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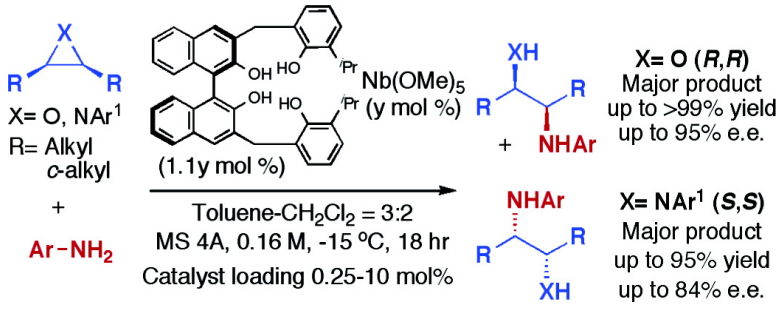

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The Development of Scalemic Multidentate Niobium Complexes as Catalysts for the Highly Stereoselective Ring Opening of *meso*-Epoxides and *meso*-Aziridines

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Abstract: The discovery and development of a new Lewis acid system based on a complex formed from niobium(V) methoxide and (*R*)-3,3′-bis(2-hydroxy-3-isopropylbenzyl)-1,1′-binaphthalene-2,2′-diol, a novel tetradentate BINOL derivative, is presented. The system was shown to be extremely effective in promoting the desymmetrative ring opening of linear and cyclic *meso*-epoxides using anilines as nucelophiles, delivering the corresponding (*R,R) anti*-amino alcohols in good to excellent yields (up to quantitative) and excellent enantioselectivity (up to 96% ee). Furthermore, the catalyst system displays a remarkable sensitivity to steric bulk at the β-carbon of the epoxide, selectively facilitating ring opening of smaller epoxides in the presence of more sterically hindered epoxides. This property was confirmed by a series of competition reactions using a mixture of *meso*-2-butene oxide and another aliphatic *meso*-epoxide, with the result that the former, less encumbered epoxide reacted preferentially with up to 98% chemical selectivity. While it was found to be most convenient to conduct the reactions with 10 mol % catalyst loading at 0.16 M, at higher overall concentration the reaction still proceeded efficiently with as little as 0.25 mol % catalyst to give the desired products with no significant reduction in yields or enantioselectivities. In addition, the current catalyst system was also found to mediate the asymmetric ring opening of nonsymmetrical *cis*-2-alkene oxides with anilines to give preferentially the corresponding (2*R*,3*R*)-2-amino-3-ols arising from ring opening at the methyl terminus, in excellent yields (up to quantitative) and good to excellent regio- and enantioselectivities (up to 18:1 and >99% ee, respectively). Intriguingly, it was discovered that the same catalyst system also promoted the ring-opening desymmetrization of aziridines with aniline nucleophiles to give the corresponding (*S,S*) vicinal diamines in good to excellent yields and enantioselectivity (up to 95% and 84% ee [>99% ee following a single recrystallization]). Catalyst systems that promote closely related reactions with opposite stereochemical outcomes in high selectivity such as the current niobium system are extremely unusual. To the best of our knowledge, this report constitutes not only the first example of the catalytic desymmetrization of both *meso*-epoxides and *meso*-aziridines but also a rare example of such complementary stereoselectivity in a catalytic reaction.

Introduction

The development of new chiral catalysts for the promotion of asymmetric reactions leading to the generation of enantiopure products is one of the most important tasks in synthetic chemistry.[1] As a result, this area has attracted a great deal of attention over nearly three decades, and the pace of development has shown no sign of abating in recent years. The majority of protocols disclosed to date involve the use of complexes of homochiral ligands and transition metals; the central role played by these reagents has led to the development of Lewis acids on the basis of almost every amenable metal in the periodic table.[2]

As a result of the attention devoted to the development of modern catalyst systems by the chemical community, the requirements placed on such systems are becoming ever more stringent. For example, in addition to promoting reactions in high yields and with high enantioselectivities, new chiral catalysts are increasingly required to possess the ability to distinguish between substrates that are closely related structural analogues. In this context, a nonenzymatic catalyst which is able to recognize the difference between methyl and ethyl groups in a substrate would be an ideal catalyst in this field.

Epoxides and aziridines are extremely useful and versatile functional elements in organic synthesis.[3] In addition to their

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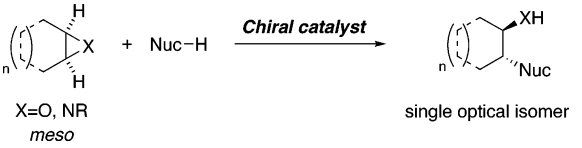
Scheme 1. Desymmetrization of *meso*-Epoxides and Aziridines by Ring Opening under the Influence of a Chiral Catalyst



presence in a diverse variety of natural products and resin precursors, their inherent reactivity toward ring opening with a wide range of nucleophiles to give products with, in the case of nonterminal epoxides and aziridines, contiguous chiral centers makes them very valuable synthetic intermediates. The higher reactivity of epoxides in particular has led to their wide use in synthesis and has been fueled by the fact that the ring-opening reaction of *meso*-epoxides proceeds smoothly with a range of nucleophiles such as with a range of mild Lewis acid catalysts to give chiral products.[4−6] Of greater synthetic interest is the use of a chiral catalyst in the ring-opening reaction which leads to the formation of chiral nonracemic products via desymmetrization of the epoxide or aziridine (Scheme 1).

In the case of epoxides, several catalyst systems that mediate the desymmetrative process using a broad array of metals and nucleophiles including TMSCN,[7] thiols,[8] $TMSN_3$,[9] alcohols,[10] anilines,[11] RLi,[12] and other carbon-centered nucleophiles[3e] have been described. As for aziridines, while several protocols for the nonstereoselective ring-opening reaction have been reported, the catalytic enantioselective version of the reaction has not been well explored. In particular, use of *meso*-aziridines as substrates has been little investigated. Although examples of ring-opening reactions of aziridines using TMSCN,[13] MeMgBr,[14] and $TMSN_3$[15] have been described, to the best of our knowledge, no methods for desymmetrisation of *meso*-aziridines using less reactive nucleophiles such as anilines have been reported. Needless to say, the introduction of such a catalyst system would be of great synthetic interest. Furthermore, the invention of a catalyst system which promotes not only the efficient and highly stereoselective ring opening of *meso*-epoxides but also of *meso*-aziridines, with aniline nucleophiles, would enhance yet further the utility of Lewis acid catalysis.

