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On the Origin of and a Solution for Uneven Efficiency by Cinchona Alkaloid-Derived, Pseudoenantiomeric Catalysts for Asymmetric Reactions

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Abstract

Cinchona alkaloid-derived chiral catalysts represent one of the most widely applied class of organocatalysts, which have been successfully utilized in the promotion of a wide variety of asymmetric reactions. Cinchona alkaloids exist in nature as pseudoenantiomers, which allow cinchona alkaloid-catalyzed reactions to provide high enantioselectivities and yields toward both enantiomers of interest in many reactions. On the other hand, the subtle structural difference between pseudoenantiomeric cinchona alkaloids could also lead to uneven efficiency that severely limits the applicability of some cinchona alkaloid-catalyzed reactions. We describe here the elucidation of the origin of and the consequent development of novel modified cinchona alkaloids to address such a problem in asymmetric imine umpolung reactions by cinchonium salts.

Graphical Abstract

Natural and modified cinchona alkaloids constitute one of the most widely applied class of organocatalysts in asymmetric synthesis.^{1,2} The existence of pseudoenantiomeric cinchona alkaloids, as exemplified by the structural pairs of cinchonine/cinchonidine and quinidine/quinine (Figure 1), is unique among natural products and allows cinchona alkaloid-derived

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Supporting Information

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X-ray Crystallographic data for catalyst QD-1 (cif)

X-ray Crystallographic data for catalyst Q-1 (cif)

X-ray Crystallographic data for catalyst epQ-1 (cif)

X-ray Crystallographic data for compound 4Bb (cif)

Experimental procedures, characterization of the product and NMR spectra (PDF).

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chiral organic catalysts to provide ready access to both enantiomers of desired chiral products in numerous reactions.³ Nevertheless, there are many examples of significant discrepancy in enantioselectivity, and usually in reactivity, for asymmetric reactions mediated by a pair of pseudoenantiomeric cinchona alkaloid-derived catalysts; namely one afforded highly enantioselective reactions producing enantioenriched products with good to high yields while the corresponding pseudoenantiomer failed to furnish the antipode of the chiral products with similar levels of enantioselectivities and yields.^{4,5} In most cases, the origin of such undesirable deterioration in the catalytic efficiency, caused by a seemingly subtle structural difference of one pseudoenantiomer vs the other, remained mysterious and the solution for this pseudoenantiomer problem proved elusive.⁶

We recently demonstrated that cinchonium salts such as cinchonine-derived catalysts **C-2** or quinidine-derived catalyst **QD-1** could activate trifluoromethyl ketimines and simple aldimines **1** as nucleophiles for highly chemo-, regio-, diastereo- and enantioselective reactions with a variety of electrophiles.⁷ These reactions provide a new approach to the enantioselective generation of chiral amines (Scheme 1). While catalysts **C-2** and **QD-1** consistently afforded exceedingly high reactivity and selectivity, the corresponding pseudoenantiomeric catalysts derived from cinchonidine **CD-2** or quinine **Q-1** are in general less efficient and selective. For reactions with relatively active electrophiles such as enals **7**, even the less efficient catalysts **CD-2** could still provide synthetically useful access to the chiral amine products *ent*-**8** with 61–89% ee values and 32–86% yield (see scheme 1a).

However, for reactions with less reactive electrophiles such as α,β -unsaturated *N*-acyl pyrroles **3**, the pseudoenantiomeric catalyst **Q-1** proceeded with drastically lower enantioselectivities and yields (32–69% ee, 22–78% yield, see Scheme 1b). As illustrated by a comparison of results obtained respectively from **QD-1** and **Q-1** catalyzed additions of trifluoromethyl imine **1J** to α,β -unsaturated *N*-acyl pyrrole **3a** (entry 1 vs 2, Table 1a), **Q-1** not only afforded significantly lower enantioselectivity of desired product **4Ja** (67% ee vs 91% ee), but also poorer chemoselectivity (63:37 vs >95:5) and regioselectivity (90:10 vs >95:5) with obviously decreased reaction conversion (83% conv. vs 95% conv.).

