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Tetrahedron Letters 45 (2004) 4213–4216
Tetrahedron Letters

Enantioselective radical cyclization of α,β-unsaturated sulfonyl compounds

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Received 11 March 2004; revised 5 April 2004; accepted 8 April 2004

Abstract—Enantioselective intramolecular radical cyclization of benzimidazolyl iodoalkenyl and iodoalkadienyl sulfones using chiral Lewis acids gave products with good enantioselectivity. Newly formed chiral centers could be induced effectively by enantioselective coordination to one of the sulfonyl oxygens.

1. Introduction

Free radical-mediated asymmetric reactions have been extensively studied.[1] There are a number of reports of the diastereoselective radical intramolecular cyclization using chiral auxiliaries, for example, (−)-8-phenylmenthyl ester,[2] Oppolzer's sultam,[3] a sulfinyl group,[4] and others.[5] However, there are only a few reports of the highly enantioselective intramolecular radical cyclization involving enantioselective radical addition to a double bond. High enantioselectivity has been reported in the reaction of vinyl radical cyclization using a chiral aluminum Lewis acid derived from Me_3Al and BINOLs.[6] Recently, we have reported allylation and hydrogen atom transfer reactions of α-sulfonyl radicals in the presence of chiral Lewis acids, which proceed with high enantioselectivity.[7] These reactions showed selective coordination of a chiral Lewis acid to one of the prochiral oxygens in the sulfonyl group, which could be a powerful strategy for the asymmetric synthesis[8] (Fig. 1). We now report an enantioselective radical cyclization of α,β-unsaturated sulfonyl compounds by selective coordination of a chiral Lewis acid to an enantiotrophic sulfonyl oxygen.

We first examined the radical 5-*exo* cyclization of benzimidazolyl ω-iodoalkenyl sulfones **1a**–**d** (Scheme 1).

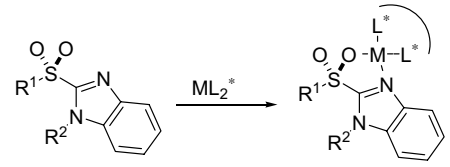

Figure 1. Asymmetric induction by the prochiral sulfonyl group.

The results are shown in Table 1. A Lewis acid (1.1 equiv) was stirred with a chiral ligand (1.2 equiv) in CH_2Cl_2 (0.01 mol/L) for 1 h at room temperature and then the ω-iodoalkenyl sulfone **1a** was added. After being stirred for 1 h at room temperature, the mixture was cooled to −78 °C. A hydrogen atom donor (2.0 equiv) and triethylborane (2.0 equiv) were added successively and the reaction mixture was stirred for an appropriate time. The reaction of *N*-benzylbenzimidazolyl sulfone **1a** using tributyltin hydride in the presence of $MgBr_2$-bis(oxazoline)-Ph **3** or $Mg(ClO_4)_2$-bis(oxazoline)-Ph **3** afforded the cyclized product **2a** in high yield but with no enantioselectivity (entries 1 and 2). On the other hand, the reaction using a combination of **3** and $Zn(OTf)_2$ gave **2a** with good enantioselectivity (entry 3). The reaction using triphenyltin hydride also gave good enantioselectivity (entry 4). The reaction using tris(trimethylsilyl)silane gave **2a** with 70% ee,[9] but a longer reaction time was required for completion of the reaction in comparison with that using tributyltin and triphenyltin hydride (entry 5 vs entries 3 and 4). Bis(oxazoline)-Ph **3** gave better enantioselectivity than other bis(oxazoline)s **4**, **5**, and **6**[10] (entries 6–8). The substituents on the nitrogen of the benzimidazolyl group

Keywords: Radical; Cyclization; Sulfone; Chiral Lewis acid.
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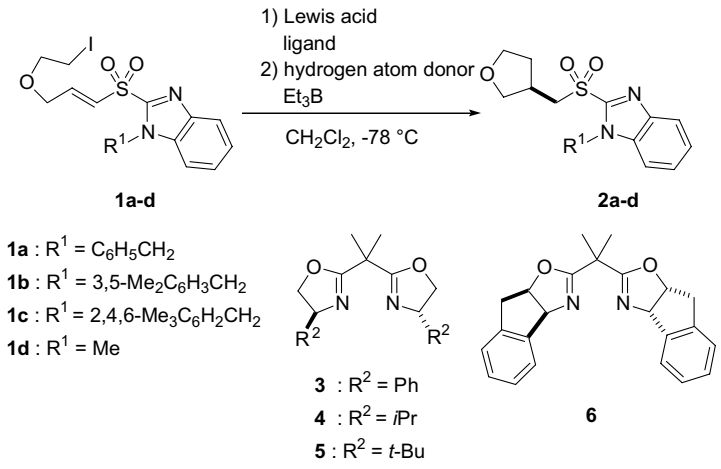
doi:10.1016/j.tetlet.2004.04.024



Scheme 1.

