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Asymmetric Catalysis

Enantioselective Desymmetrization of *meso* Epoxides with Anilines Catalyzed by a Niobium Complex of a Chiral Multidentate Binol Derivative**

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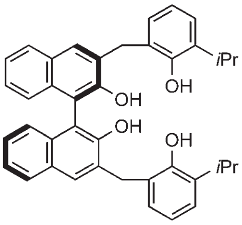
The development of new chiral catalysts for the promotion of asymmetric reactions is one of the most important tasks in organic synthesis. New chiral catalysts must not only mediate reactions with high yields and enantioselectivities, but are also increasingly required to have the ability to recognize the precise structure of substrates. For example, a nonenzymatic catalyst that could recognize the difference between methyl and ethyl groups in a substrate would be an ideal catalyst in this field.[1] We now describe homochiral multidentate complexes of binol derivatives and niobium which distinguish substrate structures strictly and catalyze the desymmetrizaton of *meso* epoxides with anilines efficiently.

We previously reported the first example of a highly enantioselective Lewis acid based on niobium(V) for Mannich-type reactions of imines with silicon enolates.[2] This species, prepared from a metal source and a binol-derived tridentate ligand, was shown to have a unique binuclear structure in which two niobium atoms were straddled by two molecules of the ligand. This arrangement, in which the metal centers are held in a spatially defined array by firm but flexible ligation, appeared to permit highly substrate-selective reactions. As niobium(V) has a high affinity for oxygen and is already heavily coordinated in our metal–ligand system, we judged that monodentate species would function most efficiently as substrates and focused accordingly on the asymmetric ring opening of *meso* epoxides[3] with anilines.[4] A series of initial experiments showed that the reaction proceeded most efficiently when the niobium atom in the complex was tetracoordinated. This finding led to the development of a new class of Lewis acid complexes formed from niobium and the tetradentate ligand **1.**

Further investigations revealed that the most effective catalyst system was Nb(OMe)$_5$–**1** in the presence of 4-Å molecular sieves with a 3:2 mixture of toluene and CH$_2$Cl$_2$ as the solvent. Following the optimization of the reaction conditions, attention was turned to the scope of the reaction.



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We conducted the reaction with a range of different epoxides and anilines,[5] with striking results (Table 1). First, it was found that the reaction of *cis*-but-2-ene oxide (**2a**) with aniline **3a** proceeded very smoothly to give the corresponding 1,2-hydroxyamine **4aa** in quantitative yield with very high enantioselectivity (Table 1, entry 1). Subsequent experiments, in which *cis*-but-2-ene oxide (**2a**) was treated with a range of substituted anilines in the presence of 10 mol% of the catalyst, further confirmed the utility of the system (Table 1, entries 2–9). These results showed that the catalyst activity was general for a broad range of aniline nucleophiles, including both electron-rich and electron-poor examples, although in the case of *ortho*-substituted anilines the chemical yield of the reaction was slightly lower. Furthermore, from a synthetic point of view, we could decrease the amount of the catalyst from 10 mol% to 0.25 mol% without significant loss of activity. On the other hand, when the reaction was conducted with the closely related epoxide substrates *cis*-hex-3-ene oxide (**2b**) and *cis*-oct-4-ene oxide (**2c**), there was hardly any turnover, and only traces of the products were formed (Table 1, entries 10 and 11). However, when we switched to epoxide substrates derived from cyclic alkenes, the ring-opened products were obtained in good to very high yields and with generally high enantioselectivities (Table 1, entries 12–16). Such outstandingly high levels of molecular recognition and selectivity are, to the best of our knowledge, unprecedented in the desymmetrization of *meso* epoxides and are a unique characteristic of the niobium–tetradentate-binol catalyst system.

To investigate the molecular-recognition ability of Nb(OMe)$_5$–**1** further, we conducted competition reactions in which the parent aniline **3a** was treated with an equimolar mixture of *cis*-but-2-ene oxide (**2a**) and another, bulkier epoxide in the presence of the catalyst (Table 2). As anticipated given the high absolute and relative reactivity of **2a**, these competition reactions proceeded smoothly with high selectivity for **2a** versus the bulkier epoxides **2i**, **2j**, or **2h** to give predominantly **4aa** in high yield and with very high enantioselectivity. Only traces of the products from the addition of the nucleophile to the other epoxide **2** were formed. In all cases, the ratio of **4aa** to the product derived from the other epoxide exceeded 60:1. To our knowledge, such high levels of chemoselectivity with a metal-based Lewis acid catalyst are unprecedented.

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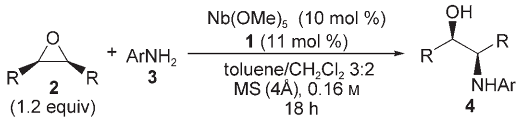
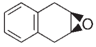
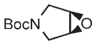
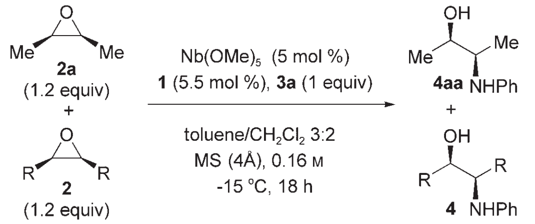
Table 1: Substrate scope with respect to the *meso* epoxide and the aniline derivative in the enantioselective desymmetrization reaction.