To gain insight into such disparity on both enantioselectivity and catalytic reactivity mediated by this pair of pseudoenantiomeric cinchona catalysts, we carried out structural analysis of both cinchona catalysts **QD-1** and **Q-1** (Figure 2).⁸ The catalytic efficiency of the cinchonium catalysts such as **QD-1** critically depends on how the quaternary nitrogen-centered tetrahedron, with C2, C6, C8, and Ca as vertices, interacts with the anionic nucleophiles.⁹ Highly enantioselective phase transfer catalysis requires that the anionic nucleophiles to be associated with great preference with only one of the four faces of this tetrahedron in cinchonium salts, where efficient chiral recognition of the reacting substrates are attained. Reaction pathways involving other faces of the cinchonium salts most likely result in low enantioselectivity of the desired products. In the X-ray structure of catalyst **QD-1** (see Figure 2a), one face of the quaternary ammonium salt was blocked by the quinuclidine backbone (C2-C6-C8). The bulky *N*-(9-anthrylmethyl) group provided an effective screening for the C2-C6-Ca face, while the 5-phenyl ring of the PYR (4-chloro-2,5-diphenylpyrimidine) group efficiently shielded the face of C2-C8-Ca. The C6-C8-Ca face where the bromide resided was the only open pocket. We therefore inferred that this face

was where the 2-azaallyl anions such as **2J** associate with the cinchonium catalyst and then selectively reacted with the electrophile in a highly enantioselective manner. By a similar analysis of the X-ray structure **Q-1**, we concluded that the C6-C8-Ca face was still the most open and was where the enantioselective reaction of opposite sense of asymmetric induction occurred. However, the respective location of the vinyl group was shown to not only render the two respective C6-C8-Ca faces in **QD-1** and **Q-1** pseudoenantiomeric but also to intrude into the C6-C8-Ca face in **Q-1** [see Figure 2b]. By making the C6-C8-Ca face more congested, the presence of the vinyl group could negatively impact the catalyst efficiency of **Q-1** either by slowing down the rate of the enantioselective reaction or diminishing its ability to exercise chiral recognition.

We envisaged that, by removing the vinyl group from **Q-1**, a new quinine-derived catalyst with a more accessible C6-C8-Ca pocket might afford improved enantioselectivity and catalytic efficiency. Following these considerations, we prepared the “vinyl deleted” catalyst **vdQ-1** [see Figure 2c].¹⁰ To our delight, we found that **vdQ-1** indeed performed significantly better than **Q-1** in terms of chemo-, regio- and enantioselectivity [entry 3 vs 2, Table 1a]. On the other hand, it was interesting to observe that **vdQ-1** was still not as effective as **QD-1** for the efficient steric control [83% ee vs 91% ee] and chemoselectivity [87/13 vs >95/5, entry 3 vs 1]. A plausible explanation of the discrepancy in catalytic efficiency between **vdQ-1** and **QD-1** was that the presence of the vinyl group in the latter by working together with the PYR group provided effective shielding of the C2-C8-Ca face, thereby contributing to the catalyst efficiency of **QD-1** by minimizing non-selective reaction pathways that could occur in the C2-C8-Ca pocket.

In principle, creating the exact enantiomer of **QD-1** would provide a catalyst of equal efficiency with the complementary sense of asymmetric induction. Unfortunately, we were not able to design a synthetic route to accomplish this task without compromising the practical accessibility of this catalyst. Nevertheless, the unexpected effect of the vinyl group confirmed the importance of effectively shielding the faces of the quaternary nitrogen-centered tetrahedron other than the face in which the desirable asymmetric reaction occurred. We therefore designed *epi***Q-1** as a new pseudoenantiomer of **QD-1** for the development of an efficient catalyst of complementary sense with the asymmetric induction. Our design was based on the considerations that the vinyl group in *epi***Q-1** would not intrude into the C6-C8-Ca face but also serve as an extra steric barrier to the C2-C6-Ca face.

