COMMUNICATION

Diastereoselective radical allylation and hydrogenation of α-(arylsulfinyl)alkyl radicals induced by chelation control

Nobuyuki Mase,† Yoshihiko Watanabe,‡ Koji Higuchi, Shuichi Nakamura and Takeshi Toru *

Department of Applied Chemistry, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466-8555, Japan. E-mail: toru@ach.nitech.ac.jp; Fax: 81-52-735-5217; Tel: 81-52-735-5217

Received (in Cambridge) 24th July 2002, Accepted 23rd August 2002
First published as an Advance Article on the web 5th September 2002

The radical allylation and the hydrogenation of α-(arylsulfinyl)alkyl radicals were examined. In the presence of a bidentate Lewis acid, high diastereoselectivities were achievable in the allylation and the hydrogenation of α-(arylsulfinyl)alkyl radicals derived through the radical β-addition to vinyl sulfoxides bearing the 2-pyridyl, the imidazol-2-yl, or the benzimidazol-2-yl groups.

Stereoselective reactions of acyclic α-(arylsulfinyl) radicals are highly attractive methods for the asymmetric 1,2-induction in inter- and intramolecular radical carbon–carbon bond formations.[1] However, it is generally difficult to accomplish high diastereoselectivity in the reaction of α-(arylsulfinyl)alkyl radicals, although there are several reactions giving high stereoselectivity.[2] In order to overcome this difficulty, we have developed new asymmetric reactions of α-(arylsulfinyl) radicals by use of either intramolecular hydrogen bonding[3] or chelation[4] with a Lewis acid between the carbonyl and the sulfinyl oxygens. We envisaged that chelation of a Lewis acid with the sulfinyl oxygen and the nitrogen of the nitrogen-containing aromatic group would control the stereochemistry in the reaction of the α-(arylsulfinyl)alkyl radicals.

The addition of a nucleophilic radical to an alkene with lower LUMO energy proceeds faster than that to an alkene with higher LUMO energy.[5] We first calculated the LUMO energies of aryl vinyl sulfoxides **1** with MOPAC 93/PM3.[6] The aryl groups bearing electron-donating substituent(s) such as *p*-tolyl and 2,4,6-trimethylphenyl groups increase the LUMO energy in comparison with phenyl vinyl sulfoxide **1a** (ΔLUMO [LUMO − LUMO (**1a**)] = 0.003 ~ 0.117 eV), in which the addition of a *tert*-butyl radical hardly takes place. Therefore, we designed the vinyl sulfoxides **1d**–**g** bearing the 2-pyridyl, the 1-methylimidazol-2-yl, the 1-methylbenzimidazol-2-yl, and the 1-benzylbenzimidazol-2-yl groups, which were shown to have lower LUMO energy than **1a** except **1e** (ΔLUMO = 0.038 ~ −0.209 eV). The chelation of $ZnBr_2$ with the sulfinyl oxygen and the nitrogen remarkably decreases the LUMO energy (ΔLUMO = −1.724 ~ −1.902 eV), and they were expected to have enough reactivity toward nucleophilic radicals.

We examined the diastereoselectivity in the radical allylation of α-(arylsulfinyl)alkyl radicals generated by the addition of *tert*-butyl radicals to vinyl sulfoxides **1**. The radical addition–allylation of vinyl sulfoxides **1** was carried out by treatment with *tert*-butyl iodide (3 equiv.) and allyltributyltin (3 equiv.) in the presence of triethylborane[7] (3 equiv.) (Table 1).

Addition–allylation of **1a** without Lewis acids gave the product **2a** in moderate yield and with no stereoselectivity (entry 1). The addition of a Lewis acid such as Et_2AlCl or methylaluminium 2,6-di-*tert*-butyl-4-methylphenoxide (MAD)[8] did not improve diastereoselectivity. *p*-Tolyl vinyl sulfoxide **1b** hardly reacts and 2,4,6-trimethylphenyl vinyl sulfoxide **1c** remained intact (entries 2 and 3). The sulfoxide **1c** did not give the product even in the presence of a Lewis acid. Without a Lewis acid, the reactions of **1d**, **1f**, and **1g** with *tert*-butyl iodide and allyltributyltin for 24 h afforded only traces of the addition–allylation products together with the formation of unidentified products (entries 4, 10, and 13). On the other hand, the addition of a Lewis acid, $Zn(OTf)_2$ or $ZnBr_2$, dramatically enhanced the reactivity of **1d**–**g** toward alkyl radicals, and the reaction was completed within 1 h to afford the addition products **2d**–**g**. Thus, the radical addition–allylation reaction of the 2-pyridyl sulfoxide **1d** with $Zn(OTf)_2$ afforded the addition–allylation product **2d** in 62% yield in a *syn*–*anti* ratio of 72 : 28 (entry 6). In the reactions of the imidazol-2-yl sulfoxides such as the 1-methylimidazol-2-yl, 1-methylbenzimidazol-2-yl, and 1-benzylbenzimidazol-2-yl sulfoxide **1e**, **1f**, and **1g**, the diastereoselectivity significantly increased up to 95 : 5 when $Zn(OTf)_2$ was used (entries 9, 12, and 14).

