Consideration of molecular arrangements in regio- and enantioselective reduction of an NAD model compound controlled by carbonyl oxygen orientation†‡

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The regio- and enantioselectivity of the reduction of an NAD model compound having axial chirality with respect to the C_3(quinolinium)–C(carbonyl) bond, 3-piperidinylcarbonyl-1,2,4-trimethylquinolinium ion (**1**), by using several reducing agents is described. Reaction of **1** with sodium hydrosulfite affords the 1,4-reduced product, 3-piperidinylcarbonyl-1,2,4-trimethyl-1,4-dihydroquinoline (**2**), with low enantioselectivity, whereas sodium borohydride promotes 1,2-reduction, affording 3-piperidinylcarbonyl-1,2,4-trimethyl-1,2-dihydroquinoline (**3**) as the sole product in a moderate enantioselectivity. When **1** was reduced by the chiral NADH model compound, 2,4-dimethyl-3-(*N*-α-methylbenzylcarbamoyl)-1-propyl-1,4-dihydropyridine (Me_2PNPH (**4**)), the regioselectivity and enantioselectivity of the reaction were significantly altered by the stereochemistry of **1** and **4**. An achiral NADH model compound, 1-propyl-1,4-dihydronicotinamide (PNAH (**5**)) exhibited both high regio- and enantioselectivities. The product selectivity reflects the change in molecular arrangement in the transition state of the reaction and reveals the relative importance of the parameters governing the molecular arrangement in the reaction.

Introduction

The asymmetric reduction of activated ketones or olefins with chiral NADH model compounds has been studied extensively.[1–11] This biomimetic molecular transformation including the non-asymmetric version of the reaction with various substrates,[12–17] has attracted considerable interest in relation to transition metal-free organic catalysts.[18–20] On the other hand, the reverse reactions, namely reductions of NAD model compounds exhibiting face-selective reduction, have been reported in a limited number.[6,8,21–26] The control of regioselectivity of the reduction is an additional requirement for this type of reaction because it often affords mixtures of 1,2-, 1,4- and 1,6-isomers.[27–29]

Several strategies for the differentiation of the nicotinamide ring face in NAD model compounds have been developed. The C3–C6,[21] C3–C5,[30] or C2–C5[26] strapped NAD model compounds undergo enantiospecific reduction from the unhindered face. Annulation in C2 and C3 results in inclination of the carbamoyl C=O bond from the plane of the nicotinamide ring, mostly activating the *syn*-face with the carbonyl oxygen in the 1,4-reduction.[6,8,23,25] The role of out-of-plane orientations of the carbonyl group in NAD/NADH model compounds in controlling the stereoselectivity has been studied extensively.[22,23,25,31]

In this article, we analyze the role of the carbonyl oxygen orientation in determining the *regio*- and *stereo*selectivity of the reduction of non-annulated NAD model compound, 3-piperidinylcarbonyl-1,2,4-trimethylquinolinium ion (**1**), which has axial chirality with respect to the C_3(quinolinium)–C(carbonyl) bond. As reported in our previous communication,[32] when (a*S*)-**1** was reduced by a chiral NADH model compound, (4*R*,9*R*)-2,4-dimethyl-3-(*N*-α-methylbenzylcarbamoyl)-1-propyl-1,4-dihydropyridine ((4*R*)-Me_2PNPH ((4*R*)-**4**), Chart 1), the main product was 1,4-dihydroquinoline (4*R*)-**2**, which is the compound where the hydride was introduced at the C4 position from the carbonyl oxygen face direction. The axial chirality was lost upon reduction, thus, axial chirality was converted to central chirality in this system. On the other hand, the present paper reveals that in the reaction of corresponding enantiomer of **1** ((a*R*)-**1**) with the same reducing agent ((4*R*)-**4**) affords 1,2-dihydroquinoline (2*S*)-**3** as a major product, which is the compound where the hydride was introduced at the C2 position from the carbonyl oxygen face direction (Scheme 1). The only difference between these two reactions is the orientation of the carbonyl group in starting material **1**; thus, the carbonyl dipole controls the regio- and stereoselectivity of the reaction. The details in determination of the absolute configuration of the product **3**, regio- and

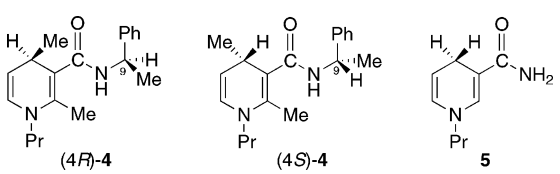

Chart 1

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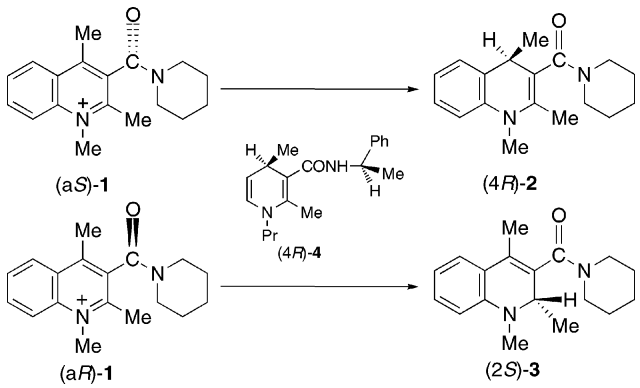


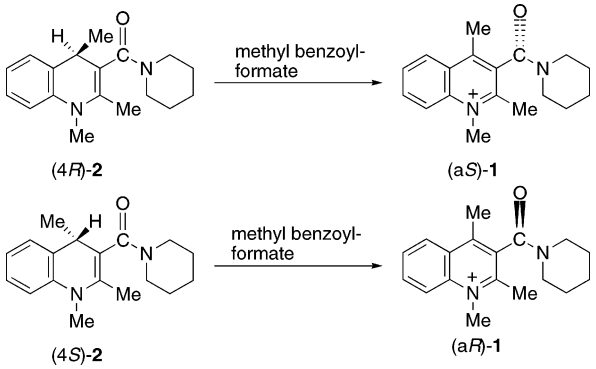
Scheme 1

enantioselectivity of the reduction with several reducing agents, and molecular arrangements at the transition states of the reactions are discussed.

