Organocatalysis

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Asymmetric Synthesis of Chiral Aldehydes by Conjugate Additions with Bifunctional Organocatalysis by Cinchona Alkaloids**

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The aldehyde is arguably the most versatile carbonyl functionality. Furthermore, it is more active than any other carbonyl functionality toward a plethora of nucleophilic reactions. This unique combination of functional versatility and activity renders chiral aldehydes highly valuable intermediates in asymmetric synthesis. The emergence of numerous catalytic enantioselective reactions that involve aldehydes as either nucleophiles or electrophiles further enhances the synthetic value of chiral aldehydes. Enantioselective transformations of the readily available prochiral aldehydes are now emerging as a fundamentally important approach toward optically active aldehydes. In particular, great strides have been made in the development of enantioselective bond formations with the α-carbon atom of prochiral aldehydes with chiral enamine catalysis,[1,2] enantioselective cycloadditions and Friedel–Crafts reactions with chiral immonium catalysis,[3] and conjugate additions of aryl boronic acids and silyl nitronates to α,β-unsaturated aldehydes by chiral transition-metal catalysis[4] and chiral phase-transfer catalysts,[5] respectively. Despite its synthetic importance, the highly enantioselective and general conjugate addition of carbonyl donors to α,β-unsaturated aldehydes remains elusive, even with considerable efforts.[6–8] Herein, we wish to report significant progress toward the development of such a reaction with cinchona-alkaloid-derived organic catalysts.

At the outset of our investigations, we were concerned that the decomposition of **3a** could be triggered by cinchona alkaloids as nucleophilic catalysts (Scheme 1) in light of the well-documented nucleophilic catalysis of 1,4-diazabicyclo-[2.2.2]octane (DABCO) and quinuclidine in the Morita–Baylis–Hillman (MBH) reaction.[9] Indeed, **3a** was found to rapidly undergo decomposition to form insoluble oligomers or polymers in the presence of DABCO, quinuclidine, or β-isocupreidine. On the other hand, mechanistic studies by us established that cinchona alkaloids, such as dihydroquinidine

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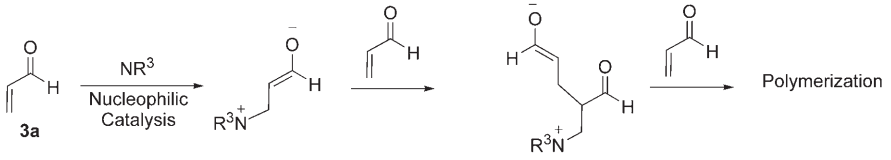
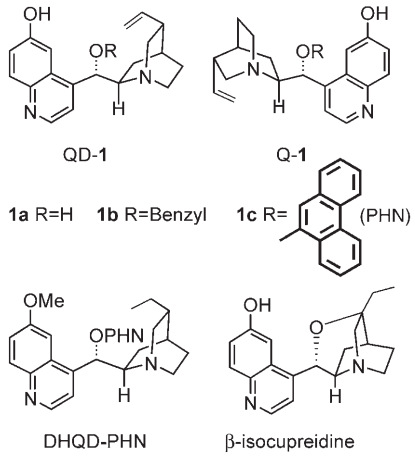


Scheme 1. Possible polymerization pathway of acrolein (**3a**) initiated by tertiary amine nucleophilic catalysis. NR^3 = achiral or chiral tertiary amine.

9-*O*-(9'-phenanthryl) ether (DHQD–PHN), as a chiral hydrogen-bond donor functioned as a general base catalyst rather than a nucleophilic catalyst for the highly enantioselective alcoholysis of *N*-carboxyanhydrides.[10] More recent mechanistic studies from our laboratories indicated that 6′-OH cinchona alkaloids **1a–c** (Scheme 2) were able to promote a

