Exploring and Exploiting New Reactivity with Novel Classes of High-Performance Multifunctional Cooperative Catalysts

Darren J Dixon
University of Oxford

Ischia Advanced School of Organic Chemistry
Ischia Island, Napoli, Italy
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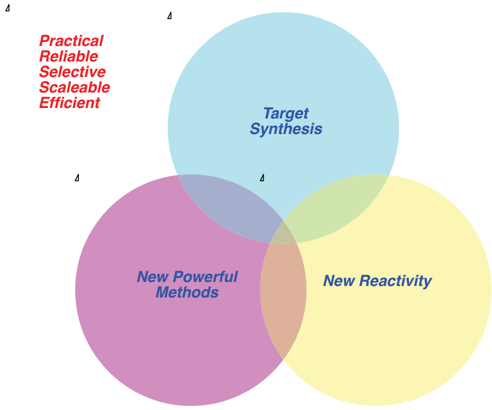
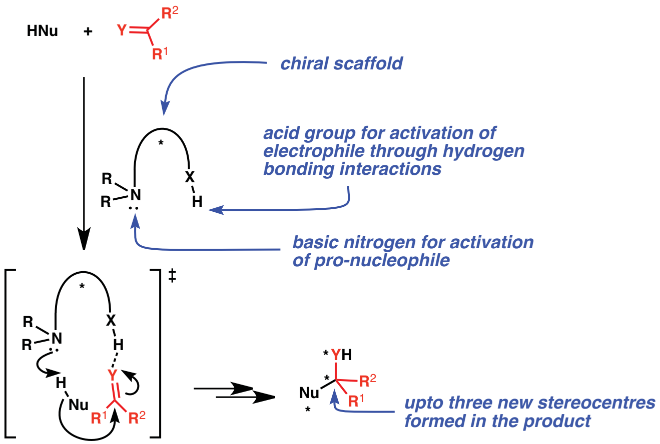
Dixon Group Research

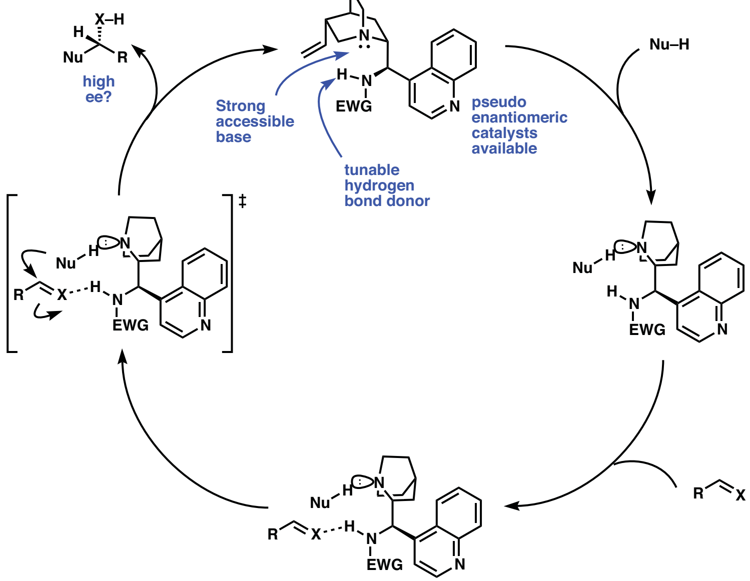


Enantioselective Bifunctional Organocatalysis

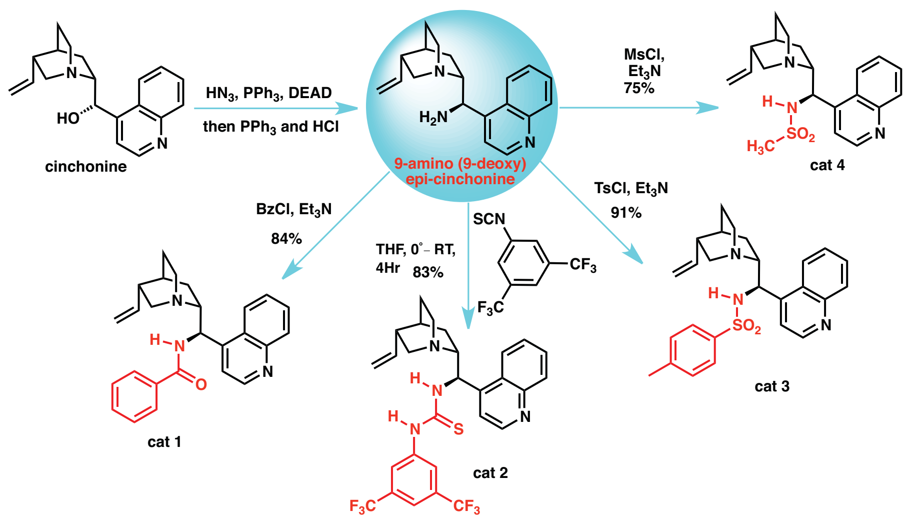


For recent selected reviews of bifunctional organocatalysis see: (a) Berkessel, A.; Groger, H. Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis; Wiley-VCH: Weinheim, 2005. b) Taylor, M. S.; Jacobsen, E. N. *Angew Chem. Int. Ed.* 2006, 45, 1520; c) Takemoto, Y. *Org. Biomol. Chem.* 2005, *3*, 4299; d) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* 2007, 107, 5713; e) Connon, S. J. *Chem. Commun.* 2008, *22*, 2499; (f) Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed.* 2008, *47*, 4638. (g) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem. Int. Ed.* 2008, *47*, 6138; (h) Pihko, P. M.; Rahaman, H. Bifunctional Acid-Base Catalysis in Enantioselective Organocatalyzed Reactions 1, 2011, 185-207; (i) Giacalone, F.; Gruttadauria, M.; Agrigento, P.; Noto, R. *Chem. Soc. Rev.* 2012, *41*, 2406; (j) Wende, C. R.; Schreiner, P. R. *Green Chem.* 2012, *14*, 1821.

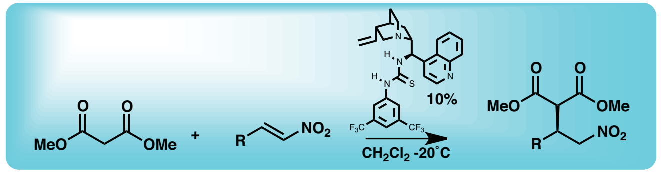
A Versatile Design for a New Family of Bifunctional Catalysts From Cinchona Alkaloids



Rapid Synthesis of a New Family of Bifunctional Catalysts



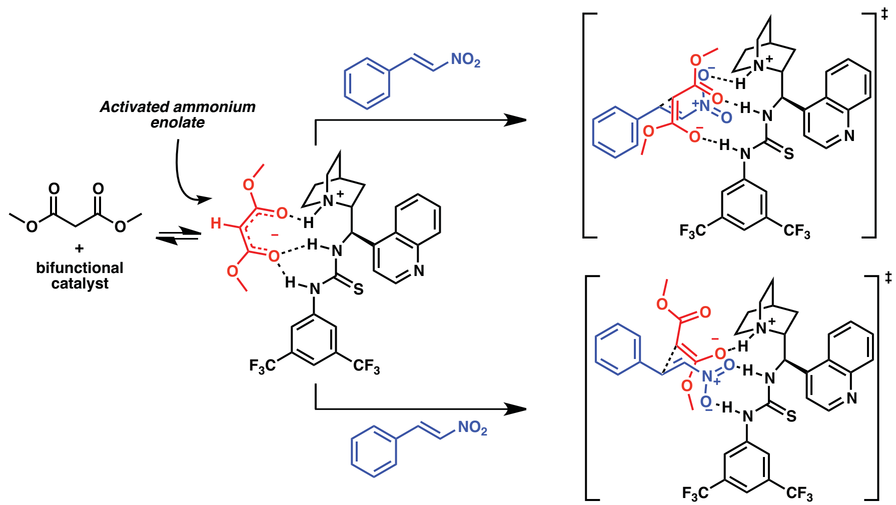
Scope of the Dimethyl Malonate Michael Addition to Nitro Alkenes



