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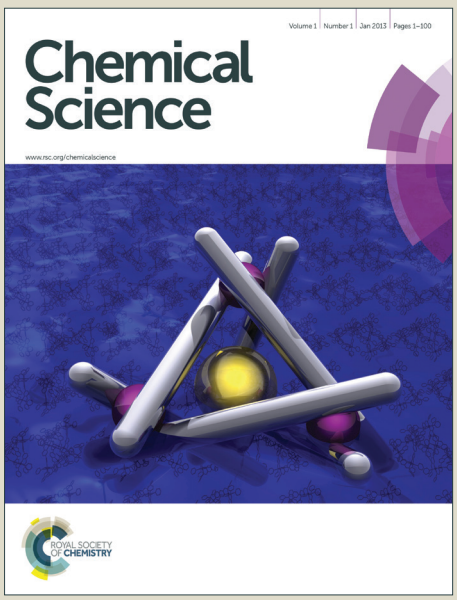

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Bimetallic Catalysis in the Highly Enantioselective Ring-Opening Reactions of Aziridines†

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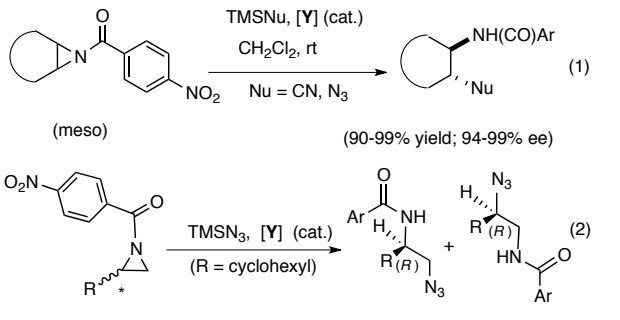
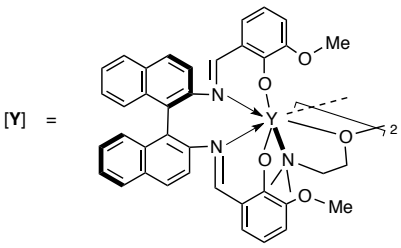
ABSTRACT: Bimetallic yttrium- and lanthanide-salen complexes, readily prepared from commercially available metal isopropoxides, 2-dimethylaminoethanol, 1,1'-binaphthyl-2,2'-diamine and 2-hydroxy-3-methoxybenzaldehyde (3 steps) catalyze highly enantioselective ring opening (~ 90-99% ee) reactions of *meso*-*N*-4-nitrobenzoyl aziridines by TMSCN and $TMSN_3$. The $TMSN_3$-mediated reactions give the highest enantioselectivities reported to date for several prototypical aziridines. Selectivity in a related ring opening by silyl isothiocyanates depends on the substituents on silicon, larger ^{t}BuSiPh$_2$SiNCS giving the best selectivities, especially when an yttrium or ytterbium complex is used as the catalyst. The bimetallic yttrium complex also effects unprecedented regiodivergent parallel kinetic resolution of racemic monosubstitued aziridines upon reaction with $TMSN_3$. In these reactions, each of the enantiomers undergoes nucleophilic addition of azide at different carbons giving two products in nearly enantiomerically pure form. To explain the dramatic differences in the selectivities between the mono- and bimetallic catalysts in these reactions, a mechanism that involves activation of both the electrophile (aziridine) and the nucleophile (azide or cyanide) at two different metals of the bimetallic complex is proposed. Molecular weight determination by vapor pressure osmometry, Diffusion Ordered NMR Spectroscopy (DOSY) and kinetic studies, which suggest first order dependence on the concentration of the catalyst, provide strong support for this proposal.

Introduction

Bimetallic catalysis is ubiquitous in nature and many of the essential processes that sustain life on our planet depend on reactions catalyzed by bimetallic enzymes.[1] The scope and efficiency of bimetallic catalysts designed to carry out highly selective organic transformations have been steadily improving during the past two decades.[2] Bimetallic activation has played a significant role in the development of catalytic enantioselective ring-opening reactions of epoxides[3-6] and aziridines,[5,7-11] which are among the most useful asymmetric transformations.[12] Mechanistic studies of these ring opening reactions have provided some of the most unequivocal evidence for a bimetallic activation mode in these catalytic transformations.[9,13-17] In 2009 we reported the discovery of a discrete dimeric yttrium salen complex [**Y**] (Eq 1) that enable the nucleophilic ring-opening reactions of *meso*-*N*-acylaziridines with $TMSN_3$ and TMSCN with exceptionally high enantioselectivities.[10] In reactions with racemic chiral aziridines, the same bimetallic Y complex promotes unprecedented regio- and enantiodivergent ring opening reactions giving two *different* products from each of the enantiomers in nearly enantiomerically pure form (Eq 2).[18] Here we report the full details of the discovery of this remarkable catalyst, along with the scope and limitations of its applications including new reactions of aziridines with silyl isothiocyanates. Since the original studies, we have also examined the key role played by the metal through a systematic comparison of the catalytic activities (and selectivities) of analogous complexes across the lanthanide series. Further we document, for the first time, structural and kinetic evidence for the bimetallic activation in the aziridine opening reactions.

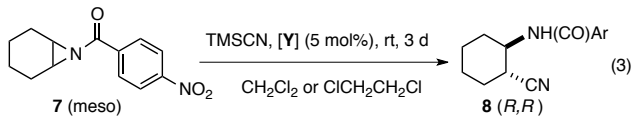




Results and Discussion

Monometallic Yttrium Complexes in Ring Opening Reactions of Aziridines

Our studies in the area started as an expansion of the application of a series of monomeric yttrium salen complexes (**1**-**4**), which we had synthesized as catalysts for trans-esterification of secondary alcohols with enol acetates[19] and ring-opening reactions of meso-epoxides.[15] Subsequently we also prepared related the Y(III)-bis-phenolate complexes **5** and **6** using previously reported ligands.[20,21] During these studies it was observed that one of these catalysts, **2a**, effected the ring-opening of *neat* epoxycyclohexane with TMSCN at room temperature at a loading level of 0.0001 equivalent (substrate: catalyst = 10,000!) in less than 4 hours.[15] Even though the best enantioselectivity observed with this catalyst was modest (77% ee), such catalytic efficiency remains unprecedented in nucleophilic ring opening reactions. We wondered whether these catalysts would be applicable to the more challenging aziridine ring opening reactions. After screening a series of *N*-acyl groups as activating groups, we recognized that the *N*-(4-nitrobenzoyl)aziridine originally used by Oguni et al[22] was the most optimum substrate for this reaction. The results of the reaction of *N*-(4-nitrobenzoyl)-7-aza-bicyclo[4.1.0]heptane (aziridine **7**) with TMSCN (Eq 3) in the presence of monomeric yttrium catalysts, listed in Figure 1, are shown in Table 1. An authentic sample of the racemic product **8** was prepared by the reaction of **7** with TMSCN in the presence of $Y(OCH_2CH_2NMe_2)_3$ or a bimetallic complex **13** (see later).



In general yttrium salen complexes are excellent catalysts for these ring-opening reactions, even though as compared to epoxides,[15] a higher loading (typically 0.05 equivalents) of the catalyst is required to complete the reaction in reasonable time. As expected, the chirality of the diamine backbone and the substituents on the salicylimine have significant effects on catalytic efficiency and selectivity. While the salen complex derived from (*R,R*)-1,2-*trans*-cyclohexanediamine and 3,5-di-*t*-butylsalicylaldehyde (**1a**) gives a quantitative yield of the product (entry 1, 52% ee, *R,R*-product), the corresponding 3-methoxysalicylimine analog, **1b** showed lower reactivity, also with formation of the *S,S*-product (18% ee). For the salens (**2a**-**2e**) derived from 2,2'-diamino-1,1-binaphthyl, the 3-methoxy analog (**2b**) gave the best result (entry 4). Salen complexes derived from (*S,S*)-1,2-diphenyl-1,2-diaminoethane (**4**, entry 8) and a carbohydrate-derived diamine (**3a, 3b**) also yielded only modest enantioselectivity. The bis-phenolate/bis-phosphine oxide complex **5** based on a binaphthol is an excellent ligand giving nearly quantitative yield, albeit with only low selectivity (entry 11).

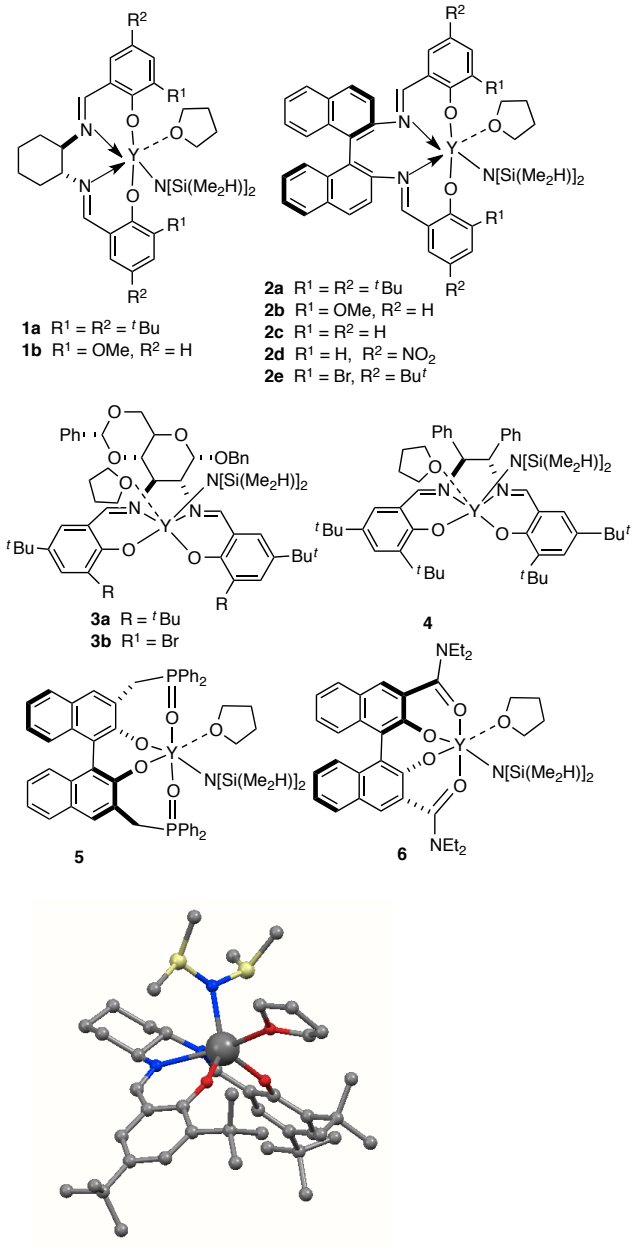
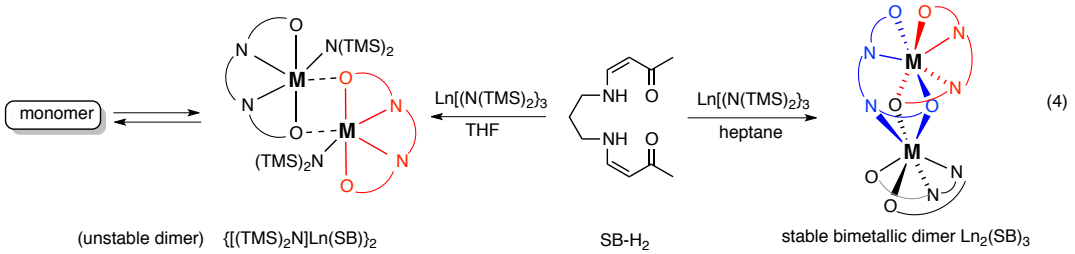


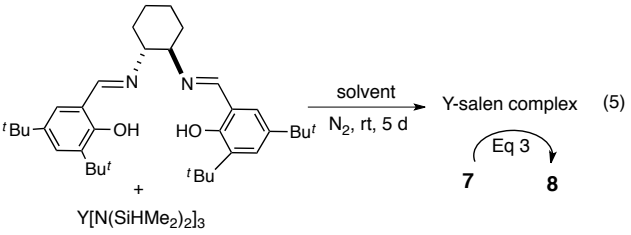
Figure 1. Monomeric Yttrium-Salen and Related Complexes and Solid-State Structure of 1a.[27]

A Bimetallic Catalyst for Ring-Opening of Aziridines

The first indications that aggregation might play a crucial role in the selectivities of these reactions appeared in our attempts to optimize the reaction by changes in the solvent. For example, the monomeric complex **1a** yielded varying selectivities (52-63% ee) of the (*R,R*) product (Eq 3) in non- coordinating solvents such as CH_2Cl_2, $ClCH_2CH_2Cl$, benzene or mixtures of these solvents.



