Asymmetric Catalysis

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Gadolinium-Catalyzed Regio- and Enantioselective Aminolysis of Aromatic *trans*-2,3-Epoxy Sulfonamides**

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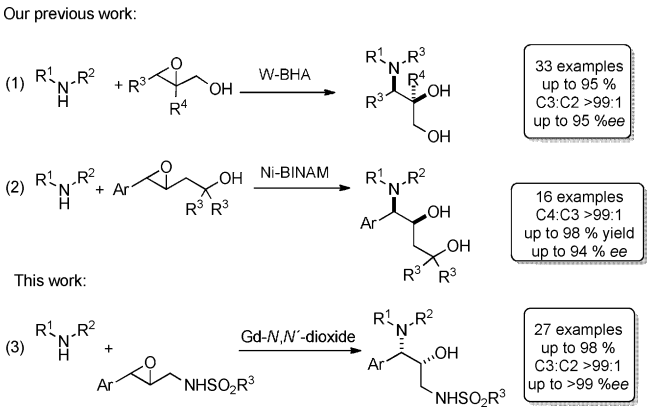
Abstract: *The first enantioselective aminolysis of aromatic trans-2,3-epoxy sulfonamides has been accomplished, which was efficiently catalyzed by a Gd-N,N′-dioxide complex. Under the directing effect of the sulfonamide moiety the ring-opening reaction proceeded selectively at the C-3 position in a highly enantioselective manner furnishing various Ts- and SES-protected 3-amino-3-phenylpropan-2-olamines as products.*

In 2012 our group developed the first asymmetric epoxidation of alkenyl sulfonamides catalyzed by Hf-BHA (bishydroxamic acid) system.[1] In 2014 our group discovered that W-salts were able to catalyze the highly regioselective ring-opening of 2,3-epoxy sulfonamides with various amines, alcohols, phenol and halides as nucleophiles.[2] The combination of asymmetric epoxidation and regioselective aminolysis of enantioenriched amino epoxides provides direct access to achieve chiral 1,3-diaminoalkan-2-ols. However, the Hf-catalyzed enantioselective epoxidation of alkenyl sulfonamides is only applicable to terminal and aliphatic olefins. As 3-amino-3-phenylpropan-2-olamine is a characteristic structural unit present in a large number of biologically active compounds and drug candidates to treat conditions ameliorated by monoamine reuptake,[3] it is highly desirable to develop a method to synthesize these compounds in a highly enantioselective manner. Recently, our group reported the first regio- and enantioselective aminolysis of 2,3-epoxy and 3,4-epoxy alcohols, which were promoted by W-BHA and Ni-BINAM (1,1′-binaphthyl-2,2′-diamine) catalytic systems, respectively (Scheme 1, Eqs. (1) and (2)).[4,5] As a continuation of our research in this field, we report the first enantioselective aminolysis of *trans*-aromatic 2,3-epoxy sulfonamides with a variety of amines as nucleophiles and a Gd-*N*,*N*′-dioxide as catalyst furnishing diverse Ts (tosyl) and SES [(2-trimethylsilyl)-ethanesulfonyl]-protected 3-amino-3-phenyl-propan-2-olamines as products in complete regiocontrol and high enantioselectivities (Scheme 1, Eq. (3)).



Scheme 1. Enantioselective aminolysis of epoxy allylic alcohols [Eq. (1)], epoxy homoallylic alcohols [Eq. (2)] and 2,3-epoxy sulfonamides [Eq. (3)].

For optimization of the reaction conditions, we used aniline (**1a**) and racemic *trans*-2,3-epoxy cinnamyl sulfonamide **2a** as standard substrates. Initially, we employed our W-BHA and Ni-BINAM catalysts for this ring-opening reaction. Unfortunately, both reactions failed to provide the product in highly enantioselective manner. (Table 1, entries 1 and 2). Then we studied this reaction using Hf-BHA as catalyst, which proved to be a good catalyst for asymmetric epoxidation of alkenyl sulfonamides. In this case the product was also obtained in low enantiomeric excess (entry 3). Furthermore, we tested [Co(salen)] and [Cr(salen)Cl] complexes, which were successful catalysts for the kinetic resolution of terminal and aromatic epoxides as well as the desymmetrization of *meso*-epoxides.[6] However, the reaction using Cr catalyst gave the product only with moderate enantioselectivity, while only traces of product were formed in the case of the Co catalyst (entries 4 and 5). Moreover, several other metal salts were studied using the BINAM-derivative **4** as ligand giving no significantly improved results (entries 6–8). We also screened some other privileged chiral ligands **7**–**10** for this kinetic resolution reaction, but in the most cases the products were obtained either in racemic form or in very low enantioselectivities (entries 9–11). Only in the case of a pipecolinic acid-derived *N*,*N*′-dioxide **10** as ligand with $La(OTf)_3$ the reaction provided the product with excellent yield and good asymmetric induction (entry 12).[7] Encouraged by this result, we then investigated scandium, yttrium, cerium, samarium and ytterbium triflate for this ring-opening reaction (entries 13–17). The best result with respect to both yield and

