Optically Active Aromatic and Heteroaromatic α-Amino Acids by a One-Pot Catalytic Enantioselective Addition of Aromatic and Heteroaromatic C−H Bonds to α-Imino Esters

Steen Saaby, Pau Bayón, Pompiliu S. Aburel, and Karl Anker Jørgensen*

Center for Catalysis, Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark

kaj@chem.au.dk

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The development of a practical one-pot catalytic enantioselective procedure for the synthesis of non-natural aromatic and heteroaromatic α-amino acids is reported. Starting from readily available starting materials and application of a chiral BINAP−Cu(I) catalyst, the optically active products are formed with readily removable N-protecting groups. The scope of the reaction is demonstrated by the addition of substituted furans, thiophenes, pyrroles, and aromatic compounds to *N*-alkoxycarbonyl-α-imino esters in good yields and with enantioselectivities up to 96% ee for the furans, 93% ee for the thiophenes, and 98% for the aromatic compounds. The protecting groups are readily removed, and various transformations of the aromatic and heteroaromatic α-amino acids are demonstrated. The coordination of the *N*-alkoxycarbonyl α-imino ester to the chiral BINAP−Cu(I) complex and the enantioselectivity of the catalyst is discussed on the basis of the DFT calculations and X-ray crystallographic data.

Introduction

Optically active α-amino acids constitute some of the most important molecules in living cells. A fundamental challenge in organic chemistry is the development of catalytic enantioselective C−C bond-forming reactions, which give access to this class of optically active building blocks using simple starting materials. A number of methods for the construction of optically active aromatic and heteroaromatic α-amino acids have been developed.[1] However, despite the relatively simple structure, the formation of these nonracemic adducts is difficult due to base-catalyzed epimerization of the acidic α-methine proton.[2]

Optically active aromatic α-amino acids are important molecular fragments in many molecules of biological importance such as cephalecins,[3] nocardicins,[4] and glycopeptides of the vancomycin family.[5] The heteroaromatic α-amino acids are also an interesting and important class of amino acids, and in particular, the furyl glycine derivatives have received increased attention due to the large number of structural equivalents and synthetic applications of the heteroaromatic moiety.[6]

The synthesis of optically active aromatic and heteroaromatic α-amino acids is a challenge in organic chemistry, and only a few research groups have succeeded in the development of a catalytic asymmetric approach to heteroaromatic α-amino acids applying either the asymmetric Strecker reaction[7] or the Sharpless amino-hydroxylation reaction,[8] giving the corresponding furfuryl α-amino cyanides or alcohols, respectively. Methods based on enzymatic or Lewis-acid-catalyzed kinetic resolution of racemic starting materials as well as the use of chiral templates have also been reported.[1a,9]

The catalytic enantioselective addition of aromatic and heteroaromatic C−H bonds to α-imino esters, an aza-Friedel−Crafts reaction,[10] is the direct approach to optically active aromatic and heteroaromatic α-amino acids. However, despite the great potential, only very few protocols for the catalytic asymmetric version of this reaction have been reported.[11,12] Recently, we communicated the catalytic formation of optically active aromatic α-amino acids by the addition of electron-rich

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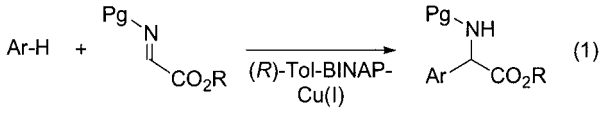
aromatic compounds to α-imino esters using chiral Lewis acid catalysis.[11] Two examples of catalytic enantioselective aza-Friedel−Crafts reactions using furan as the substrate are known from the literature; however, poor results in terms of both yield and enantiomeric excess were obtained.[12] In relation to the addition of aromatic and heteroaromatic compounds to α-imino esters, it should be noted that catalytic enantioselective addition reactions of aromatic and heteroaromatic compounds to carbonyl compounds and α,β-unsaturated systems have also recently been achieved.[13,14]

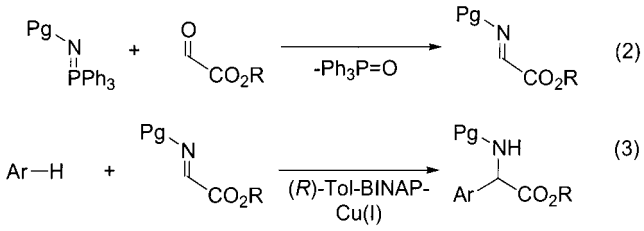
In this paper, we disclose the development of a simple one-pot procedure for the synthesis of optically active aromatic, furfuryl, thiophenyl, and pyrrolyl α-amino acid derivatives using chiral Lewis acid catalysis (eq 1). Protected aromatic and heteroaromatic α-amino acids are obtained directly by this procedure where aromatic and heteroaromatic C−H bonds are added to α-imino ester electrophiles activated by a chiral BINAP−Cu(I) catalyst.



Results and Discussion

Recently, we reported the development of a catalytic enantioselective addition of electron-rich aromatic compounds to *N*-alkoxycarbonyl α-imino esters,[11] The α-imino ester electrophiles were generated via an aza-Wittig reaction (eq 2, Scheme 1) and reacted with the aromatic substrates catalyzed by a BINAP−Cu(I) complex without any purification (eq 3, Scheme 1).

Scheme 1



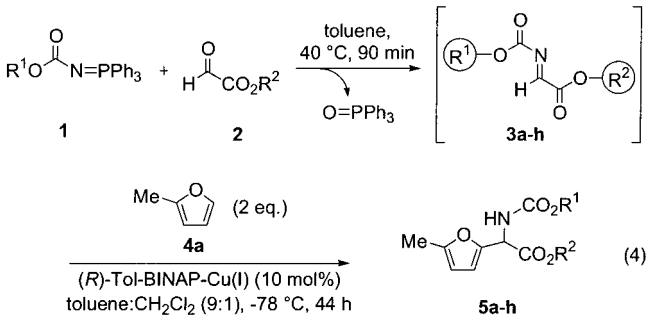
However, an attempt to extend the scope of the reaction to include also heteroaromatic compounds was met with limited success, as the reaction of 2-methylfuran **4a** with a methoxycarbonyl-protected α-imino ester **3e** afforded the corresponding furfuryl α-amino acid in poor yield (17%) and with low enantiomeric excess (41% ee). Furthermore, several of the electron-rich aromatic compounds reacted with moderate yields and enantioselectivities using the first reaction protocol.[11] These observations prompted us to develop a general reaction protocol, which was applicable for both the catalytic enantioselective addition of aromatic, as well as heteroaromatic compounds, to α-imino esters.

