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Cinchonium Betaines as Efficient Catalysts for Asymmetric Proton Transfer Catalysis: The Development of a Practical Enantioselective Isomerization of Trifluoromethyl Imines

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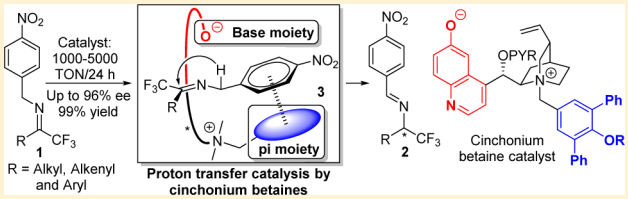
Supporting Information

ABSTRACT: We have developed a new class of cinchonium betaine catalysts bearing both a base moiety and an aromatic moiety as an *N*-substituent of the quinuclidine motif. These cinchonium betaines were found to promote proton transfer catalysis with 1000−5000 turnovers per 24 h, thereby enabling us to realize highly efficient enantioselective isomerization of trifluoromethyl imines to provide a practical access to optically active trifluoromethylated amines.



1. INTRODUCTION

We[1] and others[2] demonstrated that chiral organic catalysts containing both hydrogen-bond donor and acceptor could facilitate biomimetic 1,3-proton transfer catalysis to promote highly enantioselective olefin and imine isomerizations. These enantioselective isomerizations provide new access to valuable chiral building blocks such as α,β-unsaturated butenolides,[1a,3] α-amino acids,[2c] α,β-unsaturated cyclohexenones,[1c] and trifluoromethylated amines.[1b,2e] Among these studies, the realization of the first highly enantioselective isomerization[1b] of trifluoromethyl imines with DHQ-**3** stands as a conceptually significant progress as DHQ-**3** achieved efficient catalytic chiral recognition of nonenolate carbanions for asymmetric reactions (Figure 1).[4,5]

However, the required high catalyst loading (10 mol %) and long reaction time (48−72 h) severely hampered the application of this reaction in asymmetric synthesis. Moreover, the isomerizations with the pseudoenantiomeric catalyst DHQD-**3** proceeded with significantly lower enantioselectivity under optimized conditions (Figure 1). Consequently, this method was not able to provide useful access to the *S* enantiomers of chiral trifluoromethylated amines. These problems also apply to another cinchona alkaloid-derived bifunctional catalyst reported by Shi and co-workers for the same isomerizations.[2e] These limitations associated with existing methods highlighted both the urgent need and the challenges for the development of significantly more active and selective chiral catalysts for this promising asymmetric transformation. We wish to report in this Article the development of new chiral cinchonium betaine catalysts that afford powerful enantioselective proton transfer catalysis, which overcomes the limitations associated with existing chiral catalysts. The general scope, simple protocol for reaction execution and product isolation, and an extraordinarily low catalyst loading render this unprecedented, phase transfer catalysis-mediated enantioselective imine isomerization a practical method for the asymmetric synthesis of trifluoromethylated amines.[6−9]

2. RESULTS AND DISCUSSION

During our recent studies of C−C bond forming asymmetric umpolung reaction of imines,[10] we observed that certain cinchona alkaloid-derived chiral phase transfer catalysts promoted isomerization of trifluoromethyl imines. This observation raised the prospect of developing a new class of chiral catalysts for the promotion of asymmetric isomerizations of imines via a fundamentally different mechanism from those by acid−base bifunctional catalysts. Although highly enantioselective protonations of enol derivatives were reported,[11] a literature search revealed that phase transfer catalyst-promoted proton transfer reactions are still rare and only with modest enantioselectivity.[12]

