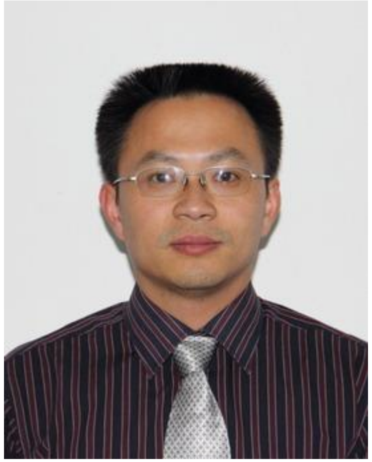
Catalytic Asymmetric Cascade Vinylogous Mukaiyama 1,6-Michael/Michael Addition of 2-Silyloxyfurans with Azoalkenes

Reporter: Bo Wu
Checker: Xiang Gao
Date: 2015/09/15

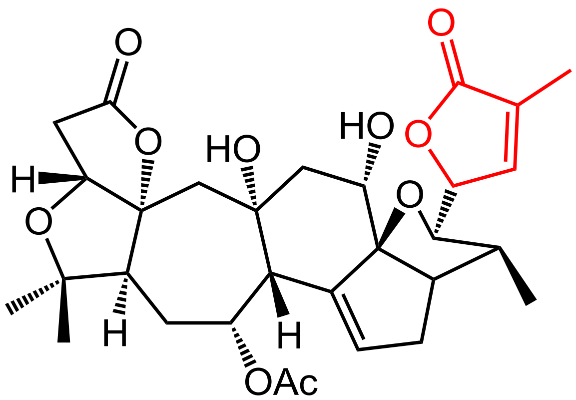


Wang, C.-J. *et al.*
J. Am. Chem. Soc. **2015**, *137*, 10124.

Chun-Jiang Wang
Wuhan University

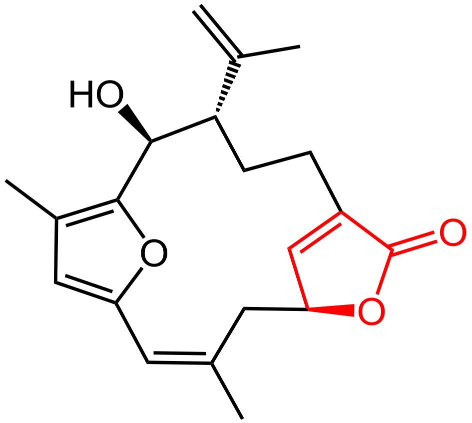
Contents

Introduction



Nortriterpednoid

Schisandra Chinensis
五味子

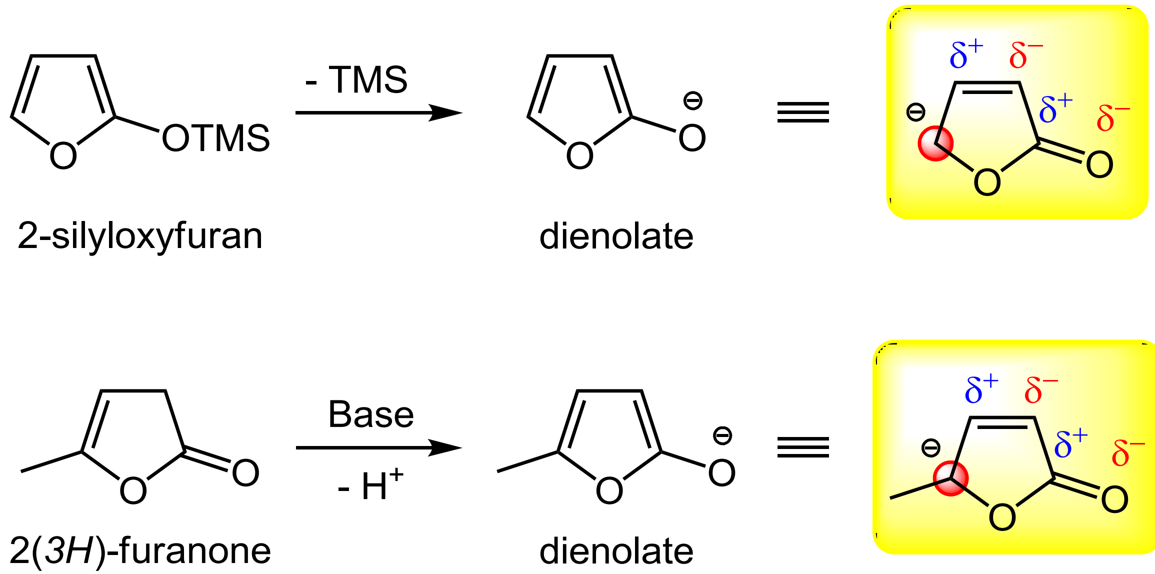


Bipinnatin J

Antillogorgia Bipinnata

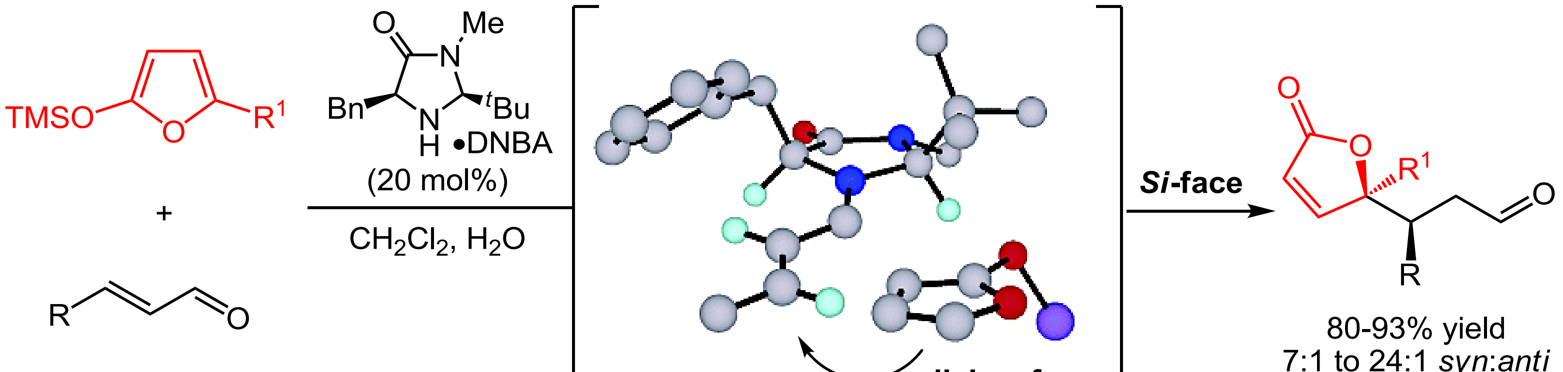
Introduction

Two approaches to generate the γ-anion of 2(*5H*)-furanone



Asymmetric Vinylogous Mukaiyama−Michael Addition of 2-Silyloxyfurans with α,β-Unsaturated Aldehydes