Table 1. Radical cyclization of benzimidazolyl ω-iodoalkenyl sulfones **1a–d**

Entry	Vinyl sulfone		Lewis acid	Ligand	Hydrogen atom donor	Time (min)	Product	Yield (%)	Ee (%)[a]
		R^1							
1	**1a**	$C_6H_5CH_2$	$MgBr_2$	**3**	Bu_3SnH	10	**2a**	97	0
2	**1a**	$C_6H_5CH_2$	$Mg(ClO_4)_2$	**3**	Bu_3SnH	1	**2a**	99	0
3	**1a**	$C_6H_5CH_2$	$Zn(OTf)_2$	**3**	Bu_3SnH	1	**2a**	99	64
4	**1a**	$C_6H_5CH_2$	$Zn(OTf)_2$	**3**	Ph_3SnH	1	**2a**	94	55
5	**1a**	$C_6H_5CH_2$	$Zn(OTf)_2$	**3**	$(TMS)_3SiH$	4.5 h	**2a**	93	70
6	**1a**	$C_6H_5CH_2$	$Zn(OTf)_2$	**4**	Bu_3SnH	1	**2a**	90	1
7	**1a**	$C_6H_5CH_2$	$Zn(OTf)_2$	**5**	Bu_3SnH	1	**2a**	90	2
8	**1a**	$C_6H_5CH_2$	$Zn(OTf)_2$	**6**	Bu_3SnH	10	**2a**	79	2
9	**1b**	3,5-$Me_2C_6H_3CH_2$	$Zn(OTf)_2$	**3**	Bu_3SnH	3	**2b**	100	67
10	**1c**	2,4,6-$Me_3C_6H_2CH_2$	$Zn(OTf)_2$	**3**	Bu_3SnH	3	**2c**	96	45
11	**1d**	Me	$Zn(OTf)_2$	**3**	Bu_3SnH	1	**2d**	92	6

[a] Determined by HPLC analysis using CHIRALPAK® AD.

were examined. The reaction of **1b** having the *N*-(3,5-dimethylphenyl)methyl group showed good enantioselectivity (entry 9), whereas *N*-(2,4,6-trimethylphenyl)-methyl- and *N*-methylbenzimidazolyl sulfones **1c** and **1d** lowered the enantioselectivity (entries 10 and 11).

We next examined the radical cyclization of iodoalkenyl and iodoalkadienyl sulfones **7**–**9** having the *N*-benzylbenzimidazolyl group (Table 2). The 6-*exo-trig* cyclization of **7** with tributyltin hydride or tris(tri-methylsilyl)silane afforded the product **10** in high yield with good enantioselectivity (entries 1 and 2). The 5-*exo-trig* cyclization of vinyl radicals derived from sulfones **8** and **9** gave **11** and **12** in high yield with good enantioselectivity using tributyltin hydride as well as tris(trimethylsilyl)silane (entries 3–6).

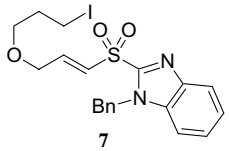
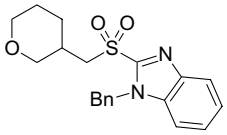
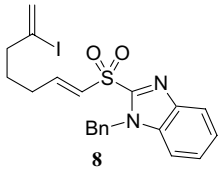
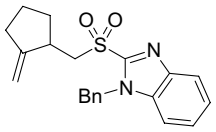
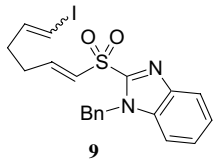
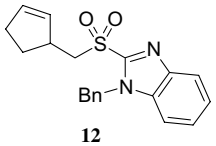
The absolute configuration of the major product **2a** was determined by comparison with (*R*)-**2a** separately prepared from (*S*)-3-tetrahydrofuranmethanol **13**[11] (Scheme 2). Treatment of **13** with TsCl, Et_3N, and $Et_3N{\cdot}HCl$ gave the tosylate **14**,[12] which was converted to the (*R*)-sulfide on treatment with 1-benzylbenzimidole-2-thiol in the presence of DBU.[13] Oxidation of the sulfide **15** with *m*-CPBA afforded the sulfone (*R*)-**2a** with 98% ee. The absolute configuration of the major enantiomer of **2a** was determined to be *R* by comparison of the value of optical rotation with that of (*R*)-**2a** derived from the chiral alcohol **13**.[14]

