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Probing the evolution of an Ar-BINMOL-derived salen–Co(III) complex for asymmetric Henry reactions of aromatic aldehydes: salan–Cu(II) *versus* salen–Co(III) catalysis†

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A new type of chiral salen–Co catalyst that features aromatic π-walls and an active Co(III) center has been developed for enantioselective Henry/nitroaldol reactions on the basis of salen–Cu catalysis. The asymmetric Henry reaction of aromatic aldehydes and nitromethane catalyzed by an Ar-BINMOL-derived salen–Co(III) complex was achieved with high yields (up to 93%) and excellent enantioselectivities (up to 98% ee). And more interestingly, it was supposed that either salan–Cu(II) or salen–Co(III) complex-catalyzed Henry reaction was an ideal model reaction for providing direct evidence of noncovalent interaction due to the distinguishable *ortho*-substituted aromatic aldehydes from *meta*- or *para*-substituted benzaldehydes in terms of enantioselectivities and yields.

Introduction

The Henry (nitroaldol) reaction is one of the most atom-economic and convenient carbon–carbon bond-forming reactions, and the resulting β-hydroxy nitroalkanes can be further converted to β-amino alcohol by reduction as well as chiral carboxylic acid and primary amines.[1] The diversity of the transformations of the Henry adducts provides potential interest and application of this process. Since the breakthrough in the catalytic asymmetric Henry reaction came from Shibasaki's group in 1992,[2] much effort has been devoted toward the development of metallic and organic catalysts as well as biocatalysts for this reaction.[3,4] And the most prominent results have been obtained in this area is zinc and copper-based catalyst system with nitrogen-centered ligands.[4–6] For example, dinuclear zinc-amino alcohol and copper-bis(oxazoline) are two classical and representative catalytic systems,[5–7] which developed by Trost[5] and Evans[6] respectively. Although great progress has been hitherto achieved, the development of novel chiral ligands and organometallic catalysis with new concept or strategy still a valuable approach to highly efficient and enantioselective Henry reaction. Herein, we described for the first time an interesting finding of aromatic-interaction-enhanced catalytic transformation with the dramatic effect of aromatic interactions between aromatic aldehydes and chiral salan–copper(II), which led to the finding of benzaldehyde and other aromatic compounds containing one phenyl ring as a key activator to assist the Henry reaction of various nonreactive aldehydes. And on the basis of these work, we report new results of our studies on the evolution of salan–Co(III) complex bearing crowed aromatic rings upon catalytic performances in the Henry reaction.

The weak non-covalent interactions such as hydrogen-bonding, π–π stacking, CH–π, cation– or anion–π, and van der Waals interaction, are the most important structural phenomena for the understanding of molecular recognition, conformational equilibria, molecular self-assembly, protein–ligand binding, molecular aggregates, and artificial metalloenzymes.[8] Especially, the importance of aromatic interactions (π–π stacking, CH–π, cation–π and anion–π interactions) in supramolecular chemistry and homogeneous catalysis has also been recognized very early and received much attention in the fields of molecule based materials and synthetic chemistry in the past decades.[9] Numerous synthetic literatures have showed that stereoselectivities of asymmetric reactions changed unexpectedly upon replacement of an alkyl moiety by an aromatic group,[10] and recent development in theory have proved that the quantum mechanical modeling or methodology could provide accurate insights into the roles of these aromatic interactions at a level of detail not previously accessible for the transition states

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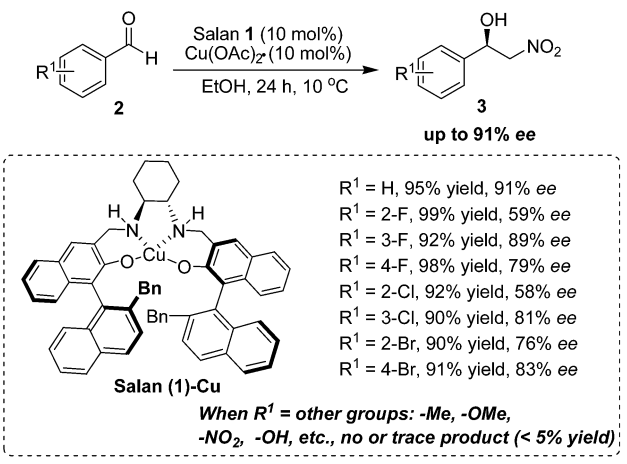
of catalytic asymmetric chemical reactions.[11] Accordingly, considerable efforts for the development of aromatic-interaction-enhanced catalytic transformations recently have been directed toward the positive and effects explanations of aromatic interactions in asymmetric catalysis.[12] Thus, wise modulation and tuning of the complementary moieties of catalyst responsible for the aromatic interactions can lead to its enantioselectivity enhancement in asymmetric reactions. However, it is difficult to develop an aromatic interactions or molecular recognition-oriented enantioselective catalysis, and there are few studies focused on the direct experimental and reaction investigation for the establishment of the crucial role of aromatic interactions in catalytic asymmetric reactions.[11,12] In this work, we want to advance the aromatic interactions as well as salan/salen–metal complex to establish a practical procedure with operationally simple and high efficiently for the metal-catalyzed Henry reactions.

