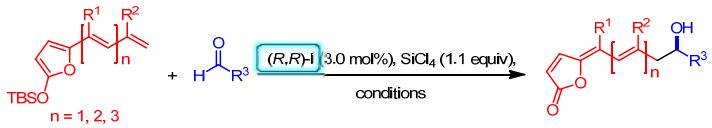
JOC **2011**, *76*, 10291

Proposed Catalytic Cycle for the Asymmetric VMMnR between Pyrrole Silyl Dienolate and *N*-Aryl Imine Acceptors

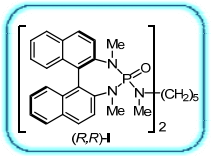


JOC **2011**, *76*, 2248; *JOC* **2011**, *76*, 10291

Catalytic, Asymmetric Hypervinylogous Mukaiyama Aldol Reactions of Extended Furan Silyl Enolates

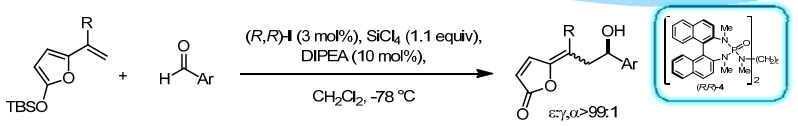


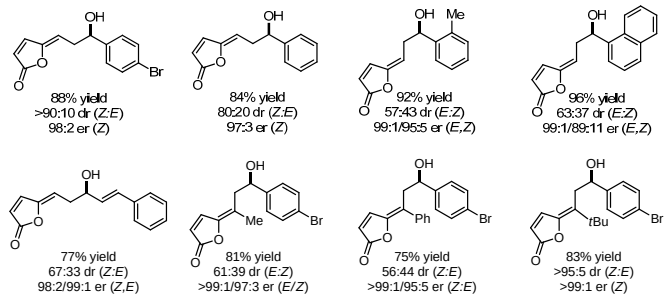
Conditions: Furan substrate (100 mg), aldehyde (1.1 equiv), DIPEA (10.0 mol%), 0.1 M in CH_2Cl_2, -78 °C, 12 h



OL **2011**, *13*, 4738

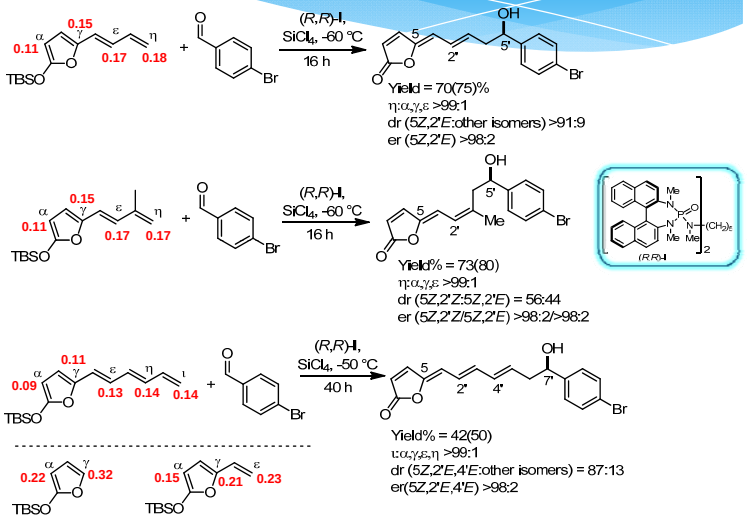
Scope of the Catalytic, Asymmetric Bis-Vinylogous Mukaiyama Aldol Reaction of Silyloxyfuran Triene Nucleophiles





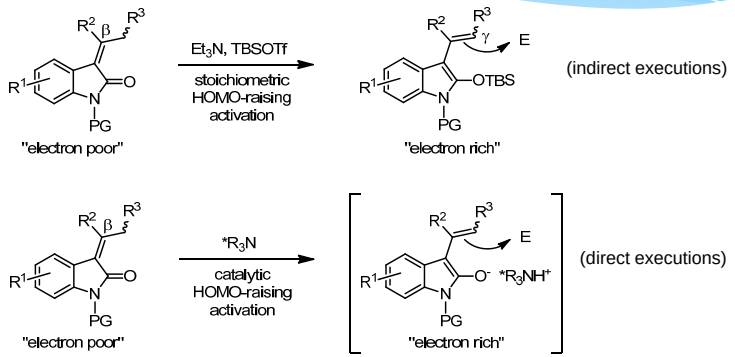
OL **2011**, *13*, 4738

Further Scope of the Catalytic, Asymmetric HVMAR of Extended Furan Nucleophiles



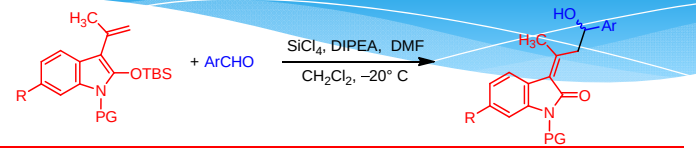
Atomic Fukui Indices in red *OL* **2011**, *13*, 4738

