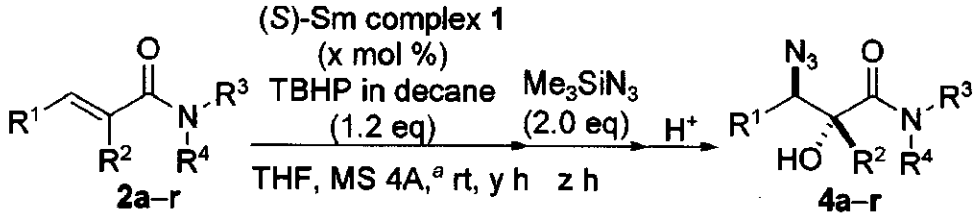
Dynamic Ligand Exchange of the Lanthanide Complex Leading to Structural and Functional Transformation: One Pot Sequential Catalytic Asymmetric Epoxidation-Regioselective Epoxide-Opening Process



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Lanthanides

^{57}La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	^{71}Lu

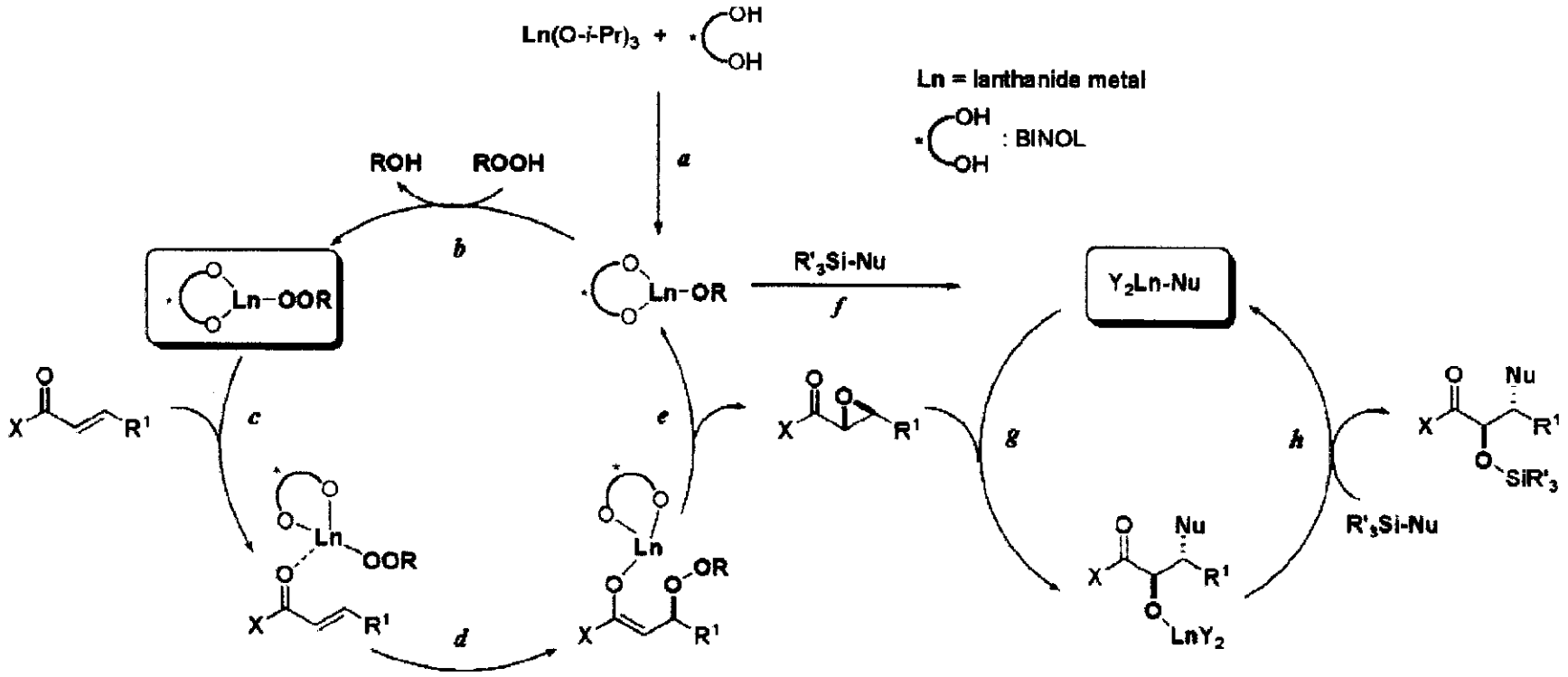
- Large coordination # enables development of lanthanide ligand complexes as Lewis acid catalysts.