Results and discussion

Very recently, we synthesized a novel chiral 1,1′-binaphthalene-2-α-arylmethanol-2′-ols (Ar-BINMOLs) that derived from BINOL through [1,2]-Wittig rearrangement.[13] The Ar-BINMOL ligands have rigid structures with C_2-axial and sp^3 carbon-central chirality, and could be acted as a supramolecular backbone due to the existence of hydrogen bonding and aromatic interactions of rotatable aromatic rings, thus we expected a high potential for the creation of a rotatable π-wall in the designed salan ligand prepared from Ar-BINMOL *via* six-step transformations.[14] Interestingly, in this case, the (*S*,*R*)-Ar-BINMOL and (*S*,*S*)-cyclohexane-1,2-diamine-derived salan ligand exhibited unusual and high level of catalytic efficiency in asymmetric Henry reaction of aldehydes in terms of enantioselectivities and conversions. As shown in Scheme 1, the salan (**1**)–copper complex exhibited good catalytic performance for non-substituted and halogen-substituted aromatic aldehydes in term of conversion and enantioselectivity. However, methyl-, methoxy-, hydroxyl-, and nitro-substituted benzaldehydes resulted in poor or no conversion.



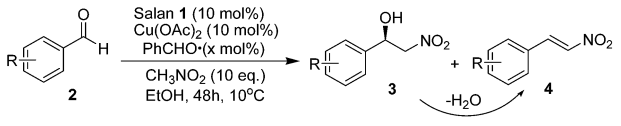
Scheme 1 Ar-BINMOL-derived salan–Cu complex-catalyzed Henry reactions.[14]

Based on the experimental results in this Henry reaction, we suggested that such unique salan ligand (**1**) bearing large aromatic π-wall led to interesting and remarkable discrimination of different aldehydes. Although the catalytic systems are highly complex and multiple parameters can have an impact on the reaction outcomes, and the reasonable mechanism is not clear at present, we can concluded the existence of aromatic π–π stacking interaction between copper ligand and substituted aromatic aldehydes was not favorable for the activation of methyl-, methoxy-, hydroxyl-, and nitro-substituted benzaldehydes by catalytic copper center. We also deduced that free benzaldehyde has the right size, shape, and functionality to interact with catalytic copper center in the salan–Cu complex and could react with nitromethane completely. On the other hand, the salan(**1**)–Cu catalyzed Henry reaction of benzaldehyde resulted in excellent enantioselectivity (91% ee) and yield (95%). On the basis of these direct findings, we hypothesized that the rational application of aromatic interaction between salan/salen–metal complex and substrate could be applied to promote the Henry reaction of methyl-, methoxy-, and other aromatic aldehydes, which encouraged us to utility the benzaldehyde as a π-molecule to initiate the Henry reaction of various nonreactive aldehydes.

To gain direct experimental information about the benzaldehyde-assisted catalytic transformations of substituted aromatic aldehydes, our investigations then focused on the effect of benzaldehyde as an activator in the Henry reaction of nonreactive aromatic aldehydes that for the salan(**1**)–copper catalyst system. We chose 2-MeO-, 3-MeO-, 4-MeO-, 2-Me, and 4-Me-substituted aromatic aldehydes for the slan(**1**)–Cu catalyzed Henry reaction under the following reactions: 10 mol% of catalyst, in ethanol, at 10 °C for 48 hours. The benzaldehyde was used with different amounts with 5 mol%, 10 mol%, and 20 mol% to provide possible regular effect on the catalytic performance of salan–Cu system.

As shown in Table 1, the catalytic activity of copper-catalyzed Henry reactions was found to be improved dramatically by benzaldehyde. For example, in contrast to the catalytic Henry reaction of 2-methoxybenzaldehyde in the absence of benzaldehyde (Entry 1), the addition of 5 mol% of benzaldehyde accelerated the reaction to give the corresponding product in 69% of total yield (Entry 2). The major product is the Henry adduct with moderate enantiomeric excess (58% ee). When the amount of benzaldehyde was increased to 10 or 20 mol%, the benzaldehyde still had positive effect on the catalytic performance of salan–Cu, while the enantioselectivity of Henry reaction was decreased largely with the addition of benzaldehyde (Entries 3 and 4). Under the similar conditions for other aromatic aldehydes, such as 3-MeO-, 4-MeO-, 2-Me, and 4-Me-substituted aromatic aldehydes (Entries 5–20), same trend that the conversion was increased obviously when larger amount of benzaldehyde was used as additive (see Fig. S1 of ESI†). Except 4-methoxybenzaldehyde, all the aldehydes evaluated in this table resulted in good to excellent conversion when 20 mol% of benzaldehyde was used as a promoter. Notably, for most of

Table 1 The effect of benzaldehyde on the catalytic Henry reaction of Me- or MeO-substituted aromatic aldehydes[a]

