Asymmetric Catalysis

DOI: 10.1002/ange.201105536

Structural Study-Guided Development of Versatile Phase-Transfer Catalysts for Asymmetric Conjugate Additions of Cyanide**

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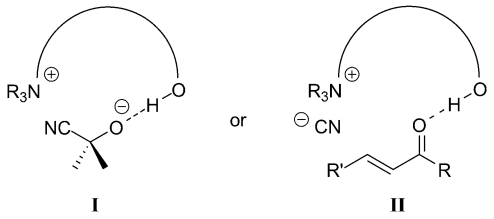
Significant advances have been made in the development of catalytic 1,2-asymmetric cyanations using both chiral metal and organic catalysts.[1] In contrast, only a few highly enantioselective catalytic conjugate additions of cyanide ions have been realized despite the potential of such transformations in providing efficient enantioselective access to synthetically valuable chiral building blocks.[2]

The first breakthroughs were reported by Jacobsen and co-workers, who described chiral Al-Salen[3] and bimetallic cooperative catalyst systems[4] for the enantioselective conjugate additions of trimethylsilyl cyanide (TMSCN) to α,β-unsaturated imides. Shibasaki, Kanai, and co-workers reported two chiral bifunctional catalysts derived from gadolinium, strontium, and different asymmetrically prepared or carbohydrate-based chiral ligands for a highly enantioselective 1,4-addition of cyanide with HCN/trialkylsilyl cyanides to α,β-unsaturated *N*-acyl pyrroles[5] and enones,[6] respectively. Feng[7] and co-workers have reported a modular titanium catalyst for the cyanation of alkylidine malonates. Very recently, Ohkuma[8] and co-workers disclosed a chiral Ru complex for the conjugate addition of TMSCN to enones. These existing reactions, while representing remarkable success in establishing general substrate scope and high catalyst efficiency, require the use of various trialkylmetal cyanides in super-stoichiometric amounts. Thus, we became interested in the development of highly enantioselective catalytic 1,4-additions of cyanide with readily accessible and easy to handle cyanation reagents.

Chiral phase-transfer catalysis has been developed as an effective strategy for the activation of practical cyanation reagents, such as KCN[9] and acetone cyanohydrin,[10] for asymmetric 1,2-additions of cyanides. On the other hand, this strategy has so far been attempted only with 1,4-additions of cyanide to nitroalkenes.[11] These attempts have so far been met with limited success. Our recent development of cupreinium salts **1**, as highly enantioselective phase-transfer catalysts for an asymmetric Darzens reaction,[12] prompted us to explore them for the asymmetric conjugate addition of cyanide. Similar to other known bifunctional phase-transfer catalysts that bear a hydrogen-bond-donor moiety,[13–15] cupreidinium salts CPD-**1**, could in principle mediate phase-transfer catalysis by their association with an anionic cyanation species, presumably a cyanide or cyanoalkoxide ion, by simultaneous ion-pair and hydrogen-bonding interactions (**I**, Scheme 1). Alternatively, CPD-**1** could promote the conjugate addition by simultaneous interactions with both the cyanation species and the enone (**II**, Scheme 1).



I II

Scheme 1. Proposed modes of activation by the bifunctional chiral catalysts.

We first investigated the asymmetric conjugate addition of acetone cyanohydrin to enone **5a**. As the equilibrium between cyanohydrin and the enone is known to favor the latter under basic conditions,[16] we reasoned that chiral phase-transfer catalysis might provide an attractive strategy to address the 1,2- vs. 1,4-chemoselectivity issue in the conjugate addition of cyanide to enones. Accordingly, enone **5a** was treated with acetone cyanohydrin in the presence of cupreidinium salt CPD-**1a** and Cs_2CO_3 in toluene/$CHCl_3$ at room temperature. We were pleased to find that the reaction proceeded cleanly to give the 1,4-adduct **6a** as the only detectable product. Although CPD-**1a** exhibited very low enantioselectivity (entry 1, Table 1), the easily modifiable 9- and N-substituents in CPD-**1** should provide valuable handles for catalyst tuning (see Scheme 2).

