JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

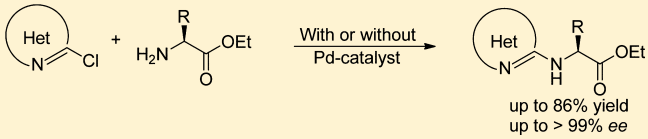
N-Heteroarylation of Chiral α-Aminoesters by Means of Palladium-Catalyzed Buchwald–Hartwig Reaction

Hassan Hammoud, Martine Schmitt,* Emilie Blaise, Frédéric Bihel, and Jean-Jacques Bourguignon

Laboratoire d'Innovation Thérapeutique, UMR 7200, Faculté de Pharmacie, Université de Strasbourg, 74, route du Rhin, BP 60024, 67401 Illkirch, France

Supporting Information

ABSTRACT: *N*-Heteroaryl-α-amino acid derivatives are valuable pharmacological agents as peptidomimetics. Classical S_NAr methods using acid catalysis and elevated temperatures could not be extended to various α-amino acids and fairly electrophilic heterocyclic partners. Here, we report a mild and versatile method of *N*-heteroarylation of chiral α-aminoesters without racemization, involving Buchwald–Hartwig conditions. It could be extended to various α-amino acids and azines. This efficient *N*-heteroarylation leads to (i) a chemical library of putative peptidomimetics combining diverse azaheterocycles with the chiral α-aminoesters and their corresponding derivatives (amides, alcohols, etc.) and (ii) arginine derivatives designed as NPFF receptor ligands.



INTRODUCTION

Synthesis of metabolically stable peptidomimetics constitutes an efficient approach in drug design.[1] The latter may result from the replacement of a critical peptidic bond by an heterocyclic amidine **III**. These compounds are prepared by classical peptidic coupling reaction of the corresponding carboxylic acid with different amines (or peptides). The critical *N*-heteroaryl-α-aminoesters **II** generally result from amination reaction of 2-chloroazines **I** with various chiral α-aminoesters (Scheme 1).

In general, the preparation of these compounds requires relatively drastic experimental conditions such as high reaction temperatures, basic solvents (NMP, DMF, DMSO) and results in low to fair yields. It is also proven or suspected to racemize, when using an optically pure α-aminoester.[2] However, if the heterocyclic iminochloride is highly reactive (i.e., heterocycles bearing electron-withdrawing groups such as nitro or cyano groups, or electrophilic azines such as pyrimidines and quinazolines), the reaction could be performed in protic solvents in milder experimental conditions.[3]

Here we describe a method of *N*-heteroarylation of different chiral α-aminoesters including Phe as a highly sterically hindered representative. The 2-chloro-4-methylquinoline **1** was chosen as a reference for our study, and then the methodology was extended to various azine systems.

RESULTS AND DISCUSSION

Before developing a palladium-catalyzed method, the scope and the limitations of the classical S_NAr amination reaction of the quinoline **1** in thermic conditions were carefully checked. In order to better estimate the different parameters of the amination reaction, we first examined the reactivity of this system in ethanol with various α-aminoesters by heating the mixture in a sealed tube at 140 °C for 8 h. As the hydrochloride salt of the title α-aminoester was used systematically, we added to the reaction medium increasing amounts of triethylamine to obtain increasing amounts of α-aminoester as the free base. The reaction was monitored by HPLC. The highly reactive glycine ester was first used in the model reaction. The α-aminoester was used in excess (2 equiv), since it is known that it may self-condense and provide the corresponding diketopiperazine.[4] After 2 h and without addition of triethylamine, we observed a complete consummation of the starting 2-chloro-4-methylquinoline **1** (Figure 1).

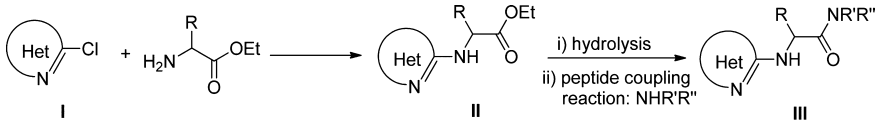
Surprisingly, the reaction medium was composed of 50% of the expected quinoline-2-yl glycinate **2a**, and 50% of the corresponding carboxylic acid identified by mass spectroscopy and resulting from important H^+ catalyzed hydrolysis of **2a** (detailed data shown in Supporting Information page S2). It clearly shows the catalytic role played by H^+ ions and their ability to partially protonate the starting iminochloride and then exacerbate its electrophilic character.[5] The best experimental conditions providing the expected α-aminoester **2a** were found with stoichiometric neutralization of the starting hydrochloride salt of ethyl glycinate (2 equiv of both glycinate salt and triethylamine), affording **2a** in a satisfactory yield (~70%) after 8 h reaction. With a large excess of triethylamine (glyOEt salt/Et_3N 2/4), the velocity of the reaction was dramatically reduced, as evidenced by both disappearance of **1** and formation of **2a**. Figure 1 clearly demonstrates (i) an acid catalytic effect for the amination reaction and (ii) an important H^+-catalyzed hydrolysis of α-amidinoester **2a** into the corresponding acid in the reaction medium.

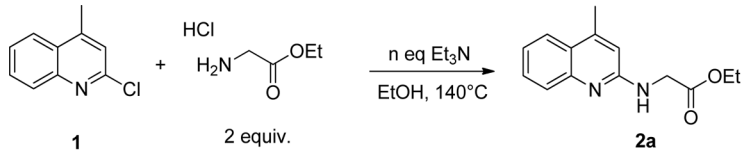
In a second set of experiments, the influence of different α-aminoesters on reactivity was checked (see Table 1). We were

Received: May 24, 2013
Published: July 11, 2013

dx.doi.org/10.1021/jo4011427 | J. Org. Chem. 2013, 78, 7930–7937

Scheme 1. Synthesis of *N*-Heteroaryl-α-aminoesters and Amides





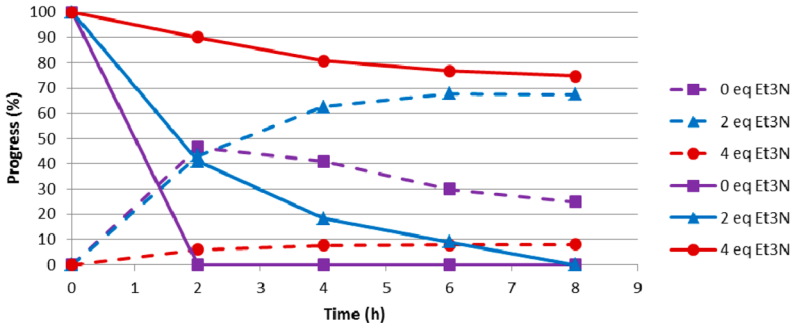
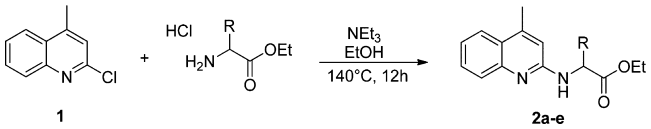


Figure 1. Influence of acid catalysis in *N*-heteroarylation of α-aminoesters. [Solid lines indicate the disappearance of starting 2-chloroquinoline **1**. Dashed lines indicate the formation of quinoline-2-yl ethylglycinate **2a**.]

Table 1. Influence of Steric Hindrance of Starting α-Aminoesters in *N*-Heteroarylation Reactions



			yield[a] (%)	
entry	no.	R	starting **1**	**2**
1	**2a**	H	0	70
2	**2b**	CH_3	47	39
3	**2c**	$(CH_2)_2SMe$	45	40
4	**2d**	$CH_2CH(Me)_2$	56	26
5	**2e**	CH_2Ph	100	0

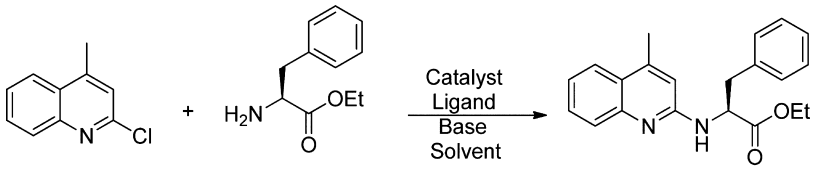
[a]Isolated product.

able to observe a clear decrease in reactivity of α-aminoesters bearing increasing steric hindrance (entries 2−5). In the case of phenylalanine (entry 5), 100% of the starting iminochloride could be recovered after 12 h of reaction, whereas moderately hindered α-aminoesters (R = Me, $(CH_2)_2$-SMe) led to about 50% completion of the reaction giving the expected compounds **2b** and **2c** in 40% yield (entries 2 and 3). Finally, this method using acid catalysis was proven to be efficient in the amination reactions of 2-chloroquinoline **1** with only fairly hindered α-aminoesters (glycine, alanine). However it was not satisfactory for *N*-heteroarylation of phenylalanine, leucine and other relatively bulky α-aminoesters.

