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Asymmetric Strecker Synthesis of α-Arylglycines

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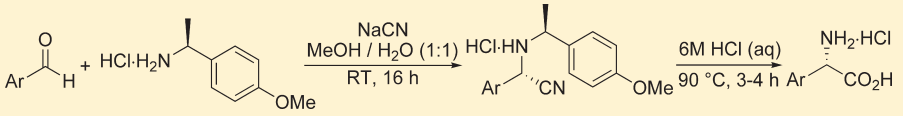
Supporting Information

ABSTRACT:



A practically simple three-component Strecker reaction for the asymmetric synthesis of enantiopure α-arylglycines has been developed. Addition of a range of aryl-aldehydes to a solution of sodium cyanide and (*S*)-1-(4-methoxyphenyl)ethylamine affords highly crystalline (*S*,*S*)-α-aminonitriles that are easily obtained in diastereomerically pure form. Heating the resultant (*S*,*S*)-α-aminonitriles in 6 M aqueous HCl at reflux resulted in cleavage of their chiral auxiliary fragments and concomitant hydrolysis of their nitrile groups to afford enantiopure (*S*)-α-arylglycines. The enantiopurities of these (*S*)-α-arylglycines were determined *via* derivatization of their corresponding methyl esters with 2-formylphenylboronic acid and (*S*)-BINOL, followed by ^{1}H NMR spectroscopic analysis of the resultant mixtures of diastereomeric iminoboronate esters.

INTRODUCTION

Enantiomerically pure α-arylglycines are non-proteinogenic α-amino acids that are found within the structures of many biologically active compounds. For example, α-arylglycine fragments are found in β-lactam antibiotics such as amoxicillin, cephalexin, and cefadroxil, and there are three separate α-arylglycine fragments contained within the structure of the glycopeptide antibiotic vancomycin.[1] They have also been widely used as privileged chiral building blocks for the preparation of drug-like molecules that exhibit a wide range of biological activities.[2] Consequently, a variety of methodologies have been developed for their asymmetric synthesis,[3] including approaches that employ chiral auxiliaries,[4] transition metal catalysts,[5] organocatalysts,[6] and biocatalysts.[7]

The asymmetric Strecker reaction is one of the most widely employed methods for synthesizing α-aminonitriles that can be hydrolyzed to give α-amino acids.[8] A number of catalytic enantioselective Strecker reactions to form α-aryl-aminonitriles that employ either metal-based catalysts[9] or organocatalysts[10] have been reported in recent years. While many of these catalytic protocols have been shown to afford enantiopure α-aryl-aminonitriles in good yield, they often employ expensive chiral catalysts or require multistep syntheses of chiral ligands. Furthermore, the majority of these catalytic protocols require the use of trimethylsilyl cyanide (TMSCN) as a nucleophile, which is an expensive, volatile, toxic reagent that is difficult to use on scale-up.[11] Many of these catalytic protocols also require a two-step process, involving nucleophilic addition of a cyanide equivalent to a preformed imine. Finally, the substrate specificity profile of a number of these catalytic protocols is limited, which can lead to the formation of scalemic α-arylglycines that are difficult to purify to greater than 95% enantiomeric excess (ee).

An alternative approach to using asymmetric catalysis is to use enantiomerically pure amines as chiral auxiliaries to perform diastereoselective Strecker reactions. The resulting α-aminonitriles can then be hydrolyzed and their auxiliary fragments removed to form enantiopure α-arylglycines. A number of different enantiomerically pure amines have been used as chiral auxiliaries for the asymmetric synthesis of α-aryl-aminonitriles.[1] Enantiopure 1-phenylethylamine (**1**) is one of the most common chiral auxiliaries for the asymmetric Strecker synthesis of α-amino acids.[12] However, while a number of procedures have been developed that afford diastereomerically enriched α-aryl-aminonitriles,[13] its use is limited due to the difficulty of selectivity removing the auxiliary fragment. 1-Phenylethylamine (**1**) fragments are usually cleaved by hydrogenolysis;[12] however, this approach has been reported to be unsuccessful for α-arylglycines due to competing cleavage of the α-aryl-aminonitrile stereocenter.[14] Panse reported that a modified procedure in which cyanogen bromide (CNBr) was added to preformed imines derived from aryl-aldehydes and (*S*)-1-phenylethylamine (**1**) allowed access to *N*-bromo-α-aminonitriles. The diastereomerically enriched *N*-bromo-α-aminonitriles were then deprotected by dehydrobromination to form benzylic imines that were hydrolyzed to afford the desired α-arylglycines. However, the ee of the resulting α-arylglycines were moderate (50% ee) due to partial racemization during the deprotection step (Scheme 1a).[13j]

Enantiopure 2-phenylglycinol (**2**) has been widely used as an effective chiral auxiliary for the synthesis of α-aryl-aminonitriles in reasonable diastereomeric excess (de).[15] Cleavage of the 2-phenylglycinol fragment of these α-aminonitriles required a

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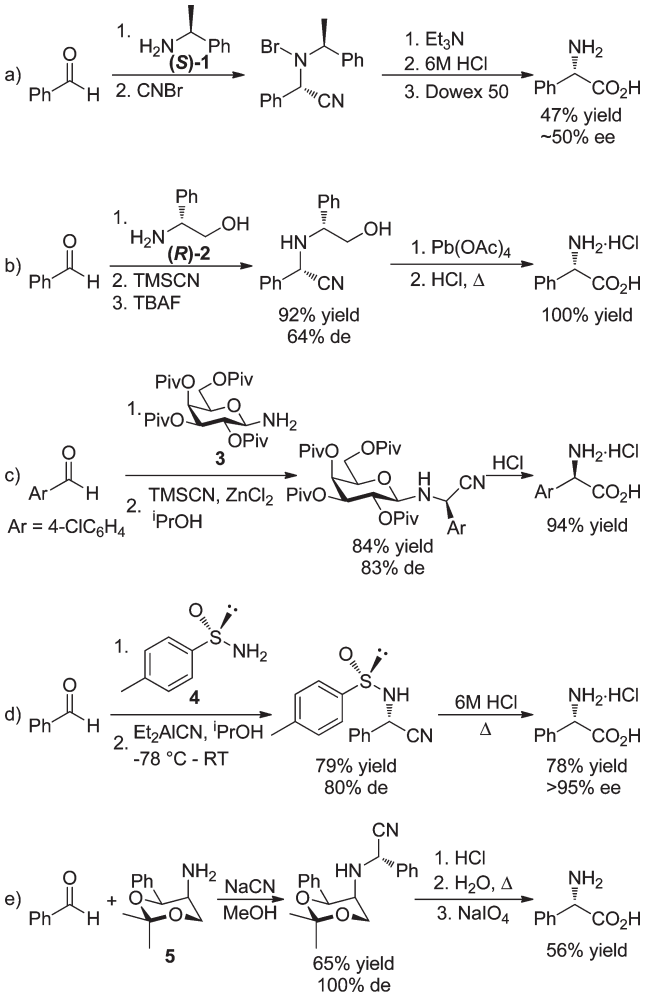
Scheme 1. Chiral Amines Previously Used As Auxiliaries for the Asymmetric Synthesis of α-Arylglycines



