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Control of Diastereoselectivity in Tandem Asymmetric Reactions Generating Nonadjacent Stereocenters with Bifunctional Catalysis by Cinchona Alkaloids

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Highly enantioselective and diastereoselective reactions or reaction cascades generating in one step chiral products with multiple stereocenters are unusually valuable for asymmetric synthesis. The full power of such reactions lies in their ability to provide, starting from the same simple prochiral precursors, selective pathways to any of the possible array of stereoisomers of a complex chiral product of interest. Ideally, this could be accomplished with a set of readily available chiral catalysts that afford complementary sense of diastereoselectivity and enantioselectivity. While complementary enantioselectivity can be readily provided by a pair of enantiomeric or pseudoenantiomeric chiral reagents, how to establish complementary diastereoselectivity in these reactions remains an important but challenging problem in asymmetric synthesis.

Significant progress has been made on the establishment of complementary diastereoselectivity with catalytic asymmetric reactions creating adjacent stereocenters.[1,2] In contrast, enantioselective and diastereoselective reactions that provide stereoselective access to all stereoisomers of a chiral product with nonadjacent stereocenters are extremely rare even for those employing a stoichiometric amount of chiral reagents.[3] In particular, to our knowledge, no such reaction mediated by a chiral catalyst has been reported. We document here the development of a new, catalytic asymmetric tandem conjugate addition−protonation reaction that generates nonadjacent stereocenters with a complementary sense of diastereoselectivity relative to that reported with the 6′-OH cinchona alkaloids **1** (Scheme 1).[4] Consequently, it is now possible to accomplish one-step and stereoselective construction of 1,3-tertiary−quaternary stereocenters in any of the four possible absolute configurations with catalytic control.

We previously reported a highly enantioselective and diastereoselective catalytic tandem conjugate addition−protonation of trisubstituted carbon nucleophiles to α-chloroacrylonitrile **4** using 6′-OH cinchona alkaloid catalyst **1** (Scheme 1). As rationalized by the transition-state model illustrated in Scheme 1,[4] the stereochemical outcome of this asymmetric tandem reaction resulted from a network of hydrogen-bonding interactions between **1** with the reacting Michael donor **X** and acceptor **Y** in the nucleophilic addition step and, subsequently, with the putative enol intermediate **I** in the protonation step. This led us to hypothesize that, by exploring bifunctional catalysts bearing the hydrogen bond donor and acceptor motifs in altered spatial relationships, an asymmetric tandem conjugate addition−protonation with a complementary sense of diastereoselectivity with respect to that promoted by **1** could be developed.

Accordingly, we investigated the reaction of 2-cyanoindanone **3a** and **4** with readily available cinchona alkaloids bearing a hydrogen bond donor at C9 (Scheme 1 and Table 1).[5] While both natural cinchona alkaloids and their C9-epimers afforded poor diastereoselectivity and enantioselectivity (entries 1−4, Table 1), the 9-thiourea cinchona alkaloids **2** were found to afford dramatically enhanced diastereoselectivity and enantioselectivity (entries 5−7, Table 1). Upon optimizations the reaction with Q-**2c** furnished

Scheme 1. Proposed Model for the Modified Cinchona Alkaloid-Catalyzed Conjugate Additions

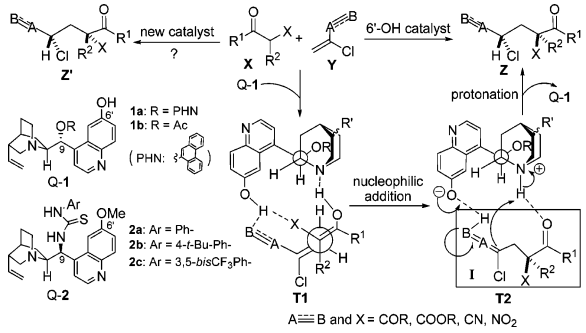
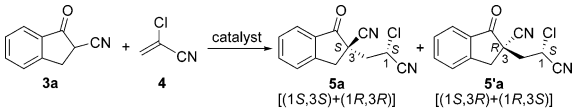
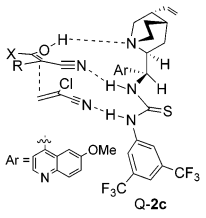


