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Cinchona Alkaloid/Ti^{IV}-Catalyzed Enantioselective Enamine–Trifluoropyruvate Condensation–Cyclization Reaction and Its Application to Drug-like Heterocycles

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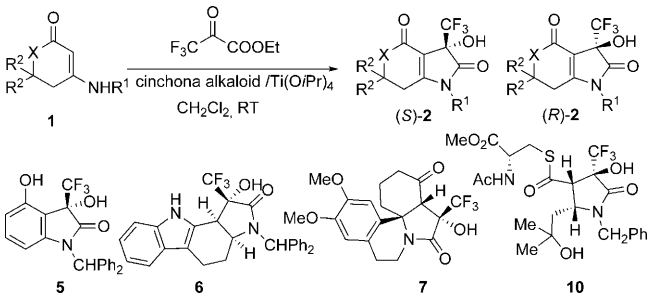
In memory of Professor Yoko Otsuka

Heterocycles are important structural motifs frequently encountered in natural products, pharmaceuticals and agrochemicals.[1] Indeed a large number of heterocycles decorated with diverse substituents have been synthesized for a wide variety of medicinal applications for over a century.[1] On the other hand, trifluoromethylated organic compounds have recently emerged expansively as promising biologically active motifs for drug design,[2] despite the fact that fluorine is "foreign" to the organic chemistry of life because only less than ten natural products containing a fluorine atom have been found.[3] Another point of interest in medicinal chemistry is the fact that the number of chiral drugs on the market has been rapidly increasing.[4] These facts led us to explore efficient routes for constructing optically pure, trifluoromethylated heterocycles to provide attractive surrogates for drug candidates.[5] Among commercially available products with a trifluoromethyl moiety on the structures, we are interested in trifluoropyruvates as building blocks for synthesizing trifluoromethylated heterocycles. Although enantioselective reactions using trifluoropyruvates have been competitively examined in recent years, such as the Friedel–Crafts reaction, the ene reaction, and others,[6] the construction of optically active heterocycles based on the trifluoropyruvate strategy is still rare.[7] In 2006, we reported the efficient synthesis of bicyclic α-hydroxy-α-trifluoromethyl-γ-lactams using a variety of enamines and ethyl trifluoropyruvate.[8] As a part of our research program for the enantioselective synthesis of fluorinated compounds,[9] we wish to report herein the first sequential, asymmetric enamine–pyruvate condensation–cyclization that provides trifluoromethyl-containing heterocycles in enantiomerically enriched form in the presence of a catalytic amount of cinchona alkaloids and Ti^{IV}. The heterocycles obtained by this reaction can be used as diverse, efficient chemical templates to yield a series of drug-like molecules with a trifluoromethylated quaternary carbon center represented by oxindole **5**, libophyllidine alkaloid-like **6**, erythrina alkaloid-like **7** and lactacystin-like **10** by conventional methods (Scheme 1).

We selected cinchona alkaloids as catalysts for the enamine–pyruvate asymmetric condensation–cyclization reaction, because of their availability on the market. When cinchonine was used as a catalyst for the reaction of enamine **1a** and ethyl trifluoropyruvate in CH_2Cl_2, the corresponding γ-lactam **2a** was provided in 80% yield with 49% *ee* (Table 1, entry 1). In the same reaction, but catalyzed by cinchonidine, 80% of **2a** was obtained with 42% *ee* with re-



Scheme 1. Cinchona alkaloid/Ti^{IV}-catalyzed enantioselective enamine–trifluoropyruvate condensation–cyclization and its application to drug-like heterocycles.