  -Ligand-accelerating effect - reaction rate is increased by addition of a suitable ligand

  -Dynamic Ligand Exchange- a nucleophilic reagent can be exchanged for a labile ligand to generate another nucleophilic catalyst.

Sharpless, K.B.; Berrisford, D. J.; Bolm, C. *Angew. Chem. Int. Ed.* **1995**, *34*, 1059.

Catalytic Cycle of Enantioselective Epoxidation and Sequential Epoxide-Opening Reaction through Dynamic Ligand Exchange of the Lanthanide Complex

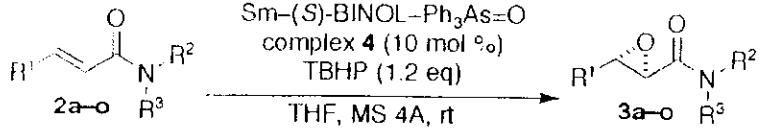


-several bonds formed without isolation of intermediate
-environmentally friendly--minimize waste

Catalytic Asymmetric Epoxidation of α,β-Unsaturated Amides

-La-BINOL-Ph_3As=O complex Asymmetric epoxidation of Enonones, α,β-Unsaturated Imidazolides

-one-pot tandem catalytic asymmetric epoxidation-Pd catalyzed epoxide opening β-aryl- α-hydroxy amides

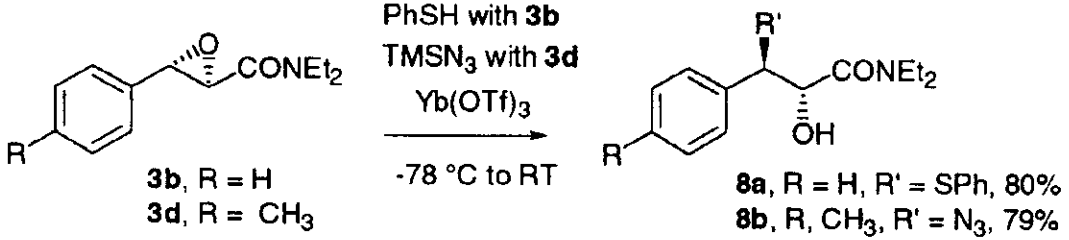


entry	substrate R^1	substrate NR^2R^3		conditions[a]	time (h)	yield[b] (%)	ee[c] (%)
1	$Ph(CH_2)_2$	CH_3NH	**2a**	A	8	99	>99
2[d]			**2a**	A	24	94	>99
3[e,f]			**2a**	A	24	91	97
4	$Ph(CH_2)_2$	BnNH	**2b**	A	6	97	>99
5[d]			**2b**	A	24	82	99
6	$Ph(CH_2)_2$	AllylNH	**2c**	A	4	95	98
7	$Ph(CH_2)_2$	cHexNH[g]	**2d**	A	11	97	>99
8	$Ph(CH_2)_2$	*t*-BuNH	**2e**	A	22	91	99
9	$Ph(CH_2)_2$	$(CH_3)_2N$	**2f**	A	3	96	99
10	$Ph(CH_2)_2$		**2g**	A	4	94	>99
11	$Ph(CH_2)_4$	CH_3NH	**2h**	A	8	81	>99
12	C_3H_7	BnNH	**2i**	A	9	94	94
13	cHex[g]	BnNH	**2j**	A	12	90	>99
14	Ph	CH_3NH	**2k**	A	24	89	>99
15			**2k**	B	18	95	99
16[e]			**2k**	B	9	92	97
17	Ph	BnNH	**2l**	B	18	91	>99
18	Ph	$(CH_3)_2N$	**2m**	B	9	96	>99
19	4-F-C_6H_4	CH_3NH	**2n**	B	20	94	99
20	4-Me-C_6H_4	CH_3NH	**2o**	B	21	89	>99

[a] Conditions A: TBHP in decane was used. MS 4A was not dried. Conditions B: TBHP in toluene was used. MS 4A was dried for 3 h at 180 °C under reduced pressure. [b] Isolated yield. [c] Determined by HPLC analysis. [d] 5 mol % of **4** was used. [e] Ph_3P=O (30 mol %) was used as an additive. [f] Dy was used as a central metal. [g] cHex = cyclohexyl.

