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Organocatalytic asymmetric Mannich-type reaction of *N*-sulfonylimines with isocyanoacetate leading to optically active 2-imidazoline-4-carboxylates

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Dedicated to Professor Henri Kagan on the occasion of his 80th birthday

ABSTRACT

The first asymmetric Mannich-type reaction of methyl isocyanoacetate with *N*-sulfonylimines catalyzed by cinchona alkaloid derivatives yielded 2-imidazolines with high diastereoselectivities and good enantioselectivities (up to >99:1 dr and 70% ee). This reaction provided a convenient route to access various substituted 2-imidazoline-4-carboxylates and related α,β-diamino acids in high enantiomeric purities.

1. Introduction

The construction of 2-imidazolines has received considerable attention because of their wide applications in the synthesis of biologically active compounds such as α,β-diamino acids and also their presence in biologically active natural products.[1,2] The Mannich-type reaction of imines with isocyanocarboxylates is an important method for accessing useful substituted 2-imidazoline compounds[2] and has been previously performed using gold, ruthenium, and copper catalysts.

The base-promoted Mannich-type reaction was first reported by Schöllkoptf et al.[3] and van Leusen et al.[4] in 1977. In 1996 Hayashi et al. realized the Au(I)-catalyzed diastereoselective Mannich-type reaction of isocyanoacetate with *N*-sulfonylimines in quantitative yields and >90:10 *cis* selectivity.[5] Lin et al. found that the *trans* isomer of 2-imidazolines could be formed preferably with 95:5 selectivity in the presence of $RuH_2(PPh_3)_4$ catalyst.[6] Other catalysts such as NHC–CuCl[7] and pincer-Pd(II)[8] compounds were also developed recently for 2-imidazoline synthesis with *trans* selectivity.

The first enantioselective reaction was achieved by Lin in 1999, using Me_2SAuCl and ferrocene-derived diphosphine ligand to afford 88% ee.[9,10] In 2008, Szabó et al. also reported another asymmetric synthesis with a chiral pincer-Pd(II) catalyst and obtained 98% yield and 86% ee for the *cis* isomer.[11]

This reaction can also be conducted in multi-component form with in situ generated imines, whereas no asymmetric version has been developed until now.[12–14]

Recently, organocatalytic systems have been developed and they sometimes challenged the metal-catalyzed systems. In particular, the use of cinchona alkaloids has been successfully applied in various organocatalytic transformations.[15–33] To the best of our knowledge, there has been no report on the organocatalytic asymmetric cyclization of general isocyanoacetates and imines, although several examples can be used for references. Jorgensen et al. performed the highly enantioselective and diastereoselective Mannich reaction of α-aryl-substituted cyanoacetates and *N*-Boc-protected α-amino esters with cinchona alkaloid **1** (Fig. 1) as an organocatalyst.[30] Gong et al. reported an organocatalytic asymmetric aldol-reaction of α-aryl isocyanoacetates with various aldehydes, providing optically active oxazolines with good stereoselectivities (up to 18:1 dr and 90% ee) by using cinchona alkaloid **2** as a catalyst.[31] For relatively inert imine substrates and the significantly decreased α-H acidity of methyl isocyanoacetate substrate (compared with α-aryl-substituted isocyanoacetate),[32,33] the development of highly efficient organocatalytic Mannich-type reactions leading to chiral 2-imidazolines, a class of medicinally relevant heterocycles, is an important challenge.

Herein we disclosed the first asymmetric catalytic Mannich-type reaction of methyl isocyanoacetate with *N*-sulfonylimines by cinchona alkaloid derivatives to yield 2-imidazolines with high diastereoselectivities and good enantioselectivities (up to >99:1 dr and 70% ee). This reaction provided a convenient method to access various substituted 2-imidazolines and related α,β-diamino acids in high enantiomeric purities.

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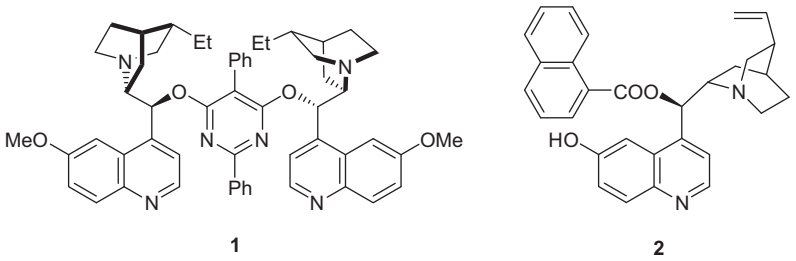
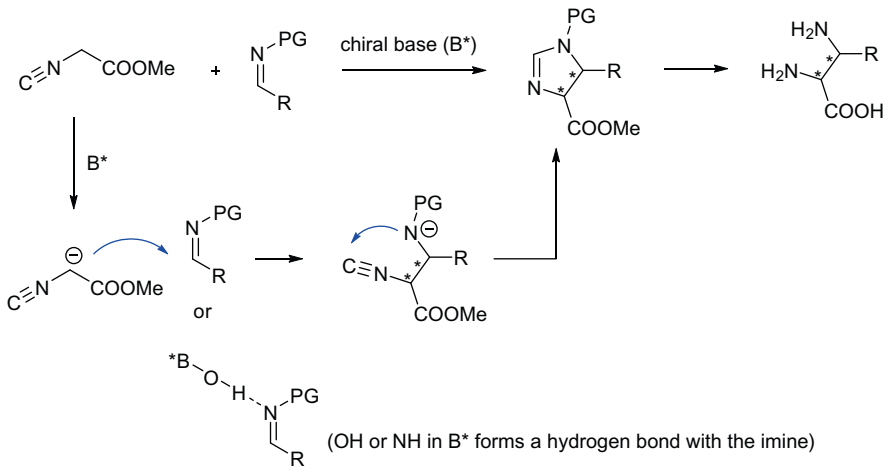
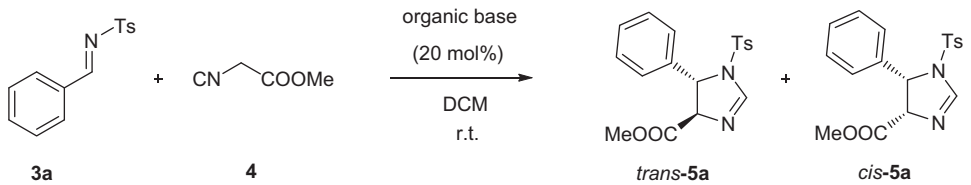