We decided to explore alternative methods by replacing the acid catalyst by other catalysts such as palladium, or copper. These catalysts were particularly developed in the recent years and applied to various fields of aromatic and heteroaromatic chemistry.[6] An Ullmann-type *N*-arylation of α-amino acids and esters has been recently described.[7] The authors were using copper iodide in presence of *N*-phenylhydrazone as catalyst and K_3PO_4 as a base in DMF solution. The method was efficient since it allowed *N*-arylation of various α-amino acids in good yields. The critical need of iodoaromatics as starting reagents in this reaction may limit the extension of the method to a large variety of aromatics and heteroaromatics. We focused our interest on palladium-catalyzed amination reactions, as largely introduced by Buchwald and Hartwig.[8] Recently, the Buchwald−Hartwig reaction was used for *N*-arylation of α-aminoesters by means of various chloro- and bromo-benzenes.[9] The yields were satisfactory, but as the authors were using a strong base such as sodium *tert*-butoxide or potassium hydroxide, they observed important racemization of resulting α-amino acid derivatives. It is noteworthy that the use of cesium carbonate as a milder base gave no reaction in their conditions. We decided to reinvestigate the palladium-catalyzed reaction, by replacing aromatic by heteroaromatic systems. In order to clearly prove the beneficial catalytic effect, we chose as a model reaction the substitution of the already used 2-chloro-4-methylquinoline **1** with the phenylalanine ethyl ester. It is important to note that in this latter case, no reaction occurred in thermic conditions (entry 5 in Table 1). A systematic evaluation by HPLC (using caffeine as an internal standard) of the ligand, catalyst, base, solvent and temperature parameters was performed at different reaction times (2−8 h). Results are summarized in Table 2. In general the use of $Pd(OAc)_2$ as catalyst in dioxane in presence of cesium carbonate was proved to be efficient in Buchwald−Hartwig reactions.[10] Different ligands were used (entries 1−5), and the best results were obtained with BINAP giving a yield of 86% (isolated product). The use of other Pd-catalysts was less satisfactory (entries 6−8). No reaction was observed with a milder base (entry 10). The use of more (entry 11) or less (entries 12−14) basic aprotic solvents was disappointing. Finally, the reaction velocity was significantly reduced at 80 or 60 °C (entries 15−16).

dx.doi.org/10.1021/jo4011427 | J. Org. Chem. 2013, 78, 7930−7937

Table 2. Optimization of *N*-Heteroarylation of Phenylalanine Ethylester with 2-Chloroquinoline 1



1 2e

						yield (%)		
entry	catalyst	ligand	base	solvent	*T* °C	2 h	4 h	8 h
1	$Pd(OAc)_2$	X-phos	Cs_2CO_3	dioxane	100	0	0	0
2	$Pd(OAc)_2$	S-phos	Cs_2CO_3	dioxane	100	4	6	6
3	$Pd(OAc)_2$	Davephos	Cs_2CO_3	dioxane	100	4	4	4
4	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	dioxane	100	68[a]	–	–
5	$Pd(OAc)_2$	BINAP	Cs_2CO_3	dioxane	100	86[a]	–	–
6	$Pd_2(dba)_3$	BINAP	Cs_2CO_3	dioxane	100	54	60	–
7	$Pd(PPh_3)_4$	BINAP	Cs_2CO_3	dioxane	100	56	64	–
8	$PdCl_2$	BINAP	Cs_2CO_3	dioxane	100	0	4	5
9	$Pd(OAc)_2$	BINAP	K_2CO_3	dioxane	100	5	9	10
10	$Pd(OAc)_2$	BINAP	Et_3N	dioxane	100	0	0	0
11	$Pd(OAc)_2$	BINAP	Cs_2CO_3	DMF	100	9	10	12
12	$Pd(OAc)_2$	BINAP	Cs_2CO_3	DCM	100	41	–	–
13	$Pd(OAc)_2$	BINAP	Cs_2CO_3	toluene	100	30	33	33
14	$Pd(OAc)_2$	BINAP	Cs_2CO_3	MeCN	100	11	13	15
15	$Pd(OAc)_2$	BINAP	Cs_2CO_3	dioxane	80	43	57	67
16	$Pd(OAc)_2$	BINAP	Cs_2CO_3	dioxane	60	33	53	64

[a]Isolated product.

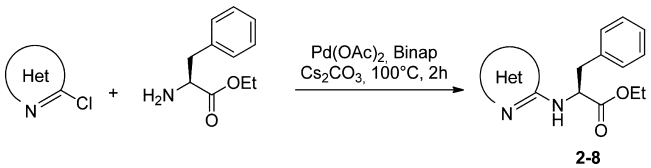
Using the optimized reaction conditions ($Pd(OAc)_2$, BINAP, Cs_2CO_3, dioxane), we checked extension of the reaction to other 2-chloroazines (Table 3). After a short reaction time (2 h), the reaction gave satisfactory yields (66−84% of expected amidine **3**−**8**) with electron-rich (entries 2, 3, 5) or electron-deficient (entries 4, 6, 7) 2-chloroazines.

Moreover we examined the generalization of the reaction to other α-aminoesters (Table 4). Besides the expected reaction products **2**, a second compound resulting from an additional *N*-heteroarylation of quinoline-2-α-aminoesters **2** took place in a significant manner with the less hindered glycinate (entry 1, 61% of **10a**). Only 20% of **10b** was observed with alanine, and no side product was observed with the most hindered α-aminoesters (entries 4−7). Our experimental conditions could be successfully applied to *N*-heteroarylation of proline and serine ethylesters, whereas no reaction occurred in the above-discussed conditions.[9]

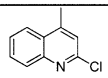
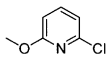
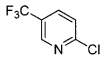
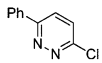
In order to avoid this side reaction observed with fairly hindered α-aminoesters, the Buchwald−Hartwig reaction was performed with their corresponding *N*-carbamates (examples given with the most reactive glycine and alanine in Table 5). With *N*-boc-α-aminoesters, the reaction gave satisfactory yields, and subsequent deprotection of intermediates **11** with TFA was nearly quantitative. **2a** and **2b** obtained from this method have the same physical characteristics (^1H and ^{13}C NMR for **2a** and **2b**, and $[\alpha]_D^{20}$ for **2b**) as that found with the previous method.

The goal of this paper is to describe a methodology that can be generalized to various heterocyclic iminochlorides, as well as to all the α-aminoesters and with no racemization. We systematically checked the optically active novel compounds (**2a−g**, **3**, **4**, **5**, **6**, **7**, **8**, **14**, **17**) resulting from coupling different pure α-aminoesters with various azines. Preparation of the corresponding diastereomeric salts by means of *S*-Mosher acid as a chiral solvating agent was particularly useful for our purposes.[11] Comparison of ^1H NMR spectra of both the pure and racemic diastereomeric salts clearly showed the optical

Table 3. Extension of the Reaction to Other 2-Chloroazines



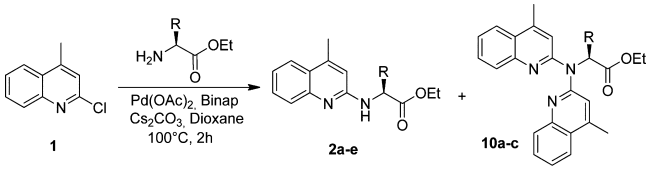
2-8

entry	2-chloroazines	No.	Yield[a] (%)
1		**2e**	86
2		**3**	70
3		**4**	78
4		**5**	71
5		**6**	75
6		**7**	84
7		**8**	66

[a]Isolated product.