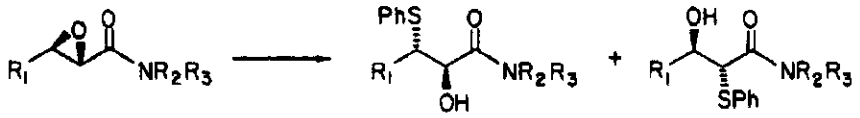
Shibasaki M. et al *J. Am. Chem. Soc.* **2002**, *124*, 14544.

Regioselective Ring Opening of α,β-Epoxy Amides



Aggarwal, V.K. *J. Am. Chem. Soc.* **2002**, *124*, 9964.

Table III. Reaction of 2,3-Epoxy Amides with Thiophenol



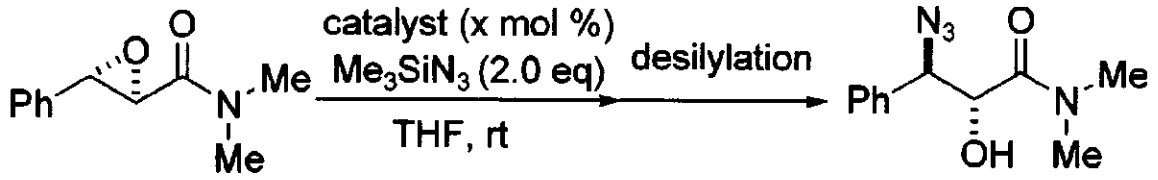
13 14 15

entry	substrate	R_1	R_2	R_3	conditns[a]	ratio 14:15	yield,[c] %
1	16	n-C_7H_{15}	H	$PhCH_2$	A	1:1.2	89
2	16	n-C_7H_{15}	H	$PhCH_2$	B	20:1	95
3	17	c-C_6H_{11}	H	$PhCH_2$	A	1:4	85
4	17	c-C_6H_{11}	H	$PhCH_2$	B	5:1	95
5	17	c-C_6H_{11}	H	$PhCH_2$	C	7:1	95
6	17	c-C_6H_{11}	H	$PhCH_2$	D	20:1	91
7	18	n-C_7H_{15}	$PhCH_2$	$PhCH_2$	A	1:11	84
8	18	n-C_7H_{15}	$PhCH_2$	$PhCH_2$	D	1:7	89

[a] A, PhSNa, THF, room temperature, 1 h; B, PhSH (2 equiv), Ti(O-*i*-Pr)$_4$ (1.5 equiv), CH_2Cl_2, room temperature, 6 h; C, PhSH (2 equiv), Ti(O-*i*-Pr)$_4$ (1.5 equiv), THF, room temperature, 6 h; D, PhSNa (1.5 equiv), Ti(O-*i*-Pr)$_4$ (1.5 equiv), THF, 0.2 h. [b] As determined by ^{1}H NMR spectroscopy on the acetylated (Ac_2O, pyr, DMAP) mixture. [c] Isolated yield of purified (flash chromatography) acetates.

Sharpless, K.B.; Chong, J.M. *J. Org. Chem.* **1985**, *50*, 1563.

Regioselective Ring Opening of α,β-Epoxy Amides

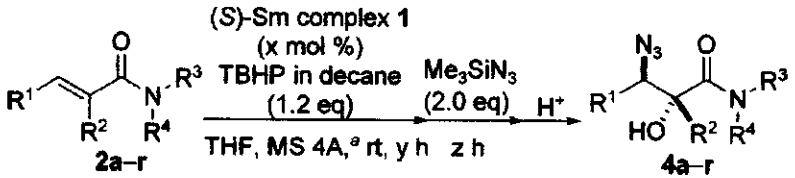


entry	catalyst	*x* (mol %)	time (h)	yield[a] (%)
1[b]	Sm(O-*i*-Pr)$_3$	5	1	99
2[b]	Sm(O-*i*-Pr)$_3$	0.2	2	97
3[b]	Sm−(*S*)-BINOL−Ph_3As=O (1:1:1) complex **1**	5	1	99
4[c]	Sm(OTf)$_3$	10	24	21

[a] Isolated yield. [b] Desilylation was conducted with 1 N HCl aq−MeOH. [c] Desilylation was conducted with KF in MeOH.