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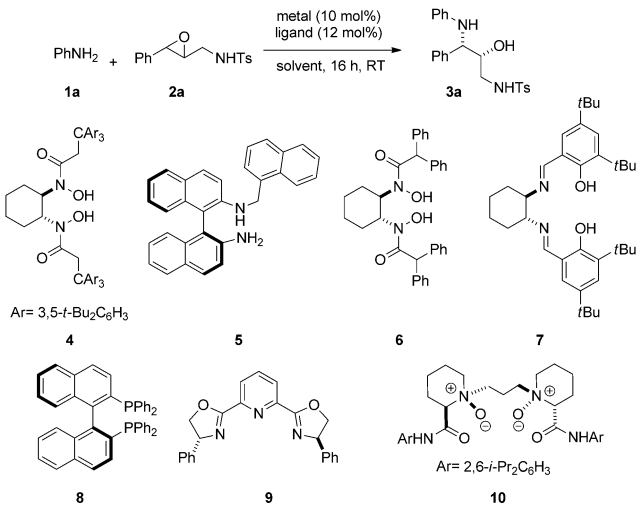
Table 1: Metals, ligands and solvents screening for the ring-opening reaction of *trans*-2,3-epoxy cinnamyl sulfonamide with aniline as nucleophile.[a]



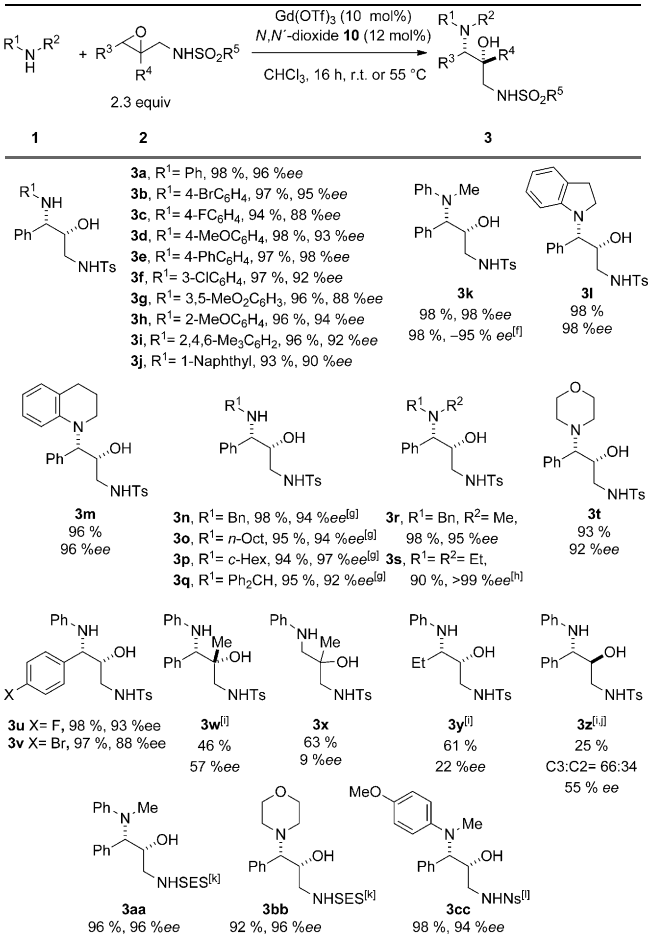
Entry	Metal	Ligand	Solvent	Yield [%][b]	*ee* [%][c]
1	$W(OEt)_6$	**4**	$CHCl_3$	78	6
2	$Ni(ClO_4)_2{\cdot}6H_2O$	**5**	$CHCl_3$	71	16
3	$Hf(OTf)_4$	**6**	$CHCl_3$	57	36
4	[d]	[d]	$CHCl_3$	traces	n.d.
5	[e]	[e]	$CHCl_3$	94	57
6	$CrCl_3{\cdot}3THF$	**5**	$CHCl_3$	61	15
7	$Co(ClO_4)_2{\cdot}6H_2O$	**5**	$CHCl_3$	81	36
8	$Mn(ClO_4)_2{\cdot}6H_2O$	**5**	$CHCl_3$	65	56
9	$Co(ClO_4)_2{\cdot}6H_2O$	**7**	$CHCl_3$	50	8
10	$Co(ClO_4)_2{\cdot}6H_2O$	**8**	$CHCl_3$	84	0
11	$Co(ClO_4)_2{\cdot}6H_2O$	**9**	$CHCl_3$	67	0
12	$La(OTf)_3$	**10**	$CHCl_3$	95	78
13	$Sc(OTf)_3$	**10**	$CHCl_3$	22	95
14	$Y(OTf)_3$	**10**	$CHCl_3$	92	60
15	$Ce(OTf)_3$	**10**	$CHCl_3$	94	83
16	$Sm(OTf)_3$	**10**	$CHCl_3$	97	94
17	$Yb(OTf)_3$	**10**	$CHCl_3$	92	60
18	$Sm(OTf)_3$	**10**	EtOAc	42	55
19	$Sm(OTf)_3$	**10**	THF	45	38
20	$Sm(OTf)_3$	**10**	MeCN	40	58
21	$Sm(OTf)_3$	**10**	*t*BuOH	67	60
22	$Sm(OTf)_3$	**10**	toluene	47	46
23	$Pr(OTf)_3$	**10**	$CHCl_3$	95	86
24	$Eu(OTf)_3$	**10**	$CHCl_3$	96	91
25	**$Gd(OTf)_3$**	**10**	**$CHCl_3$**	**98**	**96**
26	$Te(OTf)_3$	**10**	$CHCl_3$	97	80

