Catalytic Enantioselective Construction of Decalin Derivatives by Dynamic Kinetic Desymmetrization of C2-Symmetric Derivatives through Aldol–Aldol Annulation

Catalytic Enantioselective Construction of Decalin Derivatives by Dynamic Kinetic Desymmetrization of C2-Symmetric Derivatives through Aldol-Aldol Annulation

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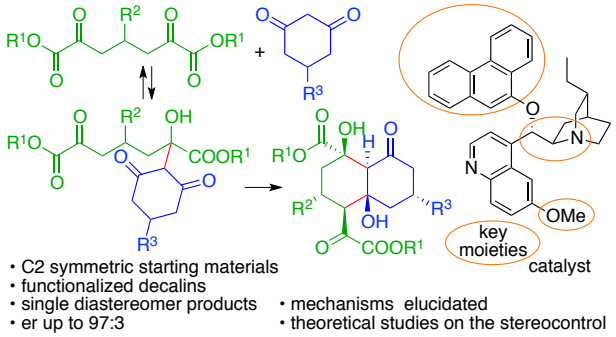
Supporting Information Placeholder

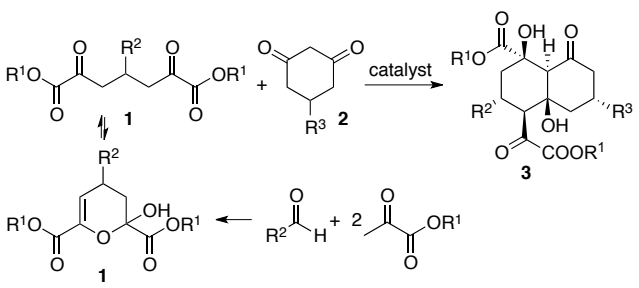


ABSTRACT: We have developed and investigated a catalytic desymmetrization reaction strategy that affords functionalized decalin derivatives with high enantioselectivities from C2-symmetric derivatives through aldol-aldol annulation. We identified the structural moieties of the catalyst necessary for the formation of the decalin derivative with high enantioselectivity. We elucidated the mechanisms of the catalyzed reactions: The first aldol reaction step was reversible and that the second aldol step was rate limiting and stereochemistry determining and was enantioselective. Using theoretical calculations guided by the experimental results, we identified the interactions between the catalyst and the transition state that led to the major enantiomer. The information obtained in this study will be useful for the development of catalysts and chemical transformations.

Introduction

Strategies and methods for the synthesis of structured ring systems bearing functional groups in highly enantiomerically enriched forms are of interest in synthetic chemistry and drug discovery efforts.[1-7] The decalin ring system is such a structured ring system that is often found in bioactive natural products and clinically used drugs.[1-8] Interest in catalytic enantioselective reactions that construct decalin derivatives has increased recently.[2a,3,6a,7b-g] To provide a new strategy to synthesize highly enantiomerically enriched, functionalized decalins, we recently reported diastereo- and enantioselective formal (4+2) cycloaddition reactions or aldol-aldol annulation reactions of C2-symmetric pyruvate derivatives **1**[8] with cyclohexane-1,3-diones **2** that afford functionalized decalin derivatives **3** (Scheme 1).[9] In the reactions, highly enantiomerically enriched decalins bearing five to six stereogenic centers, including two tetrasubstituted carbon centers, were constructed in a single transformation under mild conditions with the use of quinidine-derived dimer-type catalysts such as $(DHQD)_2AQN$.[9] Understanding the mechanisms of the reaction, including the mechanisms of the catalysis and the stereocontrol provided by the catalyst, will facilitate further development of reactions and catalysts to expand the strategies to access to structured ring systems and to synthesize complex, functionalized molecules. To address to this need, here we investigated the structural moieties of the catalyst necessary for the catalysis to afford the decalin products with high enantioselectivities from **1** and **2**, performed the reactions catalyzed by the truncated catalyst, analyzed the mechanisms of the catalyzed reactions, and determined the interactions provided by the catalyst to lead to the decalin products.