Results

Optical resolution and CD spectra of 3

The optical resolution and determination of the absolute configuration of each enantiomer of **1** and **2** have already been reported.[10] The CD spectra of **1** (Fig. S1†) further support the assignment. HPLC equipped with a chiral column (Daicel CHIRALCEL OD) is effective to separate the enantiomers of **2**, and optically active **1** was obtained by the stereospecific oxidation of chiral **2** with methyl benzoylformate in the presence of magnesium perchlorate (Scheme 2).[10,33] Due to the carbonyl rotation, it was very difficult to isolate **1** in enantiomerically pure form; however, ee > 98% was confirmed by HPLC analysis for both enantiomers of **1** used for the reaction in this paper.



Scheme 2

The enantiomers of **3** had remained unresolved under any HPLC conditions in which (4*R*)-**2** and (4*S*)-**2** are completely resolved.[10] However, the recently developed HPLC column, Daicel CHIRALPAK IA, made it possible to separate the enantiomers of **3** as well as those of **2** (eluent: hexane–iPrOH–diethylamine = 95 : 5 : 0.1). Fig. 1 shows the mirror-image CD spectra of resolved enantiomers of **3**, demonstrating the validity of the resolution and from which the absolute configuration has been determined as described below.

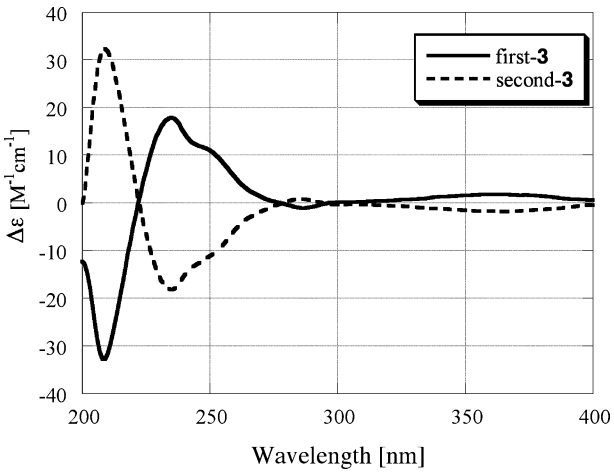
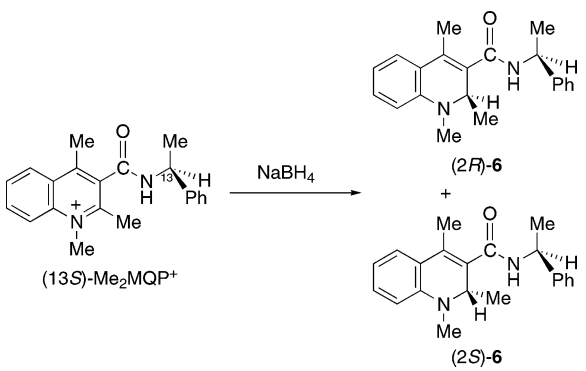


Fig. 1 CD spectra of resolved enantiomers of **3** in EtOH. The solid line represents the fast-eluting enantiomer (first-**3**) in HPLC and the broken line represents the slow-eluting enantiomer (second-**3**).

X-Ray crystallography of (2*R*,13*S*)- and (2*S*,13*S*)-1,2,4-trimethyl-3-(*N*-α-methylbenzylcarbamoyl)-1,2-dihydroquinoline ((2*R*)- and (2*S*)-1,2-Me_2MQPH (6)). Since the CD spectra for chiral 2-methyl-1,2-dihydroquinolines or corresponding pyridine derivatives structurally related to **3** with known configurations are unavailable, it is necessary to prepare a single diastereomer of a 1,2-dihydroquinoline derivative with an authentic chiral auxiliary group. Considering the crystallizing ability, optical properties and synthetic availability of the molecule, (2*R*,13*S*)- and (2*S*,13*S*)-1,2,4-trimethyl-3-(*N*-α-methylbenzylcarbamoyl)-1,2-dihydroquinoline ((2*R*)- and (2*S*)-1,2-Me_2MQPH (**6**)) were chosen as target molecules. Sodium borohydride reduction of (13*S*)-1,2,4-trimethyl-3-(*N*-α-methylbenzylcarbamoyl)quinolinium ion ((13*S*)-Me_2MQP^+)[31] is expected to afford a diastereomeric mixture of (2*R*)- and (2*S*)-**6** (Scheme 3).



Scheme 3

Upon conducting the reaction depicted in Scheme 3, one of the two diastereomers of **6** precipitated from the reaction solution. The single crystals of this compound suitable for X-ray crystallography were obtained by recrystallization from methanol. The remaining reaction solution containing both diastereomers of **6** was subjected to HPLC separation to obtain the other isomer. Single crystals suitable for X-ray crystallography for the second diastereomer were also obtained from methanol.

Fig. 2 and 3 show the ORTEP drawing of the former (precipitated from reaction solution) isomer and the separated other isomer of **6**, respectively. Since both compounds have no heavy atoms, these X-ray analyses only establish the relative stereochemistry. For the auxiliary (*S*)-phenylethylamine group, the absolute configuration of the former isomer was determined to be the 2*R* isomer and the latter was determined to be the 2*S* isomer. As found in the previous report for 2-methyl-1,2-dihydropyridine,[34] the methyl substituent on the C2 position (C11 in Fig. 2 and 3) is oriented axially to the 1,2-dihydroquinoline ring to avoid steric hindrance from the alkyl substituents on the neighboring C3 (C2 in Fig. 2 and 3) and ring nitrogen atoms. It is interesting to note that in these crystal structures, the carbonyl orientation is perpendicular to the dihydroquinoline ring and points in the same direction as the hydrogen atom from C2 (C1 in Fig. 2 and 3).