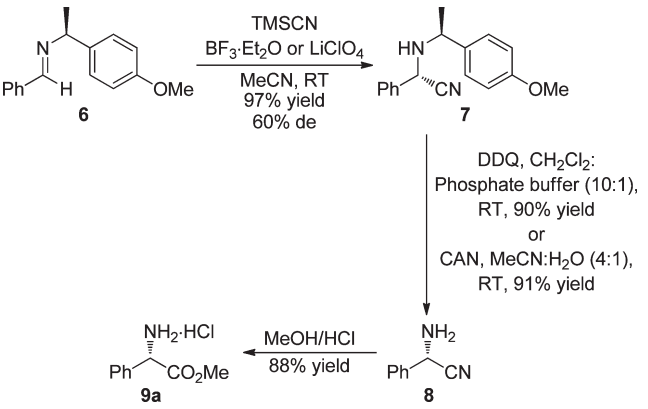
two-step process; first, lead tetraacetate was used to oxidatively cleave the amino-alcohol fragment to its corresponding imine, which was then hydrolyzed to afford the desired α-arylglycine (Scheme 1b).[15d]

Kunz and co-workers found that 1-amino-tetra-*O*-pivaloyl-β-D-galactopyranose (**3**) could control the addition of TMSCN to preformed imines using zinc chloride as a Lewis acid catalyst.[16] The diastereoselectivity of the reaction was found to be dependent on the reaction solvent, due to the difference in complexation ability of zinc chloride in polar and apolar solvents.[16b] The auxiliary could be removed by hydrolysis, with a single example of its application for the formation of an α-arylglycine (Scheme 1c).[16c]

Davis et al. have used enantiomerically pure sulfinimines (**4**) as chiral auxiliaries for the asymmetric Strecker reaction using diethylaluminium cyanide (Et_2AlCN) as a nucleophile.[17] The major diastereoisomer formed from the reaction could be isolated by recrystallization and the auxiliary removed by hydrolysis to form the α-arylglycine in good yield and high ee (Scheme 1d).[17b]

While the previous four examples of auxiliary-controlled Strecker reactions employed preformed imines, Weinges et al. have shown that (4*S*,5*S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane (**5**) can be used as an auxiliary in the three-component Strecker reaction using sodium cyanide (NaCN) as a nucleophile.

Scheme 2. (*S*)-1-(4-Methoxyphenyl)ethylamine as a Chiral Auxiliary for the Asymmetric Synthesis of (*S*)-α-Phenylglycine Methyl Ester Hydrochloride



The auxiliary initially provided α-aryl-aminonitriles with modest de (40% de), although the major diastereoisomer could be isolated in 65% yield after recrystallization. The oxidative cleavage of the auxiliary using sodium periodate was compatible with the synthesis of α-arylglycines, providing α-phenylglycine in 56% yield (Scheme 1e).[18]

As part of our studies[19] we required rapid access to a series of enantiopure α-arylglycines and decided to investigate the potential of using (*S*)-1-(4-methoxyphenyl)ethylamine (**10**) as a chiral auxiliary in the asymmetric Strecker reaction. A review of the literature revealed that Singh and co-workers had reported a single example of its use, involving Lewis acid ($BF_3 \cdot Et_2O$ or $LiClO_4$) catalyzed addition of TMSCN to preformed imine (**6**) to give chiral α-aminonitrile **7** in 60% de. The corresponding α-phenylglycine methyl ester was then obtained *via* a two-step deprotection sequence. First, treatment of α-aminonitrile **7** with either 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) or ceric ammonium nitrate (CAN) resulted in the oxidative removal of the chiral auxiliary fragment. α-Phenylnitrile **8** was then hydrolyzed to its corresponding α-phenylglycine methyl ester **9a** *via* treatment with methanolic HCl (Scheme 2).[20]

Inspired by this report, we now report a comprehensive study into using (*S*)-1-(4-methoxyphenyl)ethylamine (**10**) as a chiral auxiliary for the diastereoselective three-component Strecker synthesis of α-arylglycines. This has resulted in highly practical conditions that employ inexpensive NaCN as a nucleophile under aqueous conditions to afford diastereomerically pure crystalline α-aminonitriles in good yield. Simple acidic hydrolysis then results in removal of their chiral auxiliary fragments, with concomitant hydrolysis of their nitrile functionalities, to afford enantiopure α-arylglycines in good yield.

RESULTS AND DISCUSSION

Our aim was to develop a highly practical three-component asymmetric Strecker synthesis of α-arylglycines using a commercially available chiral auxiliary and NaCN as an inexpensive source of cyanide nucleophile (Scheme 3). In an adaptation of literature procedures,[13m,21] benzaldehyde (**11a**) was added to a solution of (*S*)-1-(4-methoxyphenyl)ethylamine hydrochloride (**10**) and NaCN in H_2O/MeOH (1:1), and the resulting solution stirred at room temperature for 16 h. After workup, ^1H NMR spectroscopic analysis of the crude reaction product revealed the

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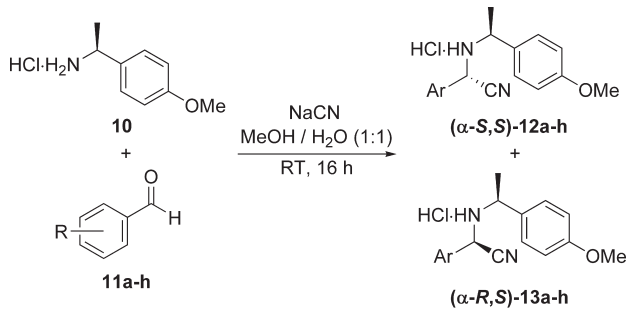
Scheme 3. Three-Component Strecker Reaction to form Chiral α-Aminonitriles Using (*S*)-1-(4-Methoxyphenyl)-ethylamine (10) as a Chiral Auxiliary



a) R = H, b) R = 4-Me, c) R = 2-Me, d) R = 4-MeO, e) R = 4-OH, f) R = 2-Br, g) R = 4-F, h) R = 3,4-(OCH_2O)

presence of a 3:1 diastereomeric ratio (dr) of α-aminonitriles (α-*S*,*S*)-**12a** and (α-*R*,*S*)-**13a**, in a combined 88% isolated yield (Table 1, entry 1).

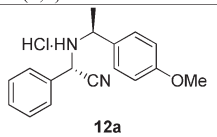
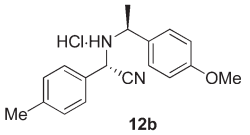
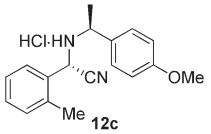
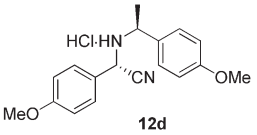
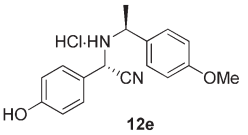
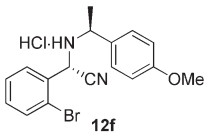
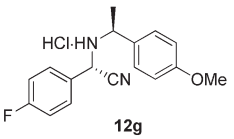
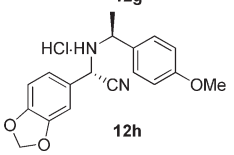
The absolute configuration of the major diastereoisomer was assigned as (α-*S*,*S*)-**12a** by comparison with spectroscopic data for this compound,[20] as well as the known preference for cyanide to undergo preferential nucleophilic attack at the *re*-face of this class of imine.[13m] Purification of the major diastereoisomer was achieved *via* fractional recrystallization of the crude reaction product from a solution of diethyl ether and saturated methanolic HCl to give the major (α-*S*,*S*)-diastereoisomer **12a** in >95% de and 62% yield.