Motivated by the possible discovery of new and powerful catalysts for enantioselective proton transfer catalysis, we began to explore cinchonium salts as catalysts for the isomerization of trifluoromethyl imine **1a**. At room temperature in the presence of aqueous KOH and 0.5 mol % cinchonium salts C-**5** and C-**6**, the model isomerization was found to proceed in very low enantioselectivity (entries 1,2, Table 1). We next examined catalyst C-**7**, which presented an electron-rich *N*-terphenyl group that was designed to engage in $\pi-\pi$ interaction with the 2-azaallylanions.[10] To our disappointment, C-**7** afforded even worse enantioselectivity (entry 3, Table 1). Moreover, imine **1a** was found to be transformed into not only the chiral amine **2a** but also the *N*-(1,1-difluoropropenyl) imine **4a**. The latter, presumably formed by the loss of fluoride from 2-azaallylanion **10a** (Figure 2a), was often the dominant product.[13]

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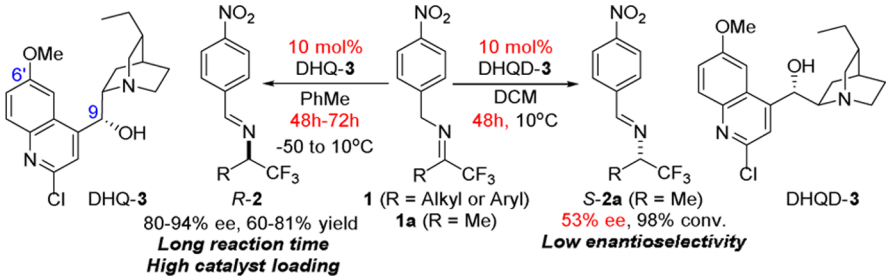
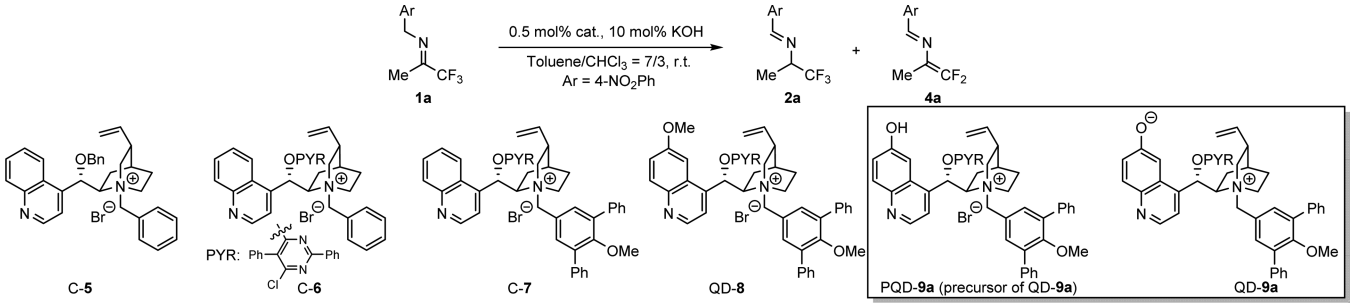


Figure 1. Drawbacks of asymmetric isomerization of trifluoromethyl imines with acid–base bifunctional catalysts.

Table 1. Asymmetric Isomerization of 1a with Cinchonium Betaine Catalysts[a]



entry	cat.	t (h)	conv. (%)[b]	ee (%)[b]	2a/4a[b]
1	C-**5**	4	16	−22	61/39
2	C-**6**	4	9	−26	45/55
3	C-7	4	10	−12	40/60
4	QD-**9a**[c]	1	100	91	97/3
5	QD-**8**	4	10	−33	34/66

[a]Reactions were run with **1a** (0.025 mmol), aqueous KOH (0.3 μL, 50 wt %, 10 mol %), and catalyst in toluene/$CHCl_3$ (7/3 v/v, 0.25 mL) at room temperature. [b]Determined by HPLC analysis. [c]The betaine catalyst QD-**9a** was generated in situ from PQD-**9a**.