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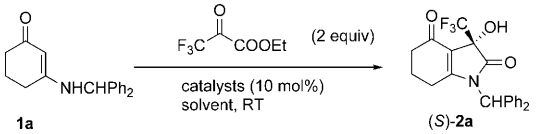
Table 1. Tandem condensation–cyclization reaction of enamine **1a** under the catalysis of cinchona alkaloids.[a]



	Cinchona alkaloid[b]/ Lewis acid	Solvent	*t* [h]	Yield [%]	*ee*[c] [%]/ *R* or *S*
1	cinchonine (CN)	CH_2Cl_2	6	80	49/*R*
2	cinchonidine (CD)	CH_2Cl_2	5	90	42/*S*
3	quinine (QN)	CH_2Cl_2	5	88	44/*S*
4	quinidine (QD)	CH_2Cl_2	5	70	14/*R*
5	$(DHQ)_2PHAL$	CH_2Cl_2	6	56	3/*S*
6	$(DHQ)_2PYR$	CH_2Cl_2	6	78	27/*S*
7	$(DHQ)_2AQN$	CH_2Cl_2	2	72	77/*S*
8	$(DHQ)_2AQN/Ti(OiPr)_4$	CH_2Cl_2	3	76	84/*S*
9	$(DHQ)_2AQN/Ti(OiPr)_4$	$CHCl_3$	4	99	82/*S*
10	$(DHQ)_2AQN/Ti(OiPr)_4$	toluene	4	89	68/*S*
11	$(DHQ)_2AQN/Ti(OiPr)_4$	Et_2O	4	99	58/*S*
12	$(DHQ)_2AQN/Ti(OiPr)_4$	THF	5	99	41/*S*
13	$(DHQ)_2AQN/Al(OiPr)_3$	CH_2Cl_2	4	73	78/*S*
14	$(DHQ)_2AQN/La(OiPr)_3$	CH_2Cl_2	4	96	80/*S*
15[d]	$(DHQ)_2AQN/Ti(OiPr)_4$	CH_2Cl_2	4	96	90/*S*
16[e]	$(DHQ)_2AQN/Ti(OiPr)_4$	CH_2Cl_2	5	93	91/*S*
17[e]	$(DHQD)_2AQN/Ti(OiPr)_4$	CH_2Cl_2	5	98	89/*R*
18[e]	$CN/Ti(OiPr)_4$	CH_2Cl_2	3	76	74/*R*
19[e]	$CD/Ti(OiPr)_4$	CH_2Cl_2	7	91	59/*S*

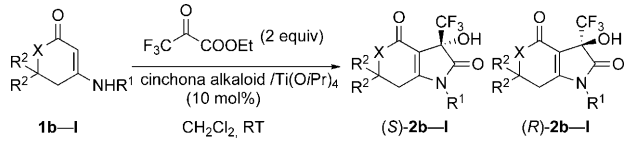
[a] Reaction conditions (unless otherwise noted): **1a** (0.15 mmol), ethyl trifluoropyruvate (2 equiv), solvent (1.0 mL), cinchona alkaloid (10 mol%), Lewis acid (10 mol%), RT, after stirring for several hours 1,2-dichloroethane was added as a co-solvent then refluxed. [b] $(DHQ)_2AQN$ = hydroquinine anthraquinone-1,4-diyl diether, $(DHQD)_2AQN$ = hydroquinidine anthraquinone-1,4-diyl diether, $(DHQ)_2PHAL$ = hydroquinine 1,4-phtalazinediyl diether, $(DHQ)_2PYR$ = hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether. [c] The *ee* values were determined by HPLC analysis. [d] CH_2Cl_2 (2.0 mL) was used. [e] CH_2Cl_2 (4.0 mL) was used.