Figure 1. Some cinchona alkaloids for organocatalytic transformations.



Scheme 1. Possible mechanism for the Mannich-type reaction.

Table 1
Screening of organic bases for the reaction of *N*-Ts imine **3a** and methyl isocyanoacetate **4**[a]



3a **4** *trans*-**5a** *cis*-**5a**

Entry	Organic base	Time (h)	Yield[b] (%)	dr[c] (*trans*/*cis*)
1	Et_3N	11	65	89/11
2	DBU	2	83	95/5
3	DMAP	25	70	91/9
4	DABCO	9	76	88/12
5	iPr_2EtN	24	70	82/18
6	(−)-Sparteine	2	82	83/17

[a] Reaction conditions: **3a** (0.20 mmol), **4** (0.22 mmol), DCM (1 mL). Reaction time was determined by TLC.
[b] Isolated yield of the two isomers after silica gel column chromatography.
[c] Determined by ^1H NMR analysis.

2. Results and discussions

2.1. Optimization of the reaction conditions

Encouraged by Gong's work,[31,33] we speculated a possible mechanism for the Mannich-type reaction catalyzed by a chiral base (Scheme 1). The chiral base could activate the acidic α-carbon atom of isocyanoacetate, hence promoting the asymmetric Mannich addition of the isocyanoacetate to imines. Subsequent intramolecular cyclization afforded 2-imidazoline-4-carboxylate, which could be converted into α,β-diamino acids after hydrolysis.

Initially experiments of the Mannich-type reaction of methyl isocyanoacetate **4** with *N*-*p*-toluenesulfonylimine **3a** were carried out in the presence of 20 mol% of an organic base. With dichloromethane as a solvent, various tertiary amines such as Et_3N, DBU, DMAP, DABCO, *i*-Pr_2EtN, and (−)-sparteine have been examined for comparison. In all cases, the reaction proceeded smoothly, giving the *trans* product of 2-imidazoline **5a** selectively in good yield. The results are summarized in Table 1. The highest yield (83%) and diastereoselectivity (95:5 dr) were achieved with a strong base (DBU, entry 2). Other tertiary amines afforded good yields but with slightly lower diastereoselectivities. In the absence of any base cat-

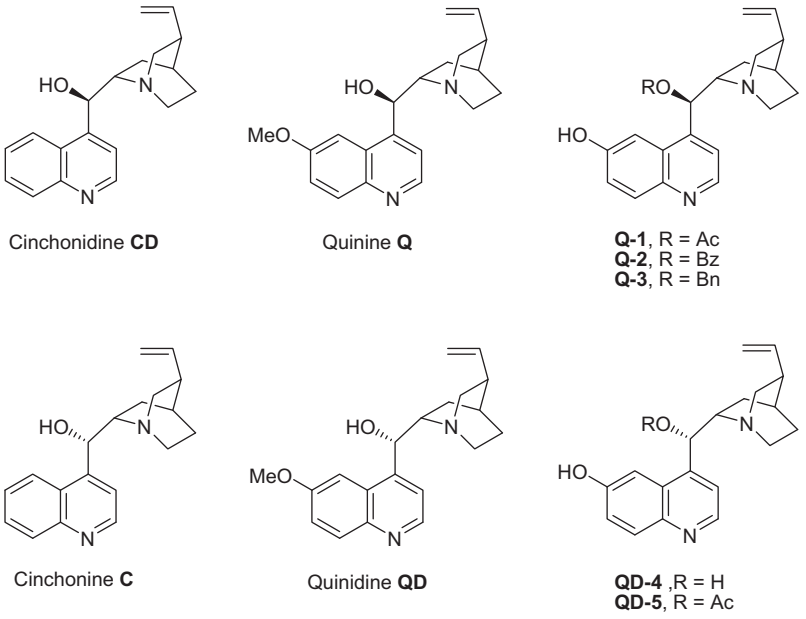


Figure 2. Cinchona alkaloid-derived catalysts tested in this study.

alyst, the reaction did not take place under otherwise identical conditions.

When (−)-sparteine was used as the chiral base in this reaction, *trans*-**5a** was obtained but in almost *racemic* form. Therefore, we turned our attention to cinchona alkaloid derivatives which have been reported as efficient organocatalysts for many asymmetric nucleophilic addition reactions. It was anticipated that activation of the less active methyl isocyanoacetate by deprotonation, followed by the subsequent cycloaddition of isocyanoesters to imines would provide optically active 2-imidazolines.