The reaction carried out in THF, on the other hand, consistently yielded the corresponding (*S,S*)-product, albeit in lower (~20% ee) selectivities. We had previously made similar observations in the ring-opening reactions of epoxycyclohexane with TMSCN in the presence of **1a**.[15] While there was little doubt about the structure of the monomeric catalyst **1a**, thanks to a solid state structure (Figure 1, bottom) derived from X-ray crystallography,[19] the nature of the catalyst in THF remains highly speculative. There is considerable evidence in the litertaure to suggest that structures of tetradentate complexes of lanthanides and yttrium depend strongly on the solvent. For example, structures of related tetradentate lanthanide Schiff base complexes, when examined as function of the solvent in which they are prepared,[23] suggest that hydrocarbon solvents favor formation of very stable dinuclear $[M_2(\mathbf{L})_3]$ complexes *held together by bridging ligands* (Eq 4). In sharp contrast, in THF, mononuclear complexes, which form weak dimers $[XM(\mathbf{L})]_2$ that readily dissociates at or above room temperature are formed (Eq 4). We reasoned that the catalytic activities of such complexes could be different, thanks in part due to the relative juxtaposition of the metals, and possibility of bimetallic activation in the more stable binuclear complexes.



In order to probe the importance of aggregation of the yttrium catalysis we prepared the complex **1a** in varying mixtures of hexane and THF, and examined the enantioselectivities in the aziridine-opening reactions. The results are shown in Table 2. We note that there is a significant deterioration of selectivity as the THF content of the solution in which the catalyst is prepared increases, eventually reversing the configuration of the major product in pure THF (entries 1-4).

Table 1. Monomeric Yttrium Catalysts for Ring-Opening Reaction of Aziridine with TMSCN[a]

Entry	Catalyst	Yield (%)	%ee (*R,R*)[b]
1	**1a**	>99	52
2	**1b**	58	-18
3	**2a**	77	<5
4	**2b**	85	55
5	**2c**	>99	30
6	**2d**	>99	14
7	**2e**	93	10
8	**4**	59	-6
9	**3a**	99	-34
10	**3b**	99	-29
11	**5**	96	47
12	**6**	38	<5

[a] see Eq 3, solvent CH_2Cl_2. [b] determined by Chiral Stationary Phase (CSP) HPLC; (–)-sign indicate (*S,S*)-isomer.

Table 2. Effect of the Solvent Used in the Preparation of the Catalyst on Enantioselectivity

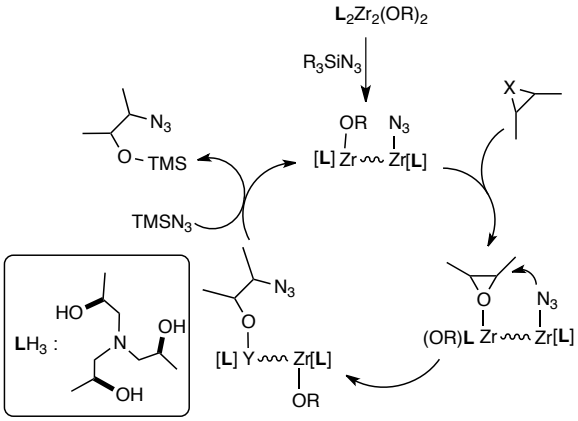
Entry	Solvent [*n*-hexane/THF (%)][a]	Yield (%)	ee (%)
1	100 : 0	>99	52 (*RR*)
2	80 : 20	88	51 (*RR*)
3	20 : 80	82	32 (*RR*)
4	0 : 100	>99	-43 (*SS*)

[a] Solvent for step 1 (Eq 5). Solvent for step 2: CH_2Cl_2

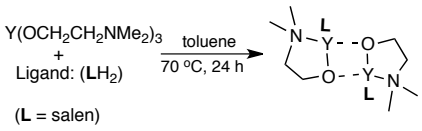
Based on the available information on the structural variations of lanthanide complexes in different solvents,[23] one could postulate the intermediates of different nuclearity as being responsible for the remarkable solvent effects. While at the outset this was only based on conjecture, it was not without some support. For example, McCleland, Nugent and Finn have invoked a dinuclear catalyst to explain the kinetic behavior of (alkanolamine)$_3$Zr-mediated ring-opening of epoxides with azides (Scheme 1).[14] In this mechanism, after an initial dimerization of the Zr complex, the electrophile (epoxide) is activated at one of the metal centers, while the nucleophile (N_3) is activated at the other metal. Our previous report[15] of the second order dependence of a monometallic Y-catalyst (**2a**) on the exceptionally facile ring-

opening reaction of epoxycyclohexane with TMSCN in nonpolar solvents is also consistent with such a hypothesis. Further anecdotal support comes from the ease with which early transition metals including yttrium and lanthanides form anion-bridged dimers.[24]

Scheme 1. Nugent-Finn Mechanism of Bimetallic Epoxide Opening Catalyzed by (triisopropanolamine)$_3$Zr Complexes



We decided to test the veracity of the bimetallic activation using *stable, discrete* bimetallic yttrium complexes prepared from yttrium *tris*-(2-dimethylaminoethoxide) and salen ligands according to Eq 6.[25,26] A solution of the ligand and the yttrium alkoxide was heated in toluene at 70 °C for 24 hours. The solvents were removed and the product was redissolved in minimum amount of CH_2Cl_2. Filtration of this solution and careful layering on the top with hexane resulted in crystallization of the product, which was used as a catalyst for the ring-opening reactions. The structures of several catalysts prepared in this fashion along with the a 3-D-rendition of a solid state structure of a key complex, **10b**, are shown in Figure 2.[27]



(6)

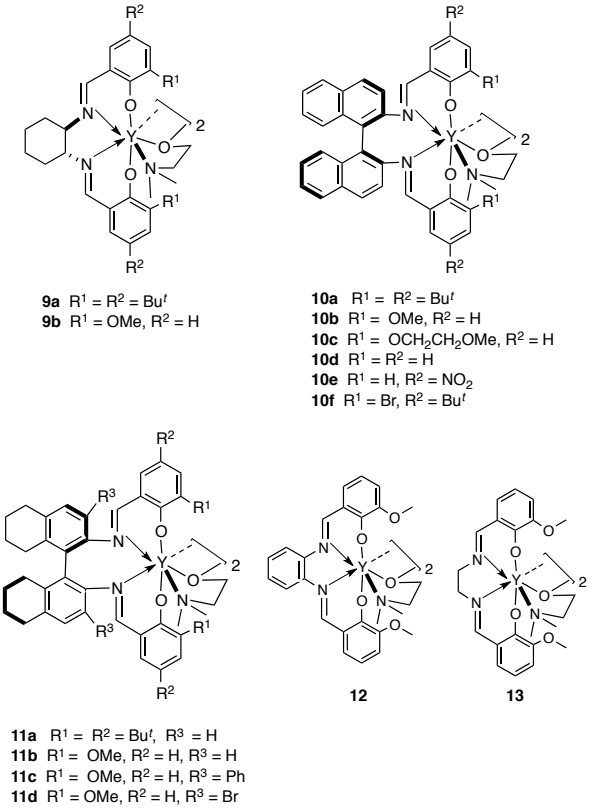


Figure 2. Structures of Bimetallic Catalysts. An enlarged rendition of the solid-state structure of 10b is included in the Electronic Supplementary Information.[27]

Ring-Opening Reactions of Aziridines

(a) With Trimethylsilyl Cyanide (TMSCN)

The catalysts **9a**, **9b**, **10a**, **10b** and **10c** were tested for the ring opening reaction of the prototypical substrate **7** using TMSCN under the optimized protocol shown in in Eq 3 and the results are shown in Table 3. The reactions were carried out in 1,2-dichloroethane using recrystallized *bimetallic* catalysts at room temperature. Compared to the typical epoxide opening reactions, the aziridine opening is sluggish, and the reactions are best carried out using 10 mol% of the catalyst. The best catalyst for this reaction was found to be **10b**, carrying a 2,2'-binaphthyl bis-imine scaffolding. The 1,2-*trans*-cyclohexanediamine-derived complexes **9a** and **9b** gave much lower selectivities. The substituents on the salicylimine fragment also play a significant role in the enantioselectivity. In the binaphthyl series, 3-methoxy substituent (**10b**) on the salicylimine gave the best selectivities (entry 4). Complexes bearing the 3-*t*-butyl substituent (**10a**) and

a 3-methoxymethyl (**10c**) gave lower selectivities (entries 3 and 5).

Table 3. Bimetallic Yttrium Catalysts for Asymmetric Ring-Opening Reaction of Aziridine 7 with TMSCN[a]

Entry	Cat.	Cat. (mol%)	Yield (%)	%ee (*R,R*) [b]
1	**9a**	5	79	37
2	**9b**	5	58	– 6
3	**10a**	10	>99	8
4	**10b**	10	>99	88 (94)[c]
5	**10c**	5	64	30

[a] see Eq 3, solvent $ClCH_2CH_2Cl$, rt, 3 d. [b] determined by CSP HPLC; (–)-sign indicates (*SS*) isomer. [c] at 0 °C.

The catalyst **10b** was tested for opening of other aziridines under the optimized conditions, and the results are shown in Table 4, columns 3 and 4. As seen in entries 1-3, the reactions with TMSCN proceeds in very good yields and enantioselectivities comparable to the highest reported values[8,9] for relatively 'small' aziridines. Perhaps reflecting the capsular nature of the catalyst, as the size of the aziridine increases, the reaction becomes increasingly slow. Thus, aziridines derived from cycloheptene **16** (entry 4), cyclooctene **17** (entry 5), 1,4-dihydronaphthalene **18** (entry 6), *Z*-stilbene **19b** (entry 8) and *E*-stilbene **19c** (entry 9) failed to react, while the one from *Z*-4-octene **19a** (entry 7) gave a lower yield under the standard conditions.

(b) With Trimethylsilyl Azide ($TMSN_3$)

The dimeric catalyst **10b** seems to be especially suitable for the aziridine opening with $TMSN_3$ (Table 4, columns 5 and 6), giving the *highest* enantioselectivities reported to-date for all substrates in Table 4 except for **18** (entry 6).[28,29] Several substrates that either reacted sluggishly or did not react at all with TMSCN give acceptable yields and selectivities in reactions with $TMSN_3$ under virtually identical conditions. For example, cycloheptene-derived aziridine (**16**, entry 4) gave excellent enantioselectivity and a modest yield in the $TMSN_3$-mediated opening, even though this substrate failed to react with TMSCN. Likewise aziridines from 1,4-dihydronaphthalene (**18**, entry 6), *Z*-4-octene (**19a**, entry 7) and *Z*-stilbene (**19b**, entry 8) react, to give acceptable yields and excellent enantioselectivities. Only aziridines derived from cyclooctene **17** (entry 5) and *E*-stilbene **19c** (entry 9) failed to react with both TMSCN and $TMSN_3$.