Entry	**2** (R)	**3** (Ar)	*T* [°C]	Product	Yield [%]	*ee* [%]
1	**2a** (Me)	**3a** (Ph)	−15	**4aa**	quant.	94[a]
2	**2a**	**3b** (2-MeC$_6$H$_4$)	−15	**4ab**	82	84
3	**2a**	**3c** (3-MeC$_6$H$_4$)	−15	**4ac**	92	93
4	**2a**	**3d** (4-MeC$_6$H$_4$)	0	**4ad**	90	91
5	**2a**	**3e** (2-MeOC$_6$H$_4$)	−10	**4ae**	95	90
6	**2a**	**3f** (4-MeOC$_6$H$_4$)	0	**4af**	99	90
7	**2a**	**3g** (3-CF$_3$C$_6$H$_4$)	−15	**4ag**	89	96
8	**2a**	**3h** (3,5-(CF$_3$)$_2$C$_6$H$_3$)	−15	**4ah**	96	96[b]
9	**2a**	**3i** (4-BrC$_6$H$_4$)	−15	**4ai**	98	95
10	**2b** (Et)	**3a**	−15	**4ba**	2[c]	38
11	**2c** (*n*Pr)	**3a**	−15	**4ca**	9[c]	84
12		**3a**	−30	**4da**	54	91[d]
13		**3a**	−30 −25	**4ea**	69 quant.	89[d] 86[e]
14	**2f** (−(CH$_2$)$_3$−)	**3a**	0 −15	**4fa**	92 59	83 86
15		**3a**	−15	**4ga**	78	89
16	**2h** (−CH$_2$OCH$_2$−)	**3a**	−15	**4ha**	77	82[f]

[a] Catalyst loading: 2 mol%: 82% yield, 91% *ee*; 1 mol%: 82% yield, 92% *ee*; 0.5 mol%: 90% yield, 90% *ee*; 0.25 mol%: 86% yield, 88% *ee*. [b] Reaction time: 48 h. [c] Yield was determined by ^{1}H NMR spectroscopy with naphthalene as an internal standard. [d] Reaction time: 72 h. [e] Reaction time: 48 h. [f] Reaction time: 24 h. Boc = *tert*-butoxycarbonyl, MS = molecular sieves.

Table 2: Competition reaction of **2a** versus other epoxides.

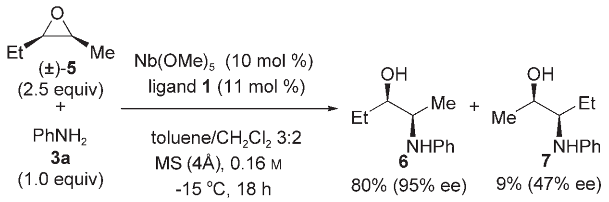


Entry	**2** (R)	**4aa** Yield [%]	**4aa** *ee* [%]	**4**[a] Yield [%]	**4aa/4**
1	**2i** (*n*Bu)	76.0	93	0.8	95.0
2	**2j** (Ph)	87.3	93	1.4	62.3
3[b]	**2h** (−CH$_2$OCH$_2$−)	95.7	92	1.5	63.8

[a] Yields of the minor product were determined by ^{1}H NMR spectroscopy with naphthalene as an internal standard. [b] Catalyst loading: 10 mol%.

Although the origin of this selectivity is still not completely understood, we believe that at least in the linear-epoxide series, the effective steric hindrance at the α position, as determined by the preferred conformation of the epoxide side chain, is of paramount importance in determining the reactivity of the Nb(OMe)$_5$–**1** system. In the case of *cis*-but-2-ene oxide (**2a**), only hydrogen atoms are present at the β carbon atom, and thus the nucleophile has a relatively unobstructed approach to the carbon atom of the epoxide group. However, with longer-chain substrates, a number of different side-chain conformations are possible, and in some of these the pendant alkyl chain partially obscures the reactive site of the complexed epoxide, thus lowering its reactivity towards ring opening.[6,7] For bicyclic epoxides, only one conformation, that in which the reactive site of the epoxide is relatively unencumbered, is possible. It may be argued that the combination of this factor and the activating effect of the inherent increased ring strain results in the similar reactivity of bicyclic epoxides to that of *cis*-but-2-ene oxide (**2a**).

To test the hypothesis that steric crowding at the β carbon atom is a decisive factor in the reactivity in our system, we conducted the niobium-catalyzed ring opening with the racemic unsymmetrically disubstituted epoxide **5** and the aniline **3a**.[8] The addition reaction proceeded smoothly and in good yield to give the amino alcohol **6**, which results from ring opening at the methyl-substituted epoxide center, with excellent enantioselectivity. The minor product **7** was produced with lower enantioselectivity. These results indicate that our catalyst system is capable of distinguishing between a methyl substituent and an ethyl substituent with a selectivity of 9.1:1.



In summary, we have discovered a Lewis acid system based on niobium alkoxides and a tetradentate binol derivative which catalyzes the desymmetrization of *meso* epoxides by ring opening with anilines. The remarkable ability of the catalyst to distinguish between different *meso* epoxides stems from its sensitivity to steric bulk at the β carbon atom of the epoxide. Further investigation of the origin of the selectivity of the reaction and the synthetic scope of the catalyst system are currently in progress.

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