[a] Unless otherwise specified, reactions were performed on a 0.25 mmol scale of aniline (**1a**) using 2.3 equiv racemic *trans*-2,3-epoxy cinnamyl sulfonamide **2a**, 10 mol% metal salts and 12 mol% ligand at RT in 8.0 mL solvent. [b] Yields of the isolated product after flash chromatography were based on aniline. [c] All enantiomeric excesses were determined by HPLC-analysis on chiral stationary phase. [d] [Co(salen)] was used as the catalyst. [e] [Cr(salen)Cl] was used as the catalyst.

enantioselectivity was obtained in the case of $Sm(OTf)_3$ (entry 16). Subsequently, a brief solvent screening was undertaken giving no better outcome (entries 18–22). The results obtained indicated that the level of facial selectivity of this ring-opening reaction is significantly influenced by the ion size of the lanthanides tested. Therefore, we then studied several lanthanide triflates with similar ion radius as Sm-$(OTf)_3$ (entries 23–26).[8] Finally, the optimum result was achieved in the case of $Gd(OTf)_3$ as catalyst (entry 25).[9]

After establishing the best reaction conditions we started to evaluate the substrate spectrum of this reaction (Table 2). We first reacted diverse primary and secondary aromatic

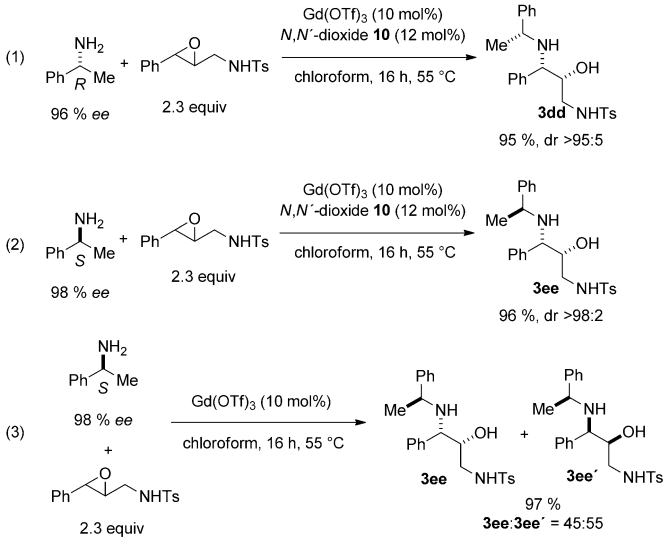
Table 2: Kinetic resolution by ring-opening reactions of *trans*-2,3-epoxy sulfonamides with various amines as nucleophiles.[11][a–e]



