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Cinchona Alkaloid Squaramide/AgOAc Cooperatively Catalyzed Diastereo- and Enantioselective Mannich/Cyclization Cascade Reaction of Isocyanoacetates and Cyclic Trifluoromethyl Ketimines

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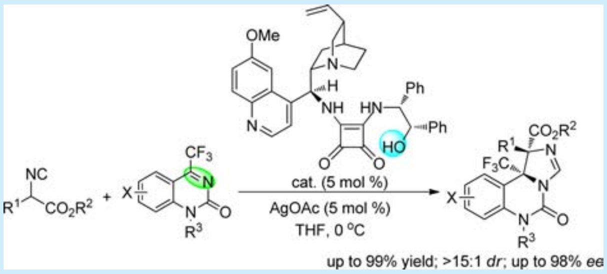
Supporting Information

ABSTRACT: An efficient diastereo- and enantioselective Mannich-type/cyclization cascade reaction of α-substituted isocyanoacetates and cyclic trifluoromethyl ketimines cooperatively catalyzed by *cinchona* alkaloid-derived multi-hydrogen-bonding donor squaramide and AgOAc has been investigated, affording the optically active trifluoromethyl-substituted tetrahydroimidazo[1,5-*c*]quinazoline derivatives in excellent yields (up to 99%) and good to excellent stereoselectivities (up to >15:1 dr, up to 98% ee) under mild conditions.



up to 99% yield; >15:1 *dr*; up to 98% *ee*

Optically active 2-imidazolines have emerged as attractive synthetic targets due to their wide applications in the synthesis of biologically active compounds,[1] cyclopalladated complexes, chiral catalysts, etc.[2] Thus far, considerable interest had been promoted to develop various excellent approaches for the asymmetric synthesis of chiral imidazolines. As one of the most efficient methods for the synthesis of imidazolines, the catalytic asymmetric Mannich-type/cyclization cascade reaction of isocyanoacetates and imines has received much attention.[3] Since Lin et al. reported the first example of an enantioselective Mannich-type reaction of isocyanoacetates and sulfonylimine catalyzed by Me_2SAuCl and a ferrocene-derived diphosphine ligand,[4] organometallic[5] and organocatalyzed[6] Mannich-type reactions of isocyanoacetates and imines have been widely investigated. However, most of these studies have been largely confined to aldimines, probably due to the lower reactivity of ketimines and the difficulties in enantiofacial discrimination for ketimines. Very recently, Dixon,[7a] Nakamura,[7b] and co-workers independently reported *cinchona*-derived aminophosphine/Ag_2O or *cinchona* alkaloid picolinamide/$Cu(OTf)_2/Cs_2CO_3$-catalyzed asymmetric Mannich-type reactions between isocyanoacetates and *N*-diphenylphosphinoyl (DPP)-protected ketimines, leading to the corresponding imidazolines that possess two consecutive tertiary−quaternary carbon stereocenters in high yields along with excellent enantioselectivities. However, only moderate stereoselectivity was obtained for the reaction of methyl 2-isocyanopropanoate and ketimine using *cinchona* alkaloid picolinamide/Et_2Zn/Cs_2CO_3 as catalyst.[7b] The highly enantioselective synthesis of chiral 2-imidazolines bearing vicinal quaternary−quaternary carbon stereocenters by the reaction of α-substituted isocyanoacetates with ketimines still remains a challenge.