In recent years, our group has reported the use of complexes of transition metals and 2,2′-binapthol (BINOL) derivatives as catalysts for a variety of transformations such as enantioselective aldol reactions,[16] hetero-Diels−Alder reactions,[17] Mannich type reactions,[18] Strecker-type reactions,[19] the allylation of imines,[20] and [3+2] cycloaddition reactions.[21] In this context, and as part of our ongoing interest in *meso*-epoxide chemistry,[22] we recently reported the invention of the first highly enantioselective Lewis acid catalyst system which shows remarkable selectivity in the

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desymmetrization reaction of closely structurally related *meso*-epoxides by ring opening with aniline nucleophiles.[23] The system in question is constructed from scalemic multidentate complexes of niobium(V) and BINOL derivatives and was discovered as part of our program of research into new, high-specification Lewis acid catalysts on the basis of less-exploited metals.[24,25] Herein, we describe in detail the development of this catalyst system and report the results of investigations into the substrate scope and selectivity of the *meso*-epoxide ring-opening reaction mediated by the same catalyst. In addition, to the best of our knowledge, the first ever desymmetrization of *meso*-aziridines with aniline nucleophiles is also described.

Results and Discussion

Development of the Multidentate-Nb(V) Catalyst System and Initial Substrate Screening. The starting point for our investigation was the Nb(V) system which we have developed as a catalyst for the Mannich-type reactions of imines with silicon enolates (Scheme 2).[26] This species, prepared from a mixture of a Nb(V) salt and novel tridentate BINOL-derived ligand **1**, was shown to catalyze the Mannich reactions in high yields and with excellent enantioselectivities. NMR and X-ray crystallographic studies suggested structure **2**, in which two niobium atoms are straddled by two equivalents of the ligand, as the most plausible catalyst species. This arrangement, in which the metal centers are held in a unique spatially well-defined binuclear array by firm but flexible ligation, facilitates highly substrate selective reactions. In view of the fact that the niobium(V) atoms at the heart of our catalyst system are already heavily coordinated, we judged that monodentate species would function most efficiently as substrates. In view of the known high oxophilicity of niobum salts, we selected epoxides as suitable substrates and decided to focus on the asymmetric ring opening of *meso*-epoxides with anilines.

Scheme 2. Mannich-Type Reaction Catalyzed by a Nb(V)/BINOL-Derived Catalyst System

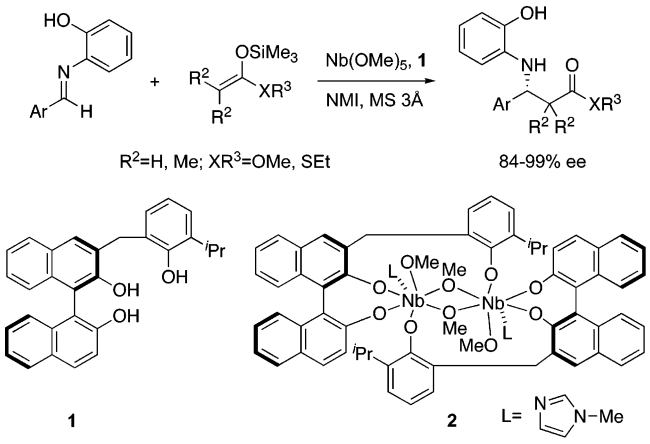
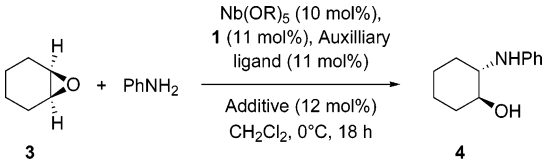


Table 1. Nb(V) Catalyzed Ring Opening of *meso*-Cyclohexene Oxide with Aniline



entry	Nb source	auxiliary ligand	additive	yield (%)[a]	ee (%)[b]
1[c]	$Nb(OMe)_5$	none	NMI[d]	18	2
2[e]	$Nb(OMe)_5$	(*R*)-BINOL	NMI[d]	21	4
3[e]	$Nb(OMe)_5$	(*S*)-BINOL	NMI[d]	29	33
4[e]	$Nb(OMe)_5$	(*S*)-BINOL	2,6-lutidine	30	27
5[e]	$Nb(OMe)_5$	2,2′-biphenol	2,6-lutidine	34	48
6	$Nb(OMe)_5$	2,2′-biphenol	2,6-lutidine	49	38
7	$Nb(OEt)_5$	2,2′-biphenol	2,6-lutidine	48	34
8	$Nb(O^nPr)_5$	2,2′-biphenol	2,6-lutidine	49	41
9	$Nb(O^iPr)_5$	2,2′-biphenol	2,6-lutidine	55	48
10	$Nb(O^tBu)_5$	2,2′-biphenol	2,6-lutidine	49	47
11	$Nb(O^iPr)_5$	2,2′-biphenol	2,6-lutidine	67	33
12	$Nb(O^iPr)_5$	2-phenylphenol	2,6-lutidine	60	41
13	$Nb(O^iPr)_5$	3-phenylphenol	2,6-lutidine	44	31
14	$Nb(O^iPr)_5$	4-phenylphenol	2,6-lutidine	49	40
15	$Nb(O^iPr)_5$	phenol	2,6-lutidine	63	38
16	$Nb(O^iPr)_5$	4-fluorophenol	2,6-lutidine	58	33
17	$Nb(O^iPr)_5$	4-^{t}butylphenol	2,6-lutidine	62	48
18	$Nb(O^iPr)_5$	2-naphthol	2,6-lutidine	56	32

[a] Isolated yields. [b] Determined by chiral high-performance liquid chromatography (HPLC). [c] 12 mol % **1**. [d] *N*-Methylimidazole. [e] In CH_2Cl_2/toluene (1:1).

We selected the ring-opening reaction of *meso*-cyclohexene oxide **3** using aniline as a nucleophile and the catalyst established for the Mannich type reaction described above as our model system. The reaction was conducted under standard reaction conditions to afford the corresponding 1,2-amino alcohol **4** in only low yield and with extremely low enantioselectivity (Table 1, entry 1). Our working model regarding the structure of the catalytic species envisaged a niobium metal center coordinated to the three alkoxide groups of the ligand

(23) For a preliminary description of our early investigations see Arai, K.; Salter, M. M.; Yamashita, Y.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 955.