-only a trace amount of 4a was observed with no catalyst after 48 h.

Table 2. One-Pot Sequential Catalytic Asymmetric Epoxidation-Regioselective Epoxide-Opening Process with Various α,β-Unsaturated Amides

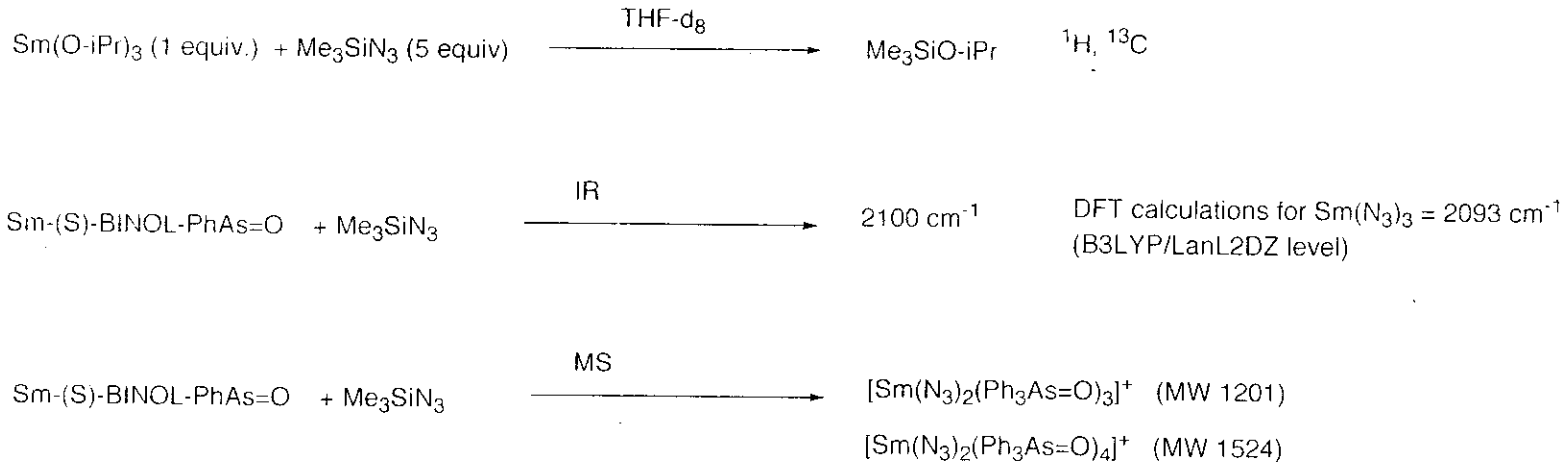


entry	substrate R¹	R²	NR³R⁴		catalyst (x mol %)	time (y/z h)	yield[b] (%)	ee[c] (%)	product
1	C_6H_5	H	NMe_2	**2a**	5	12/1	99	99	**4a**
2	C_6H_5	H	NMe_2	**2a**	2	15/2	70	99	**4a**
3	C_6H_5	H	morpholinyl	**2b**	5	11/1	99	99[d]	**4b**
4	4-$MeOC_6H_4$	H	NMe_2	**2c**	5	13/1	95	>99	**4c**
5	4-$MeOC_6H_4$	H	morpholinyl	**2d**	5	12/1	97	99[d]	**4d**
6	4-MeC_6H_4	H	NMe_2	**2e**	5	13/1	93	99	**4e**
7	4-FC_6H_4	H	NMe_2	**2f**	5	11/1	98	>99	**4f**
8	1-naphthyl	H	NMe_2	**2g**	10	11/3	98	98	**4g**
9	2-naphthyl	H	NMe_2	**2h**	5	13/1	99	>99	**4h**
10	2-naphthyl	H	NMe_2	**2h**	2	16/1	71	98	**4h**
11[e]	2-furyl	H	NMe_2	**2i**	10	11/0.5	45[f]	>99	**4i**
12	3-furyl	H	NMe_2	**2j**	5	11/1	94	>99	**4j**
13	(*E*)-PhCH=CH–	H	NMe_2	**2k**	10[g]	12/0.5	90	>99	**4k**
14	C_6H_5	H	NHMe	**2l**	10	13/8	83	99	**4l**
15	–$(CH_2)_3$–		NHBn	**2m**	10	12/5	97	96	**4m**
16	–$(CH_2)_4$–		NHBn	**2n**	10	13/1	86	99	**4n**
17	$Ph(CH_2)_2$-	H	NMe_2	**2o**	5	6/12	84	98	**4o**
18	$Ph(CH_2)_2$-	H	morpholinyl	**2p**	5	5/12	92	98	**4p**
19	*n*-propyl	H	NMe_2	**2q**	5	6/12	85	98[h]	**4q**
20	cyclohexyl	H	NMe_2	**2r**	10	6/16	75	99[h]	**4r**