There was only one literature report of the preparation of *epi*-vinyl quinine or quinidine (*epi***Q** or *epi***QD**) through a complicated synthetic route.¹¹ To establish efficient access to *epi***Q-1**, we developed an oxidation-epimerization-Wittig olefination sequence through the epimerizable aldehyde intermediate **17** for the preparation of *epi***Q-1** in 20% overall yield from quinine (Scheme 2). We next applied catalyst *epi***Q-1** to promote the model reaction of imine **1J** with α,β -unsaturated *N*-acyl pyrrole **3a**. To our delight, *epi***Q-1** mediated a highly regio-, chemo- and enantio-selective reaction, even superior to those catalyzed by **QD-1** (entry 4 vs 1, Table 1a), to furnish product **4Ja** as nearly an exclusive product. Further lowering the loading of *epi***Q-1** to 3.0 mol% did not lead to any deterioration in reaction outcomes (entry 5, Table 1a).

We next investigated whether this remarkably efficient catalysis by *epi*Q-1 could be extended from the model reaction to additions of other imines **1** to **3**. As summarized in Table 1b, the trifluoromethyl imines **1A-G** bearing simple and functionalized linear, α , β , or γ -branched aliphatic groups reacted efficiently with **3a** in not only consistently high enantioselectivity but also virtually perfect chemo- and regioselectivity, generating the corresponding chiral products **4Aa-Ga** in 92–95% ee and 91–96% yields (entries 1–7, Table 1b). Catalyst *epi*Q-1 also afforded highly efficient catalysis for reactions involving various alkenyl and aryl-substituted trifluoromethyl imines **1H-N** (entries 8–14, Table 1b). Even for the additions to the less reactive β -methyl α,β -unsaturated *N*-acyl pyrrole **3b**, the reaction furnished the desired adducts with exceedingly high diastereoselectivity and excellent enantioselectivity (*dr* > 95/5 and 90–93% ee, entries 15–17, Table 1b). In comparison, the reactions in the presence of the quinine-derived catalyst Q-1 only afforded moderate enantioselectivity and poor chemo- and regioselectivity, leading to low reaction yield in most cases (Table 1b). Interestingly, *epi*Q-1 was found to be an even more reactive and enantioselective catalyst than QD-1, as demonstrated by the employment of lower catalyst loadings and the generation of the desired chiral products with better optical purities.^{7c}

An X-ray structure of *epi*Q-1 was also successfully obtained (see Figure 2d).⁸ Gratifyingly, the considerations behind the design of *epi*Q-1 were validated, namely, by switching the orientation of the vinyl group from pointing at C6-C8-Ca pocket to the C2-C6-Ca pocket, the barrier to the active site for the desired asymmetric reaction was removed while a barrier was erected to the site for undesirable reaction pathways leading to low enantioselectivity.

Following these encouraging results, we became interested in exploring whether *epi*-vinyl cinchona catalysts were applicable to other type of reactions. We then investigated the asymmetric imine umpolung reactions with enals.^{7a} As shown in Table 2a, we reported earlier that catalyst C-2a mediated a highly chemo-, regio-, diastereo- and enantio-selective reaction of trifluoromethyl imines **1** with various enals **7** to deliver desired enantiomerically enriched amino alcohol products such as **10Ba** with high yield and excellent enantioselectivity (entry 1, Table 2a). However, this model reaction in the presence of pseudoenantiomeric catalyst CD-2a afforded the opposite enantiomeric product **10Ba** with only 78% ee (entry 2). We next examined the *epi*-vinyl catalyst *epi*CD-2a¹² and found that the reaction efficiently proceeded to the desired product with excellent yield and high optical purity (88% yield and 91% ee, entry 3). Moreover, we found that catalyst *epi*Q-2a,¹² the quinidium analogue of *epi*CD-2a, performed as a slightly better catalyst to mediate the highly efficient formation of product **10Ba** with even higher enantioselectivity (93% ee, entry 4). Further lowering catalyst loading of *epi*Q-2a to 0.1 mol%, the reaction still proceeded without any deterioration in both reaction selectivity and yield (entry 5).

The subsequent substrate scope studies revealed that the reactions of a variety of alkyl, alkenyl and aryl substituted trifluoromethyl imines **1** with acrolein (**7a**) consistently proceeded in good yields and high enantioselectivities (68–92% yield and 93–99% ee) with only 0.1 mol% catalyst loadings (entries 1–6, Table 2b). For a series of β -substituted enals such as **7b-d**, *epi*Q-2a mediated similarly highly stereoselective reactions with various trifluoromethyl imines bearing either linear or branched alkyl substituents (entries 7–12).