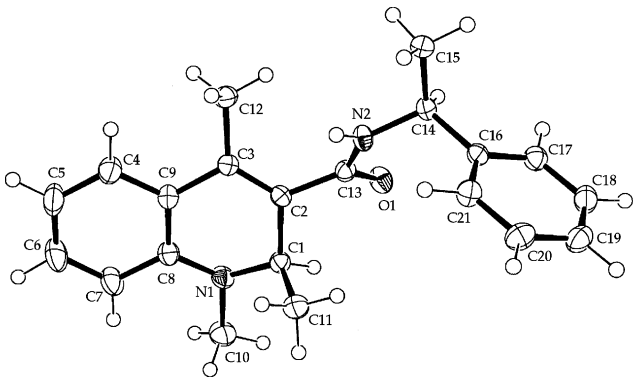


Fig. 2 ORTEP representation (50% probability) of molecular structure of (2*R*)-**6**.

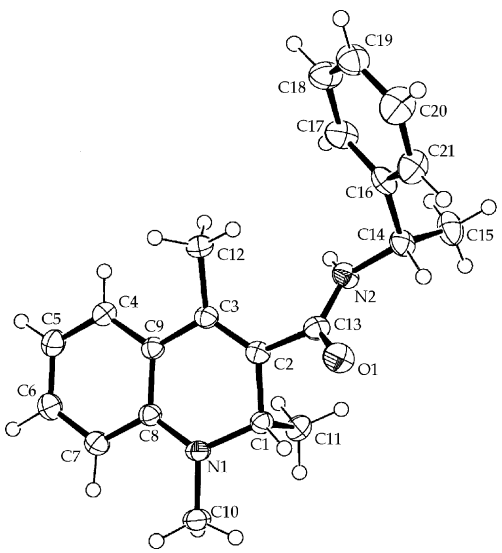


Fig. 3 ORTEP representation (50% probability) of molecular structure of (2*S*)-**6**.

CD spectra of 6 and 1,2,4-trimethyl-3-(*N*-methyl-*N*-α-methylbenzylcarbamoyl)-1,2-dihydroquinoline (1,2-Me_3MQPH (7)): determination of absolute configuration of 3. The CD spectra of (2*R*)- and (2*S*)-**6** shown in Fig. 4 did not exhibit distinct mirror images. This is because (2*R*)-**6** and (2*S*)-**6** are not enantiomers

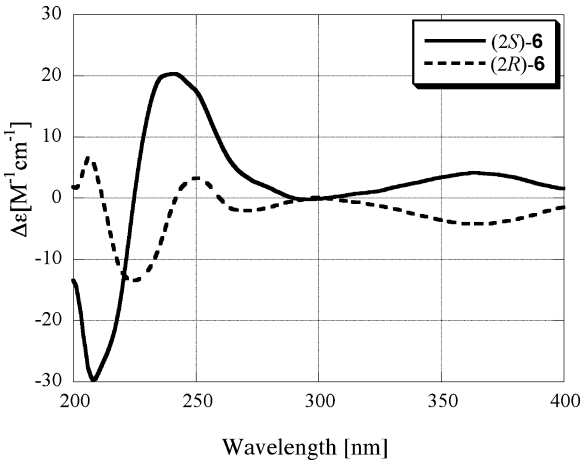


Fig. 4 CD spectra of (2*S*)-**6** (solid line) and (2*R*)-**6** (broken line) in EtOH.

but diastereomers of each other. However, compounds (2*R*)- and (2*S*)-**7** (Chart 2), which were obtained by methylation of the amide nitrogen atom in the side chain of (2*R*)- and (2*S*)-**6**, exhibited nearly mirror image CD spectra with closely related Cotton effect patterns with compound **3** (Fig. 5). Thus, the absolute configuration of both enantiomers of **3** was unambiguously determined as follows: the first-eluting isomer with a positive Cotton effect at 235 nm is (2*S*)-**3**, and the second peak on the HPLC with a negative Cotton effect at 235 nm corresponds to (2*R*)-**3**.

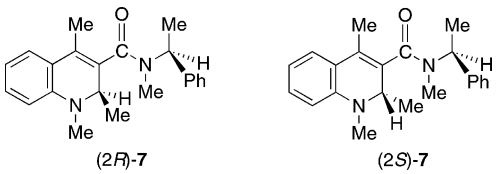


Chart 2

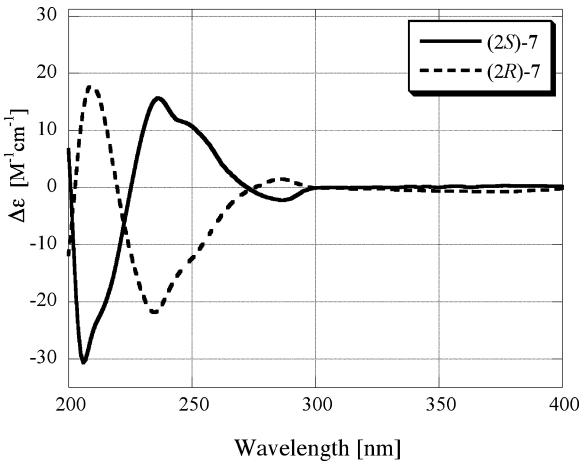


Fig. 5 CD spectra of (2*S*)-**7** (solid line) and (2*R*)-**7** (broken line) in EtOH.