Dihydroquinazolinones with a chiral trifluoromethyl moiety are an important class of heterocyclic compounds which have been characterized as potent HIV-1 non-nucleoside reverse transcriptase inhibitors, for example, drug candidates DPC 083 and DPC 961.[8] Therefore, considerable attention has been given to develop more synthetic efficient protocols for this kind of valuable framework. Contrary to the earlier work relying on chiral auxiliaries to control the stereoselectivity,[9] the catalytic asymmetric reactions of cyclic trifluoromethyl ketimines with different types of nucleophiles are more efficient and attractive.[10] In the past several years, catalytic asymmetric alkynylations,[10a,b] Mannich reaction,[10c] aza-Henry reaction,[10d] diynylation,[10e] Strecker reactions,[10f,g] decarboxylative Mannich reactions,[10h,i] hydrophosphonylation reaction,[10j] and aza-Friedel−Crafts reaction[10k] of cyclic trifluoromethyl ketimines had been widely investigated. As a part of our ongoing interest in the enantioselective reactions of isocyanoacetates with various electrophiles for the synthesis of polysubstituted chiral heterocycles,[11] we report herein the *cinchona* alkaloid-derived squaramide/AgOAc cooperatively catalyzed highly diastereo- and enantioselective Mannich-type/cyclization cascade reaction of α-substituted isocyanoacetates and trifluoromethylated cyclic ketimines, affording the corresponding optically active trifluor-

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omethyl-substituted tetrahydroimidazo[1,5-*c*]quinazoline derivatives in high yields along with excellent stereoselectivities.

In view of the concept of bifunctional H-bonding catalysis and the earlier successes in the asymmetric transformation of trifluoromethyl ketimines **2**,[10d,f−j] we envisioned that the diastereo- and enantioselective Mannich-type/cyclization cascade reaction of α-isocyanoacetates **1** and ketimines **2** may be realized in the presence of bifunctional chiral tertiary amine−thiourea or −squaramide catalysts. Thus, we initiated our study by examining the model reaction between isocyanoacetate **1a** and ketimine **2a** in the presence of quinine-derived thiourea (**3a**, 5 mol %, Figure 1) as the catalyst in THF at 0 °C. It was found that, in the absence of Ag^I salt, the reaction was sluggish and no desired product **4a** could be identified until 48 h (Table 1, entry 1). Considering that silver salts can promote the reaction between isocyanoacetates and various electrophiles,[11a,12] and encouraged by the development in the field of cooperative catalysis using *cinchona* alkaloid derivatives in combination with metal ions,[11a,12b,c,13] we assumed that *cinchona* alkaloid thiourea or squaramide/Ag^I salt cooperative catalysis could facilitate the expected Mannich-type/cyclization cascade reaction of isocyanoacetates **1** and ketimines **2**. A variety of bifunctional *cinchona* alkaloid-derived thiourea or squaramides, in combination with 5 mol % of AgOAc, were then examined in the model reaction, and the results of these experiments are summarized in Table 1. Quinine-derived thiourea **3a** exhibited high catalytic activity; the reaction was completed within 10 min, affording the desired product **4a** in high yield and good diastereoselectivity but with low enantioselectivity (Table 1, entry 2). However, quinine-derived squaramide **3b** can significantly improve the enantioselectivity along with similar dr value and yield (Table 1, entry 3). Inspired by the bifunctional amine thioureas bearing multiple hydrogen-bonding donors showing superior performance to the well-recognized aromatic thioureas,[14] we synthesized a series of *cinchona* alkaloid-derived squaramide-bearing multiple hydrogen-bonding donor catalysts **3c**−**e** and evaluated by combination with AgOAc (Table 1, entries 4−6). It was found that quinine-derived catalyst **3c** was the best for this reaction, affording **4a** in 99% yield with >15:1 dr and up to 98% ee (Table 1, entry 4). Further examination of the solvent effect revealed that the choice of solvent impacted the enantioselectivity only, and THF was still the most suitable one for the reaction (Table 1, entries 7−11). Reducing the organocatalyst loading from 5 to 3 mol % led to a slight decrease in enantioselectivity (Table 1, entry 12). The effects of temperature and silver salt were also examined, and it was found that no obvious temperature and silver salt effects were observed (Table 1, entries 13 and 14). Thus, the optimal reaction conditions have been identified as carrying out the reaction with 1.2 equiv of **1a** and 1.0 equiv of **2a** in THF (0.05 M for **2a**) at 0 °C using **3c** (5 mol %) and AgOAc (5 mol %) as the catalyst.