R	time/Hr	yield/%	ee/%
Ph	30	95	94
2-naphthyl	48	83	89
2-Cl phenyl	30	99	94
2-Br phenyl	30	95	92
3-Br phenyl	30	85	90
4-Br phenyl	48	87	90
4-Me phenyl	48	82	92
3-Me phenyl	52	92	91
2-MeO phenyl	30	96	97
2-furyl	30	93	95
2-thienyl	30	87	94
n-pentyl	72	81	87
c-hexyl	31	82	82 (at RT)

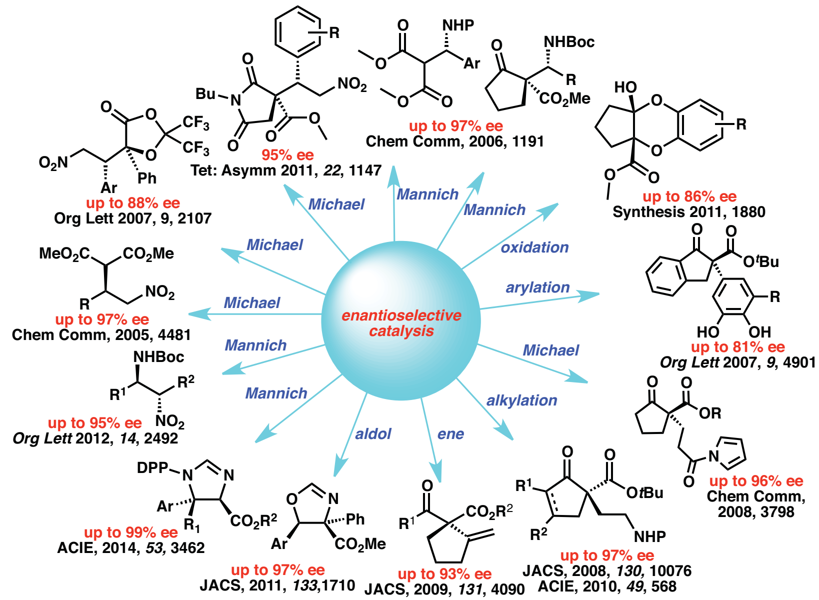
J. Ye, D. J. Dixon and P. Hynes, *Chem. Comm.* 2005, 4481
(thiophenol to enones) B. J. Li, L. Jiang, M. Liu, Y. C. Chen, L. S. Ding and Y. Wu, *Synlett*, 2005, 603
(nitromethane to chalcones) B. Vakulya, S. Varga, A. Csampa and T. Soós, *Org. Lett.*, 2005, 7, 1967
(malonate to nitroolefins) S. H. McCooey and S. J. Connon, *Angew. Chem. Int. Ed*, 2005, 6367

Possible Explanation for Enantiocontrol in Michael Addition Reaction

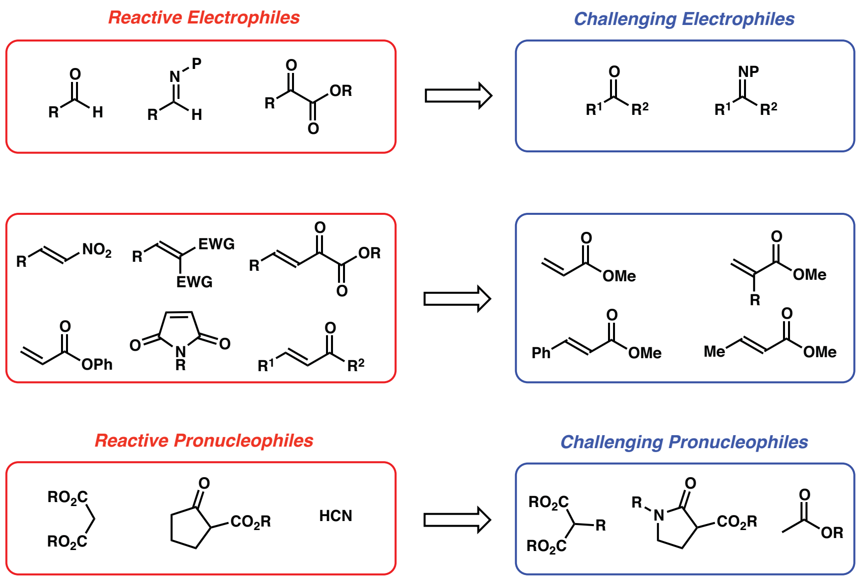


For theoretical studies on the mechanism and the bifunctionality of chiral thio urea-based organocatalysts see:
A. Hamza et al *J. Am. Chem. Soc.* 2006, 128, 13151

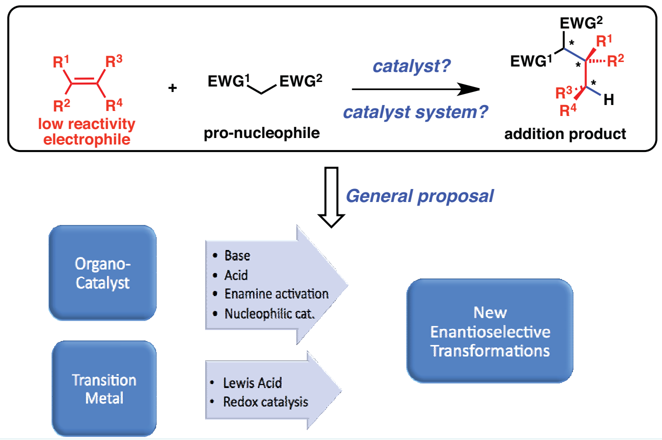
Newly Developed Catalytic Asymmetric Methodologies