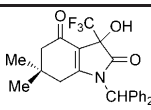
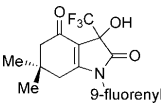
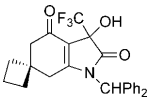
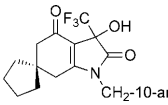
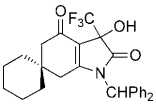
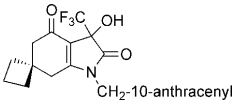
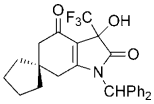
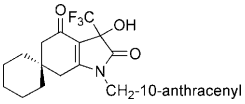
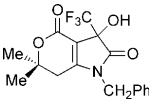
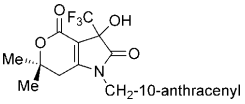
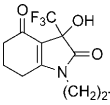
versed enantioselection (entry 2). Quinine also gave similar high yield (88%) with 44% *ee*, but quinidine provided much lower selectivity, 14% *ee* (entries 3 and 4). We next examined the reaction by use of a series of commercially available bis-cinchona alkaloids. While both $(DHQ)_2PHAL$ (hydroquinine 1,4-phthalazinediyl diether) and $(DHQ)_2PYR$ (hydroquinine-2,5-diphenyl-4,6-pyrimidinediyl diether) failed to give any improved selectivity (3–27% *ee*s, entries 5 and 6), $(DHQ)_2AQN$ (hydroquinine anthraquinone-1,4-diyl diether) provided a higher asymmetric induction with 77% *ee* (entry 7). Since almost all commercially available cinchona alkaloids were attempted, we then decided that it would be better to investigate additives to improve enantioselectivity without modifying the cinchona alkaloids. We therefore examined whether Lewis acids as additives would affect enantioselectivity.[10] As per our expectation, the use of $Ti(OiPr)_4$ as a combination catalyst increased the enantiomeric excess of **2a** to 84% *ee* (entry 8). Screening solvents such $CHCl_3$, toluene, diethyl ether and THF, as well as metal species, including $Al(OiPr)_3$ and $La(OiPr)_3$, did not further improve the selectivity (41–82% *ee*s, entries 9–14), although an *ee* over 90% was finally achieved by the combination of $(DHQ)_2AQN$ and $Ti(OiPr)_4$ at lower concentration (0.075 to 0.0375 M; entries 15 and 16). We also discovered that by using the pseudoenantiomer catalyst combination, $(DHQD)_2AQN/Ti(OiPr)_4$ ($(DHQD)_2AQN$ = hydroquinidine anthraquinone-1,4-diyl diether), a similar enantioselectivity was obtained for **2a**, albeit with the opposite (*R*) stereochemistry (89% *ee*, entry 17). This Lewis acid combination approach was effective in activating both bis-cinchona alkaloid and monomeric cinchona alkaloid catalysis. While the cinchonine/$Ti(OiPr)_4$ catalyst system allowed for the construction of (*S*)-**2a** with 74% *ee* (entries 1 vs. 19), the analogous cinchonidine/$Ti(OiPr)_4$ catalyst system afforded (*R*)-**2a** in 91% yield with 59% *ee* (entries 2 vs. 20).

With conditions now optimized, several enamines differing in the nature of the R^1 and R^2 groups were submitted to the action of our condensation system to explore the scope of the cinchona alkaloid/$Ti(OiPr)_4$ catalyst systems. On the basis of all data in Table 1, $Ti(OiPr)_4$ combinations with cinchonine (CN), cinchonidine (CD), $(DHQ)_2AQN$, or $(DHQD)_2AQN$ were selected as the catalyst. The best results of such reactions are collected in Table 2. Both enantiomers of **2** with high enantiomeric excess are equally available through this approach based on the source of cinchona alkalides. Dimethyl-substituted enamine **1b** gave product **2b** with 88% *ee* by $CN/Ti(OiPr)_4$ catalyst (Table 2, entry 1). A higher enantioselectivity of 89–93% *ee* was observed for the reaction of **1c**, which has a sterically demanding *N*-9-fluorenyl substituent (entries 3 and 4). The process was also found to be very efficient with a variety of enamines, including the substituted groups with medicinally attractive four- to six-membered spiro-cyclic structures,[11] which always gave high *ee*s ranging from 80 to 89% *ee*. The 10-anthracenylmethyl group is well tolerated in the reaction of enamines with cyclic spiro substitutions to give products in high chemical yields and high enantioselectivities, in the range of 82–89% *ee*, independent of the functional groups (Table 2, entries 7, 8, 11, and 13). Enamines with a lactone moiety **1j** and **1k** survived well in the reaction conditions to afford products **2j** and **2k** in 82–84% *ee* (entries 14 and 15). *N*-Phenethyl-substituted enamine **1l** was also nicely converted to the synthetically attractive bicyclic γ-lactam **2l** with an *R* or *S* configuration depending on the source of cinchona alkaloid, although the enantioselectivities were moderate (entry 16 and 17).