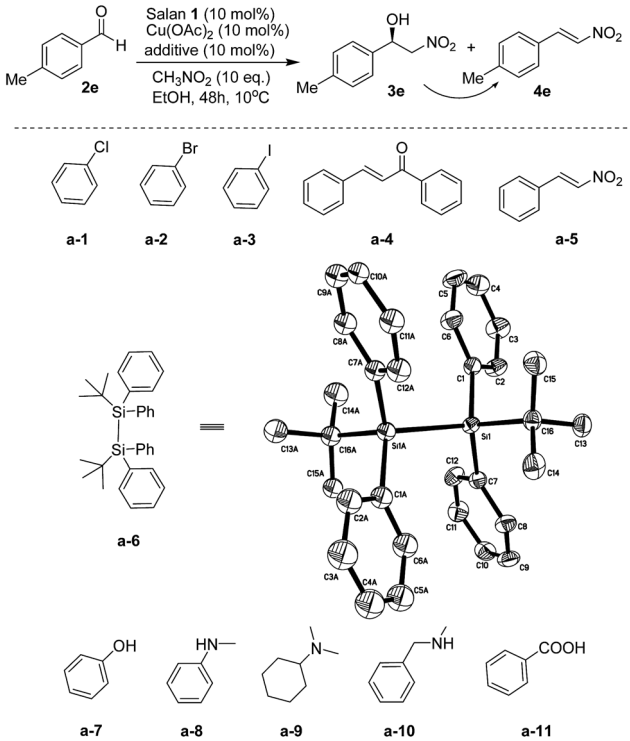


Entry	R	x (mol%)	Yield[b] (%)	3/4	ee[c] (%)
1	2-MeO	0	<5	—	—
2	2-MeO	5	69	64 : 5	58
3	2-MeO	10	58	46 : 12	11
4	2-MeO	20	88	53 : 35	5
5	3-MeO	0	<5	—	—
6	3-MeO	5	16	6 : 10	—
7	3-MeO	10	32	17 : 15	—
8	3-MeO	20	88	11 : 77	—
9	4-MeO	0	<5	—	—
10	4-MeO	5	<5	—	—
11	4-MeO	10	10	0 : 10	—
12	4-MeO	20	44	0 : 44	—
13	2-Me	0	<5	—	—
14	2-Me	5	27	27 : 0	59
15	2-Me	10	52	28 : 24	11
16	2-Me	20	>99	16 : 84	—
17	4-Me	0	<5	—	—
18	4-Me	5	30	9 : 21	—
19	4-Me	10	39	16 : 23	—
20	4-Me	20	>99	0 : 100	—

[a] All reactions were performed on a 1 mmol scale with 10 mol% of Cu salt and 10 mol % of salan ligand (**1**) at a 0.5 M concentration using 10 equiv. of nitromethane in EtOH. Reactions were run at 10 °C in a screw-capped vial for 48 h. [b] The total yield of product **3** and **4**. [c] Enantiomeric excess was determined by HPLC using chiral columns, and the absolute configuration of the major isomer was determined to be (*R*) by comparison with literature data.[4]

substrates provided in Table 1, the major products were nitroolefins **4** but not Henry adducts **3**. Thus, these experimental results supported that the effect of benzaldehyde on the salan–Cu catalyzed Henry reaction was distinctive, which was generally concordant with our hypothesis. This idea was also supported by subsequent exploring of the effect of aromatic compounds on the model Henry reaction of 4-methylbenzaldehyde and nitromethane.

As revealed in Scheme 2 and Table 2, the Henry reaction proceeded without any problem with as little as 10 mol% of chlorobenzene (Entry 1), chalcone (Entry 4), 1-(2-nitrovinyl)-benzene (Entry 5), and PhOH (Entry 7) containing one phenyl ring, giving the corresponding in good conversion. Functional groups on phenyl ring of aromatic additives, such as amines (Entries 8–10), acid (Entry 11), retarded the Henry reaction. Larger substituent on phenyl ring (for example, entry 6) was also make against the occurring of Henry addition of nitromethane to 4-methylbenzaldehyde. It should be noted that these aromatic compounds played different effect on the stereoselective Henry reaction of 4-methylbenzaldehyde led to 0–40% ee of product. It was proposed that such an experimental phenomenon driven by the unexpected force of aromatic



Scheme 2 The effect of aromatic compounds with or without functional groups on the salan–Cu-catalyzed Henry reaction (compound **a-6**, CCDC 1009555).

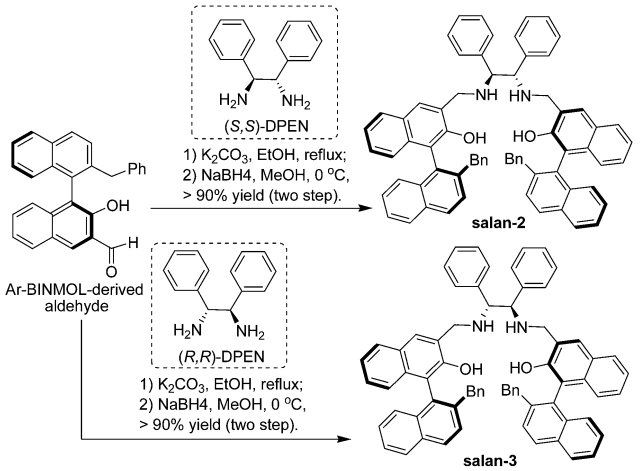
Table 2 The effect of aromatic compounds on the catalytic Henry reaction of substituted aromatic aldehydes[a]

Entry	Additive (10 mol%)	Yield[b] (%)	3/4	ee[c]/%
1	**a1**	83	83 : 0	20
2	**a2**	48	0 : 48	—
3	**a3**	53	28 : 25	0
4	**a4**	88	14 : 74	—
5	**a5**	75	19 : 56	—
6	**a6**	25	25 : 0	40
7	**a7**	70	22 : 48	5
8	**a8**	46	46 : 0	16
9	**a9**	20	20 : 0	44
10	**a10**	46	46 : 0	32
11	**a11**	<10	5 : 0	—

[a] All reactions were carried out at −10 °C in a screw-capped vial for 48 h. [b] The yield was determined by GC-MS, and the catalytic level was divided as good (>70% yield, H), moderate (40–70% yield, M), and poor (<40% yield, L). [c] Enantiomeric excess was determined by HPLC using chiral columns.