Table 1. Effect of *N*-Carboalkoxyiminophosphanes 1, Alkyl Glyoxylates 2, Solvent, and Counterion on the Catalytic Enantioselective Aza-Friedel−Crafts Reaction of *N*-Alkoxycarbonyl α-Imino Esters 3a−h with 2-Methylfuran 4a

entry	aza-ylide	R^1	R^2	imine	Lewis acid	yield[a] (%)	ee[b,c] (%)
1	**1a**	*t*-Bu	Et	**3a**	$CuPF_6$	**5a**, <20	30 (*R*)
2	**1b**	*i*-Pr	Et	**3b**	$CuPF_6$	**5b**, 61	52 (*R*)
3	**1c**	Et	Et	**3c**	$CuPF_6$	**5c**, 31	73 (*R*)
4	**1d**	Bn	Et	**3d**	$CuPF_6$	**5d**, 37	79 (*R*)
5	**1e**	Me	Et	**3e**	$CuPF_6$	**5e**, 56	84 (*R*)
6[d]	**1c**	Et	Et	**3c**	$CuPF_6$	**5c**, 25	64 (*R*)
7	**1e**	Me	Bn	**3f**	$CuPF_6$	**5f**, 21	55 (-)
8	**1e**	Me	*i*-Pr	**3g**	$CuPF_6$	**5g**, 30	79 (*R*)
9	**1e**	Me	Me	**3h**	$CuPF_6$	**5h**, 35	88 (*R*)
10	**1e**	Me	Et	**3e**	$CuClO_4$	**5e**, 29	81 (*R*)
11	**1e**	Me	Et	**3e**	CuOTf·Tol	**5e**, 31	66 (*R*)
12[e]	**1e**	Me	Me	**3h**	$CuPF_6$	**5h**, 39	90 (*R*)

[a] Isolated yields based on the aza-ylide (**1**). [b] Determined by chiral HPLC or GC (see the Supporting Information for further details). [c] The absolute configuration of **5h** was derived from a crystalline *N*-tosyl derivative **12**, which was analyzed by X-ray analysis (see the Supporting Information for further details). The configurations of **5a**−**e** were assigned by deprotection and subsequent standard protecting group transformations[18] and mutual comparison of the samples obtained. The absolute configuration of **5g** was assigned by analogy (HPLC traces). [d] Solvent: toluene. [e] Solvent: toluene/CH_2Cl_2 (19:1).

Preliminary studies revealed that low temperature (−78 °C) and the choice of solvent (toluene) was crucial for the exclusion of byproducts[15] and the enantioselectivity of the catalytic reaction. A series of reactions between **4a** and a number of different imines **3a**−**h** were conducted in the presence of (*R*)-Tol-BINAP−$CuPF_6$ as the catalyst[11,12,16] (eq 4) in order to optimize the enantioselectivity. The results are presented in Table 1.



The *N*-alkoxycarbonyl α-imino esters **3a**−**h** were prepared via an aza-Wittig reaction of the *N*-carboalkoxy-

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(15) When performing a reaction in, e.g., CH_2Cl_2 at room temperature, a substantial amount of an unidentified byproduct was formed. The molecular weight (HRMS) of the compound indicates a structure that consists of one aromatic moiety and the addition of two imine molecules.

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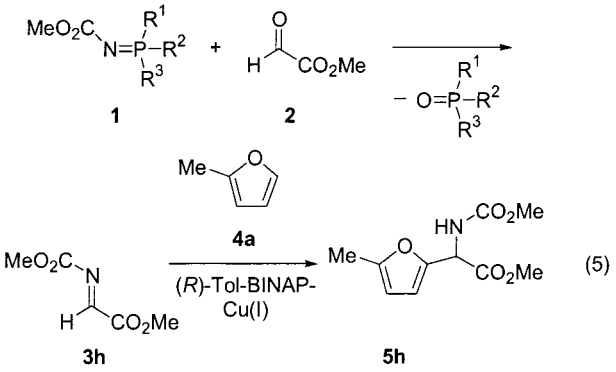
iminophosphanes **1** and the corresponding alkyl glyoxylates **2** (eq 2, Scheme 1) and used directly in the catalytic reaction (eq 3, Scheme 1) without any purification. Initially, we anticipated that the size of the imine-protecting group would affect the enantioselectivity of the reaction, and as shown in entries 1−5 in Table 1, the enantiomeric excess of the furfuryl α-amino acids **5a**−**e** increased gradually from 30% to 84% ee by reducing the steric size of the R^1-substituent of the carbamate. The same trend was observed varying the R^2-substituent on the ester functionality (Table 1, entries 5 and 7−9) as the enantiomeric excess was further increased to 88% using an imine having the smallest substituent (methyl) in both the ester and carbamate moieties. The protected furfuryl α-amino acids were formed in a regioselective manner, as the substitution only occurs at the 5-position of 2-methylfuran. A change of the copper(I) Lewis acid counterion from PF_6 to the stronger coordinating ClO_4 and TfO anions caused a reduction in both yield and enantiomeric excess from 84% to 81% and 66% ee, respectively (Table 1, entries 5, 10, and 11). The best reaction conditions in terms of enantioselectivity using the *N*-carboalkoxyiminotriphenylphosphanes as the imine precursors are outlined in entry 12. The use of imine **3h** affords the aza-Friedel−Crafts adduct **5h** in 39% isolated yield (two steps) with a high enantioselectivity of 90% ee.

The moderate yield of the optically active furfuryl α-amino acid **5h (**39%) was addressed to a low purity of the crude α-imino ester solution used in the catalytic reaction. Full conversion of the aza-ylide **1e** was monitored by ^{1}H NMR spectroscopy; however, a substantial amount of imine decomposition was detected using the reaction conditions outlined in eq 4. These observations prompted us to optimize of the reaction conditions in order to improve the yield of the reaction (eq 5). Substi-



tution of one of the phenyl groups in the aza-ylide **1** with the more electron-donating benzyl group improved the rate and purity of the first reaction step in which the imine is formed. The overall yield of the furfuryl α-amino acid was hence increased from 39% to 59%, without notably affecting the high ee value (Table 2, entry 1 vs 2). The purity of the imine derived from methyl glyoxylate and aza-ylide **1g** was excellent (ca 95%), but surprisingly the yield of **5h** decreased to 46%. We expect this observation to be a consequence of competitive coordination of the imine and the phosphine oxide to the Cu(I) catalyst. However, as long as the phosphine oxide is sufficiently bulky, the catalytic enantioselectivity of the Lewis acid complex is maintained (Table 2, entries 1−3). When the more Lewis basic tributylphosphine oxide was present