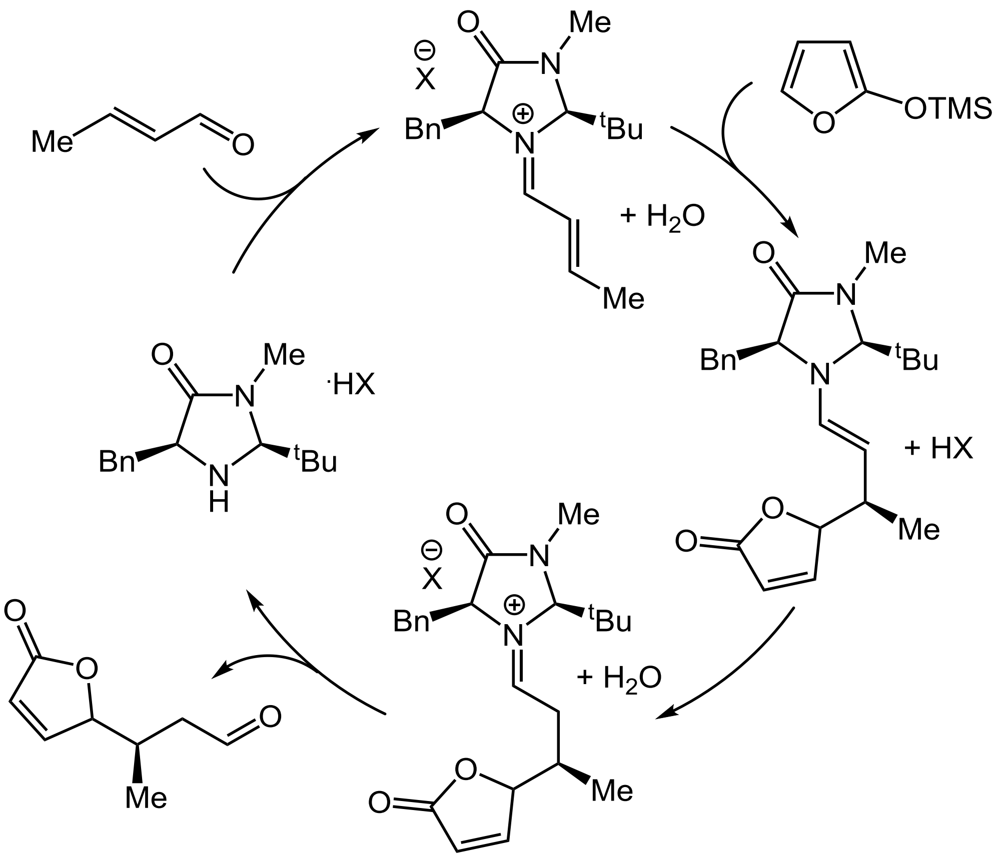
Iminium catalytic system



R = Me, ^{i}Pr, CH_2OBz, CO_2Me
R^1 = Me, H, CO_2Me

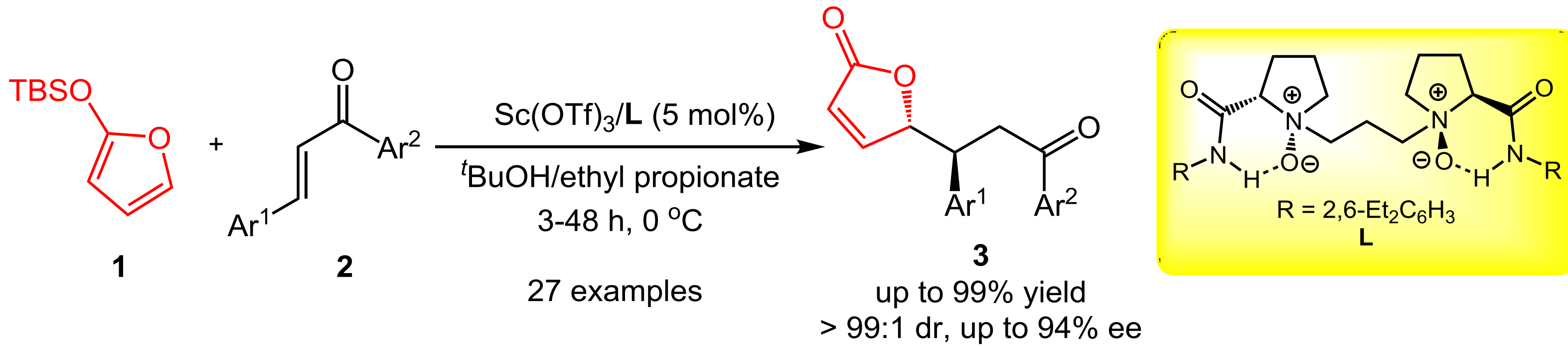
MacMillan, D. W. C. *et al. J. Am. Chem. Soc.* **2003**, *125*, 1192.

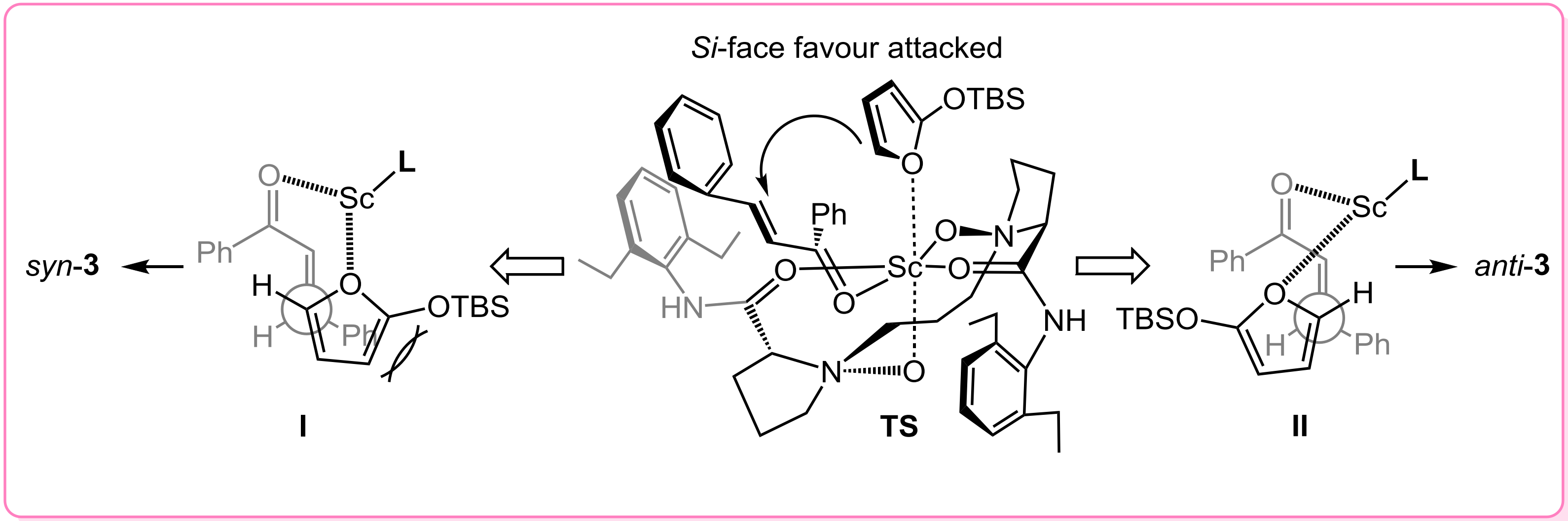
Plausible Reaction Mechanism



MacMillan, D. W. C. *et al. J. Am. Chem. Soc.* **2005**, *127*, 15051.

