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Asymmetric reduction of 2-bromo-1-phenylethylidenemalononitrile with chiral NADH models: substituent effects on enantioselectivity

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Abstract

The substituent effects on the asymmetric reduction of 2-L-1-(X-Aryl)ethylidenemalononitrile with chiral NADH model (S_S)-1-benzyl-3-(*p*-tolylsulfinyl)-1,4-dihydropyridine **1** have been investigated and a tentative transition state for the reaction is proposed.

1. Introduction

Since Ohno and co-workers[1] reported the first example of asymmetric reduction using a model of coenzyme NADH in 1975, numerous efforts have been made to construct model compounds mimicking the activity of NADH and many publications have appeared.[2] The mechanism of enantioselective hydrogen transfer in most asymmetric reductions with NADH models involves the formation of a ternary complex between the model compound, Mg^{2+} and the substrate.[3]

In our previous paper,[4] we reported that chiral NADH model (S_S)-1-benzyl-3-(*p*-tolylsulfinyl)-1,4-dihydropyridine **1** could reduce 2-bromo-1-phenylethylidenemalononitrile (BPM) enantioselectively without the addition of Mg^{2+} to give 2-phenyl-1,1-cyclopropanedinitrile (PCN) with moderate enantiomeric excess value. In order to gain more insight into the stereochemistry and mechanism of this reaction, we extended this asymmetric reduction to 1-phenylethylidene-2-*p*-tolylsulfonyloxymalononitrile **2a** and a series of 1-(X-aryl)-2-bromoethylidenemalononitriles **2b**–**2p**. Herein, we report the results.

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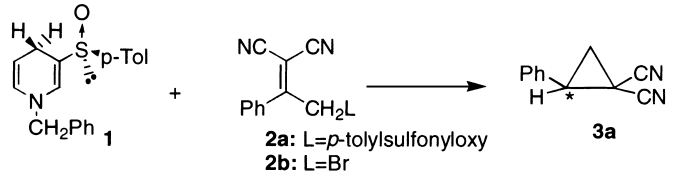
2. Results and discussion

1-Phenylethylidene-2-*p*-tolylsulfonyloxymalononitrile **2a** was chosen as the substrate because *p*-tolylsulfonyloxy is a better leaving group than bromide and the size of the *p*-tolylsulfonyloxy group is larger than that of bromine. The reduction of **2a** by compound **1** was carried out in CH_3CN at 30°C under the protection of Ar in the dark. Because **2a** is unstable in polar solvent, the chemical yield is very low. Comparing the enantiomeric excess obtained in the reduction of **2a** (51.2% e.e.) with that of **2b** (52.1% e.e.) under the same experimental conditions (Table 1), it is clear that the change of the leaving group from the methylene carbon of the substrate has little effect on the enantioselectivity of the reaction.

Table 1
Comparison of reduction of **2a** and **2b** by compound **1** in CH_3CN



Entry	Substrate	Product	Configuration[a]	Yield%[b]	Ee%[c]
1	**2a**	**3a**	S	<5	51.2
2	**2b**	**3a**	S	35.1	52.1

a. By comparision of specific rotation with authentic sample[4,5].

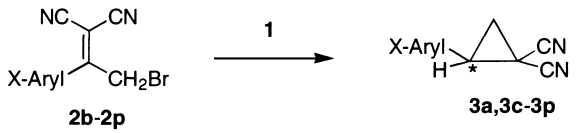
b. Isolated yields.

c. Enantiomeric excess was determined by chiral GC, see Experimental.

Secondly, the reductions of a series of differently substituted 1-(X-aryl)-2-bromo-ethylidene-malononitriles **2b**–**2p** were carried out to investigate the effect of the substituent on the enantioselectivity. The reactions were run in a mixed solvent (DMF:CH_3CN = 1:1) at 30°C under argon in the dark and the results are shown in Table 2.

Comparing the results of **2b** (entry 1) with that of other substrates (entry 2–12), it is seen that the substituents showed remarkable effects on the reactivities and enantioselectivities of the reactions. For most of the *o*-substituted substrates including α-naphthyl **2l**, only traces of products were observed by TLC (entry 8–11) except **2h** (X = F). Since a fluorine atom is the smallest among the substituents, the results implied that the presence of *o*-substituents hindered the reactions. It is also interesting to note that the enantioselectivities of reactions of *p*-substituted substrates were all lower than that of **2b** whether the substituent is electron-withdrawing or counterwise (entries 2–6, 12). Moreover, the order of enantioselectivity for the corresponding substrates (H- > F-≈Cl- > MeO- > Br- > NO_2-) bears no linear relationship with the Hammett σ_P values of the corresponding substrates, whereas the order is approximately parallel with the order of the dimensional size of the substituent groups. This seems to indicate that it is the steric effect rather than the electronic effect of substituents that plays the dominant role in enantioselectivity. In particular, the results of **2b** (entry 1) and **2m** (entry 12) clearly show that the larger the substituent, the lower the enantioselectivity. A reasonable explanation for this is that the phenyl group of the substrate must come very close to the dihydropyridine ring of compound **1** in the transition state for the reaction.