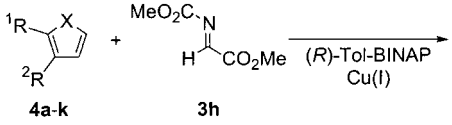
Table 2. Yield Optimization by Variation of the Electronics and Sterics of the Aza-Ylide 1

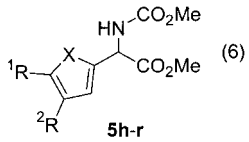
entry	aza-ylide	R^1	R^2	R^3	yield of **5h** (%)	ee of **5h** (%)
1[b]	**1e**	Ph	Ph	Ph	39	90
2[c]	**1f**	Bn	Ph	Ph	59	89
3[d]	**1g**	Bn	Bn	Ph	46	88
4[e]	**1h**	*n*-Bu	*n*-Bu	*n*-Bu	8	0

[a] (*R*)-Tol-BINAP−$CuPF_6$ (10 mol %), toluene/CH_2Cl_2 (19:1), −78 °C, 44−48 h. [b] 40 °C, 90 min, toluene, 2.0 equiv of methyl glyoxylate. [c] rt, 50 min, toluene, 1.2 equiv of methyl glyoxylate. [d] rt, 20 min, toluene, 1.1 equiv of methyl glyoxylate. [e] Nonoptimized reaction conditions.

in the reaction mixture, the catalyst complex was perturbed or decomposed completely as **5h** was formed as a racemate (Table 2, entry 4). It was found that excess amounts of **2** did not have any effects on the isolated yield of **5h**.

With the optimized reaction conditions in hand, a series of reactions of different heteroaromatic substrates **4a**−**k** were performed in order to demonstrate the scope and synthetic applicability of the reaction (eq 6). The





(6)

results are presented in Table 3. The protected 5-substituted furyl glycines **5h**−**o** were formed in generally good yields and high to excellent enantioselectivities (up to 96% ee) using the alkyl-, benzyl-, aryl-, and methoxy-substituted furans **4a**−**f** as substrates (Table 3, entries 1−6). 3-Methylfuran **4g** also reacted using the present reaction conditions, affording the furfuryl α-amino acid **5n** in a good yield, though with a slightly lower enantioselectivity (Table 3, entry 7). Disubstituted furans such as **4h** could also be used as the substrates, and the corresponding optically active heteroaromatic α-amino acid was obtained with good enantioselectivity; however, the yield was moderate due to a substantial amount of the double addition product.[15] It should be noted that the catalytic enantioselective reaction using furan as substrate was found to be sluggish, giving a mixture of isomeric products in low yield. Activated thiophenes **4i**,**j** also reacted under the optimized reaction conditions affording the optically active thiophenyl α-amino acid derivatives **5p**,**q** in high yields and excellent enantioselectivities up to 94% ee (Table 3, entries 9 and 10). The (*R*)-Tol-BINAP−$CuPF_6$ complex also catalyzed the reaction of imine **3h** with *N*-methylpyrrole **4k** with selective substitution in the 2-position. However, a drop in enantioselectivity was observed (59% ee), probably caused by the ability of the more Lewis-basic nitrogen atom in the substrate to interact with the copper(I) catalyst. This explanation was supported by the observation that lower ee values were measured when an increase of the amount of 2-methylfuran (4 equiv) was used in the reaction with the different imines. When more polar solvents such as Et_2O, THF, $C_6H_5CF_3$, CH_2Cl_2, dioxane, TBME, or $MeNO_2$ were used for the catalytic asymmetric reaction lower enantioselectivities were also found.

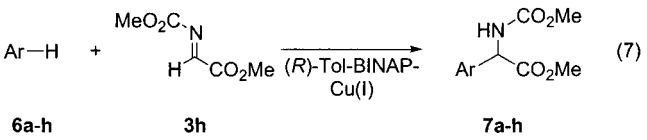
Table 3. Catalytic Asymmetric Aza-Friedel−Crafts Reactions of Different Heteroaromatic Substrates 4a−j with the *N*-Moc-Protected α-Imino Methyl Ester 3h

entry	R^1	R^2	substrate (equiv)	X	product	yield[a] (%)	ee[b] (%)
1	Me	H	**4a** (2)	O	**5h**	59	89
2	Et	H	**4b** (2)	O	**5i**	64	88
3	*t*-Bu	H	**4c** (10)	O	**5j**	33	96
4	Bn	H	**4d** (5)	O	**5k**	40[c]	95
5	*p*-MeO-Ph	H	**4e** (2)	O	**5l**	82 (45)[d]	74 (99.5)[d]
6	MeO	H	**4f** (1.2)	O	**5m**	63	96
7	H	Me	**4g** (2)	O	**5n**	55	72
8	Me	Me	**4h** (2)	O	**5o**	24	84
9	MeO	H	**4i** (1.2)	S	**5p**	75	94
10	*p*-Me_2N-Ph	H	**4j** (2)	S	**5q**	56[e]	93
11	H	H	**4k** (1.2)	NMe	**5r**	55	59

[a] Isolated yields based on the aza-ylide. [b] Determined chiral HPLC or GC (see the Supporting Information for further details). [c] A byproduct (**14**) formed in 23% yield was isolated and characterized (see the Supporting Information). [d] Numbers in parentheses refer to yield and enantiomeric excess after a single recrystallization from Et_2O/hexane. [e] Yield determined by ^1H NMR spectroscopy.

An efficient and clean synthesis of methoxycarbonyl-protected imines via the aza-ylide **1e** is limited tononpolar solvents, whereas no imine can be detected by ^1H NMR spectroscopy when the reaction is performed in, e.g., THF, although the conversion of starting material is complete. However, the imine synthesis using the more reactive benzyldiphenylphosphine derived aza-ylide **1f** is very efficient, also in polar solvents.

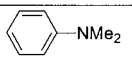
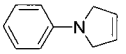
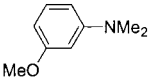
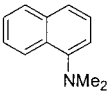
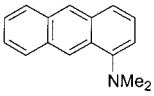
A series of electron-rich aromatic compounds **6a−h** were reacted with different imines under optimized reaction conditions providing the aromatic α-amino acid **7a−h** (eq 7) in high yields and with good to excellent enantioselectivities (up to 98% ee) (Table 4). Generally,



the results achieved using the present reaction condition were better in terms of enantioselectivity than the results previously obtained.[11] An example is that the yield and enantioselectivity increased from 68% to 81% and 72% ee to 96% ee, respectively, in the case of *meta*-methoxy-*N*,*N*-dimethylaniline **6b** as substrate, using this new procedure.

