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Phase Transfer Catalyzed Enantioselective Strecker Reactions of α-Amido Sulfones with Cyanohydrins

Raquel P. Herrera,*,† Valentina Sgarzani,‡ Luca Bernardi,‡ Francesco Fini,‡ Daniel Pettersen,‡ and Alfredo Ricci*,‡

Department of Organic Chemistry "A. Mangini", University of Bologna, V. Risorgimento 4, 40136 Bologna, Italy, and Instituto de Investigaciones Quimicas (CSIC-Use), Isla de la Cartuja, Americo Vespucio s/n, 41092 Seville, Spain

rph@alu.ua.es; ricci@ms.fci.unibo.it

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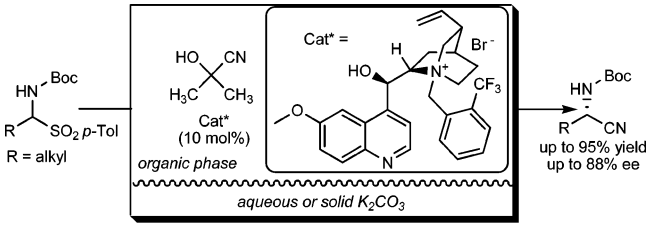

A study into the use of a chiral phase-transfer catalyst in conjunction with acetone cyanohydrin to effect the enantioselective formation of α-amino nitriles from α-amido sulfones is described. This novel catalytic asymmetric Strecker reaction is analyzed with regard to the possible mechanistic basis.

The Strecker hydrocyanation of imines[1] is the oldest known synthesis for the preparation of α-amino acids in an economical manner and under simple operational conditions.

Since α-amino acid derivatives are broadly used as chiral building blocks with important applications in complex natural products,[2] the enantioselective variants of this reaction have been intensively studied over the past years. Several successful achievements in catalytic asymmetric Strecker reactions were reported by different groups within the past few years.[3] Noteworthy, the range of suitable catalysts is broad, covering metal catalysts and, more recently, organocatalysts.[4] However most of the previously elaborated catalytic asymmetric methodologies rely on the use of anhydrous hydrogen cyanide which poses important problems to be addressed particularly when large-scale applications are considered. In this regard the possibility of employing KCN as a cyanide source has also been taken into consideration and very recently successfully applied, among the others, to an organocatalyzed asymmetric Strecker reaction.[5]

Herein we disclose the first example of the use of cyanohydrins as a CN^- source in a organocatalyzed Strecker reaction performed under phase transfer conditions and employing *N*-Boc protected α-amido sulfones as imine precursors.[6]

Acetone cyanohydrin is one of the simplest, most soluble, cheap, and on large-scale commercially available cyanide sources.[7] To date its use as cyanide source has been described for the regiospecific opening of 1,2-epoxides under mild basic conditions[8] and as a new Mitsunobu reagent in the cyanation of alcohols.[9] Furthermore, more recently a convenient procedure for the Pd-catalyzed cyanation of aryl halides has been reported.[10]

We initiated our search for an appropriate reaction system (see Table 1) with the α-amido sulfone of 3-phenylpropionaldehyde **2a**[11] and acetone cyanohydrin **3a** as model substrates in order to develop the cyanation under biphasic conditions (K_2CO_3, organic solvent). Several chiral quaternary ammonium salts derived from cinchona alkaloids were screened as potential organocatalysts together with the effects of the imine nitrogen substituent and of the addition of water.

The key elements for the success of the reaction were the easily available quinine-derived catalyst **1a** and the presence in it of an electron withdrawing group such as CF_3 at ortho position of the benzyl group, which afforded the expected product **4a** in excellent yield and 60% ee (entry 1 in Table 1). On the contrary, **1b**, in which the same functional group was installed at the para position, had significantly less efficient results (16% ee, entry 2). Also the free hydroxyl group at the position 9 plays a significant role in substrate activation since the corresponding catalyst **1c**, whose OH group had been protected in the form of benzyl ether, led to a racemic mixture (entry 3).