We also examined the radical addition–hydrogenation of the α-methyl- and the α-phenyl- substituted vinyl 2-pyridyl sulfoxides **3a** and **3b**. The results are shown in Table 2. Without a Lewis acid, the reaction gave the addition–hydrogenation products **4** or **5** with low diastereoselectivity (entries 1 and 4), whereas addition of Lewis acids such as $Zn(OTf)_2$ and $ZnBr_2$ remarkably improved the diastereoselectivity, giving the products with high diastereoselectivity (entries 2, 3, 5, and 6). The yield and the diastereoselectivity decreased when a smaller amount of the Lewis acid was used (entry 7). The chelation between the sulfoxide oxygen and the nitrogen with a bidentate Lewis acid clearly plays a crucial role in inducing high diastereoselectivity, since the monodentate Lewis acid, $BF_3{\cdot}OEt_2$, showed low diastereoselectivity (entry 8). It should be noted that the addition of cyclohexyl, isopropyl, butyl, and ethyl radicals to the vinyl sulfoxide **3b** gave the addition products with a high level of diastereoselectivity irrespective of the size of alkyl radicals (entries 9–12).

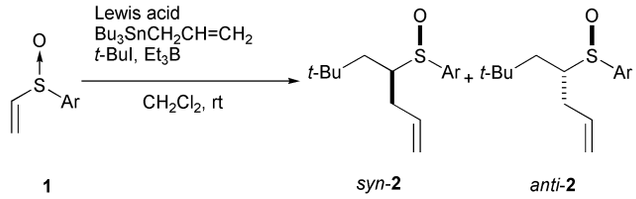
The stereochemistry of the addition–allylation and –hydrogenation products was assigned by the ^1H NMR spectral analyses of the signals due to the proton α to the sulfinyl group. These protons of the *anti*-allylation and the *syn*-hydrogenation products appear in a lower field than those of the corresponding *syn*-allylation and *anti*-hydrogenation products.

The rotational barrier about the C_{rad}–S(O) bond is known to be 2–4 kcal mol^{-1}[2d] and we also found by the PM3 calculation that there is no prominent difference in energy between the s-*cis* and the s-*trans* radical intermediates derived from **1** and **3**. Thus, the stereochemical outcome should not be rationalized by the stability of the radical intermediate, but by the difference in energy of the transition state in the reaction of the radical intermediate and allyltributyltin or tributyltin hydride. Fig. 1 illustrates presumed transition states to afford the corresponding major diastereomers *syn*-**2d**–**g** in the reactions of **1d**–**g** with allyltributyltin (TS-A) and *anti*-**4**–**9** in the reaction of **3** with tributyltin hydride (TS-B). In TS-A, the most bulky substituent is supposed to be the neopentyl group which occupies the least hindered space, whereas the bulky tributyltin hydride approaches from the least hindered side in TS-B.

† Present address: Department of Molecular Science, Faculty of Engineering, Shizuoka University, 3-5-1 Johoku, Hamamatsu 432-8561, Japan.
‡ Deceased, June 23, 2001

 DOI: 10.1039/b207249a

Table 1 Radical allylation of α-(arylsulfinyl)alkyl radicals generated by the addition of a *tert*-butyl radical to **1**



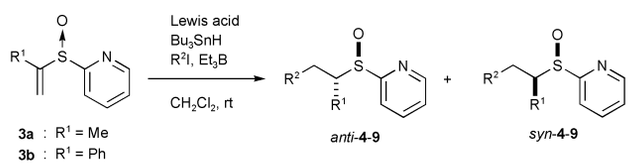
1 *syn*-**2** *anti*-**2**

a : Ar = phenyl
b : Ar = *p*-tolyl
c : Ar = 2,4,6-trimethylphenyl
d : Ar = 2-pyridyl
e : Ar = 1-methylimidazol-2-yl
f : Ar = 1-methylbenzimidazol-2-yl
g : Ar = 1-benzylbenzimidazol-2-yl