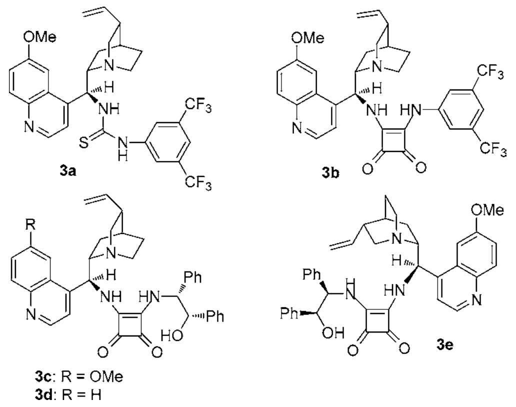
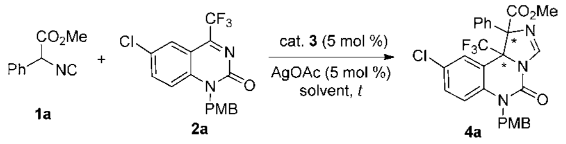


Figure 1. Evaluated organocatalysts **3**.

Table 1. Optimization of the Reaction Conditions[a]



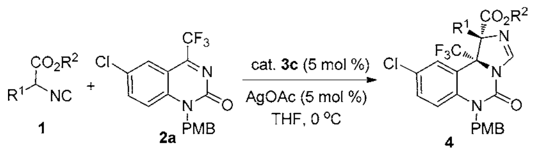
entry	catalyst	Ag^I	solvent	t (°C)	yield (%)	dr[b]	ee[c] (%)
1[d]	**3a**		THF	0	trace		nd
2	**3a**	AgOAc	THF	0	90	>15:1	29
3	**3b**	AgOAc	THF	0	92	>15:1	87
4	**3c**	AgOAc	THF	0	99	>15:1	98
5	**3d**	AgOAc	THF	0	92	>15:1	91
6	**3e**	AgOAc	THF	0	98	>15:1	−83
7	**3c**	AgOAc	toluene	0	99	>15:1	85
8	**3c**	AgOAc	DCM	0	99	>15:1	88
9	**3c**	AgOAc	Et_2O	0	99	>15:1	97
10	**3c**	AgOAc	EA	0	99	>15:1	93
11	**3c**	AgOAc	CH_3CN	0	99	>15:1	93
12[e]	**3c**	AgOAc	THF	0	99	>15:1	95
13	**3c**	AgOAc	THF	−15	99	>15:1	97
14	**3c**	$AgSbF_6$	THF	0	99	>15:1	98

[a] Unless noted otherwise, all reactions were carried out with isocyanoacetate **1a** (0.18 mmol), ketimine **2a** (0.15 mmol), catalyst **3** (5 mol %), and AgOAc (5 mol %) in solvent (3.0 mL). [b] The dr of the purified product was determined by ^1H NMR spectroscopy. [c] The ee was determined by HPLC on a chiral stationary phase. [d] For 48 h. [e] With 3 mol % of **3c** used.

Under the optimized reaction conditions, the scope of isocyanoacetates was first explored (Table 2). It was found that the reactions were not influenced by the electronic nature of the substituents; isocyanoacetates whether bearing electron-withdrawing (Table 2, entries 2−4 and 7) or electron-donating groups (Table 2, entries 5, 6, and 8) on the *para*- or *meta*-position of the aromatic ring acted as excellent substrates to react with ketimine **2a**, affording the corresponding products **4a**−**h** in high yields (91−99% yield) along with excellent stereoselectivities (>15:1 dr, 94−98% ee). However, the steric properties of the substituent played an important role in determining the reaction outcome. The presence of a substituent on the *ortho*-position of the aromatic ring significantly decreased the reactivity of isocyanoacetate, and no desired product **4i** was detected under the optimal conditions (Table 2, entry 9). Examination of the variation of the ester moiety showed that benzyl- and *tert*-butyl isocyanoacetates **1j** and **1k** reacted smoothly with **2a** to afford the desired products **4j**−**k** in similar high yields and excellent ee values, as well (Table 2, entries 10 and 11). Moreover, α-benzyl-substituted isocyanoacetate **1l** is not suitable for this reaction, affording product **4l** in high yield and good diastereoselectivity but with moderate ee value (Table 2, entry 12).