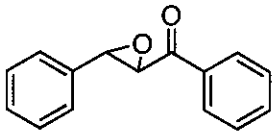
[a] MS 4A was used without prior activation (1000 mg/mmol of starting material). [b] Isolated yield. The regioselectivity was generally below the detection limit of 500 MHz ^{1}H NMR (>98:2). [c] Determined by chiral HPLC analysis. [d] ee was determined after conversion to the corresponding *N*-Boc amine. [e] The corresponding epoxide is decomposed on silica gel. [f] Isolated yield of the major anti isomer after conversion to TES ether (ref 15). [g] Gd was used as the central metal instead of Sm (ref 9d). [h] ee was determined after conversion to the corresponding benzoate.

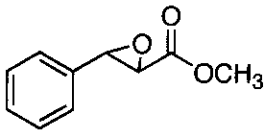
Active Species

-spectroscopic experiments

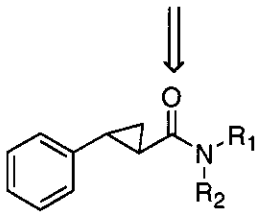


-the (S)-Sm complex also acts as a highly reactive samarium azide complex

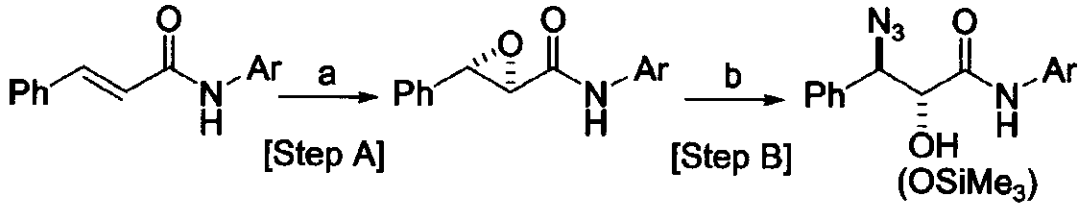


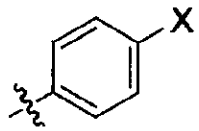


Lewis basicity of carbonyl

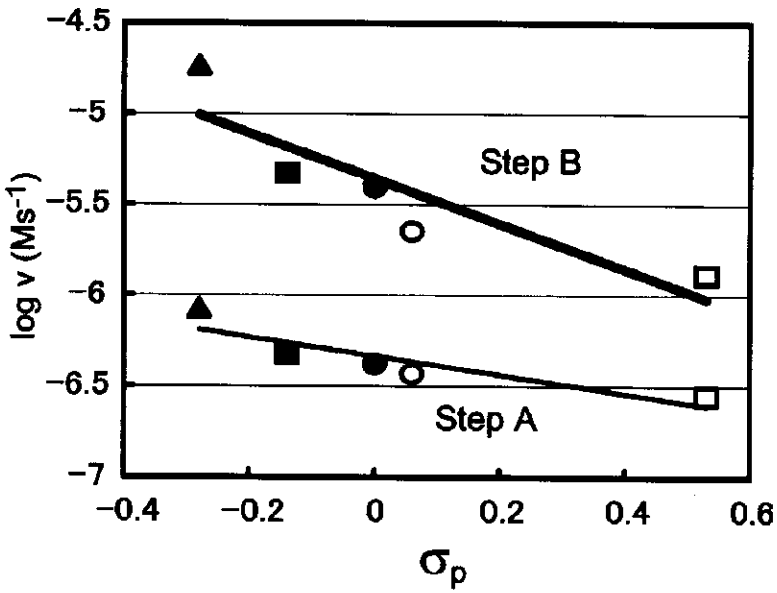


Scheme 3. Effect of Amide Moiety on the Reactivity and the Hammett Plot[a]