New Opportunities in Bifunctional Asymmetric Catalysis

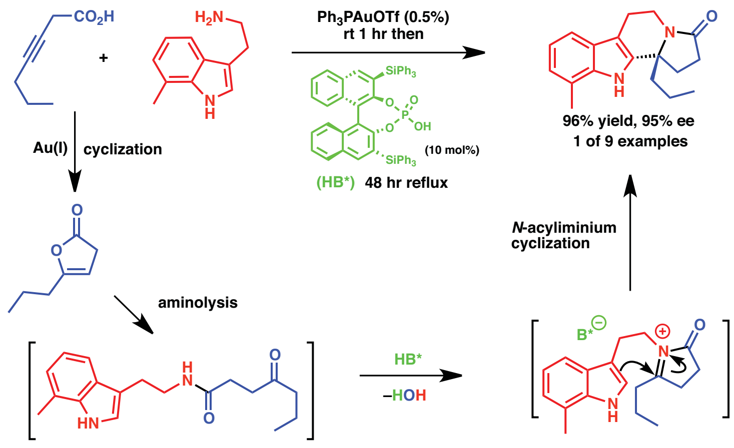


Escaping the Limits of Enantioselective Bifunctional Organocatalysis



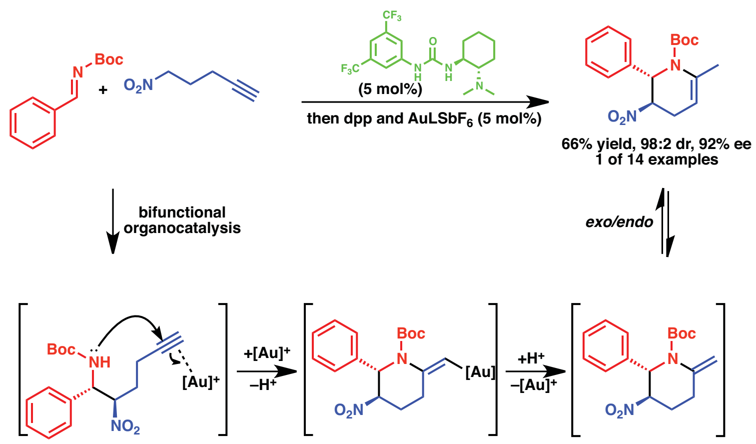
For selected reviews/highlights on the combination of organocatalysis and transition-metal catalysis, see: a) Z. Shao, H. Zhang, *Chem. Soc. Rev.* 2009, *38*, 2745-2755; b) C. Zhong, X. Shi, Eur. *J. Org. Chem.* 2010, 2999-3025 ; c) M. Rueping, R. M. Koenigs, I. Atodiresei, *Chem. Eur. J.* 2010, *16*, 9350-9365; d) N. T. Patil, *Angew. Chem. Int. Ed.* 2011, *50*, 1759-1761; e) [redacted]. Albrecht, H. Jiang, K. A. Jorgensen, *Angew. Chem. Int. Ed.* 2011, *50*, 8492-8509 ; f) N. T. Patil, V. S. Shinde, B. Gajula, *Org. Biomol. Chem.* 2012, *10*, 211-224; g) L. Stegbauer, F. Sladojevich, D. J. Dixon, *Chem. Sci.*, 2012, *3*, 942-958; h) C. C. J. Low, D. Enders, *Chem. Eur. J.* 2012, *18*, 10212-10225.

Au(I) and Chiral Bronsted Acid Cascade



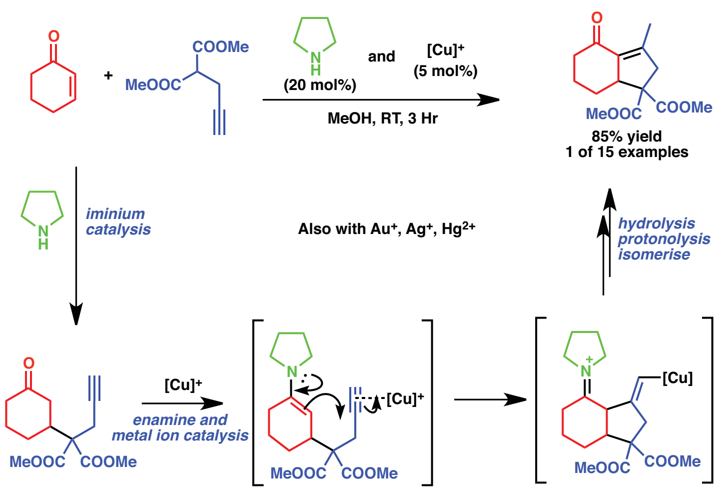
M. E. Muratore, C. A. Holloway, A. W. Pilling, R. I. Storer, G. Trevitt, D. J. Dixon *J. Am. Chem. Soc.* 2009, *131*, 10796

Au(I) and Bifunctional Organocatalyst Cascade



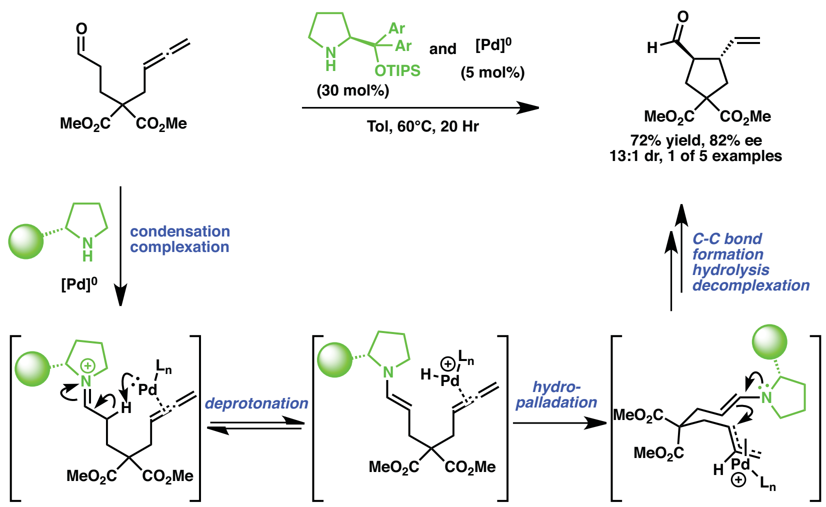
D. Barber, H. Sanganee, D. J. Dixon, *Org. Lett.* 2012, *14*, 5290

Combination Iminium, Enamine and Copper (I) Cascade Catalysis



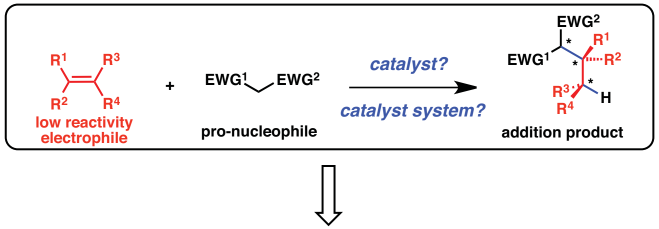
T. Yang, A. Ferrali, L. Campbell and D. J. Dixon, *Chem. Commun.* 2008, 2923

Dual Amine and Palladium Catalysis in Allene Carbocyclisation Reactions

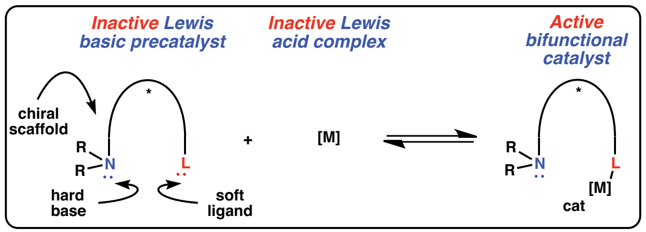


M. Li, S. Datta, D. M. Barber and D. J. Dixon, *Org. Lett.* 2012, *14*, 6350

Escaping the Limits of Enantioselective Bifunctional Organocatalysis

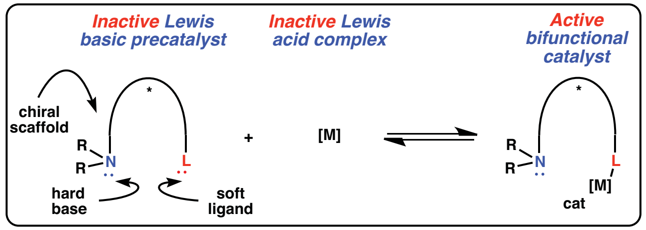


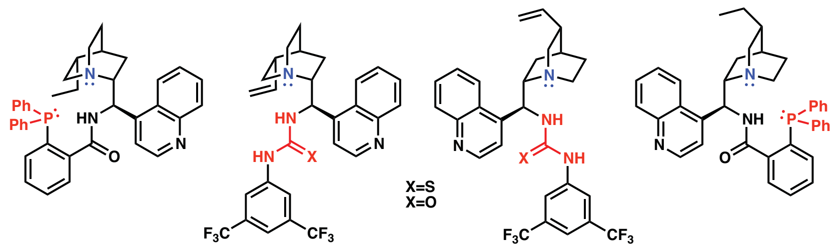
Bronsted Base / Lewis Acid Enantioselective Bifunctional Catalysis



For a relevant examples see; Casarotto, V.; Li, Z.; Boucau, J.; Lin, Y. -M. *Tetrahedron Lett*. 2007, *48*, 5561.
For reviews see; (a) Ikariya, T.; Murata, K.; Noyori, R. *Org. Biomol. Chem.* 2006, *4*, 393. (b) Muñiz, K. *Angew. Chem. Int. Ed.* 2005, *44*, 6622. (c) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Pure Appl. Chem.* 2005, *77*, 2047. (d) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett* 2005, 1491. (e) Ma, J. A.; Cahard, D. *Angew. Chem. Int. Ed.* 2004, *44*, 4566.