We obtained a single crystal X-ray structure of CPD-**1a** (Figure 1a), which revealed the possible cause of the poor asymmetric induction demonstrated by CPD-**1a**.[17] The catalytic efficiency of the cupreidinium salts critically depends on how the quaternary nitrogen-centered tetrahedron, with C2, C6, C8, and CBn (Bn = benzyl; quinine numbering) as vertices, interacts with the anionic nucleophile.[18] In order to achieve optimal efficiency, the catalyst should minimize other possible transition states by allowing the anion to preferentially associate with one face of the tetrahedron. In CPD-**1a**, one face is completely blocked by the quinuclidine backbone (C2-C6-C8), while the *N*1-benzyl and the *O*-benzyl groups

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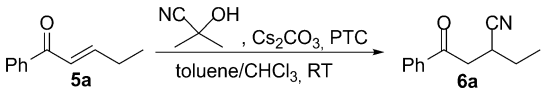
[**] We are grateful for the generous financial support of the National Institutes of Health (GM-61591).

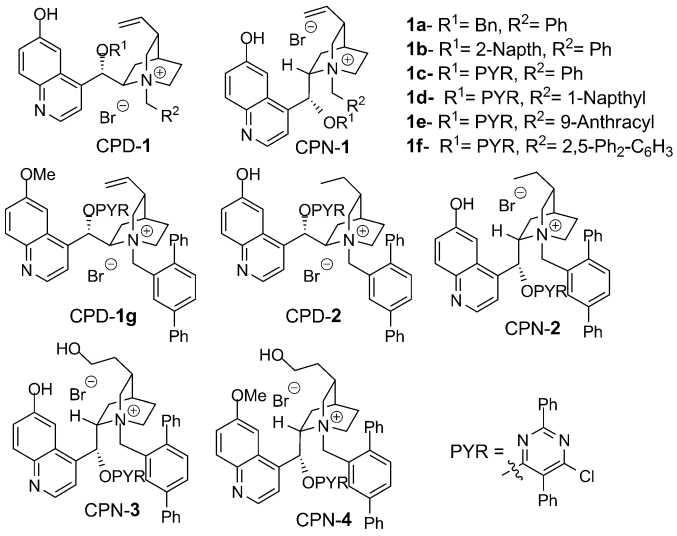
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201105536.

Table 1: Conjugate addition of cyanide to **5a**.[a]



Entry	PTC	*t* [h]	Conv.[b]	*ee*[c]
1	CPD-**1a**	25	72	8
2	CPD-**1b**	45	65	40
3	CPD-**1c**	65	72	60
4	CPD-**1d**	65	80	73
5	CPD-**1e**	65	72	82
6	CPD-**1f**	65	91	90
7[d]	CPD-**1f**	24	>95	90
8[d]	CPD-**1g**	24	>95	25
9[d]	CPD-**2**	24	>95	95
10[d,e]	CPD-**2**	24	>95	95
11[d]	CPN-**2**	24	>95	−71
12[d]	CPN-**1c**	24	>95	−16
13[d]	CPN-**1f**	24	>95	−64
14[d]	CPN-**3**	24	>95	−90
15[d,e]	CPN-**3**	96	>95	−90
16[d]	CPN-**4**	24	>95	−21

[a] Unless otherwise noted, reactions were performed with **5a** (0.05 mmol), acetone cyanohydrin (0.05 mmol) and Cs_2CO_3 (0.06 mmol) in 0.5 mL of toluene/$CHCl_3$ (7:3 v/v) with 10 mol% of catalyst. [b] % Conversion determined by GC. [c] *ee* was determined by HPLC on a chiral stationary phase, see the Supporting Information for details. [d] Acetone cyanohydrins (0.1 mmol). [e] 5.0 mol% cat. PTC = phase-transfer catalyst.



Scheme 2. Structure of the phase-transfer catalysts.

shield the C2-C6-CBn and the C2-C8-CBn faces, respectively. The C6-C8-CBn face appeared to be least hindered and the bromide ion residing on this face was also able to engage in a hydrogen-bonding interaction with the 6′-OH. Assuming the anionic nucleophile replaces the bromide in the transition state, the hydrogen-bonding interaction between the 6′-OH and the nucleophile contributes to the preferential interaction of the nucleophile with the C6-C8-CBn face. Consequently, reducing the rotational flexibility of the C9-C4′ bond could improve the catalytic enantioselectivity of the cupreidinium salt CPD-**1a**.