The absolute configuration of **2a** was determined by X-ray crystallographic analysis[12] after derivatization to the tosylhydrazone derivative **4** via bicyclic ketone **3** by stereoselective reduction of the carbon–carbon double bond under medium-pressure hydrogenation over palladium on activated carbon and conventional tosylhydrazone formation reaction (Scheme 2). Stereoselectivity of the hydrogenation observed can be explained by the approach of hydrogen, through hydrogen bonding to an adjacent hydroxyl group. The absolute stereochemistry of other trifluoromethylated compounds **2b–l** was not decided, but tentatively assumed as shown in Table 2 by analogy according to the tendency of the enantioselection of **2a** induced by cinchona alkaloids, that is, while CN, QD (QD = quinidine), and QD-type

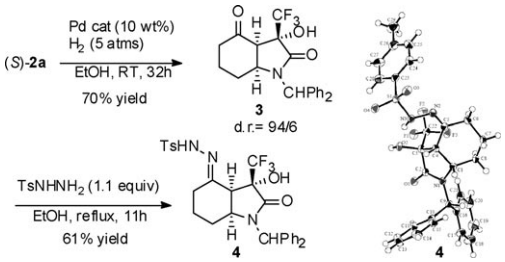
Table 2. Tandem condensation–cyclization reaction of enamine **1** under the catalysis of cinchona alkaloids/Ti(OR)$_4$.[a]



	Cinchona alkaloid	1	Product	2	Yield [%]	*ee*[b] [%]/ *R* or *S*
1	CN[c,d]	**1b**		**2b**	86	88/*R*
2	CD[c,d]	**1b**		**2b**	90	82/*S*
3	CN	**1c**		**2c**	99	89/*R*
4	CD	**1c**		**2c**	96	93/*S*
5	$(DHQD)_2AQN$	**1d**		**2d**	97	85/*R*
6	$(DHQ)_2AQN$	**1d**		**2d**	93	84/*S*
7	CN[d]	**1e**		**2e**	93	89/*R*
8	CD[d]	**1e**		**2e**	99	82/*S*
9	CN[d]	**1f**		**2f**	85	85/*R*
10	$(DHQ)_2AQN$[d]	**1f**		**2f**	93	80/*S*
11	CN	**1g**		**2g**	85	88/*R*
12	CN[d]	**1h**		**2h**	99	87/*R*
13	CN	**1i**		**2i**	99	85/*R*
14	CN[e]	**1j**		**2j**	82	84/*R*
15	CN[d,e]	**1k**		**2k**	58	83/*R*
16	$(DHQ)_2AQN$[f]	**1l**		**2l**	99	54/*S*
17	$(DHQD)_2AQN$[f]	**1l**		**2l**	97	54/*R*

[a] Reaction condition (unless otherwise noted): **1** (0.15 mmol), ethyl trifluoropyruvate (2 equiv), CH_2Cl_2 (4.0 mL), cinchona alkaloid (10 mol%), Lewis acid (10 mol%), RT, after stirring for several hours, 1,2-dichloroethane was added as a co-solvent then refluxed. [b] The *ee* value was determined by HPLC analysis. [c] Catalyst (20 mol%) was used. [d] Ti(O*n*Bu)$_4$ was used instead of Ti(O*i*Pr)$_4$. [e] Ti^{IV} (5 mol%) was used. [f] Reactions were carried out in CH_2Cl_2/THF = 1/1 (1.0 mL) without a Lewis acid.

dimers gave (*R*)-**2a**, CD, QN, and QN-type alkaloids gave (*S*)-**2a** (see, Table 1).



Scheme 2. Derivatization of **2a** to hydrazone **4** via **3** and X-ray crystallographic structure of **4**.

