Literature Report

Enantioselective Hydrogenative Desymmetrization

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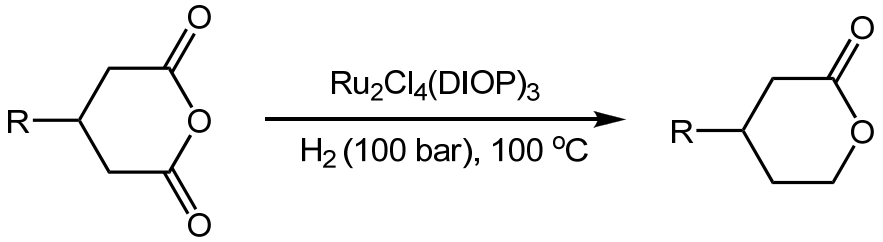
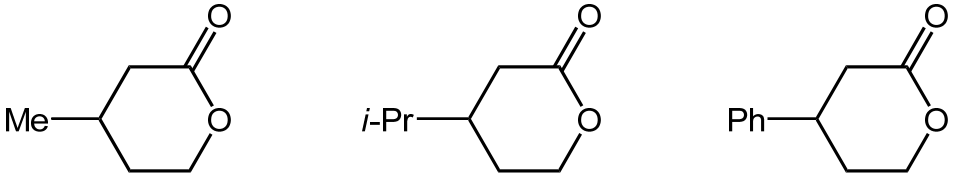
2015-03-24

Desymmetrization:

Desymmetrization in stereochemistry is the modification of a molecule that results in the loss of one or more symmetrical elements. A common application of this class of reactions involves the introduction of chirality. Typical substrates are **epoxides**, **diols**, **dienes**, and **carboxylic acid anhydrides.**

The Substrate Scope:

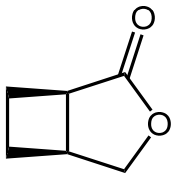




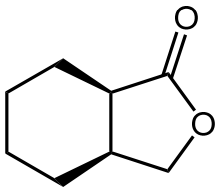
14% ee

5% ee

20% ee



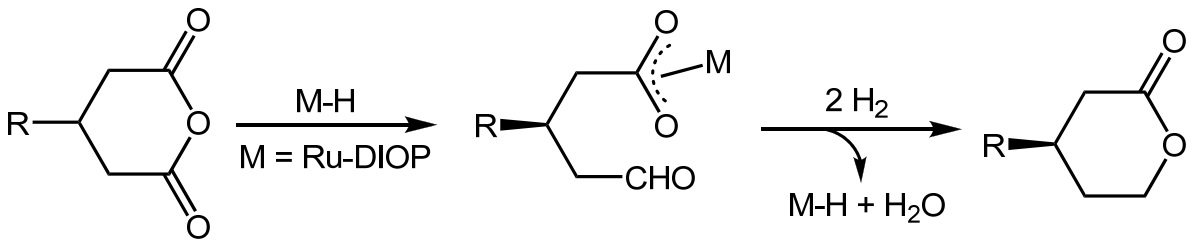
14% ee



5% ee

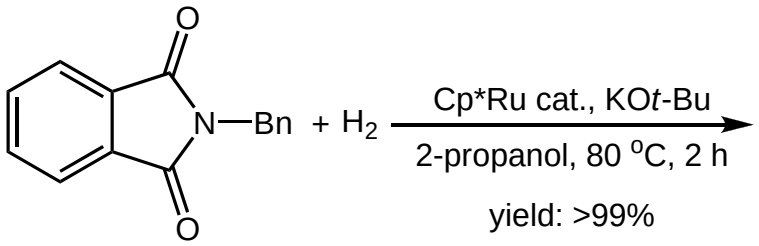
Ikariya, T. *Tetrahedron Lett*. **1981**, *22*, 4297

Plausible Reaction Process

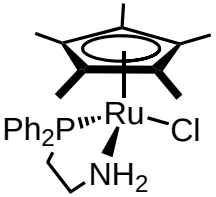


Ikariya, T. *Tetrahedron Lett*. **1981**, *22*, 4297

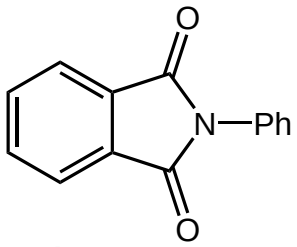
The Substrate Scope:



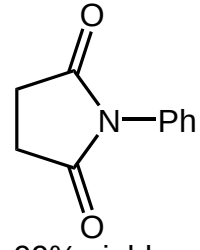
3a **4a**



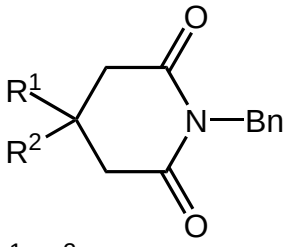
1



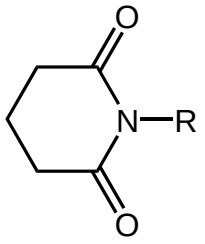
3b: >99% yield



3c: >99% yield

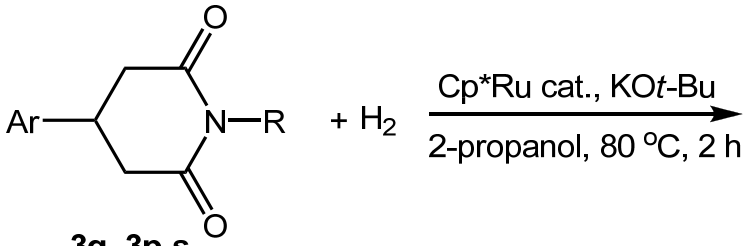


3d: R^1, R^2 = H; >99% yield
3e: R^1, R^2 = Me, H; >99% yield
3f: R^1, R^2 = Ph, H; >99% yield
3g: R^1, R^2 = 4-FC_6H_4, H; >99% yield
3h: R^1, R^2 = Me; >99% yield
3i: R^1, R^2 = Me, Et; 49% yield



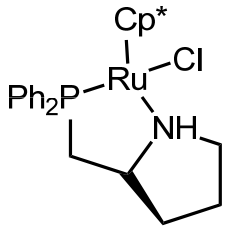
3j: R = Ph; 88% yield
3k: R = 4-$MeOC_6H_4$; >99% yield
3l: R = 4-$NO_2C_6H_4$; >99% yield

The Substrate Scope:

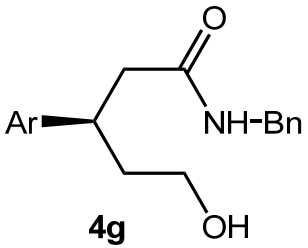


3g, 3p-s
Ar = 4-FC_6H_4

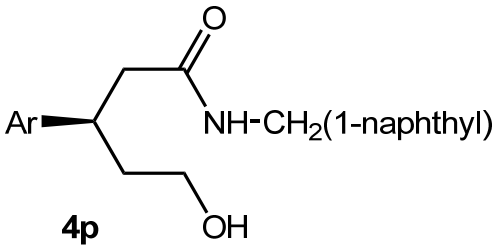
4g, 4p-s



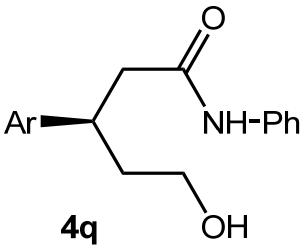
1a



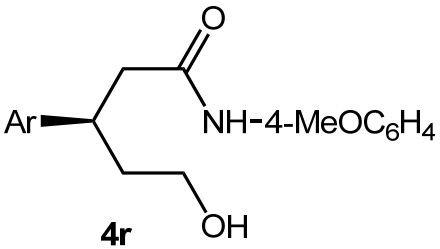
4g
>99% yield, 64% ee



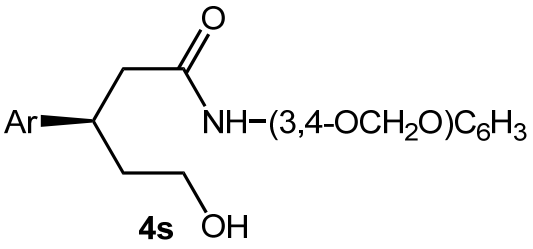
4p
>99% yield, 75% ee



4q
78% yield, 85% ee



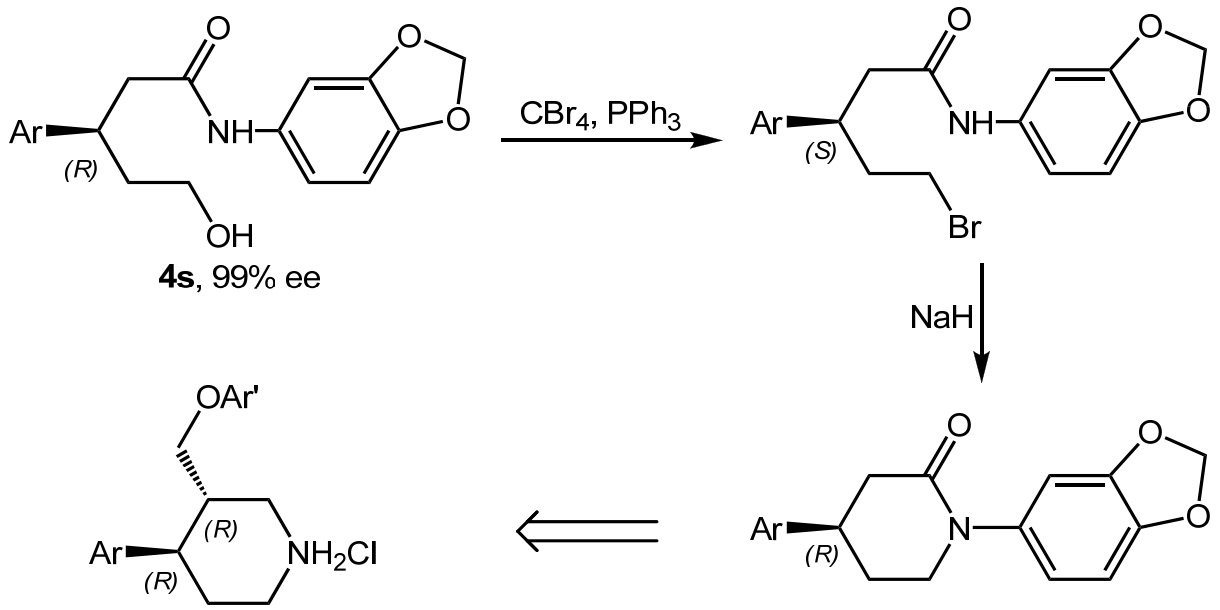
4r
90% yield, 91% ee



4s
>99% yield, 98% ee

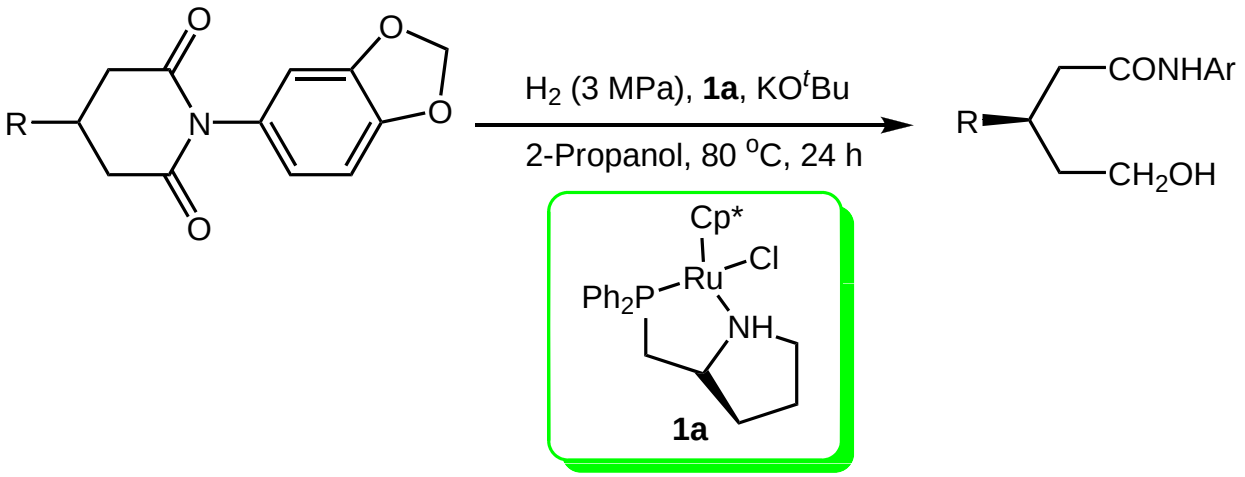
Ikariya, T. *et al*. *J. Am. Chem. Soc*. **2007**, *129*, 290

Preparation of (-)-Paroxetine



Ikariya, T. *et al*. *J. Am. Chem. Soc*. **2007**, *129*, 290

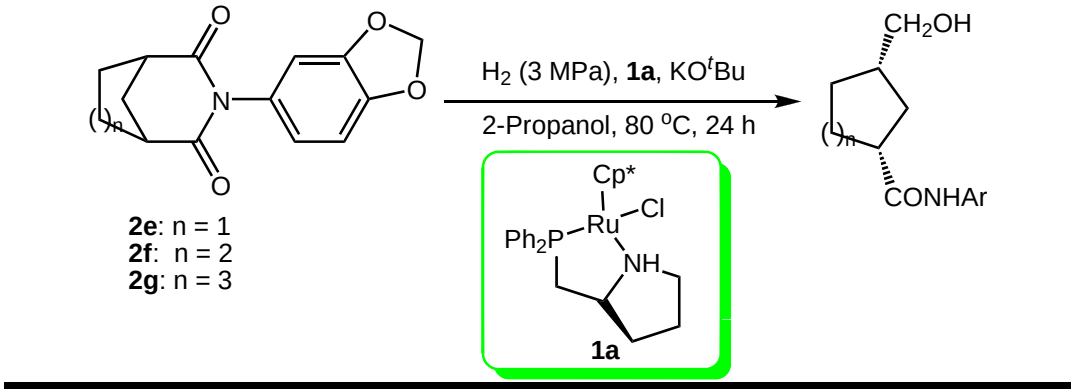
The Substrate Scope:



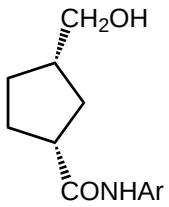
Substrate	Ee. (%)
2a (R = 4-FC_6H_4)	98
2b (R = 3,4-$Cl_2C_6H_3$)	91
2c (R = Ph)	96
2d (R = CH3)	88

Ikariya, T. *et al*. *J. Am. Chem. Soc*. **2010**, *132*, 11414

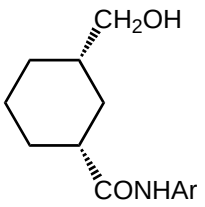
The Substrate Scope:



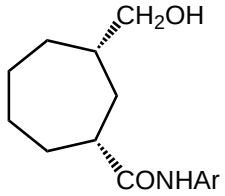
2e: n = 1
2f: n = 2
2g: n = 3



3e: ee = 94%



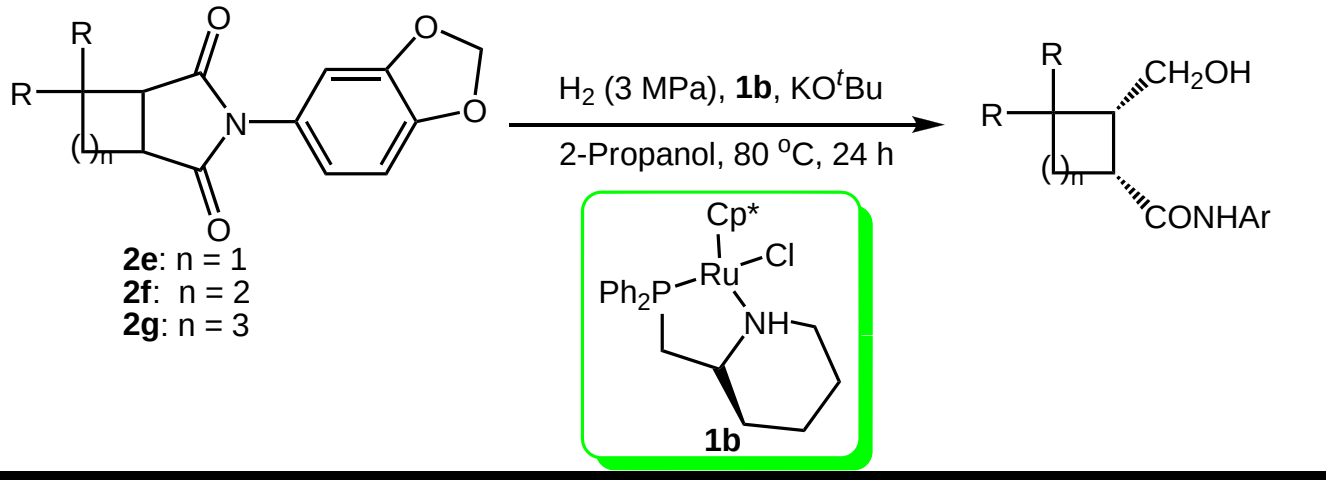
3f: ee = 94%

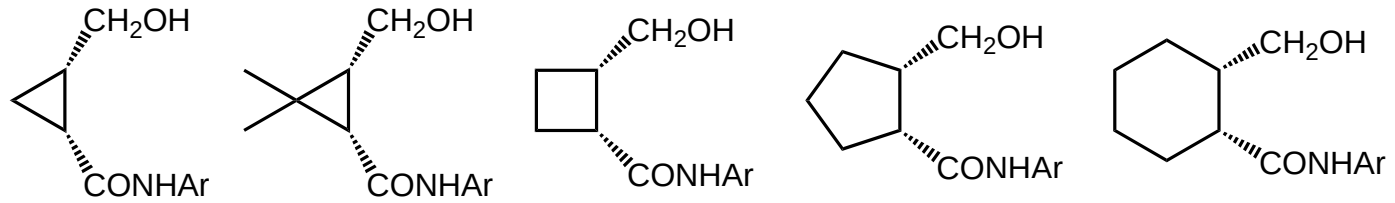


3g: ee = 93%

Ikariya, T. *et al*. *J. Am. Chem. Soc*. **2010**, *132*, 11414

The Substrate Scope:

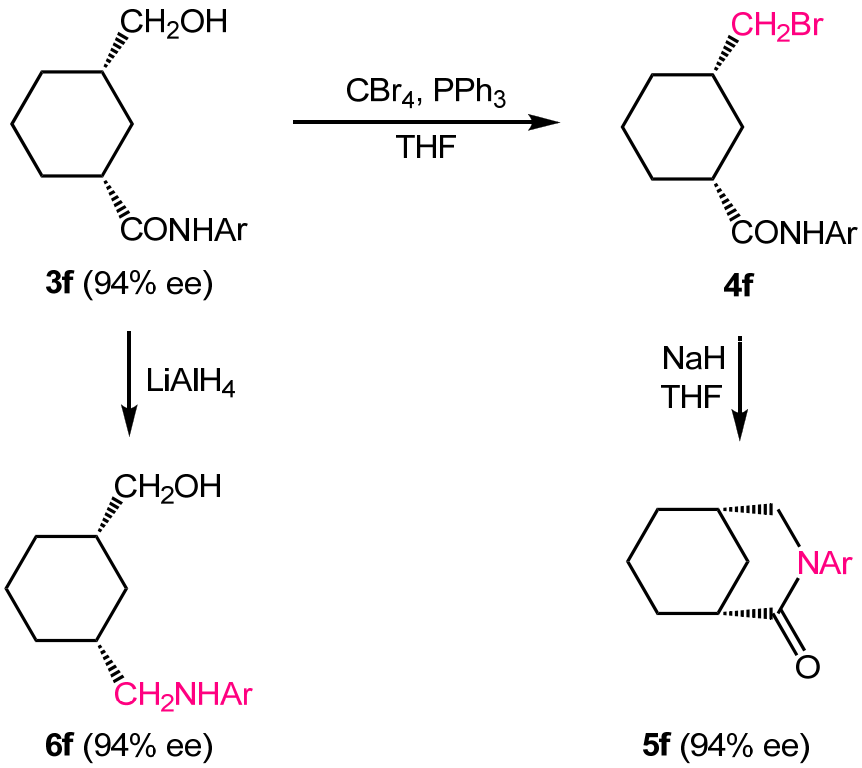




3h: ee = 62% **3i**: ee = 76% **3j**: ee = 91% **3k**: ee = 81% **3l**: ee = 92%

Ikariya, T. *et al*. *J. Am. Chem. Soc*. **2010**, *132*, 11414

Stereospecific Transformation of 3f :