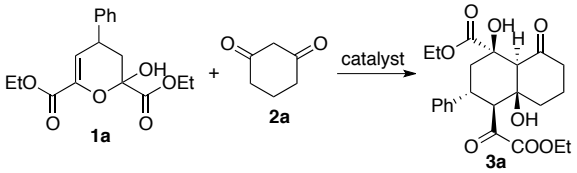
Scheme 1. Aldol-aldol annulation reactions to afford functionalized decalins



Results and Discussion

Catalyst structures. The catalyst that we previously identified, which catalyzed the reaction of **1** with **2** to afford decalin derivative **3**, was $(DHQD)_2AQN$[9] (Chart 1). To identify the structural moieties of $(DHQD)_2AQN$ that are required for the catalysis to form **3** with high enantioselectivity, we evaluated a series of truncated derivatives of $(DHQD)_2AQN$ and related molecules in catalysis of the reaction of **1a** with **2a** to afford **3a** (Table 1 and Chart 1).

Table 1. Evaluations of catalysts in the reaction of 1a with 2a to afford 3a[a]



entry	catalyst (equiv)	time (h)	yield (%)	er
1	$(DHQD)_2AQN$ (0.15)	60	70	94:6
2[b,c]	$(DHQD)_2AQN$ (0.15)	60	72	93:7
3	DHQD-PHN (0.3)	96	74	94:6
4[b]	DHQD-PHN (0.15)	168	72	94:6
5	DHQD-Nap (0.3)	120	72	91:9
6	DHQD-Ph (0.3)	120	56	86:14
7	DHQD-Bn (0.3)	120	75	74:26
8	DHQD-Me (0.3)	120	79	64:36
9	QD-PHN (0.3)	132	67	94:6
10[b]	DHQD-PHN-Nap (0.15)	144	46	91:9
11	DHCN-PHN (0.3)	120	70	75:25
12[b]	quinicoridine-PHN (0.15)	144	56	56:44
13	DHQ-PHN (0.3)	96	71	8:92

[a] Conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), and catalyst in toluene (0.5 mL)-NMP (0.06 mL) at rt (25 °C) except where noted. NMP = *N*-methyl-2-pyrrolidone. See Chart 1 for each catalyst. [b] Et_4NBr (0.05 mmol) was added. [c] Data reported in ref 9.

$(DHQD)_2AQN$ has two dihydroquinidine moieties. To determine whether the dimer-type structure is required, dihydroquinidine derivatives with various ether substituents were evaluated (Table 1, entries 3-8). DHQD-PHN, which has the 9-phenanthryl ether moiety, catalyzed the reaction of **1a** with **2a** to afford **3a** with essentially the same enantioselectivity (er 94:6) as $(DHQD)_2AQN$ (Table 1, entry 1 versus entry 3). The **3a** obtained from the DHQD-PHN-catalyzed reaction was a single diastereomer as the $(DHQD)_2AQN$-catalyzed reaction afforded the single diastereomer of **3a**. Because DHQD-PHN contains only one cinchona moiety or only one tertiary amine moiety, the loading amount used with this catalyst (0.3 equiv) was twice that used with $(DHQD)_2AQN$ (0.15 equiv). Under these catalyst loadings, the rate of the formation of **3a** in the reaction catalyzed by DHQD-PHN was similar to the rate in the same reaction catalyzed by $(DHQD)_2AQN$ (Table 1, entry 1 versus entry 3). Whereas addition of Et_4NBr favored the $(DHQD)_2AQN$-catalyzed reactions in some cases as we reported previously,[9] the addition of Et_4NBr to the DHQD-PHN-catalyzed reaction did not improve the rate of the formation of **3a** or the enantioselectivity (Table 1, entry 3 versus entry 4).