Selective Deprotection and Functional Group Transformations. A selective deprotection of the two amino functionalities and further transformations of the free aniline derivative is outlined in Scheme 2. By reaction of the aromatic α-amino acid **7a** with iodosobenzene and $TMSN_3$, and subsequent hydrolysis of the formed bis-azide, the unprotected aniline derivative **8** was isolated in a high yield of 83%. The aromatic amino group was then removed by diazotization and subsequent copper-catalyzed decomposition of the diazonium salt in saturated aqueous H_3PO_2 to give **9**. Several synthetic procedures are available for the transformation of diazonium salts into halogens or hydroxyl groups.[18] These selective transformations provide the access to versatile optically active building blocks, e.g., nonsubstituted naphthalene and anthracene derived α-amino acids (**7g**,**h**) as well as para-substituted phenylglycins. The

Table 4. Results for the Reaction of Different Aromatic Substrates with Imines

Entry	Aza-ylid	Imine		Substrate	Product[a]	Yield (%)[b]	Ee (%)[c]
1[d]	**1f**	**3h**	**6a**		**7a**	80	98 (*R*)
2[d]	**1f**	**3h**	**6b**		**7b**	70	88
3[d]	**1f**	**3h**	**6c**		**7c**	81	96
4[e]	**1e**	**3h**	**6d**		**7d**	56	97
5[d]	**1f**	**3h**	**6e**		**7e**	86	92
6[d]	**1f**	**3h**	**6f**		**7f**	47	67
7[f]	**1e**	**3e**	**6g**		**7g**	75	92
8[f]	**1d**	**3d**	**6h**		**7h**	65	89

[a] Addition of the imino electrophile occurs exclusively in the para position to the nitrogen substituent of the aromatic substrate. [b] Isolated yields based on the aza-ylide. [c] Determined chiral HPLC or GC (see the Supporting Information for further details). [d] (*R*)-Tol-BINAP−$CuPF_6$ (10 mol %), toluene/THF (3:7), −78 °C, 24 h. [e] (*R*)-Tol-BINAP−$CuPF_6$ (10 mol %), CH_2Cl_2, −78 °C, 24 h. [f] (*R*)-Tol-BINAP−$CuPF_6$ (5 mol %), CH_2Cl_2, −78 °C, 24 h.

α-methine proton of arylglycines is highly susceptible to racemization in either basic or acidic aqueous media. This problem was recognized in several attempts to remove the methoxycarbonyl protecting group using either strong basic or acidic solvolysis. However, by treatment of **7a** with TMSI in MeCN provided **11** in 84% yield. All transformations in Scheme 2 were conducted without detectable loss of optical purity, apart from the conversion of **8** into **9** where a minor loss of enantiomeric excess was observed (90% ee to 88% ee). The racemization-prone heteroaromatic α-amino acid **5h** was also selectively deprotected in high yield (>71%), although some racemization was observed (89% ee to 81% ee).

(17) For selective removal of the *N*-methoxycarbonyl protecting group: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley-Interscience: New York, 1999.

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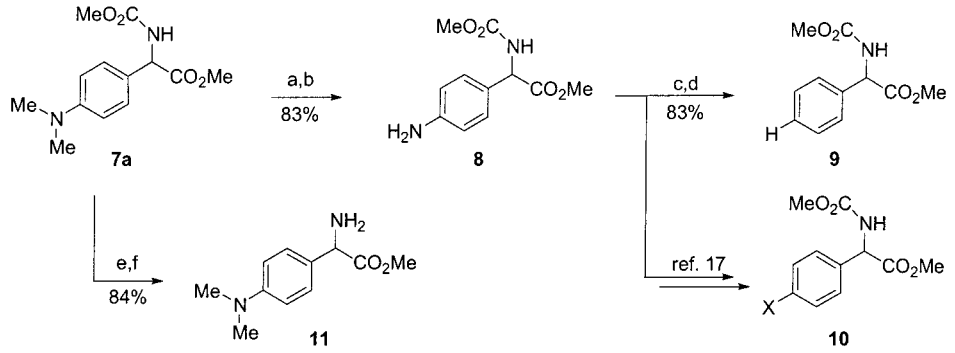
Scheme 2[a]



[a] Key: (a) PhIO, $TMSN_3$, CH_2Cl_2, −40 °C, 3 h; (b) saturated aqueous $NaHCO_3$, THF (1:1), rt, 48 h; (c) $NOBF_4$, CH_2Cl_2, 0 °C, 35 min; (d) concd aq H_3PO_2, Cu_2O (cat.), 0 °C, 40 min; (e) TMSI (1.5 equiv), CH_3CN, 60 °C, 45 min; (f) MeOH, rt, 20 min.

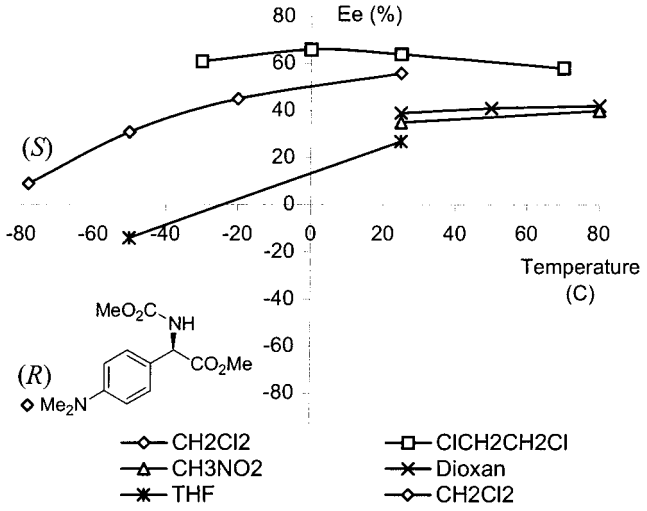
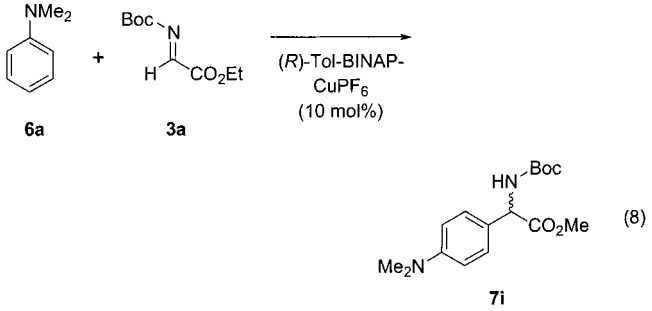