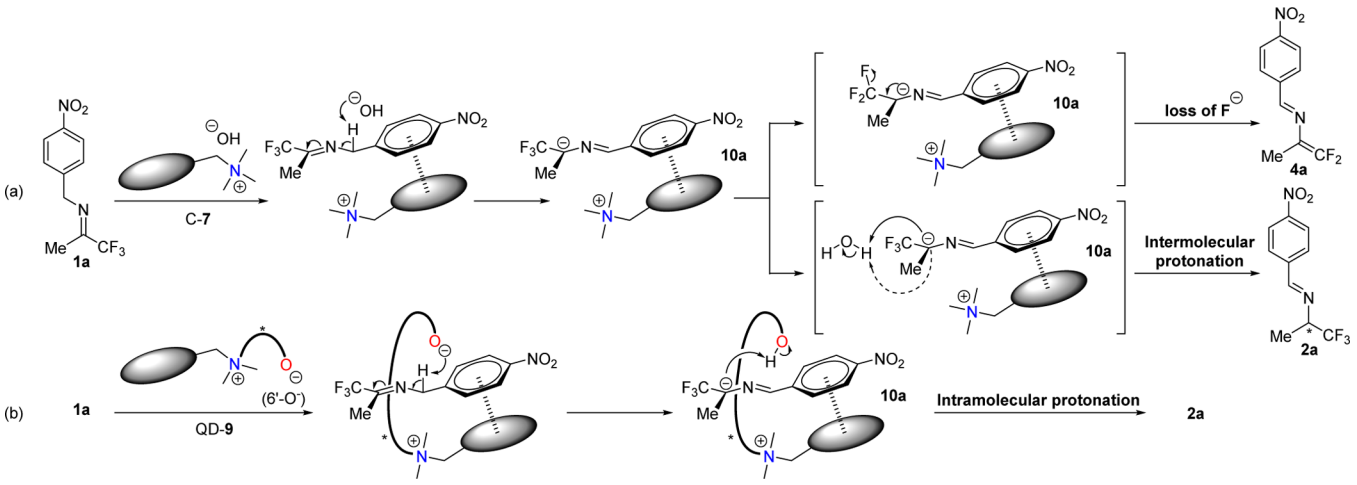


Figure 2. Working hypotheses.

These discouraging results indicated that, with cinchonium-based phase transfer catalysts, the enantioselective protonation of the 2-azaallyl anion **10a** proceeded not only with low enantioselectivity but also was too slow to establish the desired isomerization as the major reaction pathway (Figure 2a). Moreover, we suspected that the low enantioselectivity could be attributed to the difficulty in effectively biasing the two enantiotopic faces of the 2-azaallylanion **10a** toward the intermolecular protonation by water, a small proton donor. Following these considerations, we concluded that the intermolecular nature of the protonation step in these cinchonium salts-mediated isomerizations was largely responsible for the poor catalytic activity and enantioselectivity.

We postulated that we might be able to address this problem by installing an alkoxide functionality into the cinchonium salt C-7, which bears a π–π interaction moiety. As illustrated in Figure 2b, we hypothesized that such a betaine catalyst[11c,14−18] could, upon the binding of imine **1a** to the catalyst via π–π interaction, promote both the deprotonation and the protonation steps in an intramolecular-like setting. The

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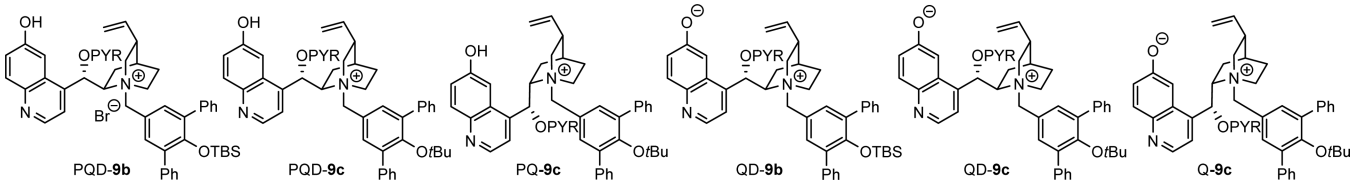
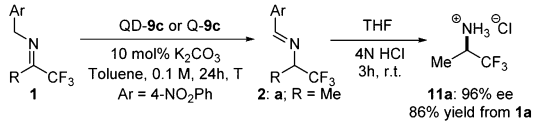
Table 2. Optimizations of Catalyst and Reaction Conditions for Enantioselective Isomerization of 1a[a]