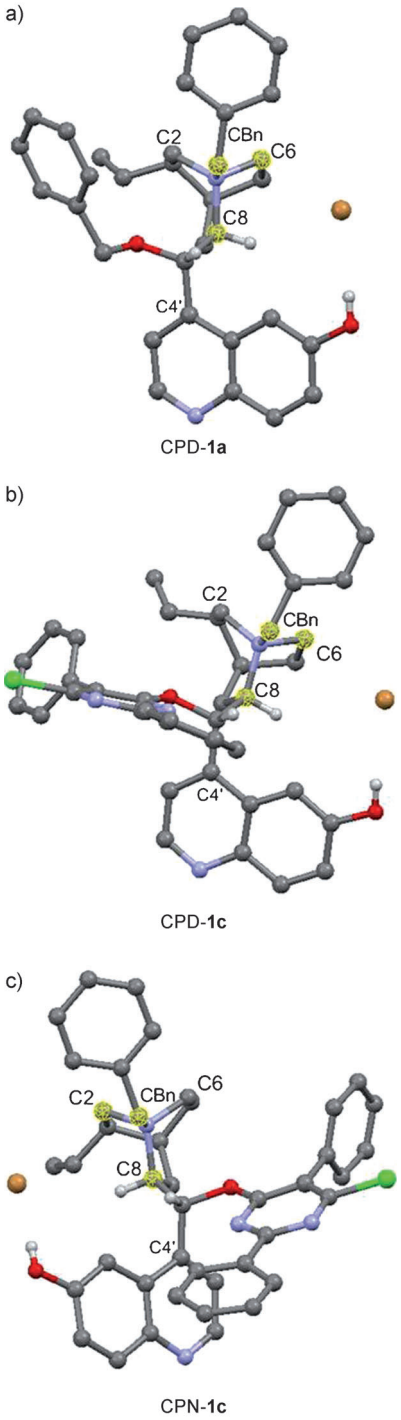


Figure 1. Single-crystal X-ray structures of cupreidinium and cupreinium salts **1**. The tetrahedral face on which the bromide ion resides is highlighted. Except for the stereogenic centers, the protons and solvent molecules have been removed for clarity. The Br···H distances are: a) CPD-**1a**: 2.41 Å, b) CPD-**1c**: 2.40 Å, c) CPN-**1c**: 2.54 Å; see the Supporting Information for full details. (C: gray, H: white, O: red, N: blue, Br: orange, Cl: green).

Based on the structure of CPD-**1a**, we reasoned that increasing the steric bulk of the 9-substiuent could in turn provide a more effective barrier to lock the quinoline ring in place and thus produce a catalyst that provides better

enantioselectivity. Following this consideration we investigated cupreidinium salts CPD-**1b** and CPD-**1c**, which afforded significantly higher enantioselectivities of 40% and 60%, respectively (entries 2 and 3, Table 1). Fortunately, we were able to obtain an X-ray structure of CPD-**1c** (**b**, Figure 1), which showed that the 9-OPYR (PYR = 6-chloro-2,5-diphenylpyrimidin-4-yl) was clearly a more effective barrier than 9-OBn (**B** vs. **A**). The structure of CPD-**1c** also suggested an additional means for catalyst tuning. Specifically, increasing the bulk of the aryl group on the tetrahedral nitrogen atom could further hinder the interaction of the nucleophile with the C2-C6-CBn face, thereby enhancing the preference for the nucleophile to associate with the C6-C8-CBn face. Subsequent investigations identified several 9-OPYR cupreidinium salts (CPD-**1d–f**) that bear various bulky N-substituents that afforded improved enantioselectivity (entries 3-6, Table 1). Among these cupreidinium salts, CPD-**1f** was found to be the most selective (entry 6, Table 1), although an increased reaction time was required to reach over 90% conversion. By increasing the amount of the cyanohydrin from 1.0 to 2.0 equivalents, the reaction time could be shortened to 24 h without compromising the enantioselectivity (entries 7, Table 1). To confirm the bifunctional nature of catalyst CPD-**1f**, CPD-**1g**, the corresponding quinidinium catalyst, was prepared and was found to furnish **6a** in only 25% *ee*, thus demonstrating the importance of the 6′OH.