In the presence of 20 mol % of commercially available cinchona alkaloid **Q** (Fig. 2), *N*-Ts imine **3a** reacted with methyl isocyanoacetate **4** to afford the desired 2-imidazoline **5a** in good yield and high diastereoselectivity, but no enantioselectivity (Table 2, entry 1). Other commercially available cinchona alkaloids showed similar results (entries 1–4). The stereochemical discrimination could be markedly improved by using cinchona alkaloids bearing two or more activating functionalities such as **Q-1** or **QD-5** (entries 5 and 9). The introduction of a hydroxyl group at the 6′-position helped to form an additional hydrogen bond with the substrate, while 9-OAc group provided proper steric hindrance to ensure higher enantioselectivity.

The effect of solvents on the catalytic Mannich-type reaction was examined in the presence of **QD-5** catalyst, and the results are listed in Table 2 (entries 9–15). It appeared that toluene was a suitable solvent with respect to reaction time, yield, diastereo-, and enantioselectivity. Acetonitrile was effective in terms of diastereoselectivity, while 1,4-dioxane afforded a higher yield with longer reaction time. Adding 4 Å molecular sieves to the reaction system led to a shorter reaction time and significantly higher enantioselectivity (entry 16).

When the catalyst loading was varied from 20 to 5 mol %, a decrease in yield but comparable enantioselectivity could be observed (entries 16–18). To balance both the yield and the selectivity, we chose 10 mol % as the catalyst ratio. Thus the optimal reaction conditions for the asymmetric Mannich-type reaction of isocyanoacetate with imines have been established. Using 10 mol % **QD-5** as a catalyst, toluene as a solvent, and 4 Å MS as the additive, 56% yield of 2-imidazoline with 91:9 diastereoselectivity and 61% enantioselectivity was obtained (entry 17). The above-mentioned reaction conditions were then employed in subsequent studies.

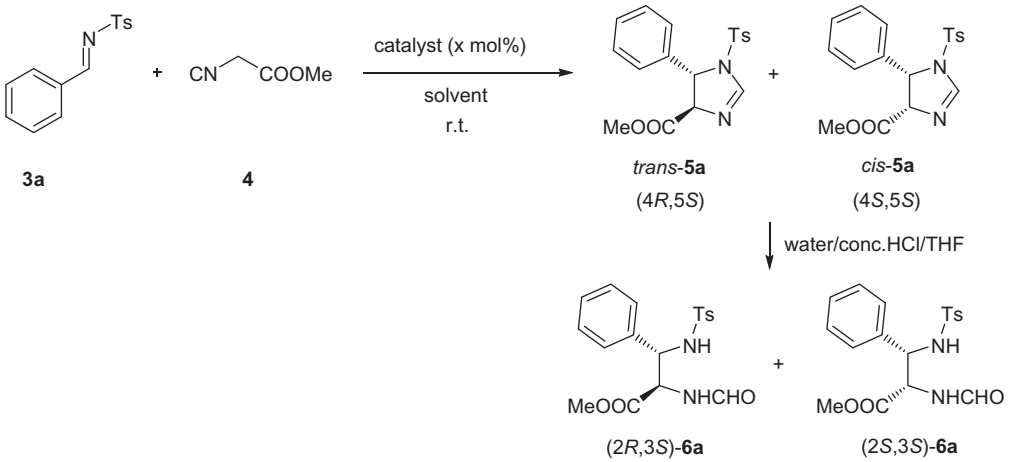
Varying the protecting group of the imine has a dramatic impact on both the rate and asymmetric induction. A strong electron-withdrawing group such as tosyl was quite necessary for the activation of the C=N bond to afford the corresponding 2-imidazoline in good yield and diastereoselectivity, while *N*-PMP or *N*-Bn protected imines led to only trace amounts of the products even after 7 days.

2-Imidazoline **5a** was converted to **6a** by hydrolysis. The absolute configuration of **6a** was determined to be (2*R*,3*S*) by comparison of the order of peak elution from HPLC analyses with the literature.[11] Thus the absolute configuration of major *trans*-**5a** was assigned as (4*R*,5*S*) while major *cis*-**5a** was assigned as (4*S*,5*S*).

The condensation reaction of **3a** with **4** in the presence of catalytic amounts of **Q** and **QD** was found to be complete within 6 h (Table 2, entries 1 and 2), indicating that the catalytic activity of **Q** and **QD** in this process was much higher than 9-protected **Q** (**Q1-3**, entries 5–7) and **QD** (**QD4-5**, entries 8 and 9), which required at least 35 h to complete the reaction. We reasoned that the stronger Brønsted basicities of **Q** and **QD** accelerated the reaction.

We also monitored the progress of the catalytic reaction in order to gain some mechanistic insights into the condensation reactions. It appeared that the *trans*/*cis* ratio and the ee for the *trans* isomer were increased very slightly in the reaction system (Table 3), high *trans* selectivity (*trans*/*cis* ratio 84:16) was obtained at the beginning of the reaction (entry 1). No isomerization of *cis*-**5a** to *trans*-**5a** was observed at the first 6 h when *cis*-**5a** was treated under the reaction conditions, which revealed that the stereoselectivity of the process was not coming from the isomerization of the thermodynamically less stable *cis*-imidazoline, but from the induction of the chiral organocatalyst. However, long reaction times caused partial isomerization of *cis*-**5a** (*trans*/*cis* 12:88 after 24 h).