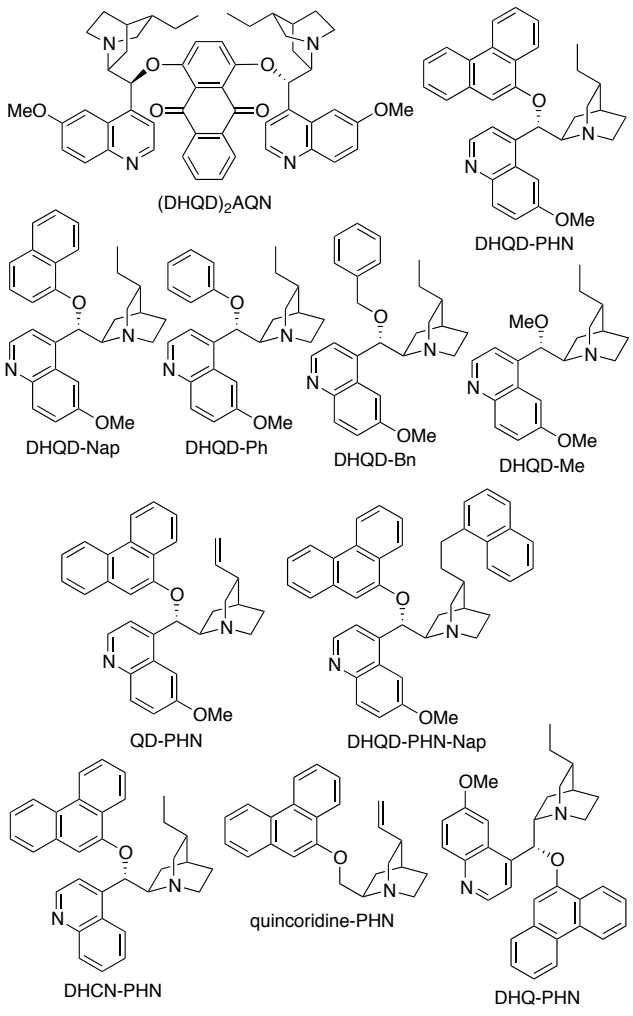
As the ether moiety became smaller (9-phenanthryl, 1-naphthyl, phenyl, benzyl, and methyl), the enantioselectivity decreased (Table 1, entries 3 and 5-8). Thus, the size of the ether moiety of the catalysts influenced the enantioselectivity. The aryl group of the ether moiety also influenced the reaction rate: The reaction catalyzed by DHQD-PHN was faster than the reaction catalyzed by DHQD-Ph (Table 1, entry 3 versus entry 6), although the difference was moderate.

The ethyl, vinyl, or naphthylethyl substituent on the quinuclidine moiety of the catalyst did not affect the enantioselectivity of the reaction (Table 1, entry 3 versus entry 9 and entry 4 versus entry 10).

The lack of methoxy group on the quinoline moiety of DHQD-PHN resulted in a notable reduction of the enantioselectivity (Table 1, entry 3 versus entry 11). The reaction catalyzed by quinicoridine-PHN, the derivative lacking the entire quinoline moiety, afforded **3a** with little enantioselectivity (Table 1, entry 12).

These results suggest that DHQD-PHN has all moieties required for the catalysis of the reactions of **1** and **2** that afford decalin derivatives with high enantioselectivities. Thus, the DHQD-PHN-catalyzed reactions were further investigated.

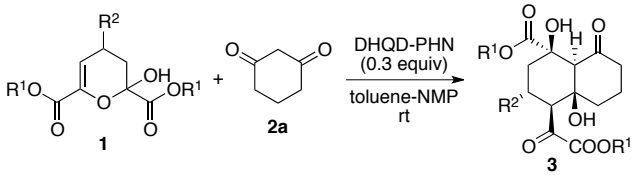
Chart 1



Substrate substituent effects in the reaction catalyzed by DHQD-PHN. To understand the reaction mechanisms and the interactions provided by the catalyst for the formation decalin ring system, substrate substituent effects were evaluated (Table 2). DHQD-PHN catalyzed the reactions of **1** bearing a substituent at the *o*-, *m*-, or *p*-position. Reactions of **1** with altered ester groups were also catalyzed efficiently by DHQD-PHN.

In the reactions of **1** bearing *p*-substituents on the phenyl group, products **3** of the reactions of **1** bearing electron-donating substituents were obtained with higher enantioselectivities (er 95:5~93:7 for methyl, methoxy, and phenyl substituents, Table 2, entries 1-3) than products **3** of the reactions of **1** bearing electron-withdrawing substituents (er 90:10 and 89:11 for cyano and nitro substituents, Table 2, entries 7 and 8). A moderate correlation between the Hammett σ_p substituent constants[10] and the enantioselectivity was observed (Supporting Information). The R^2 group is not directly connected to the C-C bond formation site of the reaction; therefore, the differences in the enantioselectivities could originate from the differences in the interactions between the substrates (or intermediates derived from the substrates) and the catalyst depending on the substituent during the catalysis.