Reduction of 1 with inorganic reducing agents

Reduction of optically active **1** was performed by sodium hydrosulfite in aqueous 0.5 M Na_2CO_3. Since a considerable extent

Table 1 Regio- and enantioselectivity in 1,2-/1,4-reduction of **1** with several reducing agents

Reductant	Configuration of **1**[a]	Product ratio[b]			Yield (%)
		2–**3**	4*R*–4*S* in **2**	2*R*–2*S* in **3**	
$Na_2S_2O_4$	a*R*	95 : 5 (0.5)	39 : 61 (5.8)	39 : 61 (7.1)	1–17[c]
	a*S*	95 : 5 (1.0)	52 : 48 (1.4)	50 : 50 (1.4)	9–40[c]
$NaBH_4$	a*R*	0 : 100	—	81 : 19 (2.4)	87
	a*S*	0 : 100	—	21 : 79 (0.7)	77
(4*R*)-**4**	a*R*	30 : 70 (1.6)	58 : 42 (2.7)	0.5 : 99.5 (0.25)	72
	a*S*	83 : 17 (2.5)	96 : 4 (1.5)	7 : 93 (1.2)	82
(4*S*)-**4**	a*R*	82 : 18 (1.2)	4 : 96 (0.7)	89 : 11 (1.3)	83
	a*S*	33 : 67 (2.8)	38 : 62 (4.0)	99 : 1 (0.3)	79
5	a*R*	88 : 12 (1.2)	7 : 93 (1.9)	2 : 98 (1.6)	7–41[c]
	a*S*	88 : 12 (0.7)	92 : 8 (2.0)	96 : 4 (3.3)	9–53[c]

[a] Enantiomeric purity of the starting materials was >98%. [b] Errors in parentheses are one standard deviations derived from at least three independent experiments. [c] Conversions determined by HPLC.

of racemization of **1** occurred during the reaction under the present conditions, we decided to stop the reaction at 15 min, at which point the racemization of **1** was found to be less than 10%. Table 1 shows the distribution of the reduction products and yield/conversion of the reaction. Although the conversion of the reaction varied from 1% to 40%, product ratios were fairly consistent. Overall, sodium hydrosulfite promotes 1,4-reduction predominantly with low enantioselectivity.

Reduction of optically active **1** with sodium borohydride was examined in methanol at 0 °C. The reaction was completed in two hours and the racemization of **1** under these reaction conditions was negligible. Table 1 shows that sodium borohydride reacts with **1** in a manner of 1,2-reduction with *anti–syn* = 4 : 1 enantioselectivity.

Reduction of 1 with NADH model compounds

The chiral NADH model compound (Me_2PNPH, **4**, Chart 1)[35] with a restricted reaction face exhibited characteristic regio- and enantioselectivity in the reduction of optically active **1** depending on the configuration of both reactant and reducing agent. When (a*S*)-**1** was reduced by (4*R*)-**4**, the main product was (4*R*)-**2**, which is the compound where the hydride was introduced at the C4 position from the carbonyl oxygen face direction. On the other hand, in the reaction of (a*R*)-**1** with (4*R*)-**4**, the major product was (2*S*)-**3**, which is the compound where the hydride was introduced at the C2 position from the carbonyl oxygen face direction (Scheme 1). Preliminary results from this reaction have been reported earlier with the exception of the enantioselectivity in **3**.[32] In this paper, we re-examined the whole set of the reactions and completed the evaluation of the selectivity as shown in Table 1.

1-Propyl-1,4-dihydronicotinamide (PNAH (**5**), Chart 1) was also employed as an NADH model compound without restriction on the reaction face of the reducing agent. This compound provides experimental evidence for the intrinsic preference of 1,2-/1,4-reduction in the reactions between NADH and NAD model compounds. Since this reaction has been found to be very slow, the reaction was stopped at 1 h to evaluate the initial selectivity of the reaction. The product ratio shown in Table 1 demonstrates that this reaction proceeds in the preference of 1,4-reduction with quite high enantioselectivity for both 1,2- and 1,4-reductions. It should be noted that the product selectivity in the reaction with **4** was not changed when the reaction was stopped at 1 h.

Discussion

The 1,2-dihydroquinolines **3**, **6** and **7** are stable compounds and the isomerization of 1,2-dihydroquinoline into 1,4-dihydroquinoline is clearly excluded in the present system in contrast to the previous report.[29] This is probably due to the axial methyl orientation of the C2 carbon as shown in the elucidated structures from X-ray crystallography,[34] forcing the C2 hydrogen into a less reactive equatorial position. Scrambling reactions between NAD and NADH model compounds[36] were also found to be negligible in the present system. Incubation of optically active **2** or **3** in the presence of racemic **1** promoted neither racemization nor 1,2-/1,4-isomerization under the present experimental conditions. Thus, the product distribution shown in Table 1 unambiguously reflects the selectivity of the reaction.

In the reaction of **1** with reducing agents, a net "hydride" reacts in four possible ways shown in Fig. 6, and the population of each transition state reflects the product distribution ((4*R*)-**2**, (4*S*)-**2**, (2*R*)-**3** and (2*S*)-**3**). In Table 1, the product ratio of **2**–**3** reveals the regioselectivity of the 1,4-/1,2-reduction, and the enantiomer ratio in **2** and **3** reflects the face selectivity of the 1,4- and 1,2-reduction, respectively.

In general, hydride reagents such as sodium borohydride afford 1,2- or 1,6-isomers, while sodium hydrosulfite or NADH model compounds give 1,4-isomers predominantly,[27,28] although some exceptions have been reported.[6] Since the 1,6-reduction is unfavorable in the present system because of the disruption of the aromaticity of the phenyl ring, sodium borohydride exclusively afforded 1,2-dihydroquinoline **3**. The face selectivity of this reaction was *anti* with respect to the carbonyl oxygen direction. The *anti* selectivity of $NaBH_4$ was reported previously[6] and understood by an electrostatic repulsion between carbonyl oxygen and the negatively-charged reducing agent in the *syn*-face attack.