dx.doi.org/10.1021/jo4011427 | J. Org. Chem. 2013, 78, 7930−7937

Table 4. Palladium-Catalyzed *N*-Heteroarylation of α-Aminoesters with 1



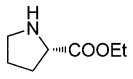
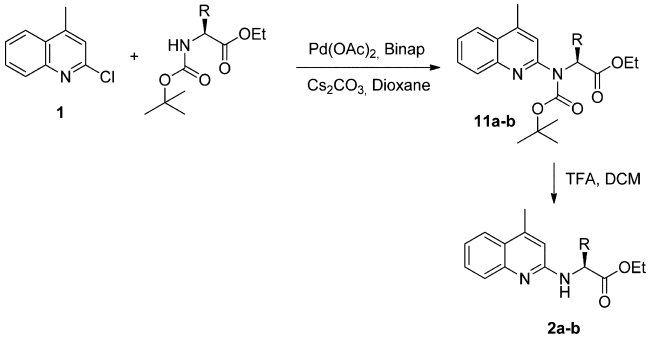
		Yield (%)			
entry	R	No.	**2**	No.	**10**
1	H	**2a**	14	**10a**	61
2	CH_3	**2b**	58	**10b**	19
3	$CH_2CH(Me)_2$	**2d**	70	**10c**	5
4	$(CH_2)_2SMe$	**2c**	73	-	0
5	CH_2Ph	**2e**	86	-	0
6	CH_2OH	**2f**	52	-	0
7		**2g**	73	-	0

Table 5. Efficient Use of *N*-Boc-α-aminoesters Derivatives of Fairly Hindered α-Aminoesters



		yield[a] (%)			
entry	R	no.	**11**	no.	**2**
1	H	**11a**	82	**2a**	92
2	CH_3	**11b**	88	**2b**	91

[a]Isolated product.

purity of our compounds (*ee* ≥ 99%), as illustrated in the Supporting Information (pages S60−S78).

A similar approach was used for phenylalanine derivatives **2**−**8** suspected to be the α-amino acids most sensitive to racemization. The method involves the preparation of the diastereomeric esters **14** and **17**, as illustrated in Scheme 2. We synthesized for this purpose the optically pure *S,S* diastereoisomer **14** by first preparing the optically pure *S,S*-Fmoc-Phe-*O*-phenylethyl **13** and reacting it with 2-chloroquinoline. In a similar manner the use of racemic phenylalanine yielded the diastereomeric mixture **16**, which was reacted with **1** to provide the quinoline derivative **17** as a diastereomeric mixture.

Comparison of ^{1}H NMR spectra of both compounds **14** and **17** (detailed in the Supporting Information page S79) clearly showed the optical purity of **14** (*ee* ≥ 99%).

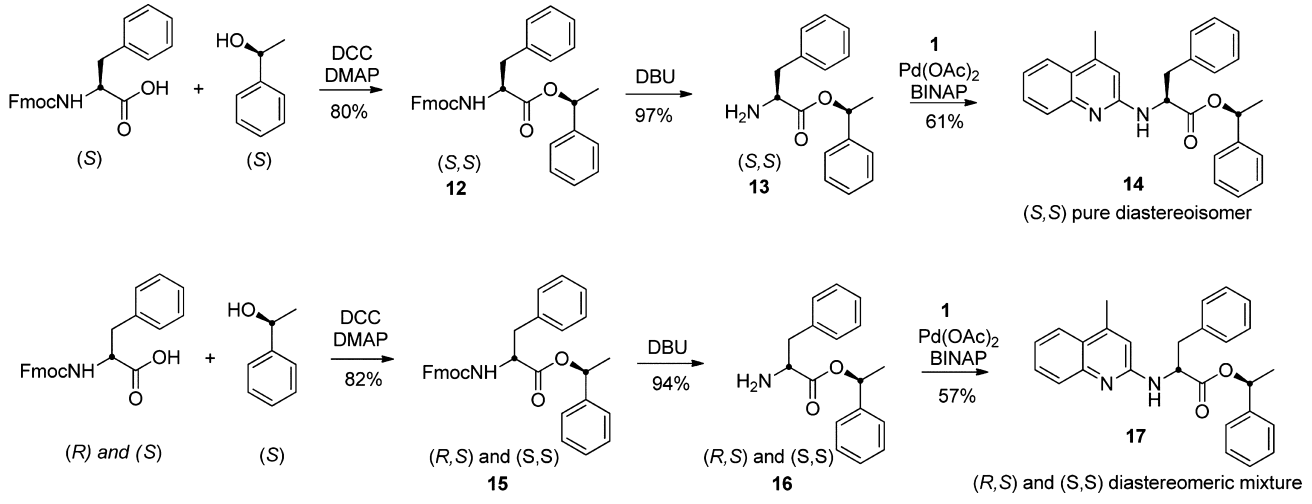
Both methods confirmed that *N*-heteroarylation of optically pure α-aminoesters in experimental conditions as described in this paper, fully conserved optical purity of the resulting *N*-heteroaryl-α-aminoester derivatives.

This efficient methodology can be used for preparing optically pure arginine derivatives as ligands of NPFF receptors.[12] The synthesis of the quinoline derivative **20** is illustrated in Scheme 3. In particular, the highly sterically hindered arginine amide **22** could be directly submitted to *N*-heteroarylation with **1**, and afforded the final compound **20** in a good yield (73%, 2 steps).

CONCLUSION

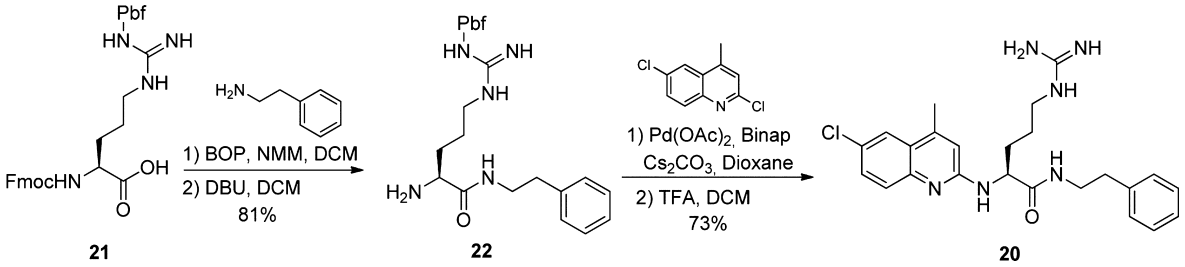
In summary, we described an efficient, versatile and non-racemizing method of *N*-heteroarylation of diverse α-aminoesters with various azines (pyridines, pyridazines, quinolines), which might be extended to other heterocyclic iminochlorides (azoles, azepines, etc). It is important to note that our method is mild and conserves chirality of the most sensitive α-amino acid esters such as phenylalanine. Therefore it constitutes a valuable method for building original chiral chemical libraries combining the domain of azaheterocycles (scaffolds) with that of chiral α-aminoesters and corresponding derivatives (decorations). These compounds may serve as intermediates leading to the corresponding carboxylic acids, amides and alcohols of great interest in medicinal chemistry (drug design, or in silico screening of libraries of peptidomimetics).

Scheme 2. Preparation of Diastereomeric Esters of 2e



dx.doi.org/10.1021/jo4011427 | J. Org. Chem. 2013, 78, 7930−7937

Scheme 3. Synthesis of Quinoline-2-yl Arginine Derivative 20



EXPERIMENTAL SECTION

General Experimental Methods. All reactions were carried out in flame-dried screw cap test tubes with magnetic stirring. Reactions were run under an inert atmosphere of argon gas. Yields refer to isolated compounds, estimated to be >97% pure as determined ^{1}H NMR, HPLC.

^{1}H NMR and ^{13}C NMR were recorded at 400 and 100 MHz, respectively, for $CDCl_3$ solutions. Chemical shifts (δ) are reported in parts per million (ppm) for ^{1}H and for ^{13}C NMR spectra. The coupling constants, J, are reported in Hertz (Hz). TMS was used as the internal reference. High-resolution mass spectra (HRMS) were recorded on a QTOF mass analyzer with electrospray ionization (ESI, Resolving Power 17000). Melting points (mp [°C]) were taken on samples in open capillary tubes. Anhydrous solvents were supplied in Sureseal bottles and were used as received avoiding further purification.

