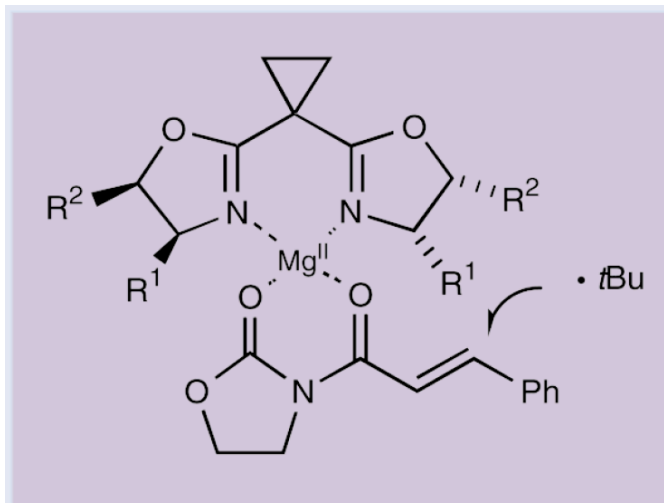


Enantioselective Free Radical Reactions

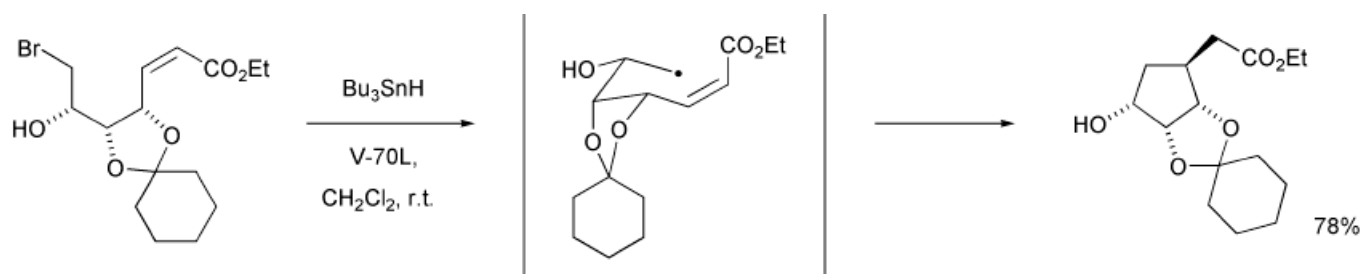


Michael Ober

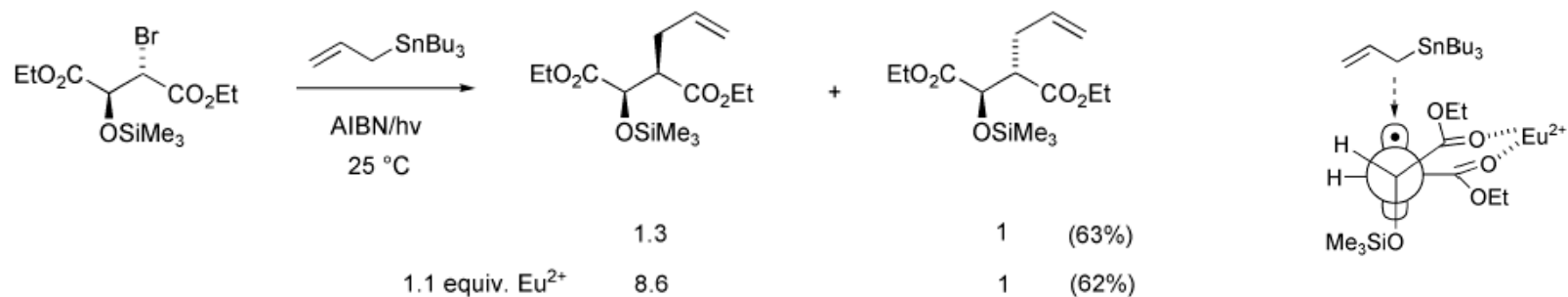
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Stereoselective Radical Reactions : The Concept

Intramolecular

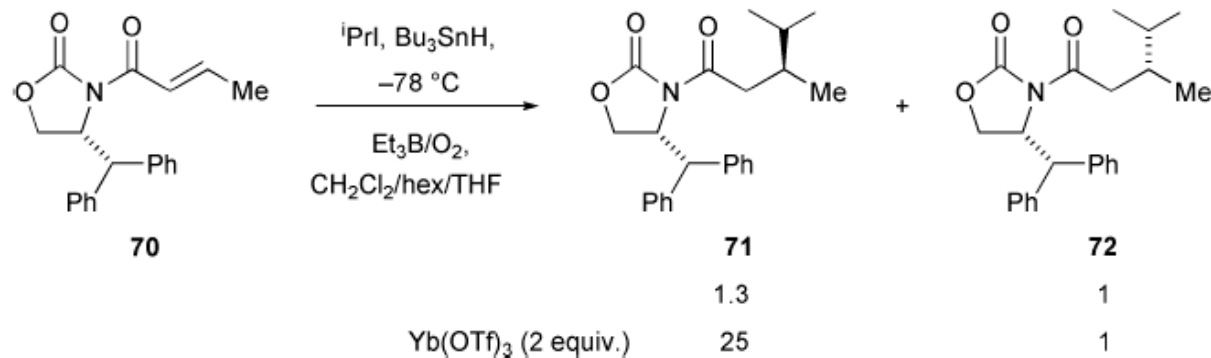


Intermolecular

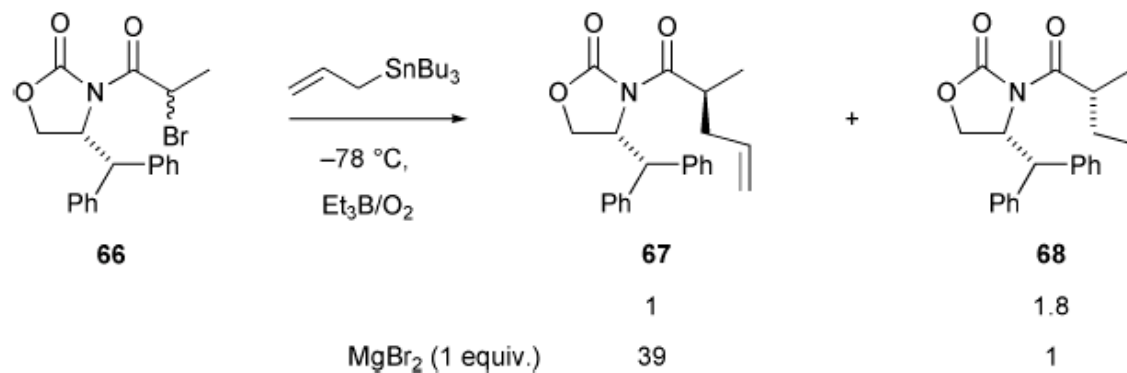


Complex Controlled Diastereoselective Reactions

Conjugate Addition



Fragmentation



Sibi, M. P. et al *J. Am. Chem. Soc.* **1999**, *121*, 751

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Complex Controlled Diastereoselective Conjugate Additions

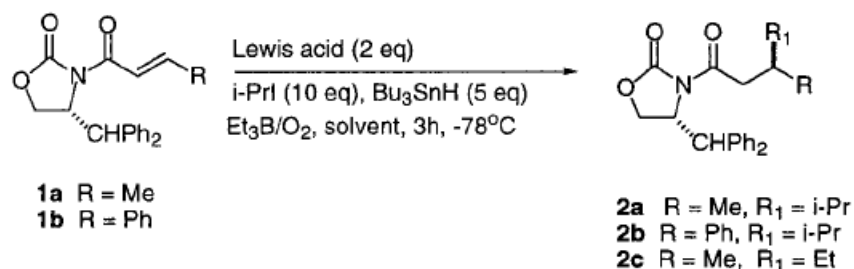


Table 1. Effect of Lewis Acids and Solvents on Diastereoselective Conjugate β -Radical Addition^a

entry	substrate	Lewis acid	solvent	product	yield (%) ^b	ratio ^c
1	(<i>R</i>)- 1a	none	CH ₂ Cl ₂	2a	30 ^{d,e}	1.3:1
2	(<i>R</i>)- 1a	Yb(OTf) ₃	CH ₂ Cl ₂ /THF (4:1)	2a	93 ^f	25:1
3	(<i>R</i>)- 1b	Yb(OTf) ₃	CH ₂ Cl ₂ /THF (4:1)	2b	94 ^f	45:1
4	(<i>R</i>)- 1a	Y(OTf) ₃	CH ₂ Cl ₂ /THF (4:1)	2a	88 ^f	24:1
5	(<i>R</i>)- 1a	Sm(OTf) ₃	CH ₂ Cl ₂ /THF (4:1)	2a	90 ^f	18:1
6	(<i>R</i>)- 1a	Sc(OTf) ₃	CH ₂ Cl ₂ /THF (4:1)	2a	82 ^f	9:1
7	(<i>R</i>)- 1a	La(OTf) ₃	CH ₂ Cl ₂ /THF (4:1)	2a	93 ^f	7:1
8	(<i>R</i>)- 1a	ZrCl ₄	CH ₂ Cl ₂ /THF (4:1)	2b	90	7:1
9	(<i>R</i>)- 1a	MgBr ₂ ·OEt ₂	CH ₂ Cl ₂ /THF (4:1)	2a	90	6:1
10	(<i>R</i>)- 1a	MgI ₂	CH ₂ Cl ₂ /ether	2a	90	6:1
11	(<i>R</i>)- 1a	MgI ₂	CH ₂ Cl ₂ /Et ₂ O (4:1)	2a	80	6:1
12	(<i>R</i>)- 1a	ZnCl ₂ (2)	CH ₂ Cl ₂ /Et ₂ O (4:1)	2a	90	6:1
13	(<i>R</i>)- 1a	ZnCl ₂ (2)	CH ₂ Cl ₂	2a	30 ^{d,g}	1.3:1
14	(<i>R</i>)- 1a	ZnCl ₂ (2)	CH ₂ Cl ₂ /THF (4:1)	2a	20 ^d	1.3:1
15	(<i>R</i>)- 1a	Zn(OTf) ₂ (2)	CH ₂ Cl ₂ /Et ₂ O (4:1)	2a	50 (20)	3:1
21	(<i>R</i>)- 1a	BF ₃ ·Et ₂ O	CH ₂ Cl ₂	2a	80 (5)	1.3:1

^a Two equivalents of the Lewis acid, 10 equiv of *i*-Pr-I, 5 equiv of Bu₃SnH, and 10 equiv of Et₃B were used at -78 °C. ^b Yields were determined by NMR integration, except when purified yields are indicated. Yields in parentheses are for the alkene reduction product. ^c Diastereomer ratios were determined by ¹H NMR (400 MHz). ^d Starting material accounted for most of the remaining mass balance. ^e Sixty percent of the starting material was recovered. ^f Purified yield. ^g The Lewis acid was insoluble.

Table 3. Effect of Solvent and Yb(OTf)₃ Stoichiometry on Selectivity^a

entry	Lewis acid (equiv)	solvent ^b	yield (%) ^c	dr ^d
1	Yb(OTf) ₃ (2)	CH ₂ Cl ₂	50 (40) ^e	1.3:1
2	Yb(OTf) ₃ (2)	CH ₂ Cl ₂ /Et ₂ O (4:1)	90	9:1
3	Yb(OTf) ₃ (2)	toluene/THF (4:1)	90	11:1
4	Yb(OTf) ₃ (2)	THF	90	15:1
5	Yb(OTf) ₃ (2)	CH ₂ Cl ₂ /THF (4:1) H ₂ O (6 equiv.)	90	20:1
6	Yb(OTf) ₃ (2)	CH ₂ Cl ₂ /THF ^a (4:1)	93	25:1
7	Yb(OTf) ₃ (2)	CH ₂ Cl ₂ /THF (4:1) H ₂ O (30 equiv.)	60	1.7:1
8	Yb(OTf) ₃ (2)	CH ₂ Cl ₂ /THF (4:1)	93	25:1
9	Yb(OTf) ₃ (1)	CH ₂ Cl ₂ /THF (4:1)	90	25:1
10	Yb(OTf) ₃ (0.3)	CH ₂ Cl ₂ /THF (4:1)	90	20:1
11	Yb(OTf) ₃ (0.1)	CH ₂ Cl ₂ /THF (4:1)	88	16:1