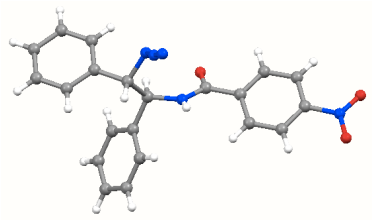
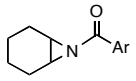
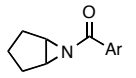
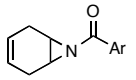
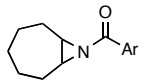
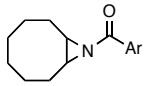
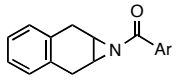
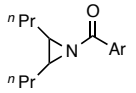
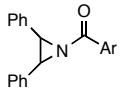
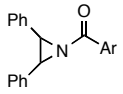


Figure 3. Solid-State Structure of (*S,S*)-2-Azido-1-(4-nitrobenzoyl)amino-1,2-diphenylethane (20, from aziridine 19b)

Table 4. Ring-Opening of Aziridines Catalyzed by Bimetallic Salen Complex 10b[a]

No	Aziridine[b]	TMSCN		$TMSN_3$	
		Y	ee[c]	Y	ee[c]
1.	 **7**	87	94	99	97
2.	 **14**	85	99	99	98
3.	 **15**	86	92	99	99
4.	 **16**	0	-	47	97
5.	 **17**	0	-	0	-
6.	 **18**	0	-	99	90
7.	 **19a** (cis)	47	82	73	92
8.	 **19b** (cis)	0	-	96	97
9.	 **19c** (trans)	0	-	0	-

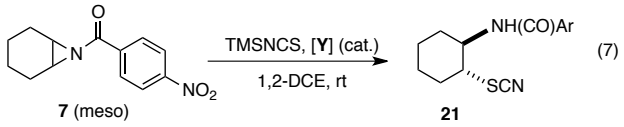
[a] See Eq 3 for procedure (10 mol% catalyst, 3 days). [b] Ar = 4-nitrophenyl, [c] %, from CSP HPLC. All (*R,R*)-products.

The stereoselectivity in the opening of **19b**, a substrate prone to S_N1-type reactivity in the presence of Lewis-acid, is especially

noteworthy. The structure of the product **20**, arising from a clean inversion of configuration, was confirmed by X-ray crystallography.[30]

(c) With Trimethylsilyl Isothiocyanate (TMSNCS)

For the synthesis of racemic β-aminothioethers from aziridines and sulfur nucleophiles, heterogeneous catalysts,[31,32] lithium perchlorate,[33] aqueous cyclodextrin[34] and indium chloride[35] have been used as effective catalysts. Uncatalyzed reaction of activated aziridines including **7** gives a mixture of the thiocyanate adduct **21** and the corresponding isothiocyanate.[36] Enantioselective ring-opening of *meso*-*N*-acylaziridines by aromatic thiols using stoichiometric amount of a Zn catalyst prepared from Et_2Zn and tartrate has been known since 1995.[22] Other catalytic methods for addition of sulfur nucleophiles use chiral alkaloid derivatives,[37] and chiral biphenanthryl phosphoric acids as organocatalysts,[38,39] the latter giving outstanding selectivities for the addition of aryl thiols. Aliphatic thiols generally give lower yields and selectivities.



In light of the excellent selectivities observed for TMSCN and $TMSN_3$ we proceeded to examine TMS-NCS (trimethylsilyl isothiocyanate) using the dimeric yttrium complexes (Eq 7). The results of the initial scouting experiments using various catalysts are shown in Table 5. Since thiocyanate is an ambidentate nucleophile capable of bonding through S or N, the structure of the adduct **21**, initially inferred from IR spectroscopy,[36] was confirmed by X-ray crystallography.[30] As before, the dimeric catalysts based on 1,2-*trans*-cyclohexanediamine (entries 1 and 2) are not as efficient or selective as the ones based on 2,2'diamino-binaphthyl. Among these the ligand **10b**, which yielded the best selectivities for TMSCN and $TMSN_3$ additions, appears to be the best for the TMSNCS addition (entry 4) giving excellent yields and ee's up to 60% in the additions to the *meso*-aziridine **7.**

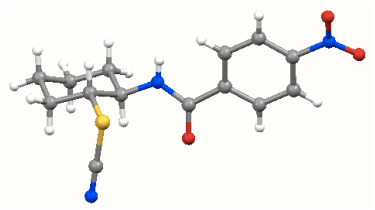


Figure 4. Solid-State Structure of **21** (Eq 7)

(d) With Larger Silyl Isothiocyanates

The substituents on the silicon in the reagent have a significant effect on the enantioselectivity of this reaction as shown in Table 6. Highest ee's were obtained with bulky silyl reagents (entry 2, Et_3Si- and entry 9, $^tBuPh_2Si$-).

Table 5. Catalyst Screening for Me_3SiNCS-Mediated Ring-Opening of *meso*-Aziridine 7[a]

Entry	Cat.	Time (d)	Yield (%)	ee (%)[b]
1	**9a**	2	32	7
2	**9b**[c]	2	75	8
3	**10a**	3	82	41
4	**10b**	3	91	57 (60)[d]
5	**10c**[c]	2	96	47
6	**10d**	1	89	23
7	**10e**	1	55	8
8	**10f**	1	87	49
9	**11a**	0.67	74	50
10	**11b**	1.25	96	34
11	**11c**[c]	2	77	60
12	**11d**	1	87	58

[a] see Eq. 7 (10 mol% catalyst, 3 days). All (*R,R*) products. [b] Determined by CSP HPLC. [c] 5 mol% cat. [d] at -3 °C, 4 d., 99% yield.

Table 6. Effect of the Silyl Reagent on the R_3SiNCS-Mediated Enantioselective Ring Opening of Aziridine 7[a]

Entry	Cat.	R_3	Yield (%)	ee[b] (%)
1	**10b**	Me_3	91	57
2	**10b**	Et_3	99	69
3	**10b**	$^tBuMe_2$	76	39
4	**10b**	$^tBuPh_2$	96	61
5	**10b**	$PhMe_2$	77	67
6	**11c**	Me_3	77	60
7	**11c**	Et_3	96	47
8	**11c**	$^tBuMe_2$	99	63
9	**11c**	$^tBuPh_2$	99	68
10	**11c**	$PhMe_2$	84	55

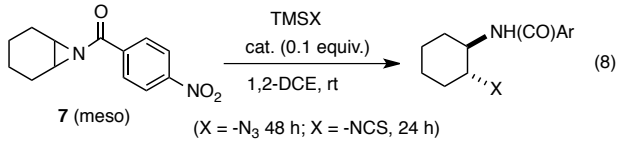
[a] See Eq. 7 (10 mol% cat., 3 d.). All (*R,R*)-products. [b] Determined by CSP HPLC.

(e) With trimethylsilyl isocyanate (TMSNCO)

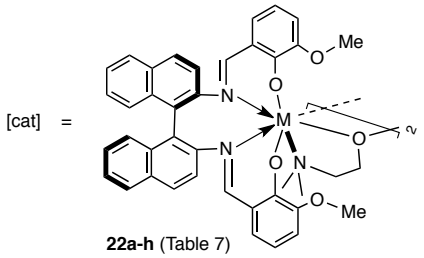
Several attempts to effect the ring opening reaction reaction of **7** with various yttrium catalysts including **10b** and **13** were unsuccessful. The starting material was recovered unchanged.

Effect of the Central Metal in Ring-Opening Reactions of meso-Aziridines. Lanthanides

Even though many metal-catalyzed ring opening reactions of meso-epoxides and meso-aziridines have been studied, systematic studies of the effect of the central metal are few.[15,40,41] As for the effect of lanthanides, Jacobsen reported that in the TMSCN-mediated opening of epoxides catalyzed by (2,5-*bis*-oxazolinylpyridine)MCl_3, there is a strong correlation of enantioselectivity with the atomic number, with the smaller ions giving the highest ee's.[4]



(8)



22a-h (Table 7)

We studied the effect of substituting the yttrium in the bimetallic complex **10b** with various lanthanides on the ring opening reactions of aziridines and the results are shown in Table 7. While all dimeric complexes with the generic structure **22** (Eq 8) carrying the salen ligand are excellent catalysts giving nearly quantitative yields, the selectivity of the reaction varies considerably. For the $TMSN_3$ reactions, except for Pr, early lanthanides with larger ionic radii (La~Gd) generally gave lower selectivities. Yttrium, and late lanthanides, Dy, Er and Yb, all with ionic radii lower than 91 pm gave the best selectivities in these reactions (>95% ee, Table 7, column 5, entries 1, 7-9). Incidentally the Lewis acidity of these late lanthanide ions and yttrium are also proportionally higher.[42] In the case of TMSNCS, a similar behavior is seen (columns 6 and 7), even though the trend is not as readily discernable.

Finally the best results in the silyl isothiocyanate-mediated reaction are obtained when the Yb catalyst is used in conjunction with a bulky silyl reagent. Thus both Et_3Si-NCS and $^tBuPh_2Si$-NCS upon reaction with **7** gave very high yields of the product **21** in ~85% ee. A recrystallization of this product from ethyl acetate/hexane gives the product in 88% ee. Under these conditions, the aziridines **14** and **15** also gave excellent yields; but the enantioselectivities were only modest (48% and 52% respectively). Increased background reaction in these more strained substrates is most likely the reason for this deterioration of selectivity.

Table 7. Effect of the Central Atom on the Ring-Opening Reactions of Aziridines with Me_3SiN_3 and Me_3SiNCS[a]

Entry	Metal	Cat.	M(III) size (pm)[b]	$TMSN_3$		Me_3SiNCS	
				Yield (%)	ee (%)	Yield (%)	ee (%)[c]
1	Y	**10b**	90.0	99	97	91	57 (69)[d]
2	La	**22a**	103.2	98	31	92	19
3	Pr	**22b**	99.0	98	87	99	66
4	Nd	**22c**	98.3	98	80	99	42
5	Sm	**22d**	95.8	99	89	99	50
6	Gd	**22e**	93.8	97	73	98	43
7	Dy	**22f**	91.2	99	99	99	61
8	Er	**22g**	89.0	99	99	99	65
9	Yb	**22h**	86.8	99	95	99	76 (88)[d]

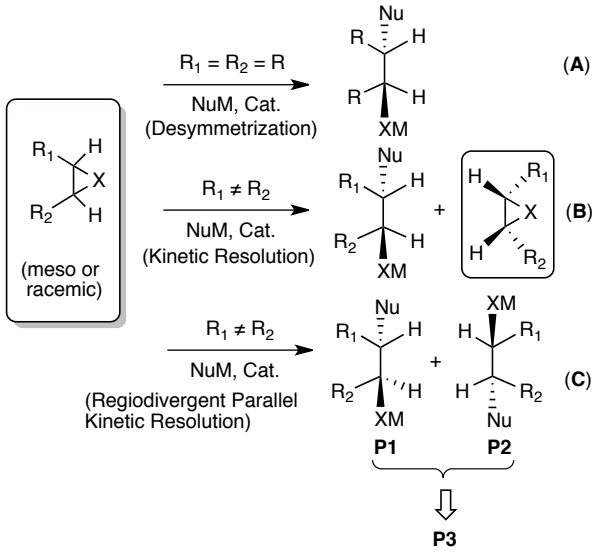
[a] See Eq 8, 10 mol% cat. [b] coordination number 6 (in picometers). [c] from CSP HPLC or CSP GC. [d] using Et_3SiNCS.

Table 8. Effect of the Trialkylsilyl Group on the Yb-Catalyzed Ring-Opening Reactions of Aziridine 7 with R_3SiNCS[a]

Entry	Substrate	R_3Si	Yield (%)	ee (%) [b]
1	**7**	Me_3Si	99	76
2	**7**	Et_3Si	99	80 (85)[c]
3	**7**	$^tBuMe_2$	98	52
4	**7**	$^tBuPh_2$	99	85 (88)[c]
5	**7**	Me_2Ph	98	66
6	**14**	Et_3Si	99	48
6.	**15**	Et_3Si	89	52

[a] See Eq 8, 10 mol% cat., **22h**, 24 h. [b] From CSP HPLC unless specified. [c] From CSP GC.