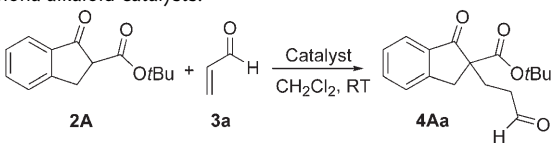


Scheme 2. Structures of cinchona-alkaloid catalysts **1**, DHQD–PHN, and β-isocupreidine. QD = quinidine, Q = quinine

variety of efficient enantioselective conjugate additions[11] as acid–base bifunctional organic catalysts from their ability to interact with the nucleophiles and electrophiles as hydrogen-bond acceptors and donors, respectively. We were pleased to find that, in stark contrast to DABCO, quinuclidine, and β-isocupreidine, 6′-OH cinchona alkaloids **1a–c** did not promote the polymerization of **3a**. These and previous results[10,11] indicate that 6′-cinchona alkaloids **1a–c** were effective general base catalysts but poor nucleophilic catalysts. We therefore suspected that **1a–c** might efficiently promote conjugate additions of carbonyl donors to **3a** without provoking polymerizations of the latter.

Our hypothesis was validated by the examination of various cinchona alkaloids as catalysts for the conjugate addition of **2A** to **3a** (Scheme 2). As summarized in Table 1, reactions with cinchona alkaloids **1a–c** rapidly went to completion to produce the 1,4-adduct **4Aa** as the only detectable product. In the presence of only 1.0 mol% of either Q-**1c** or QD-**1c**, the reaction at room temperature proceeded to completion in 15 minutes to afford chiral aldehyde **4Aa** in quantitative yield and 95% *ee* (entries 4–5, Table 1). Even with a catalyst loading of 0.1 mol%, highly enantiomerically enriched **4Aa** could still be produced in quantitative yield (entry 6, Table 1). The important role played by the 6′-OH group in the catalysis by cinchona alkaloid **1c** could be glimpsed from the dramatically lower enantioselectivity of the corresponding 6′-OMe cinchona alkaloid DHQD–PHN (entry 7 versus 3, Table 1).

Table 1: Asymmetric conjugate addition of **2A** to acrolein (**3a**) with cinchona-alkaloid catalysts.[a,b]



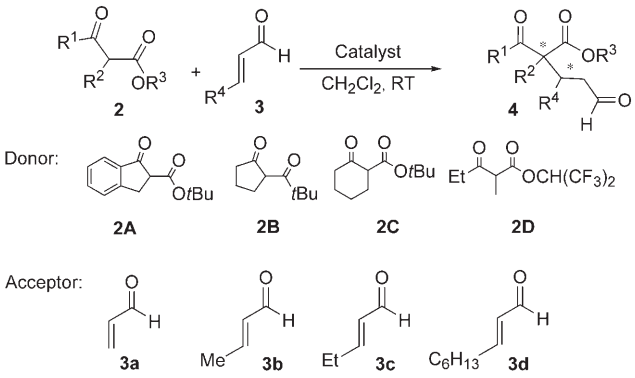
Entry	Catalyst	Loading [mol%]	*t*	Yield [%][c]	*ee* [%][d]
1	QD-**1a**	10.0	< 1 min	n.d.	39
2	QD-**1b**	10.0	< 1 min	n.d.	92
3	QD-**1c**	10.0	< 1 min	n.d.	95
4	QD-**1c**	1.0	15 min	100	95
5	Q-**1c**	1.0	15 min	100	95
6	Q-**1c**	0.1	7 h[e]	100	90
7	DHQD–PHN	10.0	< 5 min	n.d.	15

[a] Unless specified, the reaction was carried out with **2A** (0.5 M in CH_2Cl_2) and **3a** (2.5 equiv) in the presence of **1** at room temperature. [b] All the reactions went to completion in the indicated time. [c] Yield of the isolated product. [d] See the Supporting Information for the determination of the *ee* value. [e] Compound **2A** (0.2 mmol) was added to a solution of **1c** (0.5 mM) in CH_2Cl_2 (0.4 mL), and a solution of **3a** (0.26 mmol, 1.3 equiv) in CH_2Cl_2 (0.4 mL) was then added at a rate of 0.07 mL h^{-1}. n.d. = not determined.