Table 2
Mannich-type reaction of **3a** and **4** with different chiral organocatalysts[a]

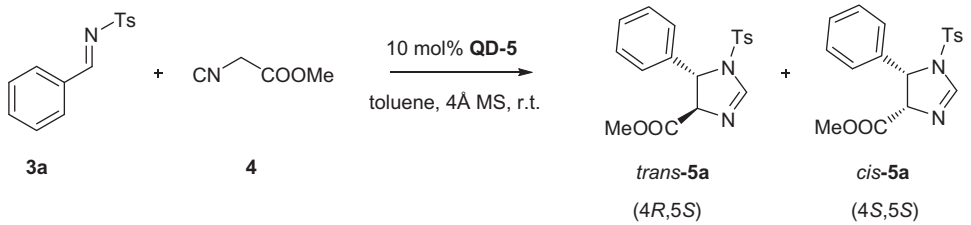


3a **4** *trans*-**5a** (4*R*,5*S*) *cis*-**5a** (4*S*,5*S*) (2*R*,3*S*)-**6a** (2*S*,3*S*)-**6a**

Entry	Catalyst	Catalyst loading (mol %)	Solvent	Time (h)	Yield[b] (%)	dr[c] (*trans*/*cis*)	ee of *trans*[d]	pK_{BH^+}[f]
1	**Q**	20	DCM	5	71	81/19	5	9.28
2	**QD**	20	DCM	6	73	93/7	5	9.28
3	**C**	20	DCM	42	59	91/9	4	9.33
4	**CD**	20	DCM	15	71	92/8	0	9.33
5	**Q-1**	20	DCM	48	42	93/7	38	8.61
6	**Q-2**	20	DCM	70	47	85/15	28	8.60
7	**Q-3**	20	DCM	48	45	93/7	17	8.77
8	**QD-4**	20	DCM	35	50	90/10	7	8.82
9	**QD-5**	20	DCM	70	46	81/19	44	8.61
10	**QD-5**	20	MeCN	72	31	93/7	2	
11	**QD-5**	20	THF	118	36	88/12	28	
12	**QD-5**	20	1,4-Dioxane	216	65	86/14	26	
13	**QD-5**	20	MeOH	60	44	82/18	1	
14	**QD-5**	20	Et_2O	36	39	84/16	32	
15	**QD-5**	20	Toluene	72	47	90/10	47	
16[e]	**QD-5**	20	Toluene	48	60	86/14	63	
17[e]	**QD-5**	10	Toluene	48	56	91/9	61	
18[e]	**QD-5**	5	Toluene	48	49	84/16	61	

[a] Reaction conditions: **3a** (0.20 mmol), **4** (0.22 mmol), solvent (1 mL). Reaction time was determined by TLC.
[b] Isolated yields of the two isomers after silica gel column chromatography.
[c] The dr was determined by ^{1}H NMR.
[d] The ee was determined by HPLC.
[e] 4 Å MS (200 mg) was added and the concentration of **3a** was increased to 0.50 mol/L.
[f] Refers to the dissociation constant of the protonated base in water, values were calculated with the use of Advanced Chemistry Development (ACD/Labs) Software V8.14 for Solaris (© 1994–2006 ACD/Labs).

Table 3
Formation of **5a** from **3a** and **4** catalyzed by **QD-5**[a]

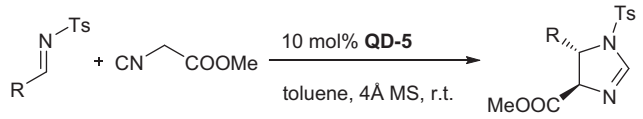


3a **4** *trans*-**5a** (4*R*,5*S*) *cis*-**5a** (4*S*,5*S*)

Entry	Time (h)	Yield[b] (%)	dr[c] (*trans*/*cis*)	ee of *trans*[d] (%)
1	6	17	84/16	58 (36)
2	12	27	85/15	59 (41)
3	18	33	87/13	60 (43)
4	24	38	89/11	60 (45)
5	36	48	90/10	60 (47)
6	48	62	91/9	60 (48)

[a] Reaction conditions: **3a** (0.50 mmol), **4** (0.55 mmol), solvent (1 mL) and 4 Å MS (200 mg).
[b] Isolated yields of the two isomers after silica gel column chromatography.
[c] The dr was determined by ^{1}H NMR.
[d] The ee was determined by HPLC. Data in parenthesis are the ee of the *cis* isomer.