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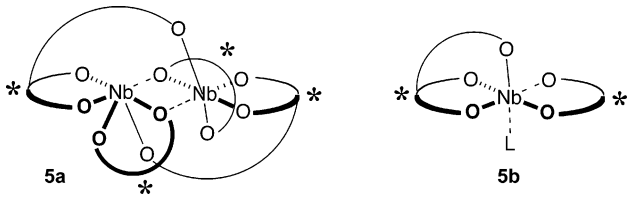


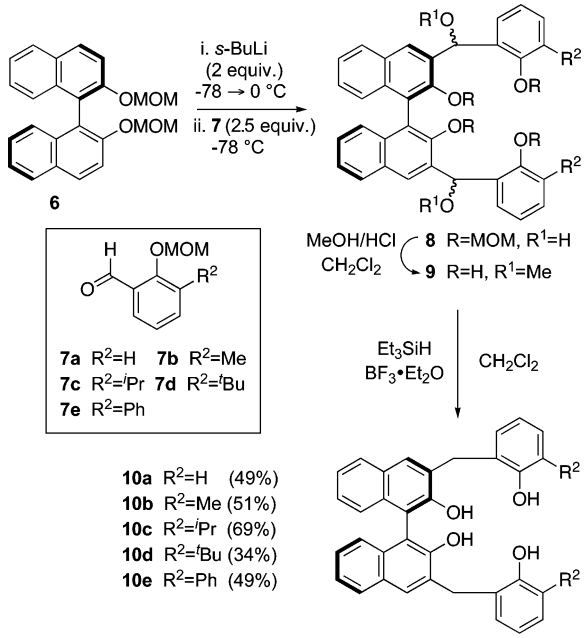
Figure 1. Postulated structures of the catalyst in the presence of auxiliary ligands.

with the two remaining coordination sites being occupied by two equivalents of the alkoxide species present in the starting $Nb(OR)_5$ salt (Figure 1). This would imply a certain lack of rigidity in the coordination sphere of the catalyst and subsequent loss of enantioselectivity in the reaction. With this in mind, the affect of adding a bidentate auxiliary ligand to the reaction with a view to creating a still more rigid structure such as **5a** or **5b** was investigated (entries 2−6).

Accordingly, the reaction was repeated in the presence of 11 mol % of (*R*)-BINOL, however, little improvement in either yield or enantioselectivity was observed (entry 2). Interestingly, use of (*S*)-BINOL led to a considerable improvement in enantioselectivity, but the absolute selectivity and yield were still low (entry 3). Use of 2,6-lutidine as an amine additive had little effect (entry 4), whereas changing the auxiliary ligand from (*S*)-BINOL to the racemic 2,2′-biphenol gave the desired product in 48% ee (entry 5) indicating that the observed increase in enantioselectivity does not require a symbiotic relationship between the chirality of ligand **1** and the auxiliary ligand. At this point, we were able to establish the absolute configuration of the major isomer unambiguously as 1*S*,2*S* by single-crystal X-ray analysis of the camphenyl ester of **4**. A survey of common Nb(V) sources (entries 6−10) revealed that those constituted from more bulky alkoxides (entries 9 and 10) gave superior results, with the *iso*-propoxide salt providing the product in the best yield and ee. Thus, $Nb(O^iPr)_5$ was adopted as the niobium source of choice for the continued development of the catalyst system.

At this stage, while the efficacy of adding an auxiliary ligand to the reaction mixture had been demonstrated, the exact role of the added species and indeed its mode of coordination (mono- or bidentate) remained unclear. ^{13}C NMR studies of the catalyst prepared from a stoichiometric amount of $Nb(OEt)_5$ with **1** (1.1 equiv) in the presence of 2,2′-biphenol (1.1 equiv) and 2,6-lutidine (1.2 equiv) in CD_2Cl_2 showed, in addition to a peak at 160 ppm corresponding to the phenoxy aromatic carbon of coordinated 2,2′-biphenol, a peak at 150 ppm which was assigned to the corresponding carbon atom of an unbound phenolic group. The result suggested that the 2,2′-biphenol was in fact binding to the metal center in monodentate fashion, an idea which was reinforced by the observation that not only did use of the monomethyl ether of 2,2′-biphenol (entry 11) as opposed to the parent diol (entry 9) in the reaction still permit the production of the ring-opened product but that it did so in markedly better yield than previously and with comparable enantioselectivity. This observation prompted us to screen many phenolic derivatives as auxiliary ligands with a view to adumbrate further the role of the latter in the reaction (entries 12−18). Although the use of 4-*tert*-butylphenol provided the ring-opening product in a respectable yield and with an enantioselectivity equal to the best level observed with other catalyst combinations observed (entry 17), the yield and the selectivity were not yet satisfactory.

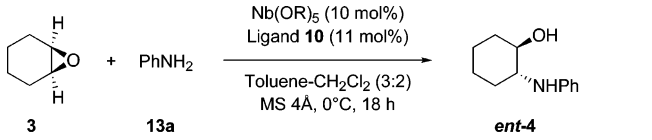
Scheme 3. Synthesis of Tetradentate Ligands **10a**−**e**



Development of a Novel Tetradentate BINOL-Derived Ligand System. Taken together, these results clearly indicated that the most effective catalyst system involved coordination of the metal center with a total of four phenoxides per niobium atom along with addition stabilization with a more weakly bound nitrogenous ligand. We then designed a new type of tetradentate ligand with all four phenoxides. Thus, BINOL protected as its *bis*-methoxymethyl ether **6** was treated with 2 equiv of *sec*-butyl lithium, and the resulting dianion was quenched at −78 °C with a range of 2-methoxymethoxybenzaldehydes **7a**−**e** to afford the resulting diol **8a**−**e**. Treatment of the latter with acidic methanol in CH_2Cl_2 resulted in cleavage of the MOM groups and the conversion of the alcohols into the corresponding methyl ethers giving tetraols **9a**−**e** which were reduced with $Et_3SiH/BF_3{\bullet}OEt_2$ to afford the desired tetradentate BINOL derivatives **10a**−**e** in good yields over three steps (see Scheme 3).

Application of these new ligands to the ring-opening reaction of *meso*-cyclohexene oxide with aniline gave interesting results (Table 2). It was discovered that while the catalyst derived from **10a** with $Nb(OMe)_5$ gave the expected 1*S*,2*S*-amino alcohol **4** in acceptable chemical yield but low enantioselectivity (entry 1), use of **10b** afforded the 1*R*,2*R* isomer as major product of the reaction (entry 2) albeit with low overall selectivity. Furthermore, it was found that switching to the ^{i}Pr-substituted ligand **10c** gave the 1*R*,2*R* product ***ent*-4** in essentially quantitative yield and with comparatively high enantioselectivity (entry 3). However, increasing the steric bulk of the ligand still further by the introduction of ^{t}Bu groups (**10d**, entry 4) led to a substantial drop-off in both yield and selectivity, whereas use of an aryl-substituted ligand (**10e**, entry 5) gave the ring-opened product in very high yield, but with the 1*S*,2*S* enantiomer as the major product. In contrast, the 6,6′-disubstituted BINOL derived tetradentate ligands **10f** and **g** again gave the 1*R*,2*R* enantiomer in very high yield but with low selectivity (entries 6 and 7). Interestingly, ligand **11** in which one of the phenoxyl groups has been converted to a methyl ether still afforded the