Table 2. Substituent effects of substrates 1 in the formation of 3 in the presence of DHQD-PHN



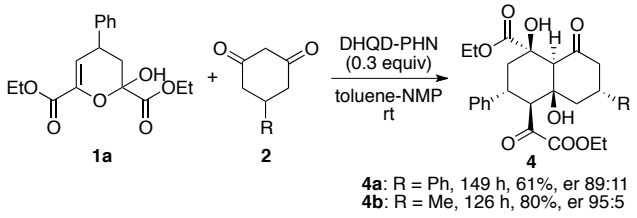
entry	R^1	R^2	**3**	time (h)	yield (%)	er
1[b]	Et	Ph	**3a**	96	74	94:6
2	Et	*p*-MeO-C_6H_4	**3b**	144	50	93:7
3	Et	*p*-Me-C_6H_4	**3c**	132	54	95:5
4	Et	*p*-Ph-C_6H_4	**3d**	90	71	93:7
5	Et	*p*-F-C_6H_4	**3e**	120	68	92:8
6	Et	*p*-Br-C_6H_4	**3f**	120	49	93:7
7	Et	*p*-CN-C_6H_4	**3g**	72	77	90:10
8	Et	*p*-NO_2-C_6H_4	**3h**	72	65	89:11
9	Et	*o*-MeO-C_6H_4	**3i**	120	69	97:3
10	Et	*m*-Br-C_6H_4	**3j**	120	74	94:6
11	Et	*o*-Br-C_6H_4	**3k**	120	66	97:3
12	Et	*o*-NO_2-C_6H_4	**3l**	114	62	93:7
13	Et	*m*-I-C_6H_4	**3m**	115	55	93:7
14	^{t}Bu	*m*-I-C_6H_4	**3n**	114	71	92:8
15[c]	Et	*p*-HC≡C-C_6H_4	**3o**	65	68	89:11
16	^{t}Bu	*p*-HC≡C-C_6H_4	**3p**	114	79	89:11
17[d]	^{t}Bu	*o*-Br-C_6H_4	**3q**	68	67	94:6

[a] Conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), and catalyst (0.03 mmol) in toluene-NMP at rt (25 °C). [b] Data from Table 1, entry 3. [c] Et_4NBr (0.5 equiv) was added. [d] A 0.05 mmol-scale reaction.

The enantioselectivities of products **3** obtained using the DHQD-PHN catalysis were similar to or slightly higher than those obtained by the $(DHQD)_2AQN$ catalysis. For example, products **3b** and **3c** were previously obtained with er 92:8 and er 93:7, respectively, under the $(DHQD)_2AQN$ catalysis,[9] and they were obtained with er 93:7 and er 95:5, respectively, under the DHQD-PHN catalysis (Table 2, entries 2 and 3). Product **3f** was obtained with er 90:10 in the presence of $(DHQD)_2AQN$[9] and with er 93:7 (Table 2, entry 6) in the presence of DHQD-PHN.

DHQD-PHN also catalyzed the reactions of **1** with **2** bearing phenyl or methyl substituent, and products **4a** and **4b** were obtained with high enantioselectivities (Scheme 2). Products **4a** and **4b** were obtained with higher enantioselectivities (er 89:11 and 95:5, respectively) in the presence of DHQD-PHN than in the presence of $(DHQD)_2AQN$ (er 80:20 and 94:6, respectively[9]).