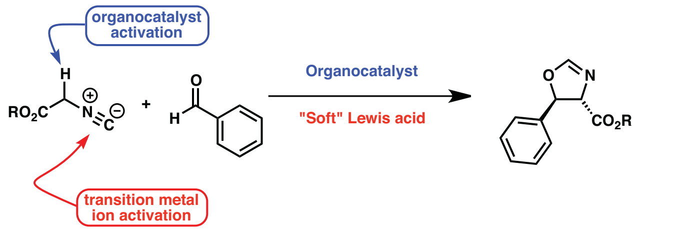
Bronsted Base / Lewis Acid Enantioselective Bifunctional Catalysis





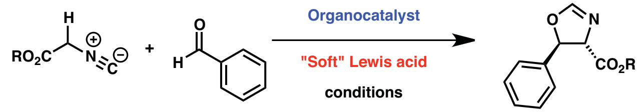
precatalysts?

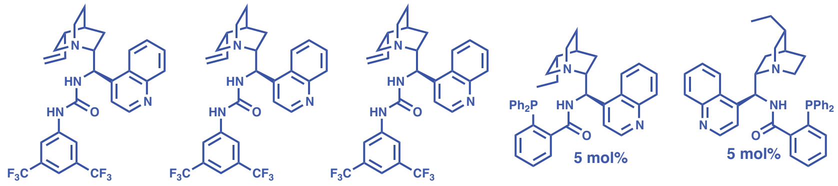
Application to the Catalytic Asymmetric Isocyanoacetate Aldol Reaction



For Au catalysed examples see: (a) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* 1986, *108,* 6405. (b) Pastor, S.D.; Togni, A. *J. Am. Chem. Soc.* 1989, *111,* 2333.

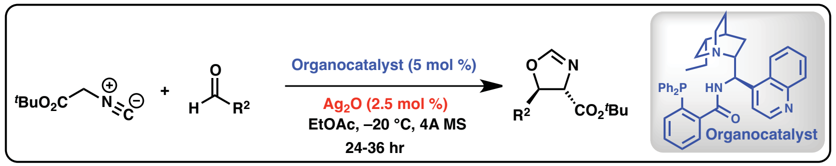
Proof of Principle Studies and Catalyst Identification

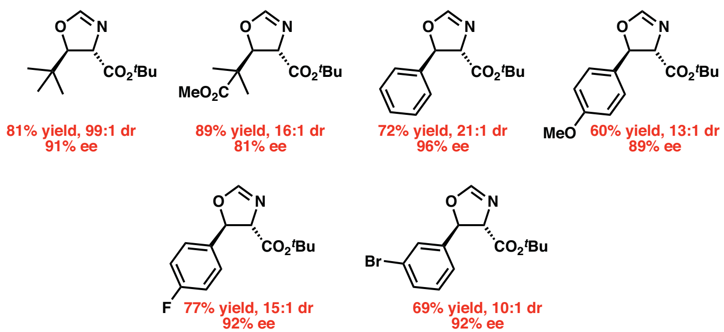




No metal traces of product	Cu(I) salts poor reactivity	Ag(I) salts good reactivity ees 20-30%	Ag_2O (2.5 mol%) EtOAc, –20 °C 100% conv, 24 hr dr 21:1, ee 96%	Ag_2O (2.5 mol%) EtOAc, –20 °C 100% conv, 24 hr dr 21:1, ee –91%

Scope of the Catalytic Asymmetric Isocyanoacetate Aldol Reaction





Sladojevich, F.; Trabocchi, A.; Guarna, A.; Dixon, D. J. *J. Am. Chem. Soc.* 2011, *133*, 1710

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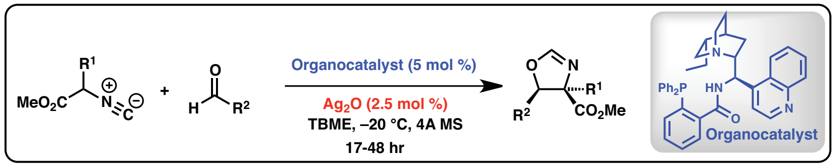
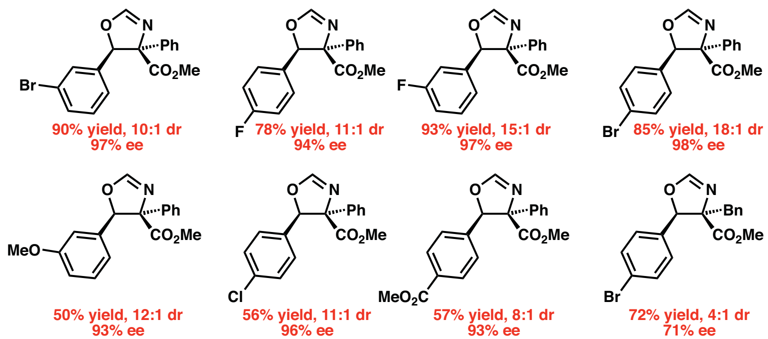
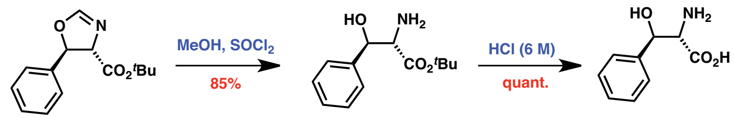




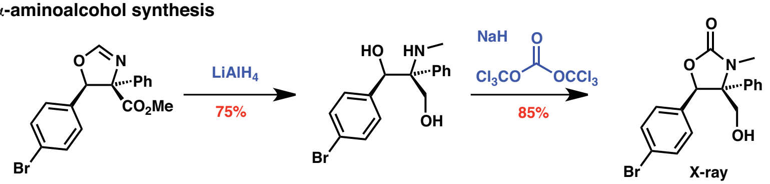
Sladojevich, F.; Trabocchi, A.; Guarna, A.; Dixon, D. J. *J. Am. Chem. Soc.* 2011, *133*, 1710

Synthetic Utility of the Isocyanoacetate Aldol Reaction

α-aminoester and α-amino acid synthesis

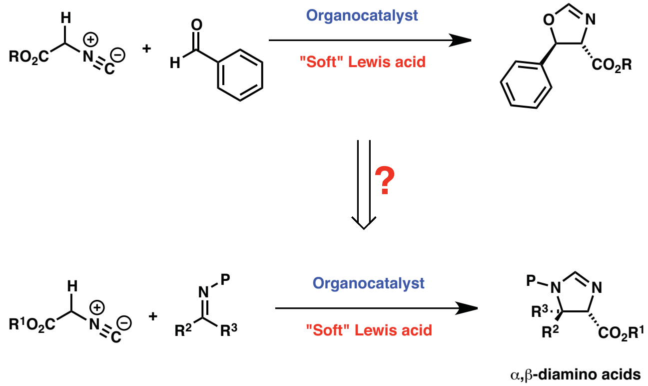


α-aminoalcohol synthesis



Sladojevich, F.; Trabocchi, A.; Guarna, A.; Dixon, D. J. *J. Am. Chem. Soc.* 2011, *133*, 1710