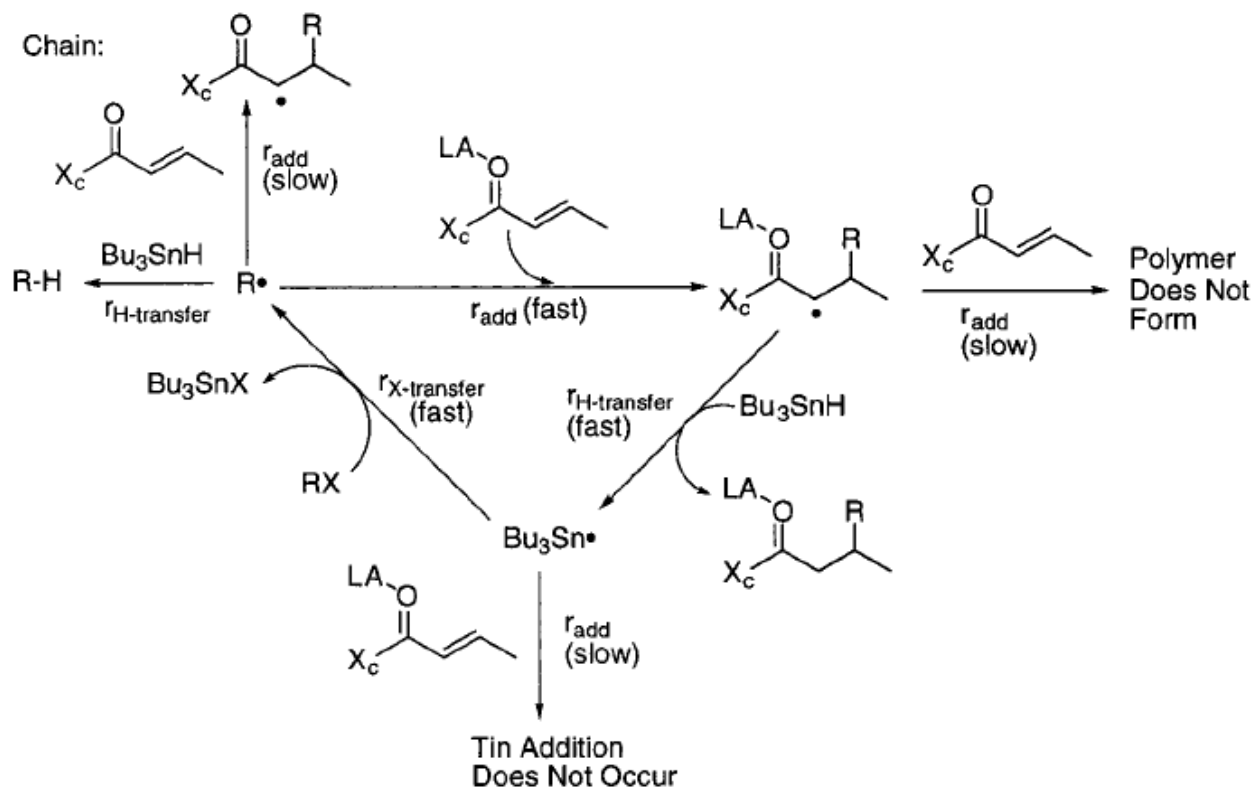
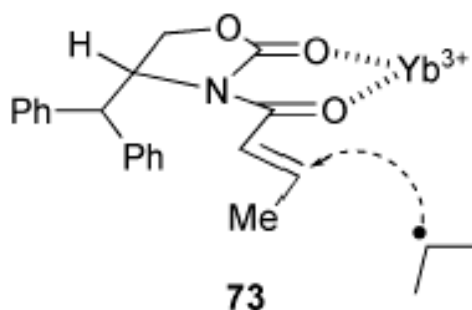
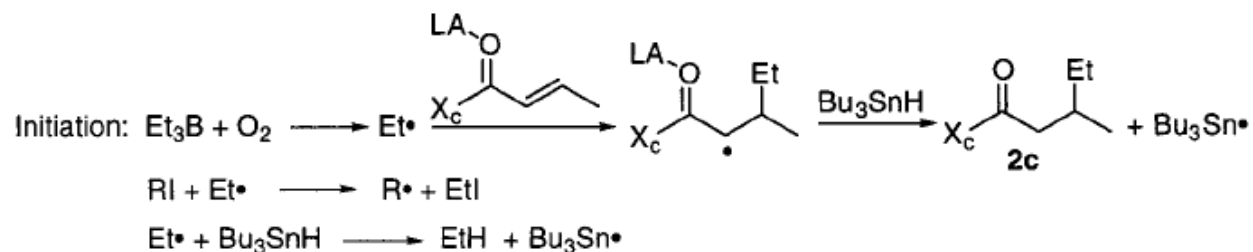
^a Five equivalents of *i*-Pr-I, 2 equiv of Bu₃SnH, and 2 equiv of Et₃B were used at -78 °C. ^b Commercial THF and CH₂Cl₂ were used without any attempt to predry or predistill them. ^c Yields are for isolated and column-purified materials. ^d Diastereomer ratios were determined by ¹H NMR (400 MHz). ^e The yield in parentheses is for the reduction product.

Table 5. Effect of Temperature on Diastereoselectivity

entry	temp (°C)	yield (%) ^a	dr ^b
1	-78	93	25:1
2	-40	90	15:1
3	0	80 (15%) ^c	5:1
4	25	30 (65%) ^c	4:1

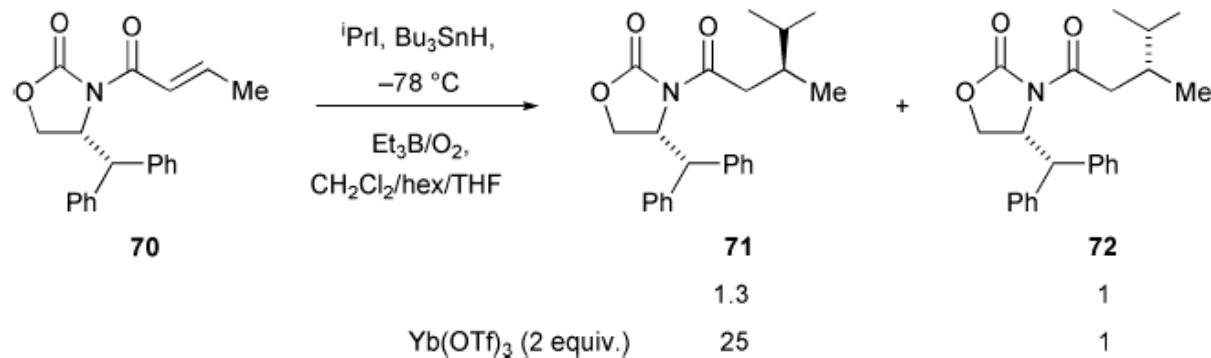
^a Yields are for isolated and column-purified materials. Five equivalents of *i*-Pr-I, 2 equiv of Bu₃SnH, and 2 equiv of Et₃B were used. ^b Diastereomer ratios were determined by ¹H NMR (400 MHz). ^c The yield in parentheses is the yield of the reduction product 5.

Complex Controlled Diastereoselective Conjugate Additions

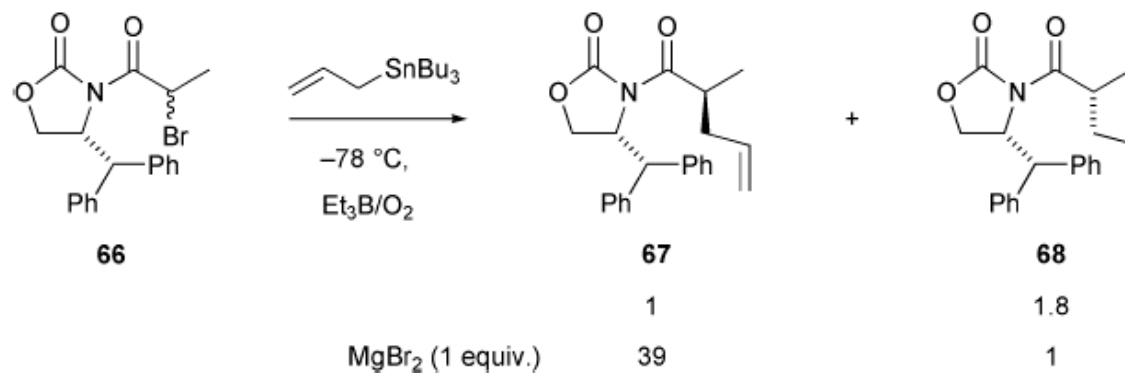


Complex Controlled Diastereoselective Reactions

Conjugate Addition



Fragmentation

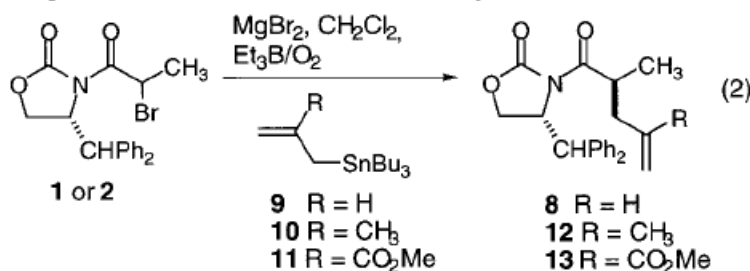


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Complex Controlled Diastereoselective Trapping of Radicals

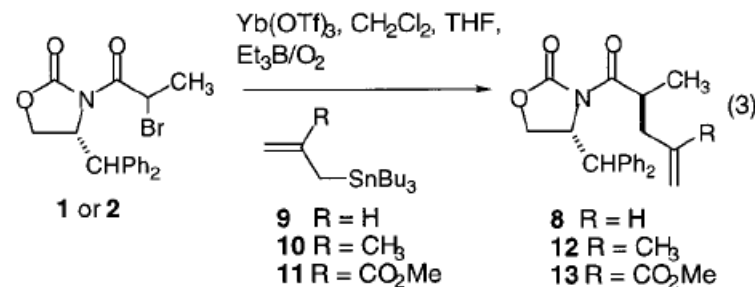
Table 2. Effect of Substrate Stereochemistry and Reaction Temperature on Product Diastereoselectivity



entry	substrate stereochem	temp	R	% yield ^{a,b}	ratio ^c
1	(R)	-78 °C	H	70	39:1 (S)
2	(S)	-78 °C	H	91	39:1 (S)
3	(R)	0 °C	H	90	> 50:1 (S)
4	(S)	0 °C	H	92	> 50:1 (S)
5	(R)	RT	H	82	> 50:1 (S)
6	(S)	RT	H	88	> 50:1 (S)
7	(R)	-78 °C	Me	78	24:1 (S)
8	(S)	-78 °C	Me	92	12:1 (S)
9	(R)	0 °C	Me	78	> 50:1 (S)
10	(S)	0 °C	Me	95	20:1 (S)
11	(R)	RT	Me	75	> 50:1 (S)
12	(S)	RT	Me	95	30:1 (S)
13	(R)	-78 °C	CO ₂ Me	25(50)	3:1 (S)
14	(S)	-78 °C	CO ₂ Me	90(10)	1:1
15	(R)	0 °C	CO ₂ Me	72	43:1 (S)
16	(S)	0 °C	CO ₂ Me	70	23:1 (S)
17	(R)	RT	CO ₂ Me	80	40:1 (S)
18	(S)	RT	CO ₂ Me	68(27)	20:1 (S)

^a Yield of isolated product. ^b Yield of recovered starting material in parentheses. ^c Diastereomer ratios were determined by ¹H NMR spectroscopy (400 MHz).

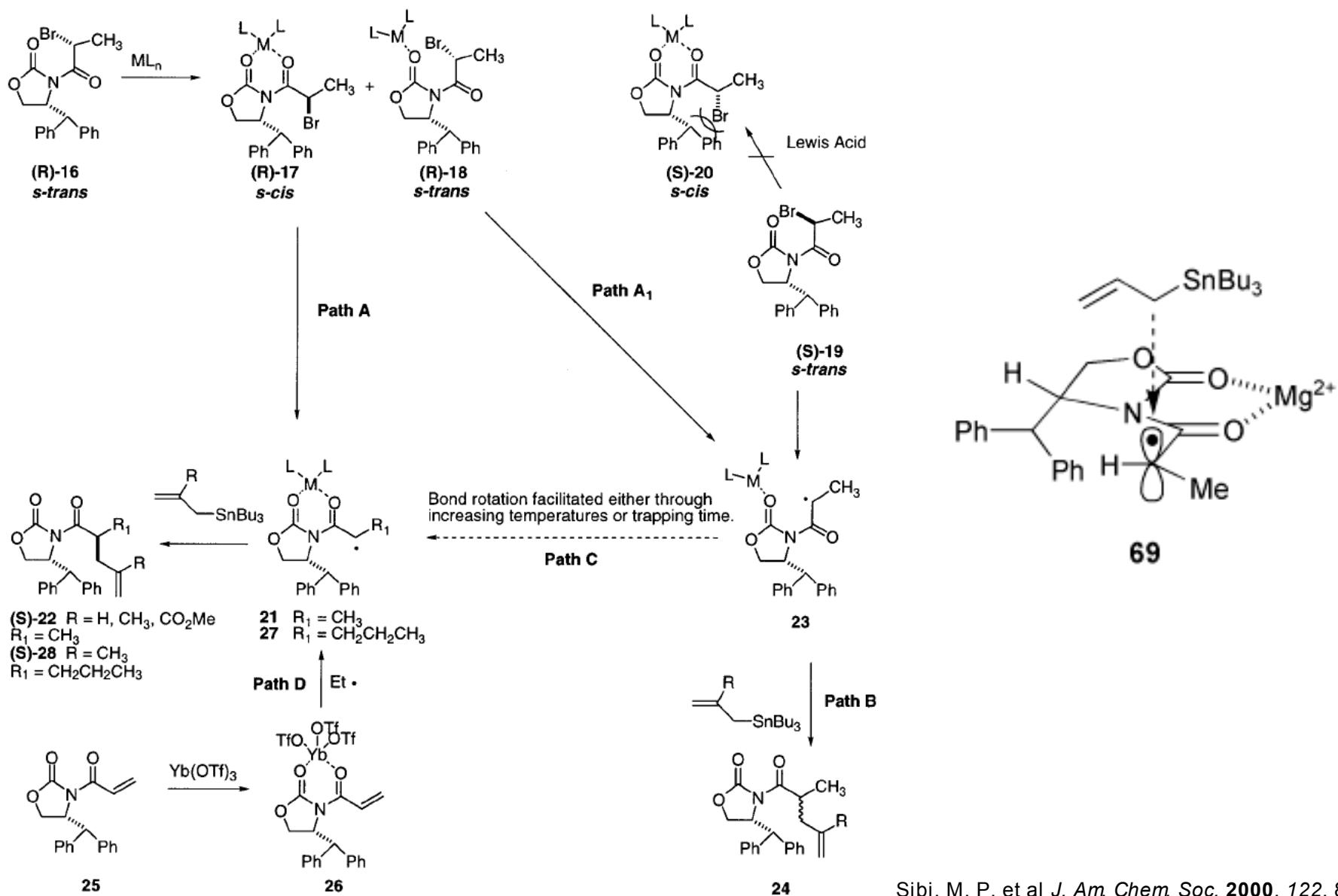
Table 3. Effect of Substrate Stereochemistry and Reaction Temperature on Product Diastereoselectivity



entry	substrate stereochem	temp	R	% yield ^{a,b}	ratio ^c
1	(R)	-78 °C	H	46 (49)	2:1 (S)
2	(S)	-78 °C	H	90	5:1 (S)
3	(R)	0 °C	H	95	50:1 (S)
4	(S)	0 °C	H	93	50:1 (S)
5	(R)	RT	H	92	> 50:1 (S)
6	(S)	RT	H	95	> 50:1 (S)
7	(R)	-78 °C	Me	81	1:1
8	(S)	-78 °C	Me	93	1:1
9	(R)	0 °C	Me	88	> 50:1 (S)
10	(S)	0 °C	Me	86	22:1 (S)
11	(R)	RT	Me	71	> 50:1 (S)
12	(S)	RT	Me	95	20:1 (S)
13	(R)	-78 °C	CO ₂ Me	41 (45)	1:2 (R)
14	(S)	-78 °C	CO ₂ Me	70 (23)	1:2 (R)
15	(R)	0 °C	CO ₂ Me	81	4:1 (S)
16	(S)	0 °C	CO ₂ Me	95	4:1 (S)
17	(R)	RT	CO ₂ Me	70	5:1 (S)
18	(S)	RT	CO ₂ Me	76	4:1 (S)