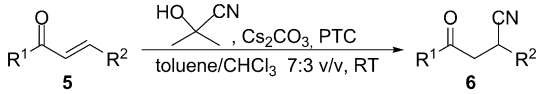
A surprising observation with the structure of cupreidinium-derived CPD-**1c** is the proximity of the vinyl group to the 9-OPYR. This observation led us to examine the impact of altering the vinyl group on the catalytic enantioselectivity. To our delight, cupreidinium salt CPD-**2**, the dihydro analogue of CPD-**1f**, was found to be noticeably more enantioselective, affording 95% *ee* for the transformation of **5a** into **6a** (entry 9 vs. 7, Table 1). Furthermore, the loading of CPD-**2** could be reduced to 5 mol% without any negative impact on the reaction (entry 10 vs. 9, Table 1).

To establish facile access to both enantiomers of **6a**, we turned our attention to the cupreinium-derived catalyst CPN-**2**. Unfortunately, the pseudoenantiomeric nature of the cinchona alkaloid had a significantly negative impact as CPN-**2** afforded drastically lower enantioselectivity than that offered by CPD-**2** (entry 11 vs. 10, Table 1). Similarly, compared to CPD-**1c**, CPN-**1c** furnished lower enantioselectivity (entry 12 vs. 3). To gain insight into this disparity in enantioselectivity between the cupreidinium and cupreinium salts, we attempted to obtain X-ray structures of CPN-**2** and CPN-**1c**. With our best efforts, only the structure of CPN-**1c** could be obtained (Figure 1c), which showed that the bromide ion resides on the C2-C8-CBn face while forming a hydrogen bond with the 6′-OH. Without the vinyl group, the two bromide-ion-binding pockets in CPD-**1c** and CPN-**1c** are enantiomeric with respect to each other. However, as represented by the structure of CPN-**1c**, the presence of the vinyl group in proximity to the anionic-binding pocket could function as a barrier to impede the incoming electrophile, thereby negatively impacting the catalytic efficiency of cupreinium salts CPN-**1c** and CPN-**2**.

We then hypothesized that this negative impact could be mitigated by converting the vinyl group into a hydrogen-bond-donor moiety as an attractive hydrogen-bonding interaction between the electrophile and this moiety could improve the catalytic efficiency of the cupreinium salts. To test this hypothesis, we prepared CPN-**3** by converting the vinyl group in CPN-**1f** into a 2-hydroxyethyl moiety. To our delight, catalyst CPN-**3** provided significantly improved enantioselectivity over that provided by either CPN-**2** or CPN-**1f** (entries 14 vs. 11 and 13, Table 1). Lowering the loading of CPN-**3** from 10 mol% to 5 mol% did not compromise enantioselectivity, although a longer reaction time was necessary to reach completion (entry 15, Table 1). To verify whether the 6′-OH in CPN-**3** is still necessary for its catalytic efficiency we also examined CPN-**4**, which produced **6a** in only 21% *ee* (entry 16, Table 1). The considerably inferior enantioselectivity afforded by CPN-**1f**, CPN-**2**, and CPN-**4** illustrates that both the 6′-OH and the aliphatic alcohol are required to achieve high efficiency with CPN-**3**.

With the development of highly enantioselective phase-transfer catalysts from both cupreidinium (CPD-**2**) and cupreinium (CPN-**3**) salts, we began to investigate the scope of these phase-transfer catalysts for the asymmetric 1,4-addition of acetone cyanohydrin. With respect to the 1,4-additon to enones, mediated by CPD-**2** and CPN-**3**, the high enantioselectivity observed with enone **5a** was found to be sustainable over a considerable range of acyclic enones that bear various linear and branched alkyl groups as the β substituent (Table 2). Notably, the length of the linear

Table 2: Conjugate addition of cyanide to **5**.[a]



