Published in final edited form as:

Angew Chem Int Ed Engl. 2011 November 4; 50(45): 10565–10569. doi:10.1002/anie.201105536.

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

Brian A. Provencher,

Department of Chemistry, Brandeis University, Waltham, MA 02454-9110(USA), Fax: (+1) 781-736-2516

Keith J. Bartelson,

Department of Chemistry, Brandeis University, Waltham, MA 02454-9110(USA), Fax: (+1) 781-736-2516

Dr. Yan Liu,

Department of Chemistry, Brandeis University, Waltham, MA 02454-9110(USA), Fax: (+1) 781-736-2516. State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Dalian 116023(China)

Prof. Bruce M. Foxman, and

Department of Chemistry, Brandeis University, Waltham, MA 02454-9110(USA), Fax: (+1) 781-736-2516

Prof. Li Deng

Department of Chemistry, Brandeis University, Waltham, MA 02454-9110(USA), Fax: (+1) 781-736-2516

Li Deng: Deng@brandeis.edu

Abstract

New phase transfer catalysts are reported for the first example of an organocatalytic asymmetric conjugate addition of cyanide with acetone cyanohydrin. Utilizing an accessible cupreidininium salt and a cyanation reagent suitable for industrial scale, this reaction holds significant promise for practical asymmetric synthesis. Additionally, the reported catalysts were developed as a result of gaining key structural insights via X-ray analysis of a series of catalysts of varying efficiencies and asymmetric induction.

Keywords

Asymmetric catalysis; Crystallography; Hydrocyanation; Michael addition; Phase-transfer catalysis

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 have been realized despite the

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

Correspondence to: Li Deng, Deng@brandeis.edu.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

potential of such transformations in providing efficient enantioselective access to synthetically valuable chiral building blocks.^[2]

The first breakthroughs were reported by Jacobsen and coworkers, who described chiral Al-Salen^[3] and bimetallic cooperative catalyst systems^[4] for the enantioselective conjugate additions of TMS-CN to $\alpha\beta$ -unsaturated imides. Shibasaki, Kanai and coworkers 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 cyanide to $\alpha\beta$ -unsaturated *N*-acyl pyrroles^[5] and enones,^[6] respectively. Feng^[7] and coworkers have reported a modular titanium catalyst for the cyanation of alkylidene malonates. Very recently, Ohkuma^[8] and coworkers disclosed a chiral Ru-complex for the conjugate addition of TMS-CN 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 superstoichiometric 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 cyanides 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 bearing a hydrogen bond donor moiety,^{[13],[14],[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, via simultaneous ion-pair and hydrogen bonding interactions (**I**, Figure 1). Alternatively, CPD-**1** could promote the conjugate addition via simultaneous interactions with both the cyanation species and the enone (**II**, Figure 1).

We first investigated the asymmetric conjugate addition of acetone cyanohydrin to enone **5a**. As the equilibrium between cyanohydrin and 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 Cs₂CO₃ in toluene/CHCl₃ 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.

We obtained a single crystal X-ray structure of CPD-**1a** (**a**, Figure 3), 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 (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 *M*-benzyl and the *O*-benzyl groups 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 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 cupreidinium salt CPD-1a.

Based on the structure of CPD-1a, we reasoned that increasing the steric bulk of the 9-substituent 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 3), which showed that the 9-OPYR 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 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) bearing 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 cyanohydrin from 1.0 to 2.0 equivalents, the reaction time could be shortened to 24 hours without compromising enantioselectivity (entries 7, Table 1). In order to confirm the bifunctional nature of catalyst CPD-1f, CPD-1g, the corresponding quinidinium catalyst, was prepared and was found to furnish 6a 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 analog of CPD-1f, was found to be noticeably more enantioselective, affording 95% ee for the transformation of 5a to 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 by CPD-2 (entry 11 vs. 10, Table 1). Similarly, compared to CPD-1c, CPN-1c furnished lower enantioselectivity (entry 12 vs. 3). In order 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 (c, Figure 3), which showed that the bromide resides on the C2-C8-CBn face while forming a hydrogen-bond with the 6'-OH. Without the vinyl group, the two bromide-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 close proximity to the anionic-binding pocket could stand 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 to a 2-hydroxyethyl moiety. To our delight, catalyst CPN-3 provided significantly improved enantioselectivity over that 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-addition 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 bearing various linear and branched alkyl groups as the β -substituent (Table 2). Notably, the length of the linear 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 bearing 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 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.

We applied CPD-2-mediated 1,4-addition of acetone cyanohydrin to develop an enantioselective route to chiral 6-phenyl-4,5-dihydropyridazin-3(2H)-ones (**10**). Compounds containing 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 1, the optically active nitrile **6a** could be converted into **10a** in an overall yield of 52% via 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 in the literature.^[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 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.