Extension to the Catalytic Asymmetric Isocyanoacetate Ketimine Mannich Reaction



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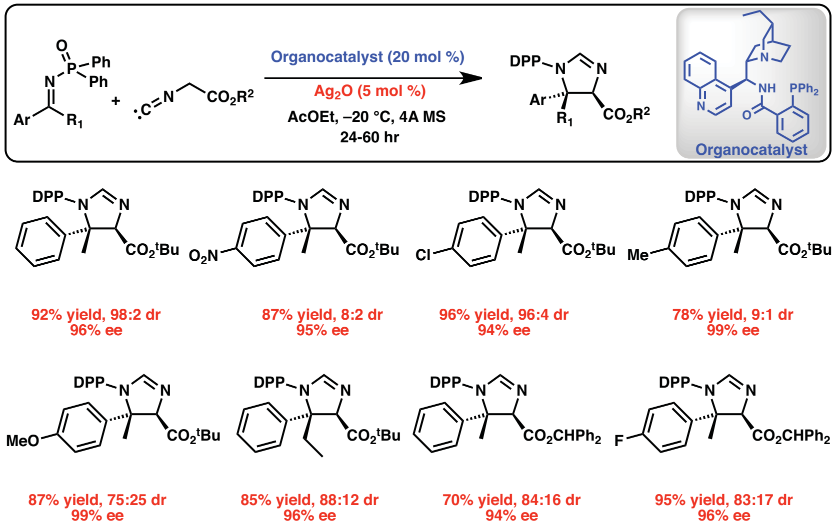
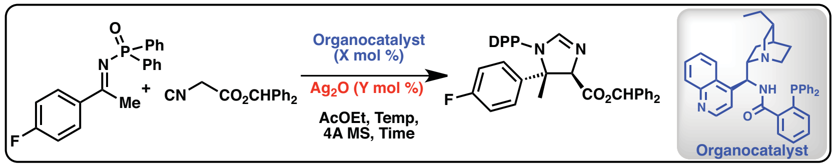
Scope of the Catalytic Asymmetric Isocyanoacetate Mannich Reaction



I. Ortín and D. J. Dixon, *Angew. Chemie. Int. Ed.* 2014, *53*, 3462-3465

Loading Studies in the Catalytic Isocyanoacetate Mannich Reaction

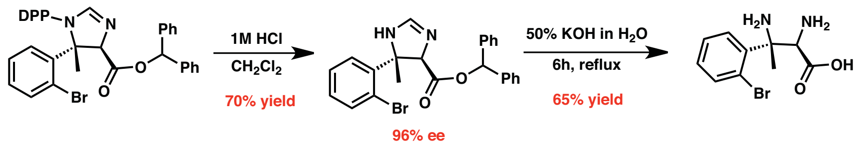


entry	X	Y	T (ºC)	Time (h)	Yield (%)	Dr[a]	Ee [b]
1	10	2.5	-20	60	87	94:6	96
2	5	1.25	-20	120	78	93:7	96
3	1	0.25	-20	160	77	92:8	95
4	1	0.25	0	60	58	87:13	94

I. Ortín and D. J. Dixon, *Angew. Chemie. Int. Ed.* 2014, 53, 3462-3465

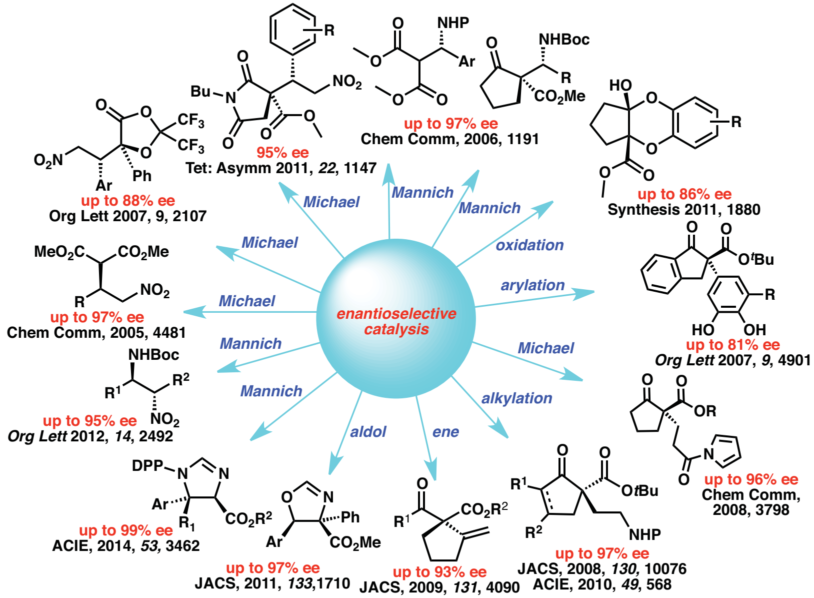
Synthetic Utility of the Isocyanoacetate Mannich Reaction

Mild DPP removal and hydrolysis of imidazoline

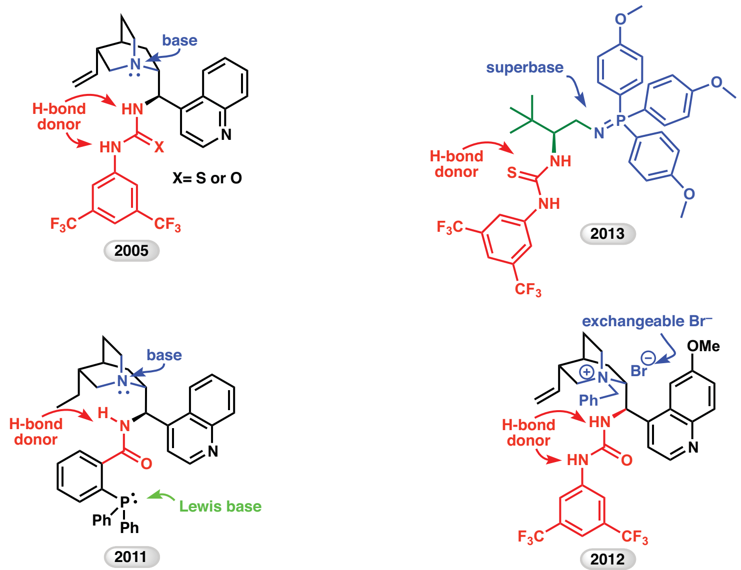


I. Ortín and D. J. Dixon, *Angew. Chemie. Int. Ed.* 2014, 53, 3462-3465

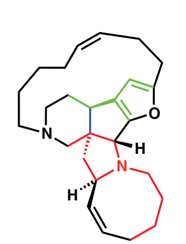
Newly Developed Catalytic Asymmetric Methodologies