(*S*),(*S*)-1-Phenylethyl 2-((((9*H*-fluoren-9-yl)methoxy)-carbonyl)amino)-3-phenylpropanoate 12. To a solution of Fmoc-phenylalanine (2 g, 5.10 mmol) in dry DCM (15 mL) were added DCC (5.10 mmol, 1 equiv) and DMAP (0.50 mmol, 0.1 equiv). The reaction mixture was first stirred at 0 °C for 10 min, and then (1*S*)-1-phenylethanol (5.10 mmol, 1 equiv) in DCM (10 mL) was added dropwise. After 2 h of stirring at room temperature, the resulting mixture was washed with water H_2O (3 × 20 mL). The organic layer was dried over Na_2SO_4, and the crude mixture was purified by flash chromatography by using EtOAc/heptane (10−90 to 40−60) as eluent to give **12** as a white solid (2 g, 80%): $[\alpha]_D^{20}$ = −78.5 (*c* 1.0, $CHCl_3$); mp 154−156 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.69 (d, 2H, J = 6.8 Hz), 7.47 (t, 2H, J = 6.8 Hz), 7.34−7.19 (m, 9H), 7.17−7.03 (m, 3H), 6.78 (d, 2H, J = 6.8 Hz), 5.89 (q, 1H, J = 5.6 Hz), 5.15 (d, 1H, J = 6.8 Hz), 4.65 (q, 1H, J = 5.6 Hz), 4.37−4.22 (m, 2H), 4.12 (t, 1H, J = 6.8 Hz), 3.06−2.90 (m, 2H), 1.50 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 170.7, 155.5, 143.9, 141.3, 140.6, 135.4, 129.4, 128.6, 128.4, 128.3, 127.7, 127.1, 126.5, 125.2, 125.1, 120.0, 73.9, 67.0, 54.7, 47.2, 38.0, 21.8; HRMS (ESI) calcd for $C_{32}H_{29}NO_4Na$ $[M + Na]^+$ 514.1991, found 514.1984.

(*S*)-1-Phenylethyl 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)-amino)-3-phenylpropanoate 15. Following the procedure of **12** starting from L,D-phenylalanine, the product **15** was obtained as a white solid (2.05 g, 82%): mp 153−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.69 (d, 2H, J = 7.0 Hz), 7.49 (t, 2H, J = 7.0 Hz), 7.34−7.17 (m, 11H), 7.08−7.06 (m, 2H), 6.76 (d, 1H, J = 7.0 Hz), 5.87−5.79 (m, 1H), 5.22−5.14 (m, 1H), 4.64−4.59 (m, 1H), 4.37−4.22 (m, 2H), 4.13 (t, 1H, J = 7.0 Hz), 3.09−2.92 (m, 2H), 1.50−1.42 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 170.8, 170.6, 155.6, 155.5, 143.9, 143.8, 143.6, 141.3, 141.2, 129.5, 129.4, 128.6, 128.5, 128.4, 128.3, 128.1, 127.7, 127.7, 127.1, 127.0, 126.6, 126.1, 125.1, 125.0, 120.0, 119.9, 73.9, 73.8, 67.0, 66.9, 54.9, 54.7, 47.2, 47.2, 38.5, 38.0, 22.0, 21.8; HRMS (ESI) calcd for $C_{32}H_{29}NO_4Na$ $[M + Na]^+$ 514.1991, found 514.1997.

(*S*),(*S*)-1-Phenylethyl 2-amino-3-phenylpropanoate 13. A solution of the protected aminoester **12** (2 g, 4.00 mmol) and DBU (8.10 mmol, 2 equiv) was dissolved in DCM (30 mL). The resulting mixture was stirred at room temperature for 2 h and then evaporated to dryness. The crude product was purified by column chromatography on silica gel by using DCM/MeOH (95/5) as eluent to give **13** as yellow oil (1.04 g, 97%): $[\alpha]_D^{20}$ = +9.7 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.29−7.23 (m, 5H), 7.22−7.11 (m, 3H), 7.00−6.97 (m, 2H), 5.87 (q, 1H, J = 6.8 Hz), 3.70−3.66 (m, 1H), 3.01−2.96 (m, 1H), 2.76−2.73 (m, 1H), 1.49−1.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 174.2, 141.2, 137.0, 129.3, 128.5, 128.4, 128.0, 126.7, 126.3, 73.0, 55.8, 40.9, 22.0; HRMS (ESI) calcd for $C_{17}H_{20}NO_2$ $[M + H]^+$ 270.1488, found 270.1485.

(*S*)-1-Phenylethyl 2-amino-3-phenylpropanoate 16. Following the procedure of **13** starting from **15**, the product was obtained by silica gel chromatography (DCM/MeOH 95/5) to give **16** as yellow oil (1 g, 94%): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.29−7.11 (m, 9H), 6.98 (d, 1H, J = 7.2 Hz), 5.87−5.78 (m, 1H), 3.70−3.64 (m, 1H), 3.03−2.96 (m, 1H), 2.88−2.71 (m, 1H), 1.49−1.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 174.4, 174.3, 141.3, 141.2, 137.3, 137.0, 129.4, 129.3, 128.5, 128.4, 128.0, 126.8, 126.7, 126.3, 126.2, 73.0, 73.0, 55.9, 55.8, 41.2, 40.8, 22.0, 22.0; HRMS (ESI) calcd for $C_{17}H_{20}NO_2$ $[M + H]^+$ 270.1488, found 270.1485.

General Procedure for the Synthesis of α-Heteroarylaminoesters (Method A). A 5 mL microwave tube was charged with 4-methyl-2-chloroquinoline **1** (1 mmol), aminoester (2 mmol), Et_3N (2 mmol) and EtOH (2 mL). The tube was sealed, and the mixture was stirred at 140 °C for 12 h. The resulting solution was cooled to room temperature. The ethanol was evaporated, and the crude residue was purified by column chromatography using EtOAc/heptane (20−80 to 30−70) as eluent to give the expected product **2a**−**d**.

General Procedure for the Synthesis of α-Heteroarylaminoesters (Method B). Reactions were carried out under argon. As a typical experiment, iminochloride (1.0 mmol, 1 equiv), amino acid ethyl ester (1.00 mmol, 1 equiv), Cs_2CO_3 (3.0 mmol, 3 equiv), BINAP (0.06 mmol, 0.06 equiv) and $Pd(OAc)_2$ (0.03 mmol, 0.03 equiv) were added to a flamed-dried microwaves tube in anhydrous dioxane (3 mL). The reaction mixture was nitrogen-flushed and then stirred at 100 °C for 3 h. Upon completion, the reaction mixture was cooled and then evaporated to dryness. The residue was diluted in water and extracted twice with EtOAc. The organic layers were combined, dried over Na_2SO_4, and then evaporated. The residue was purified by flash chromatography using EtOAc/heptane (20−80 to 60−40) as eluent to afford pure products **2**−**8**.

Ethyl 2-((4-methylquinolin-2-yl)amino)acetate 2a. Following the general procedure for the synthesis of α-heteroarylaminoesters and starting from 4-methyl-2-chloroquinoline and ethyl glycinate, **2a** was obtained as a white solid. Method A (170 mg, 70%), Method B (35 mg, 14%): mp 131−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.68 (d, 1H, J = 8.2 Hz), 7.63 (d, 1H, J = 8.0 Hz), 7.44 (td, 1H, J = 7.6 Hz, J = 2.2 Hz), 7.17 (td, 1H, J = 7.8 Hz, J= 2.0 Hz), 6.46 (s, 1H), 5.14 (s, 1H), 4.25 (s, 2H), 4.18 (q, 2H, J = 7.20 Hz), 2.45 (s, 3H), 1.24 (t, 3H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 171.5, 155.6, 147.6, 145.2, 129.2, 126.9, 124.1, 123.6, 122.3, 112.2, 61.2, 43.4, 18.71, 14.3; HRMS (ESI) calcd for $C_{14}H_{17}N_2O_2$ $[M + H]^+$ 245.1284, found 245.1285.

(*S*)-Ethyl 2-((4-methylquinolin-2-yl)amino)propanoate 2b. Following the general procedure for the synthesis of α-heteroarylaminoesters and starting from 4-methyl-2-chloroquinoline and ethyl 2-aminopropanoate, **2b** was obtained as a white solid. Method A (100 mg, 39%), Method B (150 mg, 58%): $[\alpha]_D^{20}$ = −23.4 (*c* 1.0, MeOH); mp 135−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.69−7.59 (m, 2H), 7.43 (td, 1H, J = 8.3 Hz, J = 2.2 Hz), 7.16 (td, 1H, J = 8.3 Hz, J = 2.2 Hz), 6.45 (s, 1H), 5.09 (bs, 1H), 4.81−4.77 (m, 1H), 4.19−

dx.doi.org/10.1021/jo4011427 | J. Org. Chem. 2013, 78, 7930−7937

4.11 (m, 2H), 2.47 (s, 3H), 1.44 (d, 3H, J= 7.2 Hz), 1.19 (t, 3H, J= 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 174.9, 155.4, 147.8, 144.8, 129.1, 127.1, 124.1, 123.5, 122.1, 112.3, 61.1, 49.7, 29.7, 18.6, 18.6, 14.3; HRMS (ESI) calcd for $C_{15}H_{19}N_2O_2$ $[M + H]^+$ 259.1441, found 259.1440.