Scheme 2. The reactions to afford 4

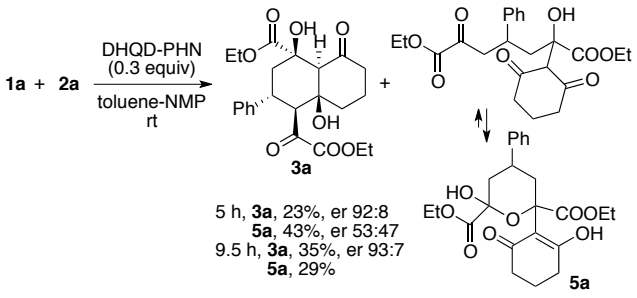


4a: R = Ph, 149 h, 61%, er 89:11
4b: R = Me, 126 h, 80%, er 95:5

The mechanisms of the catalysis by DHQD-PHN. To understand whether the product enantiomers were formed kinetically or by the thermodynamic control in the reactions catalyzed by DHQD-PHN, firstly the er of product **3a** in the reaction of **1a** with **2a** was analyzed at various time points. The er was within 94:6~95:5 from 24 h (the yield of **3a**, 57%) to 168 h (the yield of **3a**, 73%). Product **3a** had essentially the same er throughout the monitored time course of the reaction.

During the reaction of **1a** with **2a** to form **3a**, there was a lag between the consumption of **1a** and the formation of **3a**. The formation of aldol intermediate **5a** was observed before the formation of **3a** (Scheme 3). The isolated intermediate **5a** was racemic (er 53:47), whereas product **3a** was obtained with high enantioselectivity (er 92:8~93:7). These results suggest that the first aldol step to form **5a** was not enantioselective or proceeded with very little enantioselectivity and that the second aldol step to form **3a** from **5a** was highly enantioselective.

Scheme 3. Isolation of the intermediate



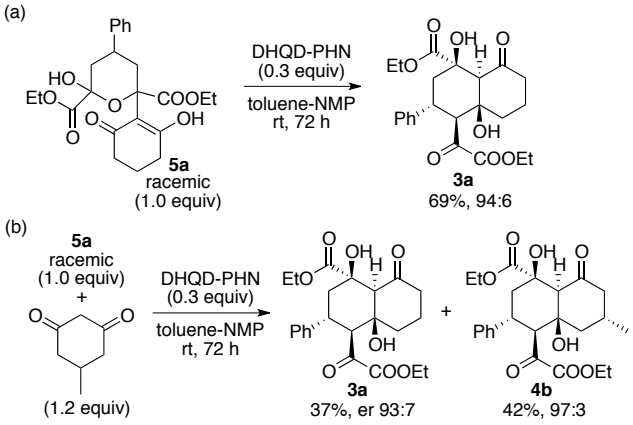
5 h, **3a**, 23%, er 92:8
5a, 43%, er 53:47
9.5 h, **3a**, 35%, er 93:7
5a, 29%

Next, the stability of product **3a** under the catalytic conditions used for the enantioselective formation of **3** was analyzed. When **3a** was treated in the presence of DHQD-PHN with or without **2a**, the er of **3a** was essentially retained, and the formation of **1a** and/or of **5a** was observed only trace (<2%) or was not detected. Further, when **3a** was treated in the presence of DHQD-PHN with 5-methylcyclohexane-1,3-dione, **3a** was

unchanged and no formation of cross product **4b** was detected. These results suggest that product **3a** was kinetically formed under the DHQD-PHN catalysis conditions and that the formed **3a** was stable.

Further, racemic intermediate **5a**, which was synthesized from **1a** and **2a** using Et_3N as catalyst, was treated with DHQD-PHN (Scheme 4a). The reaction afforded **3a** with er 94:6. When racemic **5a** was treated with DHQD-PHN in the presence of 5-methylcyclohexane-1,3-dione, product **3a** and cross product **4b** were both obtained with high enantioselectivities (Scheme 4b).