This simple Strecker protocol was then applied to a range of substituted benzaldehydes **11b**−**h** that successfully gave their corresponding (*S*,*S*)-α-aminonitriles **12b**−**h** in >95:5 dr (Table 1). It was found that the Strecker reactions of benzaldehydes (**11b**−**f**) resulted in formation of mixtures of diastereomeric α-aminonitriles whose major (α-*S*,*S*)-diastereoisomers (**12b**−**f**) precipitated directly out of the reaction mixture in >99:1 dr, thus enabling them to be collected *via* simple filtration. The major α-aminonitriles from the reactions of 4-fluorobenzaldehyde (**11g**) and piperonal (**11h**) did not directly afford crystalline precipitates. However, their major diastereoisomers (*S*,*S*)-**12g**,**h** could be purified to >99:1 dr *via* fractional recrystallization of their crude reaction products (77:23 and 80:20 dr) from ether/methanolic HCl.

The configuration of *p*-tolyl-α-aminonitrile **12b** was unequivocally assigned as (α-*S*,*S*) by X-ray crystallographic analysis (see Supporting Information). The gross structure revealed one-dimensional chains that propagate along the *a* axis as a consequence of intermolecular hydrogen-bonding between the N1-H of one molecule and the nitrile nitrogen (N2) of a lattice neighbor. The remaining α-aminonitriles (**12c**−**h**) were subsequently confirmed as having (α-*S*,*S*) configurations by hydrolysis to their corresponding α-arylglycines whose positive specific rotations were compared with known literature values for (*S*)-α-arylglycines (*vide infra*).

We then looked to develop a convenient and scalable method that would enable (α-*S*,*S*)-α-aminonitriles (**12a**−**h**) to be converted into their corresponding α-arylglycines (**14a**−**h**). While Singh has reported that treatment of (α-*S*,*S*)-α-aminonitrile **7** with CAN resulted in clean *N*-deprotection of its chiral auxiliary fragment,[20] we found that it was difficult to isolate pure α-aminonitrile **8** free from residual cerium salts. A review of the literature[22] revealed that *N*-1-(4-methoxyphenyl)ethyl groups could be removed under cationic conditions *via* treatment with

Table 1. (*S*)-1-(4-Methoxyphenyl)ethylamine (10) Directed Asymmetric Strecker Reactions

Entry	(*S*,*S*)-α-Aminonitrile	Yield (%)	dr (**12**:**13**)[a]
1	 **12a**	62 (88)[c]	>99:1[b] (76:24)[c]
2	 **12b**	77	>99:1
3	 **12c**	60	>99:1
4	 **12d**	87	>99:1
5	 **12e**	86	>99:1
6	 **12f**	58	95:5
7	 **12g**	70 (95)[c]	>99:1[b] (77:23)[c]
8	 **12h**	54 (84)[c]	>99:1[b] (80:20)[c]

[a] Determined by ^{1}H NMR spectroscopic analysis. [b] Obtained after fractional recrystallization of the crude product from Et_2O and saturated methanolic HCl. [c] Yield and dr obtained after workup, prior to purification *via* fractional recrystallization.

trifluoroacetic acid[22a] or HCOOH/Et_3SiH.[22c,g] Consequently, we reasoned that treatment of α-aminonitriles **12a**−**h** under aqueous acidic conditions might result in cleavage of their auxiliary fragment with concomitant hydrolysis of their nitrile groups, thus affording an α-arylglycine in a "one-pot" hydrolytic process. It was found that heating (α-*S*,*S*)-phenyl-α-aminonitrile **12a** in 6 M aqueous HCl at reflux for 4 h resulted in cleavage of its *N*-1-(4-methoxyphenyl)ethyl fragment, accompanied by hydrolysis of its nitrile fragment, affording (*S*)-α-phenylglycine hydrochloride (**14a**) in 60% yield. The crude ^{1}H NMR spectra also showed the presence of small amounts of (*S*)-1-(4-methoxyphenyl)ethylamine hydrochloride **10** (∼15%), resulting from a competing reaction pathway in which the α-aminonitrile was hydrolyzed to its parent aldehyde and auxiliary. Any side

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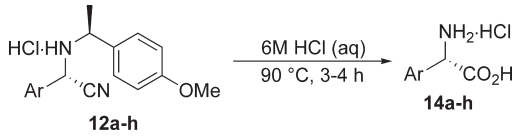
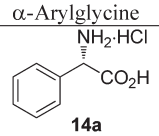
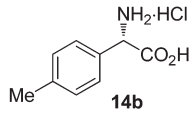
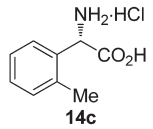
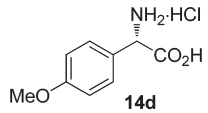
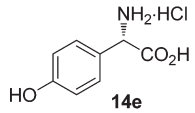
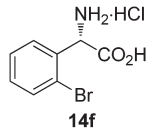
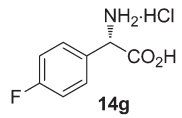
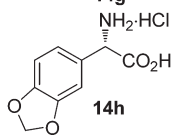
Table 2. Hydrolysis of α-Aminonitriles (12a−h) into α-Arylglycines (14a−h)

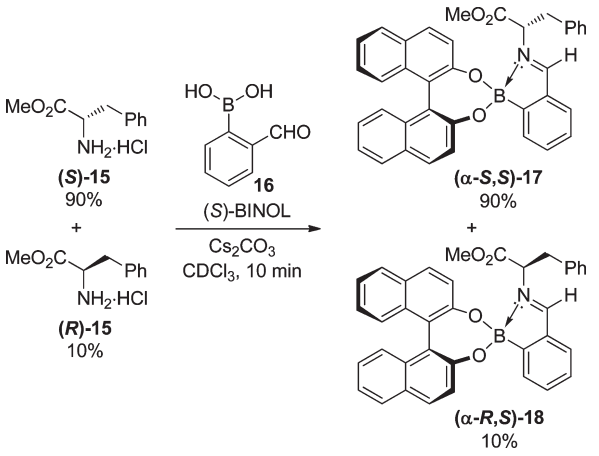


Entry	α-Arylglycine	Yield (%)	*ee* (%)[a]
1	 **14a**	60	96
2	 **14b**	56	94
3	 **14c**	80	95
4	 **14d**	52	90
5	 **14e**	81	94
6	 **14f**	80	95
7	 **14g**	63	96
8	 **14h**	64	88

[a] Determined by ^{1}H NMR spectroscopic analysis of the iminoboronate esters formed from derivatization using 2-formylphenylboronic acid (**16**) and (*S*)-BINOL (*vide infra*).

products could be conveniently removed by suspending the crude reaction mixture in chloroform and filtering the resultant suspension to give (*S*)-α-phenylglycine hydrochloride (**14a**) in 60% yield as a white solid. The configuration of the α-phenylglycine (**14a**) was confirmed by comparison of its specific rotation with that of commercially available α-phenylglycine (**14a**). These hydrolytic conditions were then applied to the remaining α-aminonitriles (**12b**−**h**) (Table 2), providing their corresponding α-arylglycines (**14b**−**h**) in reasonable yields (52−81%) and ee's (88−96%). The reduced yields observed for hydrolysis of *p*-tolyl-α-aminonitrile (**12b**) and *p*-methoxyphenyl-α-aminonitrile (**12d**) were attributed to an increase in the competing hydrolytic process that affords free auxiliary (**10**) and the parent aldehyde.