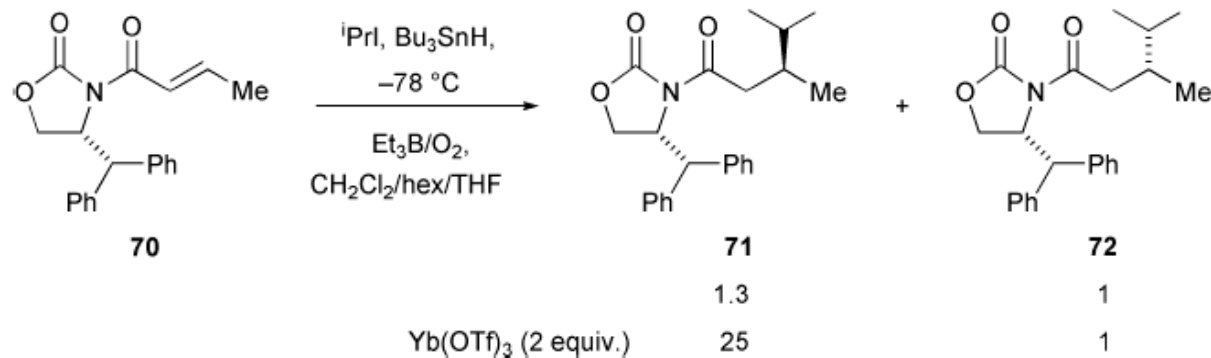
^a Yield of isolated product. ^b Yield of recovered starting material in parentheses. ^c Diastereomer ratios were determined by ¹H NMR spectroscopy (400 MHz).

Complex Controlled Diastereoselective Trapping of Radicals

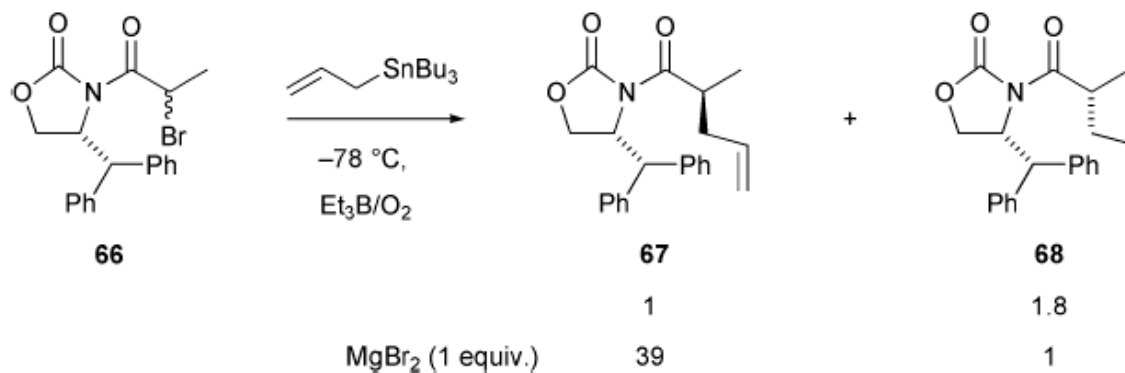


Complex Controlled Diastereoselective Reactions

Conjugate Addition



Fragmentation



Sibi, M. P. et al *J. Am. Chem. Soc.* **1999**, *121*, 751

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Enantioselective Conjugate Addition

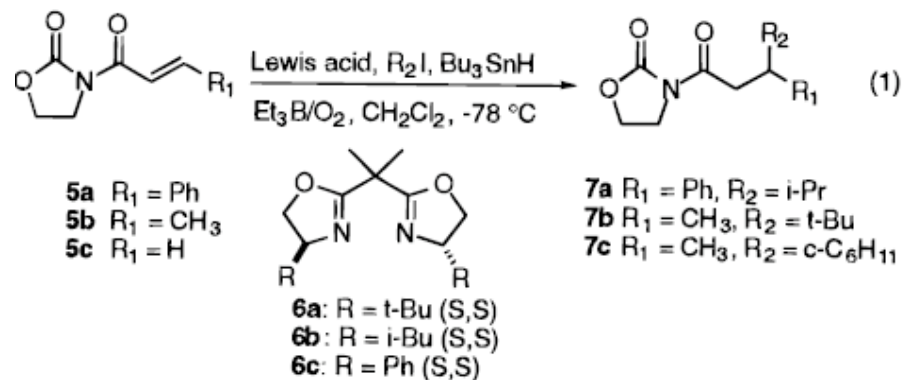


Table 1. Enantioselective Conjugate Radical Additions using Stoichiometric Chiral Lewis Acid^a

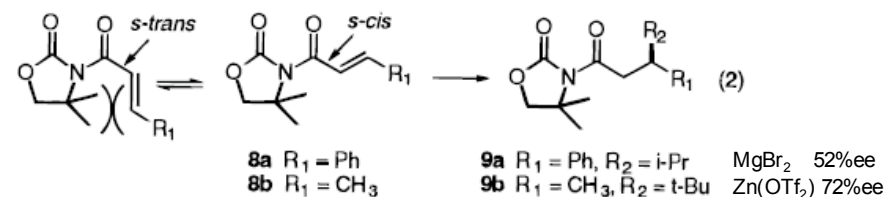
entry	substrate	product	ligand ^b	Lewis acid ^c	yield (%) ^d	ee (%) ^e
1	5a	7a	<i>SS</i> - 6a	Zn(OTf) ₂	61	37 (<i>R</i>)
2	5a	7a	<i>SS</i> - 6a	Mg(OTf) ₂	61	45 (<i>R</i>)
3	5a	7a	<i>SS</i> - 6a	MgBr ₂	92	77 (<i>R</i>)
4	5a	7a	<i>SS</i> - 6a	MgI ₂	88	61 (<i>R</i>)
5	5a	7a	<i>SS</i> - 6b	MgI ₂	88	82 (<i>R</i>)
6	5a	7a	<i>SS</i> - 6c	MgI ₂	88	47 (<i>S</i>)
7	5a	7a	<i>RR</i> - 6c	MgBr ₂	84	32 (<i>R</i>)
8	5a	7a	<i>SS</i> - 6c	Zn(OTf) ₂	88	61 (<i>S</i>)
9	5b	7c	<i>RR</i> - 6c	Zn(OTf) ₂	66	72 (<i>R</i>)
10	5b	7b	<i>RR</i> - 6c	Zn(OTf) ₂	90	82 (<i>R</i>)
11	5b	7b	<i>RR</i> - 6c	Mg(OTf) ₂	60	55 (<i>R</i>)
12	5b	7b	<i>RR</i> - 6c	Mg(ClO ₄) ₂	71	64 (<i>R</i>)
13	5b	7b	<i>SS</i> - 6a	MgBr ₂	78	82 (<i>R</i>)
14	5b	7b	<i>SS</i> - 6b	MgI ₂	88	74 (<i>R</i>)

^a For standard experimental conditions, see supporting information. ^b One equivalent of the ligand was used. ^c One equivalent of the Lewis acid was used. ^d Yields are for column or preparative TLC purified material. ^e Enantiomeric excess was determined by chiral HPLC analysis. The absolute stereochemistry of the product was determined by independent synthesis, X-ray analysis of a derivative, or hydrolysis (see supporting information for details).

Table 2. Enantioselective Radical Additions using Catalytic Chiral Lewis Acid^a

entry	substrate	product	Lewis acid/ligand	LA ^b (equiv)	yield (%) ^c	ee (%) ^d
1	5a	7a	MgI ₂ / 6b	1.0	88	82
2	5a	7a	MgI ₂ / 6b	0.5	86	79
3	5a	7a	MgI ₂ / 6b	0.2	86	67
4	5a	7a	MgI ₂ / 6b	0.05	57	40
5	5b	7b	MgI ₂ / 6b	1.0	88	74
6	5b	7b	MgI ₂ / 6b	0.2	73	66
7	5b	7b	Zn(OTf) ₂ / 6c	1.0	90	82
8	5b	7b	Zn(OTf) ₂ / 6c	0.2	71	70

^a For experimental conditions, see supporting information. ^b A 1:1 ratio of Lewis acid to ligand was used. ^c Yields are for column or preparative TLC purified material. ^d Enantiomeric excess was determined by chiral HPLC analysis.



Enantioselective Conjugate Addition

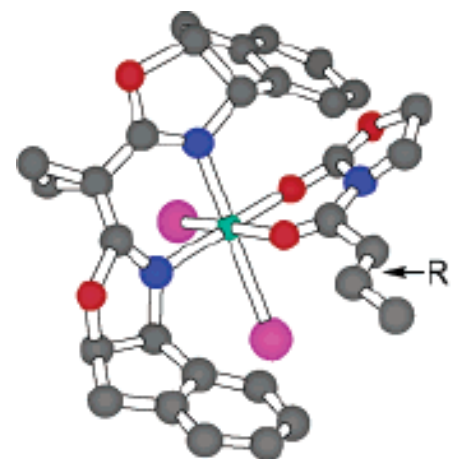
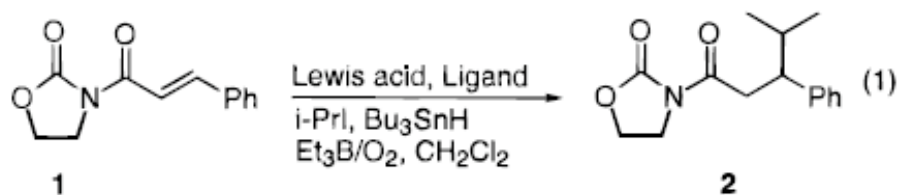
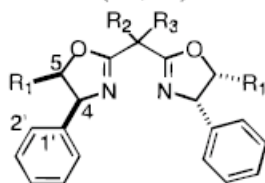
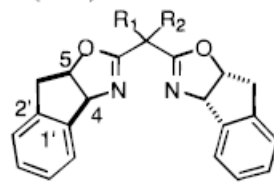


Table 1. Enantioselective Radical Additions Using MgI_2 as Lewis Acid. Effect of Ligand Structure^a

entry	ligand (stereochem)	yield ^b (%)	% ee (er) ^{c,d}	stereochemistry ^e
1	3a (<i>SS</i>)	88	47 (2.8:1)	<i>S</i>
2	3b (<i>SS</i>)	87	37 (2.1:1)	<i>S</i>
3	3c (<i>4S,5R</i>)	79	31 (2.0:1)	<i>S</i>
4	3d (<i>4S,5R</i>)	88	36 (2.1:1)	<i>S</i>
5	3e (<i>4S,5R</i>)	88	89 (17:1)	<i>R</i>
6	3f (<i>4S,5R</i>)	88	93 (28:1)	<i>R</i>
7	3g (<i>4S,5R</i>)	90	82 (10:1)	<i>R</i>
8	3h (<i>4S,5R</i>)	92	82 (10:1)	<i>R</i>



3a $R_1 = H, R_2 = R_3 = CH_3$
3b $R_1 = H, R_2, R_3 = (CH_2CH_2)$
3c $R_1 = CH_3, R_2 = R_3 = CH_3$
3d $R_1 = CH_3, R_2, R_3 = (CH_2CH_2)$



3e $R_1 = R_2 = CH_3$
3f $R_1, R_2 = (CH_2CH_2)$
3g $R_1, R_2 = (CH_2CH_2CH_2)$
3h $R_1, R_2 = (CH_2CH_2CH_2CH_2)$

Table 2. Enantioselective Radical Additions Using MgI_2 and Ligand **3f**. Effect of Stoichiometry and Temperature^a

entry	Lewis acid ^b (mol %)	T ($^{\circ}C$)	yield ^c (%)	ee ^d (%)	er ^e
1	100	-78	88	93	28:1
2	50	-78	90	96	49:1
3	40	-78	94	97	66:1
4	30	-78	91	97	66:1
5	20	-78	95	96	49:1
6	10	-78	88	95	39:1
7	5	-78	92	90	19:1
8	1	-78	29	63	4:1
9	30	-42	84	96	49:1
10	30	-20	93	95	39:1
11	30	0	91	94	32:1
12	30	25	87	93	28:1
13	20	-20	88	93	28:1
14	10	-20	83	86	13:1

^a For reactions conditions see the Supporting Information. ^b A 1:1 ratio of Lewis acid to ligand was used in all experiments.