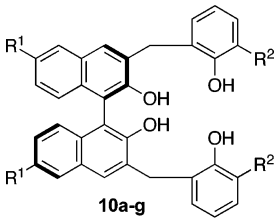
Table 2. Ring-Opening Reaction of *meso*-Cyclohexene Oxide with Aniline Catalyzed by Complexes of Nb(V) and Tetradentate Ligands



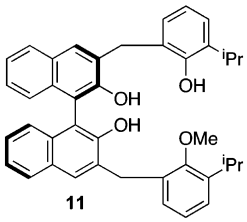
3 **13a** ***ent*-4**

(1*R*,2*R*)-2-(phenylamino)cyclohexanol

entry	Nb source	ligand	R^1	R^2	yield (%)	ee (%)
1[a]	$Nb(OMe)_5$	**10a**	H	H	64	−35
2	$Nb(OMe)_5$	**10b**	H	Me	76	25
3	$Nb(OMe)_5$	**10c**	H	^{i}Pr	quant.	70
4	$Nb(OMe)_5$	**10d**	H	^{t}Bu	63	32
5[a]	$Nb(OMe)_5$	**10e**	H	Ph	96	−18
6	$Nb(OMe)_5$	**10f**	Me	^{i}Pr	93	58
7	$Nb(OMe)_5$	**10g**	I	^{i}Pr	89	52
8	$Nb(OMe)_5$	**11**	H	^{i}Pr	83	37
9[b]	$Nb(O^iPr)_5$	**10c**	H	^{i}Pr	85	11
10[c]	$Nb(O^iPr)_5$	**10c**	H	^{i}Pr	64	66
11	$Nb(O^iPr)_5$	**10c**	H	^{i}Pr	90	68



10a-g



11

[a] (1*S*,2*S*) compound formed. [b] Reaction run in CH_2Cl_2. [c] Reaction run in toluene−CH_2Cl_2 (1:1).

same 1*R*,2*R*-amino alcohol as the majority of the tetradentate ligands examined although with somewhat reduced selectivity (entry 8).

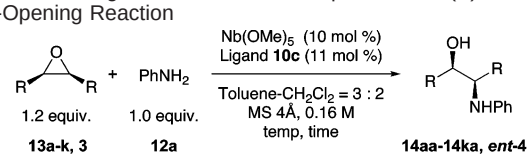
The marked preference for the ^{i}Pr substituted tetradentate ligand **10c** was in line with that observed for the tridentate system **1**, however, whereas in the latter case $Nb(O^iPr)_5$ had been the optimum niobium(V) source (using CH_2Cl_2 as solvent), the combination of $Nb(O^iPr)_5$ and **10c** in CH_2Cl_2 gave the 1*R*,2*R* product in significantly lower enantiomeric excess although in much higher chemical yield (entry 9). In mixed toluene-CH_2Cl_2 solvent systems, however, approximately the same level of enantioselectivity was observed for the catalysts derived from $Nb(O^iPr)_5$ as for that formed from $Nb(OMe)_5$ (entries 10 and 11), but as yields and selectivities were marginally better with the latter, $Nb(OMe)_5$ was adopted as the niobium source of choice.

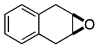
Scope of the Desymmetrization Reaction of *meso*-Epoxides. With these results in hand, we turned our attention to the scope of the reaction. Accordingly, we conducted the reaction with a range of linear and cyclic epoxides with striking results (Table 3). These investigations revealed that the reaction with *cis*-but-2-ene oxide **13a** (entry 1) and aniline **12a** proceeded very smoothly to give the corresponding 1,2-hydroxylamine **14aa** in quantitative yield and very high enantioselectivity; however, when the reaction was conducted with the closely related aliphatic *meso*-epoxides **13b**−**d** and the aromatically substituted *cis*-stilbene oxide **13e**, the reaction proceeded very sluggishly, affording the corresponding ring-opened products only in very low yields and low enantioselectivities (entries 2, 4−5) except for *cis*-oct-4-ene **13c** (entry 3, 84% ee). In contrast, on switching to cyclic *meso*-epoxide substrates, the corresponding ring-opened products were obtained in very high yields and generally high enantioselectivities (entries 6−15). The high chemoselectivity of the reaction, favoring *cis*-but-2-ene **13a** and cyclic *meso*-epoxides over other linear *meso*-epoxides is striking; such outstandingly high levels of selectivity in an epoxide ring-opening reaction are, to the best of our knowledge, unprecedented.

The high reactivity and enantioselectivity of the ring-opening was generally maintained even at lower catalyst loading although the efficiency of the reaction was found to be dependent on concentration especially at very low loadings (≤1 mol %). Accordingly, it was found that even at catalyst loadings as low as 0.5 or 0.25 mol % running the reaction at high concentration over an extended period delivered the ring-opened product in very good yield and with high enantioselectivity.

Scope of the Aniline Nucleophile. With these results in hand, we turned our attention to the scope of the aniline in the reaction. Accordingly, *cis*-but-2-ene oxide **13a** was allowed to react with a range of differently substituted anilines **12a**−**i** in the presence of 10 mol % of the catalyst under the conditions described above, affording the corresponding 1,2-amino alcohols **14aa**−**14ai** (Table 4). These experiments showed that catalyst activity was general for a wide range of different anilines with both electron-rich and electron-poor examples functioning well in the reaction, although the ring-opened product was obtained in slightly lower yield in the case of *ortho*-substituted anilines. This generality was in striking contrast to the chemoselectivity observed with respect to the epoxide component in the reaction (vide supra). In addition, we investigated the reactivity of cyclic *meso*-epoxides **13g** and **13h** with electron-poor aniline **12g** (entries 10−13). Gratifyingly, it was found that these substrates also underwent ring opening smoothly to give the anticipated products in good to excellent yields and acceptable enantioselectivity (entries 10 and 12). Lowering the temperature still further (−40 °C, entry 11; −30 °C, entry 13) and carrying out the reaction under more dilute conditions (0.08 M) afforded the ring-opened products with improved ee and in essentially the same yield.