[a] Unless otherwise specified, reactions were performed on a 0.25 mmol scale of amines **1** using 2.3 equiv racemic *trans*-2,3-epoxy sulfonamides (**2**), 10 mol% $Gd(OTf)_3$ and 12 mol% *N*,*N*′-dioxide **10** at room temperature in 8.0 mL chloroform. [b] Unless otherwise specified, the products were obtained with complete regioselectivities C3:C2 > 99:1, which were determined by ^{1}H NMR spectroscopy and HPLC analysis on chiral stationary phase. [c] Yields of the isolated products after flash chromatography were based on the amines used. [d] All enantiomeric excesses were determined by HPLC analysis on chiral stationary phase. [e] Reaction temperature: RT for **3a–h**, **3j**, **3l**, **3r**, **3u**, **3v** and **3x**; 55 °C for **3i**, **3k**, **3m**, **3n–q**, **3s**, **3t**, **3w**, and **3y–3cc**. [f] *ent*-*N*,*N*′-dioxide was used as ligand. [g] The enantiomeric excesses were determined by HPLC analysis on chiral stationary phase on the corresponding acetylated derivatives. [h] The enantiomeric excess was determined by HPLC analysis on chiral stationary phase on the corresponding trimethylsilylated derivative. [i] Reactions were performed using 20 mol% $Gd(OTf)_3$ and 24 mol% *N*,*N*′-dioxide **10**. [j] Depicted is only the relative configuration. The absolute stereochemistry is not determined. [k] SES: (2-trimethylsilyl)-ethanesulfonyl. [l] Ns: 2-nitrobenzenesulfonyl.

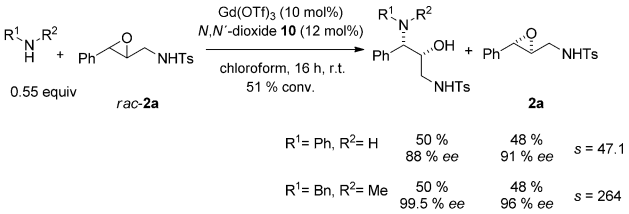
amines with the epoxide **2a**. Generally, the reactions proceeded smoothly at room temperature affording the products **3a–m** in excellent yields and enantiomeric excesses. Subsequently, we investigated the substrate scope further by employing diverse aliphatic amines as nucleophiles, which turned out to be less reactive, assumably due to the higher basicity of aliphatic amines decreasing the Lewis acidity of the Gd complex. Thus the reactions were conducted at 55 °C furnishing the products **3n–t** in high yields and enantioselectivities. Furthermore, we studied the substrate scope by varying the structure of 2,3-epoxy sulfonamides. In the cases of substituted *trans*-2,3-epoxy cinnamyl sulfonamides both reactions provided the products **3u** and **3v** in high yields and enantioselectivities. Substitution at the 2-position of the 2,3-epoxy sulfonamide showed detrimental effect to the asymmetric induction giving the product **3w** in moderate enantioselectivity. Remarkably, all the reactions mentioned above proceeded with complete regioselectivities in favor of the formation of C-3 regioisomers. When terminal and aliphatic *trans*-2,3-epoxy sulfonamides were used as substrates, the products **3x** and **3y** were obtained in low enantiomeric excesses, albeit with complete regioselectivities. In the case of the *cis*-epoxy sulfonamide as substrate the reaction proceeded with not only low facial selectivity but also low regioselectivity. Moreover, we also studied the use of SES-protected 2,3-epoxy amines as precursors for this Gd-catalyzed reaction, since SES is known as an easily removable protective group.[10] To our delight, almost the same selectivity was found in comparison to the Ts-protected epoxy amines. In addition, 2-nosyl-protected 2,3-epoxy amine also turned out to be a competent substrate.