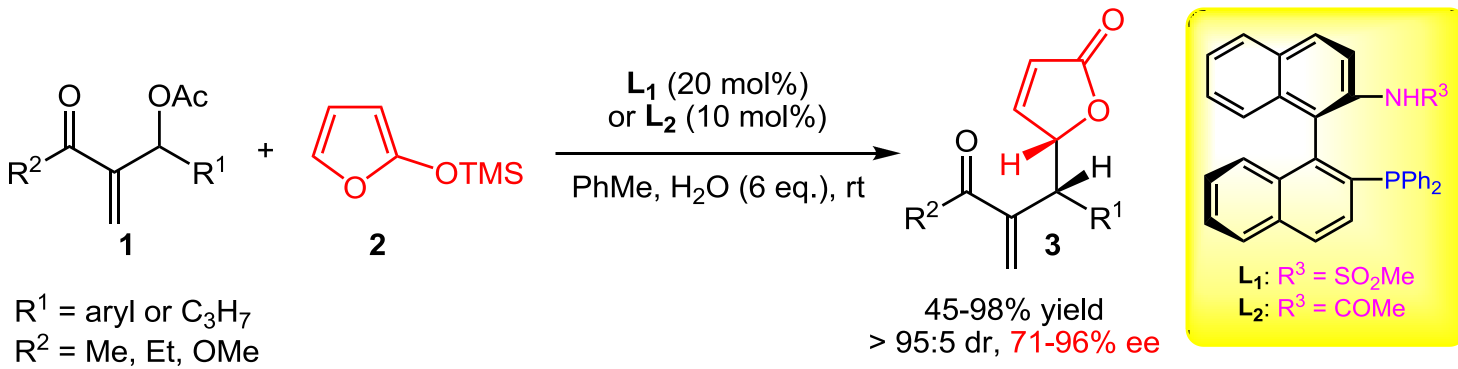
Asymmetric Vinylogous Mukaiyama–Michael Addition of 2-Silyloxyfurans with α,β-Unsaturated Ketones

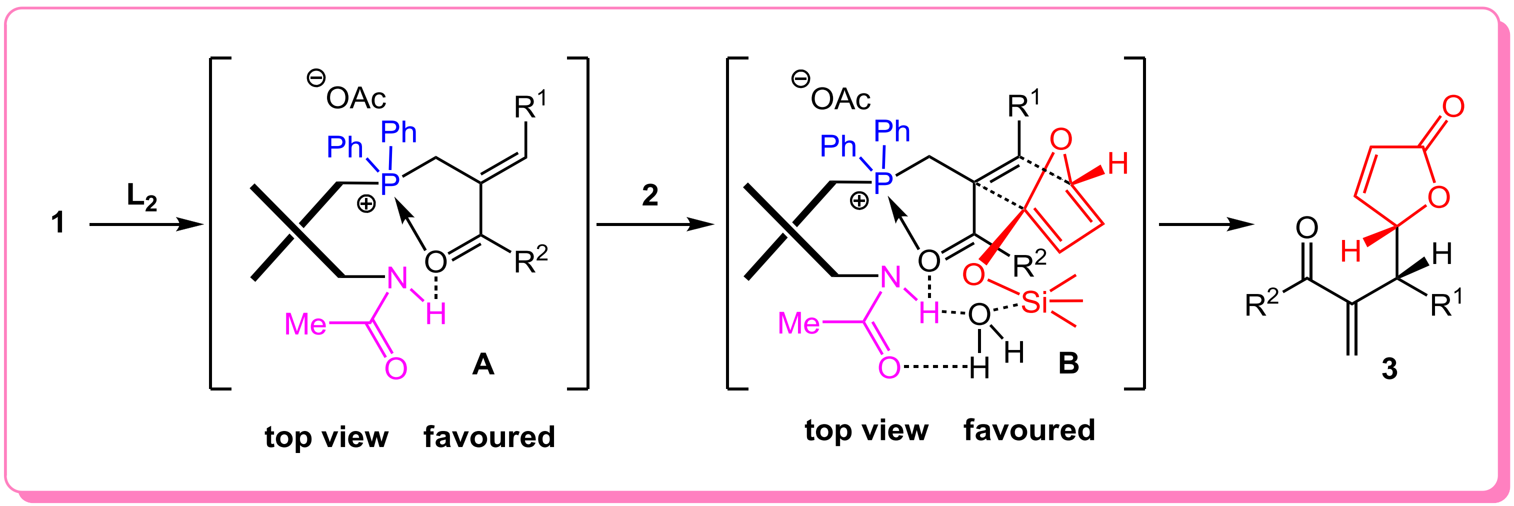




Feng, X. *et al.* *Org. Biomol. Chem.* **2011**, *9*, 5748.

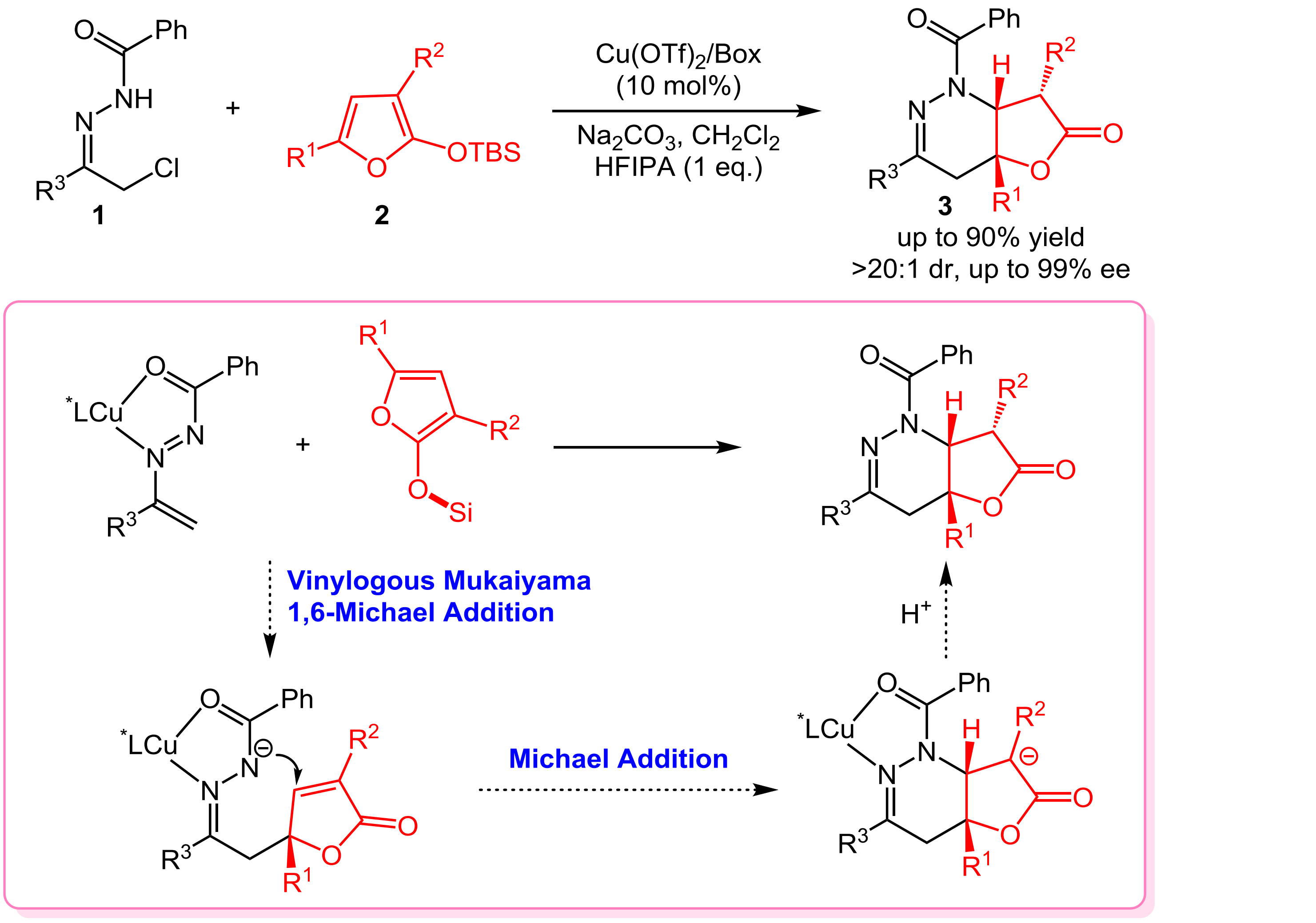
Asymmetric Vinylogous Mukaiyama−Michael Addition of 2-Silyloxyfurans with Morita-Baylis-Hillman Acetates