^c Yields are for purified and isolated materials. ^d Ee's were determined by chiral HPLC analysis using a Chiralcel OD column.

^e Enantiomeric ratios are rounded off to the nearest integer.

Enantioselective Conjugate Addition : Role of Additives

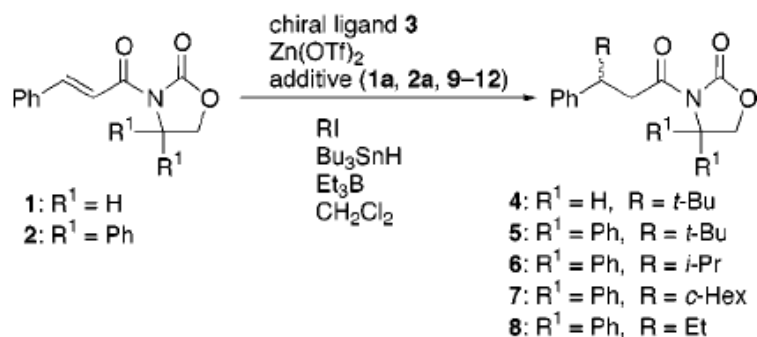


Table 1. Enantioselective Radical-Mediated Conjugate Additions of *tert*-Butyl Radical to **1** or **2** in the Presence of Zn(OTf)₂ and **3**^a

entry	substrate	additive	yield (%) ^b	ee (%) ⁴	config ⁴
1	1	none	88	9	<i>S</i>
2	1	1a	86	41	<i>S</i>
3	1	2a	78	52	<i>S</i>
4	2	none	80	3	<i>S</i>
5	2	2a	96	88	<i>R</i>

^a Stoichiometric amounts of catalysts were used (catalyst:substrate = 1:1). Zn(OTf)₂:**3**:additive = 1:1:1. All reactions were carried out by use of 2 equiv each of *t*-BuI, Bu₃SnH, and Et₃B for a substrate in CH₂Cl₂ at -78 °C. ^b Isolated yield.

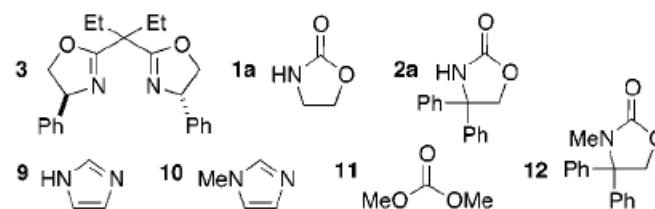


Table 2. Enantioselective Radical-Mediated Conjugate Additions of Isopropyl Radical to **2** in the Presence of **3** and Zn(OTf)₂^a

entry	additive	yield (%) ^b	ee (%) ⁸	config ⁸
1	none	72	32	<i>S</i>
2	2a	86	82	<i>R</i>
3	9	74	13	<i>S</i>
4	10	89	14	<i>S</i>
5	11	95	28	<i>S</i>
6	12	98	29	<i>S</i>

^a Stoichiometric amounts of catalysts were used (catalyst: **2** = 1:1). Zn(OTf)₂:**3**:additive = 1:1:1. All reactions were carried out by use of 2 equiv each of *i*-PrI, Bu₃SnH, and Et₃B for **2** in CH₂Cl₂ at -78 °C. ^b Isolated yield.

Enantioselective Conjugate Addition: Role of Additives

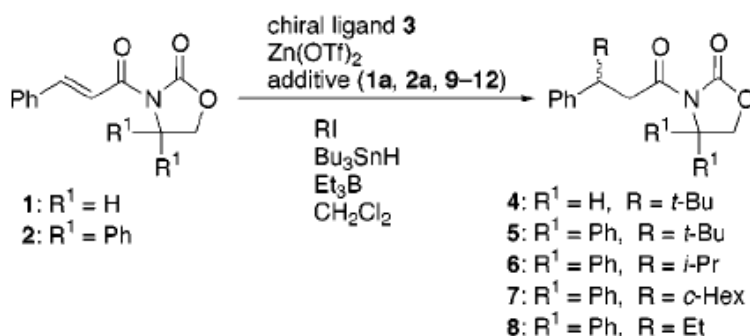


Table 3. Enantioselective Radical-Mediated Conjugate Additions of Radicals to **2** in the Presence of Zn(OTf)₂ and **3**^a

entry	R-I	chiral LA (equiv)	additive	yield (%) ^b	ee (%) ^{4,8,14}	config ^{4,8,14}
1	<i>i</i> -Pr	0.5	none	85	24	<i>S</i>
2	<i>i</i> -Pr	0.5	2a	87	84	<i>R</i>
3	<i>i</i> -Pr	0.25	2a	92	80	<i>R</i>
4	<i>t</i> -Bu	0.25	2a	72	83	<i>R</i>
5	<i>o</i> -Hex	1.0	none	80	4	<i>R</i>
6	<i>o</i> -Hex	1.0	2a	83	81	<i>R</i>
7	<i>o</i> -Hex	0.25	2a	86	84	<i>R</i>
8	Et	1.0	none	73	5	<i>R</i>
9	Et	1.0	2a	92	71	<i>S</i>
10	Et	0.25	2a	91	72	<i>S</i>

^a Stoichiometric (catalyst: **2** = 1:1) and substoichiometric (catalyst: **2** = 1:2 or 1:4) amounts of catalyst were used. Zn(OTf)₂:**3**:**2a** = 1:1:1. All reactions were carried out by use of 2 equiv each of alkyl iodide and Bu₃SnH for **2**, and Et₃B (2–4 equiv for catalyst) in CH₂Cl₂ at –78 °C. See ref 13.

^b Isolated yield.

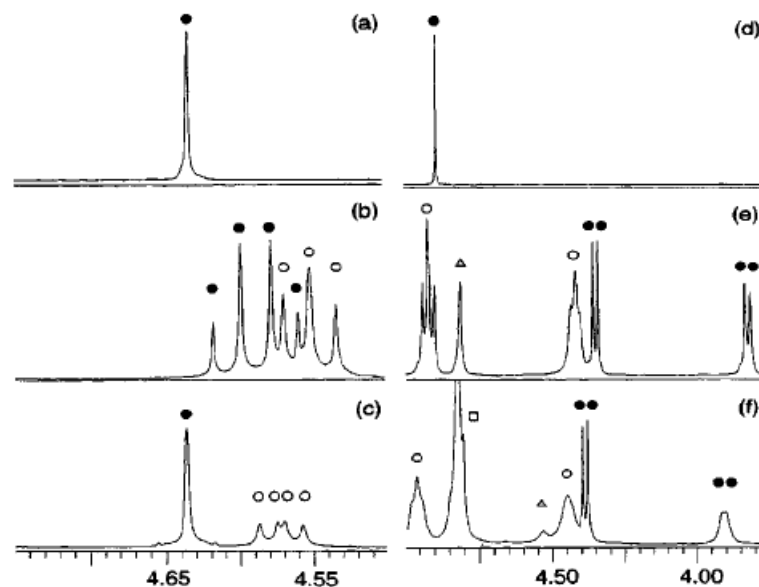
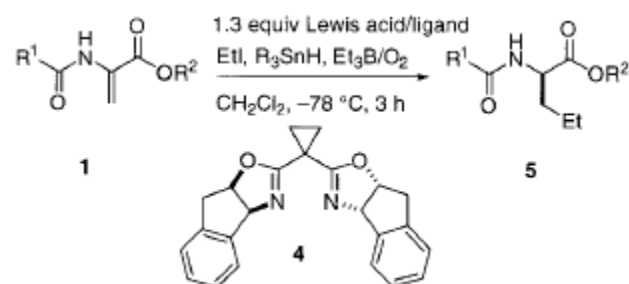
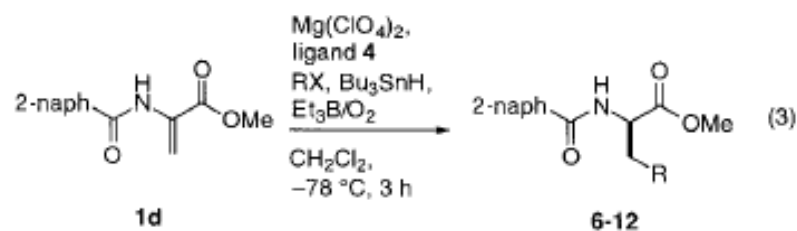


Figure 2. ¹H NMR (500 MHz) spectra: (a) **12**; (b) Zn(OTf)₂–**3** and **12**; (c) Zn(OTf)₂–**3** and **12** with 2 equiv of **2**; (d) **2a**; (e) Zn(OTf)₂–**3** and **2a**; (f) Zn(OTf)₂–**3** and **2a** with 2.5 equiv of **2**. ●: **12** or **2a**. ○: **3**. □: **2**. △: water (contamination).

Enantioselective Conjugate Addition: Manipulation of the Template



Entry	Compd	R ¹	R ²	Lewis acid	H-Atom donor (equiv)	Yield [%] ^[b]	ee [%] ^[c]
1	1a	Ph	Me	Mg(ClO ₄) ₂	Bu ₃ SnH (2)	62	17
2	1b	OBn	Me	Mg(ClO ₄) ₂	Bu ₃ SnH (2)	61	22
3	1c	1-naph	Me	Mg(ClO ₄) ₂	Bu ₃ SnH (2)	55	47
4	1d	2-naph	Me	Mg(ClO ₄) ₂	Bu ₃ SnH (2)	72	85
5	1e	2-naph	Bn	Mg(ClO ₄) ₂	Bu ₃ SnH (2)	57	68
6	1f	2-naph	<i>t</i> Bu	Mg(ClO ₄) ₂	Bu ₃ SnH (2)	56	71
7	1d	2-naph	Me	MgBr ₂	Bu ₃ SnH (2)	57	27
8	1d	2-naph	Me	MgI ₂	Bu ₃ SnH (2)	36	16
9	1d	2-naph	Me	Mg(OTf) ₂	Bu ₃ SnH (2)	33	3
10	1d	2-naph	Me	Zn(OTf) ₂	Bu ₃ SnH (2)	42	0
11	1d	2-naph	Me	Mg(ClO ₄) ₂	Bu ₃ SnH (10)	79	84
12	1d	2-naph	Me	Mg(ClO ₄) ₂	Ph ₃ SnH (2)	50	85
13	1d	2-naph	Me	Mg(ClO ₄) ₂	Ph ₃ SnH (5)	77	83
14	1d	2-naph	Me	Mg(ClO ₄) ₂	(TMS) ₃ SiH (2)	6	14



Entry	RX	Prod.	Yield [%] ^[b]	ee [%] (config.) ^[c]
1	AcBr	6	76	80
2	MeOCH ₂ Br	7	71	65
3	EtI	8	72	85 (<i>R</i>)
4	<i>t</i> BuI	9	76	79
5	<i>i</i> PrI	10	62	83 (<i>R</i>)
6	<i>c</i> HexI	11	62	55 (<i>R</i>)
7	<i>t</i> BuI	12	54	27 (<i>R</i>)

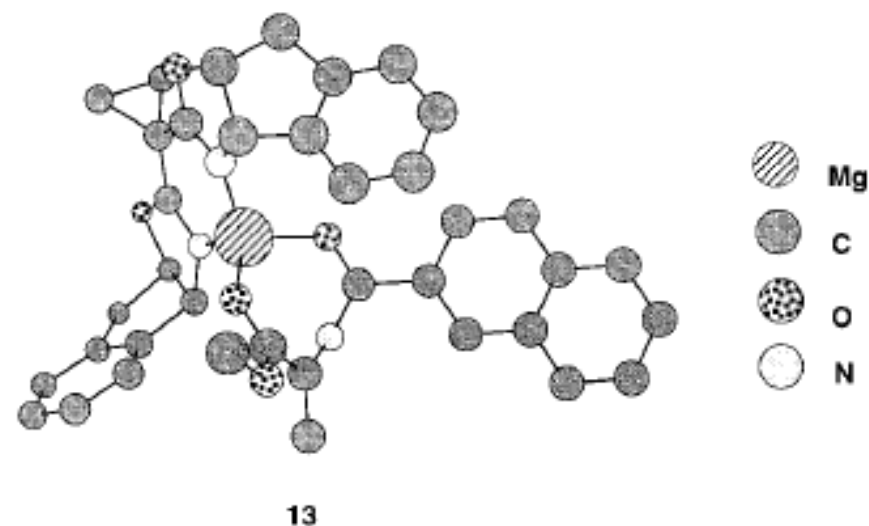
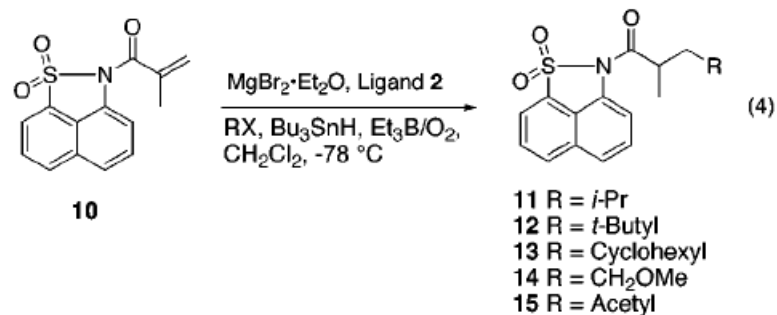
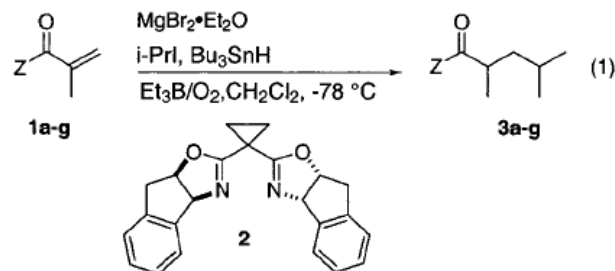


Figure 1. 7-Membered chelate. Shielding of the *Re*-face is observed.