The sterically hindered cinnamaldehyde (**7e**) was previously shown to be a considerably challenging substrate due to moderate regioselectivity (**8/9** = 78/22) and obviously decreased enantioselectivity (61% ee).^{7a} Notably, *epi*Q-**2a** catalyst promoted a highly chemo-, regio-, diastereo- and enantio-selective reaction in a highly efficient fashion (**8/9** = 93/7, dr >95/5, 91% ee, entry 13), thereby delivering the desired product **10Ae** in useful yield (73% yield).

We then explored the addition of aryl-substituted aldimines such as **1P** to acrolein (**7a**) with the newly-developed *epi*-vinyl catalyst *epi*CD-**2b**,¹² which turned out to be a considerably more powerful catalyst than either C-**2b** or CD-**2b** (entries 3 vs 1–2, Table 3).^{7a} Even at a drastically decreased loading of *epi*CD-**2b** (from 2.5 mol% to 0.5 mol%), a highly regio- and enantioselective reaction was still realized to deliver the desired product **12Pa** with good yield and excellent enantioselectivity (entry 4). The subsequent substrate scope studies revealed that *epi*CD-**2b** in 0.5–1.0 mol% catalyst loadings continued to perform better than CD-**2b** in 2.5–5.0 mol% loadings for reactions with the more challenging aryl and alkenyl-substituted aldimines **1Q–T**, furnishing the desired products **12Q–T** with improved yields (55–62% yield) and, for the first time, greater than 90% ee (entries 5–8, Table 3).

The positive impact of the *epi*-vinyl group was also observed with cinchonium catalysts developed for the umpolung additions of imines **1** to different enones **13** (Table 4).^{7b} In the model reaction of aryl-substituted aldimine **1P** and methyl vinyl ketone **13a**, *epi*CD-**2c**¹² catalyst showed better reactivity and enantioselectivity than either CD-**2c** or C-**2c**. The most dramatic improvement was on regioselectivity as reflected by the **14/15** ratio, which resulted in significantly improved yield (entry 3 vs 1–2, Table 4). Once again, decreasing the loading of *epi*CD-**2c** did not negatively impact the reaction outcomes (entry 4 vs 3, Table 4). The subsequent substrate scope studies demonstrated that the superiority of *epi*CD-**2c** could be extended to reactions between different imines (**1U–V**, **1A**, **1I**) and enones (**13a–b**) (entries 5–8, Table 4).

We recently reported the discovery of cinchonium betaine catalyst QD-**3** for the asymmetric isomerization of trifluoromethyl imines **1** to the corresponding chiral trifluoromethylated amines **6**.¹³ While the quinidine-derived catalyst QD-**3** afforded extraordinarily high catalyst turnover numbers, ranging from 500 to 5000 per 24 h, the quinine-derived catalyst Q-**3** was less efficient, affording the opposite enantiomer of the trifluoromethyl amines **6** in lower enantioselectivity and catalyst turnover numbers. The trifluoromethyl imines bearing electron-withdrawing substituents were particularly challenging substrates. As shown by the isomerization of imine **1K** mediated by QD-**3** and Q-**3**, the (*R*)- and (*S*)-enantiomers of the chiral amine **6K** were obtained in 83% and 76% ee, respectively (entries 1–2, Table 5).

We observed that the *epi*-vinyl effect was in play for these betaine catalysts. Specifically, *epi*-vinyl catalyst *epi*Q-**3**¹² was found to be a considerably superior catalyst, allowing the highly enantioselective isomerization of **1K** to proceed in 91% ee (entry 3). Even at a loading of 0.05 mol%, the reaction still proceeded to full conversion without any deterioration on the yield and enantioselectivity (entry 4). Meanwhile, catalyst Q-**3** at a loading of 0.05 mol% mediated the isomerization of **1K** to **6K** with significantly decreased enantioselectivity (61% ee, entry 5). In parallel to previous observations, the superiority of the *epi*-vinyl catalyst *epi*Q-**3** was not substrate-dependent. Excellent enantioselectivities and

quantitative yields were routinely obtained for a series of alkyl, alkenyl and aryl substituted substrates with only 0.05 mol% of *epi***Q-3** in all cases (93–96% ee and 96–98% yield, Table 5, entries 6–10).