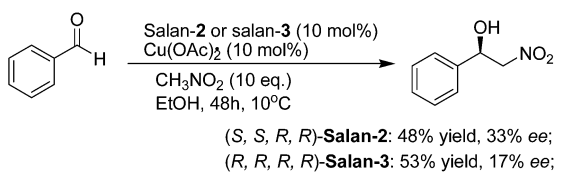
interactions, thus it was provided sight into the crucial role of aromatic additive in both the transformations and enantioselectivity of Henry reaction of aromatic aldehydes.

To highlight the specific of Ar-BINMOL-derived salan-**1** prepared from (1*S*,2*S*)-cyclohexane-1,2-diamine and (*S*)-BINOL in the Henry reaction, another type of salan ligand that derived from 1,2-diphenylethane-1,2-diamine and (*S*)-BINOL was then designed and synthesized for the Henry reaction. Two different



Scheme 3 The synthesis of salan ligand (salan-**2** and salan-**3**) from (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine (DPEN) and (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine respectively.

salan ligands (Ar-BINMOL-derived salan-**2** and salan-**3**) with both axial and sp^3 center chirality, were prepared from (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine (DPEN) and (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine respectively in high yields (Scheme 3, also see ESI†). The catalytic activity of corresponding salan–copper complex, *in situ* obtained by the reaction of salan-**2** or salan-**3** with $Cu(OAc)_2$, was investigated in the model Henry reaction of benzaldehyde and nitromethane. The chirality matching can be also evaluated in this case. As shown in Scheme 4, the Henry reaction of benzaldehyde was relatively slow as evidenced by low conversion and isolated yields in the presence of salan-**2** or salan-**3**. Unexpectedly, the enantioselectivity of the addition product was quite low (33% ee for salan-**2** and 17% ee for salan-**3**). We interpret these results as follows: whereas the lower activity found in the case of (*S*,*S*,*R*,*R*)-salan-**2** could be explained on the basis of the enhanced steric hindrance of diphenyl groups of DPEN and dibenzyl groups on binaphthyl backbone, this argument cannot be applied to (*R*,*R*,*R*,*R*)-salan-**3** because of different steric conformer of DPEN moiety. Rather, the poorer results in term of enantioselectivity and conversion afforded by latter ligand are due to the unfavorable chirality matching with different chiral sources. Notably, the enantioselectivity of present Henry reaction is mainly relay on the effect of chiral binaphthyl fragment because the use of DPEN with different stereogenic configuration did not lead to stereoselectivity reversal of corresponding product. Thus for this particular reaction, the combination use of (*S*)-BINOL derived backbone and (1*S*,2*S*)-cyclohexane-1,2-diamine as two fragments ensures



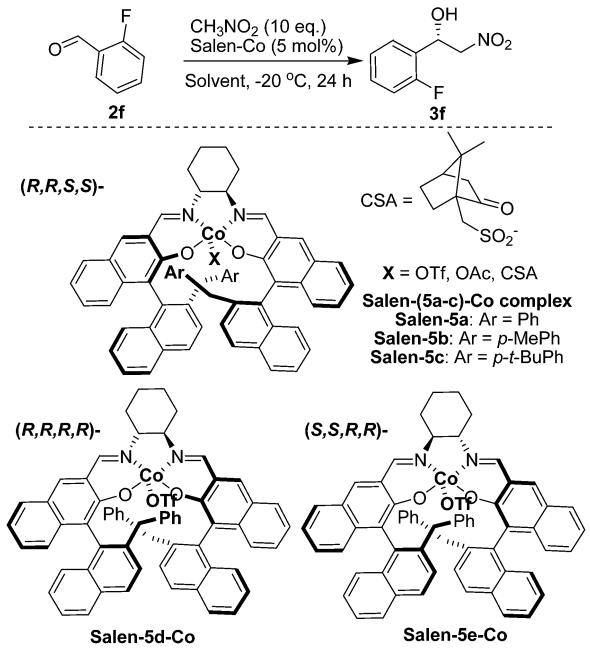
Scheme 4 DPEN-derived salan–Cu-catalyzed Henry reaction.

better control of stereoselectivity, because both the steric and electronic features of the rigid salan ligand **1** are acting in a cooperative manner combined with metal coordination and weak non-covalent aromatic interactions.

On the basis of above work, it is clear that the salan (**1**)–copper complex resulted in a quite narrow substrate scope because of its complicated and multifunctional structure similarly to the behaviour of enzyme. Thus we expected to develop a highly efficient and enantioselective Henry reaction by changing of copper center to other metal center coordinated with our Ar-BINMOL-derived salan or salen ligand. Although cobalt–salen complex has been extensively tested in various catalytic asymmetric reactions, only Yamada and Hong reported that cobalt–salen complex could be employed for the Henry reaction.[15,16] For example, an important progress reported by Hong and coworkers,[16] in which it was found that both the binuclear Co(II)–salen and self-assembled Co(III)–salen featured with hydrogen-bonding gave excellent enantioselectivity and yield. In their work, it should be noted that monomeric Co(II) or Co(III)–salen complex gave the Henry product in poor yield (<11%) and only 55–64% ee in this reaction. Thus inspired by previous studies on cobalt catalysis[17] and salan–Cu-catalyzed Henry reaction, it was expected that Ar-BINMOL-derived salen ligand featured with rotatable π-wall could be effective ligand for Co-catalyzed Henry reaction. Herein, we want to continue to disclose our new findings on the highly enantioselective Henry reaction catalyzed by monomeric salen–Co(III) complex derived from Ar-BINMOL with π-wall.