Table 3. Investigation of Substrate Scope in the Nb(V) Catalyzed Ring-Opening Reaction



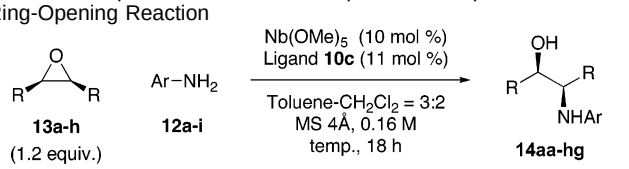
Entry	Epoxide		Product	Temp (°C)	Time (h)	Yield (%)[a]	ee (%)
1		**13a**	**14aa**	-15	18	quant.	95[b]
2		**13b**	**14ba**	-15	18	2[c]	38
3		**13c**	**14ca**	-15	18	9[c]	84
4		**13d**	**14da**	-15	18	26	31
5		**13e**	**14ea**	-15	18	21	52
6		**13f**	**14fa**	-30	72	54	91
7		**13g**	**14ga**	-30	48	69	89
8		**13g**	**14ga**	-15	72	quant.	86
9		**3**	***ent*-4**	0	18	quant.	70
10		**3**	***ent*-4**	-15	18	80	79
11		**13h**	**14ha**	0	18	92	83
12		**13h**	**14ha**	-15	18	59	86
13		**13i**	**14ia**	-15	18	78	89
14		**13j**	**14ja**	-30	42	81	87
15		**13k**	**14ka**	-15	24	77	82

[a] Isolated yields unless stated otherwise. [b] Catalyst loading: 1 mol %: 82% yield, 92% ee; 0.5 mol %: 90% yield, 90% ee; 0.25 mol %: 86% yield, 88% ee. [c] Yield determined by ^{1}N NMR vs naphthalene as internal standard.

Competition Reactions between Mixtures of *meso*-Epoxides. Having established parameters with regard to the scope of both the epoxide and aniline components, we returned to the question of the remarkable chemoselectivity of the Nb(OMe)$_5$−**10c** catalyst system. To probe this feature of our system more rigorously, we conducted a series of competition reactions in which the parent aniline **12a** was allowed to react with an equimolar mixture of *cis*-but-2-ene oxide **13a** and another, bulkier epoxide **13b**−**e**, **13j** in the presence of the catalyst (Table 5). To our delight, the competition reactions proceeded smoothly and with high chemical selectivity to give predominantly **14aa**, resulting from ring opening of **13a** with aniline, in high yield and very high enantioselectivity. Only traces of the products of addition of the nucleophile to the other epoxide **13** were formed. In all cases except for the competition between **13a** and **13c** (entry 2), the ratio of **4aa** to the product derived from the other epoxide exceeded 60:1, and in the competition reaction with *cis*-dec-5-ene oxide **13d** (entry 3) the selectivity was 98%.

Ring-Opening Reactions of Unsymmetrically Disubstituted *cis*-Epoxides. Interestingly, the high levels of selectivity observed in the competitive desymmetrization reactions were maintained in the ring opening of unsymmetrical *cis*-epoxides. Exposure of *cis*-epoxides **15a**−**c** to aniline **12a** in the presence of the Nb(V)−**10c** catalyst system (10 mol %) and MS 4A gave

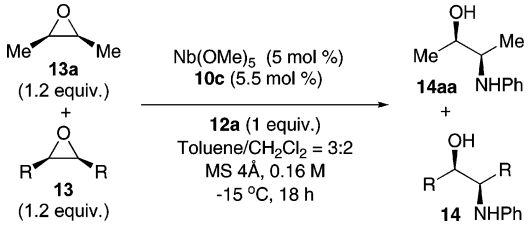
Table 4. Scope of the Aniline Nucleophile in the Epoxide Ring-Opening Reaction



entry	epoxide		Ar		temp (°C)	yield (%)[a]		ee (%)
1	Me	**13a**	Ph	**12a**	−15	quant.	**14aa**	94
2	Me	**13a**	(2-Me)Ph	**12b**	−15	82	**14ab**	84
3	Me	**13a**	(3-Me)Ph	**12c**	−15	92	**14ac**	93
4	Me	**13a**	(4-Me)Ph	**12d**	0	90	**14ad**	91
5	Me	**13a**	(2-OMe)Ph	**12e**	−10	95	**14ae**	90
6	Me	**13a**	(4-OMe)Ph	**12f**	0	99	**14af**	90
7	Me	**13a**	(3-CF$_3$)Ph	**12g**	−15	89	**14ag**	96
8	Me	**13a**	(3,5-(CF$_3$)$_2$)Ph	**12h**	−15	96	**14ah**	96
9	Me	**13a**	(4-Br)Ph	**12i**	−15	96	**14ai**	95
10		**13g**	(3-CF$_3$)Ph	**12g**	−15	98	**14gg**	83
11[b,c]		**12g**	(3-CF$_3$)Ph	**12g**	−40	94	**14gg**	90
12		**13h**	(3-CF$_3$)Ph	**12g**	−15	88	**14hg**	82
13[b,c]		**13h**	(3-CF$_3$)Ph	**12g**	−30	89	**14hg**	89

[a] Isolated yields. [b] Forty-two hours. [c] Total concentration 0.08 M.

Table 5. Competition Experiments in the Ring Opening of Epoxide Mixtures



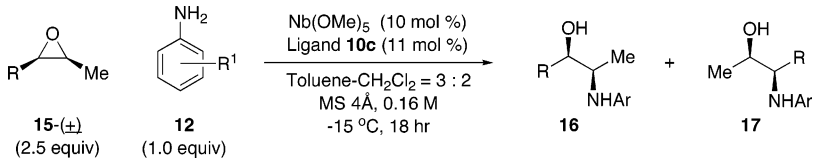
			14aa		14			chemical excess
entry	R		yield (%)[a]	ee (%)	yield (%)[b]	ee (%)		(%)[c]
1	Et	**13b**	86.2	93	1.0	56	**14ba**	98
2	Pr	**13c**	83.1	93	2.4	81	**14ca**	94
3	Bu	**13d**	76.0	93	0.8	57	**14da**	98
4	Ph	**13e**	87.3	93	1.4	74	**14ea**	97
5[d]	−CH$_2$OCH$_2$−	**13k**	95.7	92	1.5	78	**14ka**	98

[a] Isolated yield. [b] Yield determined by ^{1}H NMR after isolation of minor product, using naphthalene as internal standard. [c] Chemical excess = [(**14aa** − **14**)/(**14aa** + **14**)] × 100%. [d] 10 mol % of catalyst used.

the corresponding 1-(*N*-phenyl)amino-2-ols **16aa**−**ca**, arising from ring opening at the least hindered position of the epoxide selectively in good yields and very high enantiomeric excesses (Table 6, entries 1−4). The regioselectivity of the reaction was moderate to very good (**16**/**17** ratio up to 12:1) and in all cases the regioisomeric 2-(*N*-phenyl)amino-1-ols **17aa**−**ca** were obtained in considerably lower optical purity.