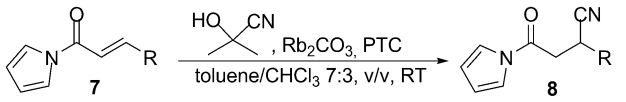
Entry	5	R^1	R^2	PTC	t [h]	Yield[b]	ee[c]
1	**5a**	Ph	Et	CPD-**2**	24	77	95 (*S*)
2	**5a**	Ph	Et	CPN-**3**	24	97	90 (*R*)
3	**5b**	Ph	Me	CPD-**2**	24	78	97 (*S*)
4	**5b**	Ph	Me	CPN-**3**	24	92	91 (*R*)
5	**5c**	Ph	*n*-C_5H_{11}	CPD-**2**	96	89	96 (*S*)
6	**5c**	Ph	*n*-C_5H_{11}	CPN-**3**	24	73	92 (*R*)
7[d]	**5d**	Ph	*i*Pr	CPD-**2**	72	69	94 (*S*)
8	**5d**	Ph	*i*Pr	CPN-**3**	24	80	93 (*R*)
9[d]	**5e**	Ph	CH_2*i*Pr	CPD-**2**	72	80	97 (*S*)
10	**5e**	Ph	CH_2*i*Pr	CPN-**3**	24	91	93 (*R*)
11[d]	**5f**	Ph	CH_2OSiEt_3	CPD-**2**	48	75	93 (*S*)
12	**5f**	Ph	CH_2OSiEt_3	CPN-**3**	24	77	87 (*R*)
13	**5g**	4-Me-C_6H_4	Me	CPD-**2**	48	78	95 (*S*)
14	**5g**	4-Me-C_6H_4	Me	CPN-**3**	24	99	92 (*R*)
15	**5h**	4-OMe-C_6H_4	Me	CPD-**2**	48	88	97 (*S*)
16	**5h**	4-OMe-C_6H_4	Me	CPN-**3**	24	98	94 (*R*)
17	**5i**	4-Cl-C_6H_4	Me	CPD-**2**	6	82	96 (*S*)
18	**5i**	4-Cl-C_6H_4	Me	CPN-**3**	4	77	90 (*R*)

[a] Unless otherwise noted, reactions were performed with **5** (0.1 mmol), acetone cyanohydrin (0.2 mmol) and Cs_2CO_3 (0.12 mmol) in 1 mL of toluene/$CHCl_3$ (7:3 v/v) with 5 mol% CPD-**2** (or 10 mol% CPN-**3a**). [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. The absolute configuration is reported in parenthesis, see the Supporting Information for details. [d] 10 mol% CPD-**2**. PTC = phase-transfer catalyst.

alkyl groups has little influence on the enantioselectivity (entries 5 and 6). Moreover, the reaction proceeded in a highly enantioselective manner with not only a δ-branched enone, but also a sterically hindered γ-branched enone (entries 7–10).[19] With respect to the ketone substituent, aromatic rings substituted with either electron-withdrawing or donating groups were well tolerated (entries 13–18, Table 2). However, enones that bear an aliphatic ketone substituent were found to be inactive for the reaction.

In addition to enones, we found that both CPD-**2** and CPN-**3** afforded high enantioselectivity for the addition of acetone cyanohydrin to β-alkyl-α,β-unsaturated *N*-acyl pyrroles. This result is particularly noteworthy as it establishes a useful method to provide ready enantioselective access to both enantiomers of synthetically important optically active β-cyano carboxylic acid derivatives (Table 3). For this reaction, Rb_2CO_3 proved to be a superior base to Cs_2CO_3 (entries 1–2 vs. 3–4, Table 3). Once again, the high enantioselectivity appeared to be independent of the steric property of the β-alkyl group affording high enantioselectivity for linear as well as γ- and δ-branched α,β-unsaturated *N*-acyl pyrroles.