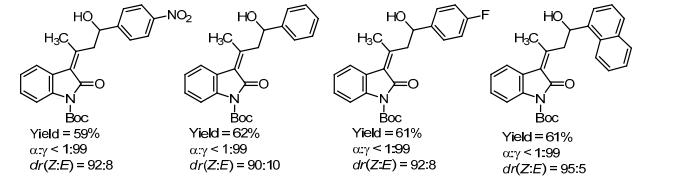
Introducing 3-Alkenyl Indole Dienolates: A Novel Progeny of Vinylogous Carbon Nucleophiles

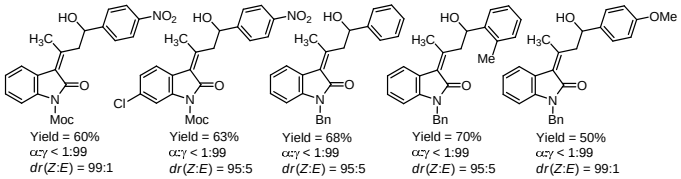


"*While 3-alkylidene oxindoles are well known for their electrophilic reactivity at C-β position, the nucleophilic properties of the related dienolate-type intermediates at C-γ position in vinylogous functionalization reactions is rarely disclosed*"

SiCl4-Assisted VMAR of Olefinic Indole Silyl Dienolates

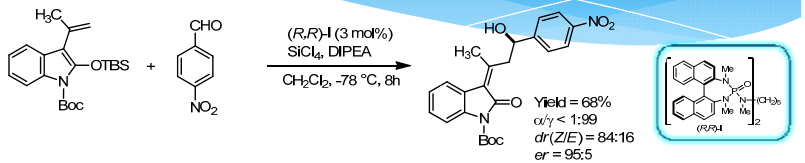


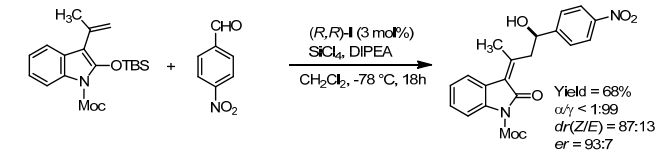


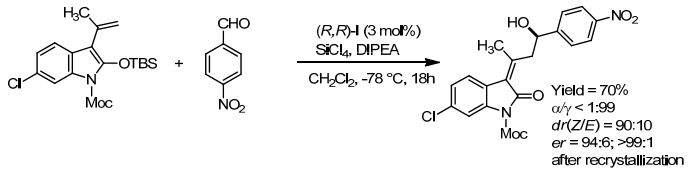


Eur. J. Org. Chem. **2012**, 466

Catalytic, Asymmetric VMAR of Olefinic Indole Silyl Dienolates

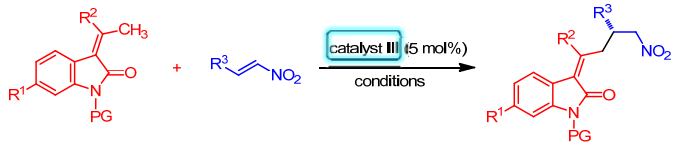




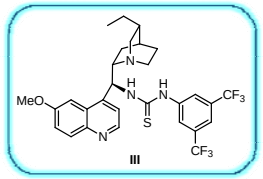


Eur. J. Org. Chem. **2012**, 466

Direct, Enantioselective Vinylogous Michael Addition of 3-Alkylidene Oxindoles to Nitroolefins

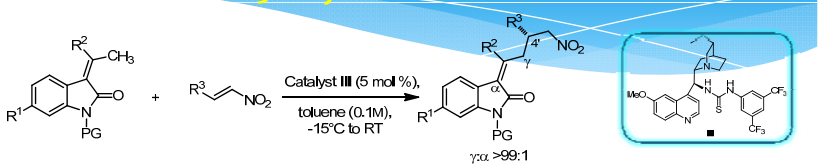


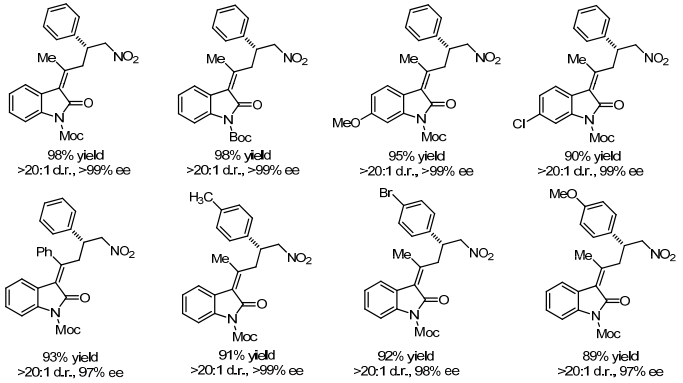
Optimized conditions (PG = Boc, Moc):
Nu:**El** molar ratio 1.2:1; 4 mL of toluene; 0.4 mmol scale; -15 °C for 24 h followed by 12 h at RT