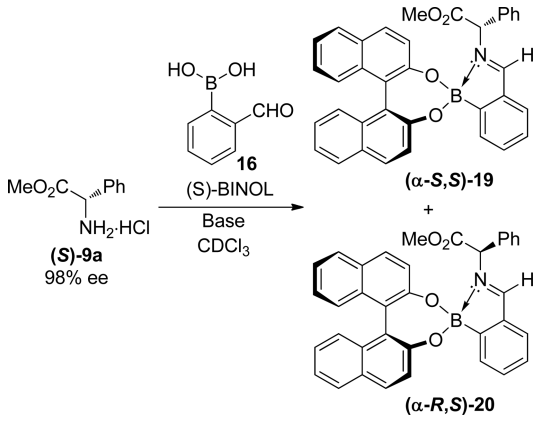
Scheme 4. Derivatization of (*S*)-Phenylalanine Methyl Ester Hydrochloride (*S*)-15 (80% ee) Affords a 9:1 dr of Iminoboronate Esters 17 and 18



It has been reported previously that direct acidic hydrolysis of optically active α-aminonitriles can potentially result in partial racemization of the α-center of α-arylglycines products.[23] Consequently, it was decided to unequivocally determine the enantiomeric excesses of the α-arylglycines **14a**−**h** using our recently published three-component chiral derivatization procedure.[24,25] This derivatization protocol involves treatment of a chiral amine of unknown enantiopurity with 2-formylphenylboronic acid (**16**) and enantiopure BINOL in $CDCl_3$. This results in formation of mixtures of diastereomeric iminoboronate esters whose ratio is easily determined by integration of appropriate pairs of diastereomeric resonances in their ^{1}H NMR spectra. Because no kinetic resolution occurs in this process, the observed dr corresponds directly to the enantiomeric ratio of the parent amine. A representative example of the analysis of a scalemic sample of phenylalanine methyl ester (*S*)-**15** of 80% ee is shown in Scheme 4.

While this derivatization protocol has been used successfully to determine the enantiomeric excess of a wide range of chiral amines,[25] Urriolabeitia and co-workers reported that "*When the NMR Tony-James* [sic] *protocol is applied, racemization was observed after the derivatization reaction. Similar results were obtained when the commercial (R)-phenylglycinate methyl ester hydrochloride was subjected to this NMR derivatization method.*"[26] In order to investigate this potential problem, we treated commercially available (*S*)-α-phenylglycine methyl ester hydrochloride (98% ee) (*S*)-**9a** with 1.1 equiv of 2-formylphenylboronic acid (**16**), (*S*)-BINOL, and cesium carbonate in $CDCl_3$ for 10 min, then filtered and acquired its ^{1}H NMR spectra. This revealed the clean formation of (α-*S*,*S*)-iminoboronate ester **19** in a 99:1 dr, with no evidence of any racemization at its α-stereocenter having occurred (Table 3, entry 1). However, we did find that leaving this derivatization reaction for extended periods of time (>1 h) resulted in epimerization of the α-stereocenter of (α-*S*,*S*)-**19**, ultimately affording a 50:50 mixture of (α-*S*,*S*)-iminoboronate ester **19** and (α-*R*,*S*)-iminoboronate ester **20** after 24 h (Table 3, entries 2 and 3). In order to address this epimerization problem, we decided to change the base from partially soluble cesium carbonate to completely insoluble potassium carbonate. This resulted in a clean derivatization reaction

Table 3. Investigating the Epimerization of Iminoboronate Complex 19



entry	base	time[a]	^{1}H NMR acquisition time	dr (**19**:**20**)[b]
1	Cs_2CO_3	10 min	10 min	99:1
2	Cs_2CO_3	5 h	5 h	94:6
3	Cs_2CO_3	24 h	24 h	53:47
4	K_2CO_3	10 min	10 min	99:1
5	K_2CO_3	10 min	24 h	99:1

[a] Reaction time before filtering excess base. [b] Determined by ^{1}H NMR spectroscopic analysis.

that was complete after 10 min, which upon filtration gave a ^{1}H NMR spectra of (α-*S*,*S*)-iminoboronate ester **19** in a 99:1 dr (Table 3, entry 4). Importantly, it was found that this filtered solution of (α-*S*,*S*)-iminoboronate **19** in $CDCl_3$ was configurationally stable, giving an identical 99:1 dr after being left for 24 h (Table 3, entry 5). This means that once the derivatization mixture has been filtered its ^{1}H NMR spectrum does not need to be acquired immediately for an accurate dr to be obtained. Therefore, we now recommend that potassium carbonate is used as a base when the ee of amines that contain relatively acidic stereocenters are determined using this three-component derivatization protocol.

Having resolved any potential epimerization problems, this derivatization protocol was then used to determine the ee of the α-arylglycines (**14a**−**h**) produced in our Strecker reactions. The α-arylglycines (**14a**−**h**) were first converted into their corresponding methyl ester hydrochlorides by heating at reflux in acidic methanol. Each α-arylglycine methyl ester was derivatized *via* treatment with 2-formylphenylboronic acid (**16**), *rac*-BINOL, and potassium carbonate in $CDCl_3$ for 10 min. The excess potassium carbonate was then filtered off, and ^{1}H NMR spectroscopic analysis was performed to afford authentic spectra of 50:50 mixtures of their corresponding diastereomeric iminoboronate esters in each case. Examination of the ^{1}H NMR spectra of each derivatization reaction revealed the presence of at least one pair of resolved diastereomeric resonances in each case, whose integrals could be used to indirectly determine the enantiopurity of their parent α-arylglycine (**14a**−**h**). A representative ^{1}H NMR spectrum that was obtained for the derivatization of (*S*)-**9a** with *rac*-BINOL is shown in Figure 1a.

The enantiomeric excess of each α-arylglycine methyl ester hydrochloride was then determined by repeating the derivatization reaction using enantiopure (*S*)-BINOL. ^{1}H NMR spectroscopic analysis of each derivatization reaction revealed that (α-*S*,*S*)-iminoboronate esters had been formed in >88% de in each case. A representative ^{1}H NMR spectrum that was obtained for the derivatization of (*S*)-**9a** with (*S*)-BINOL is shown in Figure 1b. This indicates that acidic hydrolysis of the α-aminonitriles (**12a**−**h**) to afford their corresponding α-arylglycines (**14a**−**h**) proceeds without any significant racemization of their α-stereocenters.

Finally, in order to demonstrate the applicability of our methodology, we decided to optimize the asymmetric synthesis of *p*-tolylglycine (**14b**) on a multigram scale. Therefore, the Strecker reaction of *p*-tolualdehyde (**11b**) was repeated on a 15 mmol scale to afford its (α-*S*,*S*)-aminonitrile (**12b**) that precipitated directly out of the reaction to enable its isolation in 82% yield *via* simple filtration (Scheme 5). The (α-*S*,*S*)-α-aminonitrile (**12b**) was immediately subjected to our deprotection/hydrolysis conditions by heating at reflux in 6 M HCl for 4 h. Pleasingly, the hydrolysis reaction resulted in essentially quantitative formation of the desired (*S*)-α-*p*-tolylglycine (**14b**) in 94% ee. This demonstrates that our three-component Strecker procedure can be used to rapidly produce gram quantities of enantiopure α-arylglycines in a time period of less than 24 h.

CONCLUSIONS

We have developed a practically simple three-component Strecker reaction for the asymmetric synthesis of enantiopure α-arylglycines. This protocol is based on the addition of arylaldehydes to a solution of sodium cyanide and (*S*)-1-(4-methoxyphenyl)ethylamine, which results in formation of highly crystalline (*S*,*S*)-α-aminonitriles that can are easily obtained in diastereomerically pure form. Heating the resultant (*S*,*S*)-α-aminonitriles in 6 M aqueous HCl at reflux results in cleavage of their chiral auxiliary fragments and hydrolysis of their nitrile groups to afford enantiopure (*S*)-α-arylglycines in good yield. The enantiopurities of these (*S*)-α-arylglycines were determined *via* derivatization of their corresponding methyl esters with 2-formylphenylboronic acid and (*S*)-BINOL, followed by ^{1}H NMR spectroscopic analysis of the resultant mixtures of diastereomeric iminoboronate esters.