References

1. a) Gregory RJH. *Chem Rev.* 1999; 99:3649–3682. [PubMed: 11849033] b) Brunel JM, Holmes IP. *Angew Chem Int Ed.* 2004; 43:2752–2778. c) North M, Usanov DL, Young C. *Chem Rev.* 2008; 108:5146–5226. [PubMed: 19067648]
2. a) Mander LN, Thomson RJ. *J Org Chem.* 2005; 70:1654–1670. [PubMed: 15730285] b) Nicolaou KC, Stepan AF, Lister T, Li A, Montero A, Tria GS, Turner CI, Tang Y, Wang J, Denton JRM, Edmonds DJ. *J Am Chem Soc.* 2008; 130:13110–13119. [PubMed: 18771264] c) Vázquez-Romero A, Rodríguez J, Lledó A, Verdaguer X, Riera A. *Org Lett.* 2008; 10:4509–4512. [PubMed: 18798645]
3. Sammis GN, Jacobsen EN. *J Am Chem Soc.* 2003; 125:4442–4443. [PubMed: 12683813]
4. a) Sammis GN, Danjo H, Jacobsen EN. *J Am Chem Soc.* 2004; 126:9928–9929. [PubMed: 15303860] b) Jacobsen EN, Mazet C. *Angew Chem Int Ed.* 2008; 47:1762–1765.
5. a) Mita T, Sasaki K, Kanai M, Shibasaki M. *J Am Chem Soc.* 2005; 127:514–515. [PubMed: 15643862] b) Fujimori I, Mita T, Maki K, Shiro M, Sato A, Furusho S, Kanai M, Shibasaki M. *Tetrahedron.* 2007; 63:5820–5831.
6. a) Tanaka Y, Kanai M, Shibasaki M. *J Am Chem Soc.* 2008; 130:6072–6073. [PubMed: 18419119] b) Tanaka Y, Kanai M, Shibasaki M. *J Am Chem Soc.* 2010; 132:8862–8863. [PubMed: 20536134]
7. Wang J, Li W, Liu Y, Chu Y, Lin L, Liu X, Feng X. *Org Lett.* 2010; 12:1280–1283. [PubMed: 20178336]
8. Kurono N, Nii N, Sakaguchi Y, Uemura M, Ohkuma T. *Angew Chem Int Ed.* 2011; 50:5541–5544.
9. Ooi T, Uematsu Y, Maruoka K. *J Am Chem Soc.* 2006; 128:2548–2549. [PubMed: 16492034]
10. Herrera P, Sgarzani V, Bernandi L, Fini F, Pettersen D, Ricci A. *J Org Chem.* 2006; 71:9869–9872. [PubMed: 17168611]
11. a) Bernandi L, Fini F, Fochi M, Ricci A. *Synlett.* 2008:1857–1861. b) Bernal P, Fernández R, Lassaletta J. *Chem-Eur J.* 2010; 16:7714–7718. [PubMed: 20533468]
12. Liu Y, Provencher BA, Bartelson KJ, Deng L. *Chem Sci.* 2011; 2:1301–1304. [PubMed: 22174974]
13. For cinchona alkaloid based catalysts see: Dolling UH, Davis P, Grabowski EJJ. *J Am Chem Soc.* 1984; 106:446–447. Arai S, Shirai Y, Ishida T, Shioiri T. *Chem Commun.* 1999:49–50. Fini F, Sgarzani V, Pettersen D, Herrera RP, Bernandi L, Ricci A. *Angew Chem Int Ed.* 2005; 44:7975–7978. Palomo C, Oiarbide M, Laso A, Lopez R. *J Am Chem Soc.* 2005; 127:17622–17623. [PubMed: 16351089] Berkessel A, Guixà M, Schmidt F, Neudörfl JM, Lex J. *Chem Eur J.* 2007; 13:4483–4498. [PubMed: 17348045]
14. For ephedrine based catalysts see: Loupy A, Sansoulet J, Zapparucha A, Merienne C. *Tetrahedron Lett.* 1989; 30:333–336.
15. For BINAP derived catalysts see: Ooi T, Ohara D, Tamura M, Maruoka K. *J Am Chem Soc.* 2004; 126:6844–6845. [PubMed: 15174835] He R, Shirakawa S, Maruoka K. *J Am Chem Soc.* 2009; 131:16620–16621. [PubMed: 19886657] Wang X, Lan Q, Shirakawa S, Maruoka K. *Chem Commun.* 2010; 46:321–323.
16. a) Nagata, W.; Yoshioka, M. *Organic Reactions.* Vol. 25. John Wiley & Sons, Inc; 1977. p. 255–476. b) Yang J, Shen Y, Chen FX. *Synthesis.* 2010:1325–1333.
17. CCDC 831959 – 831961 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.
18. a) Corey EJ, Xu F, Noe MC. *J Am Chem Soc.* 1979; 119:12414–12415. b) Corey EJ, Bo Y, Busch-Petersen J. *J Am Chem Soc.* 1998; 120:13000–13001.
19. The reaction with chalcone was sluggish under the reaction conditions, providing the corresponding 1,4-adduct in 30% yield (80% yield BRSM) and 48% ee after 120 hours.