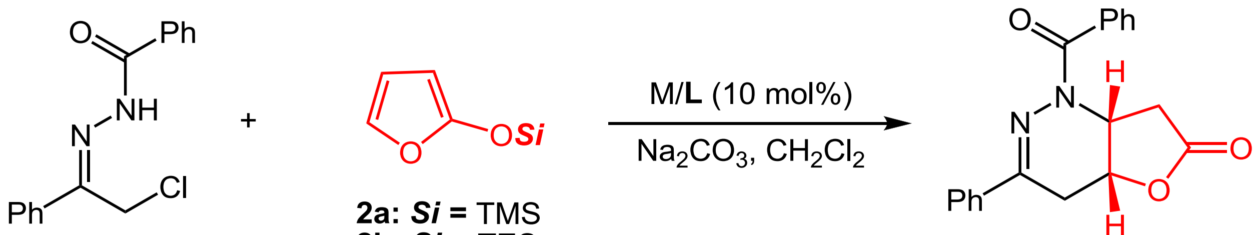
Shi, M. *et al. J. Am. Chem. Soc.* **2008**, *130*, 7207.

Asymmetric Vinylogous Mukaiyama−Michael/Michael Addition of 2-Silyloxyfurans with Azoalkenes



Wang, C.-J. *et al. J. Am. Chem. Soc.* **2015**, *137*, 10124.

Optimization of the Reaction Conditions

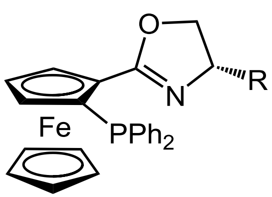


1a

2a: ***Si*** = TMS
2b: ***Si*** = TES
2c: ***Si*** = TBS

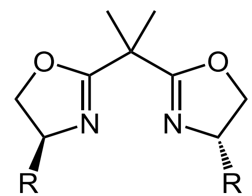
3a, >20:1 dr

Entry	2	[M]	L	Additive	T (^oC)	Yield (%)	Ee (%)
1	**2a**	--	--	--	rt	45	--
2	**2a**	$CuBF_4$	$\mathbf{L_1}$	--	rt	50	64
3	**2a**	$Cu(OTf)_2$	$\mathbf{L_1}$	--	rt	55	75
4	**2a**	$Cu(OTf)_2$	$\mathbf{L_1}$	IPA	rt	69	75
5	**2a**	$Cu(OTf)_2$	$\mathbf{L_1}$	HFIPA	rt	85	75
6	**2a**	$Cu(OTf)_2$	$\mathbf{L_1}$	H_2O	rt	71	73
7	**2a**	$Cu(OTf)_2$	$\mathbf{L_2}$	HFIPA	rt	78	10
8	**2a**	$Cu(OTf)_2$	$\mathbf{L_3}$	HFIPA	rt	82	15



(S,S_p)-Phosferrox

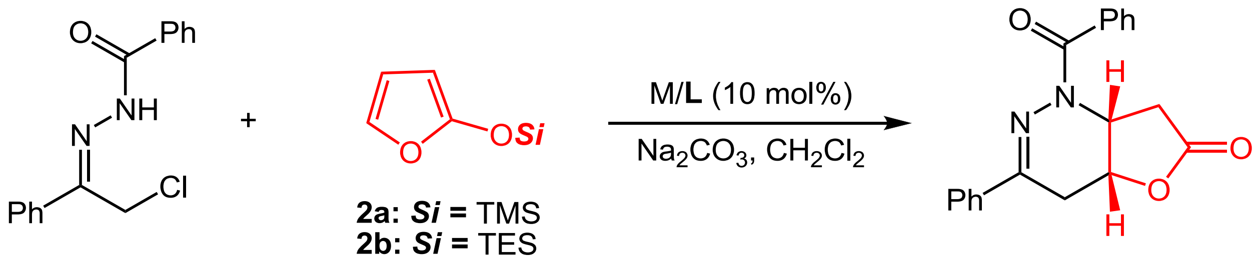
$\mathbf{L_1}$: R = ^{t}Bu
$\mathbf{L_2}$: R = ^{i}Pr
$\mathbf{L_3}$: R = Ph
$\mathbf{L_4}$: R = Bn



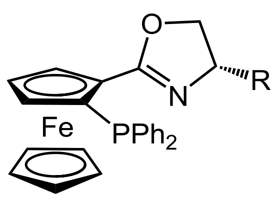
(S,S)-Bisoxazoline

$\mathbf{L_5}$: R = ^{t}Bu
$\mathbf{L_6}$: R = ^{i}Pr
$\mathbf{L_7}$: R = Ph
$\mathbf{L_8}$: R = Bn

Optimization of the Reaction Conditions

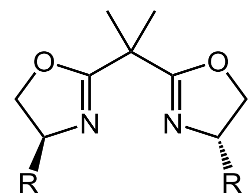


Entry	2	[M]	L	Additive	T (°C)	Yield (%)	Ee (%)
9	**2a**	$Cu(OTf)_2$	$\mathbf{L_4}$	HFIPA	rt	75	17
10	**2a**	$Cu(OTf)_2$	$\mathbf{L_5}$	HFIPA	rt	82	90
11	**2a**	$Cu(OTf)_2$	$\mathbf{L_6}$	HFIPA	rt	85	47
12	**2a**	$Cu(OTf)_2$	$\mathbf{L_7}$	HFIPA	rt	81	56
13	**2a**	$Cu(OTf)_2$	$\mathbf{L_8}$	HFIPA	rt	77	33
14	**2a**	$Cu(OTf)_2$	$\mathbf{L_5}$	HFIPA	0	87	95
15	**2b**	$Cu(OTf)_2$	$\mathbf{L_5}$	HFIPA	0	83	95
16	**2c**	$\mathbf{Cu(OTf)_2}$	$\mathbf{L_5}$	**HFIPA**	**0**	**85**	**97**



(*S*,*S*$_p$)-Phosferrox

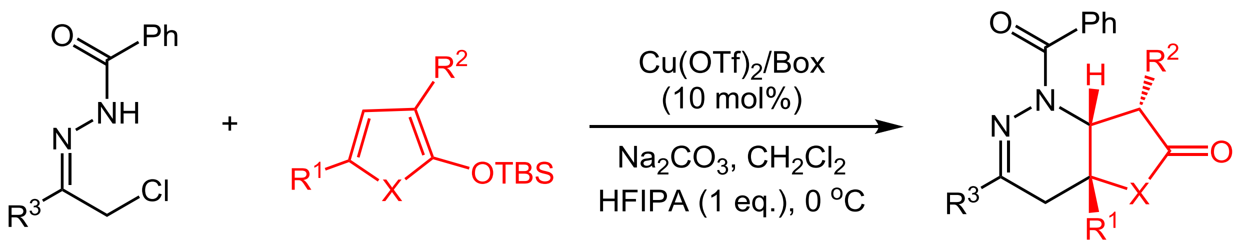
$\mathbf{L_1}$: R = ^{t}Bu
$\mathbf{L_2}$: R = ^{i}Pr
$\mathbf{L_3}$: R = Ph
$\mathbf{L_4}$: R = Bn