Ar = 

6a: X=MeO (▲)
6b: X=Me (■)
6c: X=H (●)
6d: X=F (○)
6e: X=CF_3 (□)

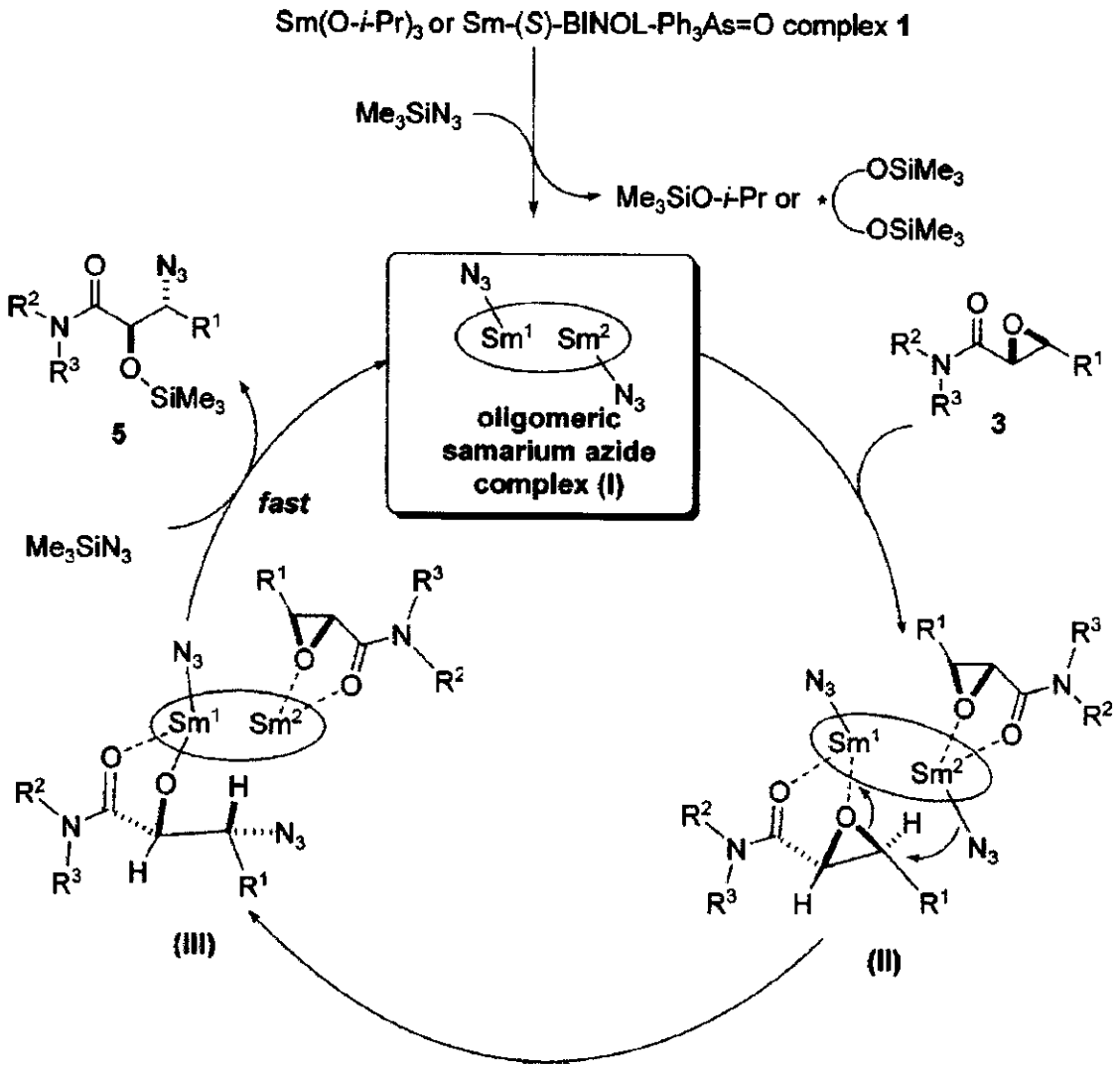


[a] (a) (*S*)-Sm complex **1** (10 mol %), TBHP in decane (1.2 equiv), THF, MS 4A, 25 °C. (b) $Sm(O\text{-}i\text{-}Pr)_3$ (10 mol %), Me_3SiN_3 (2 equiv), THF, 25 °C.