Table 1. Optimization of Reaction Conditions Using Model Substrates[a,b]



entry	catalyst	5a:5'a	ee/% of 5a
1	Quinine	1:1.8	-5
2	C9-*epi*-Q	1:1.1	-47
3	Quinidine	1:1.9	17
4	Cinchonidine	1:2.3	30
5	Q-**2a**	2.4:1	88
6	Q-**2b**	1.8:1	85
7	Q-**2c**	10:1	97
8	Q-**1a**	1:20	93[c]



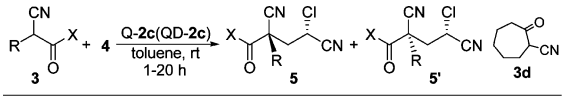
[a] Only one enantiomer was drawn for **5a** and **5′a**. [b] See Supporting Information (SI) for experimental detail. [c] ee of **5′a**.

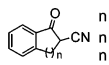
5a in 10:1 diastereomeric ratio (dr) and 97% ee. Most importantly, the sense of diastereoselectivity by **1** and **2** were found to be complementary to each other (entry 7 vs entry 8, Table 1).

These results obtained with a cyclic Michael donor implied that the switch of the sense of diastereoselectivity between the two reactions catalyzed by Q-**1a** and Q-**2c**, respectively, is independent of the geometric configuration of the double bond in the enolic form of the Michael donor **3**. Instead, it may arise from a reversal of the face of the Michael donor being exposed to the Michael acceptor in the nucleophilic addition step as a result of replacing **1a** with **2c** as the catalyst. This hypothesis received validation from analysis of the absolute configurations of the major diastereomers **5a** and **5′a** generated from reactions with Q-**2c** and Q-**1a**, respectively, which were found to have the same configuration (1*S* vs 1*S*) at the tertiary stereocenter but opposite configuration (3*S* vs 3*R*) at the quaternary stereocenter. The stereochemical outcome of the asymmetric tandem reaction catalyzed by Q-**2c** could be rationalized by *a proposed transition-state model* (Table 1), in which the putative enolic Michael donor approaches the Michael acceptor with its *si* face.[6]

10.1021/ja0670409 CCC: $37.00

Table 2. Reaction Scope[a]



entry	Michael donor		yield(5+5')/%	d.r.	ee of major isomer/%
1		n = 1 **3a**	99(99)	10:1(9:1)	97(97)[b]
2		n = 2 **3b**	94(98)	16:1(12:1)	99(97)
3		n = 3 **3c**	98(96)	9:1(9:1)	97(96)
4		**3d**	98(97)	14:1(10:1)	94(98)
5	X= OEt, R= Ph-	**3e**	98(99)	15:1(16:1)	95(95)
6[c]	Ph-	**3e**	98	25:1	97
7	4-F-Ph-	**3f**	98(98)	13:1(12:1)	95(95)
8	4-Cl-Ph-	**3g**	98	13:1	94
9	4-Br-Ph-	**3h**	98(98)	12:1(12:1)	95(94)
10	4-Me-Ph-	**3i**	100	14:1	95
11	4-MeO-Ph-	**3j**	99(99)	13:1(15:1)	95(95)
12	2-naphthyl-	**3k**	100	14:1	95
13	X= SMe, R= Me-	**3l**	98(98)	9:1(9:1)	96(96)[b]
14	allyl-	**3m**	99(98)	9:1(10:1)	95(95)

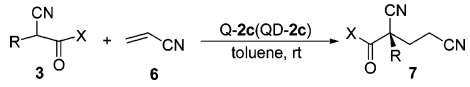
[a] See SI for experimental details. [b] For absolute configuration determination, see SI for details. [c] This reaction was run at −20 °C.