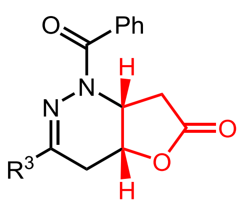
(*S*,*S*)-Bisoxazoline

$\mathbf{L_5}$: R = ^{t}Bu
$\mathbf{L_6}$: R = ^{i}Pr
$\mathbf{L_7}$: R = Ph
$\mathbf{L_8}$: R = Bn

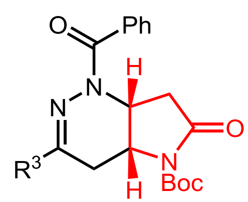
Substrate Scope



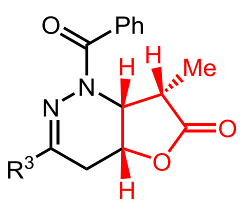
1 **2** **3** (>20:1 dr)



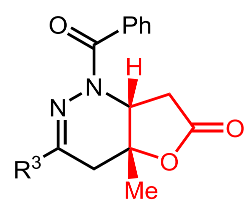
3a: R^3 = Ph, 85% yield, 97% ee
3b: R^3 = *p*-Br-C_6H_4, 86% yield, 94% ee
3c: R^3 = *p*-Me-C_6H_4, 80% yield, 96% ee
3d: R^3 = *p*-MeO-C_6H_4, 87% yield, 94% ee
3e: R^3 = *m*-Me-C_6H_4, 78% yield, 92% ee
3f: R^3 = 2-Naphthyl, 88% yield, 94% ee
3g: R^3 = PhCH=CH, 83% yield, 71% ee



3h: R^3 = Ph, 90% yield, 92% ee
3i: R^3 = *p*-Br-C_6H_4, 87% yield, 95% ee
3j: R^3 = *o*-F-C_6H_4, 82% yield, 97% ee
3k: R^3 = *p*-Me-C_6H_4, 80% yield, 98% ee

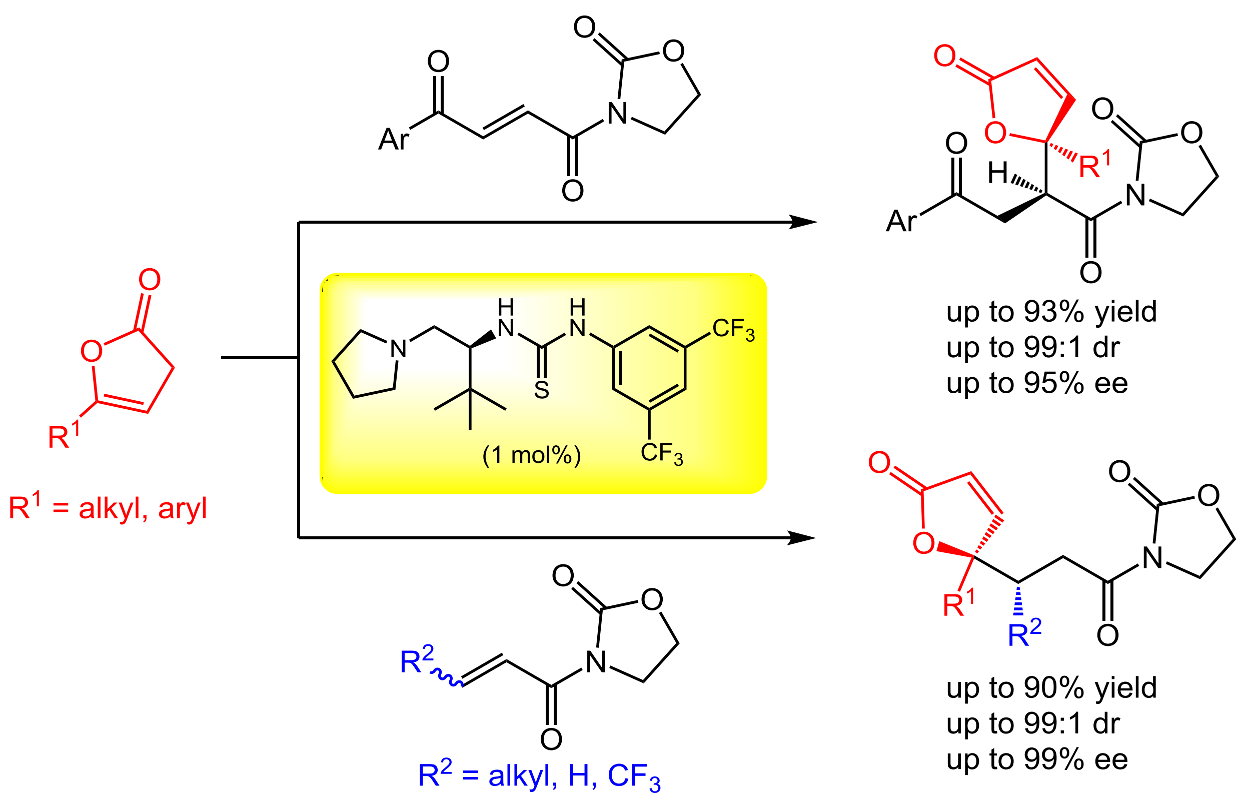


3l: R^3 = Ph, 82% yield, 97% ee
3m: R^3 = *p*-Cl-C_6H_4, 75% yield, 96% ee
3n: R^3 = *p*-CF_3-C_6H_4, 83% yield, 97% ee
3o: R^3 = *p*-Me-C_6H_4, 78% yield, 93% ee
3p: R^3 = *m*-Me-C_6H_4,75% yield, 93% ee



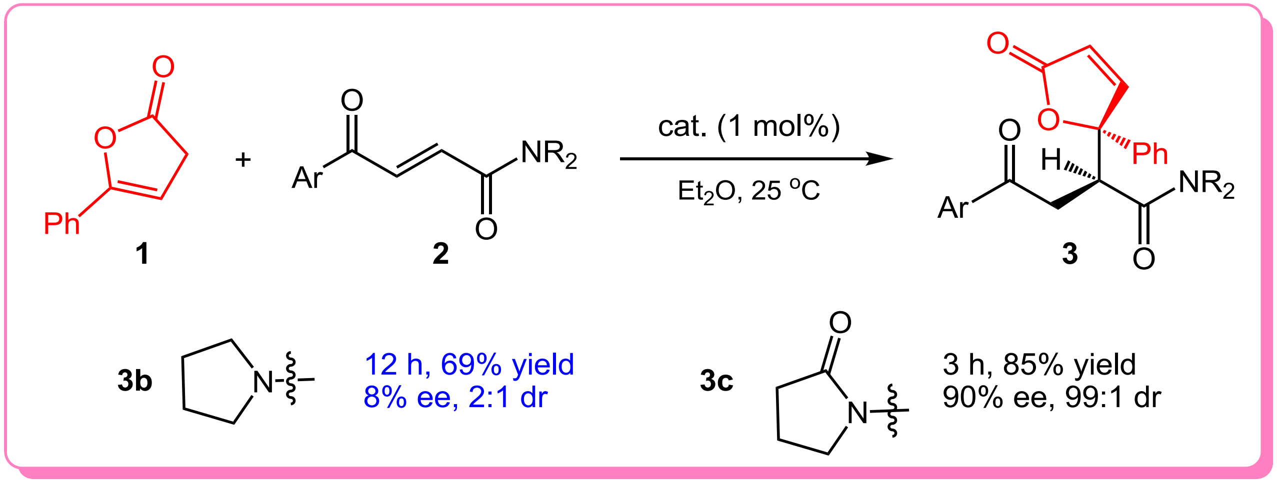
3q: R^3 = Ph, 81% yield, 97% ee
3r: R^3 = *p*-Br-C_6H_4, 86% yield, 95% ee
3s: R^3 = *p*-Cl-C_6H_4, 84% yield, 96% ee
3t: R^3 = *p*-Me-C_6H_4, 80% yield, 94% ee
3u: R^3 = *m*-Me-C_6H_4, 76% yield, 96% ee