EXPERIMENTAL SECTION

General. Commercially available (*S*)-1-(4-methoxyphenyl)ethylamine was converted to its hydrochloride salt (**10**) using 1 M HCl in Et_2O. Best results were obtained when aldehydes were purified, either by recrystallization or distillation, before use. ^{1}H NMR spectra were recorded at either 300 or 400 MHz, and $^{13}C\{^1H\}$ NMR spectra were recorded at either 75 or 100 MHz. NMR peak assignments were confirmed using 2D ^{1}H COSY where necessary. Capillary melting points are reported uncorrected. Optical rotations were recorded with a path length of 1 dm; concentrations (*c*) are quoted in g/100 mL. Infrared spectra were recorded with internal background calibration in the range 600−4000 cm^{-1}, as solutions in chloroform ($CHCl_3$), using thin films on NaCl plates (film) or KBr discs (KBr) as stated. High resolution mass spectra were recorded using electron impact (EI), chemical ionization (CI), or electrospray (ES).

General Procedure for the Synthesis of (*S*,*S*)-α-Aryl-α-[1-(4-methoxyphenyl)ethylamino]acetonitrile Hydrochlorides (12a−h). In an adaptation of literature procedures,[13m,21] (*S*)-1-(4-methoxyphenyl)-ethylamine hydrochloride (*S*)-**10** (563 mg, 3.00 mmol) and NaCN (154 mg, 3.15 mmol) were dissolved in H_2O (4 mL). MeOH (4 mL) and the corresponding aryl-aldehyde **11a**−**h** (3.00 mmol) were then added, and the mixture was stirred for 16 h. The

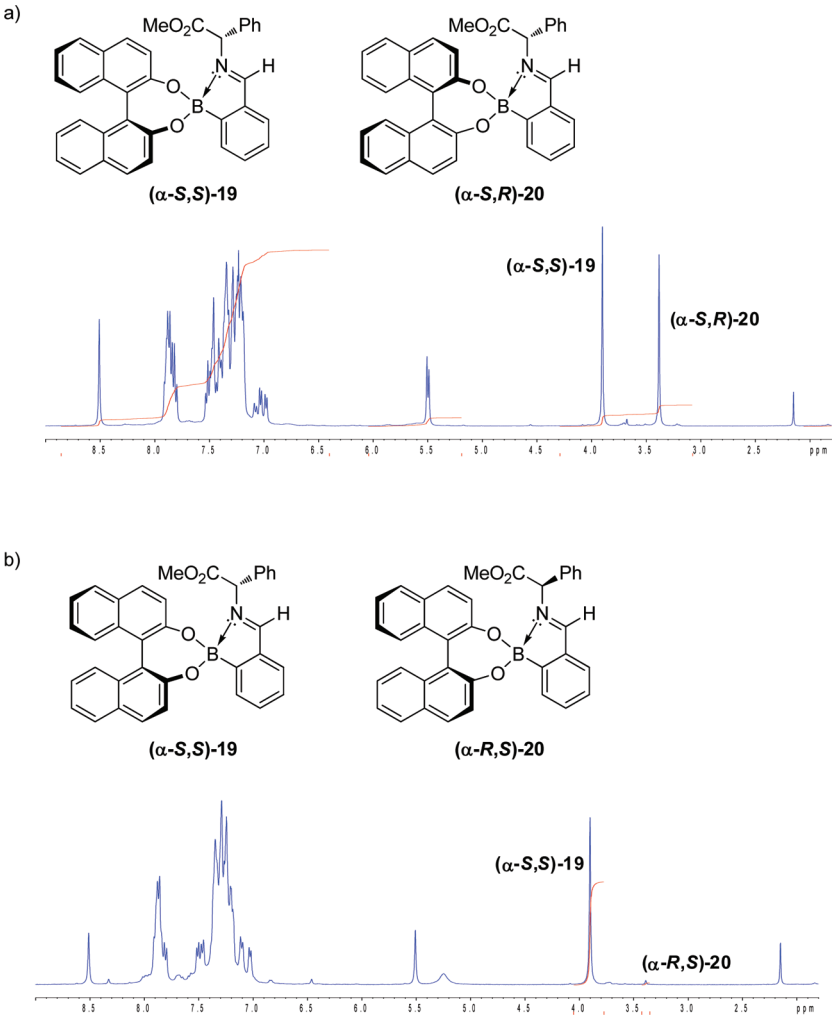
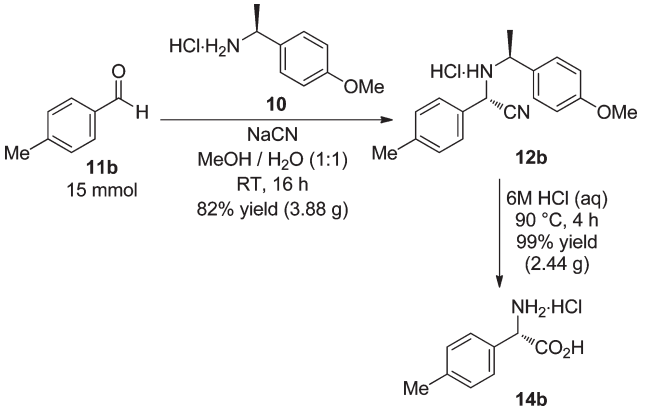


Figure 1. Representative derivatization protocol. (a) Derivatization of (*S*)-α-phenylglycine methyl ester hydrochloride (**9a**) with 2-formylphenylboronic acid (**16**) and *rac*-BINOL results in formation of a 50:50 mixture of diastereomeric iminoboronate esters (α-*S*,*S*)-**19** and (α-*S*,*R*)-**20**. (b) Derivatization of synthesized α-phenylglycine methyl ester hydrochloride (**9a**) with (*S*)-BINOL reveals a 98:2 mixture of (α-*S*,*S*)-**19**:(α-*R*,*S*)-**20**, corresponding to a 96% ee for (*S*)-α-phenylglycine (**14a**).

Scheme 5. Application of the Strecker Protocol to the Multigram Scale Synthesis of (*S*)-α-*p*-Tolylglycine (14b)



reaction was then diluted with H_2O (10 mL), and the resulting solid was collected *via* filtration and washed with *n*-hexane. If a single diastereoisomer did not precipitate out of solution, the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined CH_2Cl_2 extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude mixture was dissolved in Et_2O, and the addition of saturated methanolic HCl gave a white crystalline solid that was collected *via* filtration and washed with *n*-hexane, which corresponded to the major (α-*S*,*S*)-aminonitrile hydrochloride **12a**−**h** in >95% de.

(*S*,*S*)-α-Phenyl-α-[1-(4-methoxyphenyl)ethylamino]acetonitrile Hydrochloride (α-*S*,*S*)-12a. The title compound was synthesized according to the general procedure using benzaldehyde **11a** (0.30 mL, 3.00 mmol). After workup and recrystallization from Et_2O and saturated methanolic HCl the aminonitrile hydrochloride **12a** (562 mg, 62%) was obtained as white needles: mp 127−128 °C; $[\alpha]_D^{25}$ −95 (*c* 0.525, $CHCl_3$), −54 (*c* 0.350, MeOH); ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.49−7.46 (2H, m, Ar*H*), 7.42−7.34 (5H, m, Ar*H*), 6.93 (2H, d, *J* = 8.7 Hz, Ar*H*), 4.38 (1H, s, C*H*CN), 4.20 (1H, q, *J* = 6.5 Hz, C*H*CH_3), 3.82 (3H, s, CH_3O), 1.41 (3H, d, *J* = 6.5 Hz, CHCH_3); ^{13}C{^{1}H} NMR (75 MHz; $CDCl_3$) δ_C 161.1, 134.9, 131.3, 130.8, 130.2, 129.6, 128.9, 115.4, 114.8, 59.3, 55.8, 50.7, 20.7; *m*/*z* (CI) 266 (2%, M − HCl), 251 (25, M − HCl − Me), 240 (18, M − HCl − CN), 135 (100, C_8H_9NO). Found: C, 67.1; H, 6.40; N, 9.18. $C_{17}H_{19}ClN_2O$ requires C, 67.43; H, 6.32; N, 9.25.