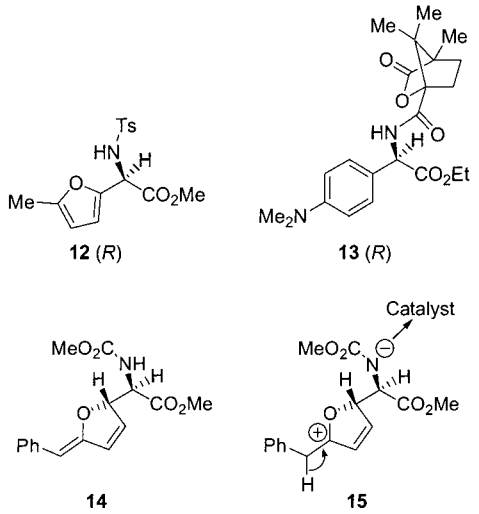
Figure 1. Enantiomeric excess of **7i** (eq 7) obtained in different solvents and at different temperatures. The enantiomeric excess and absolute stereochemistry of **7a** is shown in the lower left corner.

Mechanistic Considerations. The mode of coordination of the imines **3a**−**h** to the copper(I) catalyst is an intriguing problem as the enantioselectivity of the aromatic α-amino acids depends on the nitrogen protecting group. Performing two identical reactions except for the structure of the imine protecting group (*N*-Moc vs *N*-Boc), the absolute configuration of the product changed from *R* to *S* using the same enantiomer (*R*) of the chiral Tol-BINAP−Cu(I) complex as the catalyst (Figure 1). A series of reactions of the *N*-Boc-protected α-imino ester **3a** with *N*,*N*-dimethylaniline **6a** (eq 8) was performed in different solvents, and the enantiomeric excess was measured as a function of temperature. The results are presented in Figure 1.



It appears that the absolute configuration of the product was dependent on the N-protecting group as the *N*-Moc-protected α-imino ester **3h** gave the *R* enantiomer of the aza-Friedel−Crafts adduct **7a** (lower left corner in Figure 1), while the *N*-Boc-protected α-imino ester **3a** gave the *S* enantiomer of the aza-Friedel−Crafts adduct **7i**. The chiral induction of the reaction was also dependent on the temperature, and when, e.g., THF was used as the solvent the enantiomer in excess changed from *S* to *R* at lower temperatures. These observations could indicate that more than one reactive transition species exists in solution.

To obtain mechanistic information, the absolute configuration of the aza-Friedel−Crafts products **5h** and **7a** was resolved by X-ray analysis of the corresponding tosyl and camphanic acid derivatives **12** and **13** (see the Supporting Information). Both compounds could be assigned as the *R* configuration at the newly formed chiral center. An interesting byproduct (**14**) was formed in the catalytic enantioselective addition of 2-benzylfuran to α-imino ester **3h** (Table 3, entry 4). The formation of **14** can be explained by deprotonation at the benzylic position in the intermediate *σ*-complex **15**, rather than deprotonation at the 2-position, which would restore the aromatic furan structure. The byproduct **14** was found to have the same high level of enantiomeric excess as the expected major product **5k**; thus, **15** is believed to be a common intermediate on the two different reaction paths. The relative stereochemistry of **14** was also assigned by X-ray analysis.



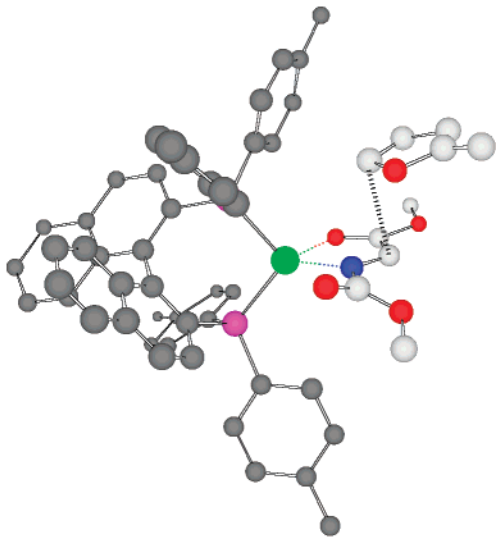


Figure 2. Calculated tetrahedral intermediate of the α-imino ester **3h** coordinated to the (*R*)-Tol-BINAP−$CuPF_6$ complex. The approach of a 2-methylfuran to the *Re*-face of the imino double bond is shown to account for both the absolute configuration of **5h** as well as the relative stereochemistry of byproduct **14** (the carbon atoms of 2-methylfuran and **1h** are light gray).

A number of different coordination modes of imine **3h** to the $CuPF_6$−(*R*)-Tol-BINAP complex is in principle possible. However, an intermediate in which the more Lewis-basic nitrogen atom and the ester carbonyl oxygen atom are coordinated to the copper(I) center is most likely. On the basis of the absolute configuration of compounds **12** and **13** (X-ray analysis), a bidentate tetrahedral five-membered coordination of imine **3h** to the (*R*)-Tol-BINAP−Cu(I) complex can be envisaged. Further support for such an intermediate has been obtained from DFT calculations[19] of the intermediate in which the α-imino ester **3h** is coordinated to the (*R*)-Tol-BINAP−Cu(I) catalyst. The optimized structure of this intermediate is shown in Figure 2. It appears from the intermediate that one of the tolyl groups of the BINAP ligand shields the *Si*-face of the α-imino ester, leaving the *Re*-face open for reaction with the aromatic substrate.

The orientation of the 2-substituted furan approaching the α-imino ester shown in Figure 2 is in agreement with the relative stereochemistry of compound **14**, which was resolved by X-ray analysis. The observed enantioselective induction is also in agreement with results obtained in a study of aza-Diels−Alder reactions in which the same catalyst was applied[12b] as well as X-ray crystallographic data obtained by Lectka.[16e]

As evident from the results in Table 1 (vide supra), the enantioselectivity of the aza-Friedel−Crafts reaction is very dependent on the choice of imine N-protecting group. Application of the more bulky carbamates, e.g., the *N*-Boc-protecting group, caused a substantial reduction in the enantioselectivity compared to the results obtained using the α-imino esters protected with the small methyl carbamate (entry 1 vs 5, Table 1). Furthermore, a much lower reaction rate was observed performing reactions of the α-imino ester **3a**. To investigate this pronounced steric effect, the structure of the α-imino ester **3a** coordinated to the (*R*)-Tol-BINAP−Cu(I) catalyst was optimized.[19] A five-membered tetrahedral intermediate with coordination of the α-imino-ester nitrogen atom and the ester carbonyl oxygen atom to the copper(I) center was anticipated as discussed above. The optimized structures of α-imino esters **3h** and **3a** coordinated to the (*R*)-Tol-BINAP−Cu(I) catalysts are shown in Figure 3.