Enantioselective Conjugate Addition: Manipulation of the Template



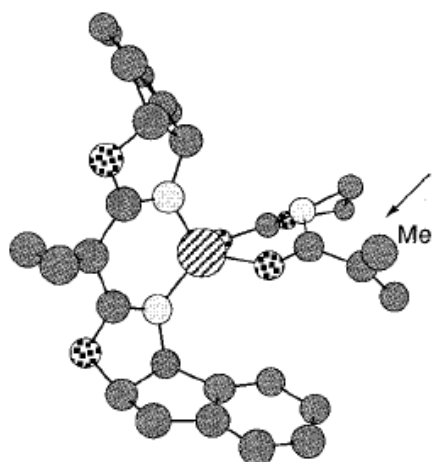
Entry	Comp	Z	Yield, % ^a	ee, % (Config)
1	1a		52	15 ^b (R)
2	1b		54	38 ^b (R)
3	1c		66	15 ^b (R)
4	1d		54	15 ^c (S)
5	1e		80	65 ^c (S)
6	1f		76	42 ^c (S)
7	1g		67	28 ^c (S)

^a Isolated yield. ^b ee determined by optical rotation of the hydrolysis product: see Supporting Information. ^c ee determined by chiral HPLC analysis.

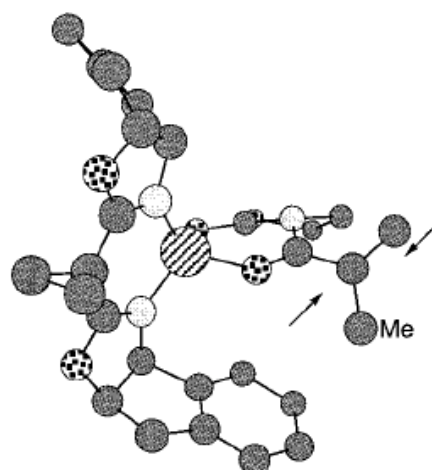
entry	product	temp, °C	Lewis acid (equiv)	hydride	yield, % ^c	ee, % ^d
1	11	-78	none ^b	Bu ₃ SnH	<5	0
2	11	-78	MgBr ₂ ·Et ₂ O (1.0)	Bu ₃ SnH	90	78
3	11	-78	MgBr ₂ ·Et ₂ O (0.3)	Bu ₃ SnH	80	80 ^e
4	11	-40	MgBr ₂ ·Et ₂ O (0.3)	Bu ₃ SnH	71	59
5	11	0	MgBr ₂ ·Et ₂ O (0.3)	Bu ₃ SnH	52	5
6	11	-78	MgBr ₂ ·Et ₂ O (1.0)	Ph ₃ SnH	59	88
7	11	-78	MgBr ₂ ·Et ₂ O (0.3)	Ph ₃ SnH	55	80
8	11	-40	MgBr ₂ ·Et ₂ O (1.0)	Ph ₃ SnH	51	42
9	12	-78	MgBr ₂ ·Et ₂ O (1.0)	Bu ₃ SnH	91	80
10	12	-78	MgBr ₂ ·Et ₂ O (0.3)	Bu ₃ SnH	84	89 ^e
11	12	-78	MgBr ₂ ·Et ₂ O (1.0)	Ph ₃ SnH	32	78
12	13	-78	MgBr ₂ ·Et ₂ O (1.0)	Bu ₃ SnH	96	89
13	13	-78	MgBr ₂ ·Et ₂ O (0.3)	Bu ₃ SnH	71	82 ^e
14	13	-78	MgBr ₂ ·Et ₂ O (1.0)	Ph ₃ SnH	72	83
15	14	-78	MgBr ₂ ·Et ₂ O (1.0)	Bu ₃ SnH	91	86
16	14	-78	MgBr ₂ ·Et ₂ O (0.3)	Bu ₃ SnH	89	90
17	14	-78	MgBr ₂ ·Et ₂ O (1.0)	Ph ₃ SnH	95	87
18	14	-78	MgBr ₂ ·Et ₂ O (0.3)	Ph ₃ SnH	93	88
19	15	-78	MgBr ₂ ·Et ₂ O (1.0)	Bu ₃ SnH	<25	18

^a Reactions were performed on a 0.2 mmol scale. ^b No Lewis acid was added. ^c Isolated yields. ^d ee's were determined from chiral HPLC analysis. ^e Reactions were performed on a 0.5 mmol scale with 30 mol % of the chiral Lewis acid.

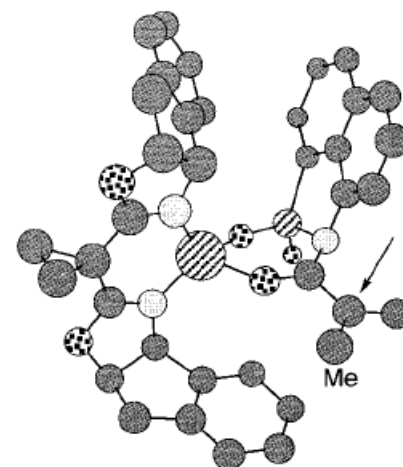
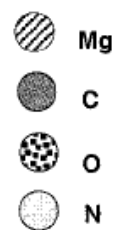
Enantioselective Conjugate Addition: Manipulation of the Template



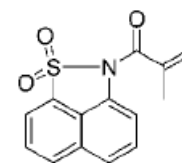
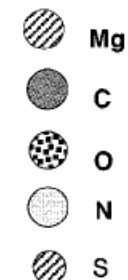
E *s-trans* rotamer
Oxazolidinone template **1e**
and Ligand **2**
Arrow shows direction
of H-atom transfer



F *s-trans* rotamer
Oxazolidinone template **1e**
and Ligand **2**
Arrow shows direction
of H-atom transfer



s-trans rotamer
G Sultam template **10**
and Ligand **2**
Arrow shows direction
of H-atom transfer



10

Enantioselective Conjugate Addition: Lost with Lanthanides

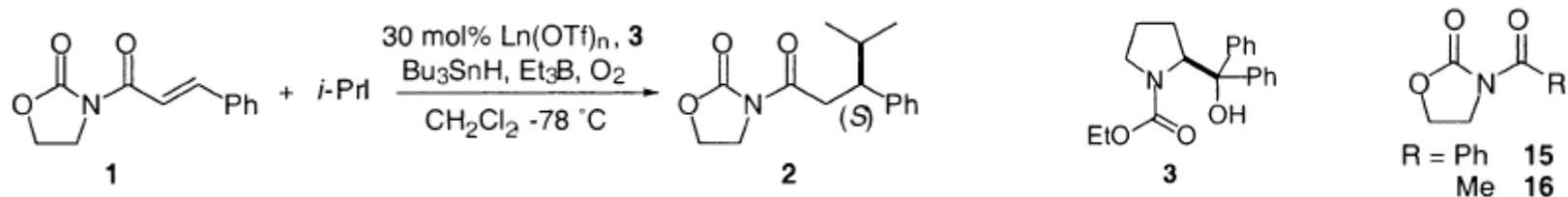


Table 1. Effect of Lewis Acid on Enantioselectivity^{a-c}

entry	Lewis acid	yield (%)	ee (%)
1	La(OTf) ₃	88	64
2	Nd(OTf) ₃	84	76
3	Sm(OTf) ₃	84	79
4	Eu(OTf) ₃	62	58
5	Y(OTf) ₃	83	62
6	Yb(OTf) ₃	87	39
7	Hf(OTf) ₄	34	0

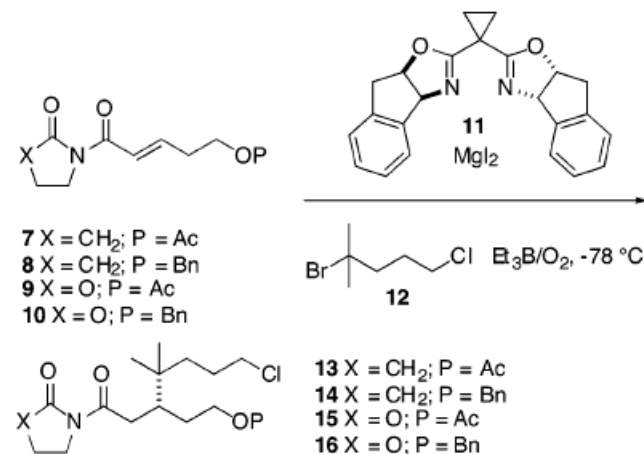
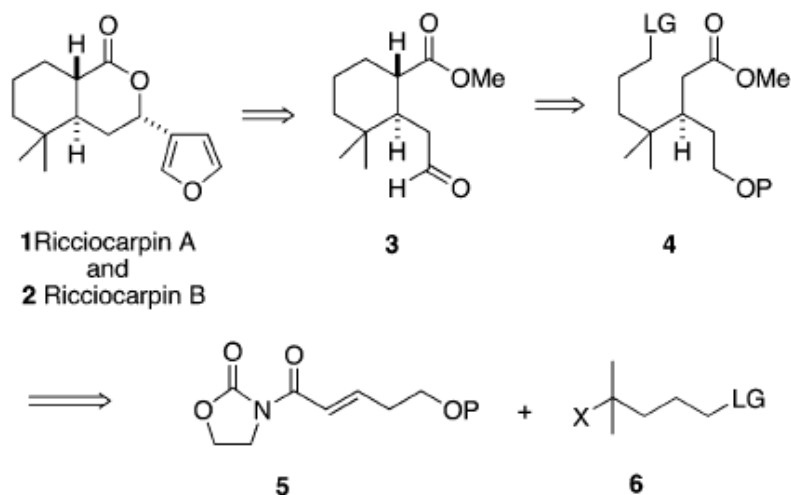
^a Entries arranged from large to small lanthanides. ^b For reaction details, see Supporting Information. Values of ees were determined using chiral HPLC. ^c Configuration of **2** was established by comparison of the HPLC retention times with that in ref 6a.

Table 2. Effect of Additives

entry	additive (equiv)	yield (%) ^a	ee (%) ^b
1	none	84	79
2	3 (1 equiv) ^c	72	64
3	3 (2 equiv) ^c	86	58
4	(±)- 2 (2 equiv)	84	49 ^d
5	HOCH ₂ CH ₂ OH (2 equiv)	73	64
6	15 (1 equiv)	84	82
7	15 (2 equiv)	67	89
8	15 (3 equiv)	63	89
9	16 (2 equiv)	95	84
10	MS 4 Å (17 mg)	67	73
11	MS 4 Å (150 mg)	45	83
12	15 (2 equiv) + MS 4 Å (150 mg)	63	92

^a Isolated yields. The amount of Lewis acid used was 30 mol %. ^b HPLC analysis was used to determine ees. ^c Amount in parentheses refers to the extra ligand added. ^d See Supporting Information for calculation of the ee.

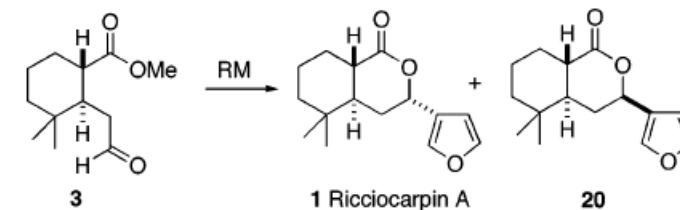
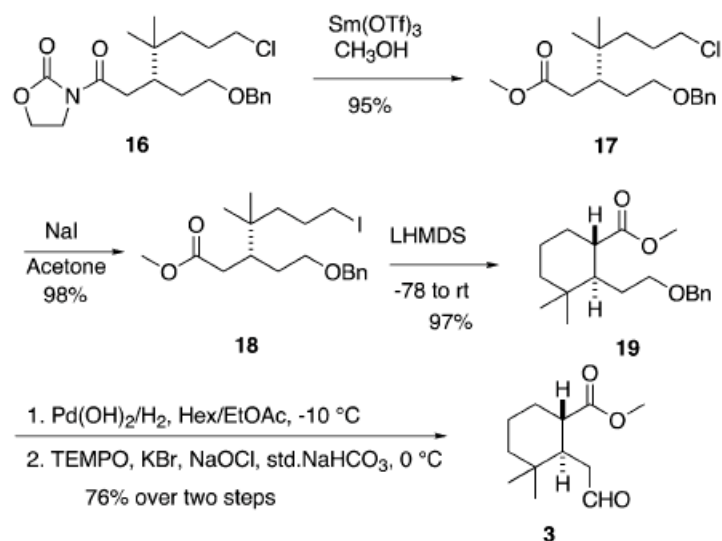
Enantioselective Conjugate Addition : Application to Synthesis



entry	sm	X	P	prod. ^a	yield, (%) ^b	ee, % ^c
1 ^d	7	CH ₂	COCH ₃	13	31	84
2 ^d	8	CH ₂	CH ₂ C ₆ H ₅	14	<10	-
3 ^d	9	O	COCH ₃	15	70	95
4 ^d	10	O	CH ₂ C ₆ H ₅	16	84	97
5 ^e	10	O	CH ₂ C ₆ H ₅	16	50	97
6 ^f	10	O	CH ₂ C ₆ H ₅	16	16	93

^a For reaction conditions, see Supporting Information. ^b Isolated yield after column purification. ^c Determined by chiral HPLC. ^d Performed with 100 mol % of the chiral Lewis acid. ^e Performed with 50 mol % of the chiral Lewis acid. ^f Performed with 30 mol % of the chiral Lewis acid.