entry	cat.	mol % of cat.	base presented in the reaction	solvent	t (h)	conv. (%)[b]	ee (%)[b]
1	QD-**9a**	0.5	no	toluene/$CHCl_3$ = 7/3	4	76	92
2	QD-**9b**	0.5	no	toluene/$CHCl_3$ = 7/3	4	97	93
3	QD-**9c**	0.5	no	toluene/$CHCl_3$ = 7/3	4	98	95
4	QD-**9c**	0.2	no	toluene/$CHCl_3$ = 7/3	24	77	95
5	QD-**9c**	0.2	solid K_2CO_3	toluene/$CHCl_3$ = 7/3	12	100	95
6	QD-**9c**	0.02	solid K_2CO_3	toluene	24	100	96[c]
7	QD-**9c**	0.01	solid K_2CO_3	toluene	24	97	96
8	Q-**9c**	0.05	solid K_2CO_3	toluene	24	100	−93

[a]Betaine catalysts QD-**9** and Q-**9c** were preformed from treatment of the corresponding precursors PQD-**9** and PQ-**9c** with base (see the Supporting Information for details). Reactions were run with **1a** (0.025 mmol) in solvent (0.25 mL) indicated. The ratio of **2a**/**4a** was determined to be greater than 99/1 by HPLC analysis. [b]Determined by HPLC analysis. [c]Absolute configuration was determined to be *R*. See the Supporting Information for details.

Table 3. Isomerization of 1 to 2 Catalyzed by QD-9c and Q-9c[a]



entry	1	R	T (°C)	mol % of cat.	yield (%)[b]	ee (%)[c]
1	**1a**	Me	rt	0.02 (0.05)	96 (96)	96 (−93)
2	**1b**	Et	rt	0.08 (0.10)	98 (97)	95 (−91)
3	**1c**	*n*-Bu	rt	0.10 (0.20)	97 (96)	96 (−90)
4	**1d**[d]	cyclohexyl	rt	0.50 (0.50)	97 (74)	94 (−86)
5	**1e**	*trans*-styryl	0	0.40 (0.40)	97 (96)	95 (−85)
6	**1f**	Ph	0	0.10 (0.10)	96 (96)	90 (−81)
7	**1g**	4-Me-C_6H_4	0	0.10 (0.10)	99 (97)	93 (−85)
8	**1h**	3-Me-C_6H_4	0	0.10 (0.10)	98 (98)	93 (−84)
9	**1i**	4-OMe-C_6H_4	0	0.10 (0.10)	99 (96)	93 (−84)
10	**1j**	4-F-C_6H_4	−20	0.20 (0.40)	97 (95)	90 (−84)
11	**1k**	4-Cl-C_6H_4	−20	0.20 (0.40)	95 (98)	88 (−81)
12	**1l**	4-Br-C_6H_4	−20	0.20 (0.40)	98 (96)	88 (−82)
13	**1m**	4-CF_3-C_6H_4	−20	0.20 (0.40)	96 (98)	83 (−76)
14	**1n**	4-COO*t*Bu-C_6H_4	−20	0.20 (0.40)	95 (94)	82 (−77)

[a]Betaine catalysts QD-**9c** and Q-**9c** were preformed from treatment of the corresponding precursors PQD-**9c** and PQ-**9** with base (see the Supporting Information for details). Reactions were run with **1** (0.2 mmol) in toluene (2.0 mL). Results in parentheses were obtained with Q-**9c**. [b]Isolated yield. [c]Determined by HPLC analysis. [d]An *E*/*Z* mixture of imine stereoisomers (*E*/*Z* = 3.2/1) was used.

protonation step should be greatly accelerated as it involved proton transfer between the alkoxide and the 2-azaallyanion intermediate located close to each other. More importantly, the spatial relationship between the phenol as the proton donor and the 2-azaallyanion interacting with the catalyst via $\pi-\pi$ and ion-pair interactions should be confined by the chiral backbone of the catalyst, thereby providing a more favorable setting for achieving fast and highly enantioselective protonation.