The optimized intermediate of α-imino ester **3h** coordinated to the catalyst (**16**, Figure 3) is shown along the α-imino ester axis, and it appears that one of the tolyl groups of the BINAP ligand effective shields the *Si*-face of the α-imino ester, leaving the *Re*-face open for reaction with the substrate. However, when the bulky *N*-Boc-protecting group of α-imino ester **3a** is used, the imine is twisted into the orientation outlined in **17** to the right in Figure 3 and the intermediate becomes almost symmetrical compared to the intermediate in **16**, which can account for the low enantioselectivity and reaction rate observed.

Conclusion

Optically active aromatic and in particular heteroaromatic α-amino acids have normally been relatively complicated to synthesize. In conclusion, we have devel-

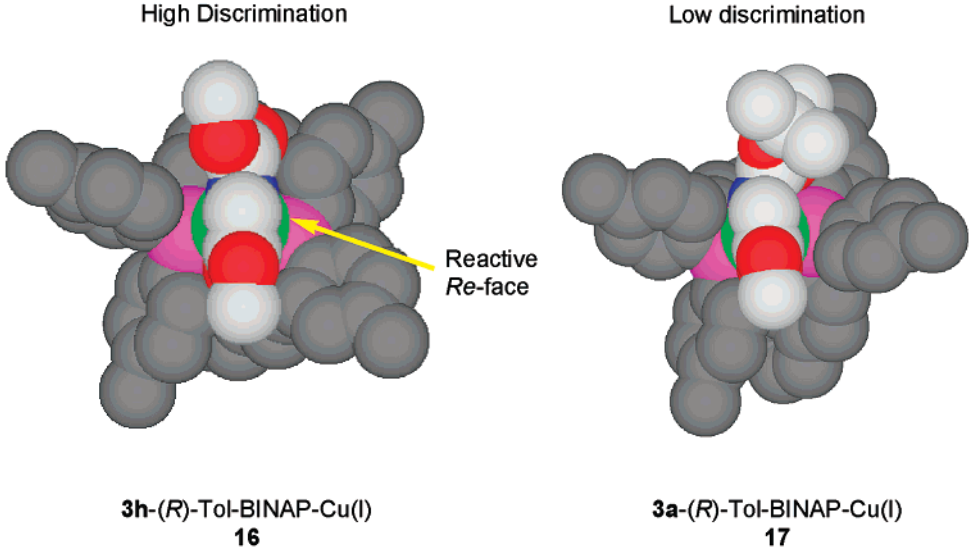


Figure 3. DFT-optimized structures of α-imino esters **3h** and **3a** coordinated to (*R*)-Tol-BINAP−Cu(I).

oped a simple one-pot procedure for the synthesis of versatile directly protected optically active aromatic and heteroaromatic α-amino acids. This new reaction gives an easy access to important chiral building blocks, using simple starting materials and an easy-available catalyst. The catalytic enantioselective reaction tolerates a number of diverse substrates and in general the products are formed in good to high yields and with enantioselectivities from 59% up to 98% ee. Selective deprotections and subsequent structural transformations of the aza-Friedel−Crafts products were conducted without notable loss of optical purity, demonstrating the practical synthetic utility of the presented reaction. The absolute stereochemistry of a number of phenyl- and furyl glycine derivatives was determined by X-ray analysis, and on the basis of experimental results, DFT calculations, and crystallographic data, the mechanism and reaction path have been disclosed.

Experimental Section

General Methods. The ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra were recorded at 300 or 400, 100, and 162 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS (δ 0) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ 77.0) for ^{13}C NMR. Solvents were dried according to standard procedures. Flash chromatography (FC) was carried out using the FlashMaster II. The enantiomeric excess (ee) of the products was determined by chiral HPLC (Daicel Chiralpak AS/AD or Daciel Chiralcel OD/OJ columns) or chiral GC (Chiraldex B-PM or G-TA columns). All solvents were dried and distilled prior to use, and all catalytic reactions were performed under nitrogen or argon atmosphere.

Materials. All glyoxylate esters were prepared by ozonolysis of the corresponding maleates and distilled prior to use.[20] All *N*-carboalkoxyiminotripenylphosphanes were prepared following literature procedures.[21] Benzyldiphenylphosphine and (*R*)-(+)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl 98%, ((*R*)-Tol-BINAP), 2-ethylfural, 2-*t*-Bu-furan, 2,3-dimethylfuran, *N*,*N*-dimethylaniline, *N*,*N*-dimethyl-1-naphthylamine, $(CuOTf)_2$·Tol, 2-methylfuran, 2-methoxyfuran, 2-methoxythiophene, 3-dimethylaminoanisole, and *N*-methylpyrrole were purchased commercially and used as received. 2-Benzylfuran,[22] 2-(4-methoxy)phenylfuran,[23] 2-(4-*N*,*N*-dimethylaminophenyl)thiophene,[24] 4-methyl-3,4-dihydro-2*H*-[1,4]oxazine (**7f**),[25] *N*-phenyl-3-pyrroline,[26] $CuPF_6$·4MeCN,[27] $CuClO_4$·4MeCN,[27] and iodosobenzene[28] were prepared according to literature procedures. *N*,*N*-Dimethyl-1-aminoanthracene, *N*,*N*-dimethylindoline, and *N*-methyl-1,2,3,4-tetrahydroquinoline were all prepared from the corresponding amines (MeI, NaH, THF, reflux, 15 h).