In conclusion, we carried out structural studies of a pair of pseudoenantiomeric cinchonium salts that demonstrated a significant discrepancy in their efficiency as catalysts to promote asymmetric umpolung reactions of imines. These structural studies revealed that the orientation of the vinyl group on the quinuclidine scaffold might play an essential role in causing the compromised efficiency of the worse performing pseudoenantiomer catalyst. Following a hypothesis-driven approach guided by these key insights gained from our structural studies, we developed novel *epi*-vinyl quinine- and *epi*-vinyl cinchonidine-based catalysts, which afford dramatically improved reactivity and stereoselectivity over those by the corresponding quinine- or cinchonidine-based catalysts. Importantly, this “*epi*-vinyl modification” proved consistently effective in improving the poor performance of several quinine- or cinchonine-derived cinchonium catalysts mediating different catalytic asymmetric imine umpolung reactions, thereby allowing these reactions to provide efficient access to not one but both enantiomers of the chiral amines of interest. We expect that this “*epi*-vinyl approach” may be applicable to address the “pseudoenantiomer problem” arising from other cinchona alkaloid-mediated asymmetric reactions.

Supplementary Material

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Figure 1.
Representative nature-originated cinchona alkaloids

Figure 2.

Crystal structures of catalyst QD-1, Q-1 and *epi*Q-1. The structure of vdQ-1 was a model based on the crystal structure of Q-1. The protons and solvent molecules have been omitted for clarity (C: grey, O: red, N: blue, Br: orange, Cl: green).

Scheme 1.

Examples of discrepancy in enantioselectivity and reactivity mediated by a pair of pseudoenantiomeric cinchona catalysts

Scheme 2.

Efficient preparation of *epi*-vinyl cinchona alkaloid phase transfer catalyst *epiQ-1*.

Table 1a.

Development of novel cinchona catalysts for generation of opposite enantiomers with high optical purities.^a

Entry	cat. (x mol%)	conv. (%) ^b	4Ja/5Ja ^b	4Ja/6J ^b	ee of 4Ja (%) ^c
1	QD-1 (5.0)	95	>95:5	>95:5	91 (<i>R</i>)
2	Q-1 (5.0)	83	90:10	63:37	67 (<i>S</i>)
3	vdQ-1 (5.0)	95	>95:5	87:13	83 (<i>S</i>)
4	epiQ-1 (5.0)	100	>95:5	>95:5	95 (<i>S</i>)
5	epiQ-1 (3.0)	99	>95:5	>95:5	95 (<i>S</i>)

^aUnless noted, reactions were performed with trifluoromethyl imine **1J** (0.025 mmol), α,β -unsaturated *N*-acyl pyrrole **3a** (0.05 mmol), aqueous KOH solution (0.25 μ L, 50 wt%, 10 mol%), mesitol (6.8 mg, 2.0 equiv.), and catalyst (x mol%) in PhMe (0.25 mL) at -40 °C for 1 h.

^bReaction conversion and product ratios were determined by ¹⁹F NMR analysis.

^cThe ee value of product **4Ja** was determined by HPLC analysis.

Table 1b.

Substrate scope studies of trifluoromethyl imines with α,β -unsaturated *N*-acyl pyrroles.^a