Sodium hydrosulfite afforded 1,4-dihydroquinolines in a low *syn* preference in the present reaction, which is in good agreement with previous results for NAD model compounds with fixed carbonyl rotations.[8,25,31] Since this reaction proceeds with partial (<10%) racemization of the starting material as described above, the actual

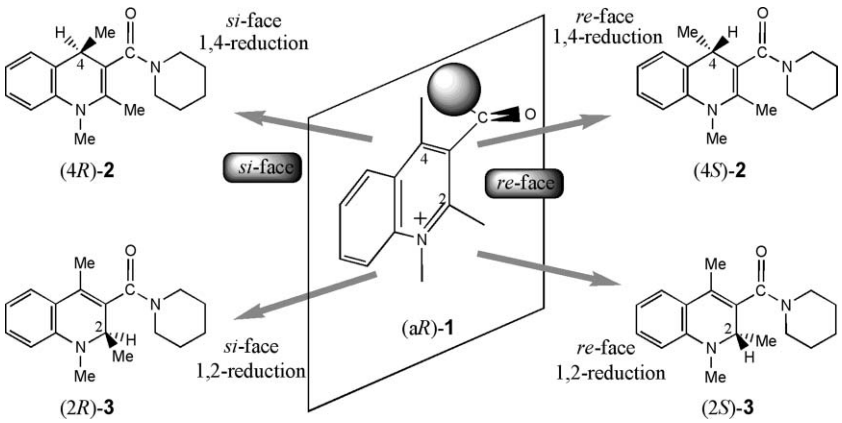


Fig. 6 Four possible methods of (a*R*)-**1** leading to different products.

stereoselectivity in this reaction may be slightly higher than the values reported in Table 1.

In the reaction of (a*S*)-**1** with (4*R*)-**4**, 1,4-reduction occurs predominantly, affording (4*R*)-**2** in a 96 : 4 enantiomer ratio. On the other hand, 1,2-reduction is the main reaction giving (2*S*)-**3** in a 99.5 : 0.5 enantiomer ratio when (a*R*)-**1** is employed with the same reducing agent. The carbonyl dipole controls the regio- and stereoselectivity of the reaction (Scheme 1). It should be noted that the phenylethylamine auxiliary in the side chain of **4** exhibits a very small effect to determine the reaction face of the substrate.[35]

As discussed in previous papers,[22,24,25,32] the following three factors in the molecular orientations in the transition state should be considered:

(i) *syn–anti* orientation of the carbonyl group of **1** with respect to the reaction face,

(ii) *cis–trans* arrangement between the carbamoyl side chains of **1** and **4**,

(iii) parallel–antiparallel (some papers used *endo–exo* notations) arrangement with respect to the ring nitrogen orientation between **1** and **4** in the π–π stacking interaction.

These parameters differentiate eight ($2^3 = 8$) possible molecular arrangements, from which half of such arrangements are excluded using **4** as a reducing agent with a restricted reaction face blocked by the 4-methyl group. For instance, the possible molecular arrangements in the reaction of (a*R*)-**1** with (4*R*)-**4** are (i) *anti–trans*–parallel, (ii) *syn–cis*–parallel, (iii) *anti–cis*–antiparallel and (iv) *syn–trans*–antiparallel (Fig. 7). Assuming that the parallel arrangement in the transition state promotes 1,4-reduction and the antiparallel arrangement leads to 1,2-reduction, the four molecular arrangements (i)–(iv) correspond to the transition states leading to (4*R*)-**2**, (4*S*)-**2**, (2*R*)-**3** and (2*S*)-**3**, respectively. The ratio in the products reveals the preferences of each parameter in this reaction in the following manner: *syn–anti* = 82 : 18, *trans–cis* = 86 : 14 and parallel–antiparallel = 30 : 70, indicating the strong dominance of the *syn–trans* arrangement with moderate antiparallel preference.

The reaction of (a*S*)-**1** with (4*R*)-**4** highlights the other set of arrangements from eight possible transition states (Fig. 8). In this case, the preferences of each parameter estimated from the product ratio of the reaction are: *syn–anti* = 81 : 19; *trans–cis* = 96 : 4 and parallel–antiparallel = 83 : 17. Here again, the strong *syn–trans* arrangement is emphasized. The parallel–antiparallel preference is inverted from that found in the reaction of (a*R*)-**1** with (4*R*)-**4**. As discussed previously,[32] the *syn–trans*–parallel arrangement is considered as the most stable transition state in the viewpoints of both theoretical[37–40] and experimental[5,6,8,10,41] investigations. The antiparallel preference found in the former reaction results from the lack of this most stable arrangement in the transition state. Since the *syn* and *trans* arrangements have strong preferences over *anti* and *cis* arrangements, respectively, the parallel preference was sacrificed in the former reaction. In order to confirm the parallel preference over antiparallel arrangement in the transition state in a single experiment, the reaction of **1** with an achiral NADH model compound **5** was investigated.

In the reaction of (a*R*)-**1** with **5**, all the eight possible arrangements in the transition state can be adopted (Fig. 9). Concomitantly, the preference of one parameter, *i.e.*, the *cis–trans* arrangement, cannot be estimated from the product ratio. The main product of this reaction was (4*S*)-**2**, indicating *syn*–parallel preference. The quantitative measures of the preference for these two parameters other than *cis–trans* arrangements were *syn–anti* = 94 : 6 and parallel–antiparallel = 89 : 11, showing the evident parallel preference.