Scheme 2. Enantioselective Ring-Opening Reactions of Small-Ring Heterocycles

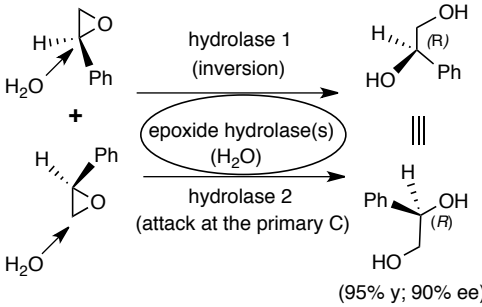


Regiodivergent Parallel Kinetic Resolution of Racemic Aziridines

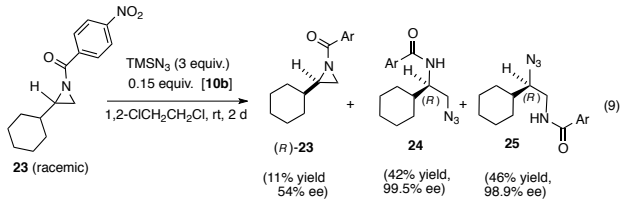
While enantioselective desymmetrization (Scheme 2, **A**) of meso-epoxides and aziridines, as well as kinetic resolution (Scheme 2, **B**) of racemic epoxides have been the subject of extensive research, an alternate approach to enantio-pure products from these substrates[43-47] which involves divergent reactions of the individual enantiomers (Scheme 2, **C**) of a racemate, has received relatively lesser attention.[48] Such an approach for the production of intermediates from racemic starting materials has at least one principal advantage over the conventional kinetic resolution (Scheme 1, **B**) in that the relative rates of reactions of the enantiomers (k_f/k_s) can remain close and need not approach the rarely observed >100 mark (assuming a first order reaction) to realize selectivities of >98% enantiomeric excess (ee).[49-51] Further if the nucleophile (Nu) is structurally related to X, the ring atom, and both X and Nu can be transformed into the same functional group, both products [**P1**] and [**P2**] (Scheme 2, **C**) maybe converted into a common intermediate [**P3**], or a congener, useful for further synthetic operations. An example is the conversion of the β-amidoazide to a diamine[28] using the Burk protocol.[51a] This avoids yet another limitation of classical kinetic resolution, viz., the maximum obtainable yield of 50% in such reactions. However, an enantiospecific catalyst that can accomplish this must meet exceedingly stringent requirements with respect to its structure and reactivity so as to promote divergent reactions of two enantiomers by appropriate recognition events. Thus far this strategy, termed 'enantioconvergent' synthesis[52] has been successful in a practical sensse only in the realm of enzyme-mediated reactions of epoxides.[53,54] In an example pertinent to this report, racemic styrene oxide has been transformed into a single, enantiomerically pure (*R*)-1,2-phenylethanediol by a combination of two recombinant microbial epoxide hydrolase

enzymes (Scheme 3) possessing complementary enantioselectivity and regioselectivity.[55,56a]

Scheme 3. Enzyme-Mediated Enantioconvergent Synthesis of (*R*)-1-Phenyl-1,2-ethanediol

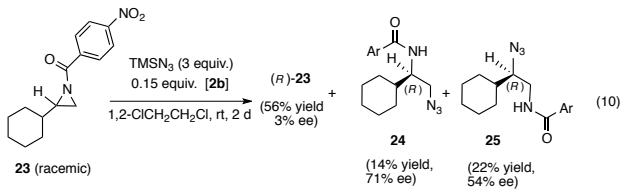


Having recognized **10b** to be an excellent catalyst for desymmetrization of meso-aziridines we turned our attention to kinetic resolution of racemic aziridines. Our studies started with an examination of the ring-opening reactions of a prototypical racemic aziridine **23** with trimethylsilyl azide ($TMSN_3$) in the presence of the dimeric yttrium-salen complex **10b**. Chiral stationary phase HPLC analysis of unconverted starting material **23** from reactions done under the most optimum conditions for kinetic resolution (rt, ratio of $TMSN_3$: **23** = 1:1 to 1:2, conversions of 50-80%) returned disappointingly low ee's for unconverted **23** even at high conversions. This surprising result, along with the presence of two new, easily separated compounds (tlc) suggested that the overall reaction appeared *not* regioselective and/or the enantiomers reacted at comparable rates. However, upon analysis of the two new products by CSP HPLC and NMR we were pleasantly surprised to find that both compounds, now identified as two regioisomeric ring-open products **24** and **25**, were formed in ~ 99% ee (Eq 9)![57] The configurations of these products were assigned by comparison of specific rotations and retention times on CSP HPLC with those of authentic samples prepared from aziridines of known configuration (see later).

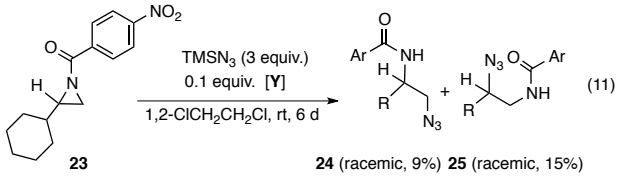


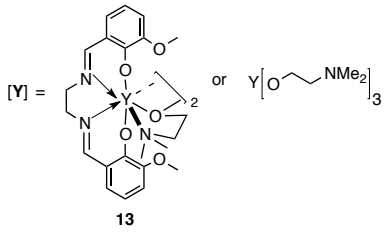
These results can be explained by regiodivergent parallel kinetic resolution (Scheme 2, **C**) of the two enantiomers of **23**. Thus, the nucleophilic attack by azide occurs exclusively at the primary position in (*R*)-**23** leading to the azido-amide **24** as the only product. In sharp contrast, the (*S*)-**23** gives a product **25**, resulting from exclusive S_N2-inversion at the secondary center. Under the optimized conditions described in Eq 9, about 11% of the starting material was recovered, and was found to have an ee of 54%, with the (*R*)-isomer predominating. This suggests that the more reactive (*S*)-enantiomer of the starting material is consumed at ~ 3.35 times faster than the slow reacting (*R*)-isomer, each of them proceeding with exceptional regio- and enantiospecificity. Since the selectivity in the ring opening of each of the enantiomers is nearly perfect (~ 99% ee for the product), the low k_f/k_s is of no consequence to the selectivity in the formation of the two products.

As is the case with the desymmetrization reactions, the monometallic catalyst **2b**, is much less selective (also less reactive) in these regiodivergent reactions (Eq 10). Under the standard conditions where the bimetallic **10b** left only 11% unreacted **23**, 56% of the starting material (**23**) was recovered in nearly racemic form in these reactions. The ring-opening products **24** (14% yield) and **25** (22% yield) were formed in 71% and 54% ee respectively.



Attempts to prepare the authentic samples of the racemic azido-amides **24** and **25** via Y-catalysis revealed yet another fascinating aspect of these reactions. The ring opening reactions of the starting aziridine **23** using an achiral salen complex derived from ethylenediamine **13** (Figure 2) or the Y-alkoxide $Y(OCH_2CH_2NMe_2)_3$ (Eq 11) are significantly slower compared to the reactions with the complex **10b** (with **23**, only 24 % overall conversion in 6 days and with $Y(OCH_2CH_2NMe_2)_3$ only 13% conversion in 10 days) under other wise similar conditions. Thus there is a significant ligand assistance[58] in the catalytic reactions of **23**.



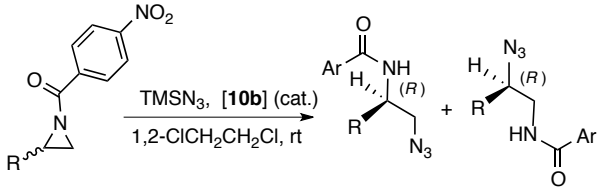


A number of structurally different aziridines were subjected to the ring-opening reactions and the results are listed in Table 9. For *all* substrates except for the *t*-butyl derivative **23h** (entry 9), the reaction is completely enantiospecific in the formation of the primary azide **24**, the nucleophilic attack taking place at the primary carbon of the (*R*)-aziridine, giving 99 %ee of the product in each case. For **23h** it is slightly lower (96 %ee). Selectivity in the formation of **25** (from the S_N2-displacement at the secondary center of the fast-reacting (*S*)-aziridine) is also impressive, less so for substrates **23d, 23e**, and **23g** (R = *n*-Bu, cyclohexylmethyl and *i*-Pr). There is some erosion in the selectivity for formation of these products, showing proportionately higher amounts of ring-opening of the (*R*)-enantiomer with displacement at the secondary position.

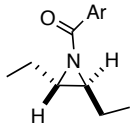
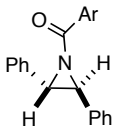
Curiously, in the case of the *t*-butylaziridine (**23h**) the normally fast reacting (*S)*- isomer was recovered along with significant amounts of unreacted (*R)*-isomer (entry 9). Attack at the neopentyl carbon is forbidden presumably because of steric congestion.

The exquisitely high enantioselectivity in these regiodivergent reactions come at a cost in terms of the scope of the substrates that are amenable to this reaction. Two examples of racemic C_2 symmetric substrates that fail to react are shown in entries 10 (**23i**) and 11 (**19c**). Recall that the cis-aziridines **19a** and **19b** do undergo the desymmetrization reaction with high ee (entries 7 and 8, Table 4).

Table 9. Regio- and Enantio-divergent Ring-Opening Reactions of Chiral Aziridines

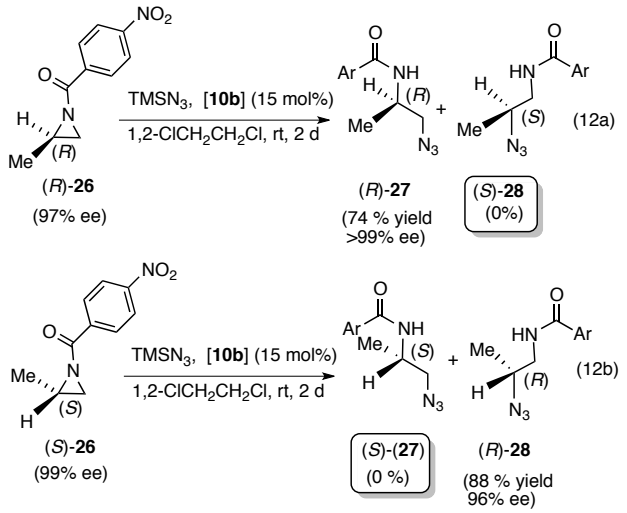


(**23** racemic) **24** **25**

Entry	Aziridine	R in **23**	Cat. (mol%)	Time (d)	Yield/%ee [a]	
					(*R*)-**24**	(*R*)-**25**
1	**23a**	cyclohexyl	15	2	42/>99	46/99
2	**23b**	cyclopentyl	15	2	33/>99	39/98
4	**23c**	benzyl	10	6	42/99	47/97
5	**23d**	*n*-Bu	10	6	32/99	48/90
6	**23e** [b]	cyclohexyl-methyl	15	2	15/>99	51/93
7	**23f**	cyclopentyl methyl	15	2	8/>99	48/96
8	**23g**	*i*-propyl	15	2	16/99	48/92
9	**23h** [c]	*t*-butyl	15	6	24/96	0/-
10	 **23i** (rac.)	--	10	3	0	0
11	 **19c** (rac.)	--	10	3	0	0

[a] isolated, >99% ee denotes that the other enantiomer was not detected in the chromatogram. [b] 24% starting material (96% ee) recovered. [c] 58% starting material (47% ee) recovered.