Although more detailed investigations of the reaction mechanism are needed, the proposed transition-state model is shown here for the reaction of **1** to give (*S*)-**2**, catalyzed by CD (Figure 1). A cinchona alkaloid/Ti(O*i*Pr)$_4$ complex

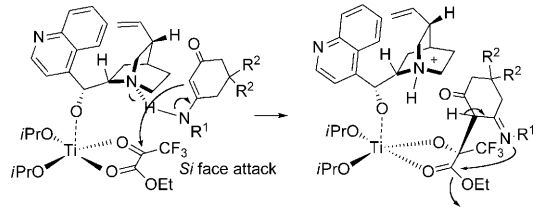
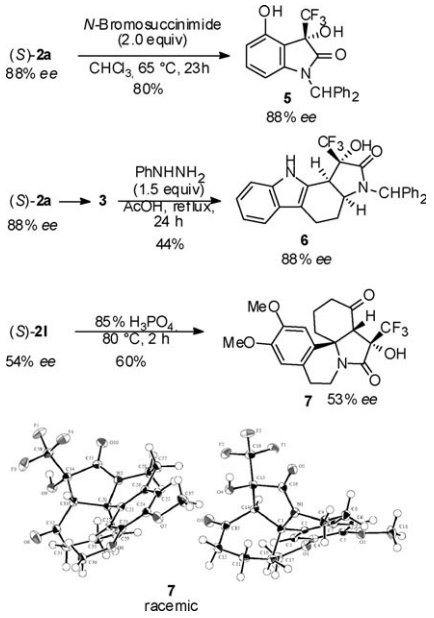


Figure 1. Proposed transition-state model to (*S*)-**2** catalyzed by CD with Ti(O*i*Pr)$_4$.

should be formed, in which the Ti^{IV} metal center captures the trifluoropyruvate, while the quinuclidine nitrogen atom of the cinchona alkaloids concurrently abstracts the proton from enamine **1**. The anion of enamine **1** approaches to the adjoining *Si* face of the enamine **1**. Thus, cooperative interaction between cinchona alkaloid, Ti^{IV}, pyruvate, and enamine **1** could play an important role to achieve high enantioselectivities of the products.

The trifluoromethylated heterocycles obtained here that retain the conjugated enamine functionality are particularly interesting substrates, since a series of functionalization steps of the moiety allows ready access to drug-like compounds. First, enamine **2a** was efficiently converted into medicinally attractive trifluoromethylated oxindole[13] **5** under the oxidation condition using NBS[14] (*N*-bromosuccinimide) in 80% without any loss of enantiomeric purity (Scheme 3, top). This transformation is important, because these types of oxindole compounds are difficult to synthesize by the direct trifluoromethylation reaction of isatin in an optically active form[15] and so far no enantioselective synthesis of this skeleton has been reported. The enamine **2a** also yielded libophyllidine-like[16] molecule **6** containing three stereocenters, a tetracyclic ring, and a trifluoromethylated tertiary alcohol unit via bicyclic ketone **3** by the straightforward application of Fischer indole synthesis[17] (Scheme 3, middle). Hence, treatment of **3** with phenylhydrazine in acetic acid under reflux afforded indole **6** in 44%. It is interesting to note that the indole formation occurred regioselectively at the less-substituted α-carbon even in a weakly acidic



Scheme 3. Synthesis of biologically attractive trifluoromethylated oxindole **5** (top), libophyllidine-like molecule **6** (middle) and erythrina alkaloid-like molecule **7** with its X-ray crystallographic structure (bottom).

medium presumably due to the steric hindrance of a neighboring trifluoromethylated quaternary carbon center.[18] We next decided to examine the stereoselective intramolecular Friedel–Crafts type conjugate addition reaction depicted in Scheme 3 (bottom). The cyclization of **2l** in the presence of H_3PO_4 under reflux condition[19] for 2 h gave an erythrina alkaloid-like molecule **7** in good yield as a single isomer without any loss of enantiopurity of the starting material **2l**. X-ray crystallographic characterization of pure racemic **7** obtained from recrystallization of **2l** with 53% *ee* was performed (Scheme 3).[12]