Entry	R ¹ , 1	3	cat. (x mol%)	conv. (%) ^b	4/5 ^b	4/6 ^b	Yield (%) ^c	ee (%) ^d
1	Me; 1A	3a	<i>epi</i> Q-1 Q-1 (0.5)	100 85	>95:5 >95:5	>95:5 >95:5	95 78 (4Aa)	94 58
2	Et; 1B	3a	<i>epi</i> Q-1 Q-1 (1.5)	100 86	>95:5 >95:5	>95:5 >95:5	96 75 (4Ba)	94 59
3	<i>n</i> -Bu; 1C	3a	<i>epi</i> Q-1 Q-1 (1.5)	100 83	>95:5 92:8	>95:5 >95:5	91 73 (4Ca)	93 46
4	CH ₂ =CH(CH ₂) ₃ ; 1D	3a	<i>epi</i> Q-1 Q-1 (1.5)	100 85	>95:5 95:5	>95:5 >95:5	94 76 (4Da)	93 63
5	Cy; 1E	3a	<i>epi</i> Q-1 Q-1 (3.0)	100 82	>95:5 91:9	>95:5 >95:5	93 60 (4Ea)	95 66
6	CyCH ₂ ; 1F	3a	<i>epi</i> Q-1 Q-1 (3.0)	97 82	>95:5 87:13	>95:5 >95:5	91 61 (4Fa)	94 69
7	PhCH ₂ CH ₂ ; 1G	3a	<i>epi</i> Q-1 Q-1 (1.5)	99 90	>95:5 >95:5	>95:5 >95:5	94 65 (4Ga)	92 58
8	PhCH=CH; 1H	3a	<i>epi</i> Q-1 Q-1 (1.5)	100 95	>95:5 77:23	>95:5 36:64	93 22 (4Ha)	96 32
9	Ph; 1I	3a	<i>epi</i> Q-1 Q-1 (2.0)	99 80	>95:5 89:11	>95:5 73:27	85 35 (4Ia)	95 59
10	4-ClC ₆ H ₄ ; 1J	3a	<i>epi</i> Q-1 Q-1 (3.0)	99 83	>95:5 90:10	>95:5 63:37	85 33 (4Ja)	95 67
11	4-CF ₃ -C ₆ H ₄ ; 1K	3a	<i>epi</i> Q-1 Q-1 (3.0)	100 93	>95:5 93:7	>95:5 56:44	80 31 (4Ka)	94 60
12	4-MeOC ₆ H ₄ ; 1L	3a	<i>epi</i> Q-1 Q-1 (3.0)	99 90	>95:5 70:30	>95:5 82:18	83 33 (4La)	95 63
13	3-MeC ₆ H ₄ ; 1M	3a	<i>epi</i> Q-1 Q-1 (2.0)	97 77	>95:5 70:30	>95:5 79:21	78 30 (4Ma)	94 60
14	2-Naphthyl; 1N	3a	<i>epi</i> Q-1 Q-1 (3.0)	98 73	>95:5 75:25	>95:5 70:30	80 28 (4Na)	95 56
15 ^e	H; 1O	3b	<i>epi</i> Q-1 Q-1 (3.0)	100 100	>95:5 90:10	>95:5 65:35	82 35 (4Ob)	90 56
16 ^e	Me; 1A	3b	<i>epi</i> Q-1 Q-1 (3.0)	100 83	90:10 65:35	>95:5 >95:5	71 42 (4Ab)	93 54
17 ^{c,f}	Et; 1B	3b	<i>epi</i> Q-1 Q-1 (3.0)	98 80	81:19 62:38	>95:5 >95:5	65 32 (4Bb)	91 54

^aUnless noted, reactions were performed with trifluoromethyl imines 1 [0.2 mmol], α,β -unsaturated *N*-acyl pyrroles 3 [0.4 mmol], mesitol [y mol%] and aqueous KOH solution (2.2 μ L, 50 wt%, 10 mol%), and catalyst [x mol%] in PhMe [2.0 mL] at indicated temperature [–20–50 °C] for 1 h, see supporting information for details. For entries 1–7, PhMe/CHCl₃ [4:1, 2.0 mL in total] was used as the solvent.

^bReaction conversion and product ratios were determined by ¹⁹F NMR analysis.

The absolute configuration of compound **4Bb** was further determined to be *R* by X-ray crystallographic analysis.⁸

Anhydrous NaOH solid powder [1.0 equiv.] was used as the base, reaction time was 0.5 h and the diastereoselectivity of the products **4** were >95:5.

The ee value of products **4** was determined by HPLC analysis.

^dYield of isolated products.

Table 2a.

Catalysts comparison for asymmetric reaction of trifluoromethyl imine **1B** with acrolein.^a

Entry	cat (x mol%)	conv. (%) ^b	Yield (%) ^c	ee (%) ^d
1	C-2a (0.2)	99	82 (10Ba)	91 (<i>S</i>)
2	CD-2a (0.2)	97	81 (10Ba)	78 (<i>R</i>)
3	<i>epi</i> CD-2a (0.2)	99	88 (10Ba)	91 (<i>R</i>)
4	<i>epi</i> Q-2a (0.2)	100	91 (10Ba)	93 (<i>R</i>)
5	<i>epi</i> Q-2a (0.1)	99	91 (10Ba)	93 (<i>R</i>)

^aUnless noted, reactions were performed with trifluoromethyl imine **1B** (0.2 mmol), acrolein **7a** (0.4 mmol), aqueous KOH solution (2.2 μL , 50 wt %, 10 mol%), and catalyst (x mol%) in PhMe (2.0 mL) at -10°C for 3 h.