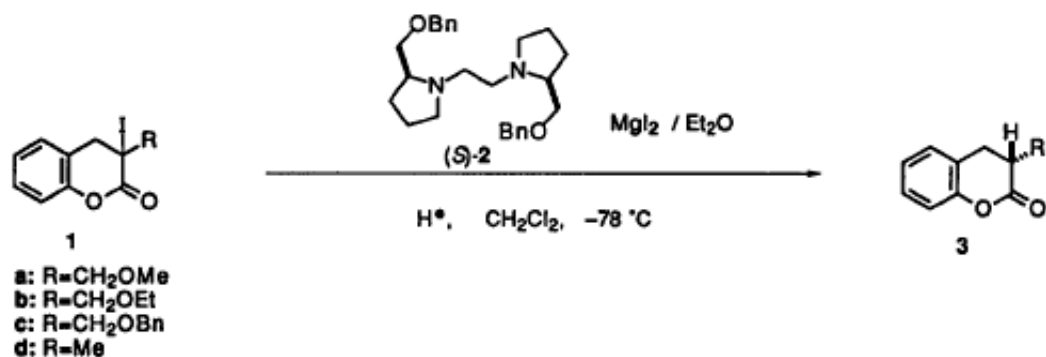
Enantioselective Conjugate Addition : Application to Synthesis



entry	RM	temp °C	solv.	time, h	yield, (%) ^b	ratio ^c 1:2 0
1		-78	THF	6	33	1:3
2		-78	Ether	5	26	1:7.8
3		-78	Ether	3	21	1:6
4 ^d		0	Ether	10	8	1:3
5		-78	THF	4	28	1:1
6		-78	Ether	4	85	5.7:1

^a For reaction conditions, see Supporting Information. ^b Isolated yield after column purification. ^c Determined by NMR. ^d Pseudoephedrine was used as a ligand.

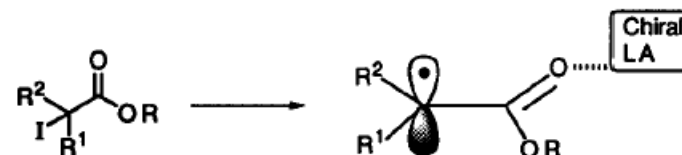
Enantioselective Radical Reactions : Hydride Transfer



Run	Substrate	Concentration of 1 (mM)	Reagent	Yield (%) ^b	ee (%)	Confign
1	1a	11	Bu ₃ SnH	75	12	R
2	1a	21	Bu ₃ SnH	81	18	R
3	1a	36	Bu ₃ SnH	88	62	R
4	1a	67	Bu ₃ SnH	83	52	R
5	1a	36	Bu ₃ SnH	50	43 ^c	R
6	1a	37	Ph ₃ SnH	74	39	R
7	1a	36	(Me ₃ Si) ₃ SiH	<i>d</i>	–	–
8	1b	21	Bu ₃ SnH	76	24	R
9	1b	37	Bu ₃ SnH	84	65	R
10	1b	35	Ph ₃ SnH	83	62	R
11	1c	21	Bu ₃ SnH	80	28	R
12	1c	38	Bu ₃ SnH	89	58	R
13	1c	35	Ph ₃ SnH	85	46	R
14	1d	35	Bu ₃ SnH	78	30	S
15	1d	30	Bu ₃ SnH ^e	82	33	S

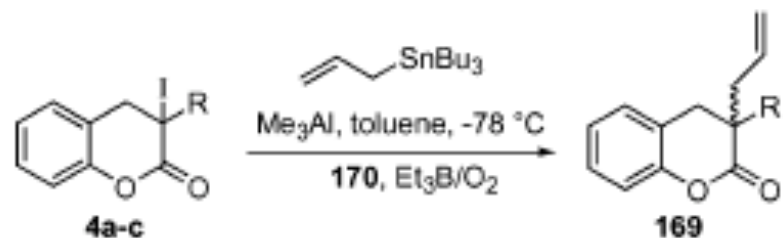
^a All reactions were carried out according to Scheme 1, unless otherwise noted. For details, see experimental section.

^b Isolated yield. ^c Reaction was carried out at –50 °C. ^d No reaction. ^e 2 equiv. of Bu₃SnH was used.

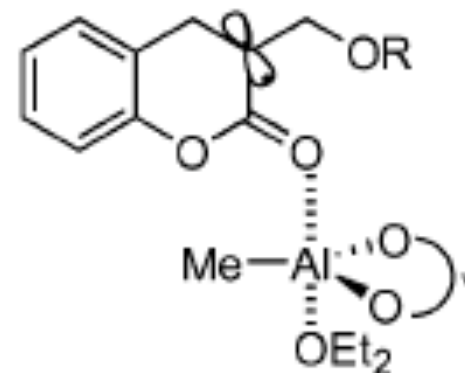
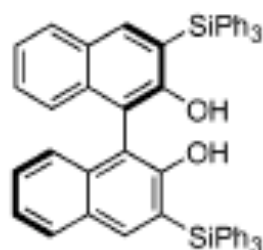


Murakata, M. et al *Chem Comm* **1995**, 481.
 Murakata, M et al *Tetrahedron*, **1999**, 55, 1029

Fragmentation and Enantioselective Trapping



Entry	R	CLA (eq.)	Additive	Yield (%)	ee (%)
1	Me	1.0	-	72	27 (<i>R</i>)
2	Me	1.0	Et_2O	84	81 (<i>R</i>)
3	CH_2OMe	1.0	-	75	10 (<i>S</i>)
4	CH_2OMe	1.0	Et_2O	85	82 (<i>R</i>)
5	CH_2OMe	1.0	$i\text{-Pr}_2\text{O}$	83	43 (<i>R</i>)
6	CH_2OMe	1.0	THF	71	33 (<i>R</i>)
7	CH_2OMe	1.0	NMP	59	3 (<i>R</i>)
8	CH_2OBn	1.0	-	72	3 (<i>S</i>)
9	CH_2OBn	1.0	Et_2O	76	91 (<i>R</i>)
10	CH_2OBn	0.2	Et_2O	73	82 (<i>R</i>)
11	CH_2OBn	0.1	Et_2O	78	71 (<i>R</i>)



Murakata, M. et al *J. Am. Chem. Soc.* **1997**, *119*, 1171;

Murakata, M. et al *Tetrahedron Asym.* **1998**, *9*, 208

Fragmentation and Enantioselective Trapping

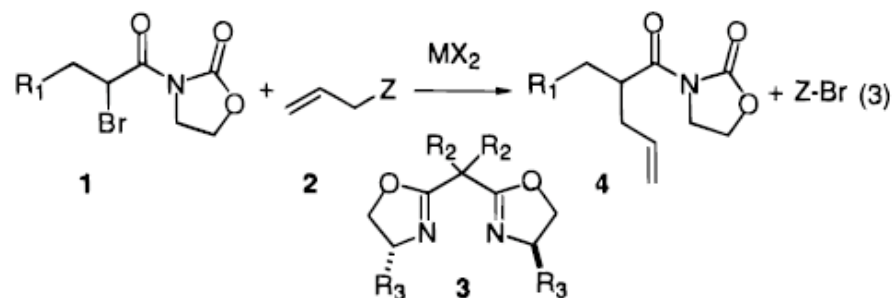
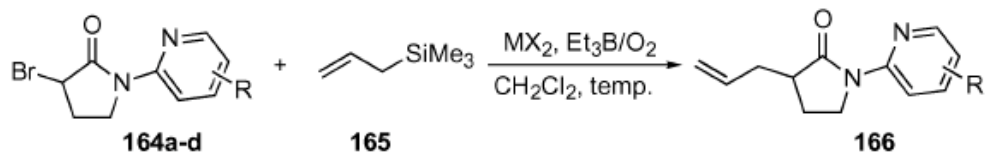


Table 1. Lewis Acid Promoted Reactions of Allylsilanes and Allylstannane^a

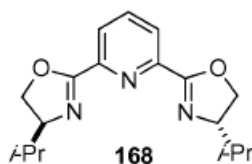
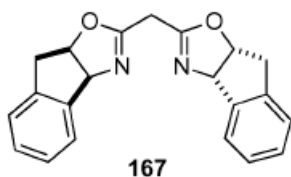
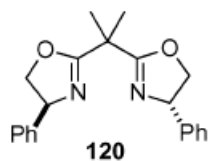
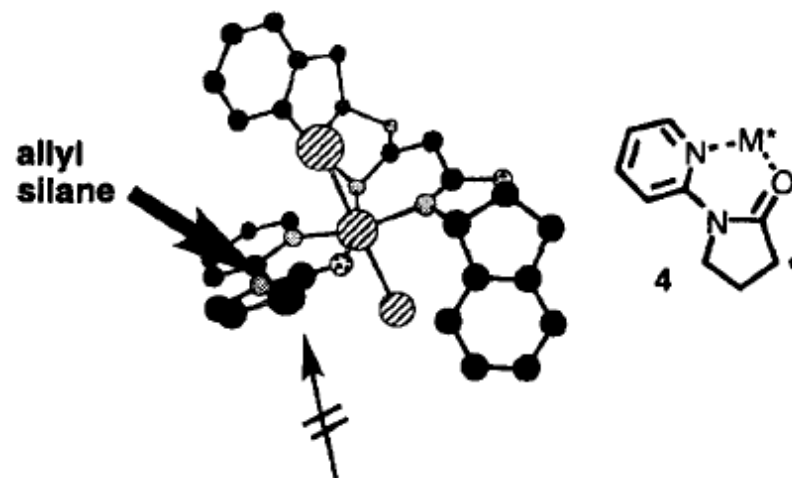
entry	R ₁	R ₂	R ₃	3 config	MX ₂	Z	yield, %	4 <i>R</i> :4 <i>S</i>
1	CH ₃	CH ₃	Ph	(<i>R,R</i>)	Zn(OTf) ₂	Sn(Bu) ₃	84 ^b	29:71
2	CH ₃	CH ₃	Ph	(<i>R,R</i>)	Zn(OTf) ₂	Si(OEt) ₃	65 ^b	20:80
3	^t Bu	CH ₃	Ph	(<i>R,R</i>)	Zn(OTf) ₂	Sn(Bu) ₃	63 ^b	87:13
4	^t Bu	CH ₃	Ph	(<i>R,R</i>)	Zn(OTf) ₂	Si(Me) ₃	88 ^c	95:5
5	^t Bu	CH ₃	Ph	(<i>R,R</i>)	MgI ₂	Si(Me) ₃	86 ^b	16:84
6	^t Bu	CH ₃	^t Bu	(<i>S,S</i>)	MgI ₂	Si(Me) ₃	61 ^c	89:11
7	^t Bu	-(CH ₂)-	^t Bu	(<i>S,S</i>)	MgI ₂	Si(Me) ₃	65 ^c	94:6
8	^t Bu	CH ₃	^t Bu	(<i>S,S</i>)	MgI ₂	Si(Me) ₃	83 ^c	91:9

^a Reaction as described in eq 3. ^b Isolated yield. ^c Yield based on GC internal standard.