As demonstrated in Scheme 2, enantioenriched chiral amines were also employed as precursors in this Gd-catalyzed kinetic resolution. Interestingly, both (*R*)- and (*S*)-α-methylbenzylamine favored the same enantiomer of the epoxide in the ring-opening process affording two different diastereomers as products both in high diastereomeric ratios (Scheme 2, Eq. (1) and (2)). Additionally, in the absence of the chiral ligand the reaction proceeded with a low diastereoselectivity in favor of the enantiomer, which was disfavored in the reaction employing the chiral *N*,*N*′-dioxide ligand (Scheme 2, Eq. (3)). These results indicate that the ligand effect is predominant over the substrate effect in this Gd-catalyzed ring-opening reaction with α-methylbenzylamines as nucleophiles.



Scheme 2. Kinetic resolution by ring-opening reactions of *trans*-2,3-epoxy cinnamyl sulfonamide **2a** with enantioenriched α-methylbenzylamines.[11]

Since this ring-opening process is a kinetic resolution of racemic 2,3-epoxy sulfonamides, we selected two reactions using an aliphatic and an aromatic amine, respectively, to determine the *s*-factor. In both cases the recovered 2,3-epoxy sulfonamide was obtained in good enantioselectivities and the *s*-factors were determined to be 47.1 and 264, respectively (Scheme 3).[12]

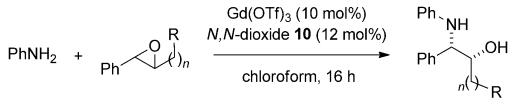


Scheme 3. Determination of the *s*-factors of the kinetic resolution of racemic *trans*-2,3-epoxy cinnamyl sulfonamide with aniline and *N*-methylbenzylamine as nucleophiles.

To study the directing effect of the sulfonamide group, first, we performed the Gd-catalyzed reaction using unfunctionalized *trans*-1-phenyl propylene oxide as substrate. In this case the product was afforded in low yield and enantioselectivity (Table 3, entry 1). Furthermore, we conducted a series of control reactions using epoxy sulfone, Boc-protected epoxy amine and Boc-protected epoxy sulfonamide as substrates. The reactions employing the epoxy sulfone and the Boc-protected epoxy amine as substrates afforded similar results in comparison to *trans*-1-phenyl propylene oxide (entries 3 and 4), while in the case of Boc-protected epoxy sulfonamide no desired product was formed (entry 5). The results revealed that the presence of NH-sulfonyl moiety as anchoring group is crucial for both the reactivity and the facial selectivity of this ring-opening reaction.

In summary, we developed an unprecedented enantioselective aminolysis of aromatic *trans*-2,3-epoxy amine derivatives with the sulfonamide moiety as directing group. This kinetic resolution was efficiently promoted by the Gd-*N*,*N*′-dioxide catalytic system. Various aromatic and aliphatic amines were successfully employed as nucleophiles for the ring opening of aromatic *trans*-2,3-epoxy sulfonamides furnishing diverse Ts- and SES-protected 3-amino-3-phenylpropan-2-olamines as products in complete regiocontrol and high enantioselectivities. Furthermore, the successful introduction of chiral amines in this Gd-catalyzed aminolysis holds promise for the use of this method to prepare structurally complex amino alcohols bearing multiple stereogenic centers.

Table 3: Enantioselective ring-opening reactions of *trans*-2,3-epoxy cinnamyl sulfonamide and its analogues with aniline as nucleophile.[11][a]



Entry	R	*n*	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	Me	0	55	21	14
2	NHTs	1	RT	98	96
3	SO_2*p*tolyl	2	55	52	26
4	NHBoc	1	55	23	30
5	BocNTs	1	55	0	–

[a] Unless otherwise specified, reactions were performed on a 0.25 mmol scale of aniline (**1a**) using 2.3 equiv racemic epoxides, 10 mol% $Gd(OTf)_3$ and 12 mol% *N*,*N*′-dioxide **10** at RT or 55 °C in 8.0 mL chloroform. [b] Yields of the isolated products after flash chromatography based on aniline. [c] All enantiomeric excesses were determined by HPLC analysis on chiral stationary phase.

Keywords: amino alcohols · gadolinium-catalysis · kinetic resolution · regioselective · ring opening

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[11] For details on the determination of the absolute stereochemistry of the amino alcohols, see the Supporting Information, pages 21–22.
[12] The selectivity factor *s* was calculated as $s = \ln[(1-C)/(1-ee)]/\ln[(1-C)(1+ee)]$, where *C* is the conversion.

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