The high specificity and identity of the products in the ring-opening were further confirmed by reactions of several enantio-pure aziridines with $TMSN_3$. An exceptionally challenging situation is illustrated with the complementary behavior of (*S*)- and (*R*)-2-methylaziridines (Eq 12a and 12b). As expected, the *(R)*-enantiomer of the aziridine **26** gives *exclusively* the primary azide (*R)*-**27** (Eq 12a), and the (*S*)-enantiomer of **26** gives the secondary azide (*R*)-**28** (Eq 12b) with *no trace of contamination with the regioisomeric product in each case*. This high regioselectivity seen in the formation of the *two different products* from the two enantiomers indicates that the nucleophile is capable of distinguishing between two electrophilic carbons that are separated by 1.46 Å in the aziridine.[59] In the formation of the primary azide (*R*-**27**), the catalyst is able to overcome the well-established preference for nucleophilic attack at the secondary position in Lewis acid-catalyzed opening of a small ring. One may speculate that such selectivity is hardly possible if only one of the components, say, the aziridine is activated. A bimetallic activation in which both the aziridine and the nucleophile (N_3^-) are activated thus looks very plausible.



Ring-opening reactions of two other sets of enantio-pure substrates (**23a**, and **23c**, Table 10) confirm the generality of these highly selective reactions. As was inferred from the previous studies with racemic substrates (Table 9), the (*S*)-aziridines react faster than the (*R*)-enantiomers in all cases under identical conditions.

Table 10. Regiospecific Ring-Opening Reactions of Enantiopure Aziridines

Entry	Aziridine (%ee)	Product	Yield (%)	ee (%)
1.	(*R*)-**23a** (95)	(*R*)-**24a**	56[a]	>99
2.	(*S*)-**23a** (97)	(*R*)-**25a**	79	96
3.	(*R*)-**23c** (99)	(*R*)-**24c**	46[b]	>99
4.	(*S*)-**23c** (99)	(*R*)-**25c**	87	97

[a] 25% (*R*)-**23a** recovered (>99% ee); [b] 20% (*R*)-**23c** recovered (92% ee).

Regiodivergent parallel kinetic ring opening of racemic aziridines is the first example of a single, small molecular-weight catalyst exhibiting such enzyme-like complementary selectivities in the ring-opening reactions of small ring compounds.[60] High yields are obtained for several 1,2-diamine derivatives from racemic aziridines in nearly enantiomerically pure (>97% ee) form. Subsequent high-yielding reactions (amide hydrolysis and azide hydrogenation) should produce the same 1,2-diamine from each of the ring-opening products[28] even though from a synthetic perspective the differentially protected primary products (vicinal azido-amides) are likely to be more valuable.

Kinetics and Mechanism of the Ring Opening Reactions

The exceptionally high enantioselectivities, especially in the regiodivergent parallel kinetic resolutions, clearly suggest a central role for both metallic centers of the catalyst in these reactions. Since anecdotal evidence in the epoxide-[15] and aziridine- (for example, see Table 2) openings (and a host of other reactions) implicate aggregation of the metallic catalyst even when a monomeric complex is used, we sought to provide further direct structural and kinetic evidence in support of a bimetallic mechanism in the reactions catalyzed by the discrete dimeric Y-complex **10b**.

Stability of the Monometallic (2b) vs Bimetallic (10b) Catalysts

NMR Spectroscopy. Recrystallized samples of the monometallic complex (**2b**) and the bridged, bimetallic complex (**10b**) were dissolved in the appropriate solvent and the spectra were recorded. Both in THF-d_8 and CD_2Cl_2, the complex **2b** gave very complex ^{1}H NMR spectra with broad peaks. In sharp contrast, the catalytically useful bridged dimer **10b** is an extremely well-behaved compound exhibiting sharp signals for the various protons and carbons. Figure 5 shows just the aromatic region of the two spectra. Full spectra are included in the Supporting Information p. S28 (**2b**) and S29 (**10b**). With the help of a series of decoupling and 2D-experiments most of these signals can be assigned,[61] and, as in solid state (Figure 2), it appears to be a C_2 -symmetric structure in solution with the expected 34 distinct down-field (δ >110 ppm) and 6 up-field (δ < 70 ppm) signals in the ^{13}C NMR spectrum. A CD_2Cl_2 solution of **10b** is quite stable for days as compared to a CD_2Cl_2 solution of the monomeric complex **2b**, which undergoes significant deterioration in ~ 24 h. While the exact nature of this change in the monomeric complex is not easily discernable because of the complex nature of the spectra, Diffusion Ordered NMR Spectra (DOSY) recorded as a function of time gives some qualitative indication of the changes in solution. The DOSY spectrum of the monomeric species **2b** in CD_2Cl_2 undergoes substantial changes when recoded over time.[61] For example –log D, a parameter related to the hydrodynamic volume of the solute goes from 8.42 at t = 0 to 8.75 at t = 12 h for the monomer, eventually returning to a value of 8.4 at 23 h. These changes could be attributed to some form of dynamic behavior in this molecule. In sharp contrast, the DOSY spectrum of the bimetallic complex **10b** in CD_2Cl_2 remains invariant (-log D = 8.40-8.45) over 40 h and beyond.

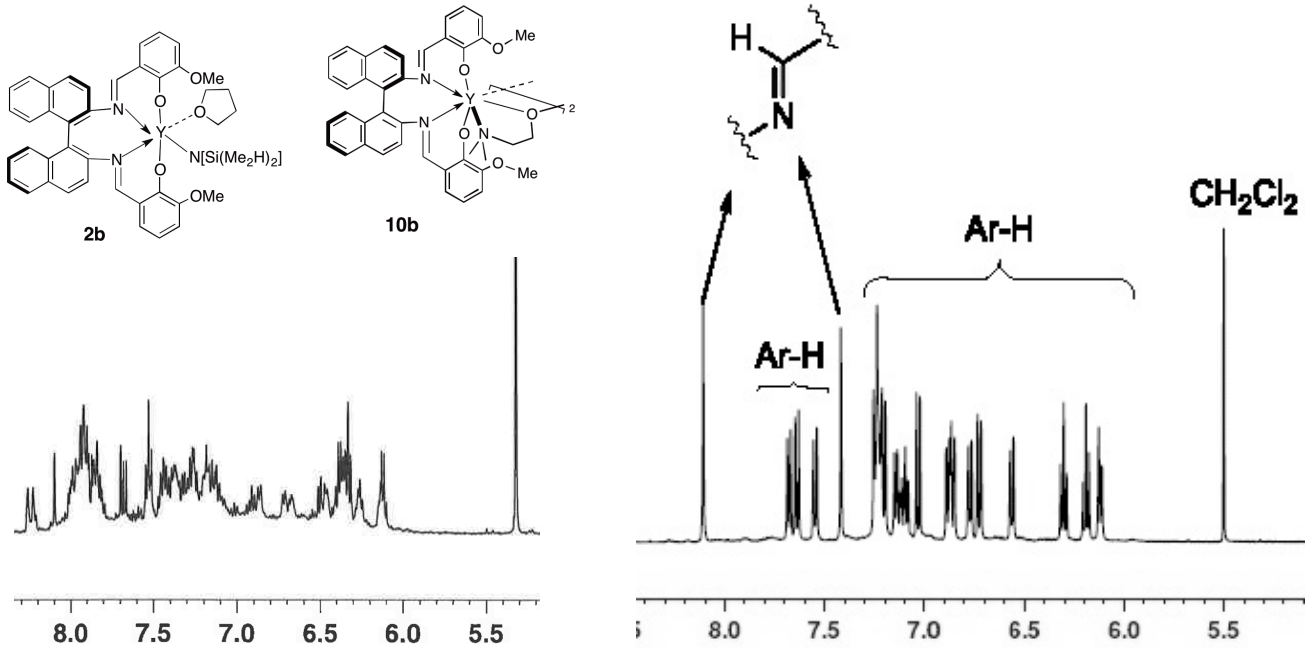


Figure 5. ^{1}H NMR Spectra of Recrystallized Monometallic (**2b**) and Bimetallic(**10b**) Catalysts. For clarity only aromatic portion is shown. Full spectra are included in the Supporting Information (pages S28 and S29).

Molecular Weights by Osmometry. A measure of the relative stability of these complexes and the state of aggregation in solution can also be gleaned by molecular weight measurements that depend on colligative properties. Among these vapor pressure osmometry (VPO) is a simple yet powerful technique.[62] The molecular weights of the monomeric and yttrium catalysts were determined using vapor pressure osmometry (VPO) using a Knauer K-7000 apparatus operated at 306 K in a rigorously inert atmosphere. The results are shown in Table 11. The monomeric complex **2b** (calculated molecular weight 843.9 g mol^{-1}) was dissolved in 1,2-dichoroethane, and, using sucrose octaacetate (calculated MW = 678.6, observed 684) as a standard, its molecular weight was determined.[30] The observed value of the molecular weight of this compound is highly dependent on the age of the solution, as was suspected from the DOSY experiments and other evidence reported earlier.[15] After a solution of **2b** was stored under inert atmosphere for 24 hours, a value of 1430 was recorded for the molecular weight, which is a clear indication of some form of aggregation in solution. The molecular weight measurements on the dimeric complex **10b** (calculated MW = 1455.3 g mol^{-1}), on the other hand, showed little tendency for change as a function of resident time in solution. After 24 hours, a value of 1483 was recorded. Molecular weight of β-lactose octaacetate (calculated MW = 677) was determined just as a test case, and the experiment gives acceptable value (observed MW = 684) within experimental error.

Table 11. Molecular Weights from VPO

Compound	Observed MW (g/mol)	Calculated MW (g/mol)
β-Lactose octaacetate (standard)	684	678.6
2b	920[a]	843.9
2b	1430[b]	843.9
10b	1483	1455.3

[a] VPO measurements recorded immediately after dissolving the compound in 1,2-DCE. [b] measurements after 24 h at rt in an inert atmosphere.

Kinetic Studies

The Y-catalyzed ring opening of aziridine by $TMSN_3$ is a reaction ideally suited for a kinetic study by in situ IR spectroscopy. The characteristic absorption signals due to $TMSN_3$, the putative metal azide,[63] and the product azide appear at 2143 cm^{-1}, 2079 cm^{-1} and 2097 cm^{-1} respectively, and each are well separated from other signals. In addition a peak at 1648 cm^{-1} whose change in intensity parallels that of the product azide peak (2097 cm^{-1}) has been tentatively assigned as belonging to an iminoether[64] intermediate.[65]

A typical kinetic experiment was run as follows with $TMSN_3$ as the limiting reagent with excess of the aziridine **7**. A two-necked glass reactor was charged with a mixture of $TMSN_3$ (11.5 mg, 0.1 mmol) and the catalyst **10b** (17.5 mg, 0.012 mmol) in 1.0 mL of 1,2-dichloroethane inside a nitrogen-filled glove box. The reactor was brought outside the box and, the apparatus was placed in a water bath maintained at 16 ± 0.2 °C.