Fragmentation and Enantioselective Trapping: Manipulation of the Template

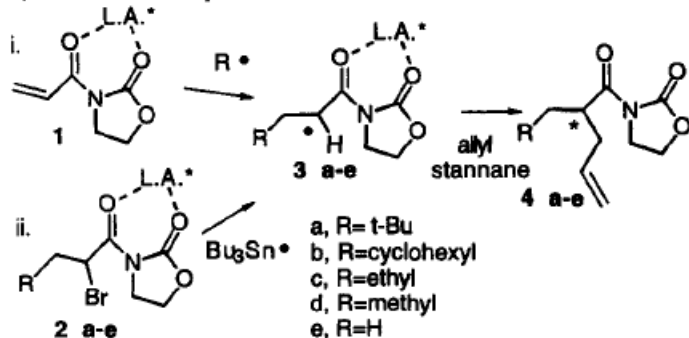


	R	Entry	Substrate	Ligand	MX ₂ (eq.)	T (°C)	Yield (%)	ee (%)
a	H	1	164a	120	Zn(OTf) ₂ (1.0)	-78	70	59 (<i>S</i>)
b	4-Me	2	164a	167	Zn(OTf) ₂ (1.0)	-78	75	96 (<i>S</i>)
c	5-Cl	3	164a	168	Zn(OTf) ₂ (1.0)	-78	42	75 (<i>R</i>)
d	5-CO ₂ Me	4	164a	167	MgBr ₂ (1.0)	-78	54	84 (<i>R</i>)
		5	164a	167	Zn(OTf) ₂ (2.0)	-78	83	>99 (<i>S</i>)
		6	164a	167	Zn(OTf) ₂ (2.0)	-20	94	95 (<i>R</i>)
		7	164a	167	Zn(OTf) ₂ (1.0)	-20	93	91 (<i>R</i>)
		8	164b	167	Zn(OTf) ₂ (1.0)	-20	85	70 (<i>R</i>)
		9	164c	167	Zn(OTf) ₂ (1.0)	-20	88	67 (<i>S</i>)
		10	164d	167	Zn(OTf) ₂ (1.0)	-20	91	80 (<i>S</i>)
		11	164a	167	Zn(OTf) ₂ (0.2)	-20	69	81 (<i>S</i>)



A Comparison

a.) Lewis acid complexed to radical



b.) Lewis acid complexed to alkene

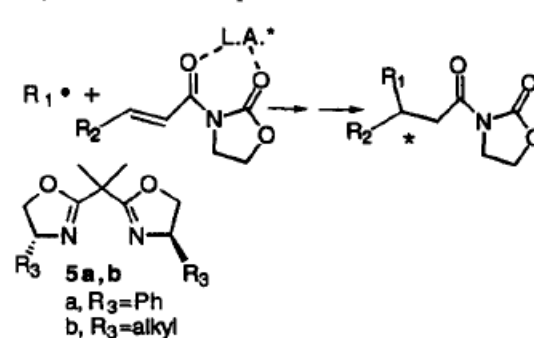
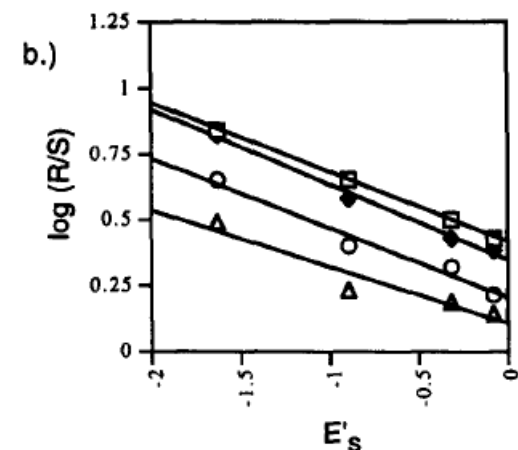
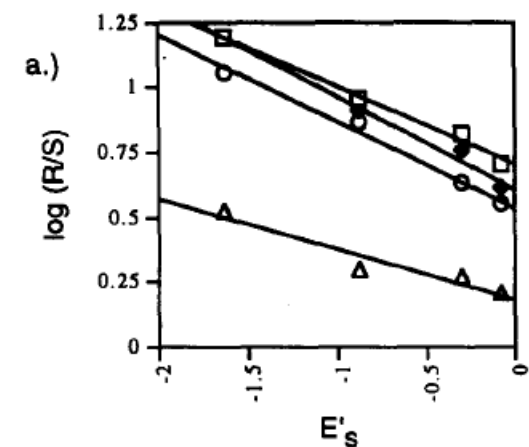


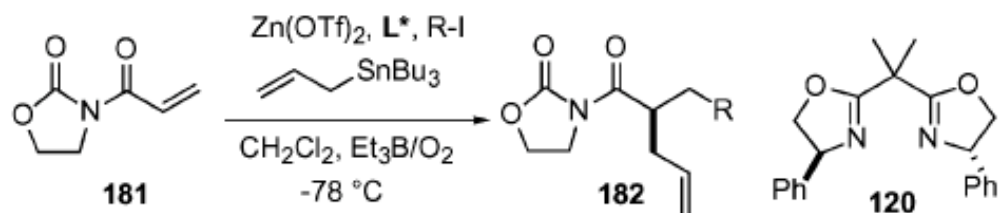
Table 1. Product Enantiomeric Excess for Reactions of R-1/1 or 2 a-d with Allyl Stannane in the Presence of Zinc Triflate and Bisoxazoline 5a at -78°C.^{a,b}

entry	Precursor	Lewis acid eq.	R=methyl	R=ethyl	R=c-hexyl	R=t-butyl
1	1	0.2	22	30	34	54
2	1	0.6	56	62	76	84
3	1	1.0	61	69	78	90
4	1	2.0	67	75	80	90
5	2	0.2	16	22	26	52
6	2	0.6	25	36	43	64
7	2	1.0	42	50	58	74
8	2	2.0	46	53	64	76

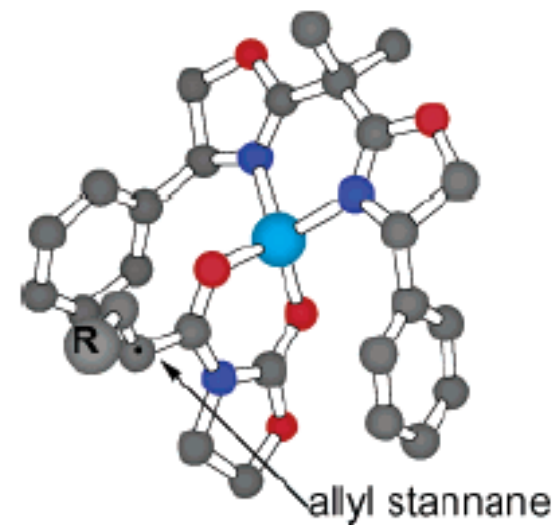
a. See Scheme 1 for a description of the transformation. b. Yields of isolated products were from 60-90%.



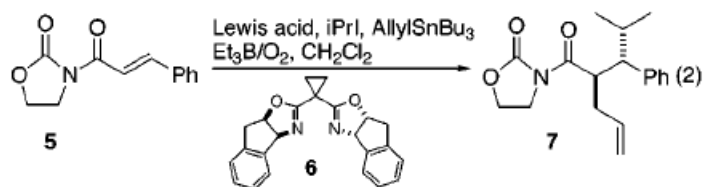
Enantioselective Radical Reactions: Tandem Reactions



Entry	RI (eq.)	L^*	181 :M: L^*	Solvent	Yield (%)	ee (%)
1	c-Hexl (10)	(<i>S,S</i>)- 120	1:1:1	CH_2Cl_2	62	50 (<i>S</i>)
2	c-Hexl (10)	(<i>S,S</i>)- 120	1:1:1	ether	90	64 (<i>S</i>)
3	c-Hexl (10)	(<i>S,S</i>)- 120	1:2:2	ether	61	80 (<i>S</i>)
4	c-Hexl (1.5)	(<i>R,R</i>)- 120	1:1:1.2	CH_2Cl_2 :pent 4:6	62	68 (<i>R</i>)
5	c-Hexl (1.5)	(<i>R,R</i>)- 120	1:2:2.4	CH_2Cl_2 :pent 4:6	92	72 (<i>R</i>)
6	<i>t</i> -Bul (5)	(<i>S,S</i>)- 120	1:1:1.2	CH_2Cl_2 :pent 4:6	78	88 (<i>S</i>)
7	<i>t</i> -Bul (5)	(<i>R,R</i>)- 120	1:1:1.2	CH_2Cl_2 :pent 4:6	92	90 (<i>R</i>)
8	<i>t</i> -Bul (5)	(<i>R,R</i>)- 120	1:2:2.1	ether	55	88 (<i>R</i>)

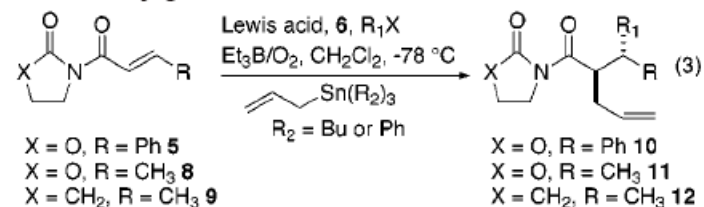


Enantioselective Radical Reactions: Tandem Reactions

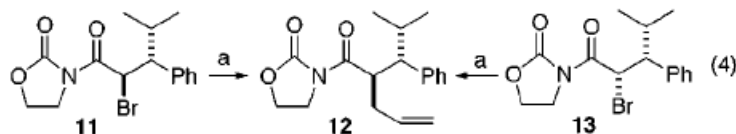


entry	Lewis acid (equiv)	temp °C	yield (%) ^a	dr ^b	ee (%) ^c
1	MgI ₂ (1)	-78	82	19:1	86
2	MgI ₂ (0.3)	-78	93	37:1	93 ^d
3	MgI ₂ (0.3)	-40	70	36:1	65
4	MgBr ₂ (0.3)	-78	90	30:1	90
5	Mg(ClO ₄) ₂ (0.3)	-78	91	40:1	87
6	Zn(OTf) ₂ (0.3)	-78	69	33:1	-43
7	Cu(OTf) ₂ (1)	-78	84 ^e	30:1	-76
8	Cu(OTf) ₂ (0.3)	-78	93 ^e	30:1	-79

^a Isolated yield. ^b Determined by NMR and HPLC. ^c Determined by HPLC. ^d Reaction using allyltriphenyltin gave **7** in 82% yield (36:1 dr and 91% ee). ^e Allyltriphenyltin was used.



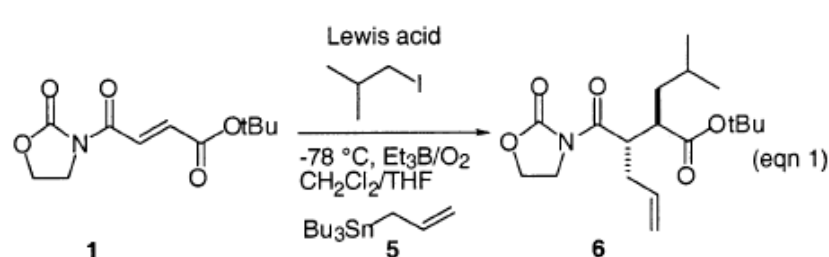
entry	sub.	R ₁ X	LA (0.3equiv)	yield (%) ^a	dr ^b	ee (%) ^c
1	5	MeOCH ₂ Br	MgI ₂	80	20:1	72
2	5	EtI	MgI ₂	79	32:1	77
3	5	c-HexI	MgI ₂	80	60:1	92
4	5	<i>i</i> -PrI	MgI ₂	93	37:1	93
5	5	<i>t</i> -BuI	MgI ₂	84	99:1	97
6	5	<i>i</i> -PrI	Cu(OTf) ₂	93 ^d	30:1	-79
7	5	<i>t</i> -BuI	Cu(OTf) ₂	90 ^d	99:1	-96
8	8	EtI	Mg(ClO ₄) ₂	83	4:1	61
9	8	c-HexI	Mg(ClO ₄) ₂	83	4:1	62
10	9	EtI	Mg(ClO ₄) ₂	83	7:1	66
11	9	c-HexI	Mg(ClO ₄) ₂	84	7:1	69
12	9	MeOCH ₂ Br	Mg(ClO ₄) ₂	83	2.4:1	53
13	9	<i>i</i> -PrI	Mg(ClO ₄) ₂	84	7:1	76
14	9	<i>i</i> -PrI	Cu(OTf) ₂	95 ^d	10:1	-76
15	9	<i>t</i> -BuI	Mg(ClO ₄) ₂	85	19:1	92
16	9	<i>t</i> -BuI	Cu(OTf) ₂	66 ^d	50:1	-83



	yield%, (dr)	yield%, (dr)	
Ligand 6	83 (12:1)	82 (7:1)	Ligand 6
no ligand	87 (5:1)	84 (6:1)	no ligand
Enantiomer of 6	87 (8:1)	84 (13:1)	Enantiomer of 6

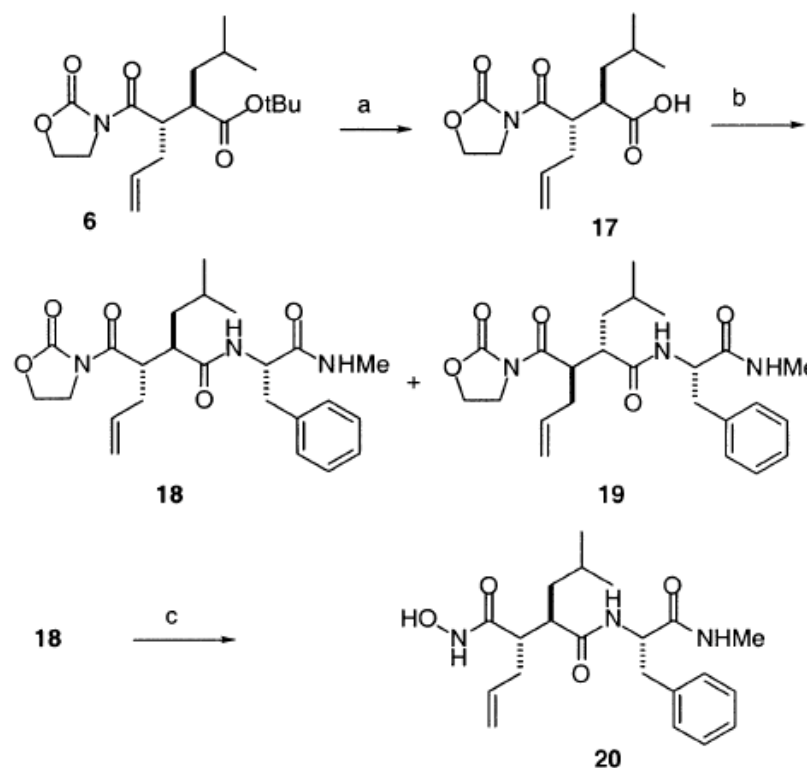
Key: ^a Mg(ClO₄)₂, AllylSnBu₃, Et₃B/O₂, CH₂Cl₂, -78 °C

Enantioselective Radical Reactions: Application to an MMP Inhibitor (Maybe?)