Multifunctional Catalysts Developed in the Dixon Group



Nakadomarin A - Structure and Biological Activity

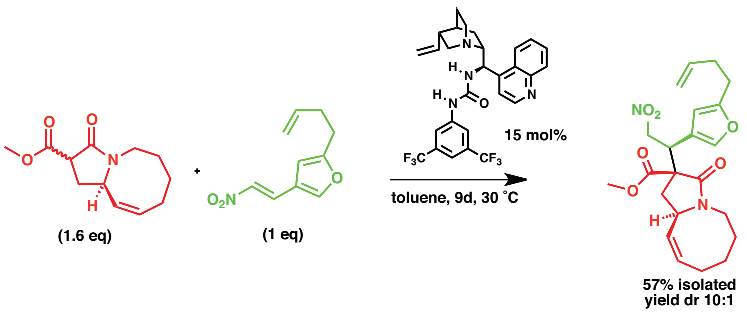


Nakadomarin A

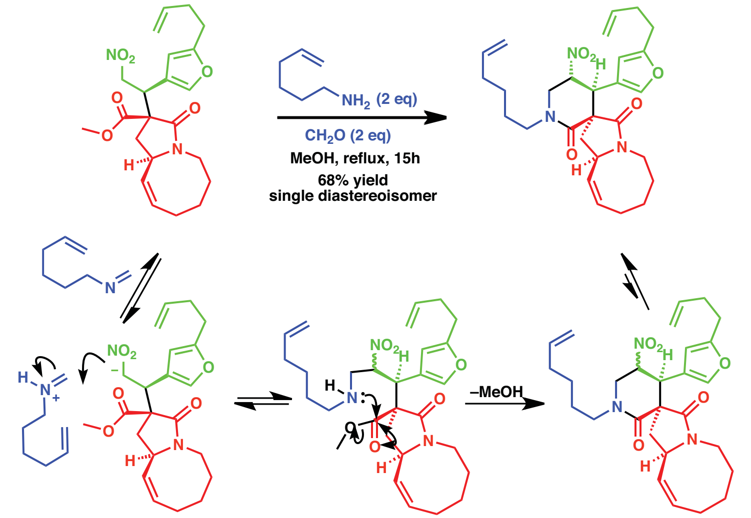
Structure:
Hexacyclic alkaloid, consisting of an 8/5/5/5/15/6 ring system
4 stereogenic carbons

Biology:
Found to be cytotoxic (murine lymphoma L1210, IC50 1.3 μg/ml)
Inhibits cyclin dependent kinase 4 (CDK4) (IC50 9.9 μg/ml)
Also antifungal and antibacterial (MIC 23 and11 μg/ml respectively)

Diastereoselective Michael Addition of 8,5-Bicyclic Pronucleophile to 2-Butenyl-Substituted Furanyl Nitro Olefin

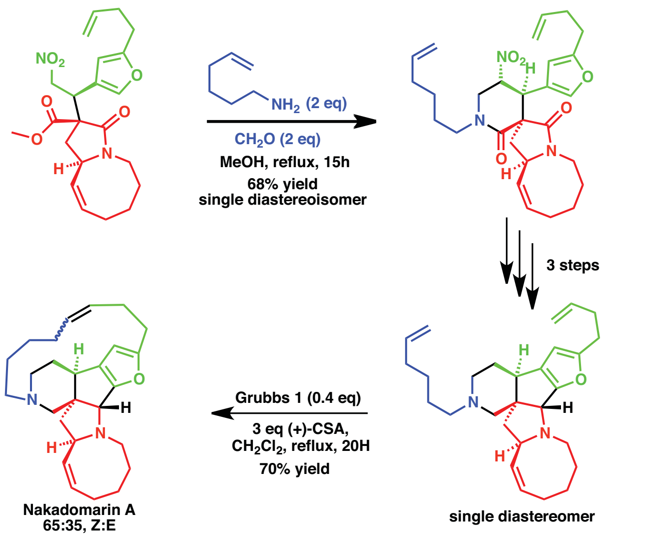


Development of a Nitro Mannich / Lactamisation Cascade to the A Ring



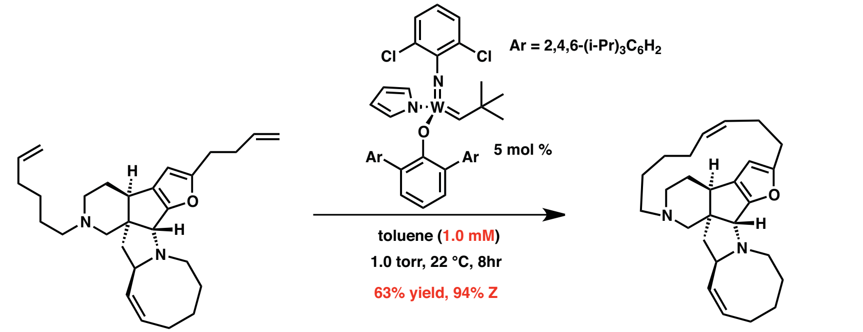
Early studies: a) Muhlstadt, M; Schultze, B. *J. Prakt. Chemie.* 1975, *317*, 919-925. b) Bhagwatheeswaran, H.; Guar, S. P.; Jain, P.C. *Synthesis*, 1976, 615. Recent developments: Jakubec, P.; Helliwell, M.; Dixon, D. J. *Org. Lett.*, 2008, *10*, 4267 and S. M.-C. Pelletier, P. C. Ray and D. J. Dixon, *Org. Lett.* 2009, *11*, 4512

Z-Selective Ring Closing Metathesis



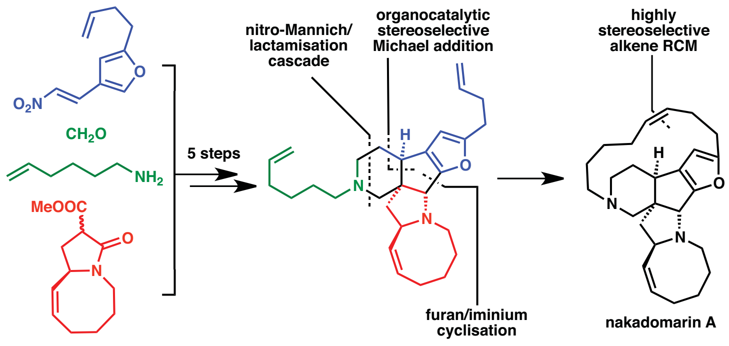
P. Jakubec, D. M. Cockfield, D. J. Dixon *J. Am. Chem. Soc.*, 2009, *131*, 16632

Route 2 Revisited: Z-Selective Catalyst Control in the Macrocyclic Alkene RCM



M. Yu, C. Wang, A. F. Kyle, P. Jakubec, D. J. Dixon, R. R. Schrock, A. H. Hoveyda, *Nature*, 2011, *479*, 88-93

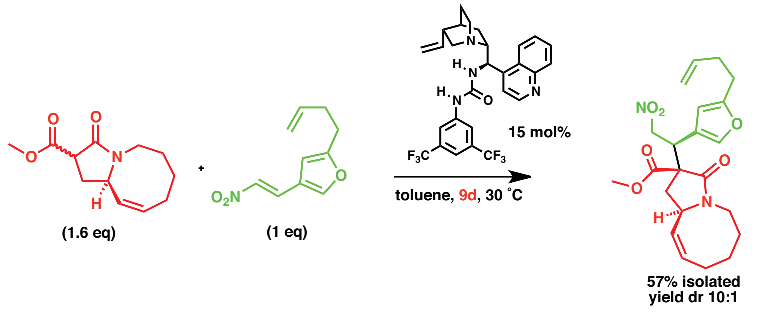
Total Synthesis of Nakadomarin A



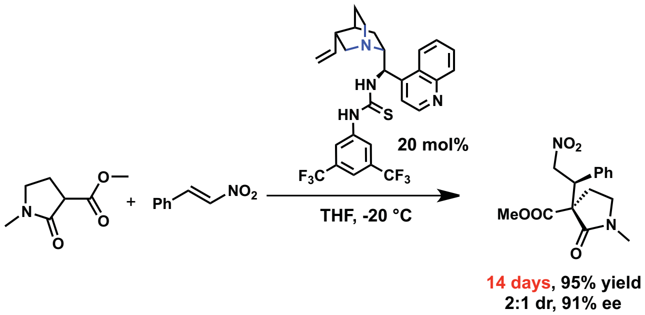
longest linear sequence: 12 steps
total step count: 16

a) Jakubec, P.; Cockfield, D. M.; Dixon D. J. *J. Am. Chem. Soc.* 2009, *131*, 16632.
b) Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* 2011, *479*, 88.