A Representative Experimental Procedure for the Synthesis of Aza-Ylids, (1a). A solution of methyl chloroformate (2.92 g, 0.031 mol), trimethylsilyl azide (4.95 g, 0.043 mol) and a few drops of pyridine in dry toluene (31 mL) is stirred at 80 °C for 30 min under an argon atmosphere. Then toluene (62 mL) is added and the solution is cooled to 0 °C. Benzyldiphenylphosphine[29] (8.56 g, 0.031 mol) is dissolved in dry degassed toluene (60 mL) and added dropwise to the previous cooled solution at 0 °C. At the end of addition, the mixture is stirred at 0 °C for 5 min and then left to warm to room temperature (approximately 30−45 min). The solvent is distilled off and the solid residue is recrystallized from EtOAc:hexane (4:1). The product **1a** is isolated as a white crystalline solid (8.0 g, 74%); mp 152−153 °C; ^{1}H NMR δ 7.67−7.62 (m, 4H), 7.49−7.45 (m, 2H), 7.39−7.34 (m, 4H), 7.08−7.03 (m, 3H), 6.85−6.82 (m, 2H), 4.04 (d, ^3J(H,H) = 14 Hz, 2H), 3.61 (s, 3H); ^{13}C NMR δ 162.9, 132.66, 132.64, 132.5, 132.4, 130.36, 130.32, 128.9, 128.8, 128.58, 128.55, 127.9, 127.32, 127.28, 126.9, 53.05, 53.02, 35.6, 33.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.9; HRMS $C_{21}H_{20}NO_2P$ $[M + Na]^+$ calcd 372.1129, found 372.1121.

A General Procedure for the Synthesis of Directly Protected α-Amino Acids. To a flame dried Schlenk tube equipped with a magnetic stirring bar is added the aza-ylide **1a** (140 mg, 0.40 mmol) and dried under vacuum at room temperature for 1 h before toluene (0.66 mL) is added by syringe. After stirring for 10 min, the suspension is added a 0.42 M solution of methyl glyoxylate in toluene (1.14 mL, 0.48 mmol) and stirred for another 15 min at ambient temperature before the white milky slurry is cooled to −78 °C. (Complete imine formation should be checked by ^{1}H NMR spectroscopy, as full conversion of the aza-ylide is crucial to achieve good results.) A catalyst solution prepared by drying $CuPF_6$·4MeCN (15 mg, 0.040 mmol) and (*R*)-Tol-BINAP (30 mg, 0.044 mmol) in a flame dried Schlenk tube under vacuum for 1 h and subsequently dissolved in a mixture of CH_2Cl_2 (0.20 mL) and toluene (2.0 mL) is added by syringe and after stirring for 30 s the aromatic substrate (0.80 mmol) is added in one portion. After 44 h, the reaction mixture is filtered through a plug of silica and eluted with Et_2O (50 mL). The crude product is concentrated in vacuo and purified by FC to give the directly protected α-amino acid.

***tert*-Butoxycarbonylamino(5-methyl-furan-2-yl)acetic acid ethyl ester 5a:** ^{1}H NMR δ 6.19 (d, ^3J(H,H) = 2.8 Hz, 1H), 5.91−5.90 (m, 1H), 5.44 (d, ^3J(H,H) = 8.0 Hz, 1H), 5.33 (d, ^3J(H,H) = 8.1 Hz, 1H), 4.26−4.16 (m, 2H), 2.25 (s, 3H), 1.44 (s, 9H), 1.19 (t, ^3J(H,H) = 7.3 Hz, 3H); ^{13}C NMR δ 169.4, 154.9, 152.5, 147.1, 109.0, 106.5, 80.2, 61.9, 51.8, 28.2, 14.0, 13.5; $[\alpha]^{rt}_D = -20.1$ (c = 1.0 in $CHCl_3$) (31% ee); GC (Chiraldex G-TA, 70−140 °C (10 °C/min), 140−145 °C (1 °C/min) then 145 °C isotherm) t_R = 38.33 min (major enantiomer), t_R = 38.96 min (minor enantiomer); HRMS $C_{14}H_{21}NO_5$ $[M + Na]^+$ calcd 306.1317, found 306.1311.

Isopropoxycarbonylamino(5-methylfuran-2-yl)acetic acid ethyl ester 5b: ^{1}H NMR δ 6.15 (d, ^3J(H,H)= 3.0 Hz, 1H), 5.85−5.84 (m, 1H), 5.49 (bd, ^3J(H,H) = 7.9 Hz, 1H), 5.23 (d, ^3J(H,H) = 8.1 Hz, 1H), 4.85 (sep, ^3J(H,H) = 6.3 Hz, 1H), 4.32−4.08 (m, 2H), 2.19 (s, 3H), 1.21−1.15 (m, 9H); ^{13}C NMR δ 169.2, 155.3, 152.6, 146.9, 109.2, 106.5, 68.9, 62.0, 52.0, 22.1, 14.0, 13.5; $[\alpha]^{rt}_D = -45.0$ (c = 0.25 in $CHCl_3$) (52% ee); GC (Chiraldex G-TA, 70−140 °C (10 °C/min), 140−145 °C (1 °C/min) then 145 °C isotherm) t_R = 36.60 min (major enantiomer), t_R = 37.55 min (minor enantiomer); HRMS $C_{13}H_{19}NO_5$ $[M + Na]^+$ calcd 292.1161, found 292.1159.

Ethoxycarbonylamino(5-methylfuran-2-yl)acetic acid ethyl ester 5c: ^{1}H NMR δ 6.22 (d, ^3J(H,H) = 3.2 Hz, 1H), 5.92−5.91 (m, 1H), 5.58 (bd, ^3J(H,H) = 6.2 Hz, 1H), 5.41 (d, ^3J(H,H) = 8.1 Hz, 1H), 4.30−4.10 (m, 4H), 2.26 (s, 3H), 1.26 (t, ^3J(H,H) = 7.4 Hz, 3H), 1.25 (t, ^3J(H,H) = 7.1 Hz, 3H); ^{13}C

(19) Density Functional Theory (DFT) calculations were performed using the Jaguar electronic structure program (Jaguar 4.0, Schrodinger, Inc., Portland, Oregon, 2000). The BLYP pure density functional was chosen, as it provides geometries similar to those of the more accurate B3LYP hybrid functional but with a substantial savings in computertime. The copper atom was given the LACVP effective core potential basis, the phosphorous atoms the polarised double-ζ 6-31G* basis, and the remaining atoms the double-ζ 6-31G basis. After convergence of the geometries the stability of the minima was tested by re-optimization after small displacements had been made in the coordinates, and it was confirmed that the same structures were recovered.

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(29) Benzyldiphenylphosphine was handled in a glovebox (air sensitive).

NMR δ 169.1, 155.6, 152.6, 146.9, 109.2, 106.5, 62.0, 61.3, 52.0, 14.4, 14.0, 13.5; $[\alpha]^{rt}_D = -73.6$ ($c = 0.25$ in $CHCl_3$) (73% ee); GC (Chiraldex G-TA, 70−140 °C (10 °C/min), 140−145 °C (1 °C/min) then 145 °C isotherm) $t_R = 34.27$ min (major enantiomer), $t_R = 35.72$ min (minor enantiomer); HRMS $C_{12}H_{17}NO_5$ $[M + Na]^+$ calcd 278.1004, found 278.1000.