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(*S,S*)-α-*p*-Tolyl-α-[1-(4-methoxyphenyl)ethylamino]actonitrile Hydrochloride (α-*S,S*)-12b. The title compound was synthesized according to the general procedure using *p*-tolualdehyde **11b** (0.35 mL, 3.00 mmol). After workup and recrystallization from Et_2O and saturated methanolic HCl the aminonitrile hydrochloride **12b** (739 mg, 77%) was obtained as white needles: mp 118−119 °C; $[\alpha]_D^{25}$ −100 (*c* 0.510, $CHCl_3$), −28 (*c* 0.360, MeOH); ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.39−7.33 (4H, m, Ar*H*), 7.20 (2H, d, *J* = 8.0 Hz, Ar*H*), 6.92 (2H, d, *J* = 8.6 Hz, Ar*H*), 4.34 (1H, s, C*H*CN), 4.19 (1H, q, *J* = 6.5 Hz, C*H*CH_3), 3.82 (3H, s, CH_3O), 2.35 (3H, s, ArCH_3), 1.40 (3H, d, *J* = 6.5 Hz, CHC*H*$_{>3}$); ^{13}C{^{1}H} NMR (75 MHz; $CDCl_3$) δ_C 159.3, 138.9, 135.1, 132.5, 129.7, 128.2, 127.2, 119.3, 114.4, 56.3, 55.4, 52.1, 25.0, 21.3; IR (film, cm^{-1}) ν_{max} = 3304 (NH), 2228 (CN); *m*/*z* (EI) 265 (24%, M − HCl − Me), 253 (45, M − HCl − HCN), 238 (64, M − HCl − HCN − Me), 135 (100, C_8H_9NO). Found for the free base form: C, 77.1; H, 7.19; N, 9.86. $C_{18}H_{20}N_2O$ requires C, 77.1; H, 7.19; N, 9.99.

(*S,S*)-α-*o*-Tolyl-α-[1-(4-methoxyphenyl)ethylamino]acetonitrile Hydrochloride (α-*S,S*)-12c. The title compound was synthesized according to the general procedure using *o*-tolualdehyde **11c** (0.35 mL, 3.00 mmol). After filtration, the aminonitrile hydrochloride **12c** (570 mg, 60%) was obtained as white plates: mp 129−132 °C; $[\alpha]_D^{25}$ −189 (*c* 0.475, $CHCl_3$), −109 (*c* 0.525, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.57−7.55 (1H, m, Ar*H*), 7.38 (2H, d, *J* = 8.7 Hz, Ar*H*), 7.28−7.15 (3H, m, Ar*H*), 6.92 (2H, d, J = 8.6 Hz, Ar*H*), 4.39 (1H, s, C*H*CN), 4.20 (1H, q, *J* = 6.4 Hz, C*H*CH_3), 3.83 (3H, s, CH_3O), 2.14 (3H, s, ArCH_3), 1.40 (3H, d, *J* = 6.4 Hz, CHC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz; $CDCl_3$) δ_C 159.7, 136.7, 134.9, 133.8, 131.5, 129.5, 128.8, 127.7, 127.0, 119.5, 114.5, 56.7, 55.7, 50.6, 24.7, 19.0; $\nu_{max}(CHCl_3)/cm^{-1}$ 3338 (NH), 2222 (CN); *m*/*z* (CI) 265 (12%, M − Me), 253 (22, M − HCN), 135.0 (100, C_8H_9NO). Found: C, 77.0; H, 7.03; N, 9.86. $C_{18}H_{20}N_2O$ requires C, 77.11; H, 7.19; N, 9.99.

(*S,S*)-α-(4-Methoxyphenyl)-α-[1-(4-methoxyphenyl)ethyl)-amino]-acetonitrile Hydrochloride (α-*S,S*)-12d. The title compound was synthesized according to the general procedure using *p*-methoxybenzaldehyde **11d** (0.37 mL, 3.00 mmol). After filtration, the aminonitrile hydrochloride **12d** (871 mg, 87%) was obtained as a white solid, mp 109−111 °C; $[\alpha]_D^{20}$ −27.4 (*c* 0.475, MeOH); ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.40−7.35 (4H, m, Ar*H*), 6.95−6.86 (4H, m, Ar*H*), 4.32 (1H, s, C*H*CN), 4.18 (1H, q, *J* = 6.6 Hz, C*H*CH_3), 3.82 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 1.40 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C 160.1, 159.3, 135.1, 128.5, 128.2, 127.5, 119.3, 114.4, 56.3, 55.5, 55.4, 51.8, 24.9; IR (film, cm^{-1}) ν_{max} = 3306 (NH), 2227 (CN); HRMS *m*/*z* (ES) 297.1605, $C_{18}H_{21}N_2O_2$ $[M + H]^+$ requires 297.1603.

(*S,S*)-α-(4-Hydroxyphenyl)-α-[1-(4-methoxyphenyl)ethyl)-amino]-acetonitrile hydrochloride, (α-*S,S*)-12e. The title compound was synthesized according to the general procedure using *p*-hydroxybenzaldehyde **11e** (0.37 g, 3.00 mmol). After filtration, the aminonitrile hydrochloride **12e** (819 mg, 86%) was obtained as a white solid, mp 132−134 °C; $[\alpha]_D^{20}$ −40.7 (*c* 0.590, MeOH); ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.37 (2H, app d, *J* = 8.7 Hz, Ar*H*), 7.30 (2H, app d, *J* = 8.4 Hz, Ar*H*), 6.92 (2H, app d, *J* = 8.7 Hz, Ar*H*), 6.81 (2H, app d, *J* = 8.7 Hz, Ar*H*), 4.30 (1H, s, C*H*CN), 4.16 (1H, q, *J* = 6.4 Hz, C*H*CH_3), 3.82 (3H, s, OCH_3), 1.40 (3H, d, *J* = 6.4 Hz, CHC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C 159.3, 156.4, 135.0, 128.7, 128.2, 127.3, 119.3, 115.9, 114.4, 56.3, 55.5, 51.8, 24.9; IR (film, cm^{-1}) ν_{max} = 3261 (NH), 2228 (CN); HRMS *m*/*z* (ES) 305.1255, $C_{17}H_{18}N_2NaO_2$ $[M + Na]^+$ requires 305.1266.