Importantly, with Q-**1c** or QD-**1c**, conjugate additions of a wide range of cyclic and acyclic α-alkyl β-ketoesters (**2A–D**) to **3a** at room temperature generated the corresponding 1,4-adducts containing only an all-carbon quaternary stereocenter in 91–95% *ee* and virtually quantitative yield (entries 1–5, Table 2). Moreover, unprecedented highly diastereoselective and enantioselective conjugate additions to various β-substituted α,β-unsaturated aldehydes (**3b–d**) could be accomplished with 6′-OH cinchona alkaloid **1b** to afford the corresponding chiral aldehydes containing adjacent quaternary–tertiary stereocenters with 18–25:1 d.r. and 92–99% *ee* in nearly quantitative yield (entries 6–8, Table 2).

In light of the presence of all-carbon benzylic quaternary stereocenters in biologically interesting compounds,[12] we attempted the conjugate addition of α-phenyl α-cyanoacetate (**5A**) to **3a**. Unfortunately, all known 6′-OH cinchona alkaloids (**1a–e**),[11] including **1b** and **1c**, that demonstrated high enantioselectivity and considerable generality for the conjugate additions of α-alkyl β-ketoesters **2** with **3a** (see above) gave unsatisfactory enantioselectivities (entries 1–5, Table 3). Taking advantage of the readily tunable characteristics of 6′-OH cinchona alkaloids **1**, we explored the development of a new catalyst to attain an efficient enantioselective conjugate addition of **5A** to **3a**. Catalyst screening studies along this line of inquiry led to the discovery that catalyst **1f**, a structurally novel 6′-OH cinchona alkaloid,

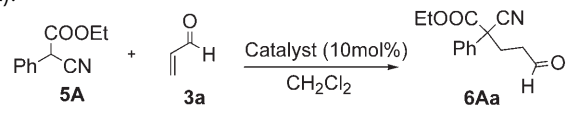
Table 2: Asymmetric conjugate addition of α-substituted-β-keto esters **2** to α,β-unsaturated aldehyde **3** with bifunctional cinchona-alkaloid catalysts **1b** and **1c**.[a]

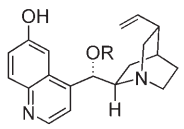


Entry	2	3	Catalyst	Loading [mol%]	*t*	Yield [%][b]	*ee* [%][c]	d.r.[d]
1[e]	**2A**	**3a**	QD-**1c** (Q-**1c**)	1.0	15 min	100 (100)	95 (95[f])	–
2[e]	**2A**	**3a**	Q-**1c**	0.1	7 h[g]	100	90[f]	–
3	**2B**	**3a**	QD-**1c** (Q-**1c**)	1.0	44 h	98 (99)	93[f] (90)	–
4	**2C**	**3a**	QD-**1c** (Q-**1c**)	10.0	30 h	98 (99)	98 (90)	–
5	**2D**	**3a**	QD-**1c** (Q-**1c**)	10.0	36 h[h]	100 (100)	91 (90)	–
6	**2A**	**3b**	QD-**1b**	10.0	8 h	100	99[i]	18:1
7	**2A**	**3c**	QD-**1b**	10.0	12 h	97	92[i]	20:1
8	**2A**	**3d**	QD-**1b**	10.0	24 h	98	98[i]	25:1

[a] Unless specified, the reaction was performed by treatment of **2** (0.3 mmol) with **3** (0.75 mmol, 2.5 equiv) and the catalyst in CH_2Cl_2 (0.6 mL) at 23 °C. The results in parentheses were obtained with Q-**1c**. [b] Yield of the isolated product. [c] See the Supporting Information for the determination of the *ee* value. [d] Determined by ^{1}H NMR spectroscopic analysis of the crude products. [e] The reaction was carried out with 1.3 equivalents of **3a**. [f] The absolute configuration was determined to be *R* (see the Supporting Information). [g] Compound **2A** (0.2 mmol) was added to a solution of **1c** (0.5 mM) in CH_2Cl_2 (0.4 mL), and a solution of **3a** (0.26 mmol, 1.3 equiv) in CH_2Cl_2 (0.4 mL) was then added at a rate of 0.07 mL h^{-1}. [h] A solution of **3a** (0.5 mmol, 2.5 equiv) in CH_2Cl_2(0.4 mL) was added to a solution of **2D** (0.2 mmol) and **1c** (0.02 mmol, 10.0 mol%) in CH_2Cl_2 (0.4 mL) at −36 °C and at a rate of 0.07 mL h^{-1}. [i] For the major diastereomer of **4**.