Ikariya, T. *et al*. *J. Am. Chem. Soc*. **2010**, *132*, 11414

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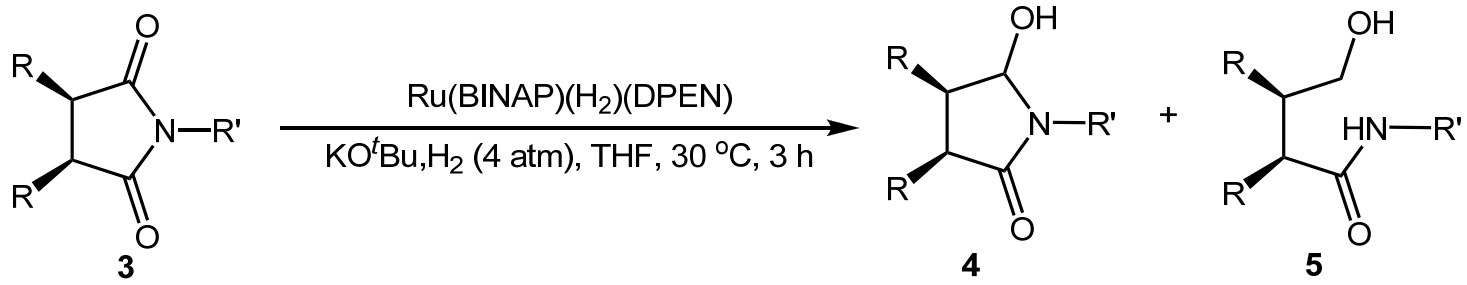
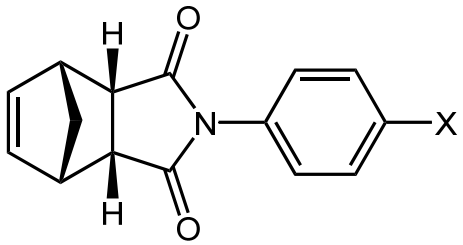
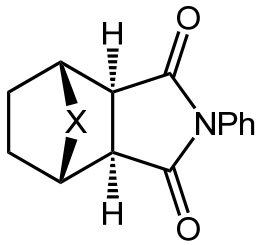
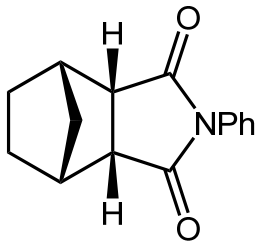




3a, X = H
3b, X = F
3c, X = NMe_2
3d, X = OMe



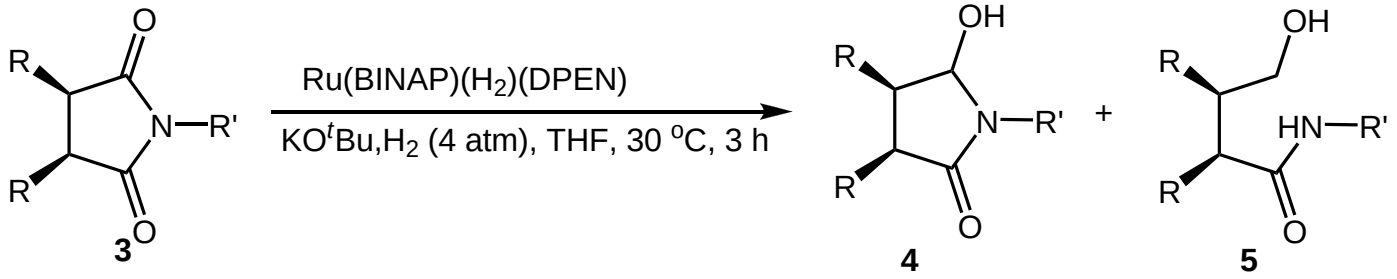
3e, X = none
3f, X = O



3g

Bergens, S. H. *et al*. *J. Am. Chem. Soc*. **2010**, *132*, 12832

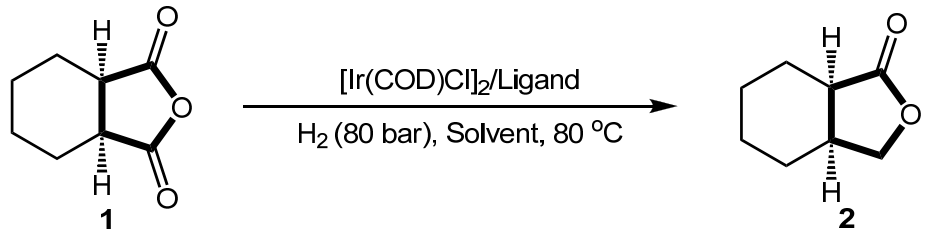
The Substrate Scope:

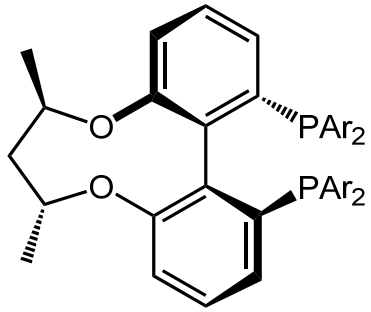


entry	imide	Time (H)	**4** (%)	**5** (%)	d.r. of **4**	Ee of **4** (%)
1	**3a**	3	70	12	>99:1	83
2	**3b**	17	98	0	>99:1	96
3	**3c**	17	99	0	>99:1	97
4	**3d**	17	92	0	>99:1	97
5	**3e**	17	98	0	>99:1	95
6	**3f**	57	90	trace	97:3	88
7	**3g**	6	97	trace	93:7	92
8	**3h**	17	44	0	>99:1	92

Bergens, S. H. *et al*. *J. Am. Chem. Soc*. **2010**, *132*, 12832

Optimization of the Conditions:



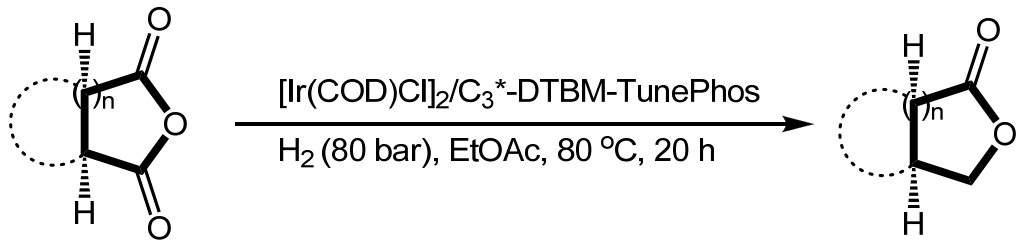


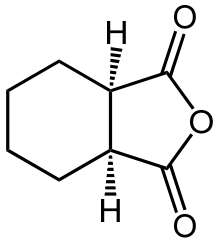
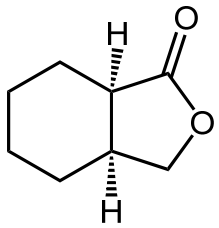
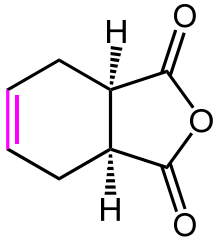
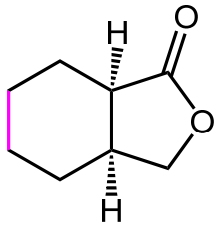
L1 Ar = 4-MeO-3,5-^{t}Bu$_2$-C$_6$H$_2$
L2 Ar = 3,5-^{t}Bu$_2$-C$_6$H$_3$
L3 Ar = 3,5-Me$_2$-C$_6$H$_3$
L4 Ar = 4-Me-C$_6$H$_4$
L5 Ar = C$_6$H$_5$

entry	L	Solvent	Conv.	Ee (%)
1	**L1**	EtOAc	>99	91
2	**L1**	THF	75	90
3	**L1**	toluene	20	90
4	**L1**	DCE	30	97
5	**L2**	EtOAc	>99	90
6	**L3**	EtOAc	>99	68
7	**L4**	EtOAc	>99	63
8	**L5**	EtOAc	>99	61

Zhang, X. *et al*. *Org. Lett*. **2013**, *15*, 1740

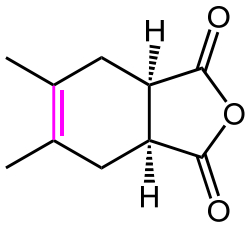
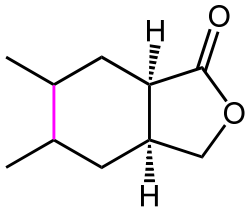
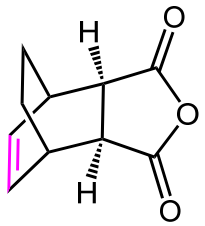
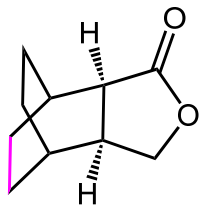
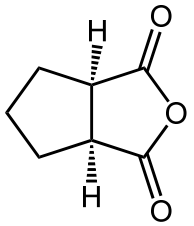
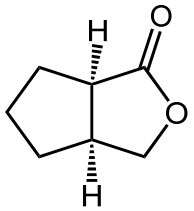
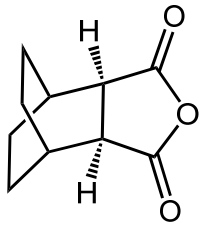
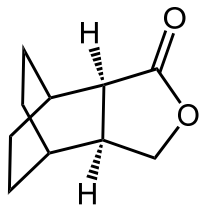
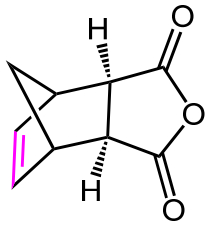
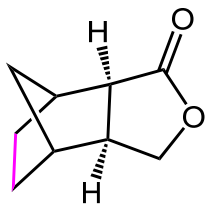
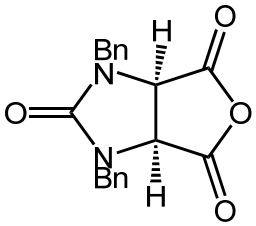
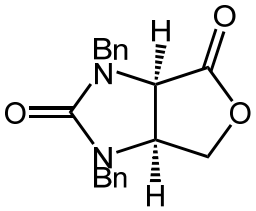
The Substrate Scope:



Anhydrides	Lactones	Ee (%)
		91
		90

Zhang, X. *et al*. *Org. Lett*. **2013**, *15*, 1740

The Substrate Scope:

Anhydrides	Lactones	Ee (%)	Anhydrides	Lactones	Ee (%)
		94			99
		80			99
		87			96

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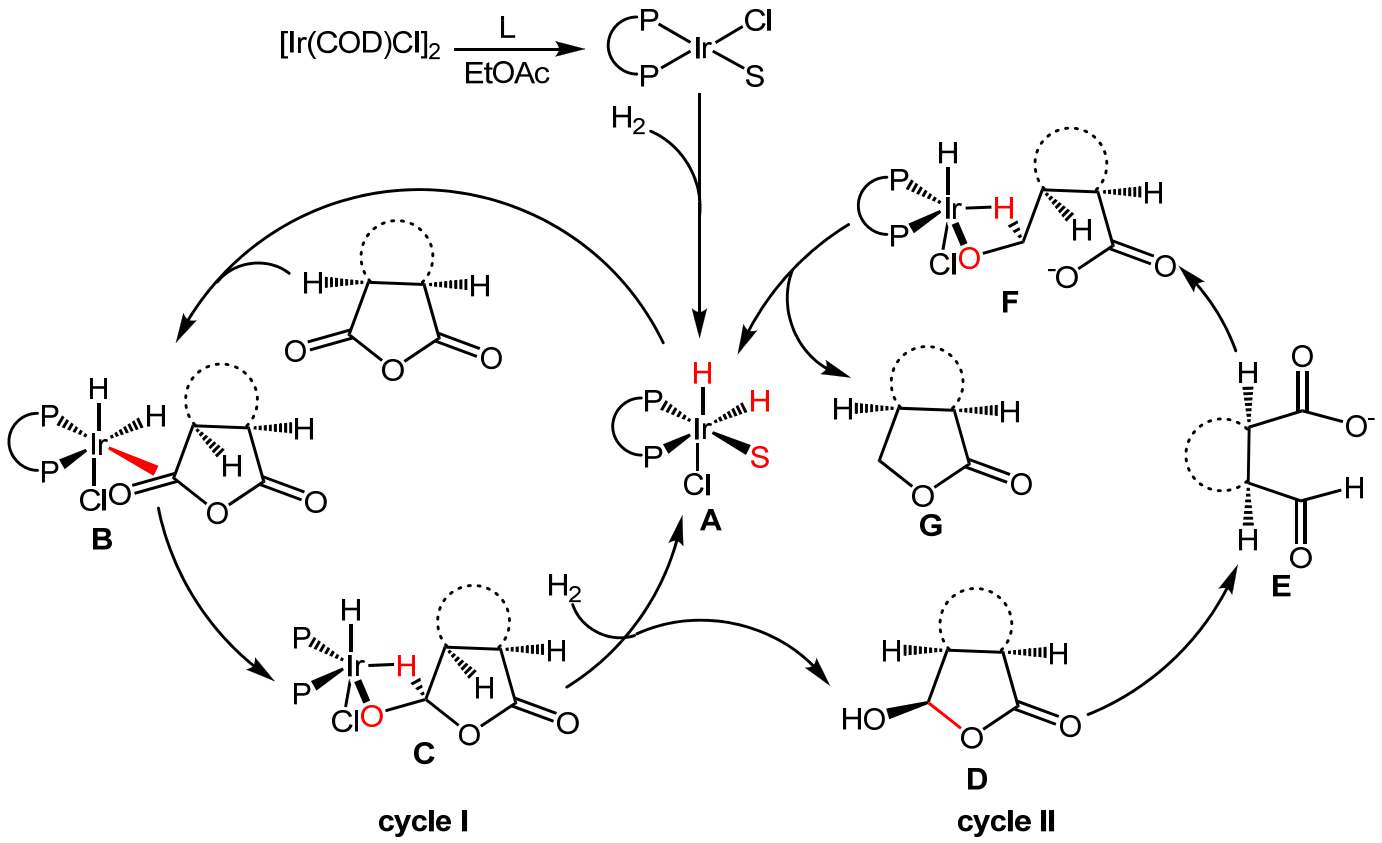
Plausible Reaction Mechanism:



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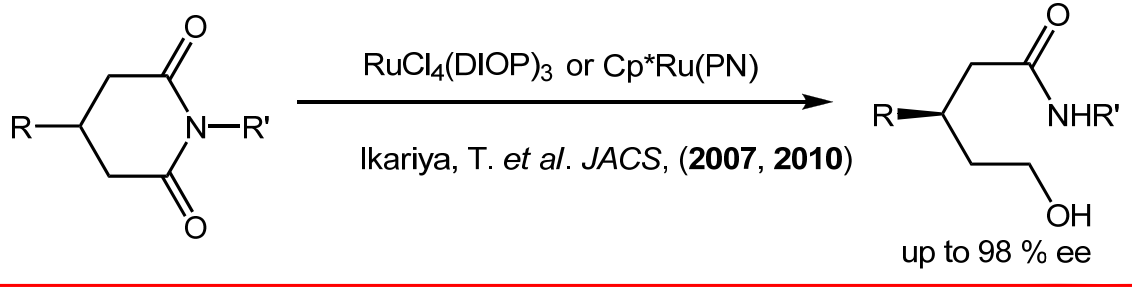
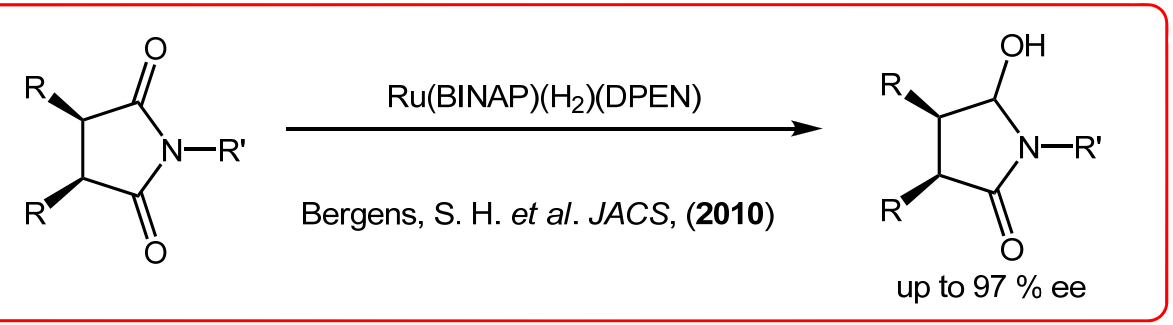
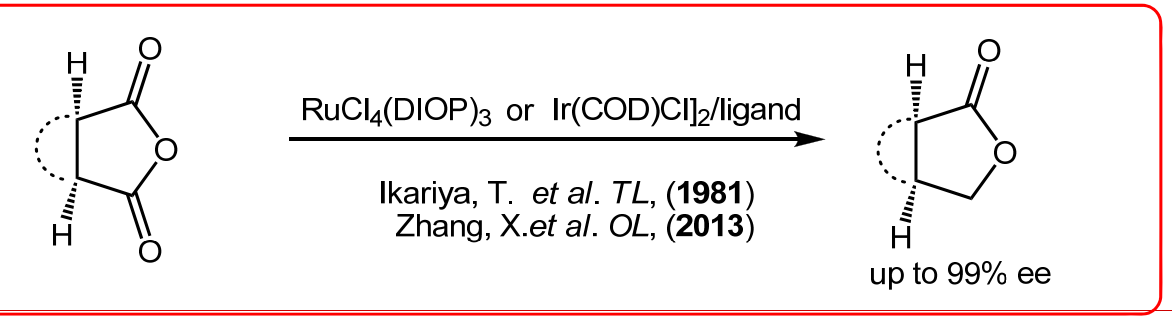
Summary:


RuCl4(DIOP)3 or Cp*Ru(PN)
Ikariya, T. et al. JACS, (2007, 2010)
up to 98 % ee


Ru(BINAP)(H2)(DPEN)
Bergens, S. H. et al. JACS, (2010)
up to 97 % ee


RuCl4(DIOP)3 or Ir(COD)Cl]2/ligand
Ikariya, T. et al. TL, (1981)
Zhang, X.et al. OL, (2013)
up to 99% ee

The asymmetric desymmetrization (ADS) of prochiral molecules in symmetrical bifunctional compounds has proven to be a straightforward and powerful strategy in asymmetric syntheses. In particular, ADS of meso compounds is a remarkably valuable transformation in organic synthesis because it breaks the symmetry of the molecule without incorporating new stereogenic centers. Stereoselective catalytic desymmetrization of meso-anhydrides has been developed as an advantageous methodology in the synthesis of many biologically active compounds, such as lactones and their derivatives

In conclusion, we have developed a novel and practical method to desymmetrize meso-anhydrides into lactones *via* Ir/C3*-DTBM-TunePhos (**L1**), which contains bulky biaryl bisphosphine, catalyzed asymmetric hydrogenation under high temperature. In the presence of a catalytic amount of the catalyst, asymmetric hydrogenation of various meso-anhydrides proceeded smoothly and afforded the corresponding enantiomerically enriched lactones in high yields and with good to excellent enantioselectivities. Study of the desymmetrization of other meso-carbonyl compounds as well as further modification of steric environment in C3*-TunePhos ligand family is in progress and will be reported in due course.