(*S*)-Ethyl 2-((4-methylquinolin-2-yl)amino)-4-(methylthio)-butanoate 2c. Following the general procedure for the synthesis of α-heteroarylaminoesters and starting from 4-methyl-2-chloroquinoline and ethyl 2-amino-4-(methylthio)butanoate, **2c** was obtained as a white solid. Method A (127 mg, 40%), Method B (232 mg, 73%): $[\alpha]_D^{20}$ = −6.5 (*c* 0.85, MeOH); mp 130−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.69 (d, 1H, *J* = 8.4 Hz), 7.61 (d, 1H, *J* = 8.4 Hz), 7.45 (td, 1H, *J* = 8.4 Hz, *J* = 2.0 Hz), 7.19−7.15 (m, 1H), 6.47 (s, 1H), 5.16 (s, 1H), 4.95−4.94 (m, 1H), 4.17−4.14 (m, 2H), 2.59−2.54 (m, 2H), 2.46 (s, 3H), 2.30−2.21 (m, 1H), 2.09−2.02 (m, 4H), 1.23−1.18 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 173.6, 155.4, 147.6, 145.0, 129.2, 127.1, 124.1, 123.5, 122.2, 112.3, 61.3, 53.2, 32.2, 30.3, 18.7, 15.6, 14.3; HRMS (ESI) calcd for $C_{17}H_{23}N_2O_2S$ $[M + H]^+$ 319.1474, found 319.1469.

(*S*)-Ethyl 4-methyl-2-((4-methylquinolin-2-yl)amino)-pentanoate 2d. Following the general procedure for the synthesis of α-heteroarylaminoesters and starting from 4-methyl-2-chloroquinoline and ethyl 2-amino-4-methylpentanoate, **2d** was obtained as a white solid. Method A (168 mg, 56%), Method B (210 mg, 70%): $[\alpha]_D^{20}$ = −49.4 (*c* 1.0, MeOH); mp 142−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.68 (d, 1H, *J* = 8.4 Hz), 7.61 (d, 1H, *J* =8.4 Hz), 7.43 (td, 1H, *J* = 8.4 Hz, *J* = 2.2 Hz), 7.18 (td, 1H, *J* = 8.4 Hz, *J* = 2.2 Hz), 6.44 (s, 1H), 4.83−4.78 (m, 2H), 4.17−4.07 (m, 2H), 2.46 (s, 3H), 1.75−1.58 (m, 3H), 1.21 (t, 3H, *J* = 7.8 Hz), 1.01−0.91 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 174.8, 155.7, 147.8, 144.8, 129.0, 127.1, 124.1, 123.5, 122.1, 112.2, 60.9, 52.6, 42.2, 25.1, 23.0, 22.3, 18.7, 14.3; HRMS (ESI) calcd for $C_{18}H_{25}N_2O_2$ $[M + H]^+$ 301.1909, found 301.1907.

(*S*)-Ethyl 2-((4-methylquinolin-2-yl)amino)-3-phenylpropanoate 2e. Following the general procedure for the synthesis of α-heteroarylaminoesters and starting from 4-methyl-2-chloroquinoline and ethyl 2-amino-3-phenylpropanoate, **2e** was obtained as a white solid. Method A (0%), Method B (287 mg, 86%): $[\alpha]_D^{20}$ = −14.6 (*c* 0.8, MeOH); mp 115−117 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.67−7.61 (m, 2H), 7.44 (td, 1H, *J* = 8.2 Hz, *J* = 1.8 Hz), 7.21−7.11 (m, 6H), 6.38 (s, 1H), 5.11−5.06 (m, 1H), 4.97 (s, 1H), 4.14−4.05 (m, 2H), 3.21 (qd, 2H, *J* = 8.2 Hz, *J* = 2.0 Hz), 2.42 (s, 3H), 1.15 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 173.2, 155.1, 147.8, 144.9, 136.8, 129.5, 129.1, 128.4, 127.1, 126.8, 124.1, 123.5, 122.2, 112.4, 61.1, 54.9, 38.1, 18.7, 14.2; HRMS (ESI) calcd for $C_{21}H_{23}N_2O_2$ $[M + H]^+$ 335.1754, found 335.1753.

(*S*)-Ethyl 3-hydroxy-2-((4-methylquinolin-2-yl)amino)-propanoate 2f. Following the general procedure for the synthesis of α-heteroarylaminoesters and starting from 4-methyl-2-chloroquinoline and ethyl 2-amino-3-hydroxypropanoate, **2f** was obtained as a brown solid. Method A (0%), Method B (142 mg, 52%): $[\alpha]_D^{20}$ = +15.8 (*c* 1.0, MeOH); mp 111−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.69 (dd, 1H, *J* = 7.2 Hz, *J* = 1.2 Hz), 7.58 (dd, 1H, *J* = 7.2 Hz, *J* = 1.2 Hz), 7.46 (td, 1H, *J* = 7.2 Hz, *J* = 1.2 Hz), 7.21−7.17 (m, 1H), 6.52 (s, 1H), 5.68 (s, 1H), 4.81 (t, 1H, *J* = 2.8 Hz), 4.23−4.15 (m, 3H), 3.85−3.81 (m, 1H), 2.46 (s, 3H), 1.35 (t, 3H, *J* = 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 171.3, 155.7, 146.5, 145.8, 129.5, 126.2, 123.9, 123.5, 122.6, 112.6, 66.2, 62.01, 58.2, 18.7, 14.2; HRMS (ESI) calcd for $C_{15}H_{19}N_2O_3$ $[M + H]^+$ 275.1390, found 275.1394.

(*S*)-Ethyl 1-(4-methylquinolin-2-yl)pyrrolidine-2-carboxylate 2g. Following the general procedure for the synthesis of α-heteroarylaminoesters and starting from 4-methyl-2-chloroquinoline and ethyl pyrrolidine-2-carboxylate, **2f** was obtained as a brown solid. Method A (0%), Method B (207 mg, 73%): $[\alpha]_D^{20}$ = +26.1 (*c* 0.9, MeOH); mp 131−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.65 (dd, 1H, *J* = 8.0 Hz, *J* = 1.2 Hz), 7.54 (d, 1H, *J* = 8.0 Hz), 7.41−7.36 (m, 1H), 7.11−7.06 (m, 1H), 6.49 (s, 1H), 4.61−4.58 (m, 1H), 4.15−4.02 (m, 2H), 3.67−3.63 (m, 1H), 3.51−3.49 (m, 1H), 2.46 (s, 3H), 2.21−2.19 (m, 1H), 2.07−1.93 (m, 3H), 1.15 (t, 1H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 174.3, 154.7, 148.1, 144.8, 129.03, 127.06, 123.5, 123.3, 121.5, 110.1, 60.6, 59.9, 47.2, 30.1, 24.4, 19.1, 14.3; HRMS (ESI) calcd for $C_{17}H_{21}N_2O_2$ $[M + H]^+$ 285.1597, found 285.1604.

Ethyl 2-(bis(4-methylquinolin-2-yl)amino)acetate 10a. Following the general procedure for the synthesis of α-heteroarylaminoesters (Method B) and starting from 4-methyl-2-chloroquinoline and ethyl glycinate, **10a** was obtained as a white solid (120 mg, 61%): mp 189−191 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.77 (d, 4H, *J* = 8.2 Hz), 7.51 (td, 2H, *J* = 8.2 Hz, J= 2.2 Hz), 7.32 (td, 2H, *J* = 8.2 Hz, *J* = 2.2 Hz), 7.16 (s, 2H), 5.11 (s, 2H), 4.12 (q, 2H, *J* = 8.0 Hz), 2.51 (s, 6H), 1.68 (t, 3H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 171.2, 155.2, 147.5, 145.3, 129.43, 128.4, 125.5, 124.3, 123.6, 115.6, 60.8, 50.6, 19.1, 14.3; HRMS (ESI) calcd for $C_{24}H_{24}N_3O_2$ $[M + H]^+$ 386.1861, found 386.1859.

Ethyl 2-(bis(4-methylquinolin-2-yl)amino)propanoate 10b. Following the general procedure for the synthesis of α-heteroarylaminoesters (Method B) and starting from 4-methyl-2-chloroquinoline and ethyl 2-aminopropanoate, **10b** was obtained as a white solid (75 mg, 19%): mp 197−199 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.93 (d, 4H, *J* = 7.6 Hz), 7.63 (td, 2H, *J* = 7.6 Hz, *J* = 2.2 Hz), 7.61 (td, 2H, *J* = 7.6 Hz, *J* = 2.2 Hz), 7.27 (s, 2H), 4.22 (q, 2H, *J* = 7.2 Hz), 3.67−3.59 (m, 1H), 2.61 (s, 6H), 1.27 (t, 3H, *J* = 7.2 Hz), 1.13 (d, 3H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 171.4, 155.3, 147.6, 145.5, 129.5, 128.6, 125.7, 124.5, 123.7, 111.9, 60.9, 55.8, 50.7, 23.7, 16.9, 14.4; HRMS (ESI) calcd for $C_{25}H_{26}N_3O_2$ $[M + H]^+$ 400.2020, found 400.2026.