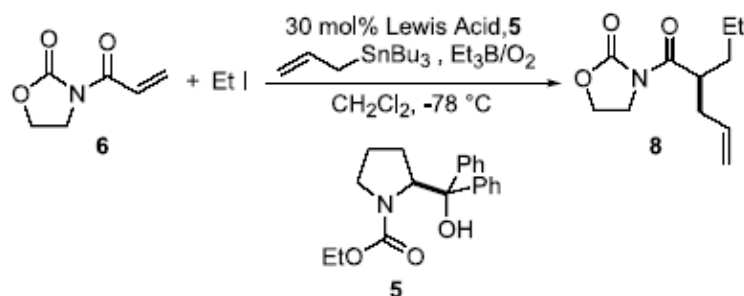
entry	Lewis acid	time (h)	yield (%) ^b	dr ^c
1		4	44	≥ 99:1
2	MgI ₂	6	26	≥ 99:1
3	Mg(ClO ₄) ₂	4	70	≥ 99:1
4	Mg(OTf) ₂	2	58	≥ 99:1
5	Al(OTf) ₃	4	41	≥ 99:1
6	In(OTf) ₃	4	43	≥ 99:1
7	Sc(OTf) ₃	4	56	≥ 99:1
8	Y(OTf) ₃	2	91	≥ 99:1
9	Sm(OTf) ₃	2	85	≥ 99:1
10	Yb(OTf) ₃	4	67	≥ 99:1

^a For reaction conditions, see Supporting Information. ^b Isolated yield.
^c Diastereomer ratio determined by ¹H NMR (500 MHz).



^a Key: (a) TFA, CH₂Cl₂, 98%. (b) EDCI/HOBT/amino acid/DMF 63% yield (36% of **18** and 27% of **19**). (c) (i) THPONH₂/Sm(OTf)₃/THF, (ii) dilute HCl workup, 75% over two steps.

Those Problematic Lanthanides

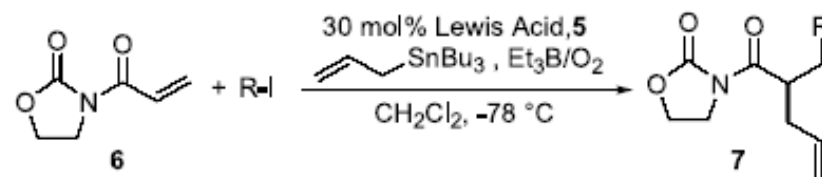


Entry	Lewis acid	Yield (%) ^a	ee (%) ^b
1	La(OTf) ₃	56	0
2	Ce(OTf) ₄	53	0
3	Sm(OTf) ₃	35	52
4	Er(OTf) ₃	35	37
5	Y(OTf) ₃	61	70
6 ^c	Y(OTf) ₃	50	20
7	Yb(OTf) ₃	45	50
8	Yb(NTf ₂) ₃	22	7
9	Sc(OTf) ₃	10	10

^a Isolated yields.

^b Chiral HPLC analysis.

^c 300 mg MS 4 Å was used.



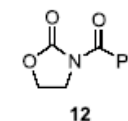
Entry	R	Product	Yield (%) ^a	ee (%) ^b
1	ClCH ₂ -	7a	56	42
2	Et	8	61	70
3 ^c	Et	8	46	66
4	<i>n</i> -Pr	7b	57	60
5	<i>n</i> -Bu	7c	41	38
6	<i>i</i> -Pr	7d	50	56
7 ^d	<i>i</i> -Pr	7d	67	68
8	<i>t</i> -Bu	7e	40	24
9 ^c	<i>t</i> -Bu	7e	48	24
10 ^d	<i>t</i> -Bu	7e	46	42
11	<i>c</i> -Hex	7f	53	31

^a Isolated yields.

^b Chiral HPLC analysis.

^c 100 mol% of the chiral Lewis acid was used.

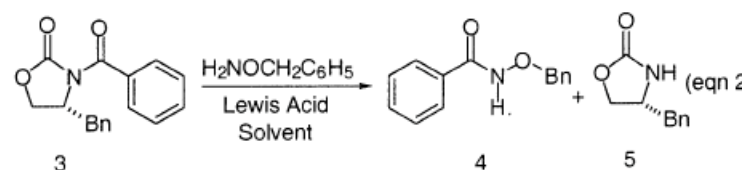
^d 2 equiv. of **12** was used as an additive.



Conclusions

- Radicals can behave as expected under controlled circumstances, when harnessed this represents a powerful methodology
- Diastereoselective radical reactions are well established and fairly well understood
- Extension to enantioselective radical reactions is still a developing field with much work need in a better understanding of the factors which control the yield and enantioselectivity of the reaction
- Ligand design and the identification of catalytic protocols have contributed to much of the recent success.
- Little application toward total synthesis has been accomplished

Table 1. Conversion of *N*-Benzoyloxazolidinone to *O*-Benzylhydroxamide^a



entry	Lewis acid (equiv)	amine (equiv)	solvent ^b	yield, ^c %
1	Sm(OTf) ₃ (1.0)	2	THF	90
2	Sm(OTf) ₃ (1.0)	2	ether	83
3	Sm(OTf) ₃ (1.0)	2	CH ₃ CN	88
4	Sm(OTf) ₃ (1.0)	5	THF	91
5	Sm(OTf) ₃ (0.5)	2	THF	90
6	Sm(OTf) ₃ (0.3)	2	THF	78
7	Yb(OTf) ₃ (1.0)	2	THF	68
8	Yb(OTf) ₃ (1.0)	2	ether	50
9	Eu(OTf) ₃ (1.0)	2	THF	80
10	Eu(OTf) ₃ (1.0)	2	ether	85
11	La(OTf) ₃ (1.0)	2	THF	50
12	La(OTf) ₃ (1.0)	2	ether	80

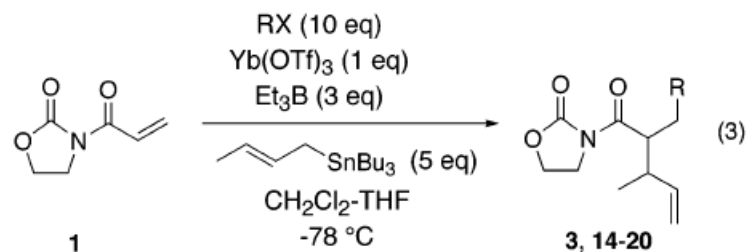
^a Reactions were carried out at rt. ^b An average concentration of 0.1–0.2 M was employed. ^c Isolated yields for column purified materials.

Table 3. Chemoselectivity and Scope of the Method^a

Entry	Acyl Oxazolidinone	Substrate concentration M	Hydroxylamine	Time h	Product	Yield ^b %
1.		0.1	BnONH ₂ (2)	5		70
2.		0.1	BnONH ₂ (2)	5		87
3.		0.5	BnONH ₂ (4)	5		70
4.		0.5	BnONH ₂ (4)	5		84
5.		0.1	BnONH ₂ (2)	1		98
6.		0.1	BnONH ₂ (2)	1		90
7.		0.2	MeONHMe (4) ^c	72		75
8.		0.2	NH ₂ OH (4) ^c	72		60

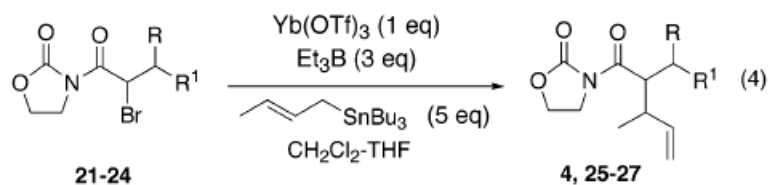
^a Reactions were carried out at room temperature using 0.3 equiv of Sm(OTf)₃ as catalyst. ^b Isolated yields for column purified materials. ^c The reaction was carried out by in situ generation of the amine (4 equiv) from the corresponding hydrochloride using triethylamine (3.8 equiv).

Enantioselective Radical Reactions: Tandem Reactions



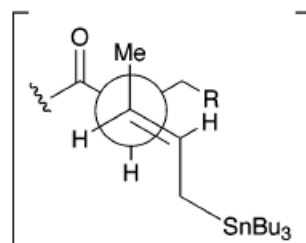
entry	RX	product	yield (%) ^a	dr ^b
1	EtI	3 R = Et	68	3.5:1
2	MeOCH ₂ Br	14 R = MeOCH ₂	48	2.0:1
3	<i>t</i> -BuI	15 R = <i>t</i> -Bu	63	2.6:1
4	<i>n</i> -Bu	16 R = <i>n</i> -Bu	58	3.4:1
5	<i>i</i> -PrI	17 R = <i>i</i> -Pr	63	3.0:1
6	<i>c</i> -hexyl I	18 R = <i>c</i> -hexyl	62	3.5:1
7	adamantyl I	19 R = adamantyl	69	5.6:1
8	<i>t</i> -BuI	20 R = <i>t</i> -Bu	75	5.4:1

^a Isolated yield. ^b Diastereomer ratio was determined by ¹H NMR (500 MHz).



entry	starting material	temp °C	product	yield (%) ^a	dr ^b
1	21 R = R ¹ = H	-78	25	78	3.0:1
2	22 R = H, R ¹ = Me	-78	26	78	2.1:1
3	23 R = H, R ¹ = Et	-78	3	85	2.9:1
4	24 R = R ¹ = Me	20	27	74	1:1
5	24 R = R ¹ = Me	-78	27	82	1.2:1

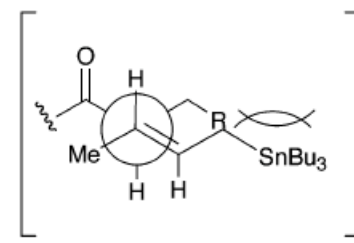
^a Isolated yield. ^b Diastereomer ratio was determined by ¹H NMR (500 MHz).



A favored



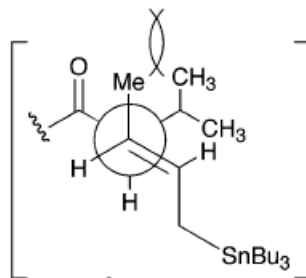
syn product



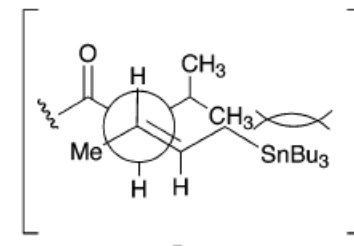
B disfavored



anti product

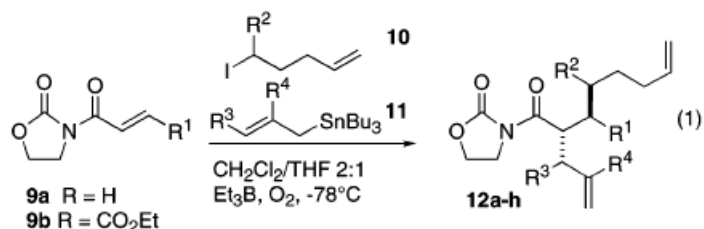


C



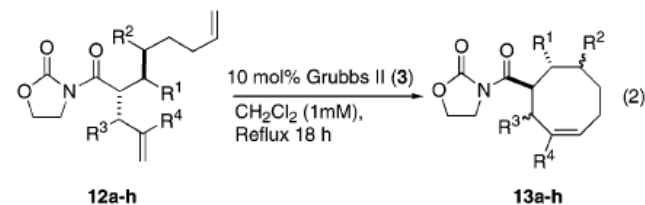
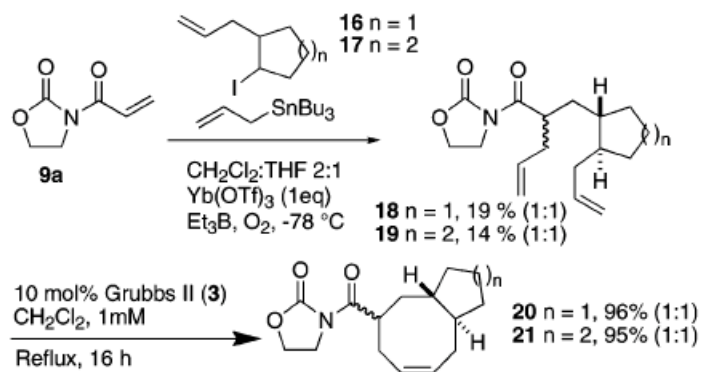
D

Enantioselective Radical Reactions: Tandem Reactions



entry	Lewis acid/ equiv	R ¹	R ²	R ³	R ⁴	product	% yield ^b
1	Y(OTf) ₃ /0.3	H	H	H	H	12a	49
2	Yb(OTf) ₃ /1.0	H	CH ₃	H	H	12b	51
3	Y(OTf) ₃ /0.3	H	H	CH ₃	H	12c	50
4	Y(OTf) ₃ /0.3	H	H	H	CH ₃	12d	47
5	Y(OTf) ₃ /0.3	CO ₂ <i>t</i> Bu	H	H	H	12e	40
6	Yb(OTf) ₃ /1.0	CO ₂ <i>t</i> Bu	CH ₃	H	H	12f	72
7	Y(OTf) ₃ /0.3	CO ₂ <i>t</i> Bu	H	CH ₃	H	12g	49
8	Y(OTf) ₃ /0.3	CO ₂ <i>t</i> Bu	H	H	CH ₃	12h	47

^a For reaction conditions see Supporting Information. ^b Isolated yields after chromatography. Diastereomer ratio was determined by NMR.



entry	diene	product	% yield ^c
1	12a	13a	43
2	12b	13b	88
3	12c	13c	33
4	12d	13d	60
5	12e	13e	70
6	12f	13f	70
7	12g	13g	19
8	12h	13h	63

^a For reaction conditions see Supporting Information. The diastereomeric ratios for the products were the same as of those for the starting dienes.
^b Isolated yields after column chromatography.