Under the optimized conditions the **2c**-catalyzed reactions with a variety of cyclic α-substituted cyanoketones **3a**−**d** and acyclic α-substituted cyanoesters **3e**−**m** proceeded in high diastereoselectivity (9−25:1 dr), enantioselectivity (94−99% ee), and excellent yield (94−100%) (Table 2). Moreover, quinine(Q)- and quinidine-(QD)-derived **2c** afforded similarly high stereoselectivities and yields (entries 1−5, 7, 9, 11, 13−14, Table 2). Thus, with the complementary diastereoselectivities afforded by **1** and **2c**, respectively, for reactions with a variety of Michael donors (**3a**−**d**, **3e**, **3h**, **3l**),[7] the asymmetric tandem conjugate addition−protonation allowed the stereoselective construction of the 1,3-tertiary−quaternary stereocenters in any of the possible configurations from the same starting materials.[7] To our knowledge, these results constitute the first example of such a complete stereocontrol for a catalytic asymmetric transformation creating nonadjacent stereocenters. Such catalyst-controlled constructions of 1,3-tertiary−quaternary centers have been applied by us to accomplish the asymmetric total syntheses of manzacidins A[4] and C[8] via a common sequence of reactions.

The remarkable catalytic efficiency demonstrated by **2c** for the conjugate addition with α-chloroacrylonitrile **4** prompted us to explore its ability to promote an enantioselective conjugate addition with acrylonitrile **6**. In spite of its obvious synthetic value, no highly enantioselective catalytic conjugate addition to acrylonitrile (**6**) has been reported. At least due partially to its weak activity as a Michael acceptor, acrylonitrile (**6**) appears to be a particular challenging Michael acceptor for catalytic asymmetric conjugate additions. For example, although **1a** is highly effective for asymmetric conjugate additions with nitroalkenes,[6b,9a] α,β-unsaturated sulfones,[9b] ketones,[9c] aldehydes,[9d] and α-chloroacrylonitrile,[4] the addition of α-phenyl α-cyanoacetate **3e** to acrylonitrile (**6**) with QD-**1a** produced the corresponding 1,4-adduct **7e** in only 44% ee. Thus, we were delighted to find that **2c** was able to promote this challenging asymmetric conjugate addition in drastically enhanced enantioselectivity (entry 3, Table 3). Furthermore the high efficiency by **2c** could be extended to a range of different Michael donors (Table 3). To our knowledge, these results constitute the first documentation of a highly enantioselective catalytic conjugate addition to acrylonitrile (**6**).

In conclusion, with readily accessible bifunctional organic catalysts, we developed an unprecedented highly enantioselective catalytic conjugate addition with acrylonitrile and an asymmetric tandem conjugate addition−protonation of high enantioselectivity and a unique sense of diastereoselectivity. The development of the latter demonstrates that hydrogen-bonding-based cooperative catalysis not only is applicable to the development of highly

Table 3. Asymmetric Michael Addition of **3** to Acrylonitrile **6**[a]



entry	donor	yield/%	ee/%	entry	donor	yield/%	ee/%
1	**3a**	100	93[b]	7	**3i**	92	90
2	**3b**	92	94	8	**3j**	85	90
3	**3e**	95(93)	89(90)	9[c]	**3j**	97	87
4	**3f**	84(87)	88(90)	10	**3k**	89	89
5	**3g**	96(96)	88(89)	11	**3l**	80	93[b]
6	**3h**	89(82)	89(89)	12	**3m**	82	91

[a] See SI for experimental details. [b] For absolute configuration determination, see SI for details. [c] This reaction was run at 50 °C.

enantioselective and diastereoselective tandem reactions but also could be manipulated to achieve diastereoselective control in such reactions, thereby allowing catalyst-controlled, direct and stereoselective construction of two nonadjacent stereocenters in any of the possible configurations from simple precursors.

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Supporting Information Available: Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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