Ethyl 2-((*tert*-butoxycarbonyl)(4-methylquinolin-2-yl)-amino)acetate 11a. Following the general procedure for the synthesis of α-heteroarylaminoesters (Method B) and starting from 4-methyl-2-chloroquinoline and *N*-boc-ethyl glycinate, **11a** was obtained as a white solid (282 mg, 82%): mp 102−104 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.81−7.74 (m, 3H), 7.35 (td, 1H, *J* = 8.2 Hz, *J* = 1.8 Hz), 7.17 (td, 1H, *J* = 8.2 Hz, *J* = 1.8 Hz), 4.77 (s, 2H), 4.14 (q, 2H, *J* = 7.2 Hz), 2.58 (s, 3H), 1.41 (s, 9H), 1.18 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 170.2, 153.9, 152.9, 146.2, 145.0, 129.1, 128.8, 125.9, 125.1, 123.5, 118.1, 82.1, 60.9, 48.2, 28.2, 19.0, 14.3; HRMS (ESI) calcd for $C_{19}H_{25}N_2O_4$ $[M + H]^+$ 345.1809, found 345.1806.

Ethyl 2-((*tert*-butoxycarbonyl)(4-methylquinolin-2-yl)-amino)propanoate 11b. Following the general procedure for the synthesis of α-heteroarylaminoesters (Method B) and starting from 4-methyl-2-chloroquinoline and *N*-boc-ethyl 2-aminopropanoate, **11b** was obtained as a white solid (315 mg, 88%): mp 131−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.91−7.84 (m, 3H), 7.35 (td, 1H, *J* = 7.2 Hz, *J* = 1.8 Hz), 7.17 (td, 1H, *J* = 7.2 Hz, *J* = 1.8 Hz), 4.24 (q, 2H, *J* = 7.2 Hz), 3.25−3.17 (m, 1H), 2.68 (s, 3H), 1.56 (s, 9H), 1.30 (t, 3H, *J* = 7.2 Hz), 1.09 (d, 3H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 171.9, 154.01, 153.0, 146.3, 145.2, 129.2, 128.9, 126.1, 125.3, 123.6, 115.5, 82.2, 67.8, 48.3, 36.9, 28.3, 19.2, 14.4; HRMS (ESI) calcd for $C_{20}H_{27}N_2O_4$ $[M + H]^+$ 359.1965, found 359.1966.

(*S*)-Ethyl 3-phenyl-2-(pyridin-2-ylamino)propanoate 3. Following the general procedure for the synthesis of α-heteroarylaminoesters (Method B) and starting from 2-chloropyridine and ethyl 2-amino-3-phenylpropanoate, **3** was obtained as a white solid (189 mg, 70%): $[\alpha]_D^{20}$ = −19.7 (*c* 1.0, MeOH); mp 89−91 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.02 (dd, 1H, *J* = 5.0 Hz, *J* = 2.0 Hz), 7.31 (td, 1H, *J* = 8.5 Hz, *J* = 2.0 Hz), 7.22−7.09 (m, 5H), 6.53−6.51 (m, 1H), 6.33 (d, 1H, *J* = 8.5 Hz), 4.82−4.74 (m, 2H), 4.08 (q, 2H, *J* = 8.5 Hz), 3.14 (qd, 2H, *J* = 8.5 Hz, *J* = 5.6 Hz), 1.13 (t, 3H, *J* = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 173.1, 157.2, 147.9, 137.2, 136.6, 129.4, 128.5, 126.9, 113.6, 108.7, 61.1, 55.3, 38.3, 14.2; HRMS (ESI) calcd for $C_{16}H_{19}N_2O_2$ $[M + H]^+$ 271.1441, found 271.1446.

(*S*)-Ethyl 2-((6-methylpyridin-2-yl)amino)-3-phenylpropanoate 4. Following the general procedure for the synthesis of α-heteroarylaminoesters (Method B) and starting from 6-methyl-2-chloropyridine and ethyl 2-amino-3-phenylpropanoate, **4** was obtained as a white solid (221 mg, 78%): $[\alpha]_D^{20}$ = −23.7 (*c* 1.0, MeOH); mp 98−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.22−7.11 (m,

dx.doi.org/10.1021/jo4011427 | J. Org. Chem. 2013, 78, 7930−7937

6H), 6.39 (d, 1H, J = 8.5 Hz), 6.13 (d, 1H, J = 8.5 Hz), 4.75−4.71 (m, 2H), 4.10−4.02 (m, 2H), 3.54−3.09 (m, 2H), 2.28 (s, 3H), 1.12 (t, 3H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 173.1, 156.7, 137.6, 136.7, 129.4, 128.4, 126.8, 112.8, 104.9, 60.9, 55.7, 38.4, 24.3, 14.2; HRMS (ESI) calcd for $C_{17}H_{21}N_2O_2$ $[M + H]^+$ 285.1600, found 285.1605.

(*S*)-Ethyl 3-phenyl-2-(pyrimidin-2-ylamino)propanoate 5. Following the general procedure for the synthesis of α-heteroarylaminoesters (Method B) and starting from 2-chloropyrimidine and ethyl 2-amino-3-phenylpropanoate, **5** was obtained as a pink solid (192 mg, 71%): $[\alpha]_D^{20}$ = −12.5 (c 1.0, MeOH); mp 103−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.21 (d, 2H, J = 8.0 Hz), 7.21−7.11 (m, 5H), 6.49 (t, 1H, J = 4.0 Hz), 5.53 (d, 1H, J = 8.0 Hz), 4.87−4.83 (m, 1H), 4.09 (q, 2H, J = 8.0 Hz), 3.13 (qd, 2H, J = 4.0 Hz, J = 8.2 Hz), 1.12 (t, 3H, J = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 172.3, 161.4, 158.0, 136.3, 129.4, 128.5, 126.9, 111.5, 61.2, 55.2, 38.2, 14.1; HRMS (ESI) calcd for $C_{15}H_{18}N_3O_2$ $[M + H]^+$ 272.1393, found 272.1397.

(*S*)-Ethyl 2-((6-methoxypyridin-2-yl)amino)-3-phenylpropanoate 6. Following the general procedure for the synthesis of α-heteroarylaminoesters (Method B) and starting from 6-methoxy-2-chloropyridine and ethyl 2-amino-3-phenylpropanoate, **6** was obtained as a white solid (225 mg, 75%): $[\alpha]_D^{20}$ = +38.9 (c 1.0, MeOH); mp 139−141 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.24−7.09 (m, 6H), 5.97 (d, 1H, J = 7.8 Hz), 5.91 (d, 1H, J = 7.8 Hz), 4.77−4.65 (m, 3H), 4.08 (q, 2H, J = 7.8 Hz), 3.76 (s, 3H), 3.89−3.11 (m, 2H), 1.12 (t, 3H, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 173.2, 163.5, 156.1, 139.8, 136.7, 129.9, 128.5, 126.9, 99.7, 98.14, 60.9, 55.6, 53.1, 38.4, 14.2; HRMS (ESI) calcd for $C_{17}H_{21}N_2O_3$ $[M + H]^+$ 301.1547, found 301.1553.

(*S*)-Ethyl 3-phenyl-2-((5-(trifluoromethyl)pyridin-2-yl)-amino)propanoate 7. Following the general procedure for the synthesis of α-heteroarylaminoesters (Method B) and starting from 5-trifuloromethyl-2-chloropyridine and ethyl 2-amino-3-phenylpropanoate, **7** was obtained as a white solid (284 mg, 84%): $[\alpha]_D^{20}$ = −31.3 (c 1.0, MeOH); mp 143−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.25 (s, 1H), 7.45−7.41 (m, 1H), 7.21−7.12 (m, 3H), 7.06 (d, 1H, J = 7.8 Hz), 6.33−6.29 (m, 1H), 5.27−5.19 (m, 1H), 4.89−4.84 (m, 1H), 4.09 (q, 2H, J = 7.8 Hz), 3.63−3.14 (m, 2H), 1.16 (t, 3H, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 172.6, 172.5, 158.9, 145.8, 145.8, 136.3, 134.1, 129.3, 128.5, 127.5, 125.8, 123.2, 120.5, 116.7, 116.4, 116.1, 115.7, 108.2, 61.4, 55.1, 38.0, 29.7, 14.1; HRMS (ESI) calcd for $C_{17}H_{18}F_3N_2O_2$ $[M + H]^+$ 339.1305, found 339.1306.