ACIE **2012**, *51*, 6200

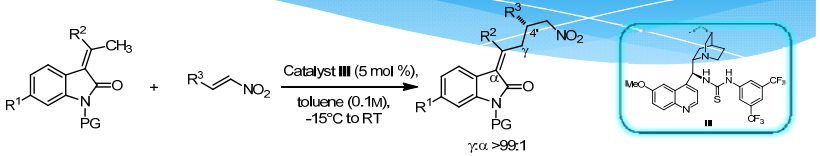
Generality of the Direct, Organocatalytic Asymmetric VMcR of 3-Alkylidene Oxindoles with Nitroolefins

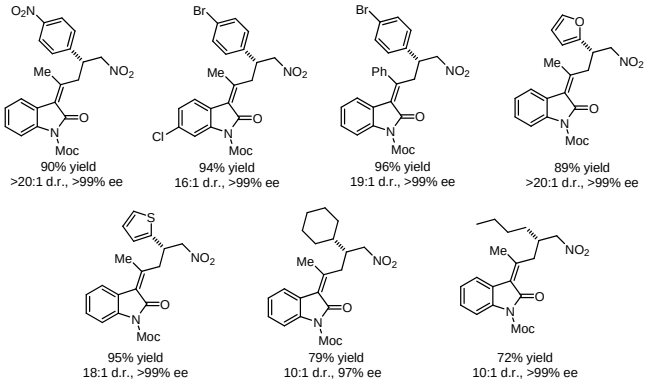




ACIE **2012**, *51*, 6200

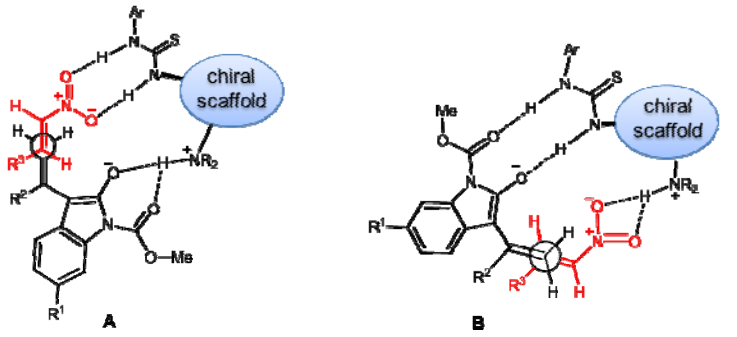
Generality of the Direct, Organocatalytic Asymmetric VMcR of 3-Alkylidene Oxindoles with Nitroolefins





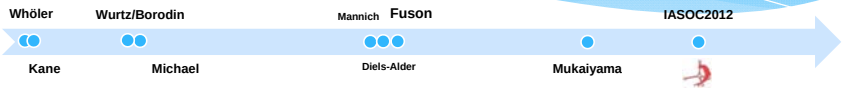
ACIE **2012**, *51*, 6200

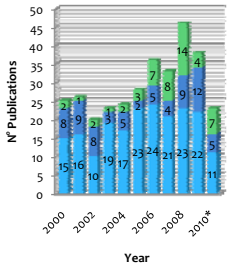
Possible Models of Dual Activation of the Nucleophilic and Electrophilic Reaction Components by the Cinchona-Thiourea Catalyst

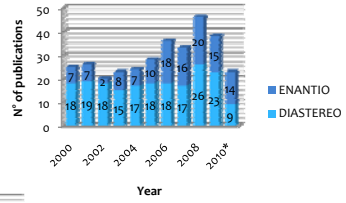


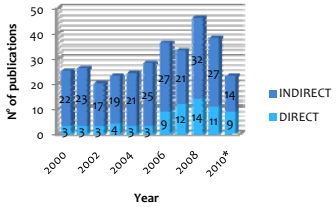
ACIE **2012**, *51*, 6200

Vinylogous and Hypervinylogous Aldol/Mannich/Michael Reactions: Perspectives









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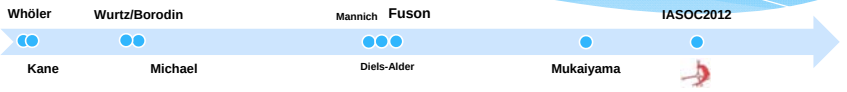

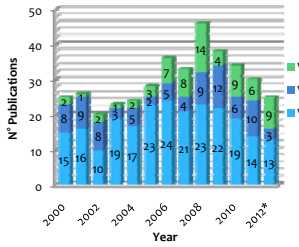

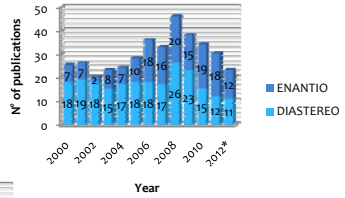

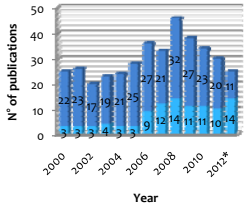

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