Guided by these considerations, we employed PQD-**9a** as a precursor of the cinchonium betaine catalyst QD-**9a** (Table 1). Initially, betaine QD-**9a** was examined for the isomerization of **1a** under the same conditions as those applied to catalysts C**5**-C7. We expected that QD-**9a** could be formed in situ via deprotonation of the PQD-**9a** by KOH. To our delight, the isomerization of **1a** went to completion in 1 h with 0.5 mol % of QD-**9a** to afford the desired chiral amine **2a** in 91% ee as virtually the only detectable product (entry 4, Table 1). In contrast, the quinidine-derived cinchonium salt QD-**8** afforded poor chemoselectivity and enantioselectivity, thereby showing the critical role played by the phenoxide of QD-**9a** for the efficient promotion of the enantioselective isomerization. The opposite sense of asymmetric induction by QD-**9a** versus that by C**5**-C7 and QD-**8** indicated that QD-**9a** exercised its enantioselectivity via a distinct mechanism. This notion is consistent with the working hypothesis of our catalyst design as outlined in Figure 2.

To further test whether the betaine QD-**9** was indeed responsible for the dramatically improved catalytic activity and selectivity, we carried out an isomerization with the preformed betaine QD-**9a** under base-free conditions. Specifically, we first treated PQD-**9a** with solid KOH in toluene/$CHCl_3$ for 15 min, when PQD-**9a** was shown by ^{1}H NMR analysis to be converted

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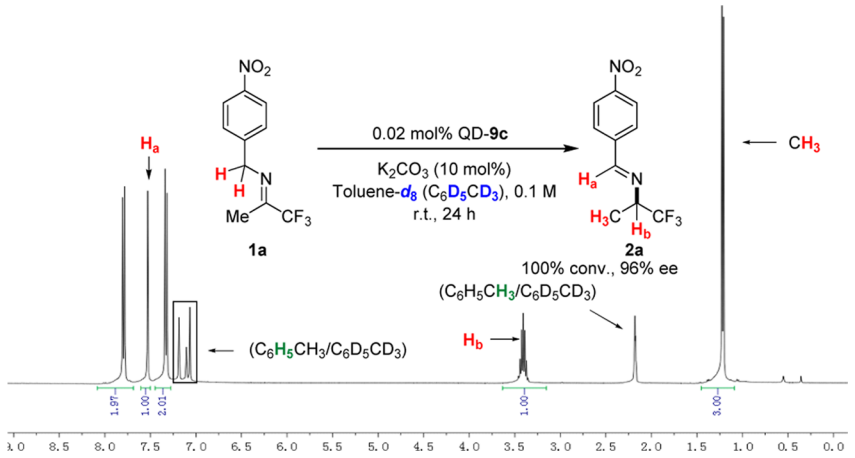

Figure 3. ^{1}H NMR spectra of **2a** isolated from labeling experiment in toluene-d_8 at 298 K using the standard reaction conditions.

into the betaine QD-**9a**.[19] The desired amount of the QD-**9a** solution in toluene/$CHCl_3$ then was added to a solution of imine **1a** in toluene/$CHCl_3$. After 4 h the isomerization was shown to proceed to 76% conversion to afford *R*-**2a** as the only detectable product in 92% ee (entry 1, Table 2). Upon further optimization by catalyst tuning (entries 2,3, Table 2), we were able to accomplish the isomerization in 98% conversion and 95% ee by employing betaine QD-**9c**.