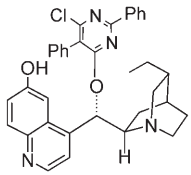
Table 3: Conjugate addition of α-phenyl α-cyanoacetate **5A** to acrolein (**3a**).[a,b]





QD-**1d** R=Benzoyl

QD-**1e** R=Acetyl



DHQD-**1f**

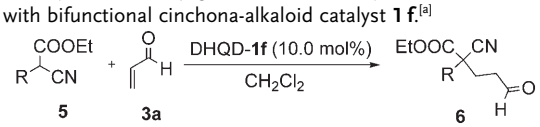
Entry	Catalyst	*T* [°C]	*t*	*ee* [%][c]
1	QD-**1a**	23	< 2 min	8
2	QD-**1b**	23	< 2 min	27
3	QD-**1c**	23	< 2 min	41
4	QD-**1d**	23	< 2 min	42
5	QD-**1e**	23	< 2 min	48
6	DHQD-**1f**	23	< 2 min	60
7	DHQD-**1f**	−50	< 20 min	85
8	DHQD-**1f**	−50	6 h[d]	91

[a] Unless specified, the reaction was carried out with **5A** (0.5 M in CH_2Cl_2) and **3a** (1.3 equiv) in the presence of **1** (10 mol%) at the indicated temperature. [b] All the reactions went to completion in the indicated time. [c] See the Supporting Information for the determination of the *ee* value. [d] A solution of **3a** (0.26 mmol, 1.3 equiv) in CH_2Cl_2 (0.4 mL) was added to a solution of **5A** (0.2 mmol) and DHQD-**1f** (0.02 mmol, 10.0 mol%) in CH_2Cl_2 (0.4 mL) at a rate of 0.07 mL h^{-1}.

could afford significantly higher enantioselectivity than **1a–e** (entry 6 versus 1–5, Table 3). In particular, the conjugate addition of **5A** to **3a** with DHQD-**1f** at −50 °C afforded the corresponding 1,4-adduct **6A** in 85% *ee* (entry 7, Table 3). Upon a slow addition of **3a** to a solution of **5A** and DHQD-**1f** in dichloromethane, the enantioselectivity could be further improved to 91% *ee* (entry 8, Table 3). It should be noted that DHQD-**1f** was prepared on a multigram scale from dihydroquinidine by a four-step sequence[13] in 70% overall yield. Importantly, DHQD-**1f** afforded synthetically useful enantioselectivity and high yields for conjugate additions to **3a** with α-cyanoacetates (**5A–E**) bearing a range of α-aryl and -heteroaryl groups (entries 1–5, Table 4).