^bReaction conversion was determined by ^{19}F NMR analysis.

^cYield of isolated product.

^dThe ee value of product **10Ba** was determined by HPLC analysis.

Table 2b.

Substrate scope studies for the reaction of trifluoromethyl imines with various enals catalyzed by *epiQ*-2a.^a

Entry	R ¹ ; 1	R ² ; 7	t (h)	Yield (%) ^b	ee (%) ^c
1 ^d	Me; 1A	H; 7a	3	88 (10Aa)	95
2 ^d	<i>n</i> -Bu; 1C	H; 7a	3	83 (10Ca)	93
3	PhCH=CH; 1H	H; 7a	1	92 (11Ha)	97
4	Ph; 1I	H; 7a	3	73 (11Ia)	99
5	4-CF ₃ C ₆ H ₄ ; 1K	H; 7a	3	73 (11Ia)	98
6	4-MeOC ₆ H ₄ ; 1L	H; 7a	3	68 (11La)	97
7 ^e	Me; 1A	Me; 7b	5	82 (10Ab)	94
8 ^e	Et; 1B	Me; 7b	5	84 (10Bb)	93
9 ^e	<i>n</i> -Bu; 1C	Me; 7b	5	80 (10Cb)	93
10 ^e	CyCH ₂ ; 1F	Me; 7b	5	53 (10Fb)	94
11 ^e	Me; 1A	Et; 7c	5	64 (10Ac)	94
12 ^e	Me; 1A	<i>n</i> -Hex; 7d	12	55 (10Ad)	97
13 ^{e,f}	Me; 1A	Ph; 7e	8	73 (10Ae)	91

^a Unless noted, reactions were performed with trifluoromethyl imines **1** (0.2 mmol), enals **7** (0.4 mmol), aqueous KOH (2.2 μL, 50 wt%, 10 mol%), and *epiQ*-2a (0.1 mol%) in PhMe (2.0 mL) at -20 °C for indicated time.

^b Yield of isolated product.

^c The ee value of product **10** or **11** was determined by HPLC analysis.

^d Reactions were performed at -10 °C through slow addition, see supporting information for details.

^e 0.2 mol% catalyst loading was used, the dr values of product **10** (entries 7–13) were >95/5.

^f The regioselectivity of **8/9** = 93/7, see supporting information for details.

Table 3.

Catalysts comparison and substrate scope studies for reaction of aldimines with acrolein.^a

Catalyst comparison

Entry	R ¹ ; 1	Cat (x mol%)	t (h)	Yield (%) ^b	ee (%) ^c
1	Ph; 1P	C-2b (2.5)	8	55 (12Pa)	93 (<i>S</i>)
2	Ph; 1P	CD-2b (2.5)	8	52 (12Pa)	89 (<i>R</i>)
3	Ph; 1P	<i>epi</i> CD-2b (2.5)	3	61 (12Pa)	93 (<i>R</i>)
4	Ph; 1P	<i>epi</i> CD-2b (0.5)	8	60 (12Pa)	93 (<i>R</i>)

Substrate scope studies

5	4-MeOC ₆ H ₄ ; 1Q	<i>epi</i> CD-2b (1.0)	12	56 (12Qa)	94 (<i>R</i>)
6	4-MeO ₂ CC ₆ H ₄ ; 1R	<i>epi</i> CD-2b (0.5)	5	62 (12Ra)	91 (<i>R</i>)
7	PhCH=CH; 1S	<i>epi</i> CD-2b (0.5)	12	60 (12Sa)	90 (<i>R</i>)
8	4-BrC ₆ H ₄ CH=CH; 1T	<i>epi</i> CD-2b (0.5)	12	55 (12Ta)	90 (<i>R</i>)

^a Unless noted, reactions were performed with aldimines **1** (0.2 mmol), acrolein (**7a**, 0.4 mmol), aqueous KOH solution (2.2 μL, 50 wt%, 10 mol%), and catalyst (x mol%) in PhMe (2.0 mL) at 0 °C for indicated time.