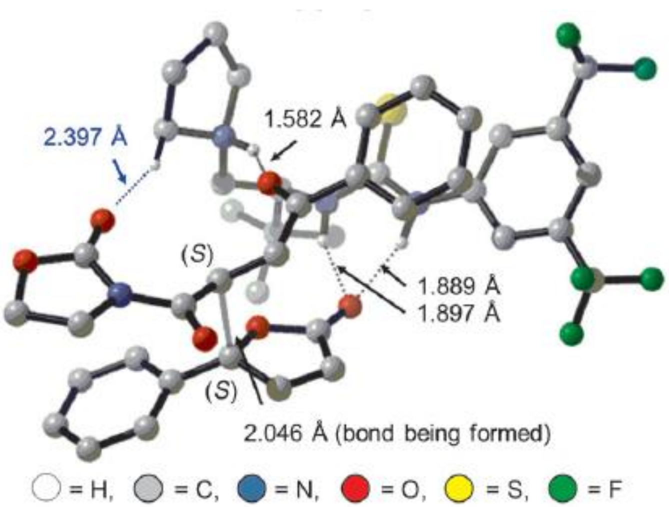
Asymmetric Vinylogous Michael Addition of Furanones with α,β-Unsaturated Ketones

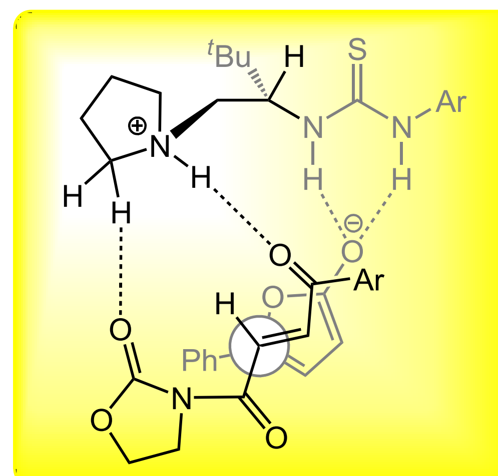


Jiang, Z. *et al. Angew. Chem. Int. Ed.* **2012**, *51,* 10069.

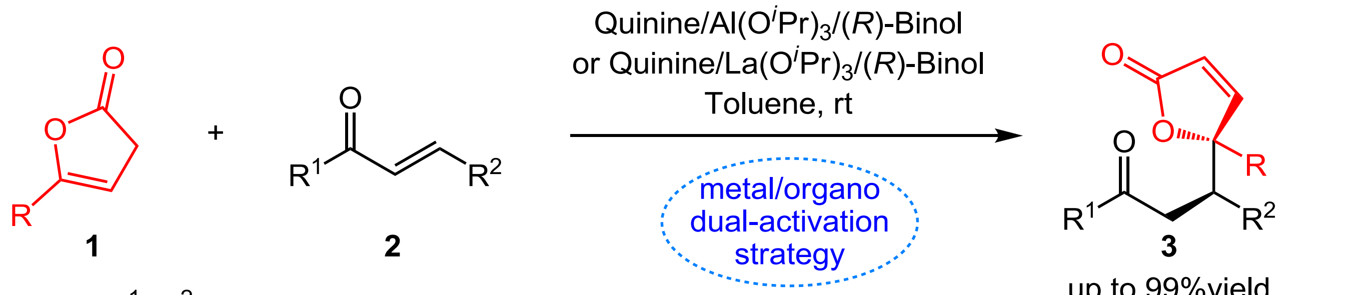
Asymmetric Vinylogous Michael Addition of Furanones with α,β-Unsaturated Ketones







Asymmetric Vinylogous Michael Addition of Furanones with α,β-Unsaturated Ketones



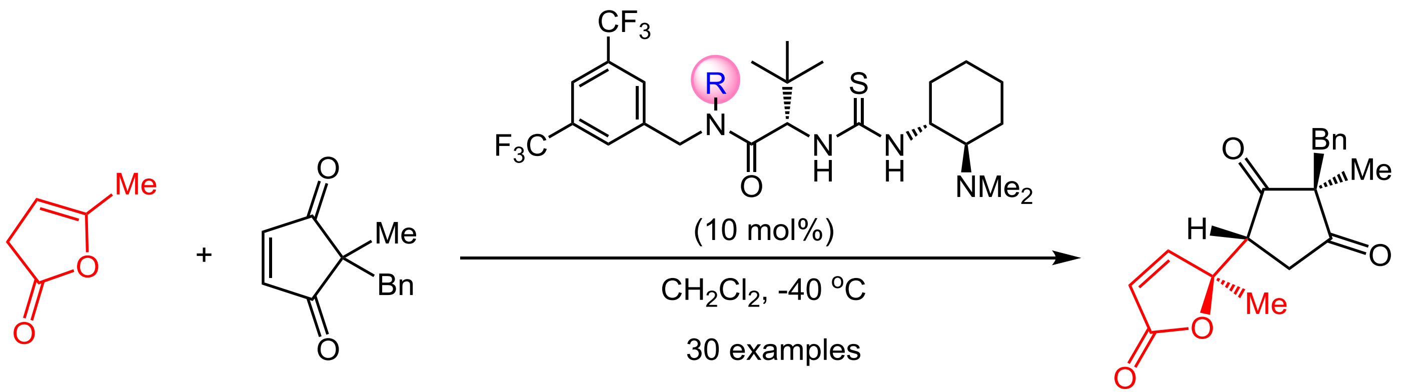
1 **2** **3**

R, R^1, R^2 = aryl, alkyl

up to 99%yield
up to >20:1 dr
up to 99% ee

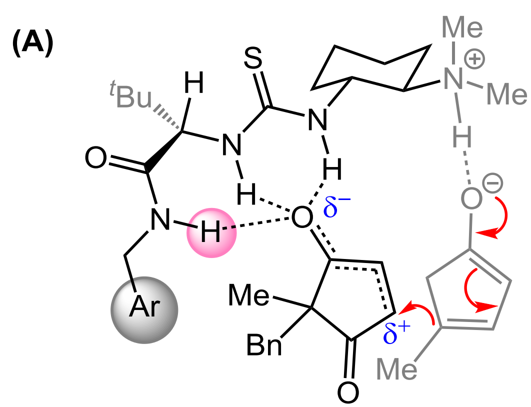
Wang, R. *et al. Chem.−Eur. J.* **2013**, *19*, 4691.