Entry	Substrate	Lewis acid[a]	Time/h	Product	Yield (%)	Ratio *syn* : *anti*
1	**1a**	None	15	**2a**	51	50 : 50
2	**1b**	None	24	**2b**	22[b]	50 : 50
3	**1c**	None	24	**2c**	–[c]	—
4	**1d**	None	24	**2d**	<5	—
5	**1d**	$ZnBr_2$	1	**2d**	38	53 : 47
6	**1d**	$Zn(OTf)_2$	1	**2d**	62	72 : 28
7	**1e**	None	5	[d]	—	—
8	**1e**	$ZnBr_2$	0.5	**2e**	60	72 : 28
9	**1e**	$Zn(OTf)_2$	1	**2e**	98	95 : 5
10	**1f**	None	24	**2f**	<5	—
11	**1f**	$ZnBr_2$	0.5	**2f**	42	85 : 15
12	**1f**	$Zn(OTf)_2$	0.2	**2f**	54	95 : 5
13	**1g**	None	24	**2g**	<5	—
14	**1g**	$Zn(OTf)_2$	0.5	**2g**	61	95 : 5

[a] The reaction was carried out in the presence of 1.1 equiv. of a Lewis acid. [b] The sulfoxide **1b** was recovered in 63% yield. [c] The starting sulfoxide **1c** remained unreacted. [d] The addition-hydrogenation product was obtained in 88% yield.

Table 2 Hydrogenation of α-(2-pyridylsulfinyl)alkyl radicals generated by the addition of alkyl radicals to **3**



3a : R^1 = Me
3b : R^1 = Ph

anti-**4**-**9** *syn*-**4**-**9**

Entry	Substrate	Lewis acid[a]	R^2	Time/h	Product	Yield (%)	Ratio *syn* : *anti*
1	**3a**	None	*t*-Bu	24	**4**	25	63 : 37
2	**3a**	$Zn(OTf)_2$	*t*-Bu	0.5	**4**	95	84 : 16
3	**3a**	$ZnBr_2$	*t*-Bu	1	**4**	99	74 : 26
4	**3b**	None	*t*-Bu	24	**5**	80	62 : 38
5	**3b**	$Zn(OTf)_2$	*t*-Bu	1	**5**	86	92 : 8
6	**3b**	$ZnBr_2$	*t*-Bu	2	**5**	99	96 : 4
7	**3b**	$ZnBr_2$[b]	*t*-Bu	2	**5**	48	70 : 30
8	**3b**	$BF_3{\cdot}OEt_2$	*t*-Bu	4	**5**	81	58 : 42
9	**3b**	$ZnBr_2$	c-Hex[c]	4	**6**	60	96 : 4
10	**3b**	$ZnBr_2$	i-Pr[c]	7	**7**	42	96 : 4
11	**3b**	$ZnBr_2$	Bu[c]	5	**8**	72	96 : 4
12	**3b**	$ZnBr_2$	Et[c]	7	**9**	60	96 : 4

[a] Lewis acids (1.1 equiv.) were used unless otherwise noted. [b] $ZnBr_2$ (0.2 equiv.) was used. [c] Et_3B (10 equiv.) and R^2I (10 equiv.) were used.

In summary, the diastereoselectivity as well as the reactivity of the vinyl sulfoxides were enhanced by the chelation of the bidentate Lewis acids between the sulfinyl oxygen and the nitrogen.

Experimental

General procedure for the radical addition–allylation and –hydrogenation of aryl vinyl sulfoxides 1 and 3

The radical reaction was carried out by adding an alkyl iodide (3 equiv.), allyltributyltin or tributyltin hydride (3 equiv.), and triethylborane (3 equiv.) to a 0.01 mol L^{-1} solution of the aryl vinyl sulfoxide **1** or **3** in CH_2Cl_2. In the reaction with a Lewis acid, a mixture of **1** or **3** and a Lewis acid (1.1 equiv.) was stirred for 30 min before addition of other reagents. In the reaction without a Lewis acid, after stirring for an appropriate time, the reaction mixture was evaporated under reduced pressure to give the crude product. In the case using a Lewis acid, the reaction mixture was poured into saturated aqueous NaH_2PO_4. The aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated to give the crude product. The crude product obtained in each reaction was purified by column chromato-