Increasing steric hindrance in the cyanide source, such as in benzophenone (**3b**) and fluorenone (**3c**) cyanohydrins, was detrimental for the enantioselection (compare entries 1, 4, and 5 in Table 1). Finally it was possible to further improve the enantioselectivity of the reaction by careful optimization of the reaction conditions. For example, the ee of product **4a** could be enhanced to 68% ee (entry 6) by simply using more dilute conditions in conjunction with aqueous base and lower temperature (−20 °C). The occurrence of an effective catalytic

* To whom correspondence should be addressed. (A.R.) Phone: +39(051)-2093635. Fax: +39(051)2093654.
† Instituto de Investigaciones Quimicas.
‡ University of Bologna.

(1) Strecker, V. A. *Liebigs. Ann. Chem.* **1850**, *75*, 27−51.
(2) (a) Schultz, P. G.; Ellman, J. A.; Mendel, D. *J. Am. Chem. Soc.* **1991**, *113*, 2758−2760. (b) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889−917.
(3) (a) Yet, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 875−877 and references cited therein. (b) Kobayashi, S; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069−1094.
(4) (a) Gröger, H. *Chem. Rev.* **2003**, *103*, 2795−2828. (b) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157−160. (c) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012−10014. (d) Huang, J.; Corey, E. J. *Org. Lett.* **2004**, *6*, 5027−5029.
(5) Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2548−2549.
(6) During the preparation of this manuscript a paper on the use of an NEt_3/acetone cyanohydrin as a catalytic system for the three-component Strecker-type, α-amino nitrile synthesis appeared: Paraskar, A. S.; Sudalai, A. *Tetrahedron Lett.* **2006**, *47*, 5759−5762.
(7) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649−3682.
(8) Mitchell, D; Koenig, T. M. *Tetrahedron Lett.* **1992**, *33*, 3281−3284.
(9) Tsunoda, T.; Uemoto, K.; Nagino, C.; Kawamura, M.; Kaku, H.; Ito, S. *Tetrahedron Lett.* **1999**, *40*, 7355−7358.
(10) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1661−1664.
(11) For the preparation of α-amido sulfones see (a) Pearson, W. H.; Lindbeck, A. C.; Kampf, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 2622−2636. (b) Mecozzi, T; Petrini, M. *J. Org. Chem.* **1999**, *64*, 8970−8972.

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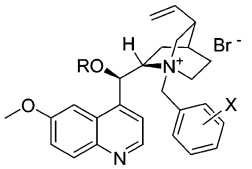
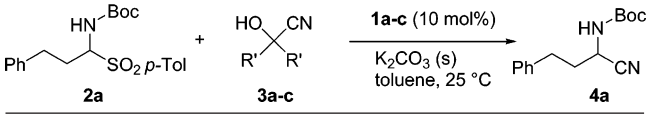
TABLE 1. Initial Screening and Optimization of Reaction Conditions[a]



1a X = *o*-CF_3, R = H
1b X = *p*-CF_3, R = H
1c X = *o*-CF_3, R = CH_2Ph



entry	cyanohydrin	R′	catalyst	time [h]	yield %[b]	ee %[c]
1	**3a**	Me	**1a**	5	95	60
2	**3a**	Me	**1b**	5	89	16
3	**3a**	Me	**1c**	5	90	0
4	**3b**	Ph	**1a**	18	80	20
5	**3c**	−(9-fluorenyl)−	**1a**	42	83	26
6	**3a**	Me	**1a**	42	95	68[d]

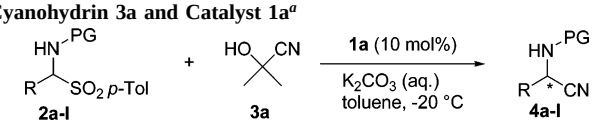
[a] The reactions were carried out at 25 °C using 0.1 mmol of α-amido sulfone, 0.2 mmol of cyanohydrin, 0.5 mmol of K_2CO_3(s) and 0.01 mmol of catalyst in 2 mL toluene. [b] Yields are given for isolated products. [c] The enantiomeric excess was determined by chiral HPLC. [d] Reaction performed at −20 °C with 5 mL toluene and aqueous K_2CO_3 (50% w/w).

behavior promoted by **1a**, was ascertained by the eightfold rate enhancement in the reaction with a catalytic loading of 10 mol %, run under the conditions shown in Table 1, with respect to the uncatalyzed reaction[12] and highlighted the minor role played by the background reaction. Interestingly, the presence of the in situ generated imine was never detected, thus suggesting that deprotonation followed by sulfinate ion release may occur in the rate determining step.