To further broaden the substrate scope, a variety of cyclic ketimines **2** bearing electron-withdrawing, electron-donating, or

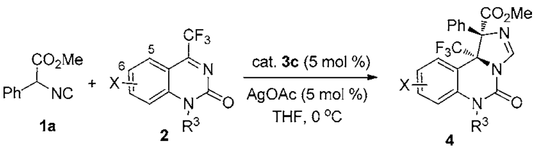
Table 2. Substrate Scope of Isocyanoacetates 1[a]



entry	1 (R^1, R^2)	4	yield (%)	dr[b]	ee[c] (%)
1	**1a** (Ph, Me)	**4a**	99	>15:1	98
2	**1b** (4-FC_6H_4, Me)	**4b**	95	>15:1	98
3	**1c** (4-ClC_6H_4, Me)	**4c**	99	>15:1	97
4	**1d** (4-BrC_6H_4, Me)	**4d**	99	>15:1	98
5	**1e** (4-MeC_6H_4, Me)	**4e**	99	>15:1	97
6	**1f** (4-MeOC_6H_4, Me)	**4f**	99	>15:1	95
7	**1g** (3-FC_6H_4, Me)	**4g**	91	>15:1	94
8	**1h** (3-MeC_6H_4, Me)	**4h**	99	>15:1	96
9	**1i** (2-BrC_6H_4, Me)	**4i**	nr		
10	**1j** (Ph, Bn)	**4j**	99	>15:1	97
11	**1k** (Ph, *t*-Bu)	**4k**	99	>15:1	95
12	**1l** (Bn, Me)	**4l**	98	>15:1	58

[a] All reactions were carried out with isocyanoacetates **1** (0.18 mmol), ketimine **2a** (0.15 mmol), catalyst **3c** (5 mol %), and AgOAc (5 mol %) in THF (3.0 mL) at 0 °C for 10 min. [b] The dr of the purified product was determined by ^{1}H NMR spectroscopy. [c] The ee was determined by HPLC on a chiral stationary phase.

Table 3. Substrate Scope of Ketimines 2[a]

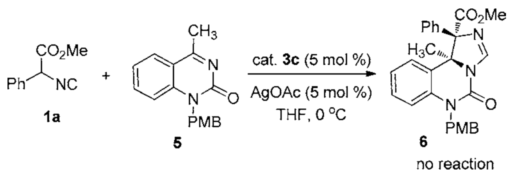


entry	2 (X, R^3)	4	yield (%)	dr[b]	ee[c] (%)
1	**2b** (6-F, PMB)	**4m**	95	>15:1	98
2	**2c** (6-Me, PMB)	**4n**	91	>15:1	97
3	**2d** (6-MeO, PMB)	**4o**	98	>15:1	95
4	**2e** (5-Me, PMB)	**4p**	81	>15:1	98
5	**2f** (H, PMB)	**4q**	76	>15:1	97
6	**2g** (6-Cl, TMB)	**4r**	99	>15:1	98
7	**2h** (6-Cl, H)	**4s**	99	>15:1	91

[a] All reactions were carried out with isocyanoacetate **1a** (0.18 mmol), ketimines **2** (0.15 mmol), catalyst **3c** (5 mol %). and AgOAc (5 mol %) in THF (3.0 mL) at 0 °C for 10 min. [b] The dr of the purified product was determined by ^{1}H NMR spectroscopy. [c] The ee was determined by HPLC on a chiral stationary phase.