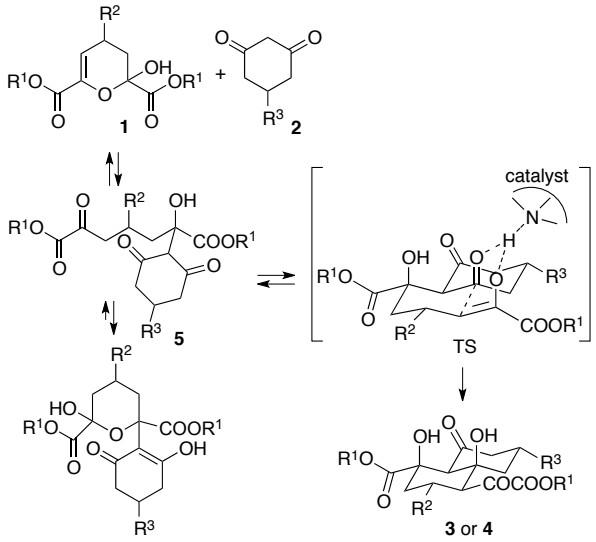
Scheme 4. Reactions of intermediate 5a



These results indicate that intermediate **5a** was reversibly formed during the reaction of **1a** with **2a** in the presence of DHQD-PHN and that only one enantiomer of one diastereomer of **5a** was selectively converted to **3a**. Thus, the formation of **3a** from **1a** with **2a** occurs through a dynamic kinetic desymmetrization. The results also suggest that, in the reaction of **1** with **2** to form **3** or **4** in the presence of DHQD-PHN, the formation of **3** or **4** from intermediate **5** is the rate-limiting step, and the stereochemistry of product **3** or **4** is kinetically determined at this step (Scheme 5). A chair-like conformation of the transition state would be used in the formation of the decalin ring in the presence of the catalyst, and this would lead to the formation of the single diastereomer decalin product. The tertiary amine group of catalyst DHQD-PHN is likely involved in the formation of the enolate of **5** by acting as a base, and the protonated form of the tertiary amine group is likely involved in the formation of the C-C bond in the second aldol reaction through the activation of the ketone carbonyl group.

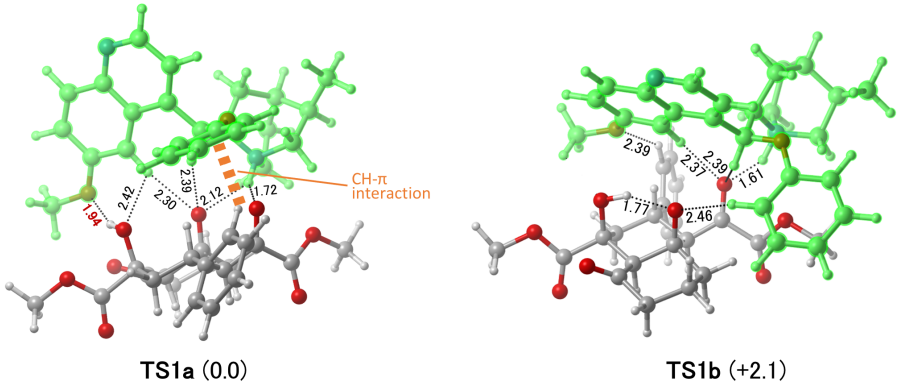
Whereas desymmetrization reactions have been used for the synthesis of decalin derivatives[6,7b-d] and related ring derivatives,[6b,7b,d,11] these reported reactions only desymmetrize a single substrate per transformation. Reactions involving desymmetrization of both starting materials are rare. In the DHQD-PHN-catalyzed reactions of **1** and **2**, both starting materials **1** and **2** are desymmetrized to afford **3** as single diastereomers with high enantioselectivities. Under the DHQD-PHN catalysis, the reversible formation of **5** from **1** and the selective use of one isomer of **5** among all possible enantiomers and diastereomers enable the double desymmetrization that leads to the diastereo- and enantioselective formation of the decalin derivatives.

Scheme 5. Pathway and transition state of the reactions catalyzed by DHQD-PHN



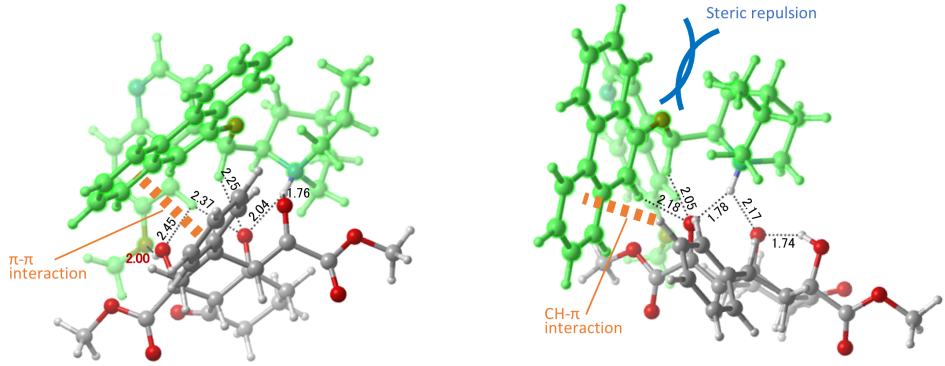
Theoretical studies on the mechanisms of the stereocontrol exerted by DHQD-PHN. To elucidate the mechanism of the stereocontrol provided by DHQD-PHN in the formation of **3** or **4** from **1** and **2**, density functional theory (DFT) calculations (M06-2x/6-31G*)[12] were conducted on the reaction of **5** to form **3**,[13] which is the rate- and stereo-determining step. Because the ether moiety of the DHQD-derived catalysts influenced the enantioselectivity of the reaction, the transition state models in the reaction catalyzed by DHQD-PHN and by DHQD-Ph were studied, and transition states **TS1a**, **TS1b**, **TS2a**, and **TS2b** were identified (Figures 1 and 2).[13,14]