-Lewis-basic carbonyl coordinates to the samarium more efficiently and enhances the nucleophilicity of the active samarium azide complex

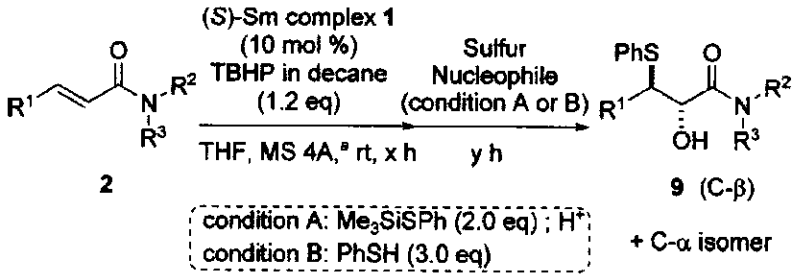
Catalytic Cycle of Epoxide Opening with Azide

Initial rate kinetics
1.08 [$Sm(O\text{-}iPr)_3$]
0.04 [$TMSN_3$]



Other Nucleophiles: Me_3SiSPh, PhSH

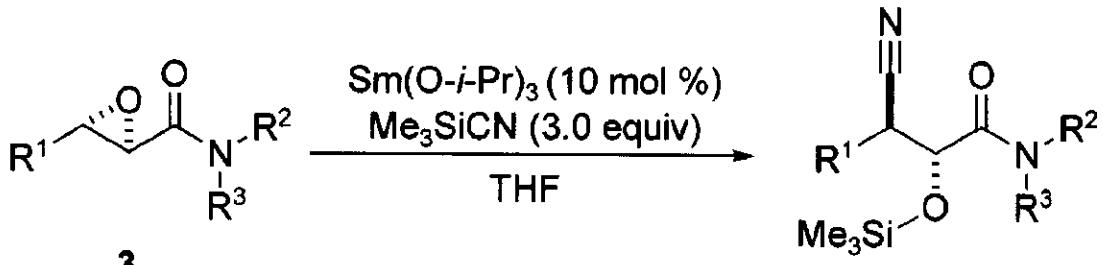
Table 5. One-Pot Sequential Process with a Sulfur Nucleophile



	substrate								
entry	R^1	NR^2R^3		condition	time *x*/*y* (h)	yield[b] (%)	ratio[c] (C-β:C-α)	ee[d] (%)	product
1	C_6H_5	NMe_2	**2a**	A	11/1	86	92:8	99	**9a**
2	C_6H_5	NMe_2	**2a**	B	11/1	93	94:6	99	**9a**
3	C_6H_5	morpholinyl	**2b**	A	11/1.5	85	95:5	99	**9b**
4	C_6H_5	morpholinyl	**2b**	B	11/1.5	91	96:4	99	**9b**
5	4-$MeOC_6H_4$	NMe_2	**2c**	A	11/1	83	96:4	>99	**9c**
6	4-$MeOC_6H_4$	NMe_2	**2c**	B	11/1	90	98:2	>99	**9c**
7	C_6H_5	NHMe	**2l**	A	15/2	70	>98:2	99	**9l**
8	C_6H_5	NHMe	**2l**	B	13/4	74	>98:2	99	**9l**
9	$Ph(CH_2)_2$—	NHMe	**2s**	A	11/2	76	92:8	99	**9s**
10	$Ph(CH_2)_2$—	NHMe	**2s**	B	6/2	72	90:10	99	**9s**
11	cyclohexyl	NHMe	**2t**	A	15/73	75	85:15	99	**9t**
12	cyclohexyl	NHMe	**2t**	B	14/76	74	80:20	99	**9t**

[a] MS 4A was used without prior activation (1000 mg/mmol of starting material). [b] Isolated yield. [c] Determined by ^1H NMR analysis. [d] Determined by chiral HPLC analysis.