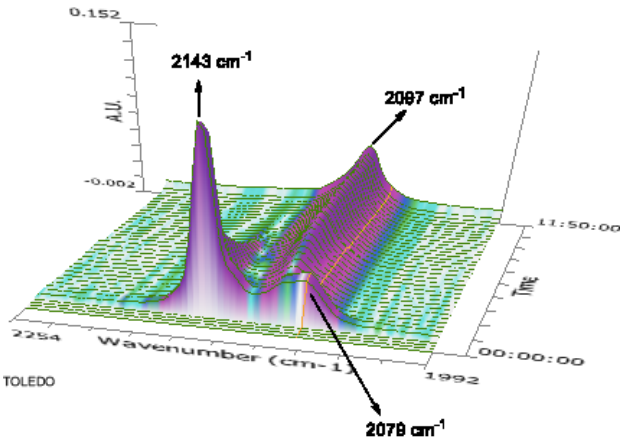


Figure 6. Typical Kinetic Run. Stacked IR Spectra Shows Disappearance of $TMSN_3$ (2143 cm^{-1}) and Appearance of the Product (2097 cm-1) and Active Species [Y]-N_3 (2079 cm^{-1})

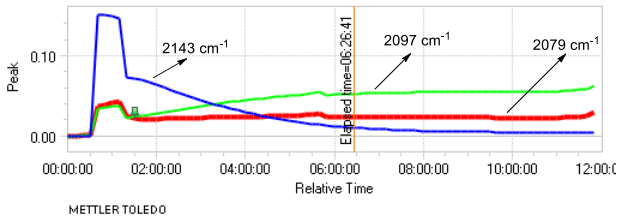


Figure 7. Profiles of Absorbances for $TMSN_3$ and the Product and Active Species [L]Y-N_3 as a Function of Time

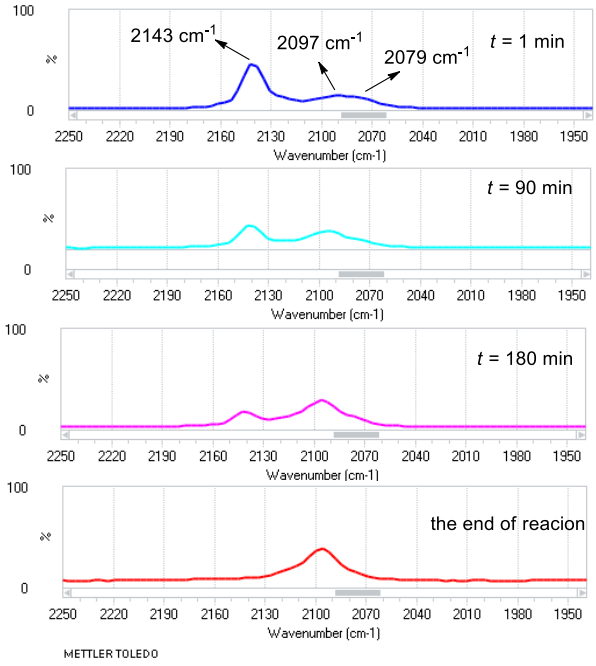


Figure 8. The Azide Peaks as a Function of Time

With rigorous exclusion of moisture, and under copious flow of nitrogen, the IR probe was introduced through the large opening of the reactor. After equilibration, the aziridine **7** (61.5 mg, 0.25 mmol) dissolved in 1.0 mL of 1,2-dichloroethane was introduced through a serum stopper on the side-arm. IR spectra were collected at 10-minute intervals.

A stack of spectra [6 mol% of catalyst (0.006 M) with respect to $TMSN_3$], showing the relevant peaks is shown in Figure 6. Figure 7 shows the profiles of peaks as a function of time. Individual spectra at t = 1 min, 90 min and 180 min and at the end of the reaction are shown in Figure 8.

The assignment of the peak at 2079 cm^{-1} to a metal azide follows from the in situ experiment in which stoichiometric amount of $TMSN_3$ is added to the catalyst. As shown in Figure 9, rapid disappearance of the peak at 2143 cm^{-1} and the corresponding appearance of the peak at 2079 cm^{-1} strongly suggest the formation of a metal azide. Note that the intensity of this peak remains virtually unchanged through out a typical kinetic experiment (Figure 7), confirming its presence as the likely steady-state intermediate.

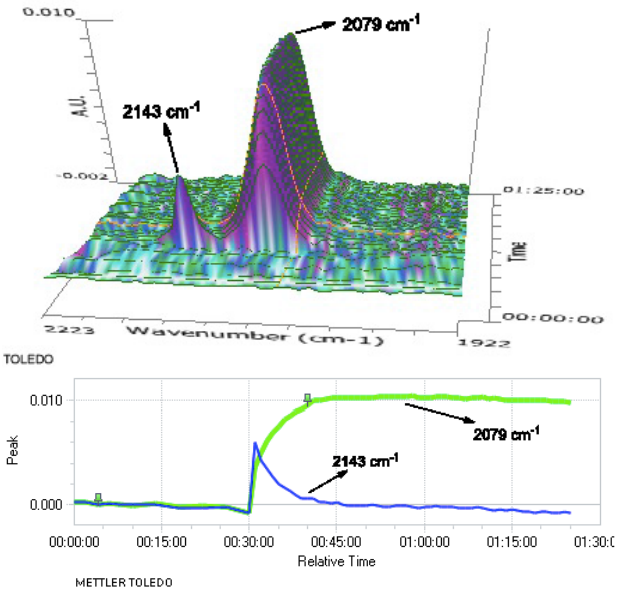


Figure 9. Stacked IR Spectra Showing Disappearance of $TMSN_3$ (2143 cm^{-1}) and Appearance of the Active Species, [Y]-N_3 (2079 cm^{-1})

Kinetic runs were carried out in a 3-fold concentration range of the catalyst with the following equivalents: 0.04, 0.06, 0.10 and 0.12. The absorbance data was plotted with $\ln[(a^o)/(a^o-x)]$ vs time (min) where a^o is the initial absorbance of $TMSN_3$ and (a^o – x) is the absorbance of remaining $TMSN_3$ at time t (Figure 10).

As can be seen in Figure 10, this is an exceptionally well-behaved system, and gives highly reliable data from which k_{obs} values can be calculated from the slope of the $\ln[a_0/(a_0-x)]$ vs t graph. These values for 4 different concentrations are listed in Table 12. A plot of catalyst concentration vs k_{obs} (Figure 11), which gives a straight line with excellent fit (R^2 = 0.99988), is consistent with a first order dependence of the catalyst concentration on the ring-opening reaction. A similar plot of $[cat]^{0.5}$ vs k_{obs}, suggesting a dissociation of the dimer followed by catalysis by monometallic species showed relatively poorer fit.[30] This data taken together with the low enantioselectivity observed (Table 1, entry 4) upon use of structurally related monomeric catalysts (e. g., **2b**) provide strong support for the bimetallic mechanism in these reactions.

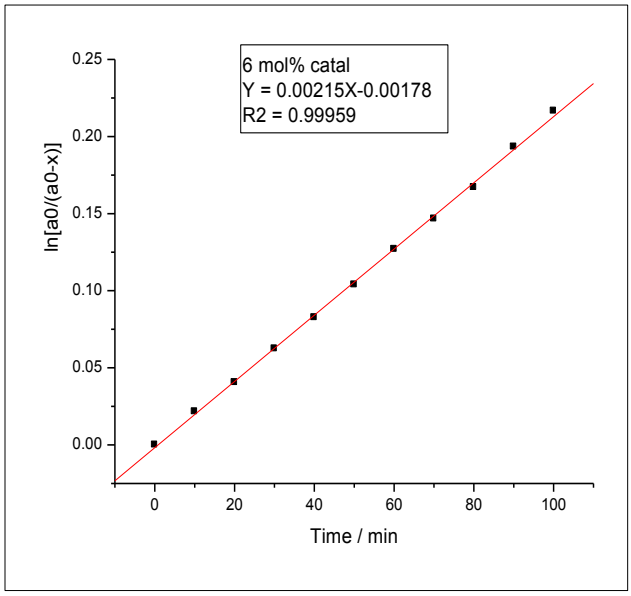


Figure 10. Pseudo-First Order Plot of $\log[(TMSN_3)_0/(TMSN_3)_t]$ vs t for Aziridine Opening Reaction (See Supporting Information for Similar plots with Other Catalyst Concentrations)

Table 12. Data Table k_{obs}, [cat]

[cat.] M	k_{obs} (min^{-1})
0.002	0.00060
0.003	0.00215
0.005	0.00508
0.006	0.00654

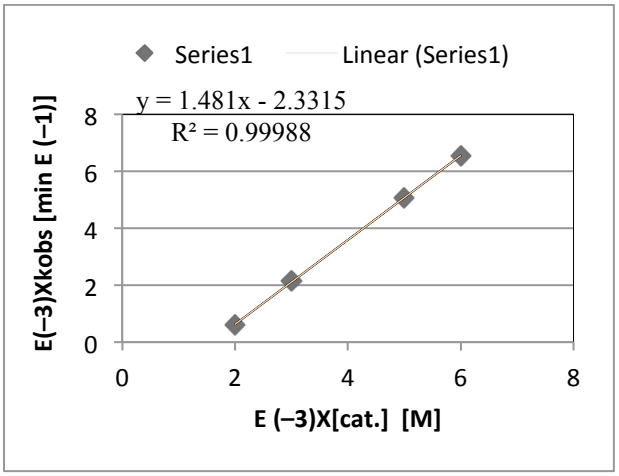
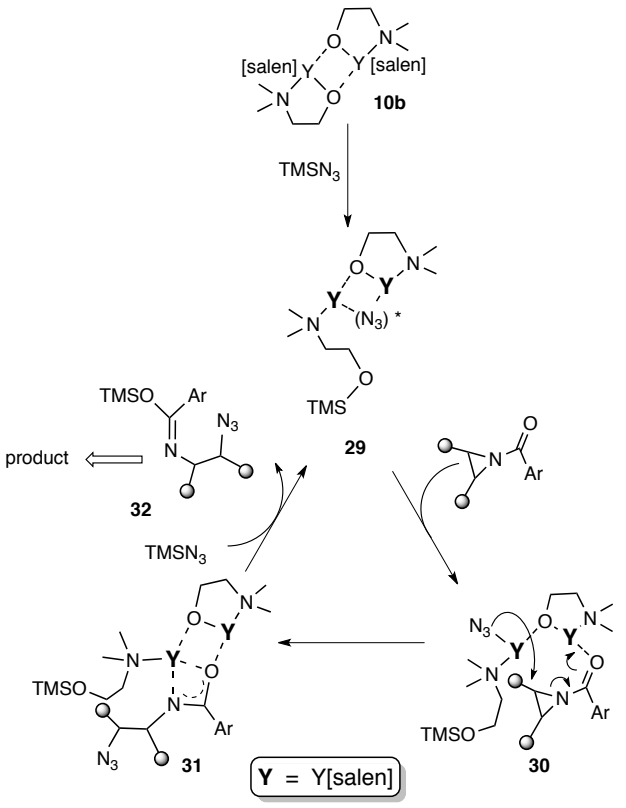


Figure 11. Linear k_{obs} vs [cat]^1 Indicating a Unimolecular Reaction in the Bimetallic Catalyst

A Mechanistic Proposal

One possible mechanism consistent with all the observations is shown in Scheme 4. In this mechanism, the reaction is initiated with the formation of the Y-azide by a metathesis reaction of [**L**]Y–O bond in the dimeric complex with $TMSN_3$ to form the intermediate **29**, tentatively identified as the species responsible for the IR absorption at 2079 cm^{-1}. The nature of the bridging interaction between the azide and the two Y atoms is purposely left vague, since both linear and terminal bridging are well known in lanthanides.[66-68] Activation of the aziridine by the second Y and an internal nucleophilic reaction results in the formation of yet another intermediate, one possible structure of which is depicted in **31**. Oxygen or nitrogen silylation of **31** leads to the silylether derivative of the product (**32**), returning the catalyst as the steady state species **29**. Lack of reactivity of the bulky aziridines can be rationalized by the reluctance of a bulky substrate to enter the cavity at the bottom of which sits the Y_2O_2-core (see the 3D-representation of the solid-state structure of **10b** in Figure 2), or any structurally related putative intermediates generated from **10b** in the initial steps.

Scheme 4. One Possible Mechanism Consistent with the Available Data



Summary and Conclusions

Based on our initial work on the use of monometallic yttrium-salen complexes for TMSX-mediated ring opening reactions of epoxides and aziridines, the structures of these complexes, and, their propensity to form dimers, a set of binuclear complexes (e. g., **10b**) were synthesized and tested for desymmetrization of meso-aziridines and related reactions. Enantioselectivities observed for the $TMSN_3$ and TMSCN mediated ring opening reactions using **10b** as a catalyst are among the highest reported to-date for several aziridines. The reaction has been extended to R_3Si-NCS additions, which gave excellent yields and surprisingly high ee's for the β-amino-alkyl thiocyanate, given the prevalence of an uncatalyzed background reaction. The rate of this thermal background reaction, especially with Me_3SiNCS, can be suppressed with the use of bulky (Et_3Si and *t*-$BuPh_2Si$) isothiocyanate reagents. Use of Yb instead of Y also improves the selectivity in selected cases.

The ligands developed for yttrium for these reactions can be used to prepare the corresponding bimetallic lanthanide complexes. A systematic examination of these complexes across the lanthanide series suggests that the smaller ions (e.g., Dy, Er and Yb) are just as effective as yttrium in many of these ring-opening reactions.