Diastereoselective Michael Addition of 8,5-Bicyclic Pronucleophile to 2-Butenyl-Substituted Furanyl Nitro Olefin

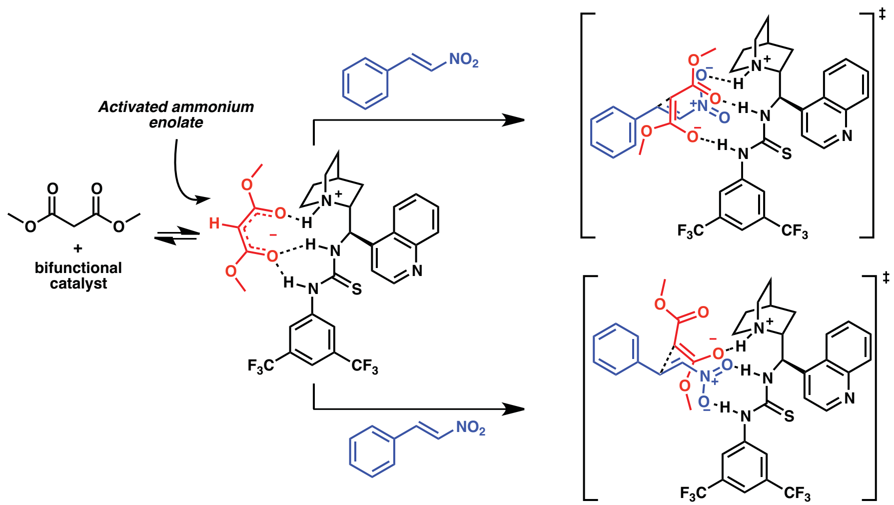


Limitations of Tertiary Amine Bifunctional Organocatalysts



P. Jakubec, M. Heliwell, D. J. Dixon, *Org. Lett.* 2008, *10*, 4267-4270

Possible Explanation for Enantiocontrol in Michael Addition Reaction



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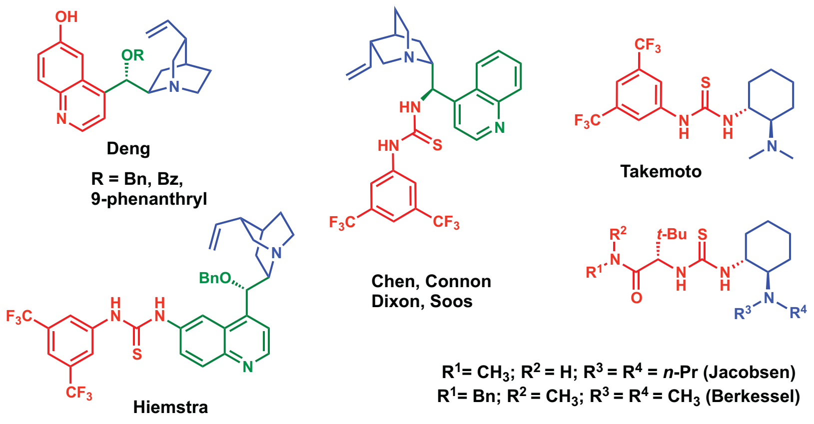
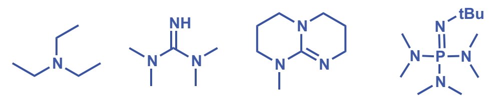
A. Hamza et al *J. Am. Chem. Soc.* 2006, 128, 13151

Common Bifunctional Bronsted basic / H-bond Donor Organocatalysts



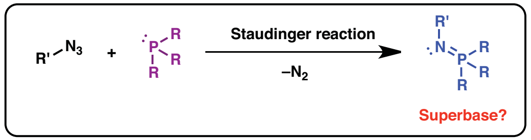
Nitro-Mannich Reaction of Nitromethane to DPP-Ketimines

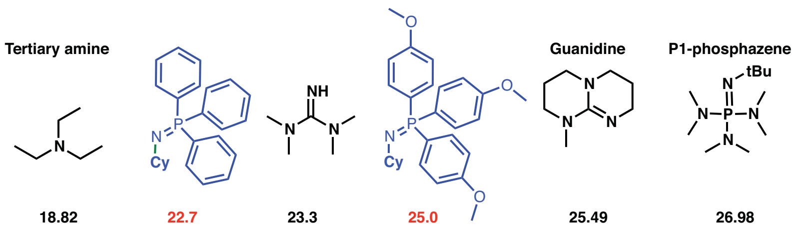
Tertiary amine	Guanidine		P1-phosphazene
No reaction	14 h, 91%	15 h, 90%	8 h, 89%
	TMG	MTBD	*t*-Bu-P1



N. K. Pahadi, H. Ube, M. Terada, *Tetrahedron. Lett.* 2007, *48*, 8700-8703

Organic Superbases

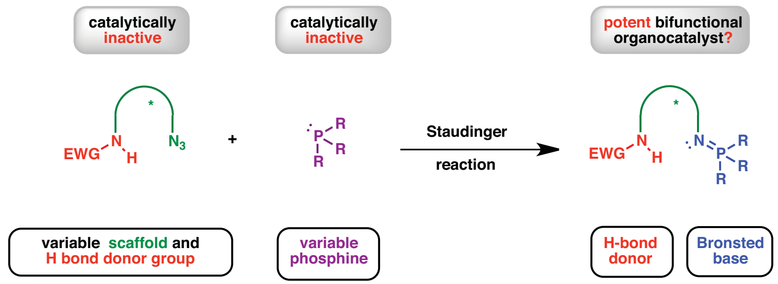




18.82	22.7	23.3	25.0	25.49	26.98
pK_{BH+} (CH_3CN)		TMG		MTBD	*t*-Bu-P1

Ishikawa, T. Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts (Wiley, 2009).

Design of New Class of Superbase Bifunctional Bronsted Basic / H-bond Donor Organocatalysts