We attempted to further reduce catalyst loading, but failed to accomplish a completed reaction with 0.2 mol % of QD-**9c** (entry 4, Table 2). Subsequently, we found that the presence of a solid base such as K_2CO_3 was highly beneficial for maintaining the activity of the betaine catalyst (entry 5 vs 4, Table 2). Upon optimizations of solvent, a highly enantioselective and complete isomerization of **1a** could be consistently accomplished in 24 h in toluene with only 0.02 mol % of QD-**9c** (entry 6, Table 2). Notably, the conversion only suffered very slightly with 0.01 mol % of QD-**9c** without compromising enantioselectivity, reaching 97% in 24 h. These results showed that the cinchonium betaine catalyst-mediated asymmetric proton transfer catalysis proceeded with an extraordinarily high catalyst turnover rate (entry 7, Table 2). Gratifyingly, a highly enantioselective isomerization of **1a** into *S*-**2a** could be accomplished with 0.05 mol % of quinine-derived betaine Q-**9c** (entry 8, Table 2). Thus, the cinchonium betaine catalysts not only are far superior to existing organocatalysts in terms of catalyst efficiency but also bring a decisive synthetic advantage by offering useful access to either the *R* or the *S* enantiomer of the trifluoromethylated amines **2**.

We next investigated the substrate scope. Excellent enantioselectivity could be readily accomplished for a variety of aliphatic trifluoromethyl imines of varying length (**1a**−**1c**) with QD-**9c** in 0.02−0.10 mol % loading (entries 1−3, Table 3). For the sterically more hindered cyclohexyl trifluoromethyl imine **1d**, a catalyst loading of 0.50 mol % was required to achieve a highly enantioselective and complete isomerization in 24 h (entry 4, Table 3). Interestingly, we found that QD-**9c** promoted an unprecedented isomerization of α,β-unsaturated imine **1e** in excellent enantioselectivity and yield. It is noteworthy that the reaction proceeded without the formation of the olefin isomerization side product. The scope of the reaction was readily extended to a wide range of aryl trifluoromethyl imines (entries 6−12, Table 3). In most cases, a loading of 0.10−0.20 mol % of QD-**9c** was sufficient in affording a complete and highly enantioselective isomerization of imines **1** within 24 h to generate the corresponding optically active chiral aryl trifluoromethylated amines **2** in close to quantitative yields. Aryl trifluoromethyl imines bearing a strongly electron-withdrawing substituent such as **1m** and **1n** proved to be more challenging substrates; nonetheless, a quantitative reaction with good enantioselectivity could be mediated by 0.20 mol % of QD-**9c**. Importantly, isomerizations with betaine Q-**9c** in similarly low loading afforded the opposite enantiomer of the chiral trifluoromethylated amine in excellent yield and in only slightly lower optical purities (Table 3). The isomerization typically proceeded so cleanly that a simple filtration of the reaction mixture through a plug of deactivated silica gel followed by solvent removal furnished amines **2** in pure form as determined by NMR analysis. The NMR-pure isomerization product **2a**, without further purification, could be hydrolyzed to give the desired chiral trifluoromethylated amine **11a** in 86% yield and 96% ee.[1b]

To validate that the methine hydrogen in **2a** came from one of the benzylic hydrogen in **1a**, we first carried out the QD-**9c**-catalyzed isomerization of **1a** in toluene-d_8 using the standard reaction conditions. We next carried out the same isomerization with dry K_2CO_3 in anhydrous toluene-d_8 in drybox.[19] As shown by ^{1}H NMR analyses (Figure 3 and S-Figure 6), we found the chiral amine **2a** was formed without incorporation of deuterium. We also investigated a QD-**9c**-catalyzed isomerization of **1a** in toluene-d_8 with 40% KOD in D_2O, instead of K_2CO_3, as the base. We found that **2a** was formed in 92% ee and, once again, without incorporation of deuterium.[19] These results indicated that the methine hydrogen in **2a** indeed came from the benzylic hydrogen in **1a**, which was consistent with our hypothesis of how a cinchonium betaine like QD-**9c** mediated this highly enantioselective 1,3-proton transfer (Figure 2b). To verify that the $\pi-\pi$ interaction between imines **1** and catalyst **9c** played an important role to the catalysis by **9c** (Figure 2b), we investigated the isomerizations of both imines **1a**′ and **1a**″, which were derived by replacing the 4-NO_2 benzyl group in **1a** with a benzyl group and 4-carboxylatebenzyl group, respectively (Figure 4). Catalyst **9c** was found to be inactive toward the isomerization of imine **1a**′ and afforded significantly worse enantioselectivity (84% ee vs 96% ee) and lower conversion (43% vs 100%) for the isomerization of **1a**″. These results indicated that the 4-NO_2 benzyl group not only rendered imine **1a** more active toward the QD-**9c**-catalyzed isomerization but also played an important role in the substrate-catalyst chiral recognition.