Starting from commercially available (1*S*,2*S*)-cyclohexane-1,2-diamine or (1*R*,2*R*)-cyclohexane-1,2-diamine with chiral Ar-BINMOL that derived from (*S*)-BINOL or (*R*)-BINOL (Ar = Ph, *p*-Me-Ph, or *p*-*t*Bu-Ph), a new type of chiral Ar-BINMOL-derived salen ligands (**5a–e**) could be synthesized in good overall yields (see ESI†). We hypothesized that the Ar-BINMOL-derived salen bearing rotatable π-wall is a highly attractive ligand in the construction of cobalt-centered π-pocket for the recognition and activation of aromatic aldehyde in this Henry reaction. Initially, we evaluated the performance of Ar-BINMOL-derived salen (**5a**) in the asymmetric cobalt-catalyzed Henry reaction of 2-fluorobenzaldehyde with nitromethane (Scheme 5) because the 2-fluorobenzaldehyde led to low enantioselectivity in salan–Cu catalyst system (2-F, only 59% ee in Scheme 1, line 2).

Table 3 summarizes the optimal results of the initial studies on solvent effect. The data clearly demonstrates the superiority of toluene as a solvent in term of yield and ee value (Entry 9) compared to other solvents (Entries 1–8). The reaction conditions were then further optimized with regard to base and counterion. As shown in Table 3, it was found that TEA, TMEDA, and K_2CO_3 were not effective base to activate nitromethane because of low conversion and inferior enantioselectivity in this reaction (Entries 11–14). In addition, no addition of organic base and the use of phosphine led to almost no reaction (Entries 10 and 13). The metal oxidation state of cobalt proved to be pivotal, and a Co(III)–salen complex with counterion is crucial to the reaction yield. Both Co(II)-based salen complex and Co(III)–salen complex with acetate (OAc) were found to be ineffective catalysts in this Henry reaction (Entries 15 and 16). Although



Scheme 5 Ar-BINMOL-derived salen–Co catalyzed Henry reaction of 2-fluorobenzaldehyde (**2f**) with nitromethane.

Table 3 Salen–Co-catalyzed Henry reaction of 2-fluorobenzaldehyde (**2f**): optimization of reaction conditions[a]

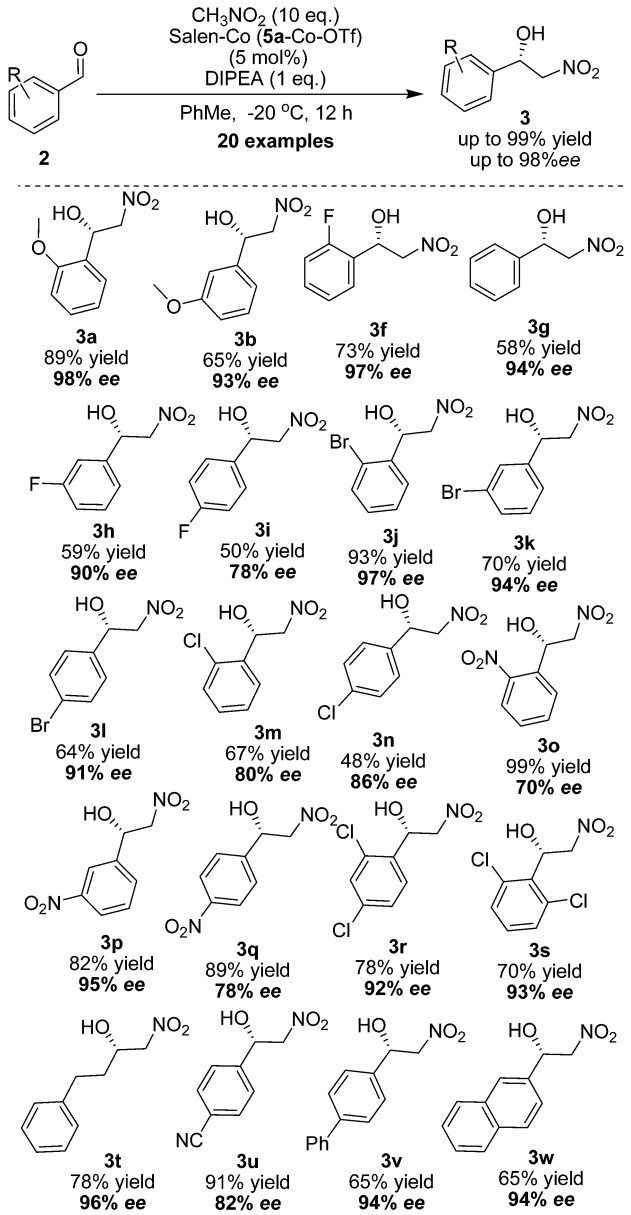
Entry	Salen	X	Base	Sol.	Yield[b] (%)	ee[c] (%)
1	**5a**	OTf	DIPEA	DCM	80	87
2	**5a**	OTf	DIPEA	Et_2O	45	50
3	**5a**	OTf	DIPEA	THF	36	88
4	**5a**	OTf	DIPEA	PhCl	80	67
5	**5a**	OTf	DIPEA	PhI	83	57
6	**5a**	OTf	DIPEA	MeOH	40	14
7	**5a**	OTf	DIPEA	EtOH	50	50
8	**5a**	OTf	DIPEA	DCE	58	41
9	**5a**	OTf	DIPEA	PhMe	**73**	**97**
10	**5a**	OTf	—	PhMe	<5	—[d]
11	**5a**	OTf	TEA	PhMe	35	68
12	**5a**	OTf	TMEDA	PhMe	80	81
13	**5a**	OTf	PPh_3	PhMe	<5	—[d]
14	**5a**	OTf	K_2CO_3	PhMe	75	22
15	**5a**	—	DIPEA	PhMe	<5	—[d]
16	**5a**	OAc	DIPEA	PhMe	<5	—[d]
17	**5a**	CSA	DIPEA	PhMe	53	90
18	**5b**	OTf	DIPEA	PhMe	66	87
19	**5c**	OTf	DIPEA	PhMe	40	73
20[e,f]	**5a**	OTf	DIPEA	PhMe/Et_2O	**71**	**98**
21[e,f]	**5d**	OTf	DIPEA	PhMe/Et_2O	47	59
22[e,f,g]	**5e**	OTf	DIPEA	PhMe/Et_2O	70	−89