In the case of *cis*-*β*-methylstyrene oxide **15d** however, the regioselectivity was reversed and 1-phenyl-1-(phenylamino)-propan-2-ol **17da** was isolated as the major product in good yield but with only moderate enantioselectivity (49% ee), whereas minor product **16da** was obtained in much lower yield but in much higher optical purity (85% ee). This was not entirely unexpected and is indicative of a competing Lewis acid assisted S$_N$1-type background reaction that proceeds via an intermediate benzylic cation which is trapped by the aniline in a largely nonstereoselective manner. It is reasonable to speculate that the

Table 6. Nb-Catalyzed Ring Opening of Unsymmetrical *cis*-Epoxides



15-(±) (2.5 equiv) **12** (1.0 equiv) **16** **17**

entry	**15** (R)		**13** (R^1)		yield (%)[a]	**16** (ee)[b]	**17**	**16/17**
1	Et	**15a**	H	**12a**	89	**16aa** (95)	**17aa**	9.1/1
2	Pr	**15b**	H	**12a**	88	**16ba** (98)	**17ba**	3.4/1
3[d]	Pr	**15b**	H	**12a**	83	**16ba** (98)	**17ba**	3.7/1
4	$PhCH_2CH_2$	**15c**	H	**12a**	82	**16ca** (97)	**17ca**	12.0/1
5	Ph	**15d**	H	**12a**	92	**16da** (85)[e]	**17da**	1/5.6
6	Et	**15a**	2-OMe	**12e**	67	**16ae** (95)	**17ae**	8.1/1
7	Et	**15a**	2-Me	**12b**	63	**16ab** (88)	**17ab**	10.4/1
8	Pr	**15b**	2-OMe	**12e**	79	**16be** (98)	**17be**	4.3/1
9	Pr	**15b**	2-Me	**12b**	66	**16bb** (85)	**17bb**	7.2/1
10	$PhCH_2CH_2$	**15c**	2-OMe	**12e**	95	**16ce** (98)	**17ce**	8.5/1
11	$PhCH_2CH_2$	**15c**	2,6-Me_2	**12j**	quant.	**16cj** (94)	**17cj**	7.0/1
12	$PhCH_2CH_2$	**15c**	2-Cl	**12k**	quant.	**16ck** (94)	**17ck**	11.4/1
13	$PhCH_2CH_2$	**15c**	3-Cl	**12l**	82	**16cl** (99)	**17cl**	15.0/1
14	$PhCH_2CH_2$	**15c**	3-CF_3	**12g**	90	**16cg** (>99)	**17cg**	18.0/1
15	$PhCH_2CH_2$	**15c**	4-Me	**12d**	83	**16cd** (86)	**17cd**	5.6/1
16	$PhCH_2CH_2$	**15c**	4-F	**12m**	87	**16cm** (97)	**17cm**	13.0/1
17	$PhCH_2CH_2$	**15c**	4-Cl	**12n**	83	**16cn** (98)	**17cn**	14.0/1
18	$PhCH_2CH_2$	**15c**	4-Br	**12i**	83	**16ci** (94)	**17ci**	12.0/1

[a] Combined yield of **16** + **17**. [b] Determined by Chiralpak HPLC. (ee of major regioisomer only). [c] Ratio calculated from ^{1}H NMR. [d] Reaction run at 0 °C. [e] Major isomer **17da** obtained in 49% ee.

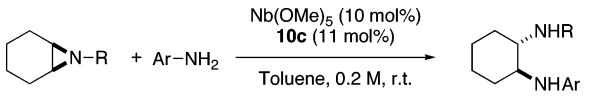
minor product is generated by a different, more stereoselective catalyst-mediated S_N2-type pathway. Next, we examined the effect of varying the substituent on the aniline ring in the reaction with *cis*-epoxides **15a**−**c** and were pleased to find that ring opening occurred smoothly in all cases. In the cases of the all-aliphatic epoxides **15a** and **15b** (entries 6−9), the reactions with *o*-anisidine **12e** and *o*-toluene **12b** proceeded in moderate combined yield and moderate to good regioselectivity, affording the major products **16ae**−**ab** with good to excellent enatioselectivity. In line with the previously observed trend, except for **17ae** (entry 6), the minor regioisomer was formed in substantially lower ee than the corresponding major regioisomer. On switching to oxirane **15c** (entries 10−18), the yield of the reaction improved dramatically and the corresponding 1,2-amino alcohols were obtained in up to quantitative yields with good to excellent regioselectivity (**16**/**17** up to 18:1, entry 14) and very high enantioselectivity with anilines bearing both electron-donating (entries 10−11, 14) and electron-withdrawing substituents (entries 12−13, 15−18) in the 2-, 3-, or 4-position.

Desymmetrization of *meso*-Aziridines Using Aniline Nucleophiles. Having demonstrated the effectiveness of our catalyst system in mediating the desymmetrization of *meso*-epoxides, we sought further to broaden the applicability of the catalyst system to include other monodentate electrophiles. Accordingly, we turned our attention to the ring-opening reaction of *meso*-aziridines as they and their ring-opened derivatives are useful intermediates for the synthesis of versatile nitrogen-containing compounds. While several protocols for the nonstereoselective ring opening of aziridines have been described, catalytic enantioselective versions have not been well explored, and in particular, use of *meso*-aziridines as substrates has been little investigated.[3b] Although as described above examples of ring-opening reactions of aziridines using reactive nucleophiles such as TMSCN,[13] MeMgBr,[14] and $TMSN_3$[15] to afford the corresponding enantioenriched products have been reported, to the best of our knowledge, no methods for desymmetrization of *meso*-aziridines using anilines as nucleophiles have been reported.

We selected aziridines **18a**−**e** and aniline **12a** as model substrates for our initial studies and screened many aziridines using catalyst systems derived from $Nb(OMe)_5$ and either BINOL ligands **1** or **10c**. Although the catalysts derived from Nb(V) and tridentate ligand **1** showed high activity in the ring-opening reaction, the diamine products were generated in racemic or near-racemic forms. By contrast, application of the catalyst formed with tetradentate ligand **10c** to the reaction of *N*-phenyl aziridine **18a** with *p*-toluidine **12d** at room temperature obtained the corresponding ring-opened product in relatively good yield albeit with low enantioselectivity (Table 7, entry 1). We next examined the effect of adding molecular sieves to the reaction mixture and were pleased to discover that when carried out in the presence of either 4 Å or 3 Å MS, the reactions proceeded with both impoved yields and enatioselectivities (entries 2 and 3), although less inspiring results were obtained with 5 Å MS. It was further found that *N*-benzyl aziridine **18b** and *N*-diphenylmethylene aziridine **18c** showed moderate enantioselectivity (entries 5 and 6) although longer reaction time or higher temperatures failed to provide the products in higher yields. Interestingly, when activated aziridines (**18d** and **18e**) bearing electron-withdrawing groups on the nitrogen were used, the ring-opening reactions proceeded in very poor yield or not at all (entries 7 and 8). These results imply that the efficiency of the reaction is governed by the availability of the aziridine nitrogen lone pair for coordination to the catalyst rather than by the ability of the nitrogen center to act as a leaving group in the ring opening.