Table 4
Mannich-type reaction of various *N*-Ts imines **3a–n** and methyl isocyanoacetate **4**[a]



3a-n **4** *trans*-**5a-n** (4*R*,5*S*)

Entry	R	Product	Time (h)	Yield[b] (%)	dr[c] (*trans*/*cis*)	ee of *trans*[d] (%)
1	Phenyl **a**	**5a**	48	56	91/9	61
2	4-Methylphenyl **b**	**5b**	48	57	95/5	70
3	4-Methoxyphenyl **c**	**5c**	72	49	98/2	68
4	3-Methoxyphenyl **d**	**5d**	84	34	>99/1	50
5	2-Methoxyphenyl **e**	**5e**	84	47	>99/1	50
6	2,5-Dimethoxyphenyl **f**	**5f**	84	44	>99/1	38
7	4-Chlorophenyl **g**	**5g**	48	50	96/4	48
8	4-Bromophenyl **h**	**5h**	60	48	95/5	48
9	4-Nitrophenyl **i**	**5i**	72	61	94/6	5
10	4-Isopropylphenyl **j**	**5j**	72	35	91/9	62
11	*4-tert*-Butylphenyl **k**	**5k**	72	43	92/8	58
12	2-Naphthyl **l**	**5l**	72	78	98/2	53
13	2-Furyl **m**	**5m**	48	62	95/5	18
14	2-Thienyl **n**	**5n**	60	79	95/5	52

[a] Reaction conditions: **3** (0.50 mmol), **4** (0.55 mmol), toluene (1 mL). Reaction time was determined by TLC.
[b] Isolated yields of the two isomers after silica gel column chromatography.
[c] Determined by ^{1}H NMR of the crude product.
[d] Determined by HPLC after purification.

2.2. Scope and limitation of the catalytic system

Next we investigated the scope of the imine substrates. A variety of aromatic and heteroaromatic imines were used in the Mannich-type reaction, affording the desired 2-imidazoline products in good yields and stereoselectivities (Table 4). In all cases, *trans* 2-imidazolines were obtained preferably (dr up to 99/1). The steric effects of the aromatic rings of the imines on the enantioselectivity of the reaction were significant. The less sterically hindered *para*-methoxy-substituted imine afforded 68% ee for the preferable *trans*-adduct, while both *ortho*- and *meta*-methoxy substituted imines gave 50% ee (entries 3–5). Hindered 2,5-dimethoxy substituted imine offered only 38% ee (entry 6). In the presence of **QD-5** organocatalyst, the highest enantioselectivity (70% ee) was achieved in the condensation reaction of imine **3b** and methyl isocyanoester **4** (entry 2).

We also found that the enantioselectivity was affected by the electronic properties of the substituents on the phenyl rings of the imines. For example, a strong electron-withdrawing *para*-NO_2 group afforded a poor ee value for the *trans*-adduct (entry 9), while moderate electron-withdrawing Cl and Br groups provided better ees (entries 7 and 8); higher ees were obtained with electron-donating groups such as methyl and methoxy (entries 2 and 3).

The **QD-5**-catalyzed reaction also worked well for heteroaromatic *N*-Ts imine **3m** and **3n**, affording good yields and diastereoselectivities, albeit at lower enantioselectivity for the *trans*-**5m** adduct (entries 13 and 14).

3. Conclusions

In conclusion, we have developed the first organocatalytic asymmetric cycloaddition of methyl isocyanoacetate to various *N*-sulfonylimines by using cinchona alkaloid-derived catalysts to form 2-imidazolines with high diastereoselectivities and good enantioselectivities. The simplicity of operation, mild reaction conditions, high yields, and high stereoselectivity of the nucleophilic addition offer promise for the synthesis of nitrogen-heterocyclic compounds as well as useful α,β-diamino acids.

4. Experimental

4.1. General methods

All reactions were carried out in flame-dried glassware under a nitrogen atmosphere. All solvents were freshly distilled prior to use. Unless otherwise stated, commercial reagents were purchased from Alfa Aesar, Acros, Aldrich, or Shanghai Aladdin chemical companies and were used without further purification. Purification of the reaction products was carried out by flash column chromatography using Qing Dao Sea Chemical Reagent silica gel (200–300 mesh). ^{1}H NMR spectra were recorded on a Bruker Avance III spectrometer (400 MHz) and the spectra were referenced internally to the residual proton resonance in $CDCl_3$ (δ = 7.26 ppm), or with tetramethylsilane (TMS, δ = 0.00 ppm) as the internal standard. Chemical shifts were reported as parts per million (ppm) in the δ scale downfield from TMS. ^{13}C NMR spectra were recorded on a Bruker (400 MHz) spectrometer with complete proton decoupling, and chemical shifts were reported in ppm from TMS with the solvent as the internal reference ($CDCl_3$, δ = 77.0 ppm). HPLC analyses were conducted on a Shimadzu 10A instrument using Daicel Chiralcel OD-H, AD-H, or AS-H column (0.46 cm diameter × 25 cm length). Mass spectra were recorded on an ESI-ion trap mass spectrometer (Shimadzu LCMS-IT-TOF). Optical rotations were recorded on a Perkin–Elmer polarimeter (Model 341). Analytical TLC was performed using EM separations percolated silica gel 0.2 mm layer UV 254 fluorescent sheets.

The cinchona alkaloid derivatives **Q**, **QD**, **C**, **CD** were commercially available. **Q-1**, **Q-2**, **Q-3** and **QD-4**, **QD-5** were prepared as previously described.[23–25] All *N*-sulfonylimines **3** and methyl isocyanoacetate **4** were prepared according to literature methods.[34–37]

4.2. General procedure for the Mannich-type cycloaddition reaction

Methyl isocyanoacetate **4** (50 μL, 0.55 mmol) was added in a dropwise manner to a mixture of *N*-sulfonylimine **3** (0.50 mmol), catalyst **QD-5** (17.6 mg, 10 mol %), and 4 Å MS (200 mg) in 1 mL toluene at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at ambient temperature until the imine was consumed (monitored by TLC). Then the solvent was removed to yield a crude mixture of 2-imidazoline. The *trans*/*cis* ratio was determined by ^{1}H NMR spectroscopy. The product was purified by flash column chromatography with petrol ether/ethyl acetate as eluent. The ee values were determined by HPLC analyses. Absolute configurations of the major products were determined by comparison of the order of peak elution from HPLC analyses with literature values.[11]