Asymmetric Vinylogous Michael Addition of Furanones with Cyclopentenediones

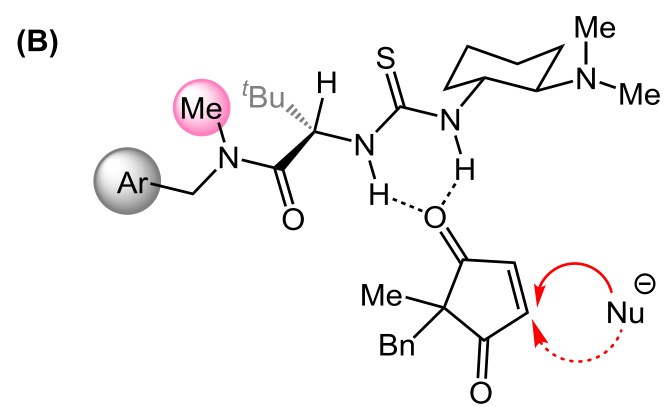


with R = Me, 17:1 dr, 50% ee

with R = H, >20:1 dr, 98% ee



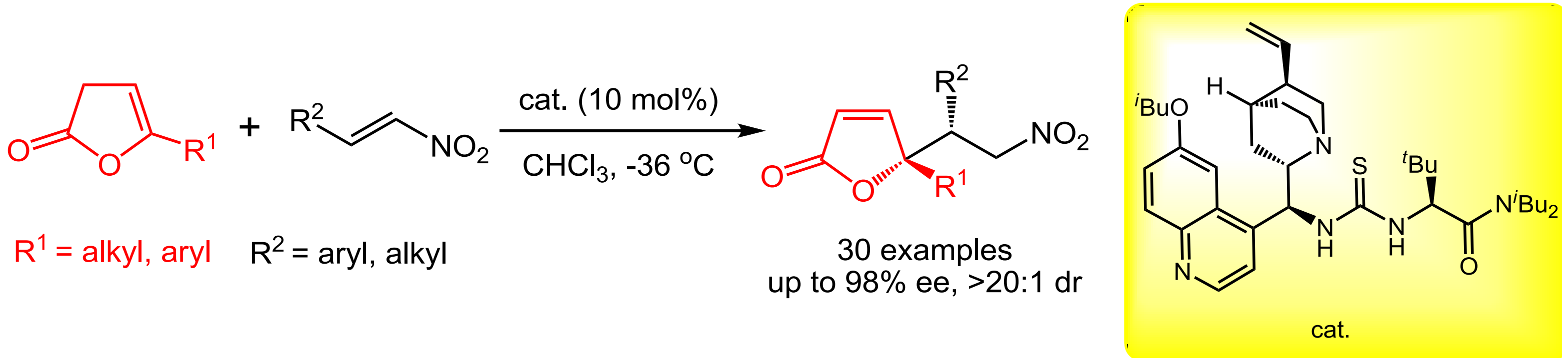
Top face approach is hindered by the bulky aryl group



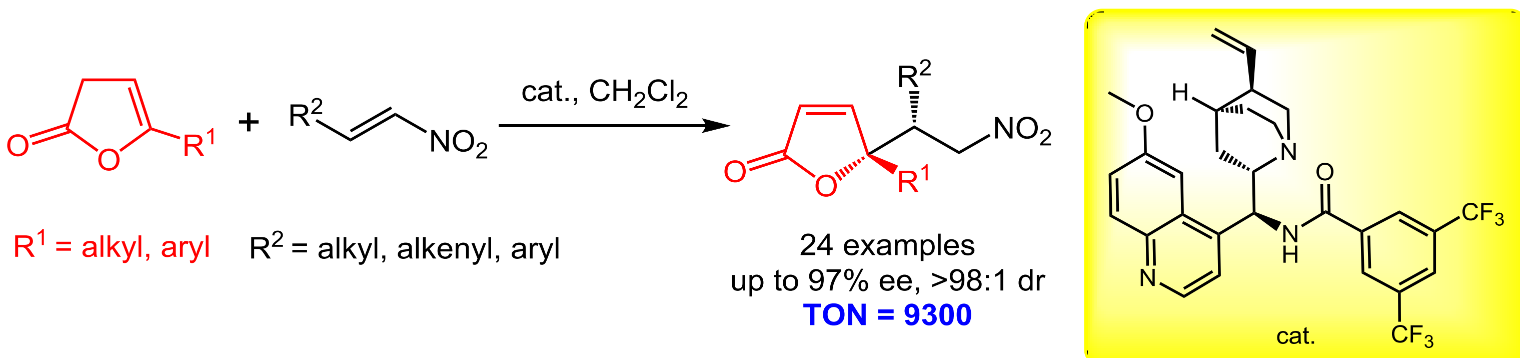
Nucelophilic approach is possible from both the olefin faces

Mukherjee, S. *et al. Chem. Sci.* **2014**, *5*, 1627.

Asymmetric Vinylogous Michael Addition of Furanones with Nitroalkenes



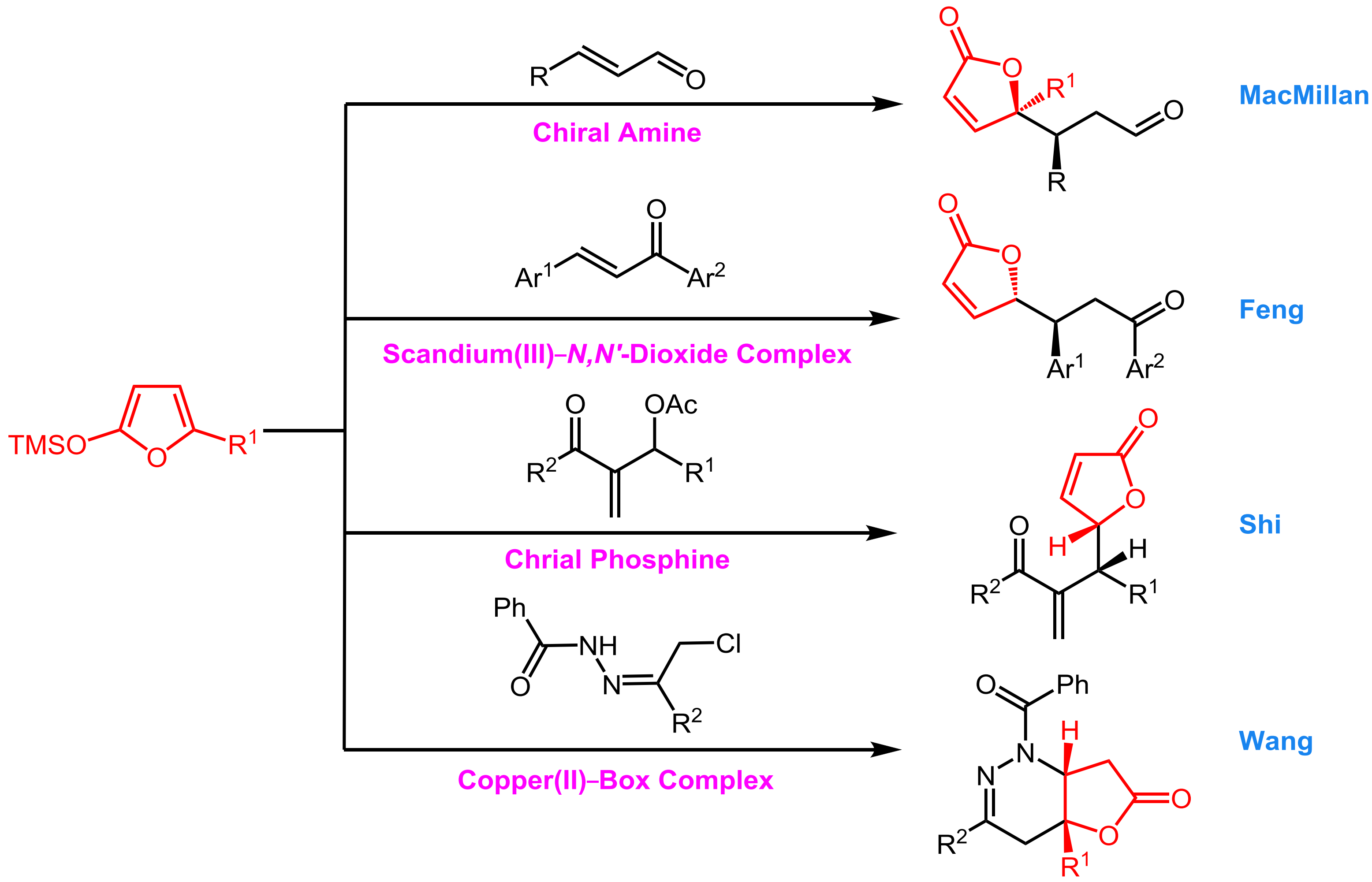
Mukherjee, S. *et al. Chem. Commun.* **2012**, *48*, 5193.