^b Yield of isolated product.

^c The ee value of product **12** was determined by HPLC analysis.

Table 4.

Catalysts comparison and substrate scope studies for the reaction of imines with enones.^a

Catalyst comparison							
Entry	1	13	Cat (x mol%)	t (h)	14/15 ^b	Yield (%) ^c	ee (%) ^d
1	1P	13a	C-2c (2.5)	12	71:29	50 (16Pa)	82 (<i>S</i>)
2	1P	13a	CD-2c (2.5)	12	66:34	45 (16Pa)	80 (<i>R</i>)
3	1P	13a	<i>epi</i> CD-2c (2.5)	6	83:17	71 (16Pa)	86 (<i>R</i>)
4	1P	13a	<i>epi</i> CD-2c (1.0)	12	82:18	70 (16Pa)	86 (<i>R</i>)
Substrate scope studies							
5	1U	13a	<i>epi</i> CD-2c (1.0)	8	82:18	68 (16Ua)	86 (<i>R</i>)
6	1V	13b	<i>epi</i> CD-2c (1.0)	12	83:17	71 (16Vb)	86 (<i>R</i>)
7 ^e	1A	13b	<i>epi</i> CD-2c (0.2)	5	>95:5	91 (14Ab)	85 (<i>R</i>)
8 ^e	1I	13a	<i>epi</i> CD-2c (0.2)	24	>95:5	93 (14Ia)	90 (<i>S</i>)

^aUnless noted, reactions were performed with imines **1** (0.2 mmol), enones **13** (0.4 mmol), aqueous KOH solution (2.2 μL, 50 wt%, 10 mol%), and catalyst (x mol%) in PhMe (2.0 mL) at 0 °C for indicated time.

^bProduct ratios were determined by ¹H NMR or ¹⁹F NMR analysis.

^cYield of isolated product.

^dThe ee value of products **16** or **14** was determined by HPLC analysis.

^eReactions were performed at -50 °C.

Table 5.

Catalysts comparison and substrate scope studies for catalytic asymmetric isomerization of trifluoromethyl imines.^a

Catalyst comparison

Entry	R ¹ ; 1	Cat (x mol%)	t (h)	Yield (%) ^b	ee (%) ^c
1	4-CF ₃ C ₆ H ₄ ; 1K	QD-3 (0.2)	24	96 (6K)	83 (<i>R</i>)
2	4-CF ₃ C ₆ H ₄ ; 1K	QD-3 (0.2)	24	98 (6K)	76 (<i>S</i>)
3	4-CF ₃ C ₆ H ₄ ; 1K	<i>epi</i> Q-3 (0.2)	12	97 (6K)	91 (<i>S</i>)
4	4-CF ₃ C ₆ H ₄ ; 1K	<i>epi</i> Q-3 (0.05)	24	98 (6K)	91 (<i>S</i>)
5	4-CF ₃ C ₆ H ₄ ; 1K	Q-3 (0.05)	24	96 (6K)	61 (<i>S</i>)

Substrate scope studies

6 ^d	Me; 1A	<i>epi</i> Q-3 (0.05)	24	96 (6A)	96 (<i>S</i>)
7 ^d	Cy; 1E	<i>epi</i> Q-3 (0.05)	24	96 (6E)	96 (<i>S</i>)
8	PhCH=CH; 1H	<i>epi</i> Q-3 (0.05)	24	96 (6H)	94 (<i>S</i>)
9	Ph; 1I	<i>epi</i> Q-3 (0.05)	24	98 (6I)	94 (<i>S</i>)
10	4-ClC ₆ H ₄ ; 1J	<i>epi</i> Q-3 (0.05)	24	98 (6J)	93 (<i>S</i>)

^a Unless noted, reactions were performed with trifluoromethyl imines **1** (0.2 mmol), solid K₂CO₃ (2.8 mg, 10 mol%) and catalyst (x mol%) in PhMe (2.0 mL) at -20 °C for indicated time.

^b Yield of isolated product.

^c The ee value of product **6** was determined by HPLC analysis.

^d Reactions were performed at room temperature.