(*S*)-Ethyl 3-phenyl-2-((6-phenylpyridazin-3-yl)amino)-propanoate 8. Following the general procedure for the synthesis of α-heteroarylaminoesters (Method B) and starting from 6-phenyl-3-chloropyridazine and ethyl 2-amino-3-phenylpropanoate, **8** was obtained as a white solid (230 mg, 66%): $[\alpha]_D^{20}$ = −165.7 (c 1.0, MeOH); mp 253−255 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.16 (d, 1H, J = 9.6 Hz), 7.81−7.79 (m, 2H), 7.56 (d, 1H, J = 9.6 Hz), 7.46−7.45 (m, 3H), 7.21−7.12 (m, 5H), 4.87−4.81 (m, 1H), 4.13 (q, 2H, J = 7.2 Hz), 3.28 (dd, 1H, J = 12.0 Hz, J = 4.0 Hz), 3.11 (dd, 1H, J = 12.0 Hz, J = 8.0 Hz), 1.16 (t, 3H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 171.6, 156.4, 151.9, 137.5, 133.0, 132.9, 132.5, 130.5, 130.4, 129.7, 128.3, 128.0, 125.3, 63.1, 57.7, 38.6, 14.4; HRMS (ESI) calcd for $C_{21}H_{22}N_3O_2$ $[M + H]^+$ 348.1709, found 348.1715.

(*S*)-(*S*)-1-Phenylethyl 2-((4-methylquinolin-2-yl)amino)-3-phenylpropanoate 14. Following the general procedure for the synthesis of α-heteroarylaminoesters (Method B) and starting from 4-methyl-2-chloroquinoline and **13**, **14** was obtained as a white solid (250 mg, 61%): $[\alpha]_D^{20}$ = −15.5 (c 1.0, $CHCl_3$); mp 111−113 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.03 (d, 1H, J = 8.2 Hz), 7.88 (d, 1H, J = 8.2 Hz), 7.69−7.60 (m, 3H), 7.47 (t, 2H, J = 7.6 Hz), 7.17−7.04 (m, 7H), 6.53 (s, 1H), 5.97 (q, 1H, J = 7.6 Hz), 5.53 (s, 1H), 4.19 (t, 1H, J = 7.6 Hz), 3.45−3.40 (m, 1H), 3.25−3.20 (m, 1H), 2.42 (s, 1H), 1.48 (d, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 171.5, 155.6, 147.4, 144.3, 138.0, 129.7, 129.5, 129.3, 129.0, 128.1, 127.4, 126.3, 125.9, 123.7, 123.6, 121.9, 121.1, 112.1, 58.3, 42.1, 29.8, 22.8, 18.8; HRMS (ESI) calcd for $C_{27}H_{27}N_2O_2$ $[M + H]^+$ 411.2067, found 411.2069.

(*R,S*)-(*S*)-1-Phenylethyl 2-((4-methylquinolin-2-yl)amino)-3-phenylpropanoate 17. Following the general procedure for the synthesis of α-heteroarylaminoesters (Method B) and starting from 4-methyl-2-chloroquinoline and **16**, **17** was obtained as a white solid (233 mg, 57%): mp 105−107 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.65−7.59 (m, 3H), 7.54−7.51 (m, 1H), 7.44−40 (m, 2H), 7.23−7.12 (m, 17H), 7.06−7.04 (m, 3H), 6.89−6.87 (m, 2H), 6.33 (s, 1H), 6.27 (s, 1H), 5.86−5.78 (m, 2H), 5.13−4.96 (m, 4H), 3.21−3.16 (m, 3H), 3.07−3.04 (m, 1H), 2.36 (s, 3H), 2.29 (s, 3H), 1.48 (d, 3H, J = 6.8 Hz), 1.34 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 172.8, 172.6, 155.3, 155.2, 147.8, 147.7, 146.6, 144.9, 144.8, 141.3, 141.1, 136.9, 136.5, 129.6, 129.5, 129.2, 129.1, 128.8, 128.5, 128.4, 127.9, 127.8, 127.2, 126.8, 126.7, 126.5, 126.1, 125.3, 124.2, 124.1, 123.7, 123.5, 123.4, 122.2, 122.1, 114.7, 112.5, 112.4, 73.2, 73.1, 55.3, 55.0, 38.2, 37.8, 22.0, 21.9, 18.9, 18.6; HRMS (ESI) calcd for $C_{27}H_{27}N_2O_2$ $[M + H]^+$ 411.2067, found 411.2066.

General Procedure for *N*-Boc Deprotection of 11. Compound **11** (0.5 mmol) and trifluoroacetic acid (2 mL) were mixed in DCM (2 mL). After 1 h, TFA and DCM were evaporated, the crude sample was washed with saturated aqueous $NaHCO_3$ solution (20 mL), and the product was extracted with ethyl acetate (3 × 15 mL). On drying with sodium sulfate, the filtrate was evaporated to dryness to afford **2a** or **2b** as white solids.

Ethyl 2-((4-methylquinolin-2-yl)amino)acetate 2a. Following the general procedure for *N*-Boc deprotection, **2a** was obtained as a white solid (91 mg, 75%): mp 130−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.69 (d, 1H, J = 8.0 Hz), 7.64 (d, 1H, J = 8.0 Hz), 7.45 (td, 1H, J = 7.6 Hz, J = 2.2 Hz), 7.19 (td, 1H, J = 7.6 Hz, J= 2.2 Hz), 6.46 (s, 1H), 5.68 (s, 1H), 4.26 (s, 2H), 4.18 (q, 2H, J = 7.2 Hz), 2.45 (s, 3H), 1.23 (t, 3H, J = 6.2 Hz).

(*S*)-Ethyl 2-((4-methylquinolin-2-yl)amino)propanoate 2b. Following the general procedure for *N*-Boc deprotection, **2b** was obtained as a white solid (103 mg, 80%): $[\alpha]_D^{20}$ = −23.8 (c 1.0, MeOH); mp 136−139 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.65 (d, 1H, J = 8.0 Hz), 7.60 (d, 1H, J = 8.0 Hz), 7.44 (td, 1H, J = 8.0 Hz, J = 2.2 Hz), 7.13 (td, 1H, J = 8.0 Hz, J = 2.2 Hz), 6.40 (s, 1H), 5.08−5.10 (m, 1H), 4.88−4.76 (m, 1H), 4.09−4.18 (m, 2H), 2.40 (s, 3H), 1.46 (d, 3H, J= 7.0 Hz), 1.22 (t, 3H, J= 7.2 Hz).

(*S*)-2-Amino-*N*-(pbf)-5-guanidino-*N*-phenethylpentanamide 22. BOP (4 mmol, 1.3 equiv) was added to a solution of Fmoc-L-Arg (Pbf)-OH (3 mmol) and NMM (4 mmol, 1.3 equiv) in DCM (12 mL). The resulting mixture was then stirred at rt for 10 min, and after this time, phenethylamine (4 mmol, 1.3 equiv) was added to the solution. After 12 h at rt, the mixture was washed with a saturated solution of $NaHCO_3$ (20 mL), HCl 1 N (20 mL), and then H_2O (20 mL). The organic phase was dried (Na_2SO_4) and filtered, and then the solvent was removed under reduced pressure. The crude residue was redissolved in anhydrous DCM (30 mL), and DBU (5.2 mmol, 2 equiv) was added. The final solution was stirred at rt until TLC showed complete consumption of starting material (1 h). The solvent was evaporated under a vacuum, and the residue was purified by chromatography on silica gel (DCM, then DCM/MeOH 95/5) to give the desired product as a white solid (1.22 g, 81%): $[\alpha]_D^{20}$ = +3.9 (c 0.35, $CHCl_3$); mp 89.2−91.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.40 (bs,1H), 7.18−7.06 (m, 5H), 6.23 (s, 3H), 3.42−3.35 (m, 3H), 3.08 (bs, 2H) 2.89−2.85 (m, 5H), 2.71 (t, 2H, J = 7.2 Hz), 2.48 (s, 3H), 2.41 (s, 3H), 2.00 (s, 3H), 1.63 (bs, 2H), 1.42−1.49 (m, 2H), 1.37 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 173.9, 169.1, 158.8, 156.6, 138.8, 138.2, 132.9, 132.2, 128.8, 128.7, 128.5, 126.4, 124.9, 117.6, 86.4, 60.8, 54.1, 43.3, 40.5, 35.6, 31.6, 28.6, 25.3, 19.3, 17.9, 12.5; HRMS (ESI) calcd for $C_{27}H_{40}N_5O_4S$ $[M + H]^+$ 530.2795, found 530.2800.