Figure 2 shows a steric requirement in the transition state for the formation of (*R*)-**2a** from **1a**. In this plausible transition state, the *pro-R* oxygen of the sulfonyl group and the nitrogen atom of the benzimidazolyl group in **1a** are coordinated with tetrahedral zinc[15] and the complex is well arranged to avoid the severe steric repulsion between the alkenyl and the phenyl groups on the bis(oxazoline) ring. As a result, this transition state turned out to be similar to those assumed in our previous reports for the allylation and hydrogen atom transfer to α-sulfonyl radicals, in which the *pro-R* sulfonyl oxygen is coordinated with tetrahedral zinc. In the present cyclization, the carbon radical attacks the *Si*-face of the double bond to afford (*R*)-**2a**.

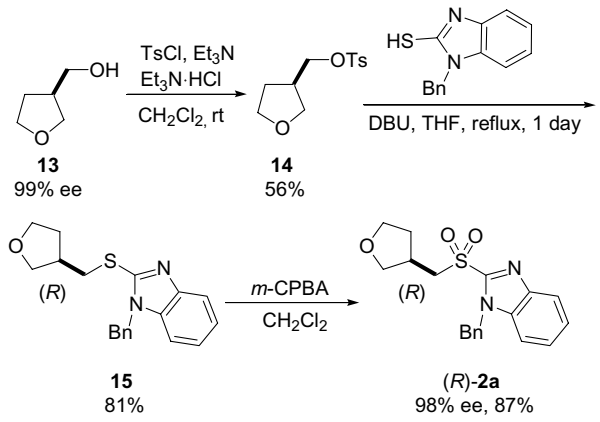
2. Conclusion

In conclusion, we have demonstrated that selective coordination of a chiral Lewis acid to one of the enantiotrophic sulfonyl oxygens is an efficient method for the

Table 2. Radical cyclization of iodoalkenyl and iodoalkadienyl sulfones **7**–**9**

Entry	Vinyl sulfone	Hydrogen atom donor	Time	Product	Yield (%)	Ee (%)[a]
1	 **7**	Bu_3SnH	0.5 h	 **10**	97	62
2		$(TMS)_3SiH$	5 h		62	59
3	 **8**	Bu_3SnH	5 min	 **11**	67	60
4		$(TMS)_3SiH$	2.5 h		66	66
5	 **9**	Bu_3SnH	3 min	 **12**	93	60
6		$(TMS)_3SiH$	3.5 h		96	50

[a] Determined by the HPLC analysis using Chiralcel OJ-H and CHIRALPAK® AD.



Scheme 2.

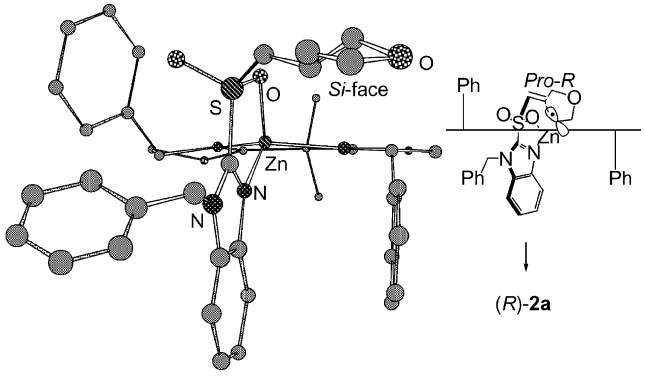


Figure 2. Plausible transition state for the radical cyclization of *N*-benzylbenzimidazolyl ω-iodoalkenyl sulfone **1a**.

asymmetric radical cyclization. We are currently engaged in further application and extension of this methodology.

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