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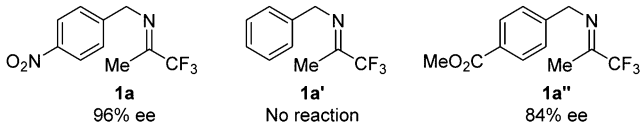

Figure 4. Isomerization of imines **1a**′ and **1a**″ with QD-**9c**.

3. CONCLUSION

Our exploratory studies of cinchonium betaines have led to the discovery of a new class of catalysts for enantioselective proton transfer catalysis. These new catalysts afforded a remarkably high catalyst turnover rate for the promotion of asymmetric isomerizations of trifluoromethyl imines.[20] Consequently, a broad range of alkyl, alkenyl, and aryl trifluoromethyl imines could be converted in a highly enantioselective manner into either enantiomer of the corresponding optically active trifluoromethylated amines with typically 0.02−0.10 mol % of the cinchonium betaines. With a mechanistically distinct mode of catalysis, this reaction should provide a complementary approach to existing methods for the asymmetric synthesis of trifluoromethylated amines.

4. EXPERIMENTAL SECTION

4.1. General Procedure for the Asymmetric Isomerization of Alkyl Trifluomethyl Imines 1a to 1d with Catalyst QD-9c. To a solution of catalyst PQD-**9c** (3.1 μmol, 3.0 mg) in toluene (180 μL) was added ground K_2CO_3 (0.065 mmol, 9.0 mg). The suspension was then stirred vigorously at room temperature for 2 h. After standing for 10 min, a portion of the clear solution (90 μL) was collected and diluted with toluene (810 μL). A portion of this diluted solution of QD-**9c** in toluene (0.040−1.0 μmol, 23 to 580 μL) was placed into a vial (3.7 mL), to which were added sequentially toluene (1.977−1.42 mL), ground K_2CO_3 (0.020 mmol, 2.8 mg), and trifluoromethyl imine **1** (0.20 mmol). The mixture then was allowed to stir at room temperature for 24 h. The reaction mixture was allowed to pass through a plug of deactivated silica gel[21] to remove the catalyst. The deactivated silica gel plug was then washed with diethyl ether (2.0−4.0 mL). The filtrate was concentrated in vacuo to give trifluoromethylated amines **2**.

4.2. General Procedure for the Asymmetric Isomerization of Alkenyl or Aryl Trifluomethyl Imines 1e to 1n with Catalyst QD-9c. To a solution of catalyst PQD-**9c** (3.1 μmol, 3.0 mg) in toluene (180 μL) was added ground K_2CO_3 (0.065 mmol, 9.0 mg). The suspension was then stirred vigorously at room temperature for 2 h. After standing for 10 min, a portion of the clear solution (90 μL) was collected and diluted with toluene (810 μL). A portion of this diluted solution of QD-**9c** in toluene (0.20−0.80 μmol, 120−460 μL) was placed into a vial (3.7 mL), to which were added sequentially toluene (680−340 μL) and ground K_2CO_3 (0.020 mmol, 2.8 mg). After the mixture was stirred at the designated temperature in Table 3 for 20 min, the solution of imine **1** (0.20 mmol) in toluene (1.2 mL) was added in one portion (the imine solution was also stirred at the specified temperature for 20 min). The mixture then was allowed to stir at the specified temperature for 24 h. The reaction mixture was allowed to pass through a plug of deactivated silica gel to remove the catalyst. The deactivated silica gel plug was then washed with diethyl ether (2.0−4.0 mL). The filtrate was concentrated in vacuo to give trifluoromethylated amines **2**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08727.

Detailed experimental procedures, and characterization of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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