[a] Reaction conditions: 0.5 mmol of aldehyde, 10 eq. $MeNO_2$, 5 mol% of salen–Co catalyst, 1.0 eq. of DIPEA. And the reaction time is 12 hours except special note. [b] Isolated yields. [c] The ee value was determined by HPLC with chiral column and the absolute configuration of **3f** was *S*-isomer except additional notes (see ESI). [d] The yield is very poor (<5%) or almost no product was detected, thus the ee value of trace product was not determined. [e] PhMe : Et_2O is 2 : 1. [f] The reaction time is 72 h. [g] The absolute configuration of **3f** was *R*-isomer.

anion of camphorsulfonate (CSA) gave good enantioselectivity (90% ee, Entry 17), trifluoromethanesulfonate (OTf) was still the best choose in term of yield and enantioselectivity. Interestingly, the further modification and application of Ar-BINMOL-derived salens (**5b** and **5c**) was not successfully in this reaction (Entries 18 and 19), whereas the introduction of Me and *t*-Bu to benzyl motif of Ar-BINMOL-derived salen resulted in only 87% ee and 73% ee respectively (**5b** and **5c**, Entries 18–19). Thus notably, under the optimized conditions, excellent enantioselectivity (97% or 98% ee) and good isolated yield (71–73%) were achieved in the reaction between nitromethane and 2-fluorobenzaldehyde (Entry 9 and Entry 20). However, it should be noted that the reaction time is different largely (12 h in toluene and 72 h in toluene–Et_2O).

Notably and interestingly, (*R*,*R*,*R*,*R*)-salen–Co(III) (**5d**) and (*S*,*S*,*R*,*R*)-salen–Co(III) (**5e**) derived from (*S*)-BINOL-derived aldedyde with (*R*,*R*)-cyclohexane-1,2-diamine or (*S*,*S*)-cyclohexane-1,2-diamine respectively exhibited inferior activity in both catalytic activity and enantiomeric induction, being incapable of achieving good yield and high enantioselectivity even with 72 hours (only 59% ee and reversed absolute configuration of 89% ee respectively, Entries 21 and 22). This result showed that the stereochemistry of Ar-BINMOL backbone play crucial role in this salen–Co(III)-catalyzed Henry addition of nitromethane to aromatic aldehydes. Thus, the mismatching between different chiral sources, C_2-axial binaphthol or Ar-BINMOL and sp^3 central chiral phosphine, revealed that the geometric orientation of BINOL-derived cyclohexane-1,2-diamine was crucial to the enantioselective induction in this nitroaldol reaction.[18]

The (*R*,*R*,*S*,*S*)-salen (**5a**)–Co(III) catalyst was then applied to enantioselective Henry reactions of various aldehydes with nitromethane (Scheme 6). As shown in Scheme 6, the scope of the catalytic enantioselectivity in this Henry reactions was demonstrated by treatment of various aromatic aldehydes in the presence of 5 mol% of (*R*,*R*,*S*,*S*)-salen–Co(III) and 1 eq. DIPEA (*N*,*N*-diisopropylethylamine) at −20 °C for 12 h. In most of cases, the Henry reactions of various aromatic aldehydes were clean and proceeded in good yields with excellent enantioselectivities. It should be also noted that there are several interesting findings from these reaction results: (1) most of aromatic aldehydes led to good yields and enantioselectivities. It is clear that better yields and ees are recorded for substrates functionalized in the 2-position. And interestingly, aromatic aldehydes bearing electron-donating groups (such as OMe) and electron-withdrawing groups (such as NO_2) at 3-position of aromatic ring also led to the same level of good yields and enantioselectivity. For example, 3-methoxybenzaldehyde could give the desired product in 92% ee, while 3-nitrobenzaldehyde (**2p**) resulted in 95% ee. However, the enantioselectivity in the Henry reaction of 2-nitrobenzaldehyde (**2o**) and 4-nitrobenzaldehyde (**2q**) was decreased largely to only 70–78% ee, which showed the electronic effect of substrate is obviously for aromatic aldehydes with strong electron-withdrawing group. In other words, the enantioseletive induction of Ar-BINMOL-derived salen–Co(III) was not good for aromatic aldehydes with strong electron-withdrawing group because of weak coordination and aromatic