(*S*)-2-(6-Chloro-4-methylquinolin-2-yl)amino)-5-guanidino-*N*-phenethylpentanamide 20. Following the general procedure for the synthesis of α-heteroarylaminoesters (Method B) and starting from 6-chloro-4-methyl-2-chloroquinoline and **22**, pbf derivatives were obtained as a brown solid without further purification. This product (0.5 mmol) and trifluoroacetic acid (3 mL) were mixed in DCM (3 mL). After 1 h, TFA and DCM were evaporated, and the crude sample was purified by inverse flash chromatography using methanol 10−80%

dx.doi.org/10.1021/jo4011427 | J. Org. Chem. 2013, 78, 7930−7937

in water as eluent to give **20** as a white solid (331 mg, 73%): $[\alpha]_D^{20}$ = +13.3 (*c* 0.8, $CHCl_3$); mp 198.3−199.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.58 (d, 1H, *J* = 2.2 Hz), 7.48 (d, 1H, *J* = 7.4 Hz), 7.39 (dd, 1H, *J* = 7.4 Hz, *J* = 2.2 Hz), 7.12−7.07 (m, 4H), 7.04−7.00 (m, 1H), 6.94 (s, 1H), 3.92 (t, 1H, *J* = 6.8 Hz), 3.45−3.52 (m, 1H), 3.29−3.34 (m, 3H), 2.69−2.78 (m, 2H), 2.36 (s, 3H), 1.87−1.95 (m, 2H), 1.59−1.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 172.7, 158.4, 155.7, 151.1, 146.6, 142.7, 134.5, 134.2, 132.6, 132.4, 132.0, 129.9, 129.6, 126.5, 118.2, 56.3, 44.6, 44.2, 38.9, 32.3, 26.9, 21.2; HRMS (ESI) calcd for $C_{24}H_{30}ClN_6O$ $[M + H]^+$ 453.2164, found 453.2165.

Use of *S*-Mosher Acid As a Chiral Solvation Agent. Diastereomeric salts were prepared directly in an NMR tube by mixing 10 mg of the α-aminoester derivatives with 1 equiv of a standard solution of *S*-Mosher acid in $CDCl_3$ or in MeOD. All salts except for that of **8** were dissolved in $CDCl_3$. Because of the low solubility in $CDCl_3$, the salt of **8** was dissolved in MeOD. Racemic and enantiomerically pure compounds **2b−g** and enantiomerically pure compounds of phenylalanine derivatives **3−8** were used as a starting material for syntheses of those salts.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Influence of acid catalysis, optical purity studies, ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mschmitt@unistra.fr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This project was supported by the Alsace region (Région Alsace), the University of Strasbourg (UdS), and the National Center of Scientific Research (CNRS). We thank Mr. Patrick Wehrung for providing the high-resolution mass spectra.

■ REFERENCES

(1) (a) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699. (b) Callahan, F. J.; Bean, J. W.; Burgess, J. L.; Eggleston, D. S.; Hwang, S. M.; Kopple, K. D.; Koster, P. F.; Nichols, A.; Peishoff, C. E.; Samenen, J. M.; Vaskpo, J. A.; Wong, A.; Huffman, W. F. *J. Med. Chem.* **1992**, *35*, 3970. (c) Ho, K. K.; Auld, D. S.; Bohnstedt, A. C.; Conti, P.; Dokter, W.; Erickson, S.; Feng, D.; Inglese, J.; Kingsbury, C.; Kultgen, S. G.; Liu, R. Q.; Masterson, C. M.; Ohlmeyer, M.; Rong, Y.; Rooseboom, M.; Roughton, A.; Samama, P.; Smit, M. J.; Son, E.; Louw, J. V. D.; Vogel, G.; Webb, M.; Wijkmans, J.; You, M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2724. (d) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244. (e) Belvisi, L.; Gennari, C.; Mielgo, A.; Potenza, D.; Scolastico, C. *Eur. J. Org. Chem.* **1999**, *1999*, 289. (f) Ramanathan, S. K.; Keeler, J.; Lee, H. L.; Reddy, D. S.; Lushington, G.; Aubé, J. *Org. Lett.* **2005**, *7*, 1059. (g) Blomberg, D.; Brickmann, K.; Kihlberg, J. *Tetrahedron.* **2006**, *62*, 10937.

(2) (a) Du, W.; Jewell, J. P.; Lin, L. S.; Colandrea, V. J.; Xiao, J. C.; Lao, J.; Shen, C. P.; Bateman, T. J.; Reddy, V. B. G.; Ha, S. N.; Shah, S. K.; Fong, T. M.; Hale, J. J.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5195. (b) Chandrika, P. M.; Yakaiah, T.; Rao, A. R. R.; Narsaiah, B.; Reddy, N. C.; Sridhar, V.; Rao, J. V. *Eur. J. Med. Chem.* **2008**, *43*, 846. (c) Bursavich, M. G.; Lombardi, S.; Gilbert, A. M. *Org. Lett.* **2005**, *7*, 4113.

(3) (a) Chayer, S.; Essassi, E. M.; Bourguignon, J. J. *Tetrahedron Lett.* **1998**, *39*, 841. (b) Ho, K. K.; Auld, D. S.; Bohnstedt, A. C.; Conti, P.; Dokter, W.; Erickson, S.; Feng, D.; Inglese, J.; Kingsbury, C.; Kultgen, S. G.; Liu, R. Q.; Masterson, C. M.; Ohlmeyer, M.; Rong, Y.; Rooseboom, M.; Roughton, A.; Samama, P.; Smit, M. J.; Son, E.; Louw, J.; Vogel, G.; Webb, M.; Wijkmans, J.; You, M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2724.

(4) (a) Santos, C.; Mateus, M. L.; Santos, A. P.; Moreira, R.; Oliveira, E.; Gomes, P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1595. (b) Falorni, M.; Giacomelli, G.; Porcheddu, A.; Taddei, M. *Eur. J. Org. Chem.* **2000**, *8*, 1669. (c) Goolcharran, C.; Borchardt, R. T. *Pharm. Sci.* **1997**, *87*, 283. (d) Witiak, D. T.; Nair, R. V.; Schmid, F. A. *J. Med. Chem.* **1985**, *28*, 1228.

(5) Maghioros, G.; Schlewer, G.; Wermuth, C. G. *New J. Chem.* **1983**, *11*, 667.

(6) (a) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2010**, *1*, 13. (b) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338.

(7) Jiang, Q.; Jiang, D.; Jiang, Y.; Fu, H.; Zhao, Y. *Synlett* **2007**, *12*, 1836.

(8) (a) Hartwig, J. F. *Synlett* **1997**, *4*, 329. (b) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, *348*, 23. (c) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609. (d) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (e) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (f) Yang, B.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (g) Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 15914. (h) Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 3505. (i) Sheng, Q.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 4109. (j) Vo, G. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 11049. (k) Maes, B. U. W.; Kosmrlj, J.; Lemiere, G. L. F. *J. Heterocycl. Chem.* **2002**, *39*, 535. (l) Jonckers, T. H. M.; Maes, B. U. W.; Lemiere, G. L. F.; Dommisse, R. *Tetrahedron* **2001**, *57*, 7027. (m) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *21*, 7240.

(9) Ma, F.; Xie, X.; Ding, L.; Gao, J.; Zhang, Z. *Tetrahedron* **2011**, *67*, 9405.

(10) (a) Salomé, C.; Schmitt, M.; Bourguignon, J. J. *Tetrahedron Lett.* **2012**, *53*, 1033. (b) Salomé, C.; Schmitt, M.; Bourguignon, J. J. *Tetrahedron Lett.* **2009**, *50*, 3798.

(11) (a) Navratilova, H. *Chirality* **2001**, *13*, 731. (b) Parker, D. *Chem. Rev.* **1991**, *91*, 1441.

(12) Simonin, F.; Schmitt, M.; Laulin, J. P.; Laboureyras, E.; Jhamandas, J. H.; MacTavish, D.; Matifas, A.; Mollereau, C.; Laurent, P.; Parmentier, M.; Kieffer, B. L.; Bourguignon, J. J.; Simonnet, G. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 466.