Table 2
The reduction of 1-(X-aryl)-2-bromoethylidenemalononitriles by compound **1**



2b-2p **3a,3c-3p**

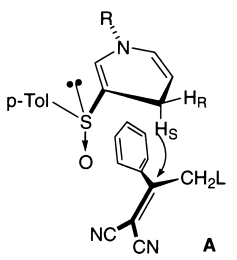
Entry	X-Aryl	Substrate	Product	Yields%[a]	Configuration[b]	Ee%[c]
1	Phenyl	**2b**	**3a**	56	S	53.2
2	*p*-NO_2-Phenyl	**2c**	**3c**	72	S	13.1
3	*p*-F-Phenyl	**2d**	**3d**	57	S	37.5
4	*p*-Cl-Phenyl	**2e**	**3e**	52	S	37.1
5	*p*-Br-Phenyl	**2f**	**3f**	47	S	16.3
6	*p*-MeO-Phenyl	**2g**	**3g**	61	S	27.2
7	*o*-F-Phenyl	**2h**	**3h**	27	S	21.3
8	*o*-Cl-Phenyl	**2i**	**3i**	traces		
9	*o*-Br- Phenyl	**2j**	**3j**	traces		
10	*o*-MeO-Phenyl	**2k**	**3k**	traces		
11	α-Naphthyl	**2l**	**3l**	traces		
12	β-Naphthyl	**2m**	**3m**	66	S	21.1

a. Isolated yields.

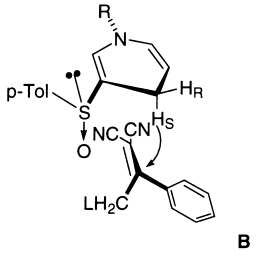
b. Because the configuration of the major isomer of **3a** is *S* and the optical rotation of other reduction products (**3c-3h**, **3m**) is also negative, the configurations of the major isomers of other products should be *S* , see Experimental.

c. Enantiomeric excess was determined by chiral GC and chiral HPLC, see Experimental.

Taking into account the stereospecific hydrogen transfer of compound **1**[6] and the configurations of the major *S*-isomer of cyclopropane products (**3a**, **3c**–**3h**, **3m**) as well as the steric hindrance between substrates and the S–O group of compound **1**, the substrate could come close to the dihydropyridine ring of compound **1** in the transition state via two modes of approach as follows:



A



B

Although the steric hindrance in mode **B** as a whole may appear to be less than that in mode **A**, mode **A** is more probable than mode **B** due to the following considerations: (1) it is unlikely that the substituents, especially those in the *p*-position, in mode **B** could affect the enantioselectivity by steric effect because of the distance from the reaction center, while in mode **A** the X-aryl group lies right underneath the dihydropyridine ring, so that substituents could decrease the enantioselectivity through steric interactions (the possible interaction is between the lone electron pair of

the N atom of the dihydropyridine ring and the substituents at the *p*-position) in agreement with the experimental results; (2) it is also unlikely that *o*-substituents except F in mode **B** could hinder the reactions so markedly that practically no product is obtained, while in mode **A** the repulsion between the S–O group and the *o*-substituents could be large enough to hinder the reactions; and (3) in mode **A**, substituents linked with the methylene carbon of the substrate have little steric hindrance with the dihydropyridine ring, so the change of substituent at this end should have little effect on enantioselectivity in consistence with the experimental results. Therefore, it is likely that the reaction takes place via transition state **A**.[7]

In conclusion, the effect of substituents on the enantioselectivity of asymmetric reduction of the title compound **2** with chiral NADH model **1** has been shown to be governed mainly by steric effects and a tentative transition state for the reaction is suggested. Further experiments aimed at seeking more insight into the mechanism and structure–reactivity of the reaction are being planned.