4.2.1. (4*R*,5*S*)-4-(Methoxycarbonyl)-5-phenyl-*N*-tosyl-2-imidazoline 5a[5]

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, J = 2.2 Hz, 1H), 7.46 (d, J = 8.3 Hz, 2H), 7.25–7.15 (m, 7H), 5.08 (d, J = 7.5 Hz, 1H), 4.66 (dd, J = 7.5, 2.2 Hz, 1H), 3.71 (s, 3H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.8, 150.2, 144.8, 138.1, 134.4, 129.8, 128.9, 128.5, 127.3, 127.0, 79.8, 63.8, 52.9, 21.6. HPLC conditions: Daicel Chiralcel OD-H column, *i*-PrOH/hexane 5:95, flow rate 0.8 mL/min, UV detection at 254 nm, t_{major} = 29.1 min, t_{minor} = 32.9 min.

4.2.2. (4*R*,5*S*)-4-(Methoxycarbonyl)-5-(4-methylphenyl)-*N*-tosyl-2-imidazoline 5b

$[\alpha]_D^{20} = +40$ (*c* 1.0, THF, 70% ee). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, J = 2.2 Hz, 1H), 7.47 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 8.1 Hz, 2H), 7.04 (s, 4H), 5.01 (d, J = 7.5 Hz, 1H), 4.65 (dd, J = 7.5, 2.2 Hz, 1H), 3.70 (s, 3H), 2.41 (s, 3H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.8, 150.1, 144.7, 138.4, 135.1, 134.5, 129.7, 129.5, 127.4, 126.9, 79.9, 63.7, 52.8, 21.6, 21.1. HRMS (ESI-TOF): *m*/*z* calcd for $C_{19}H_{21}N_2O_4S$ $[M+H]^+$: 372.1144; found: 372.1149. HPLC conditions: Daicel Chiralcel OD-H column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, UV detection at 254 nm, t_{major} = 8.9 min, t_{minor} = 9.7 min.

4.2.3. (4*R*,5*S*)-4-(Methoxycarbonyl)-5-(4-methoxyphenyl)-*N*-tosyl-2-imidazoline 5c[5]

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, J = 2.4 Hz, 1H), 7.46 (d, J = 7.8 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.2 Hz, 2H), 6.76 (d, J = 8.2 Hz, 2H), 5.05 (d, J = 7.5 Hz, 1H), 4.66 (dd, J = 7.5, 2.4 Hz, 1H), 3.78 (s, 3H), 3.70 (s, 3H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.9, 159.8, 150.0, 144.6, 134.6, 130.0, 129.7, 128.3, 127.3, 114.2, 79.8, 63.5, 55.3, 52.8, 21.6. HPLC conditions: Daicel Chiralcel OD-H column, *i*-PrOH/hexane 25:75, flow rate 1.0 mL/min, UV detection at 254 nm, t_{minor} = 11.7 min, t_{major} = 13.3 min.

4.2.4. (4*R*,5*S*)-4-(Methoxycarbonyl)-5-(3-methoxyphenyl)-*N*-tosyl-2-imidazoline 5d

$[\alpha]_D^{20} = +22$ (*c* 1.0, THF, 50% ee). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, J = 2.2 Hz, 1H), 7.47 (d, J = 8.3 Hz, 2H), 7.19–7.13 (m, 3H), 6.79–6.76 (m, 2H), 6.58 (s, 1H), 5.07 (d, J = 7.5 Hz, 1H), 4.66 (dd, J = 7.5, 2.2 Hz, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.7, 159.9, 150.1, 144.8, 139.4, 134.5, 129.9, 129.7, 127.3, 119.4, 114.2, 112.0, 79.8, 63.7, 55.1, 52.8, 21.5. HRMS (ESI-TOF): *m*/*z* calcd for $C_{19}H_{20}N_2NaO_5S$ $[M+Na]^+$: 388.1093; found: 388.1105. HPLC conditions: Daicel Chiralcel AS-H column, *i*-PrOH/hexane 25:75, flow rate 1.0 mL/min, UV detection at 254 nm, t_{major} = 13.4 min, t_{minor} = 28.6 min.

4.2.5. (4*R*,5*S*)-4-(Methoxycarbonyl)-5-(2-methoxyphenyl)-*N*-tosyl-2-imidazoline 5e

$[\alpha]_D^{20} = +24$ (*c* 1.0, THF, 50% ee). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (d, J = 2.0 Hz, 1H), 7.45 (d, J = 8.2 Hz, 2H), 7.29–7.22 (m, 2H), 7.18 (d, J = 8.1 Hz, 2H), 6.91 (t, J = 7.4 Hz, 1H), 6.63 (d, J = 8.2 Hz, 1H), 5.29 (d, J = 7.0 Hz, 1H), 4.68 (dd, J = 7.0, 1.8 Hz, 1H), 3.68 (s, 3H), 3.55 (s, 3H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.3, 156.9, 149.7, 149.6, 144.3, 134.7, 129.9, 129.5, 127.3, 125.2, 120.5, 110.6, 77.9, 61.0, 54.9, 52.6, 21.5. HRMS (ESI-TOF): *m*/*z* calcd for $C_{19}H_{20}N_2NaO_5S$ $[M+Na]^+$: 388.1093; found: 388.1094. HPLC conditions: Daicel Chiralcel AS-H column, *i*-PrOH/hexane 25:75, flow rate 0.8 mL/min, UV detection at 254 nm, t_{minor} = 9.0 min, t_{major} = 10.0 min.