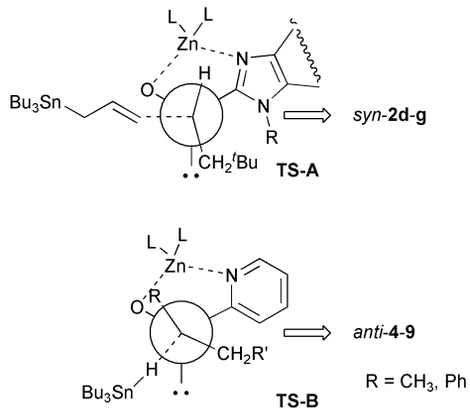


Fig. 1 Presumed transition states for allylation and hydrogenation of the α-(arylsulfinyl)alkyl radical derived from **1d**–**g** and **3**

graphy to give the respective addition–allylation and –hydrogenation products.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research (07750950 and 09750932) from the Ministry of Education, Science, Sports and Culture of Japan.

Notes and references

1 D. P. Curran, N. A. Porter, B. Giese, *Stereochemistry of Radical Reactions*; VCH, Weinheim, 1995 .

2 For high diastereoselective reactions of α-sulfinyl radicals, see: (*a*) B. B. Snider, B. Y.-F. Wan, B. O. Buckman and B. M. Foxman, *J. Org. Chem.*, 1991, **56**, 328; (*b*) A. L. J. Beckwith, R. Hersperger and J. M. White, *J. Chem. Soc., Chem. Commun.*, 1991, 1151; (*c*) A. De Mesmaeker, A. Waldner, P. Hoffmann and T. Mindt, *Synlett*, 1993, 871; (*d*) P. Renaud, P.-A. Carrupt, M. Gerster and K. Schenk, *Tetrahedron Lett.*, 1994, **35**, 1703; (*e*) P. Renaud and T. Bourquard, *Tetrahedron Lett.*, 1994, **35**, 1707; (*f*) P. Renaud, T. Bourquard, M. Gerster and N. Moufid, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1601; (*g*) P. Renaud and T. Bourquard, *Synlett*, 1995, 1021; (*h*) M. Zahouily, G. Caron, P.-A. Carrupt, N. Knouzi and P. Renaud, *Tetrahedron Lett.*, 1996, **37**, 8387; (*i*) P. Renaud, T. Bourquard, P.-A. Carrupt and M. Gerster, *Helv. Chim. Acta*, 1998, **81**, 1048.

3 (*a*) N. Mase, Y. Watanabe and T. Toru, *Tetrahedron Lett.*, 1999, **40**, 2797; (*b*) N. Mase, Y. Watanabe, T. Toru, T. Kakumoto and T. Hagiwara, *J. Org. Chem.*, 2000, **65**, 7083.

4 (*a*) T. Toru, Y. Watanabe, M. Tsusaka and Y. Ueno, *J. Am. Chem. Soc.*, 1993, **115**, 10464; (*b*) N. Mase, Y. Watanabe, Y. Ueno and T. Toru, *J. Org. Chem.*, 1997, **62**, 7794; (*c*) T. Toru, Y. Watanabe, N. Mase, M. Tsusaka, T. Hayakawa and Y. Ueno, *Pure Appl. Chem.*, 1996, **68**, 711; (*d*) N. Mase, Y. Watanabe and T. Toru, *J. Org. Chem.*, 1998, **63**, 3899; (*e*) N. Mase, Y. Watanabe and T. Toru, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 2957; (*f*) N. Mase, Y. Watanabe, Y. Ueno and T. Toru, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1613.

5 (*a*) B. Giese, *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 753; (*b*) B. Giese, *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press, Oxford, 1986 .

6 (*a*) J. J. P. Stewart, *J. Comp. Chem.*, 1989, **10**, 210; (*b*) For the zinc parameter for PM3, see: J. J. P. Stewart, *J. Comp. Chem.*, 1991, **12**, 320.

7 K. Nozaki, K. Oshima and K. Utimoto, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 403.

8 For reviews, see: (*a*) T. Ooi, K. Maruoka, in *Lewis Acids in Organic Synthesis*, ed. H. Yamamoto, Wiley, Weinheim, 2000, vol. 1, pp. 191–282; (*b*) T. Ooi and K. Maruoka, *J. Synth. Org. Chem. Jpn.*, 1996, **54**, 200.

9 (*a*) T. Sato and J. Otera, *Synlett*, 1995, 365; (*b*) K. Nakamura, M. Higaki, S. Adachi, S. Oka and A. Ohno, *J. Org. Chem.*, 1987, **52**, 1414 . See also ref. 2*d–f* and 2*h*.