The larger energy difference between the transition state models leading to the major enantiomer and the minor enantiomer in the DHQD-PHN catalysis (4.2 kcal/mol) than the energy difference between those in the DHQD-Ph catalysis (2.1 kcal/mol) is in agreement with the experimental results that the DHQD-PHN catalysis afforded **3a** with higher enantioselectivity than the DHQD-Ph catalysis (Table 1, entry 3 versus entry 6). In **TS2a**, a hydrogen bond between the hydroxy group of **5** and the methoxy group on the quinoline moiety of DHQD-PHN and π-π stacking interactions between the phenyl group of **5** and the 9-phenanthryl group of the catalyst are observed; these attractive non-covalent interactions are not present in **TS2b**. Thus, the tertiary amine moiety, the methoxy group of the quinoline moiety, and the 9-phenanthryl group of DHQD-PHN are the key moieties for the catalysis and the stereocontrol (see Supporting Information for detailed interactions in TSs and additional discussions).



TS1a (0.0) **TS1b** (+2.1)

Figure 1. Transition state structures **TS1a** and **TS1b** that lead to the major enantiomer and the minor diastereomer, respectively, in the formation of **3** from **5** catalyzed by DHQD-Ph.[13] DHQD-Ph is highlighted in green. The relative energies (kcal/mol) are in parentheses. Distances are shown in Å. See Supporting Information for details. See also pdb files.



TS2a (0.0) **TS2b** (+4.2)

Figure 2. Transition state structures **TS2a** and **TS2b** that lead to the major enantiomer and the minor diastereomer, respectively, in the formation of **3** from **5** catalyzed by DHQD-PHN.[13] DHQD-PHN is highlighted in green. The relative energies (kcal/mol) are in parentheses. Distances are shown in Å. See Supporting Information for details. See also pdb files.

Conclusion

We have developed catalytic enantioselective aldol-aldol annulation reactions of C2-symmetric pyruvate derivatives with C2-symmetric cyclohexane-1,3-diones that afford functionalized decalin derivatives bearing five or six stereogenic carbon centers with high enantioselectivities in the presence of cinchona-derived catalysts. Based on experimental results and on theoretical studies, we identified the key structural moieties of the catalyst and the interactions between the catalyst and the transition state that result in the formation of the decalin derivatives with high enantioselectivities. We found that the first aldol reaction step was reversible and that the second-aldol reaction step was the rate-limiting step and the stereochemistry-determining step and was enantioselective. The reaction proceeded by dynamic kinetic desymmetrization, and both starting materials were desymmetrized to form the decalin products. Three moieties of DHQD-PHN, the tertiary amine, the methoxy group of the quinoline moiety, and the 9-phenanthryl group at the ether moiety, had especially important roles in the catalysis and the stereocontrol. This study provides insights into the catalysis and the mechanisms that result in the formation of functionalized structured ring systems and in the stereocontrol achieved by non-covalent interactions and will be useful for the further development of catalysts and chemical transformation methods to construct ring systems and functionalized molecules.

Experimental Section

All experimental details are presented in the Supporting Information.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data of compounds, additional results, computational details, additional discussions, NMR spectra, HPLC chromatograms, and cartesian coordinates (PDF)

TS1a, TS1b, TS2a, and TS2b (pdb)

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Notes

The authors declare no competing financial interest.

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