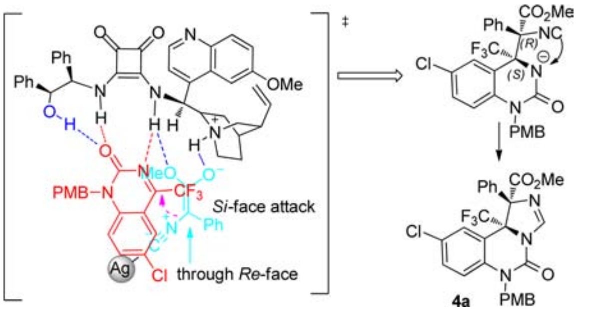
electron-neutral substituents on the phenyl ring were also evaluated. Ketimines **2b−g** proceeded in the Mannich-type/cyclization cascade reaction with **1a**, affording the corresponding products **4m−r** in good to high yields and excellent enantioselectivities (Table 3, entries 1−6). It should be noted that, different from previous reports on these types of cyclic ketimine-involved reactions[10c,d,h,i,k] in which the N-substituted benzyl protecting group at the ketimine substrate is very important for achieving the high level of asymmetric induction, N-H-substituted ketimine **2h** also gave the desired product **4s** in good enantioselectivity (91% ee) in our case (Table 3, entry 7). Moreover, with replacement of the trifluoromethyl group on the quinazolinones with a methyl group, a dramatic decrease in the reactivity was observed and no desired product **6** was detected (Scheme 1). This result indicated that the strong electron-withdrawing trifluoromethyl group is pivotal for this Mannich/cyclization cascade reaction to occur.

Scheme 1. Asymmetric Mannich-Type/Cyclization Cascade Reaction of Isocyanoacetate 1a and Ketimine 5



The relative and absolute configurations of the major diastereomer of **4d** were assigned as (1*R*,10b*S*) by single-crystal X-ray analysis[15] (see Figure S1 in the Supporting Information), and the other products were deduced by an analogue. A plausible transition state model, based on the experimental results and commonly accepted mechanisms, is proposed in Scheme 2. In this model, the *α*-proton of isocyanoacetate **1a** is easily deprotonated by the quinuclidine nitrogen of catalyst **3c** due to the activation of Ag^I chelating to the terminal carbon of the isocyano group, resulting in a single H-bonding interaction between the OH group of the enolized isocyanoacetate and the tertiary amine and a weak hydrogen bonding between the OMe group of the enolized isocyanoacetate and the NH in the squaramide moiety. Simultaneously, cyclic *N*-acyl ketimine **2a** was activated and oriented by hydrogen bonding with the NH and OH groups of the multi-hydrogen-bonding donor squaramide catalyst **3c**, thus forcing the isocyanoacetate enolate only to be delivered through the *Re* face to the *Si* face of the C═N and leading to the formation of two newly generated stereocenters with (*R*,*S*) configuration. Subsequently, a 5-*endo-dig* cyclization would occur by an intramolecular reaction between the amino group of the resulting Mannich intermediate and the isocyano group assisted by electrophilic silver isocyanide activation to afford the observed cyclic product **4a**.

Scheme 2. Proposed Transition State Model



In conclusion, we have developed the first example of a multi-hydrogen-bonding donor squaramide/AgOAc cooperative catalytic system for the highly diastereo- and enantioselective Mannich-type/cyclization cascade reaction of *α*-aryl isocyanoacetates and trifluoromethyl-substituted cyclic ketimines. A wide variety of isocyanoacetates and trifluoromethylated cyclic ketimines were tolerated in this reaction, leading to optically active trifluoromethyl-substituted tetrahydroimidazo-[1,5-*c*]quinazoline derivatives in excellent yields (up to 99%) and excellent stereoselectivities (up to >15:1 dr, up to 98% ee) under mild conditions. Investigations aimed at expanding this kind of bifunctional organo/metal cooperative catalysis with *cinchona* alkaloid squaramide scaffolds to other valuable transformations are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental procedure and characterization data of the products. Copies of NMR spectra and HPLC analysis spectra of compounds **4**, and X-ray structural data (CIF) of compound **4d** (CCDC 995270). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) CCDC 995270 (**4d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.