We reasoned that the relatively modest levels of enantioselectivity observed in these trials might be due to competition

Table 7. Investigation of Conditions in the Nb-Catalyzed Ring-Opening Reaction of Cyclohexene-Derived Aziridines with Anilines **12a,d**

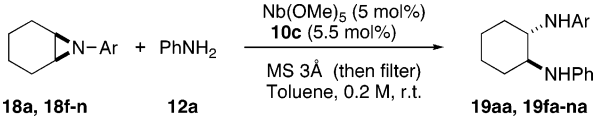


18a-e **12a,d** **19aa-ea, 19ad**

entry	aziridine (R)	aniline **13**	additive	time (h)	yield (%)[a]		ee (%)[b]
1	**18a** Ph	**12d** (4-Me)Ph	none	41	73	**19ad**	21
2	**18a** Ph	**12d** (4-Me)Ph	MS 4Å	44	92	**19ad**	48
3	**18a** Ph	**12d** (4-Me)Ph	MS 3Å	43	96	**19ad**	53
4[c]	**18a** Ph	**12d** (4-Me)Ph	MS 5Å	96	32	**19ad**	57
5	**18b** Bn	**12a** Ph	MS 4Å	24	25	**19ba**	40
6	**18c** $CHPh_2$	**12d** (4-Me)Ph	MS 4Å	44	80	**19cd**	40
7	**18d** Ts	**12a** Ph	MS 4Å	24	10	**19da**	0
8	**18e** Bz	**12a** Ph	MS 4Å	48	n.r.[d]	**19ea**	n.d.[e]

[a] Determined by ^{1}H NMR using dibenzylether as an internal standard. [b] Determined by chiral HPLC analysis. [c] The reaction was performed at −10 °C. [d] n.r. = no reaction. [e] n.d. = not determined.

Table 8. Effect of Changing *N*-Phenyl Ring Substitution



18a, 18f-n **12a** **19aa, 19fa-na**

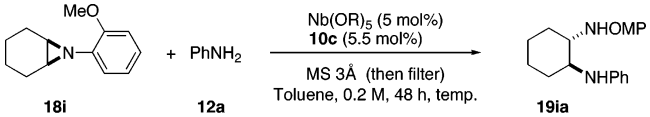
entry	aziridine (Ar)	time (h)	yield (%)[a]		ee (%)[b]
1	**18a** (Ph)	40	86	**19aa**	62
2	**18f** (4-F)Ph	62	77	**19fa**	59
3	**18g** (4-NO_2)Ph	72	9	**19ga**	53
4	**18h** (4-MeO)Ph	62	92	**19ha**	70
5	**18i** (2-MeO)Ph	46	89	**19ia**	74
6	**18j** (3-MeO)Ph	78	93	**19ja**	56
7	**18k** (2-HO)Ph	40	86	**19ka**	11
8	**18l** (2-EtO)Ph	78	96	**19la**	72
9	**18m** (2-PhO)Ph	72	89	**19ma**	70
10	**18n** (2,4-$(MeO)_2$Ph	62	92	**19na**	69

[a] Determined by ^{1}H NMR using dibenzylether as an internal standard. [b] Determined by chiral HPLC analysis.

with a nonstereoselective background reaction catalyzed by the molecular sieves in the reaction mixture. The existence of such a competition reaction was confirmed by carrying out the corresponding control reaction in which aziridine **18a** and aniline **12a** were stirred together in toluene in the presence of MS 3 Å without the catalyst for 24 h affording the corresponding racemic ring-opened product in 60% yield. This was in direct contrast to the reactions involving *meso*-epoxides in which no ring opening mediated by molecular sieves was observed at the low temperatures (−15 °C) used for those reactions. We therefore sought to re-engineer our catalyst preparation conditions and developed a new procedure in which the catalyst was formed in the presence of molecular sieves which were then filtered off before the addition of the substrate and the nucleophile. Gratifyingly, application of this new protocol to the benchmark ring-opening reaction of **18a** with **12a** gave the desired product in improved chemical yield and enantioselectivity (86% and 62% ee, respectively) (Table 8, entry 1). Using the new procedure, we then investigated the effect of placing substituents on the aromatic ring of a series of *N*-aryl aziridines **18f**−**n** on reactivity and selectivity (Table 8).

Examination of these data clearly showed that *N*-aryl aziridines having para- electron-withdrawing substituents on the aryl

Table 9. Investigation of Niobium Source and Temperature in the Ring Opening of **18i** and **12a**



18i **12a** **19ia**
OMP=*o*-MeOPh

entry	Nb source (R)	temp (°C)	yield (%)[a]	ee (%)[b]
1	Me	22	89	74
2	Et	22	85	66
3[c]	^{i}Pr	22	93	81
4	^{t}Bu	22	91	53
5	^{i}Bu	22	81	79
6	^{i}Pr	15	92	82
7	^{i}Pr	5	90	84 (>99)[d]
8	^{i}Pr	0	81	82
9	^{i}Pr	−5	74	80
10	^{i}Pr	−10	79	80
11	^{i}Pr	−15	81	80

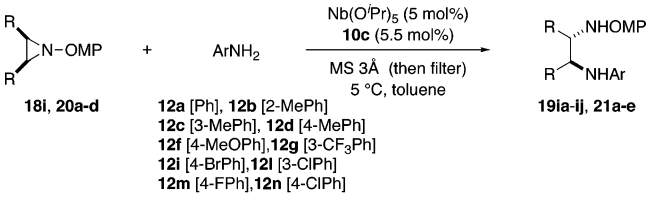
[a] Isolated yields. [b] Determined by chiral HPLC analysis. [c] Reaction run for 24 h. [d] ee after single recrystallization.

moiety (entries 2 and 3) gave much less satisfactory results in terms of both reactivity and enantioselectivity than those examples in which the aryl ring bears electron-releasing groups (entries 4−10). In particular, *N*-(*p*-NO_2)Ph aziridine **18g** (entry 3) showed very low reactivity presumably because of low electron density on the nitrogen atom, leading to poorer coordination of the aziridine to the catalyst metal center (vide supra). On the other hand, introduction of an electron-donating OMe group in the para-position of the *N*-aryl substituent activated the aziridine **18h** toward ring opening giving the corresponding diamine **19ha** in excellent yield with improved enantioselectivity (entry 4). Closer examination showed that *o*-OMe-susbstituted aziridine **18i** gave the best result in terms of enantioselectivity (entry 5), although the *m*-OMe system **18j** afforded the product in slightly improved yield with lower enantioselectivity (entry 6). Aziridines bearing other ortho-electron-donating substituents gave comparable results (**18l** and **18m**, entries 8 and 9) as did *N*-(2,4-dimethoxyphenyl) substituted aziridine **18n** (entry 10). While the importance of the presence of electron-donating substituents is not yet completely understood, it may be possible that the alkoxy group acts as a supplementary binding point for a niobium center in the catalyst and helps to fix the aziridine in a favorable orientation in the catalyst chiral pocket. Furthermore, derivatization of an enantioenriched sample of **19aa** obtained under these conditions allowed us to confirm the absolute stereochemistry of the major enantiomer as 1*S*,2*S* by comparison of its physical data with that of the known system.[28] This absolute configuration is the opposite to that obtained in the analogous ring opening of *meso*-epoxides (vide supra) and further illustrates the complementarity and synthetic utility of our system.