4.2.6. (4*R*,5*S*)-4-(Methoxycarbonyl)-5-(2,5-dimethoxyphenyl)-*N*-tosyl-2-imidazoline 5f

$[\alpha]_D^{20} = +19$ (*c* 1.0, THF, 38% ee). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (d, J = 2.1 Hz, 1H), 7.50 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 6.81 (d, J = 3.0 Hz, 1H), 6.77 (dd, J = 8.9, 3.1 Hz, 1H), 6.60 (d, J = 8.9 Hz, 1H), 5.27 (d, J = 7.0 Hz, 1H), 4.67 (dd, J = 7.0, 2.0 Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.56 (s, 3H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.2, 153.5, 151.0, 149.8, 144.4, 134.6, 129.5, 127.4, 115.0, 114.4, 111.6, 78.3, 60.5, 55.8, 55.5, 52.6, 21.5. HRMS (ESI-TOF): *m*/*z* calcd for $C_{20}H_{23}N_2O_6S$ $[M+H]^+$: 418.1199; found: 418.1210. HPLC conditions: Daicel Chiralcel OD-H column, *i*-PrOH/hexane 25:75, flow rate 0.8 mL/min, UV detection at 254 nm, t_{major} = 9.7 min, t_{minor} = 10.9 min.

4.2.7. (4*R*,5*S*)-4-(Methoxycarbonyl)-5-(4-chlorophenyl)-*N*-tosyl-2-imidazoline 5g[6]

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, J = 2.2 Hz, 1H), 7.47 (d, J = 8.3 Hz, 2H), 7.23–7.19 (m, 4H), 7.10 (d, J = 8.4 Hz, 2H), 5.04 (d, J = 7.5 Hz, 1H), 4.62 (dd, J = 7.5, 2.2 Hz, 1H), 3.71 (s, 3H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.6, 150.0, 145.1, 136.6, 134.6, 134.2, 129.9, 129.0, 128.3, 127.3, 79.8, 63.1, 52.9, 21.6. HPLC conditions: Daicel Chiralcel OD-H column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, UV detection at 254 nm, t_{minor} = 10.0 min, t_{major} = 11.5 min.

4.2.8. (4*R*,5*S*)-4-(Methoxycarbonyl)-5-(4-bromophenyl)-*N*-tosyl-2-imidazoline 5h

$[\alpha]_D^{20} = +20$ (*c* 1.0, THF, 48% ee). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, J = 2.0 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 5.03 (d, J = 7.5 Hz, 1H), 4.62 (dd, J = 7.5, 2.2 Hz, 1H), 3.70 (s, 3H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.5, 150.0, 145.1, 137.1, 134.2, 131.9, 129.9, 128.6, 127.3, 122.7, 79.7, 63.2, 52.9, 21.6. HRMS (ESI-TOF): *m*/*z* calcd for $C_{18}H_{18}BrN_2O_4S$ $[M+H]^+$: 436.0092; found: 436.0094. HPLC conditions: Daicel Chiralcel AS-H column, *i*-PrOH/hexane 25:75, flow rate 1.0 mL/min, UV detection at 254 nm, t_{major} = 10.6 min, t_{minor} = 23.1 min.

4.2.9. (4*R*,5*S*)-4-(Methoxycarbonyl)-5-(4-nitrophenyl)-*N*-tosyl-2-imidazoline 5i[6]

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 2.2 Hz, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 5.13 (d, J = 7.6 Hz, 1H), 4.63 (dd, J = 7.6, 1.5 Hz, 1H), 3.72 (s, 3H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.2, 150.2, 147.9, 145.6, 145.4, 133.6, 130.1, 127.8, 127.4, 124.1, 79.8, 62.9, 53.1, 21.6. HPLC conditions: Daicel Chiralcel AD-H column, *i*-PrOH/hexane 25:75, flow rate 1.0 mL/min, UV detection at 254 nm, t_{minor} = 43.0 min, t_{major} = 45.9 min.

4.2.10. (4*R*,5*S*)-4-(Methoxycarbonyl)-5-(4-isopropylphenyl)-*N*-tosyl-2-imidazoline 5j

$[\alpha]_D^{20} = +35$ (*c* 1.0, THF, 62% ee). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, *J* = 2.2 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.12 (d, *J* = 8.2 Hz, 2H), 7.06–7.01 (m, 4H), 5.10 (d, *J* = 7.4 Hz, 1H), 4.68 (dd, *J* = 7.4, 2.1 Hz, 1H), 2.81–2.88 (m, 1H), 3.70 (s, 3H), 2.37 (s, 3H), 1.20 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.9, 150.0, 149.4, 144.5, 135.2, 134.8, 129.6, 127.3, 127.0, 126.8, 79.8, 63.7, 52.8, 33.8, 24.0, 23.9, 21.5. HRMS (ESI-TOF): *m*/*z* calcd for $C_{21}H_{25}N_2O_4S$ $[M+H]^+$: 400.1457; found: 400.1470. HPLC conditions: Daicel Chiralcel OD-H column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, UV detection at 254 nm, t_{major} = 7.3 min, t_{minor} = 8.5 min.