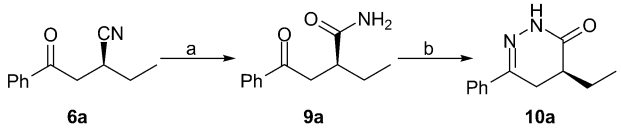
Table 3: Conjugate addition of acetone cyanohydrin to **7**.[a]



Entry	**7**	R	PTC	*t* [h]	Yield[b]	*ee*[c]
1[d]	**7a**	Et	CPD-**2**	24	>95[e]	86
2[d]	**7a**	Et	CPN-**3**	24	>95[e]	78
3	**7a**	Et	CPD-**2**	48	83	95 (*S*)
4	**7a**	Et	CPN-**3**	24	94	90 (*R*)
5	**7b**	Me	CPD-**2**	48	79	97 (*S*)
6	**7b**	Me	CPN-**3**	24	77	92 (*R*)
7	**7c**	*n*-C_5H_{11}	CPD-**2**	96	87	96 (*S*)
8	**7c**	*n*-C_5H_{11}	CPN-**3**	24	84	92 (*R*)
9	**7d**	*i*Pr	CPD-**2**	48	83	95 (*S*)
10	**7d**	*i*Pr	CPN-**3**	24	71	91 (*R*)
11	**7e**	CH_2*i*Pr	CPD-**2**	96	78	98 (*S*)
12	**7e**	CH_2*i*Pr	CPN-**3**	24	80	94 (*R*)
13	**7f**	CH_2CH_2Ph	CPD-**2**	96	75	95 (*S*)
14	**7f**	CH_2CH_2Ph	CPN-**3**	24	70	93 (*R*)

[a] Unless otherwise noted, reactions were performed with **7** (0.1 mmol), acetone cyanohydrin (0.2 mmol) and Rb_2CO_3 (0.12 mmol) in 1 mL of toluene/$CHCl_3$ (7:3 v/v) with 10 mol% CPD-**2** (or 10 mol% CPN-**3a**). [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. The absolute configuration is reported in parenthesis, see the Supporting Information for details. [d] Cs_2CO_3 (0.12 mmol) used instead of Rb_2CO_3. PTC = phase-transfer catalyst.

We applied the CPD-**2**-mediated 1,4-addition of acetone cyanohydrin to develop an enantioselective route to chiral 6-phenyl-4,5-dihydropyridazin-3(2*H*)-ones (**10**). Compounds that contain this chiral heterocyclic scaffold have exhibited a diverse range of biological properties such as antihypotensive activity,[20] platelet aggregation,[21] and positive inotropic behavior.[22] As summarized in Scheme 3, the optically active nitrile **6a** could be converted into **10a** in an overall yield of



Scheme 3. Synthesis of 6-Phenyl-4,5-dihydropyridazin-3(2*H*)-ones. a) 12 N HCl, 0 °C, 82% yield, 95% *ee*; b) NH_2NH_2, pTsOH, EtOH, 75 °C, 63% yield, 95% *ee*.

52% by a two-step sequence: 1) stirring of **6a** in 12.0 N HCl at 0 °C to form amide **9a**; 2) heating the intermediate **9a** in ethanol with hydrazine in the presence of a catalytic amount of *p*-toluenesulfonic acid. This route should be applicable to the synthesis of a range of analogues of **10a**. To the best of our knowledge, only a chiral auxiliary-mediated asymmetric synthesis of **10** has been reported so far.[23]

In summary, we have developed a new class of chiral catalysts, CPN-**3**, for the asymmetric 1,4-addition of cyanide. As only chiral metal catalysts were found to be effective prior to this study, these chiral phase-transfer catalysts provide a new efficient approach toward the development of these synthetically important asymmetric transformations. Several noteworthy features of these phase-transfer-catalyst-mediated asymmetric transformations include the use of an accessible organic catalyst as well as a practical cyanation reagent and the ability to provide access to both enantiomers of the 1,4-adducts derived from α,β-unsaturated ketones and N-acyl pyrroles. Such features should render these reactions valuable additions to synthetic methodology. It is particularly noteworthy that the successful development of these new chiral catalysts resulted from several key, yet non-intuitive insights gained from structural studies of a series of catalyst candidates of varying enantioselectivity.

Received: August 4, 2011
Published online: September 14, 2011

Please note: Minor changes have been made to this manuscript since its publication in *Angewandte Chemie* EarlyView. The Editor.

Keywords: asymmetric catalysis · crystal structures · hydrocyanation · Michael addition · phase-transfer catalysis

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