With these insights into the optimized reaction conditions, we explored the scope of the reaction using a range of aliphatic α-amido sulfones and acetone cyanohydrin **3a** as starting materials (Table 2). Catalyst **1a** proved to be highly effective for the hydrocyanation of a variety of *N*-Boc α-amido sulfones. The (*S*)-configured α-aminonitriles[13] were obtained throughout with excellent yields and high ee's, and the size of the aliphatic group did appear to slightly dictate the levels of enantioselectivity (entries 1−9). No changes of the products ee's were observed even after prolonged times, thus supporting the suitability of the reaction conditions employed. *N*-Boc proved to be the most suitable protection, since the reaction run with *N*-Cbz α-amido sulfone **2l** led to a sizable decrease of the enantioselection (compare entries 1 and 10).

Catalyst **1a** displays a remarkably substrate scope in the asymmetric hydrocyanation of aldimines, since it accommodates substrates bearing α-substituents ranging from methyl to *tert*-alkyl moieties. This would enable, among the others, a straightforward synthesis of enantiomerically enriched *tert*-leucine, a target of considerable utility as chiral building block, by simultaneous *N*-Boc deprotection and CN hydrolysis in acidic medium.[14]

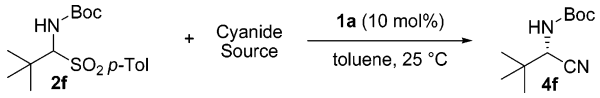
TABLE 2. Asymmetric Catalytic Strecker Reactions with Cyanohydrin 3a and Catalyst 1a[a]



entry	α-amido sulfone	R	PG	product	yield %[b]	ee %[c]
1	**2a**	$Ph(CH_2)_2$	Boc	**4a**	95	68
2	**2b**	$PhCH_2$		**4b**	95	79
3	**2c**	Me		**4c**	85	78
4	**2d**	CH_3CH_2		**4d**	88	80
5	**2e**	*i*-Pr		**4e**	92	82
6	**2f**	*t*-Bu		**4f**	85	88
7	**2g**	$CH_3(CH_2)_5$		**4g**	95	72
8	**2h**	$(CH_3)_2CHCH_2$		**4h**	90	68
9	**2i**	Cy		**4i**	95	50
10	**2l**	$Ph(CH_2)_2$	Cbz	**4l**	79	40

[a] The reactions were carried out at −20 °C for 42 h using 0.1 mmol of α-amido sulfone, 0.2 mmol of cyanohydrin, 0.5 mmol of aqueous K_2CO_3 (50% w/w) and 0.01 mmol of catalyst in 5 mL toluene. [b] Yields are given for isolated products. [c] The enantiomeric excess was determined by chiral HPLC or GC.

TABLE 3. Supplementary Experiments with Different Cyanide Sources[a]



entry	cyanide source	base (5 equiv)	acetone	time h	conversion %[b]	ee %[c]
1	**3a**	K_2CO_3(s)		3	>95	70
2	KCN			5	>95	40
3	KCN		2.5 equiv	5	>95	54
4	TMSCN	K_2CO_3(s)		2	>95	35
5	TMSCN	K_2CO_3(s)	2.5 equiv	2	>95	52

[a] The reactions were carried out at 25 °C for the stated time using 0.1 mmol of α-amido sulfone **2f**, 0.2 mmol of cyanide source, and 0.01 mmol of catalyst **1a** in 2 mL toluene. [b] Conversions determined by ^1H NMR.[c] The enantiomeric excess was determined by chiral GC.

As shown in Table 3, a few ancillary experiments carried out on **2f** at room-temperature revealed that in all cases the enantiomeric excesses, using more conventional CN^- ion sources like KCN (entry 2) and TMSCN (entry 4), were substantially lower with respect to the value obtained with cyanohydrin **3a** (entry 1). Undoubtedly in these reactions the operativity of other pathways leading to the Strecker product formation without recognition of the catalytic species is likely, and a direct transfer of the nucleophile to the imine will probably compete with that occurring via **1a**/CN^- ion pair (entries 2 and 4 in Table 3), as suggested by the moderate enantioselection observed.