(*S,S*)-α-(2-Bromophenyl)-α-[1-(4-methoxyphenyl)ethyl-amino]-acetonitrile Hydrochloride (α-*S,S*)-12f. The title compound was synthesized according to the general procedure using 2-bromobenzaldehyde **11f** (0.35 mL, 3.00 mmol). After filtration, the aminonitrile hydrochloride **12f** (662 mg, 58%) was obtained as white plates: mp 117.0−118.5 °C; For a sample with *ca.* 90% de $[\alpha]_D^{25}$ −166 (*c* 0.525, $CHCl_3$), −116 (*c* 0.490, MeOH); ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.63−7.56 (2H, m, Ar*H*), 7.42−7.35 (3H, m, Ar*H*), 7.28−7.21 (1H, m, Ar*H*), 6.93−6.90 (2H, m, Ar*H*), 4.66 (1H, s, C*H*CN), 4.18 (1H, q, *J* = 6.6 Hz, C*H*CH_3), 3.83 (3H, s, CH_3O), 1.74 (1H, brs, N*H*), 1.42 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz; $CDCl_3$) δ_C 159.7, 135.2, 134.5, 134.1, 131.0, 129.7, 128.9, 128.6, 123.7, 118.9, 114.4, 56.7, 55.7, 52.8, 24.9; $\nu_{max}(CHCl_3)/cm^{-1}$ 3333 (NH), 2228 (CN); *m*/*z* (CI) 346 (3%, M^+), 344 (3%, M^+), 331 (66, M − Me), 329 (66, M − Me), 318 (69, M − CN), 304 (12, M − CN − Me − H), 302 (12, M − CN − Me − H), 135 (100, C_8H_9NO). Found: C, 59.2; H, 4.86; N, 8.10. $C_{17}H_{17}BrN_2O$ requires C, 59.14; H, 4.96; N, 8.11.

(*S,S*)-α-(4-Fluorophenyl)-α-[1-(4-methoxyphenyl)ethyl-amino]-acetonitrile Hydrochloride (α-*S,S*)-12g. The title compound was synthesized according to the general procedure using 4-fluorobenzaldehyde **11g** (0.32 mL, 3.00 mmol). After workup and recrystallization from Et_2O and saturated methanolic HCl the aminonitrile hydrochloride **12g** (674 mg, 70%) was obtained as white needles: mp 137−138 °C; $[\alpha]_D^{25}$ −53 (*c* 0.510, MeOH); ^{1}H NMR (300 MHz; $(CD_3)_2SO$) δ_H 7.66−7.58 (2H, m, Ar*H*), 7.39 (2H, d, *J* = 8.6 Hz, Ar*H*), 7.23−7.17 (2H, m, Ar*H*), 6.87 (2H, d, *J* = 8.6 Hz, Ar*H*), 5.19 (1H, s, C*H*CN), 4.16 (1H, q, *J* = 6.5 Hz, C*H*CH_3), 3.64 (3H, s, OCH_3), 1.49 (3H, d, *J* = 6.5 Hz, CHC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz; $(CD_3)_2SO$) δ_C 159.7, 132.1 (d, *J* = 9.0 Hz, $C_{Ar}HC_{Ar}HC_{Ar}F$), 129.8, 129.4, 128.8, 124.3 (d, *J* = 207 Hz, $C_{Ar}F$), 116.0 (d, *J* = 22.1 Hz, $C_{Ar}HC_{Ar}F$), 114.5, 114.2, 56.8, 55.2, 48.2, 20.3; *m*/*z* (CI) 284 (2%, M − HCl), 269 (21, M − HCl − Me), 258 (29, M − HCl − CN), 135 (100, C_8H_9NO). Found: C, 63.4 ; H, 5.74; N, 8.67. $C_{17}H_{18}ClFN_2O$ requires C, 63.65; H, 5.66; N, 8.73.

(*S,S*)-α-(Benzo[d][1,3]dioxol-5-yl)-α-[1-(4-methoxyphenyl)-ethylamino]-acetonitrile Hydrochloride (α-*S,S*)-12h. The title compound was synthesized according to the general procedure using piperonal **11h** (0.45 g, 3.00 mmol). After workup and recrystallization from Et_2O and saturated methanolic HCl the aminonitrile hydrochloride **12h** (558 mg, 54%) was obtained as a white solid: mp 116−119 °C; $[\alpha]_D^{22}$ −60 (*c* 0.55, $CHCl_3$); ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.64 (2H, d, *J* = 8.7 Hz, Ar*H*), 7.24−7.22 (1H, m, Ar*H*), 7.01−6.79 (4H, m, Ar*H*), 5.91 (2H, s, CH_2), 4.57 (1H, s, C*H*CN), 4.41 (1H, q, *J* = 6.8 Hz, C*H*CH_3), 3.84 (3H, s, OCH_3), 1.66 (3H, d, *J* = 6.4 Hz, CHC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz; CD_3OD) δ_C 160.9, 150.1, 150.0, 148.3, 130.0, 129.8, 125.2, 124.6, 115.1, 114.9, 110.7, 108.8, 102.0, 58.9, 55.5, 50.3, 20.6; IR (film, cm^{-1}) ν_{max} = 3032 (NH), 2049 (CN); HRMS *m*/*z* (ES) 311.1382, $C_{18}H_{19}N_2O_3$ $[M + H]^+$ requires 311.1396.

General Procedure for the Synthesis of (*S*)-α-Arylglycine Hydrochlorides 14a−h. The corresponding aminonitrile hydrochloride (**12a**−**h**) was treated with 6 M aqueous HCl (amount corresponding to a 0.1 M solution), and the mixture was heated at 90 °C for *ca.* 3−4 h. The reaction mixture was allowed to cool to room temperature and extracted with Et_2O. The organic extract was discarded, and the aqueous layer was concentrated *in vacuo* to dryness to give a white/yellowish solid. The crude was suspended in $CDCl_3$ (using a sonicator) and filtered to give the corresponding (*S*)-α-arylglycine hydrochloride (**14a**−**h**) as a white solid.

(*S*)-α-Amino-α-phenylacetic Acid Hydrochloride (*S*)-14a. The title compound was synthesized according to the general procedure using aminonitrile (*S,S*)-**12a** (124 mg, 0.47 mmol) and 5 mL of 6 M aqueous HCl. The title compound **14a** was obtained as a white solid (53 mg, 60%);$[\alpha]_D^{20}$ +152 (*c* 0.100, 1 M HCl); ^{1}H NMR (400 MHz; D_2O) δ_H 7.47−7.42 (5H, m, Ar*H*), 5.07 (1H, s, C*H*CO_2H); ^{13}C{^{1}H} NMR (100 MHz; D_2O) δ_C 171.2, 131.9, 130.2, 129.7, 128.1, 56.9; *m*/*z* (CI) 152 (6%, M − HCl), 135 (39, M − HCl − NH_3), 107 (100, M − HCl − CO_2H).

(*S*)-α-Amino-α-*p*-tolylacetic Acid Hydrochloride (*S*)-14b. The title compound was synthesized according to the general procedure

using aminonitrile (*S*,*S*)-**12b** (150 mg, 0.53 mmol) and 5 mL of 6 M aqueous HCl. The title compound **14b** was obtained as a white solid (60 mg, 56%); $[\alpha]_D^{20}$ +70 (*c* 0.100, H_2O); ^1H NMR (300 MHz; D_2O) δ_H 7.29 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.26 (2H, d, *J* = 8.5 Hz, Ar*H*), 5.02 (1H, s, C*H*CO_2H), 2.28 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz; D_2O) δ_C 171.1, 140.8, 130.1, 128.8, 128.0, 56.6, 20.3; IR (film, cm^{-1}) ν_{max} = 2976 (br, NH), 2880 (br, OH), 1727 (C═O); HRMS *m*/*z* (ES) 166.0870, $C_9H_{12}NO_2$ $[M + H]^+$ requires 166.0868.

(*S*)-α-Amino-α-*o*-tolylacetic Acid Hydrochloride (*S*)-14c. The title compound was synthesized according to the general procedure using aminonitrile (*S*,*S*)-**12c** (300 mg, 1.07 mmol) and 11 mL of 6 M aqueous HCl. The title compound **14c** was obtained as a white solid (173 mg, 80%); $[\alpha]_D^{25}$ +90 (*c* 0.100, 5 M HCl); ^1H NMR (300 MHz; D_2O) δ_H 7.41−7.20 (4H, m, ArH), 5.05 (1H, s, C*H*CO_2H), 2.04 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz; D_2O) δ_C 170.8, 137.4, 131.5, 130.3, 129.8, 127.1, 126.8, 53.1, 18.8, *m*/*z* (CI) 166 (8%, M − Cl), 149.0 (26, M − Cl − NH_3), 120 (100, M − HCl − CO_2H).