Analogue-based drug discovery has served as a mainstream in drug development during the past 100 years.[20] Homologues, isosteres, isomers, and transformation of ring systems are some of the important key words for designing novel analogues. However, finding promising lead compounds is still a hard task by this strategy, and a novel concept of structural modifications of drugs is unquestionably required. We finally attempted the design of drug-like structures to show the utility of these heterocycles **2** as medicinal chemistry templates. As the enamine compound **2j** contains a couple of functional groups, we envisioned it as a useful template for drug-like molecules, fluorinated pseudo-lactacystin (Figure 2). Lactacystin, a microbial metabolite, is a potent and selective proteasome inhibitor isolated from bacteria of the genus *Streptomyces* in 1991.[21g,h] The first total synthesis of lactacystin was developed by Corey in 1992.[21f] Since then, a number of total synthesis and structural modifications of lactacystin have been extensively reported.[21a–d] Pseudo-lactacystin was design as an alternative pseudo-isomer of lactacystin based on the "degradation and recombination concept". The molecular formula, functional

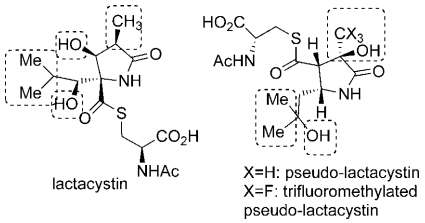
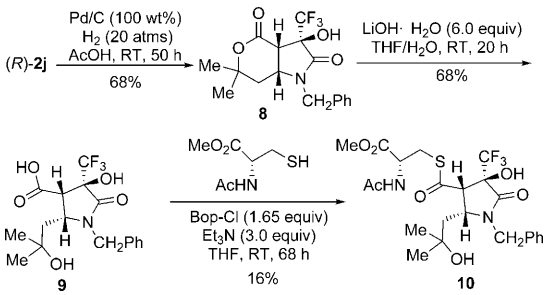


Figure 2. Structures of lactacystin and our designed pseudo-lactacystin and its fluorinated analogue.

groups, and basic cyclic core of pseudo-lactacystin are the same as lactacystin, but their combination is different. The trifluoromethylated analogue of pseudo-lactacystin would also be attractive as a drug-like molecule for highly specific reasons based on the use of trifluoromethylated functional groups in medicinal chemistry.[2] The synthesis of a trifluoromethylated pseudo-lactacystin analogue was achieved as follows. Stereoselective reduction of the olefinic moiety on (*R*)-**2j** was performed under similar hydrogenation conditions to the reduction of (*S*)-**2a** detailed above (68%; see also Scheme 2) followed by the hydrolysis of the lactone moiety to furnish **9** in 68% yield. A coupling reaction of the resulting acid **9** with methyl-*N*-acetylcysteine by Bop-Cl (bis(2-oxo-3-oxazolidinyl)phosphonic chloride) in the presence of Et_3N in THF gave the desired trifluoromethylated



Scheme 4. Synthesis of trifluoromethylated lactacystin-like molecule **10**.

pseudo-lactacystin **10** in 16% yield (Scheme 4).

In conclusion, we have developed a cinchona alkaloid/Ti^{IV}-catalyzed enantioselective enamine–trifluoropyruvate condensation reaction. By employing suitable pseudoenantiomeric cinchona alkaloids as catalysts, both enantiomers of the trifluoromethylated heterocycles with an asymmetric quaternary carbon center can be obtained selectively. Although the exact role of Ti^{IV} is still a matter of debate, this is the first example of an asymmetric enamine–pyruvate condensation–cyclization reaction. The series of products **2** are attractive medicinal chemistry templates and were readily converted to drug-like trifluoromethylated heterocycles. The biological activities of the designed molecules and further application of this methodology are now under investigation.

Acknowledgements

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Keywords: asymmetric synthesis · drug design · fluorine · organocatalysts · titanium

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