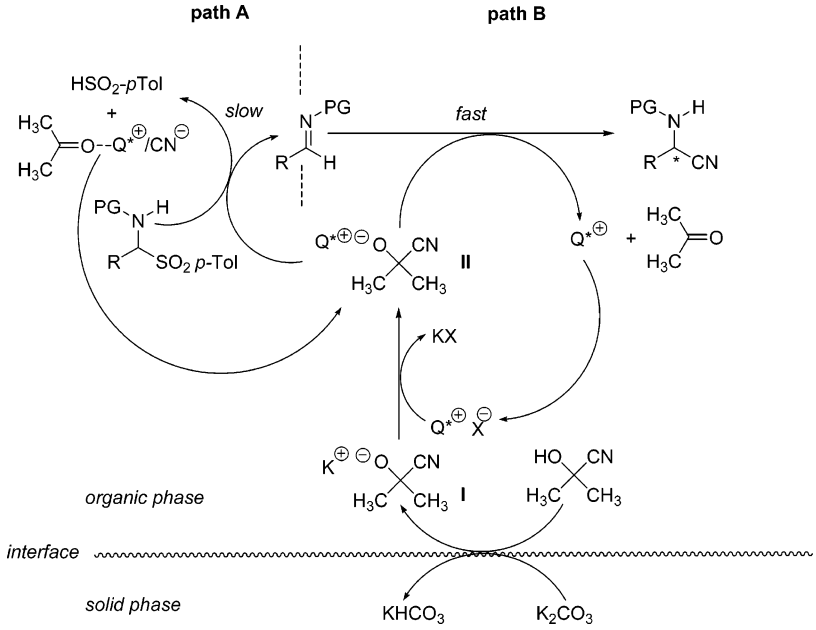
Furthermore, most interestingly, an addition of 2.5 equiv acetone produced a remarkable enhancement of the enantioselection (compare entries 2, 3 and 4, 5). This prompted us to shed some light on the mechanism of this PTC reaction. The focus was first addressed toward the reaction pathway in which

(12) The uncatalyzed reaction goes through itself in 40 hours.

(13) The absolute configuration of the optically active compounds **4b** and **4h** was determined by comparison of the measured optical rotation with literature values: Boeijen, A.; Liskamp, R. M. J. *Eur. J. Org. Chem.* **1999**, 2127−2135. The remaining absolute configurations were assigned by analogy to further adducts.

(14) Banphavichit, V.; Chaleawlertumpon, S.; Bhanthumnavin, W.; Vilaivan, T. *Synth. Commun.* **2004**, *34*, 3147−3160.

SCHEME 1. Hypothetical Mechanism for the Strecker Reaction of α-Amido Sulfones and Cyanohydrin 3a Catalyzed by 1a



α-amido sulfones are converted into imines: in the presence of K_2CO_3 and 10 mol % of phase transfer catalyst this reaction took place after more than 1 day, whereas the combination K_2CO_3 /cyanohydrin/PTC afforded complete disappearance of the precursor within 3 h. A cyanohydrin-derived anionic species, generated at the interface, might therefore act as the effective base in the α-amido sulfone-imine transformation. A sketch of a mechanistic proposal is shown in Scheme 1.

According to this proposal the conjugate base of the cyanohydrin **I** might form with the chiral quaternary ammonium salt a lipophilic ion pair **II** that in path **A** releases the CN^- ion promoting deprotonation of the precursor and its conversion into an imine. The already mentioned catalysis promoted by **1a**, is strongly suggestive of an intervention of the organocatalytic species in this rate-determining step.[15] In the presence of the in situ formed imine, **II** will then deliver in path **B** the CN^- ion to the electrophilic carbon. The possibility that in ion pair **II** the catalyst might accommodate in its chiral pocket a more complex anionic species than CN^- is supported by the lowering of both yields and enantioselectivity observed with cyanohydrins **3b** and **3c** (see Table 1), since one could easily assume that the accommodation of these bulkier systems would be much more difficult. Furthermore, the beneficial effect on the enantioselection owing to addition of acetone to the reactions in the presence of KCN or TMSCN (see Table 3), most likely leading to in situ generation of **I**, provides further support to the above-reported interpretation of the reaction pathways. According to this mechanism, the CN^- will thus play the sequential role of catalytic base and stoichiometric nucleophile. This is also consistent with the fact that the reaction described in Table 2 for **2f**, performed with only 1.1 equiv of cyanohydrin **3a**, afforded the expected α-amino nitrile in 85% yield and 89% ee without any erosion of efficiency and enantioselectivity.