3. Experimental

3.1. Materials

(S_S)-1-Benzyl-3-(*p*-tolylsulfinyl)-1,4-dihydropyridine **1** was prepared according to the literature[6a] with some modifications.[8] 1-Phenylethylidene-2-*p*-tolylsulfonyloxymalononitrile (TOSPM) was prepared from 2-bromo-1-phenylethylidenemalononitrile (BPM) by exchange reaction with silver *p*-tolylsulfonate.[9] All 1-aryl-2-bromo-ethylidenemalononitriles were prepared from the corresponding ketones according to the literature.[10]

3.2. Typical procedure for reduction of 1-aryl-2-bromoethylidenemalononitrile with *1*

A mixture of **1** (0.01 mmol) and 1-aryl-2-bromo-ethylidenemalononitrile (0.012 mmol) was stirred in the mixed solvent (DMF–CH_3CN) at 30°C for 12 h under an Ar atmosphere in the dark. The reaction mixture was treated with water and extracted with ether. Usual work-up and purification by SiO_2 column chromatography [hexane:AcOEt (10:1)] gave light yellow oily or solid product.

3.3. 2-Phenyl-1,1-cyclopropanedinitrile (PCN)

^{1}H NMR (200 MHz) δ: 2.27 (2H, d, J = 9.0 Hz), 3.38 (1H, t, J = 9.0 Hz), 7.28–7.47 (5H, m) ppm; anal. calcd for $C_{11}H_8N_2$: C, 78.57; H, 4.76; N, 16.67; found: C, 78.32; H, 4.84; N, 16.55; $[\alpha]_D^{25} = -103.7$ ($c = 0.30$, CH_3COCH_3); 53.2% e.e., GC t_R (–)-isomer: 11.82 min (76.6%); t_R (+)-isomer: 12.13 min (23.4%); cp-Cyclodex-236 M, column temperature: 161°C; HPLC t_R (–)-isomer: 12.97 min (76.8%); t_R (+)-isomer: 14.02 min (23.2%); CHI-TBB, *i*-PrOH:hexane, 2:98, 1.0 mL/min.

3.4. 2-(p-NO_2-Phenyl)-1,1-cyclopropanedinitrile (p-NO_2-PCN)

^{1}H NMR (200 MHz) δ: 2.35 (2H, dm, J = 9.0 Hz), 3.31 (1H, t, J = 9.0 Hz), 7.50, 8.31 (4H, AA′BB′ type, J = 4.8 Hz) ppm; anal. calcd for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.29; N, 19.72; found: C,

61.58; H, 3.21; N, 19.42; $[\alpha]_D^{25} = -34.0$ ($c = 0.30$, CH_3COCH_3); 13.2% e.e., HPLC t_R (–)-isomer: 15.09 min (56.6%); t_R (+)-isomer: 17.70 min (43.4%); CHI-TBB, *i*-PrOH:hexane, 20:80, 1.0 mL/min.

3.5. 2-(p-*F*-Phenyl)-1,1-cyclopropanedinitrile (p-*F*-PCN)

^{1}H NMR (500 MHz) δ: 2.25 (2H, dm, J = 9.0 Hz), 3.25 (1H, t, J = 9.0 Hz), 7.14 (2H, m), 7.29 (2H, m) ppm; anal. calcd for $C_{11}H_7N_2F$: C, 70.97; H, 3.76; N, 15.05; found: C, 70.57; H, 4.10; N, 14.48; $[\alpha]_D^{25} = -65.5$ ($c = 0.09$, CH_3COCH_3); 37.5% e.e., HPLC t_R (–)-isomer: 16.08 min (68.7%); t_R (+)-isomer: 18.20 min (31.3%); CHI-TBB, *i*-PrOH:hexane, 2:98, 1.0 mL/min.

3.6. 2-(p-*Cl*-Phenyl)-1,1-cyclopropanedinitrile (p-*Cl*-PCN)

^{1}H NMR (200 MHz) δ: 2.25 (2H, d, J = 10.0 Hz), 3.25 (1H, t, J = 10.0 Hz), 7.20, 7.45 (4H, AA′BB′ type, J = 8.0 Hz) ppm; anal. calcd for $C_{11}H_7N_2Cl$: C, 65.35; H, 3.46; N, 13.86; found: C, 65.22; H, 3.51; N, 13.53; $[\alpha]_D^{25} = -64.3$ ($c = 0.30$, CH_3COCH_3); 37.1% e.e., GC t_R (–)-isomer: 15.95 min (68.5%); t_R (+)-isomer: 16.25 min (31.5%); cp-Cyclodex-236 M, column temperature: 179°C.