The bimetallic catalyst **10b** upon reaction with chiral monosubstitued aziridines and $TMSN_3$ brings about unprecedented regiodivergent parallel kinetic resolution. The catalyst accelerates the reaction of both members of the racemic mixture, but does so along divergent pathways, inducing opposing regioselectivity in its respective encounters with the Y-reagent. An advantage of this approach is that when azide is used as the nucleophile, the full racemic mixture of an aziridine can be transformed into a set of desirable resolved products, in this case, 1,2-diamines.

The exact origin of the specificity of the bimetallic catalysts remains speculative. It is conceivable that the capsular nature of the catalyst, as revealed by a solid-state structure (Figure 2), helps to coordinate the electrophile (the aziridine) and the nucleophile (the azide) in specific orientations during the activation process. Each of the diastereomeric complexes has a different electrophilic carbon favorably juxtaposed for attack by the nucleophile, which is linked to the second metal within the confines of the cavity. Some support for this conjecture comes from the lack of selectivity when a structurally related monometallic complex is used, and the strict first order dependence of the ring-opening reaction on the concentration of the bimetallic reagent. Lack of reactivity when sterically demanding aziridines such as the ones derived from cyclooctene or *trans*-stilbene, also supports this notion. Vapor pressure osmometry and NMR studies suggest that while the C_2-symmetric bimetallic catalyst is quite robust in solution for the duration of the reaction, the monometallic species undergo significant aggregation.

The results disclosed in this paper add to a growing list of impressive applications of homo- and heteronuclear bimetallic complexes for highly selective carbon-carbon and carbon-heteroatom bond forming reactions. By all indications interest in this area of research continue to burgeon with applications being sought in small molecule as well as polymer[16,69,70] chemistry.

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[†] **Electronic Supplementary Information (ESI) Available**. Full experimental details for the preparation of previously undisclosed catalysts and substrates, typical protocols for desymmetrization and regiodivergent kinetic resolution, 1H and 13C NMR spectra of key compounds, CSP HPLC and CSP GC of key ring-opening products, HR-DOSY spectra for **2b** and **10b**, details of VPO and in situ IR kinetics, CIF for **20** and **21**. Crystallographic data for structures **20** and **21** have been deposited at The Cambridge Crystallographic Data Centre. CCDC 967684-967685 contains the supplementary crystallographic data for this paper, which can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif.

Notes and References

(1) (a) R. H. Holm, P. Kennepohl, E. I. Solomon, *Chem. Rev.* 1996, **96**, 2239. This article appears in an issue of *Chemical Reviews* entirely devoted to 'Bioinorganic Enzymology'. Several other articles in this issue (1996, **96** (7), 2239-3042) also deal with bimetallic enzymes. (b) H. Steinhagen, G. Helmchen, *Angew. Chem. Int. Ed.* 1996, **35**, 2339. (c) J. A. Cricco, E. G. Orellano, R. M. Rasia, E. A. Ceccarelli, A. J. Vila, *Coord. Chem. Rev.* 1999, **190-192**, 519. (d) C. Belle, J.-L. Pierre, *Eur. J. Inorg. Chem.* 2003, 4137. (e) E. L. Hegg, *Acc. Chem. Res.* 2004, **37**, 775. (f) M. J. Hawk,R. M. Breece, C. E. Hajdin, K. M. Bender, Z. Hu, A. L. Costello, B. Bennett, D. L. Tierney, M. W. Crowder, *J. Am. Chem. Soc.* 2009, **131**, 10753.

(2) For reviews, see: (a) M. Shibasaki, M. Kanai, S. Matsunaga, N. Kumagai, "Multimetallic Multifunctional Catalysts for Asymmetric Reactions", In *Bifunctional Molecular Catalysis*; T. Ikariya, M. Shibasaki, Eds. 2011; Vol. 37, pp. 1-30. (b) B. G. Cooper, J. W. Napoline, C. M. Thomas, *Catal. Rev. Science Engg.* 2012, **54**, 1. (c) M. Cokoja, C. Bruckmeier, B. Rieger, W. A. Herrmann, F. E. Kühn, *Angew. Chem. Int. Ed.* 2011, **50**, 8510. (d) R. M. Haak, S. J. Wezenberg, A. W. Kleij, *Chem. Commun.* 2010**,** **46**, 2713. (e) M. Shibasaki, M. Kanai, S. Matsunaga, N. Kumagai, *Acc. Chem. Res.* 2009, **42**, 1117. (f) E. Jacobsen, *Acc. Chem. Res.* 2000, **33**, 421. (g) J.-A. Ma, D. Cahard, *Angew. Chem. Int. Ed.* 2004, **43**, 4566. For a few notable recent contributions, see the following references and those cited in them: (h) V. Annamalai, E. F. DiMauro, P. J. Carroll, M. C. Kozlowski, *J. Org. Chem.* 2003, **68**, 1973. (i) M. Mazet, E. N. Jacobsen, *Angew. Chem. Int. Ed.* 2008, **47**, 1762. (j) Q.-X. Guo, Z.-J. Wu, Z.-B. Luo, Q.-Z. Liu, J.-L. Ye, S.-W. Luo, L.-F. Cun, L. Z. Gong, *J. Am. Chem. Soc.* 2007, **129**, 13927. (k) M. H. Yang, C. J. Zhu, F. Yuan, Y. J. Huang, Y. Pan, *Org. Lett.* 2005, **7**, 1927. (l) S. Mouri, Z. Chen, H. Mitsunuma, M. Furutachi, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* 2010, **132**, 1255. (m) Z. Zhang, Z. Wang, R. Zhang, K. Ding, *Angew. Chem. Int. Ed.* 2010, **49**, 6746. (n) A. Matsuzawa, T. Mashiko, N. Kumagai, M. Shibasaki, *Angew. Chem. Int. Ed.* 2011, **50**, 7616. (o) J. A. Kalow, A. G. Doyle, *J. Am. Chem. Soc.* 2011, **133**, 16001. (p) P. Gopinath, T. Watanabe, M. Shibasaki, *Org. Lett.* 2012, **14**, 1358.

(3) K. B. Hansen, J. L. Leighton, E. N. Jacobsen, *J. Am. Chem. Soc.* 1996, **118**, 10924.

(4) S. E. Schaus, E. N. Jacobsen, *Org. Lett.* 2000, **2**, 1001.

(5) K. Arai, S. Lucarini, M. M. Salter, K. Ohta, Y. Yamashita, K. Kobayashi, *J. Am. Chem. Soc.* 2007, **129**, 8103.

(6) R. M. Thomas, P. C. B. Widger, S. M. Ahmed, R. C. Jeske, W. Hirahata, E. B. Lobkovsky, G. W. Coates, *J. Am. Chem. Soc.* 2010, **132**, 16520.

(7) Z. Li, M. Fernandez, E. N. Jacobsen, *Org. Lett.* 1999, **1**, 1611.

(8) T. Mita, I. Fujimori, I.; R. Wada, J. Wen, M. Kanai, M. Shibasaki, M. *J. Am. Chem. Soc.* 2005, **127**, 11252.

(9) I. Fujimori, T. Mita, K. Maki, M. Shiro, A. Sato, S. Furusho, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* 2006, **128**, 16438.

(10) B. Wu, J. R. Parquette, T. V. RajanBabu, *Angew. Chem. Int. Ed. Engl.* 2009, **48**, 1126.

(11) Y. J. Xu, L. Q. Lin, M. Kanai, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* 2011, **133**, 5791.

(12) Other reports on stereoselective opening of aziridines, see: (a) K. Ohmatsu, Y. Hamajima, T. Ooi, *J. Am. Chem. Soc.* 2012, **134**, 8794. (b) J. Cockrell, C. Wilhelmsen, H. Rubin, A. Martin, J. B. Morgan, *Angew. Chem. Int. Ed.* 2012, **51**, 9842. (c) A. Marti, S. Peruncheralathan, C. Schneider, *Synthesis* 2012, **44**, 27. (d) A. Marti, L. Richter, C. Schneider, *Synlett* 2011, 2513. (e) S. Nakamura, M. Hayashi, Y. Kamada, R. Sasaki, Y. Hiramatsu, N. Shibata, T. Toru, *Tetrahedron Lett.* 2010, **51**, 3820. (f) S. Peruncheralathan, H. Teller, C. Schneider, *Angew. Chem. Int. Ed.* 2009, **48**, 4849. (g) G. D. Sala, A. Lattanzi, *Org. Lett.* 2009, **11**, 3330. (h) S. Minakata, Y. Murakami, M. Satake, I. Hidaka, Y. Okada, M. M. Komatsu, *Org. Biomol. Chem.* 2009, **7**, 641. (i) S. E. Larson, J. C. Baso, G. Li, J. C. Antilla, *Org. Lett.* 2009, **11**, 5186. (j) E. B. Rowland, G. B. Rowland, E. Rivera-Otero, J. C. Antilla, *J. Am. Chem. Soc.* 2007, **129**, 12084. (k) W. H. Leung, W. L. Mak, E. Y. Y. Chan, T. C. H. Lam, W. S. Lee, H. L. Kwong, L. L. Yeung, *Synlett* 2002, 1688. (l) P. Muller, P. Nury, *Helv. Chim. Acta* 2001, **84**, 662. (m) M. Hayashi, K. Ohno, H. Hoshimi, N. Oguni, *Tetrahedron* 1996, **52**, 7817.

(13) R. G. Konsler, J. Karl, E. N. Jacobsen, *J. Am. Chem. Soc.* 1998, **120**, 10780.

(14) B. W. McCleland, W. A. Nugent, M. G. Finn, *J. Org. Chem.* 1998, **63**, 6656. Similar models have been invoked to rationalize reactivity and selectivity in other nucleophile-electrophile combinations, although rigorous evidence for the operation of bimetallic mechanisms is seldom offered, see ref. 2. For some notable exceptions, see: (a) R. G. Konsler, J. Karl, E. N. Jacobsen, *J. Am. Chem. Soc.* 1998, **120**, 10780. (b) Y. N. Belokon, B. Green, N. S. Ikonnikov, V. S. Larichev, B. V. Lokshin, M. A. Moscalenko, M. North, C. Orizu, A. S. Peregudov, G. I. Timofeeva, *Eur. J. Org. Chem.* 2000, 2655. (c) Q.-X. Guo, Z.-J. Wu, Z.-B. Luo, Q.-Z. Liu, J.-L. Ye, S.-W. Luo, L.-F. Cun, L.-Z. Gong, *J. Am. Chem. Soc.* 2007, **129**, 13927. (d) C. Mazet, E. N. Jacobsen, *Angew. Chem. Int. Ed.* 2008, **47**, 1762.

(15) B. Saha, M.-H. Lin, T. V. RajanBabu, *J. Org. Chem.* 2007, **72**, 8648.

(16) R. M. Thomas, P. C. B. Widger, S. M. Ahmed, R. C. Jeske, W. Hirahata, E. B. Lobkovsky, G. W. Coates, *J. Am. Chem. Soc.* 2010, **132**, 16520.

(17) J. A. Kalow, A. G. Doyle, *J. Am. Chem. Soc.* 2011, **133**, 16001.

(18) B. Wu, J. R. Parquette, T. V. RajanBabu, *Science* 2009, **326**, 1662.

(19) M.-H. Lin, T. V. RajanBabu, *Org. Lett.* 2002, **4**, 1607.

(20) Y. Hamashima, D. Sawada, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* 1999, **121**, 2641.

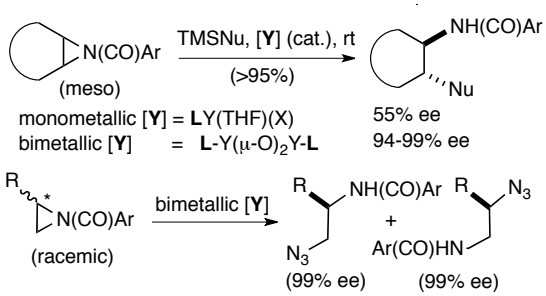
(21) H. Kitajima, K. Ito, Y. Aoki, T. Katsuki, *Bull. Chem. Soc. Jpn.* 1997, **70**, 207.