Interestingly, in the reaction of (a*R*)-**1** with (4*R*)-**4**, the enantioselectivity in **2** is very poor compared to the other face selectivities (Table 1). The molecular arrangement leading to these compounds is *anti–trans*–parallel for the (4*R*)-**2** and *syn–cis*–parallel for the (4*S*)-**2** (Fig. 7). The observed small preference for the (4*R*)-product indicates that *trans* preference for the arrangement of two carboxamide groups would be the dominant factor over the *syn* orientation of the carbonyl group in **1**. As a consequence, the relative order of importance between these three parameters should be: *trans–cis* arrangement for the carboxamide groups > *syn–anti* orientation of carbonyl oxygen > parallel–antiparallel arrangements of heteroaromatic rings.

Conclusion

The absolute configuration assignment for separated isomers of 1,2-dihydroquinoline **3** has been achieved. In the reduction of NAD model compound **1** with NADH model compounds **4** and **5**, the *syn–trans*–parallel arrangement in the transition state of the reaction was proven to be the most stable in energy. This clear-cut conclusion was obtained by the combined use of

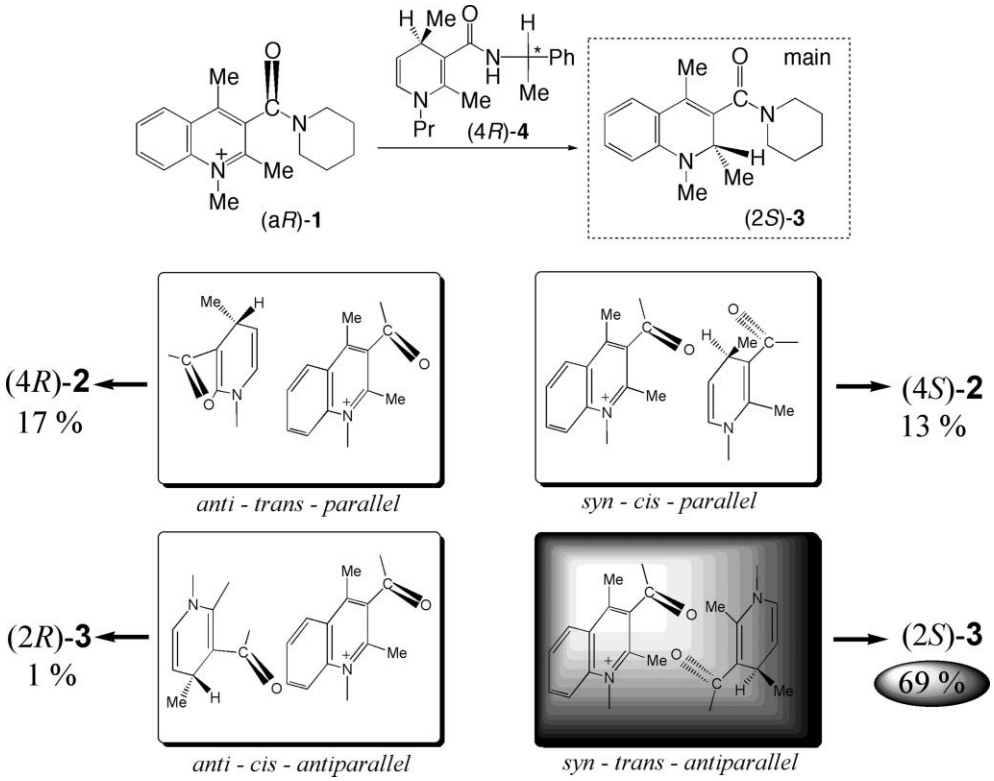


Fig. 7 Molecular arrangements in the transition state for the reaction of (a*R*)-**1** with (4*R*)-**4**.

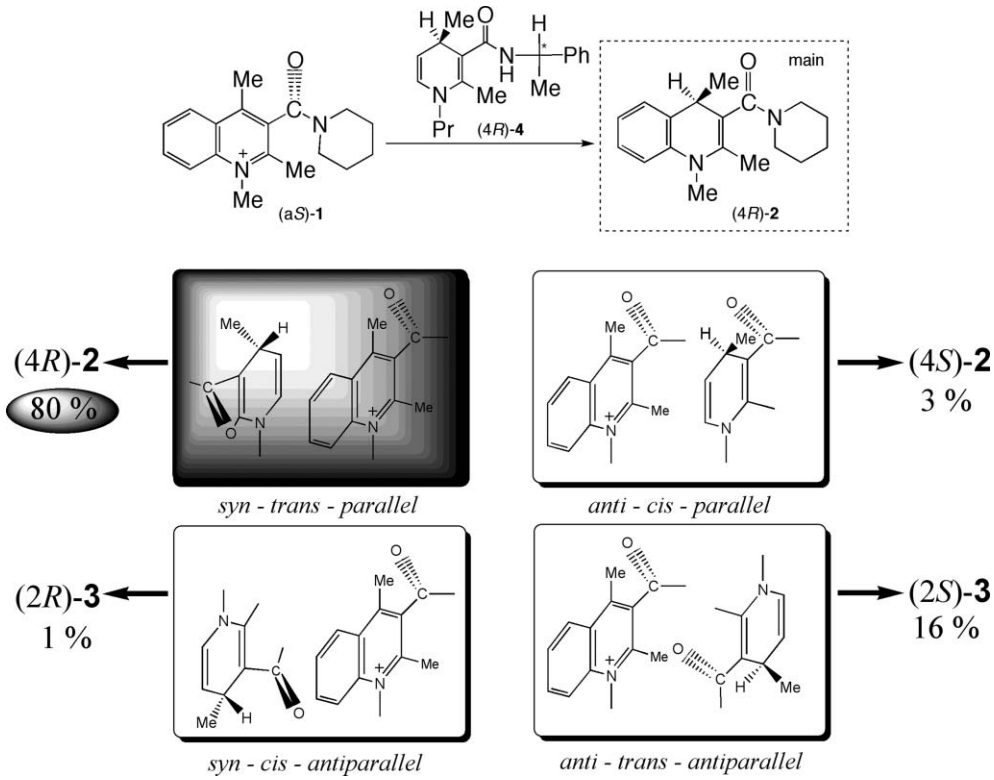


Fig. 8 Molecular arrangements in the transition state for the reaction of (a*S*)-**1** with (4*R*)-**4**.