20. Curran WV, Ross A. *J Med Chem.* 1974; 17:273–281. [PubMed: 4204335] b) McEvoy FJ, Allen GR. *J Med Chem.* 1974; 17:281–286. [PubMed: 4811221]
21. Thygesen M, Lehmann HD, Gries J, Koenig H, Kretzschmar R, Kunze J, Lebkuecher R, Lenke D. *J Med Chem.* 1983; 26:800–807. [PubMed: 6854582]
22. Sircar I, Duell BL, Bobowski G, Bristol JA, Evans DB. *J Med Chem.* 1985; 28:1405–1413. [PubMed: 2864447]
23. Lim YJ, Angela M, Buonora PT. *Tetrahedron Lett.* 2003; 44:7799–7801.

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

Figure 2.
Structure of the Phase Transfer Catalysts.

Figure 3.

Single Crystal X-Ray Structures of Cupreidin and Cuprein salts **1**. The tetrahedral face on which the bromide resides is highlighted. Except for the chiral 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 supporting information for full details. (C-grey, H-white, O-red, N-blue, Br- orange, Cl-green)

Scheme 1.

Synthesis of 6-Phenyl-4,5-dihydropyridazin-3(2H)-ones. [a] 12 N HCl, 0°C, 82% yield, 95% ee; [b] NH₂NH₂, pTsOH, EtOH, 75°C, 63% yield, 95% ee.

Table 1

Conjugate Addition of Cyanide to **5a**.^a

Entry	PTC	Time (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 noted, reactions were performed with 0.05 mmol of **5a** and 0.05 mmol acetone cyanohydrin, 0.06 mmol Cs₂CO₃ in 0.5 mL of Toluene/CHCl₃ (7:3 v/v) with 10 mol% of catalyst.

^b % Conversion determined by GC.

^c Ee was determined by chiral HPLC, see supporting information for details.

^d 0.1 mmol acetone cyanohydrin.

^e 5.0 mol% cat

Table 2

Conjugate Addition of Cyanide to **5**.^a

Entry	5	R¹	R²	PTC	Time (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	<i>n</i> -C ₅ H ₁₁	CPD-2	96	89	96 (S)
6	5c	Ph	<i>n</i> -C ₅ H ₁₁	CPN-3	24	73	92 (R)
7 ^d	5d	Ph	<i>i</i> -Pr	CPD-2	72	69	94 (S)
8	5d	Ph	<i>i</i> -Pr	CPN-3	24	80	93 (R)
9 ^d	5e	Ph	CH ₂ - <i>i</i> -Pr	CPD-2	72	80	97 (S)
10	5e	Ph	CH ₂ - <i>i</i> -Pr	CPN-3	24	91	93 (R)
11 ^d	5f	Ph	CH ₂ -OSiEt ₃	CPD-2	48	75	93 (S)
12	5f	Ph	CH ₂ -OSiEt ₃	CPN-3	24	77	87 (R)
13	5g	4-Me-C ₆ H ₄	Me	CPD-2	48	78	95 (S)
14	5g	4-Me-C ₆ H ₄	Me	CPN-3	24	99	92 (R)
15	5h	4-OMe-C ₆ H ₄	Me	CPD-2	48	88	97 (S)
16	5h	4-OMe-C ₆ H ₄	Me	CPN-3	24	98	94 (R)
17	5i	4-Cl-C ₆ H ₄	Me	CPD-2	6	82	96 (S)
18	5i	4-Cl-C ₆ H ₄	Me	CPN-3	4	77	90 (R)

^aUnless noted reactions were performed with 0.1 mmol of **5** and 0.2 mmol acetone cyanohydrin, 0.12 mmol Cs₂CO₃ in 1 mL of Toluene/CHCl₃ (7:3 v/v) with 5 mol% CPD-2(or 10 mol% CPN-3a).

\$watermark-text

\$watermark-text

\$watermark-text

 b Isolated yield. c Determined by chiral HPLC. The Absolute configuration is reported in parenthesis, see supporting information for details. d 10 mol% CPD-2.

Table 3

Conjugate Addition of Acetone Cyanohydrin to **7**.^a

Entry	7	R	PTC	Time (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	<i>n</i> -C ₅ H ₁₁	CPD-2	96	87	96 (S)
8	7c	<i>n</i> -C ₅ H ₁₁	CPN-3	24	84	92 (R)
9	7d	<i>i</i> Pr	CPD-2	48	83	95 (S)
10	7d	<i>i</i> Pr	CPN-3	24	71	91 (R)
11	7e	CH ₂ <i>i</i> Pr	CPD-2	96	78	98 (S)
12	7e	CH ₂ <i>i</i> Pr	CPN-3	24	80	94 (R)
13	7f	CH ₂ CH ₂ Ph	CPD-2	96	75	95 (S)
14	7f	CH ₂ CH ₂ Ph	CPN-3	24	70	93 (R)

^aUnless noted reactions were performed with 0.1 mmol of **7** and 0.2 mmol acetone cyanohydrin, 0.12 mmol Rb₂CO₃ in 1 mL of Toluene/CHCl₃ (7:3 v/v) with 10 mol% CPD-2 (or 10 mol% CPN-3a).^bIsolated yield.^cDetermined by chiral HPLC. The Absolute configuration is reported in parenthesis, see supporting information for details.^d0.12 mmol Cs₂CO₃ used instead of Rb₂CO₃