(*S*)-α-Amino-α-(4-methoxyphenyl)acetic Acid Hydrochloride (*S*)-14d. The title compound was synthesized according to the general procedure using aminonitrile (*S*,*S*)-**12d** (210 mg, 0.70 mmol) and 7 mL of 6 M aqueous HCl. The title compound **14d** was obtained as a white solid (79 mg, 52%); $[\alpha]_D^{22}$ +41.7 (*c* 0.120, H_2O); ^1H NMR (300 MHz; D_2O) δ_H 7.38 (2H, app d, *J* = 8.9 Hz, Ar*H*), 7.03 (2H, app d, *J* = 8.9 Hz, Ar*H*), 4.99 (1H, s, C*H*CO_2H), 3.81 (3H, s, OCH_3); $^{13}C\{^1H\}$ NMR (75 MHz, D_2O) δ_C 160.4, 130.0, 124.8, 115.3, 56.7, 55.7; IR (film, cm^{-1}) ν_{max} = 2969 (OH), 1733 (C═O); HRMS *m*/*z* (ES) 182.0809, $C_9H_{12}NO_3$ $[M + H]^+$ requires 182.0817.

(*S*)-α-Amino-α-(4-hydroxyphenyl)acetic Acid Hydrochloride (*S*)-14e. The title compound was synthesized according to the general procedure using aminonitrile (*S*,*S*)-**12e** (200 mg, 0.70 mmol) and 7 mL of 6 M aqueous HCl. The title compound **14e** was obtained as a white solid (116 mg, 81%); $[\alpha]_D^{22}$ +58.5 (*c* 0.205, H_2O); ^1H NMR (300 MHz; D_2O) δ_H 7.31 (2H, app d, *J* = 8.6 Hz, Ar*H*), 6.91 (2H, app d, *J* = 8.6 Hz, Ar*H*), 5.04 (1H, s, C*H*CO_2H); $^{13}C\{^1H\}$ NMR (75 MHz, D_2O) δ_C 171.7, 157.4, 130.2, 123.9, 116.6, 56.6; IR (film, cm^{-1}) ν_{max} = 3000 (O−H), 1728 (C═O); HRMS *m*/*z* (ES) 168.0643, $C_8H_{10}NO_3$ $[M + H]^+$ requires 168.0661.

(*S*)-α-Amino-α-(2-bromophenyl)acetic Acid Hydrochloride (*S*)-14f. The title compound was synthesized according to the general procedure using aminonitrile (*S*,*S*)-**12f** (246 mg, 0.71 mmol) and 8 mL of 6 M aqueous HCl. The compound **14f** was obtained as a white solid (151 mg, 80%); $[\alpha]_D^{25}$ +60 (*c* 0.515, 1 M HCl); ^1H NMR (300 MHz; D_2O) δ_H 7.64 (1H, d, *J* = 7.7 Hz, Ar*H*), 7.38−7.33 (2H, m, Ar*H*), 7.31−7.25 (1H, m, Ar*H*), 5.45 (1H, s, C*H*CO_2H); $^{13}C\{^1H\}$ NMR (75 MHz; D_2O) δ_C 169.7, 133.0, 131.2, 130.5, 129.0, 128.0, 123.1, 55.5; ν_{max}(KBr)/cm^{-1} 3409 (OH), 1747 (C═O), 1405 (OH); *m*/*z* (CI) 232 (29%, M − HCl), 230 (29%, M − HCl), 215 (14, M − HCl − NH_3), 213 (14, M − HCl − NH_3), 186 (100, M − HCl − CO_2H), 184 (100, M − HCl − CO_2H).

(*S*)-α-Amino-α-(4-fluorophenyl)acetic Acid Hydrochloride (*S*)-14g. The title compound was synthesized according to the general procedure using aminonitrile (*S*,*S*)-**12g**· (77 mg, 0.24 mmol) and 3 mL of 6 M aqueous HCl. The title compound **14g** was obtained as a white solid (31 mg, 63%); $[\alpha]_D^{22}$ +132 (*c* 0.100, 1 M HCl); ^1H NMR (300 MHz; D_2O) δ_H 7.39−7.34 (2H, m, Ar*H*), 7.10 (2H, app t, *J* = 8.7 Hz, Ar*H*), 5.05 (1H, s, C*H*CO_2H); $^{13}C\{^1H\}$ NMR (75 MHz; D_2O) δ_C 170.7, 163.3 (d, *J* = 246.9 Hz, $C_{Ar}F$), 130.5 (d, *J* = 9.2 Hz, $C_{Ar}HC_{Ar}HC_{Ar}F$), 127.6 (d, *J* = 3.1 Hz, $C_{Ar}H(C_{Ar}H)_2C_{Ar}F$), 116.7 (d, *J* = 22.2 Hz, $C_{Ar}HC_{Ar}F$), 56.1; *m*/*z* (CI) 170 (12%, M − Cl), 153 (36, M − Cl − NH_2), 124 (100, M − HCl − CO_2H).

(*S*)-α-Amino-α-(benzo[*d*][1,3]dioxol-5-yl)acetic Acid (*S*)-14h. The title compound was synthesized according to the general procedure using aminonitrile (*S*,*S*)-**12h** (275 mg, 0.79 mmol) and 8 mL of 6 M aqueous HCl. The title compound **14h** was obtained as a white solid (118 mg, 64%); $[\alpha]_D^{20}$ +48 (*c* 0.415, H_2O); ^1H NMR (300 MHz; D_2O) δ_H 7.01−6.94 (3H, m, Ar*H*), 6.03 (2H, s, CH_2), 5.07 (1H, s, C*H*CO_2H); $^{13}C\{^1H\}$ NMR (75 MHz; D_2O) δ_C 171.6, 149.0, 148.4, 125.7, 123.0, 109.5, 108.4, 102.2, 57.0; IR (film, cm^{-1}) ν_{max} = 2985 (br, NH), 2915 (br, OH), 1734 (C═O); HRMS *m*/*z* (ES) 196.0610, $C_9H_{10}NO_4$ $[M + H]^+$ requires 196.0610.

General Procedure for the Determination of the Enantiomeric Excess of the Synthesized (*S*)-α-Arylglycine Hydrochlorides. The α-arylglycines hydrochlorides **14a**−**h** were converted to their respective methyl ester hydrochloride derivatives in quantitative yield by heating them at reflux at 85 °C in 3 M aqueous HCl in MeOH for 12 h, followed by simple evaporation of the solvent. The α-amino ester hydrochloride (1 equiv) and K_2CO_3 (1.1 equiv) were suspended in a minimum amount of $CDCl_3$. 2-Formylphenylboronic acid (**16**) (1.1 equiv), (*S*)-(BINOL) (1.1 equiv), 4 Å molecular sieves, and $CDCl_3$ were then added in order to produce a 0.1 M solution of the α-amino ester hydrochloride. The solution was stirred for 10 min before being filtered through a small pad of Celite and the solution analyzed by ^1H NMR spectroscopy.

■ ASSOCIATED CONTENT

Supporting Information. ^1H and ^{13}C NMR spectra of α-aminonitriles **12a**−**h** and α-arylglycines **14a**−**h** and CIF file for (α-*S*,*S*)-**12b**. This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data for compound (α-*S*,*S*)-**12b** have also been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 811794.

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