3.7. 2-(p-*Br*-Phenyl)- 1,1-cyclopropanedinitrile (p-*Br*- PCN)

^{1}H NMR (200 MHz) δ: 2.24 (2H, dm, J = 9.0 Hz), 3.25 (1H, t, J = 9.0 Hz), 7.17, 7.56 (4H, AA′BB′ type J = 6.2 Hz) ppm; anal. calcd for $C_{11}H_7N_2Br$: C, 53.66; H, 2.84; N, 11.38; found: C, 53.39; H, 3.04; N, 11.20; $[\alpha]_D^{25} = -12.5$ ($c = 0.20$, CH_3COCH_3); 23.3% e.e., HPLC t_R (–)-isomer: 26.71 min (61.7%); t_R (+)-isomer: 31.40 min (38.3%); CHI-TBB, *i*-PrOH:hexane, 2:98, 1.0 mL/min.

3.8. 2-(p-*MeO*-Phenyl)- 1,1-cyclopropanedinitrile (p-*MeO*- PCN)

^{1}H NMR (200 MHz) δ: 2.20 (2H, d, J = 9.0 Hz), 3.26 (1H, t, J = 9.0 Hz), 3.81 (3H, s), 6.93, 7.22 (4H, AA′BB′ type, J = 8.0 Hz) ppm; anal. calcd for $C_{12}H_{10}N_2O$: C, 72.73; H, 5.05; N, 14.14; found: C, 72.76; H, 5.15; N, 14.48; $[\alpha]_D^{25} = -31.0$ ($c = 0.20$, CH_3COCH_3); 27.2% e.e., HPLC t_R (–)-isomer: 10.80 min (63.6%); t_R (+)-isomer: 11.80 min (36.4%); CHI-TBB, *i*-PrOH:hexane, 5:95, 1.0 mL/min.

3.9. 2-(o-*F*-Phenyl)- 1,1-cyclopropanedinitrile (o-*F*-PCN)

^{1}H NMR (500 MHz) δ: 2.28 (2H, dm, J = 9.0 Hz), 3.36 (1H, t, J = 9.0 Hz), 7.16–7.45 (4H, m) ppm; anal. calcd for $C_{11}H_7N_2F$: C, 70.97; H, 3.76; N, 15.05; found: C, 70.60; H, 4.00; N, 15.01; $[\alpha]_D^{25} = -26.3$ ($c = 0.08$, CH_3COCH_3); 23.1% e.e., HPLC t_R (–)-isomer: 14.45 min (61.6%); t_R (+)-isomer: 15.53 min (38.4%); CHI-TBB, *i*-PrOH:hexane, 2:98, 1.0 mL/min.

3.10. 2-β-Naphthyl-1,1-cyclopropanedinitrile (β-NCN)

^{1}H NMR (500 MHz) δ: 2.33 (H, dd, J = 9.3 Hz), 2.42 (1H, dd, J = 8.6 Hz), 3.47 (1H, t, J = 9.0 Hz), 7.42 (1H, t, J = 6.5 Hz), 7.55 (2H, m), 7.75 (1H, s), 7.87 (2H, m), 7.92 (1H, d, J = 8.5 Hz) ppm; anal. calcd for $C_{15}H_{10}N_2$: C, 82.57; H, 4.59; N, 12.84; found: C, 82.99; H, 5.09; N, 12.36;

$[\alpha]_D^{24} = -37.0$ ($c = 0.20$, CH_3COCH_3); 21.2% e.e., HPLC t_R (–)-isomer: 15.48 min (60.6%); t_R (+)-isomer: 18.21 min (39.4%); CHI-TBB, *i*-PrOH:hexane, 2:98, 1.0 mL/min.

Acknowledgements

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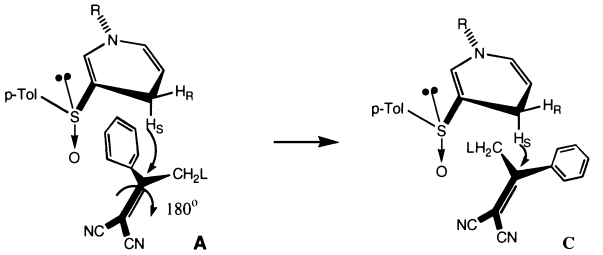
7. Through rotating the substrate by 180° around the axis of the C=C double bond in transition state **A**, the *R*-isomer could be formed via transition state **C**. Comparing transition states **A** and **C**, it is seen that transition state **C** would be of higher energy because of the steric interactions between the two methylene hydrogens of the substrate and the 1,4-dihydropyridine moiety and would be less favorable.



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