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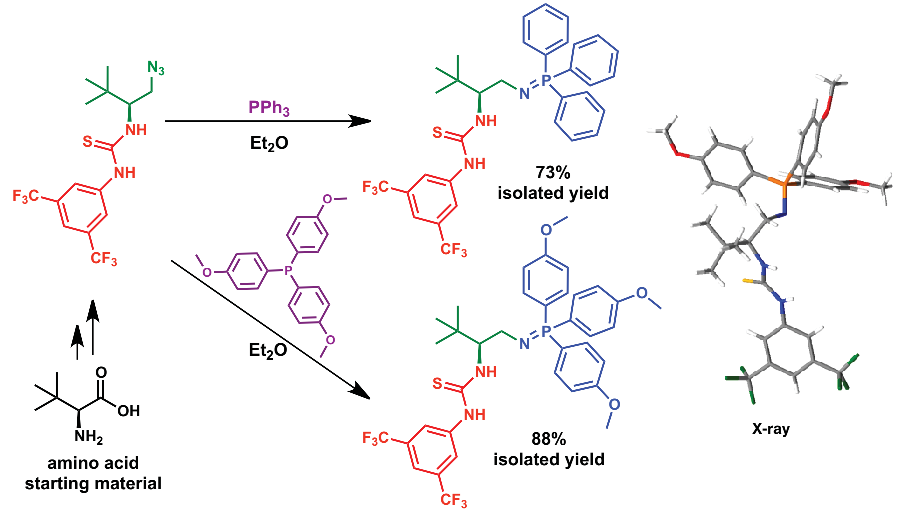
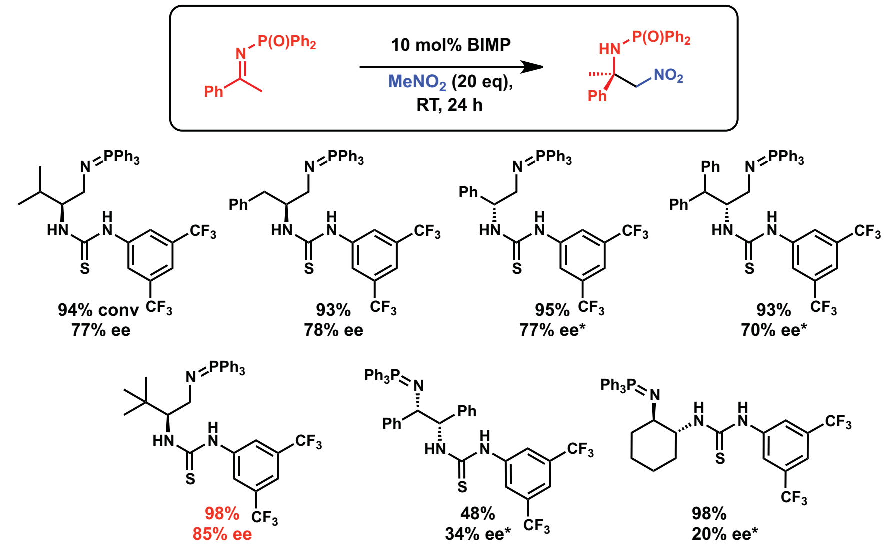
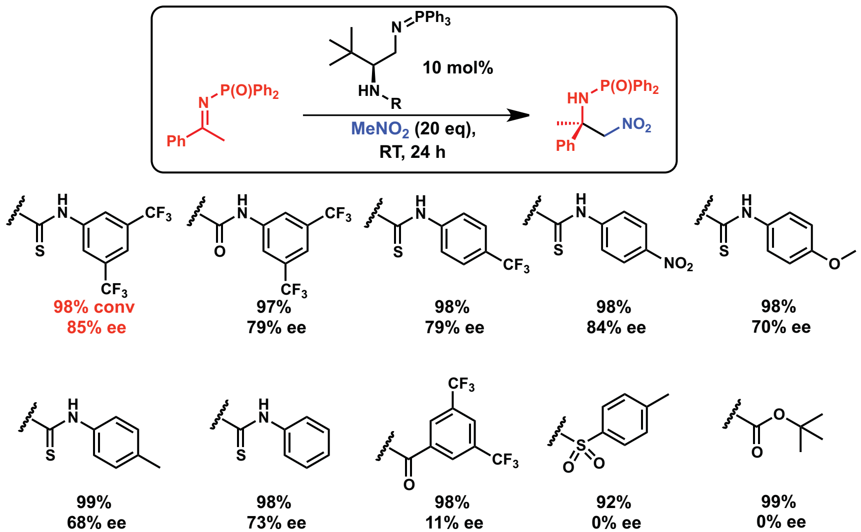
Synthesis of New Superbase Bifunctional Iminophosphorane (BIMP) Organocatalysts



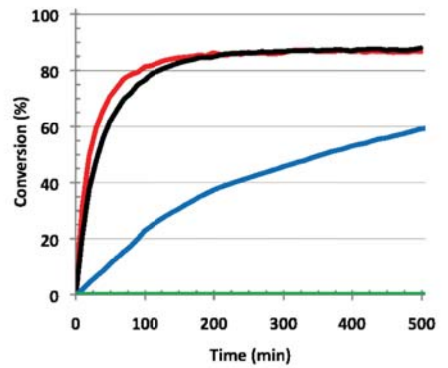
Catalyst Scaffold Screen

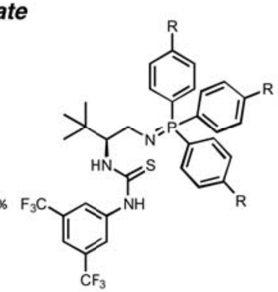


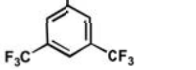
H-Bond Donor Screen



Effect of Basicity on Reaction Rate

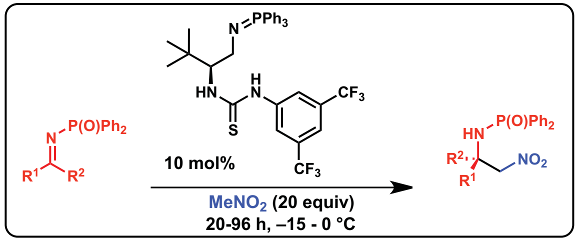


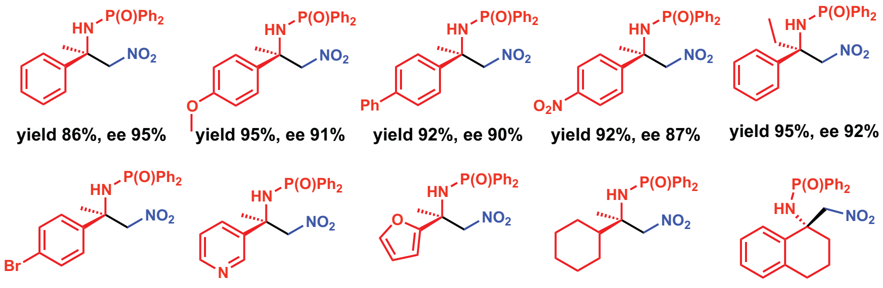




^{1}H NMR kinetic experiments performed on 0.161 mmol of ketimine, 20 eq $MeNO_2$ and 10 mol% catalyst in THF-d[8].

Scope of the BIMP Catalysed Nitro-Mannich Reaction to Ketimines





yield 86%, ee 95% | yield 95%, ee 91% | yield 92%, ee 90% | yield 92%, ee 87% | yield 95%, ee 92%

yield 84%, ee 90% | yield 97%, ee 82% | yield 97%, ee 84% | yield 71%, ee 78% | yield 40%, ee 92%

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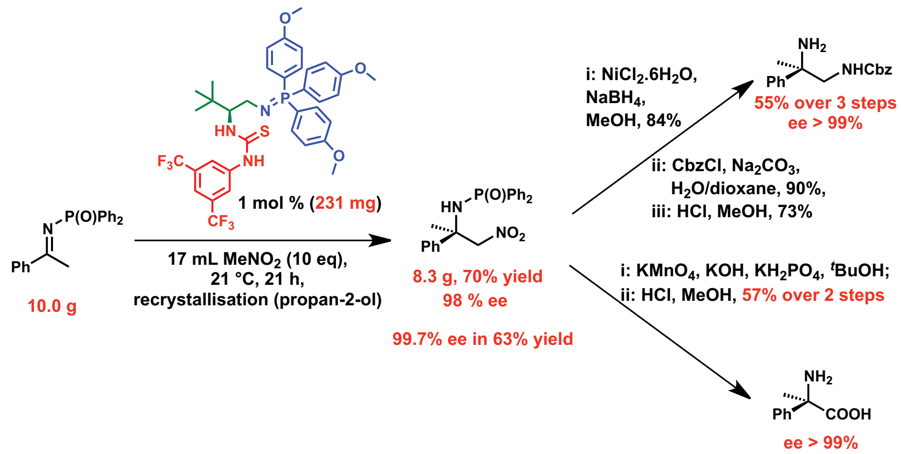
Preparative Scale of Nitro-Mannich Reaction



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Prof Amir Hoveyda
Dr Rob Paton
Kelvin Jackson

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