4.2.11. (4*R*,5*S*)-4-(Methoxycarbonyl)-5-(4-*tert*-butylphenyl)-*N*-tosyl-2-imidazoline 5k

$[\alpha]_D^{20} = +32$ (*c* 1.0, THF, 58% ee). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66 (d, *J* = 2.2 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.1 Hz, 2H), 7.04 (d, *J* = 8.1 Hz, 2H), 5.14 (d, *J* = 7.4 Hz, 1H), 4.68 (dd, *J* = 7.4, 2.1 Hz, 1H), 3.70 (s, 3H), 2.36 (s, 3H), 1.27 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.8, 151.6, 149.9, 144.4, 134.9, 134.7, 129.6, 127.3, 126.8, 125.7, 79.8, 63.6, 52.8, 34.5, 31.3, 21.5. HRMS (ESI-TOF): *m*/*z* calcd for $C_{22}H_{27}N_2O_4S$ $[M+H]^+$: 414.1613; found: 414.1627. HPLC conditions: Chiralcel OD-H column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, UV detection at 254 nm, t_{major} = 6.9 min, t_{minor} = 8.3 min.

4.2.12. (4*R*,5*S*)-4-(Methoxycarbonyl)-5-(2-naphthyl)-*N*-tosyl-2-imidazoline 5l[8]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.77–7.64 (m, 4H), 7.59 (d, *J* = 2.1 Hz, 1H), 7.49–7.46 (m, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.18 (dd, *J* = 8.5, 1.0 Hz, 1H), 6.97 (d, *J* = 7.9 Hz, 2H), 5.30 (d, *J* = 7.4 Hz, 1H), 4.78 (dd, *J* = 7.4, 2.2 Hz, 1H), 3.72 (s, 3H), 2.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.8, 150.1, 144.7, 134.9, 134.5, 133.2, 132.9, 129.6, 129.0, 128.0, 127.6, 127.3, 126.8, 126.6, 126.5, 123.8, 79.8, 64.1, 52.9, 21.4. HPLC conditions: Daicel Chiralcel AD-H column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, UV detection at 254 nm, t_{major} = 19.7 min, t_{minor} = 28.8 min.

4.2.13. (4*R*,5*S*)-4-(Methoxycarbonyl)-5-(2-furyl)-*N*-tosyl-2-imidazoline 5m[6]

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56 (d, *J* = 2.0 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.16 (s, 1H), 6.39 (d, *J* = 3.2 Hz, 1H), 6.25 (s, 1H), 5.30 (d, *J* = 7.6 Hz, 1H), 4.92 (dd, *J* = 7.6, 2.0 Hz, 1H), 3.73 (s, 3H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.5, 149.4, 148.5, 144.6, 143.4, 134.7, 129.8, 127.2, 110.7, 110.5, 75.6, 56.9, 53.0, 21.6. HPLC conditions: Daicel Chiralcel AD-H column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, UV detection at 254 nm, t_{major} = 17.4 min, t_{minor} = 21.5 min.

4.2.14. (4*R*,5*S*)-4-(Methoxycarbonyl)-5-(2-thienyl)-*N*-tosyl-2-imidazoline 5n[8]

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58 (d, *J* = 2.2 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.30–7.20 (m, 3H), 7.01 (dd, *J* = 3.2, 0.7 Hz, 1H), 6.88 (dd, *J* = 5.0, 3.5 Hz, 1H), 5.46 (d, *J* = 7.4 Hz, 1H), 4.77 (dd, *J* = 7.4, 2.2 Hz, 1H), 3.71 (s, 3H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.4, 149.6, 144.8, 141.0, 134.6, 129.8, 127.4, 127.3, 126.8, 126.7, 80.0, 59.6, 53.0, 21.5. HPLC conditions: Daicel Chiralcel AS-H column, *i*-PrOH/hexane 25:75, flow rate 1.0 mL/min, UV detection at 254 nm, t_{major} = 13.1 min, t_{minor} = 19.3 min.

4.2.15. Methyl 2-formylamino-3-[(4-methylphenyl)sulfonyl]-amino-3-phenylpropanoate 6a[8,9,11]

Compound **6a** was obtained by stirring a mixture of water (0.073 g, 4.0 mmol), HCl (37%, 0.132 g, 0.37 mmol), THF (5 mL), and 2-imidazoline **5a** (0.233 g, 0.65 mmol) for 8 h at room temperature. The crude mixture was purified by chromatography using CH_2Cl_2/MeOH (80:1) as eluent to afford **6a**. The NMR data of **6a** were identical with the literature values.[8] HPLC conditions: Daicel Chiralcel OJ-H column, *i*-PrOH/hexane 15:85, flow rate 1.0 mL/min, UV detection at 210 nm, *syn* diastereomer t_r(2*R*,3*R*) = 21.9 min, t_r(2*S*,3*S*) = 40.5 min, *anti* diastereomer t_r(2*S*,3*R*) = 10.8 min, t_r(2*R*,3*S*) = 14.7 min. Specific rotation: $[\alpha]_D^{20} = +8.0$ (*c* 1.0, THF); corresponding to a *trans*/*cis* ratio of 91:9 for which the enantiomeric excess was *trans* 61% and *cis* 48%.

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