Me_3CN

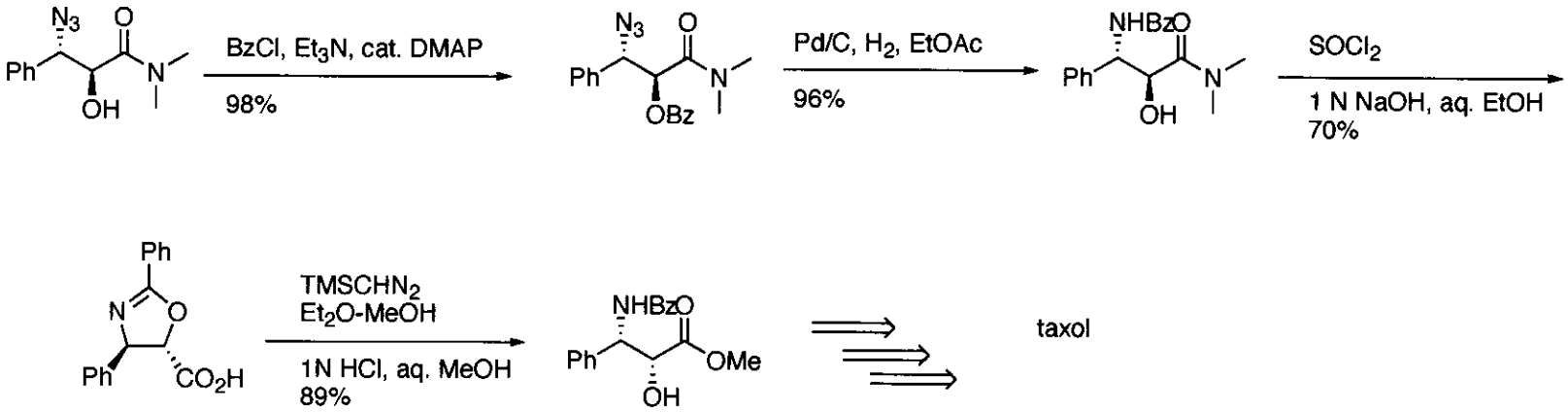


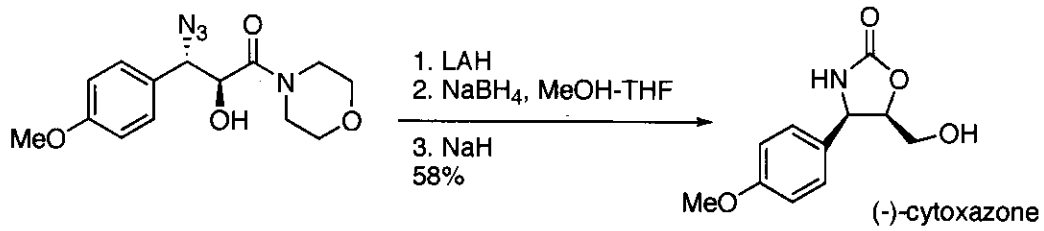
	substrate			temp	time	yield[a]	ratio[b]	
entry	R^1	NR^2R^3		(°C)	(h)	(%)	(C-β:C-α)	product
1	C_6H_5	NMe_2	**3a**	rt	24	81	88:12	**10a**
2	C_6H_5	NHMe	**3l**	rt	39	80	93:7	**10l**
3	$Ph(CH_2)_2$-	NMe_2	**3o**	rt	36	57	86:14	**10o**
4	$Ph(CH_2)_2$-	NMe_2	**3o**	50	36	71	85:15	**10o**

[a] Isolated yield. [b] Determined by ^1H NMR analysis.

-one-pot sequential procedure resulted in slugglish epoxide opening

Applications towards natural products





Summary

-a convenient catalytic asymmetric approach to α-hydroxy,β-azido amides has been realized by dynamic ligand exchange of a lanthanide complex

-mechanistic spectroscopic studies confirmed the generation of the samarium azide complex

-high Lewis basicity of the amide moiety has a key role in both the high reactivity of the epoxidation and epoxide-opening reactions

-extended to other nucleophiles such as thiols

-future work- one-pot epoxidation/cyanation