(22) M. Hayashi, K. Ohno, H. Hoshimi, N. Oguni, *Tetrahedron* 1996, **52**, 7817.

(23) S. A. Schuetz, M. A. Erdmann, V. W. Day, J. L. Clark, J. A. Belot, *Inorg. Chim. Acta* 2004, **357**, 4045.
(24) (a) Ti: G. Boche, K. Mobüs, K. Harms, M. Marsch, *J. Am. Chem. Soc.* 1996, **118**, 2770. Y: (b) $(Ln)Y(\mu\text{-}Cl)]_2$ (several chloride bridged dimers): W. J. Evans, C. H. Fujimoto, J. W. Ziller, *Chem. Commun.* 1999, 311. (c) $Y(L)(\mu\text{-}OH)]_2$ (a hydroxide bridged dimer): C. M. Mascarenhas, S. P. Miller, P. S. White, J. P. Morken, *Angew. Chem. Int. Ed.* 2001, **40**, 601. (d) $Y(L)(\mu\text{-}OR)]_2$ (an alkoxide bridged dimer): T. M. Ovitt, G. W. Coates, *J. Am. Chem. Soc.* 2002, **124**, 1316. CN-bridged complexes: (e) C. E. Plecnik, S. Liu, S. S. Shore, *Acc. Chem. Res.* 2003, **36**, 499. (f) S. Tanase, *Coord. Chem. Rev.* 2006, **250**, 2501. Azide bridged complexes: (f) H. Schumann, C. Janiak, J. Pickardt, *J. Organomet. Chem.* 1988, **349**, 117. (g) H.-C. Wang, M. Xue, Q. Guo, J.-P. Zhao, F.-C. Liu, J. Ribas, *J. Solid State Chem.* 2012, **187**, 143. (h) X.-C. Huang, C. Zhou, H.-Y. Wei, X.-Y. Wang, *Inorg. Chem.* 2013, **52**, 7314.
(25) S. L. McLain, T. M. Ford, N. E. Drysdale, *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* 1992, **33**, 463.
(26) Reference 24(d).
(27) Crystallographic data for the solid state-structures **1a** and **10b** were previously deposited at The Cambridge Crystallographic Data Centre. CCDC 181773 (**1a**) and CCDC 701484 (**10b**) contains the supplementary crystallographic data for this paper, which can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif.
(28) Y. Fukuta, T. Mita, N. Fukuda, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* 2006, **128,** 6312.
(29) E. B. Rowland, G. B. Rowland, E. Rivera-Otero, J. C. Antilla, *J. Am. Chem. Soc.* 2007, **129**, 12084.
(30) See ESI for details.
(31) B. Das, R. Ramu, B. Ravikanth, K. R. Reddy, *Tetrahedron Lett.* 2006**, 47,** 779.
(32) B. Das, V. S. Reddy, R. Ramu, D. N. Kumar, *Catal. Commun.* 2006, **7**, 997.
(33) J. S. Yadav, B. V. S. Reddy, B. Jyothirmai, M. S. R. Murty, *Tetrahedron Lett.* 2005, **46**, 6385.
(34) M. S. Reddy, M. Narender, Y. V. D. Nageswar, K. R. Rao, *Tetrahedron Lett.* 2005, **46**, 6437.
(35) S. Peruncheralathan, M. Henze, C. Schneider, *Tetrahedron Lett.* 2007, **48**, 6743.
(36) N. Prusinowska, J. Gawronski, *Synthetic Commun.* 2009, **39**, 2795.
(37) Z. Wang, X. Sun, S. Ye, W. Wang, B. Wang, J. Wu, J. *Tetrahedron-Asymmetry* 2008, **19**, 964.
(38) G. D. Sala, A. Lattanzi, *Org. Lett.* 2009, **11**, 3330.
(39) S. E. Larson, J. C. Baso, G. Li, J. C. Antilla, *Org. Lett.* 2009, **11**, 5186.
(40) E. N. Jacobsen, *Acc. Chem. Res.* 2000, **33**, 421.
(41) M. Shibasaki, S. Matsunaga, N. Kumagai, N. *Synlett* 2008, 1583.
(42) R. Anwander, "Principles of Organolanthanide Chemistry", In *Lanthanides: Chemistry and Use in Organic Synthesis*; S. Kobayashi, Ed.; Springer: Berlin, 1999; Vol. 2, pp. 1-61.
(43) L. C. Miller, R. Sarpong, R. *Chem. Soc. Rev.* 2011, **40**, 4550.
(44) R. R. Kumar, H. B. Kagan, *Adv. Synth. Catal.* 2010, **352**, 231.
(45) E. Vedejs, M. Jure, *Angew. Chem. Int. Ed.* 2005, **44**, 3974.
(46) J. R. Dehli, V. Gotor, *Chem. Soc. Rev.* 2002, **31**, 365.
(47) A. Gansauer, C. A. Fan, F. Keller, P. Karbaum, P. *Chem. Eur. J.* 2007, **13**, 8084.
(48) Examples of chemo- and regiodivergent kinetic resolutions in which constitutionally different products are formed are still relatively rare. For notable examples, see: (a) R. Webster, A. Boyer, M. J. Fleming, M. Lautens, *Org. Lett.* 2010, **12**, 5418. (b) R. Webster, C. Böing, M. Lautens, *J. Am. Chem. Soc.* 2009, **131**, 444. (c) C. K. Jana, A. Studer, *Angew. Chem. Int. Ed.* 2007, **46**, 6542. (d) A. Gansauer, C. A. Fan, F. Keller, J. Keil, *J. Am. Chem. Soc.* 2007, **129**, 3484. (e) H. M. L. Davies, X. Dai, M. S. Long, *J. Am. Chem. Soc.* 2006, **128**, 2485. (f) M. Pineschi, F. Del Moro, P. Crottti, V. Di Bussolo, F. Macchia, *J. Org. Chem.* 2004, **69**, 2099. (g) K. Tanaka, K.; F. C. Fu, *J. Am. Chem. Soc.* 2003, **125**, 8078. (h) F. Bertozzi, P. Crotti, F. Macchia, M. Pineschi, B. L. Feringa, *Angew. Chem. Int. Ed.* 2001, **40**, 930. (i) G. R. Cook, S. Sankaranarayanan, *Org. Lett.* 2001, **3**, 3531. (j) B. D. Brandes, E. N. Jacobsen, *Synlett* 2001, 1013. (k) Y. Chen, L. Deng, *J. Am. Chem. Soc.* 2001, **123**, 11302. (l) C. Bolm, O. Beckmann, C. Palazzi, *Can. J. Chem.* 2001, **79**, 1593. (m) M. S. Visser, A. H. Hoveyda, *Tetrahedron* 1995, **51**, 4383. (n) M. P. Doyle, A. B. Dyatkin, A. V. Kalinin, D. A. Ruppar, S. F. Martin, M. R. Spaller, S. Liras, *J. Am. Chem. Soc.* 1995, **117**, 11021. (o) C. Bolm, G. Schlingloff, *J. Chem. Soc., Chem. Commun.* 1995, 1247. (p) S. F. Martin, M. R. Spaller, S. Liras, B. Hartmann, *J. Am. Chem. Soc.* 1994, **116**, 4493.
(49) H. B. Kagan, J. C. Fiaud, "Kinetic Resolution", In *Topics in Stereochemistry*; E. L. Eliel, S. H. Wilen, Eds.; John Wiley: 1988; Vol. 18, pp. 249-330.
(50) S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow, E. N. Jacobsen, *J. Am. Chem. Soc.* 2002, **124**, 1307.
(51) M. Tokunaga, J. Kiyosu, Y. Obora, Y. Tsuji, *J. Am. Chem. Soc.* 2006, **128**, 4481.
(51a) Burk, M. J.; Allen, J. G. *J. Org. Chem.* 1997, **62**, 7054-7057. The β-amido-azide from **7** has been converted into *trans*-1,2-diaminocyclohexane by trans-amidation with $(boc)_2O$/DMAP, acid-mediated deprotection and hydrogenation of the resulting azide.[28]
(52) K. Faber, *Chem. Eur. J.* 2001, **7**, 5004.
(53) U. T. Strauss, U. Felfer, K. Faber, K. *Tetrahedron: Asymmetry* 1999, **10**, 107.
(54) Yields of more than 50% can be obtained in special cases where the epoxide can undergo racemization under hydrolytic conditions. This is an example of the well-known dynamic kinetic resolution, and is distinctly different from the strategy outlined here. See, ref. 50. This paper also illustartes a rare instance in which the slow reacting enantiomer from a classical kinetic resolution with exceptionally high k_f/k_s is transformed into the same initial product in a subsequent chemical reaction.
(55) S. Hwang, C. Y. Choi, E. Y. Lee, *Biotechnology and Bioprocess Engineering* 2008, **13**, 453.
(56) (a) W. Kroutil, M. Mischitz, K. Faber, *J. Chem. Soc., Perkin Trans 1* 1997, 3629. (b) For the conversion of a β-acylamidoazide to a 1,2-diamine, see ref 28.
(57) (a) See ESI for experiemental details, spectroscopic and analytical data including chromatograms from chiral stationary phase separations. The enantiomeric excesses were determined by chiral phase liquid chromatography where base-line separtion of the enantiomers were observed. (b) The starting racemic aziridines were prepared by reaction of the appropriate alkene substrate with IN_3 followed by reduction with $LiAlH_4$ and acylation with 4-nitrobenzoyl chloride. The enantiopure *N*-acyl aziridines were prepared from the corresponding α-amino acids via $LiAlH_4$ reduction, Mitsunobu reaction and benzoylation. See ref. 18 for details.
(58) For other examples, see: (a) D. J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem. Int. Ed.* 1995, **34**, 1059. (a) In yttrium chemistry: M.-H. Lin, T. V. RajanBabu, *Org. Lett.* 2002, **4**, 1607.
(59) N. W. Mitzel, J. Riede, C. Kiener, *Angew. Chem. Int. Ed. Engl.* 1997, **36**, 2215.
(60) For another recent example in the Ti(III)-mediated epoxide-opening, see: A. Gansauer, L. Shi, M. Otte, *J. Am. Chem. Soc.* **2010**, *132*, 11858.
(61) See ESI for the ^1H, ^{13}C, ^1H-^1H COSY, HMQC, time-dependent DOSY spectra of **10b**. DOSY spectra of **2b** recorded at time intervals t = 0, 7.5 12 and 23 h are also included there.
(62) *ACS Symposium Series*; A. L. Wayda, M. Y. Darensbourg, Eds.; Amrican Chemical Society: Washington, DC, 1987.

(63) S. Tosaki, R. Tsuji, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* 2005, **127**, 2147.
(64) B. Baccar, *J. Mol. Structure* 1971, **7**, 369.
(65) See ESI for the IR spectrum in the range 1560-1720 cm^{-1}, and the time-dependent profile of the peak at 1648 cm^{-1}.
(66) X.-C. Huang, C. Zhou, H.-Y. Wei, X.-Y. Wang, *Inorg. Chem*. 2013, **52**, 7314, and references cited therein.
(67) H.-C. Wang, M. Xue, Q. Guo, J.-P. Zhao, F.-C.Liu, J. Ribas, *J. Solid State Chem.* 2012, **187**, 143.
(68) H. Schumann, C. Janiak, J. Pickardt, *J. Organomet. Chem.* 1988, **349**, 117.
(69) I. Yu, A. Acosta-Ramirez, P. Mehrkhodavandi, P. *J. Am. Chem. Soc.* 2012, **134**, 12758.
(70) M. R. Kember, F. Jutz, A. Buchard, A. J. P. White, C. K. Williams, *Chem. Sci.* 2012, **3**, 1245.

TOC Graphic



• Structural and kinetic evidence for bimetallic mechanism