In conclusion, we have accomplished the first organocatalyzed phase-transfer enantioselective cyanation of in-situ-generated aliphatic aldimines using acetone cyanohydrin **3a** as a cyanide ion source. The ready preparation and stability of the simple chiral quininium salt, the convenient experimental procedure, and the easy access to the α-amino acids in the natural (*S*)-form are good assets of the enantioselective Strecker process described herein.

(15) HPLC analysis performed on several samples at various reaction times did not show evidences in favour of enantiomeric enrichment of the unreacted α-amido sulfone.

Experimental Section

General Procedure for the Catalytic Enantioselective Strecker Reaction of α-Amido Sulfones 2a−l with Cyanohydrin 3a. To a solution of α-amido sulfone **2a**−**l** (0.1 mmol) in toluene (5 mL) was added *N*-(*o*-trifluoromethyl)quininium bromide **1a** (0.01 mmol, 5.6 mg) followed by acetone cyanohydrin (0.2 mmol, 18 μL). After the resulting solution was cooled to −20 °C, K_2CO_3(aq) 50% w/w (0.5 mmol, 90 μL) was added in one portion. The reaction mixture was then vigorously stirred at the same temperature without any precaution to exclude moisture or air. After 42 h, the reaction was quenched with saturated $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was then purified by chromatography on silica gel (CH_2Cl_2).

Products **4a**,**b**, **4d**−**f**, **4h**,**i** are known compounds in literature and spectroscopical data are consistent with previously reported values.[14] The absolute configuration of the optically active compounds **4b**,**h** was determined by comparison of the measured optical rotation with literature values.[13] All other absolute configurations were assigned by analogy to further adducts.

(*S*)-*tert*-Butyl 1-Cyano-3-phenylpropylcarbamate (4a).[14] Obtained as a white solid in 95% yield (24.7 mg). The ee of the product was determined by HPLC using an AD-H column (*n*-hexane/*i*-PrOH = 98:2, flow rate 0.75 mL/min, λ = 254 nm, τ_{maj} = 42.7 min, τ_{min} = 38.8 min); $[\alpha]^{25}_D$ −11.4 (*c* 0.38, dioxane), 68% ee.

(*S*)-*tert*-Butyl 1-Cyano-2-phenylethylcarbamate (4b).[14] Obtained as a white solid in 95% yield (23.4 mg). The ee of the product was determined by HPLC using an AD-H column (*n*-hexane/*i*-PrOH = 95:5, flow rate 0.75 mL/min, λ = 254 nm, τ_{maj} = 22.7 min, τ_{min} = 21.3 min); $[\alpha]^{25}_D$ −11.5 (*c* 0.42, dioxane), 79% ee. [Lit. (*S* enantiomer): $[\alpha]^{25}_D$ −16.4 (*c* 0.98, dioxane)].[13]

(*S*)-*tert*-Butyl 1-Cyanoethylcarbamate (4c). Obtained as a white solid in 85% yield (14.4 mg). The ee of the product was determined

by GC using a RT-BetaDEX-sm chiral column (isothermal 130 °C, injector temp = 235 °C, detector temp = 250 °C, using N_2 as carrier gas, τ_{maj} = 17.0 min, τ_{min} = 17.5 min); mp 101−103 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.78 (br s, 1H), 4.62 (br s, 1H), 1.54 (d, J = 7.2 Hz, 3H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 154.4, 109.9, 81.1, 29.6, 28.2, 19.7. ESIMS: *m*/*z* 193 [M + Na]$^+$. Anal. Calcd for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.34; H, 8.31; N, 16.50. $[\alpha]^{25}_D$ −54.3 (*c* 0.36, dioxane), 78% ee.

(*S*)-*tert*-Butyl 1-Cyanopropylcarbamate (4d).[14] Obtained as a white solid in 88% yield (16.2 mg). The ee of the product was determined by GC using a RT-BetaDEX-sm chiral column (isothermal 150 °C, injector temp = 235 °C, detector temp = 250 °C, using N_2 as carrier gas, τ_{maj} = 9.7 min, τ_{min} = 9.9 min); $[\alpha]^{25}_D$ −50.5 (*c* 0.49, dioxane), 80% ee.