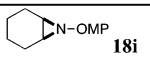
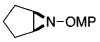
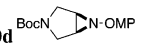
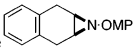
Having established *o*-methoxyophenyl (OMP) as the optimum protecting group for the aziridine nitrogen, we re-examined the effect of different niobium sources on the yield and selectivity of the reaction. A comprehensive screen of niobium alkoxides in the benchmark reaction of *o*-Me-substituted aziridine **18i** with aniline **12a** revealed that the ring-opening reaction proceeded most efficiently with $Nb(O^iPr)_5$ as the metal source, affording

(28) Aoyama, H.; Tokunaga, M.; Kiyosu, J.; Iwasawa, T.; Obora, Y.; Tsuji, Y. *J. Am. Chem. Soc.* **2005**, *127*, 10474.

Table 10. Investigation of Scope of the Aniline Nucleophile



18i, **20a-d** **12a** [Ph], **12b** [2-MePh] **12c** [3-MePh], **12d** [4-MePh] **12f** [4-MeOPh],**12g** [3-CF_3Ph] **12i** [4-BrPh],**12l** [3-ClPh] **12m** [4-FPh],**12n** [4-ClPh] **19ia-ij**, **21a-e**

Entry	Aziridine (R)	Aniline	Time (h)	Yield (%)[a]		ee (%)[b]
1	 **18i**	**12a**	48	90	**19ia**	84 (>99)[c]
2		**12b**	48	55	**19ib**	47 (85)[c]
3		**12c**	48	78	**19ic**	77 (>99)[c]
4		**12d**	48	82	**19id**	76 (90)[c]
5		**12f**	48	69	**19if**	60 (94)[c]
6		**12g**	48	89	**19ig**	74 (>99)[c]
7		**12i**	48	94	**19ii**	81 (>99)[c]
8		**12l**	21	85	**19il**	84 (>99)[c]
9		**12m**	20	85	**19im**	81 (97)[c]
10		**12n**	20	95	**19in**	84 (>99)[c]
11[d]	**20a** (Me)	**12i**	27	86	**21ai**	53
12[d,e]	**20b** (^{n}Pr)	**12a**	25	64	**21ba**	61
13[d]	**20b** (^{n}Pr)	**12i**	27	87	**21bi**	62
14[f]	**20c** 	**12a**	8	85	**21ca**	50
15[d]	**20d** 	**12a**	48	57	**21da**	60 (95)[c]
16[f]	**20e** 	**12a**	24	79	**21ea**	63 (>99)[c]

[a] Isolated yields. [b] Determined by chiral HPLC analysis. [c] ee after a single recrystallization. [d] Reaction run at room temperature (rt). [e] 20 mol % catalyst. [f] Reaction run at 0 °C.

the desired diamine product **19ia** at room temperature in 93% yield and 81% ee (Table 9, entry 3). Furthermore, it was discovered that lowering the reaction temperature still further to 5 °C gave the product with higher enantioselectivity and with no deleterious effect on yield (entry 7). However, no advantage was found in going to even lower temperatures, as under such conditions both yield and enantioselectivity were gradually eroded.

Scope of the Aniline Nucleophile in the Desymmetrization of *meso*-Aziridines. Having identified the optimal catalyst and reaction conditions (5 mol % $Nb(O^iPr)_5$, 5.5 mol % **10c**, MS 3 Å removed by filtration, toluene, 5 °C), we proceeded to probe the substrate scope of the reaction (Table 10). Screening several readily available anilines revealed that the reaction had broad generality for this class of nucleophile, giving the desired 1,2-diaryl amines in good to high yields with moderate to good enantioselectivity in the majority of cases.

In the case of ortho-substituted aniline **12b** (entry 2) and those with an electron-donating substituent (**12f**, entry 5), less satisfactory results in terms of both reactivity and selectivity were obtained. The best results were obtained using anilines with electron-withdrawing groups such as CF_3 or a halogen atom at either the meta or para position. We also examined a range of monocyclic aziridines **20a**, **20b**, and bicyclic azridines **20c**−**20e**. In general, the substrates showed good to high reactivity, but selectivities were lower than those observed in the analogous ring-opening reaction of the benchmark [4.1.0] system **18i**. Within the range of substrates examined, the bicyclic aziridines **20c**−**20e** were found to be more reactive than their monocyclic counterparts **20a** and **20b**, presumably because of the effects of greater release of ring strain in the reaction of the bicyclic systems. In addition, all the final 1,2-diamine products were obtained as solids and in the great majority of cases could be isolated as essentially single enantiomers after a single recrystallization. This straightforward operation further enhances the synthetic utility of the current methodology and provides a new protocol for the synthesis of enantiopure or highly enantioenriched C_2-symmetric and non-C_2-symmetric 1,2-diamines.

Conclusion

In summary, we have discovered and developed a Lewis acid system on the basis of niobium alkoxides and a tetradentate BINOL derivative which catalyzes the desymmetrative ring opening of both *meso*-epoxides and *meso*-aziridines with anilines giving the corresponding (*R*,*R*)-1,2-amino alcohol and (*S*,*S*)-1,2-diamine products in good to excellent yields and very high to excellent enantioselectivity. Furthermore, the catalyst displays a remarkable ability to distinguish between different *meso*-epoxides stemming from its sensitivity to steric bulk at the β-carbon of epoxides. In the ring-opening reactions of both epoxides and aziridines, formation of the catalyst in the presence of molecular sieves was found to be important for the realization of high yields and selectivity. The synthetic utility of the system is further enhanced by its ability to promote the asymmetric ring opening of nonsymmetric *cis*-epoxides with anilines with good to excellent regio- and enantioselectivity. To the best of our knowledge, the protocol described herein constitutes the first report not only of the catalytic enantioselective desymmetrization of both *meso*-epoxides and *meso*-aziridines with anilines but also of a nonenzymic catalyst system that provides stereochemically complementary products for two different but closely related reactions, and as such we believe that it will be of significant interest to the chemical community.

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Supporting Information Available: Full experimental procedures and spectral data for all compounds used in the study. This material is available free of charge via the Internet at http://pubs.acs.org.

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