Hatanaka, Y. *et al. Org. Lett.* **2015**, *17*, 3026.

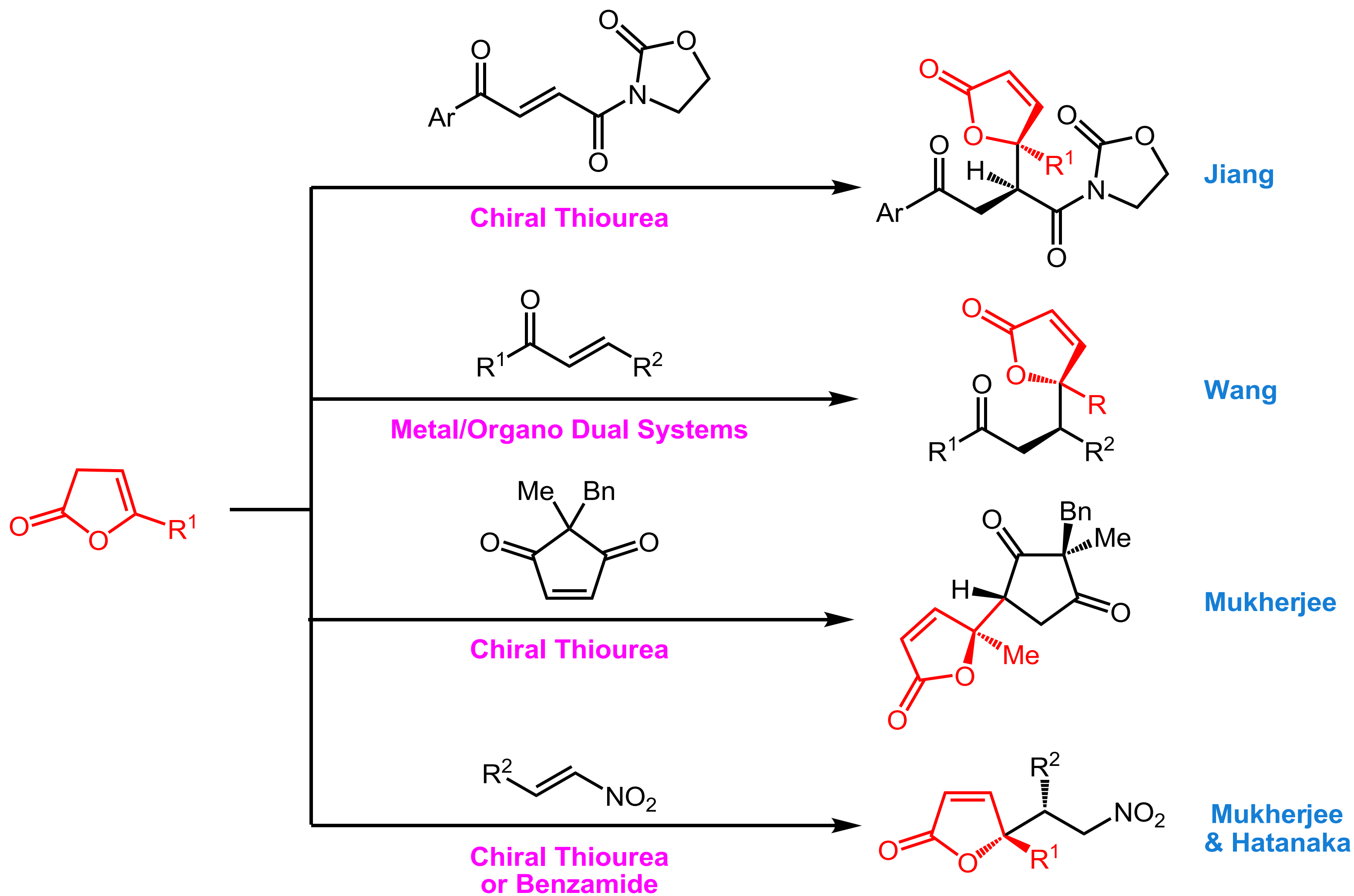
Summary

Asymmetric Vinylogous Mukaiyama Michael Addition of 2-Silyloxyfurans



Summary

Asymmetric Vinylogous Michael Addition of Furanones



Development of a practical methodology for the construction of enantioenriched γ-butyrolactones and γ-butenolides represents an important research topic in organic synthesis because of their prevalence as the core structures in a number of biologically interesting natural and synthetic compounds. In this context, elaboration of 2-silyloxyfurans as the readily accessible nucleophilic synthons of the γ-anion of 2(*5H*)-furanone by means of vinylogous Mukaiyama−aldol, Mukaiyama−Michael, and Mukaiyama−Mannich-type additions has been, thus far, the well-established method for electrophilic attack at the C5 position. Considering that an electron-deficient unsaturated lactone moiety in butenolide is a potential Michael acceptor easily trapped by a built-in nucleophile group, we envision that 2-silyloxyfurans could be utilized as dipole-type synthons in the cascade reaction by sequentially reacting as a nucleophile and an electrophile, giving rise to fused butyrolactone.

This cascade approach involves the nucleophilicity on C5 of the 2-silyloxyfuran and the electrophilicity of C4 of the formed butenolide. Surprisingly, however, this kind of asymmetric cascade annulation with 2-silyloxyfurans has received much less attention despite numerous examples of butyrolactone stereogenicity found in natural alkaloids and biologically active compounds.

In conclusion, we have successfully developed an unprecedented Cu(II)-catalyzed asymmetric cascade vinylogous Mukaiyama 1,6-Michael/Michael addition of 2-silyloxyfurans with in situ formed azoalkenes. The key feature of the current methodology is that furan-based dienoxysilanes could be utilized as efficient dipole-type synthons. This cascade annulation process provides a straightforward approach to a variety of biologically important and structurally complicated fused butyrolactones in good yield with high regioselectivity and excellent stereoselectivity. The studies of carbon isotope effects measured by ^{13}C NMR indicated a stepwise mechanism for this annulation. Further efforts are currently underway to understand the origin of stereoselectivity control and application of this methodology in organic synthesis.