(*S*)-*tert*-Butyl 1-Cyano-2-methylpropylcarbamate (4e).[14] Obtained as a white solid in 92% yield (18.2 mg). The ee of the product was determined by GC using a RT-BetaDEX-sm chiral column (isothermal 150 °C, injector temp = 235 °C, detector temp = 250 °C, using N_2 as carrier gas, τ_{maj} = 9.7 min, τ_{min} = 10.0 min); $[\alpha]^{25}_D$ −44.2 (*c* 0.55, dioxane), 82% ee.

(*S*)-*tert*-Butyl 1-Cyano-2,2-dimethylpropylcarbamate (4f).[14] Obtained as a white solid in 85% yield (18.0 mg). The ee of the product was determined by GC using a RT-BetaDEX-sm chiral column (isothermal 150 °C, injector temp = 235 °C, detector temp = 250 °C, using N_2 as carrier gas, τ_{maj} = 9.0 min, τ_{min} = 9.4 min); $[\alpha]^{25}_D$ −48.8 (*c* 0.57, dioxane), 88% ee.

(*S*)-*tert*-Butyl 1-Cyanoheptylcarbamate (4g). Obtained as a colorless oil in 95% yield (22.8 mg). The ee of the product was determined by GC using a RT-BetaDEX-sm chiral column (isothermal 150 °C, injector temp = 235 °C, detector temp = 250 °C, using N_2 as carrier gas, τ_{maj} = 53.0 min, τ_{min} = 55.1 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.78 (br s, 1H), 4.56 (br s, 1H), 1.82−1.73 (m, 2H), 1.46 (s, 9H), 1.36−1.25 (m, 8H), 0.88 (t, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 154.1, 119.0, 81.2, 42.3, 33.4, 31.4, 28.4, 28.2, 25.2, 22.4, 14.0. ESIMS: *m*/*z* 263 [M + Na]$^+$. Anal. Calcd for $C_{13}H_{24}N_2O_2$: C, 64.97; H, 10.07; N, 11.66. Found: C, 64.83; H, 10.05; N, 11.62. $[\alpha]^{25}_D$ −26.6 (*c* 0.88, dioxane), 72% ee.

(*S*)-*tert*-Butyl 1-Cyano-3-methylbutylcarbamate (4h).[14] Obtained as a white solid in 90% yield (19.1 mg). The ee of the product was determined by GC using a RT-BetaDEX-sm chiral column (isothermal 140 °C, injector temp = 235 °C, detector temp = 250 °C, using N_2 as carrier gas, τ_{maj} = 25.9 min, τ_{min} = 27.4 min); $[\alpha]^{25}_D$ −34.4 (*c* 0.68, dioxane), 68% ee. [Lit. (*S* enantiomer): $[\alpha]^{25}_D$ −58.9 (*c* 0.98, dioxane)].[13]

(*S*)-*tert*-Butyl Cyano(cyclohexyl)methylcarbamate (4i).[14] Obtained as a white solid in 95% yield (22.6 mg). The ee of the product was determined by GC using a RT-BetaDEX-sm chiral column (isothermal 180 °C, injector temp = 235 °C, detector temp = 250 °C, using N_2 as carrier gas, τ_{maj} = 17.5 min, τ_{min} = 17.7 min); $[\alpha]^{25}_D$ −13.8 (*c* 0.68, dioxane), 50% ee.

Benzyl 1-Cyano-3-phenylpropylcarbamate (4l). Obtained as a white solid in 79% yield (23.2 mg). The ee of the product was determined by HPLC using an AD-H column (*n*-hexane/*i*-PrOH = 95:5, flow rate 0.75 mL/min, λ = 254 nm, τ_{maj} = 30.4 min, τ_{min} = 36.4 min); mp 81−83 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.38−7.17 (m, 10H), 5.14 (s, 2H), 5.00 (br s, 1H), 4.57 (br s, 1H), 2.82 (dt, J = 7.3, 1.9 Hz, 2H), 2.18−2.10 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 155.0, 138.9, 135.5, 128.8, 128.6, 128.5, 128.4, 128.3, 126.8, 118.3, 67.8, 42.3, 34.8, 31.4. ESIMS: *m*/*z* 317 [M + Na]$^{+\cdot}$. Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.57; H, 6.18; N, 9.50. $[\alpha]^{25}_D$ −10.0 (*c* 0.12, dioxane), 40% ee.

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Supporting Information Available: General experimental information and ^{1}H NMR spectra of catalyst **1a** and of products **4a**−**l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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