Scheme 6 Ar-BINMOL-derived salen–Co(III)-catalyzed Henry reactions.

interaction between salen–Co(III) and electron-defect substrate (**2o** or **2q**). (2) The position of substituent was proved to be sensitive and pivotal, in which the *ortho*-substituted groups significantly improved the reaction yield enantioselectivity. For example, fluorine-substituted benzaldehyde, the decreased order of enantioselective induction is 2-F > 3-F > 4-F. And similarly, for bromobenzaldehyde and methoxybenzaldehyde, the Henry reaction of *ortho*-substituted benzaldehyde led to better enantioselectivity and yield than that of *meta*- or *para*-substituted benzaldehyde correspondingly. These reaction results suggest that the selective recognition to *ortho*-substituted benzaldehydes is ascribe to the difference in the molecular size of aromatic aldehydes and possible aromatic-aromatic interaction between the phenyl rings of Ar-BINMOL-derived salen–Co(III) and the aromatic ring of aldehydes. Except 3-phenylpropanal (**2t**), the salen–Co(III) complex showed a significantly decreased activity in the Henry reaction of aliphatic aldehyde. Almost no yield and enantioselectivity was observed for cyclohexanecarbaldehyde (<5% yield). Similarly to previous report on salan–Cu(II)-catalyzed Henry reaction, these reaction results probably show acceleration of the Henry reaction by *ortho*-substituent-mediated weak coordination and π–π interaction between salen–Co(III) catalyst and aromatic aldehydes. Thus we examined the ability of the salen–Co(III) to discriminate aromatic aldehydes in a competitive reaction of 2-fluorobenzaldehyde and cyclohexanecarbaldehyde. In this case, the salen–Co(III) did more selectively catalyze the Henry reaction of 2-fluorobenzaldehyde than that of cyclohexanecarbaldehyde. The nitroaldol addition of nitromethane to cyclohexanecarbaldehyde was almost not occurred under this reaction conditions (<5% yield).

Thus in our case, the experimental results showed the Henry reaction was an ideal model reaction for distinguishing *ortho*-substituted aromatic aldehydes from *meta*- or *para*-substituted benzaldehydes (Fig. S2, see ESI†). To obtain a better understanding of the unusual reactivity of aromatic aldehydes in this salen–Co(III)-catalyzed Henry reaction, theoretical calculations were performed using Gaussian 09 suite of programs.[19] The HOMO and LUMO data of *o*-fluorobenzaldehyde, *m*-fluorobenzaldehyde, and *p*-fluorobenzaldehyde are shown in Fig. 1 (also see ESI†). It is noteworthy that the general electrophilic activity of fluoro-substituted benzaldehydes with theoretical calculation would be different from that of experimental results (2-F> 3-F > 4-F).

Thus according to the specifically crowded structure of the present salen–Co(III) complex, the π-wall of phenyl substituent on salen ligand significantly influenced the weak coordination and aromatic π–π stacking interaction between salen–Co(III) complex and aldehydes, and the desired reaction environment can be affected by the rotatable π-wall to give optimal reaction

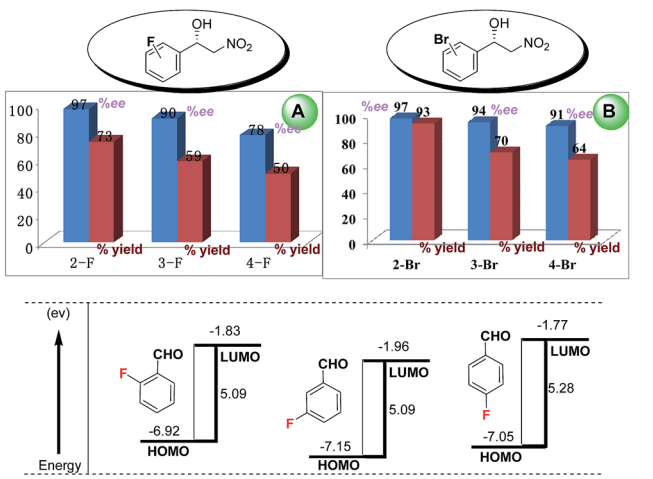


Fig. 1 The comparison of enantioselectivities and yields in the salen–Co (**1a**) catalyzed Henry reaction of F- or Br-substituted aromatic aldehydes.

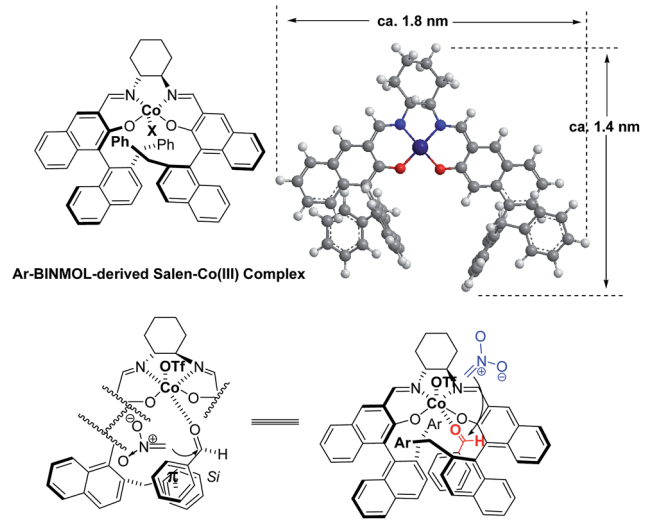


Fig. 2 Assumed transition state for the nanoscale salen–Co(III)-catalyzed Henry reaction.

model with high stereoselectivity. On the basis of present experimental results, a proposed transition state for the salen–Co(**5a**)-catalyzed Henry reaction as depicted in Fig. 2 may be envisioned, which could account for the observations.