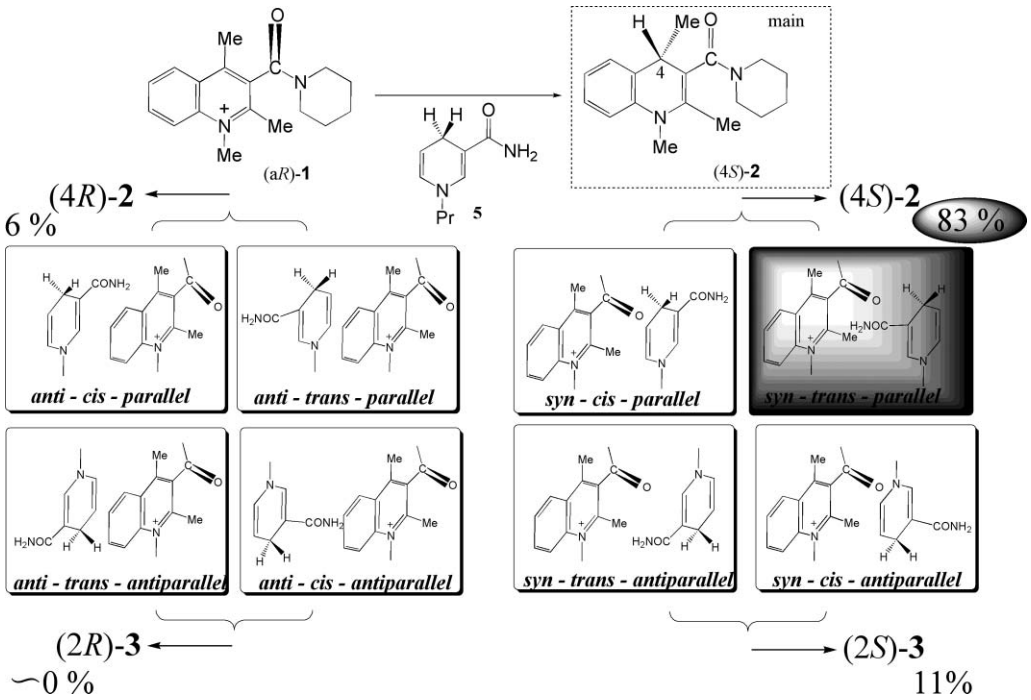


Fig. 9 Molecular arrangements in the transition state for the reaction of (a*R*)-**1** with **5**.

reaction-face-restricted and unrestricted NADH model compounds. Although the assumption that the 1,2-reduction proceeds *via* antiparallel arrangement remains to be proven, the importance of the entropy contribution of the NADH model compounds may support this idea.[11,42,43] The present results demonstrate the important contribution of the carboxamide group of the NAD model compounds for controlling the entire reaction pathway and provide valuable information for future organic catalyst design for highly stereoselective reactions.

Experimental

(2*R*,13*S*)- And (2*S*,13*S*)-1,2,4-trimethyl-3-(*N*-α-methylbenzylcarbamoyl)-1,2-dihydroquinoline ((2*R*)- and (2*S*)-1,2-Me_2MQPH (6))

To an argon-filled flask containing (13*S*)-1,2,4-trimethyl-3-(*N*-α-methylbenzylcarbamoyl)quinolinium iodide[31] ((13*S*)-Me_2MQP^+ I^-) (0.53 g, 1.19 mmol) and sodium borohydride (0.11 g, 2.85 mmol), methanol (23 mL) was injected and the reaction mixture was stirred for two hours at room temperature in the dark. The resulting yellow precipitate was separated by filtration to give diastereomerically pure (2*R*)-**6** (70 mg, 0.22 mmol) in 18% yield. The other diastereomer was obtained from the filtrate by HPLC purification (column: Daicel CHIRALPAK IA 0.46ϕ × 25 cm; eluent: hexane–iPrOH–diethylamine = 95 : 5 : 0.1) to give 13 mg of (2*S*)-**6** (from 20 mg of diastereomer mixture containing (2*R*)-**6**–(2*S*)-**6** = 25 : 75). Both compounds were recrystallized from methanol to afford single crystals suitable for X-ray crystallography.

(2*R*)-6. ^{1}H NMR ($CDCl_3$) δ 1.05 (d, J = 8.4 Hz, 3H), 1.58 (d, J = 9.6 Hz, 3H), 2.11 (s, 3H), 2.89 (s, 3H), 4.20 (q, J = 8.4 Hz, 1H), 5.26 (dq, J = 9.6, 10.4 Hz, 1H), 5.95 (d, J = 10.4 Hz, 1H), 6.51 (d, J = 10.8 Hz, 1H), 6.70 (t, J = 9.2 Hz, 1H), 7.14–7.36 (m, 7H).

^{13}C NMR ($CDCl_3$) δ 15.5, 21.6, 36.0, 49.0, 56.7, 111.4, 111.6, 116.8, 123.2, 124.8, 126.1, 127.4, 128.7, 129.7, 131.2, 143.0, 144.5, 168.2.

Anal. calcd for $C_{21}H_{24}N_2O$: H, 7.55; C, 78.72; N, 8.74. Found: H, 7.62; C, 78.44; N, 8.70%.