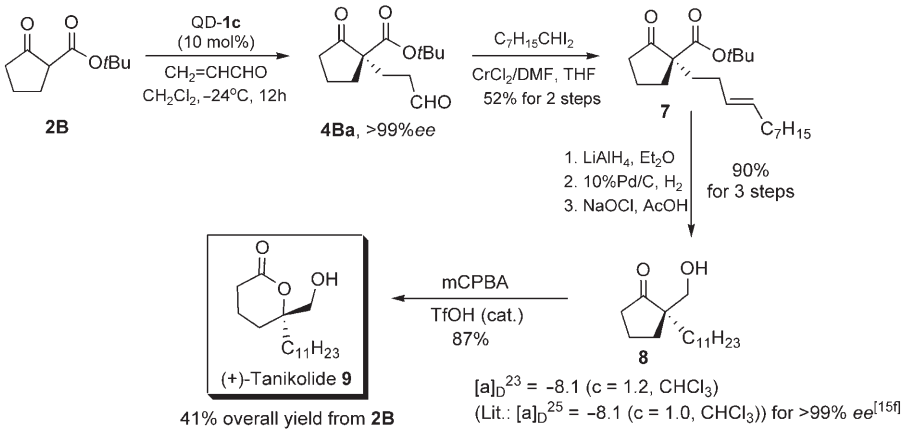
We applied this reaction to the development of a concise enantioselective total synthesis of (+)-tanikolide (**9**) to explore its synthetic utility.[14,15] Our approach features the conjugate addition of β-ketoester **2B** to **3a** catalyzed by QD-**1c** as the asymmetric induction step (see Scheme 3). We performed the conjugate addition at −25 °C with 10 mol% of QD-**1c** to achieve optimum enantioselectivity. The reaction occurred smoothly to provide the desired chiral aldehyde **4Ba** in quantitative yield with virtually perfect enantioselectivity (> 99% *ee*). The aliphatic side chain of **9** was then introduced by the olefination of aldehyde **4Ba** with 1,1-diiodooctane by following the procedure of Takai and co-workers with modifications.[16] Subsequent straightforward functional-group transformations converted keto ester **7** into keto alcohol **8** by a three-step sequence of in an overall yield of

Table 4: Asymmetric conjugate addition of α-cyano esters **5** to acrolein (**3a**) with bifunctional cinchona-alkaloid catalyst **1f**.[a]



Entry	5	R	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**5A**	Ph	−50	6	100	91
2	**5B**	*p*-Cl-Ph	−50	6	98	88
3	**5C**	*m*-Cl-Ph	−50	8	100	80
4[d]	**5D**	*p*-MeO-Ph	−50	8	99	95
5	**5E**	2-thienyl	−78	8	90	87

[a] Unless specified, a solution of **3a** (0.26 mmol, 1.3 equiv) in CH_2Cl_2 (0.4 mL) was added to a solution of **5** (0.2 mmol) and DHQD-**1f** (0.02 mmol, 10.0 mol%) in CH_2Cl_2 (0.4 mL) at a rate of 0.07 mL h^{-1}. [b] Yield of the isolated product. [c] See the Supporting Information for the determination of the *ee* value. [d] A solution of **3a** (0.26 mmol, 1.3 equiv) in CH_2Cl_2 (0.4 mL) was added to a solution of **5D** (0.2 mmol) and DHQD-**1f** (0.02 mmol, 10.0 mol%) in CH_2Cl_2 (0.8 mL) at a rate of 0.07 mL h^{-1}.



Scheme 3. Catalytic enantioselective total synthesis of (+)-tanikolide. DMF = dimethylformamide, Tf = trifluoromethanesulfonyl.

90%. A Baeyer–Villiger oxidation of **8** with *m*-chloroperbenzoic acid (*m*CPBA) furnished **9** in 87% yield. In comparison to existing enantioselective syntheses of (+)-**9**,[15] our route is concise and affords tanikolide in virtually optically pure form and favorable overall yield. Moreover, this route should be useful for the asymmetric synthesis of analogues of tanikolide.

In summary, we have developed the first highly efficient and general asymmetric conjugate addition of carbonyl donors to α,β-unsaturated aldehydes. Critical to establishing a wide scope of carbonyl donors is the development of a new and readily accessible 6′-OH cinchona alkaloid catalyst **1f**, which is uniquely effective for conjugate additions to α,β-unsaturated aldehydes with α-aryl α-cyanoacetates as donors. With broad scope for both the α-substituted β-dicarbonyl donors and the α,β-unsaturated aldehydes and the use of readily available chiral organic catalysts that are easily recyclable[13] and compatible with air and moisture, the current reaction should open new opportunities for asymmetric synthesis that involve the construction of tetrasubstituted carbon stereocenters. This possibility is demonstrated in the development of a concise, high-yielding, and flexible enantioselective synthesis of the biologically interesting natural product tanikolide.

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