For modelling purposes, the structure of *o*-fluorobenzaldehyde and (*R*,*R*,*S*,*S*)-salen (**5a**)–Co(III) catalyst were considered for the modular construction of transition state for the salen–Co(III)-catalyzed Henry reaction. As shown in Fig. S3 (see ESI†), the optimized structure of the most reasonable catalyst–substructure complexes was provided on the basis of experimental results (Fig. 2). Because of asymmetric character of the Ar-BINMOL-derived backbone and substrate, the coordination of oxygen of aldehyde with cobalt center was impacted largely by two different naphthyl rings of salen ligand, therefore the orientations of *o*-fluorobenzaldehyde can occur within the catalyst–substrate complex, leading to highly enantioselective Henry addition. In other words, one of the naphthyl ring of salen ligand could also discriminate different molecular interaction between substituted-benzaldehyde and (*R*,*R*,*S*,*S*)-salen (**5a**)–Co(III) catalyst for the steric repulsion of naphthyl group: the aromatic interaction as well as coordination between catalyst and fluorobenzaldehyde could be weakened with the order of *o*-F > *m*-F > *p*-F substituted aldehyde, which is inconsistent with that of reaction results. Also notably, the nanoscale Ar-BINMOL-derived salen–Co(III) with rotatable π-wall is totally different from simple salen–Co(III) complex in shape, volume, and chirality, thus resulting in the larger difference in their activity and selectivity for Henry reaction.[20]

Conclusions

In summary, it was found firstly that the benzaldehyde or similar aromatic compounds could work as a π-molecule to enhance the catalytic activity of nanoscale Ar-BINMOL-derived salan(**1**)–Cu to initiate the Henry reaction of various nonreactive aldehydes, which led to the determination of aromatic interactions enhanced salan(**1**)–Cu-catalyzed Henry reaction of nonreactive aldehydes, and thus provided a indirect experimental evidence in the aromatic additive initiated enantioselective reaction. More importantly in this work, a new type of chiral salen–Co catalyst that features aromatic π-wall and active Co(III) center has been developed for highly enantioselective Henry/nitroaldol reactions. The asymmetric Henry reaction of aromatic aldehydes and nitromethane catalyzed by Ar-BINMOL-derived salen (**5a**)–Co(III) complex was achieved with high yields (up to 99%) and excellent enantioselectivities (up to 98% ee). And more interestingly, it was supposed that the salen–Co(III) complex-catalyzed Henry reaction was an ideal model reaction for providing direct evidence of noncovalent interaction due to the distinguishing *ortho*-substituted aromatic aldehydes from *meta*- or *para*-substituted benzaldehydes in term of enantioselectivities and yields. We believed that the attractive noncovalent interactions of aromatic rings with other groups can influence and control the stereoselectivity of various catalytic transformations. Further efforts will be devoted to apply such salen–Co(III) complex with chiral π-wall to noncovalent interaction-oriented asymmetric catalysis and enantioselective synthesis of functional organic molecules.

Experimental section

General

All reagents and solvents were used directly without purification. Flash column chromatography was performed over silica (200–300 mesh). Reactions were monitored by thin layer chromatography using silica gel. ^{1}H NMR and ^{13}C NMR (500 and 125 MHz, respectively) spectra were recorded in $CDCl_3$, ^{1}H NMR chemical shifts are reported in ppm relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$ at 7.26 ppm, $(CD_3)_2CO$ at 2.05 ppm). ^{13}C NMR chemical shifts are reported in ppm from tetramethyl silane (TMS) with the solvent resonance as the internal standard ($CDCl_3$ at 77.20 ppm). Thin layer chromatography was performed using silica gel; F_{254} TLC plates and visualized with ultraviolet light. HPLC was carried out with a Waters 2695 Millennium system equipped with a photodiode array detector. The ESI-MS analysis of the samples was operated on an LCQ advantage mass spectrometer (ThermoFisher Company, USA), equipped with an ESI ion source in the positive ionization mode, with data acquisition using the Xcalibur software (Version 1.4).

General procedure for the asymmetric salen–Co(III)-catalyzed Henry reaction

To a screw cap vial containing a stir bar, cobalt complex (26.5 mg, 0.025 mmol, 5% mmol) was added. And then 2 mL toluene, 2-fluorobenzaldehyde (53 μL, 0.5 mmol), and DIPEA (83 μL, 0.5 mmol) was added to the vial. The reaction mixture was cooled down to −20 °C, and then CH_3NO_2 (0.27 mL, 5 mmol) was added. The mixture was continued to stir at −20 °C for 12 h. The reaction mixture was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 10/1) to give the nitroaldol

adduct as a colorless oil. All these molecules have been confirmed by NMR, IR, and GC-MS or HRMS. The detailed experimental procedures and characteristics of corresponding products were provided in Supporting Information.

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