Crystal data for (2*R*)-**6**: $C_{21}H_{24}N_2O$, monoclinic, space group $P2_1$ with a = 12.3636(10) Å, b = 5.2242(4) Å, c = 13.3704(11) Å, β = 97.482(2)°, V = 856.24(12) Å^3, Z = 2, R = 0.051, R_w = 0.102.‡

(2*S*)-6. ^{1}H NMR ($CDCl_3$) δ 1.10 (d, J = 6.6 Hz, 3H), 1.58 (d, J = 6.9 Hz, 3H), 2.12 (s, 3H), 2.89 (s, 3H), 4.16 (q, J = 6.0 Hz, 1H), 5.27 (m, 1H), 5.88 (d, J = 7.5 Hz, 1H), 6.52 (d, J = 8.1 Hz, 1H), 6.70 (t, J = 7.5 Hz, 1H), 7.14–7.38 (m, 7H).

^{13}C NMR ($CDCl_3$) δ 15.5, 15.7, 21.6, 36.1, 49.0, 56.8, 111.5, 116.8, 123.2, 124.8, 126.3, 127.6, 128.8, 129.8, 131.1, 142.8, 144.6, 168.2.

Anal. calcd for $C_{21}H_{24}N_2O$: H, 7.55; C, 78.72; N, 8.74. Found : H, 7.37; C, 78.64; N, 8.74%.

Crystal data for (2*S*)-**6**: $C_{21}H_{24}N_2O$, orthorhombic, space group $P2_12_12_1$ with a = 5.3478(10) Å, b = 13.519(3) Å, c = 23.990(5) Å, V = 1734.4(6) Å^3, Z = 4, R = 0.039, R_w = 0.115.‡

(2*R*,13*S*)-1,2,4-Trimethyl-3-(*N*-methyl-*N*-α-methylbenzylcarbamoyl)-1,2-dihydroquinoline ((2*R*)-1,2-Me_3MQPH ((2*R*)-7))

To an argon-filled flask containing (2*R*)-**6** (30 mg, 0.094 mmol) and patassium *tert*-butoxide (69 mg, 0.61 mmol), dry THF (4.7 mL) was injected. After stirring for 20 min, methyl iodide (0.08 mL, 1.3 mmol) was added and the reaction mixture was stirred for two days at room temperature in the dark. After the precipitate

was removed by filtration, the filtrate was evaporated, dissolved in dichloromethane, washed with water, dried over Na_2SO_4, and evaporated to give 12.2 mg of crude product. This material was purified by HPLC (Daicel CHIRALCEL OD 2.0ϕ × 25 cm; eluent = hexane–iPrOH–diethylamine = 95 : 5 : 0.1) to give 7.5 mg (0.022 mmol, 24% yield) of pure (2*R*)-**7** as a white powder.

(2*R*)-7. ^{1}H NMR ($CDCl_3$) δ 1.01 (br.d, J = 6.0 Hz), 1.16 (d, J = 6.6 Hz), 1.24 (br.), 1.57–1.67 (m, 3H), 1.93 (s), 2.00 (s), 2.08 (s), 2.70 (s), 2.73 (s), 2.78 (s), 2.88 (s), 2.91, (s), 3.79–3.86 (m), 4.46 (br.), 5.56 (q, J = 6.9 Hz), 6.16 (br.q), 6.26 (br.q), 6.52 (m), 6.74 (m), 7.15–7.39 (m).

^{13}C NMR ($CDCl_3$) δ 15.0, 15.3, 15.8, 16.1, 18.6, 27.2, 29.7, 36.0, 49.6, 49.9, 56.7, 57.3, 111.0, 111.5, 116.3, 116.9, 123.4, 124.2, 124.3, 126.4, 127.4, 128.5, 128.7, 129.2, 130.2, 140.8, 144.2, 170.9.

ESI-MS: m/z 357.19353 (M + Na^+. $C_{22}H_{26}N_2ONa$ requires 357.19428).

(2*S*,13*S*)-1,2,4-Trimethyl-3-(*N*-methyl-*N*-α-methylbenzylcarbamoyl)-1,2-dihydroquinoline ((2*S*)-1,2-Me_3MQPH ((2*S*)-7))

Starting from a diastereomeric mixture of **6** (60 mg (0.19 mmol), (2*R*)-**6**–(2*S*)-**6** = 20 : 80), a similar procedure to that above afforded 54.3 mg of crude product. Recrystallization of this material from methanol afforded 17 mg (0.051 mmol) of diastereomerically pure (2*S*)-**7** (34% yield based on (2*S*)-**6**).

(2*S*)-7. ^{1}H NMR ($CDCl_3$) δ 1.08 (br.), 1.19 (d, J = 6.0 Hz), 1.25 (br.d), 1.57 (s), 1.59 (s), 1.69 (s), 1.85 (s), 2.01 (s), 2.07 (s), 2.69 (br.), 2.77 (br.), 2.86 (s), 2.90 (s), 2.94 (s), 3.80 (br.q), 3.96 (q, J = 6.3 Hz), 4.45 (br.), 5.63 (q, J = 6.9 Hz), 6.14 (m), 6.54 (m), 6.73 (m), 7.20–7.38 (m).

^{13}C NMR ($CDCl_3$) δ 15.0, 16.1, 17.6, 17.7, 26.9, 29.9, 36.1, 36.4, 36.5, 49.4, 50.5, 56.3, 56.4, 57.3, 57.6,111.3, 111.5, 111.6, 116.8, 116.9, 123.5, 124.2, 124.4, 126.0, 126.8, 127.3, 128.5, 129.3, 130.0, 130.4, 139.8, 140.3, 144.0, 144.2, 170.2, 170.8.

ESI-MS: m/z 357.19287 (M + Na^+. $C_{22}H_{26}N_2ONa$ requires 357.19428).

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