Benzyloxycarbonylamino(5-methylfuran-2-yl)acetic acid ethyl ester 5d: ^{1}H NMR δ 7.40−7.30 (m, 5H), 6.22 (d, ^3J(H,H) = 2.6 Hz, 1H), 5.92−5.91 (m, 1H), 5.72 (bd, ^3J(H,H) = 8.1 Hz, 1H), 5.43 (d, ^3J(H,H) = 8.2 Hz, 1H), 5.12 (s, 2H), 4.29−4.14 (m, 2H), 2.25 (s, 3H), 1.25 (t, ^3J(H,H) = 7.1 Hz, 3H); ^{13}C NMR δ 169.0, 155.4, 152.7, 146.7, 136.1, 128.5, 128.2, 128.1, 109.3, 106.6, 67.1, 62.1, 52.1, 14.0, 13.5; $[\alpha]^{rt}_D = -84.4$ ($c = 1.0$ in $CHCl_3$) (79% ee); HPLC (Daciel Chiralcel OD, hexane/2-propanol 97/3, 1 mL/min) $t_R = 17.0$ min (minor enantiomer), $t_R = 25.9$ min (major enantiomer); HRMS $C_{17}H_{19}NO_5$ $[M + Na]^+$ calcd 340.1161, found 340.1164.

Methoxycarbonylamino(5-methylfuran-2-yl)acetic acid ethyl ester 5e: ^{1}H NMR δ 6.20 (d, ^3J(H,H) = 2.8 Hz, 1H), 5.90−5.89 (m, 1H), 5.68 (bd, ^3J(H,H) = 7.2 Hz, 1H), 5.40 (d, ^3J(H,H) = 8.3 Hz, 1H), 4.28−4.15 (m, 2H), 3.67 (s, 3H), 2.23 (s, 3H), 1.24 (t, ^3J(H,H) = 7.0 Hz, 3H); ^{13}C NMR δ 169.1, 156.0, 152.6, 146.8, 109.2, 106.5, 62.0, 52.4, 52.1, 14.0, 13.5; $[\alpha]^{rt}_D = -103.4$ ($c = 1.0$ in $CHCl_3$) (81% ee); GC (Chiraldex B-PM, 70 °C (isotherm 5 min), 70−150 °C (2 °C/min) then 150 °C isotherm) $t_R = 45.44$ min (minor enantiomer), $t_R = 45.72$ min (major enantiomer); HRMS $C_{11}H_{15}NO_5$ $[M + Na]^+$ calcd 264.0848, found 264.0849.

Methoxycarbonylamino(5-methylfuran-2-yl)acetic acid benzyl ester 5f: ^{1}H NMR δ 7.34−7.25 (m, 5H), 6.20 (d, ^3J(H,H) = 3.2 Hz, 1H), 5.91−5.90 (m, 1H), 5.64 (bd, ^3J(H,H) = 8.3 Hz, 1H), 5.49 (d, ^3J(H,H) = 8.2 Hz, 1H), 5.25−5.17 (m, 2H), 3.69 (s, 3H), 2.23 (s, 3H); ^{13}C NMR δ 169.0, 156.1, 152.7, 146.6, 135.2, 128.5, 128.3, 127.9, 109.5, 106.6, 67.5, 52.5, 52.2, 13.5; $[\alpha]^{rt}_D = -45.2$ ($c = 0.25$ in $CHCl_3$) (55% ee); HPLC (Daicel Chiralpak AS, hexane/2-propanol 97/3, 1 mL/min) $t_R = 17.6$ min (minor enantiomer), $t_R = 27.8$ min (major enantiomer); HRMS $C_{16}H_{17}NO_5$ $[M + Na]^+$ calcd 326.1004, found 326.1003.

Methoxycarbonylamino(5-methylfuran-2-yl)acetic acid isopropyl ester 5g: ^{1}H NMR δ 6.19 (d, ^3J(H,H) = 3.2 Hz, 1H), 5.91−5.89 (m, 1H), 5.64 (bd, ^3J(H,H) = 7.0 Hz, 1H), 5.37 (d, ^3J(H,H) = 8.3 Hz, 1H), 5.07 (sep, ^3J(H,H) = 6.3 Hz, 1H), 3.69 (s, 3H), 2.24 (s, 3H), 1.26 (d, ^3J(H,H) = 6.3 Hz, 3H), 1.18 (d, ^3J(H,H) = 6.2 Hz, 3H); ^{13}C NMR δ 168.6, 156.1, 152.5, 147.0, 109.1, 106.5, 69.8, 52.4, 52.2, 21.6, 21.4, 13.5; $[\alpha]^{rt}_D = -70.4$ ($c = 0.5$ in $CHCl_3$) (79% ee); GC (Chiraldex B-PM, 70−140 °C (10 °C/min), 140−160 °C (2 °C/min) then 160 °C isotherm) $t_R = 16.11$ min (minor enantiomer), $t_R = 16.35$ min (major enantiomer); HRMS $C_{12}H_{17}NO_5$ $[M + Na]^+$ calcd 278.1004, found 278.1006.

Methoxycarbonylamino(5-methylfuran-2-yl)acetic acid methyl ester 5h: ^{1}H NMR δ 6.21 (d, ^3J(H,H) = 3.2 Hz, 1H), 5.91−5.90 (m, 1H), 5.69 (bd, ^3J(H,H) = 6.9 Hz, 1H), 5.42 (d, ^3J(H,H) = 8.2 Hz, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 2.24 (s, 3H); ^{13}C NMR δ 169.6, 156.0, 152.7, 146.6, 109.4, 106.5, 52.9, 52.4, 51.9, 13.4; $[\alpha]^{rt}_D = -123.0$ ($c = 1$ in $CHCl_3$) (87% ee); HPLC (Daicel Chiralpak AS, hexane/2-propanol 97/3, 1 mL/min) $t_R = 19.2$ min (minor enantiomer), $t_R = 25.2$ min (major enantiomer); HRMS $C_{10}H_{13}NO_5$ $[M + Na]^+$ calcd 250.0691, found 250.0692.

(5-Ethylfuran-2-yl)methoxycarbonylaminoacetic acid methyl ester 5i: ^{1}H NMR δ 6.22 (d, ^3J(H,H) = 2.4 Hz, 1H), 5.92−5.91 (m, 1H), 5.68 (bd, ^3J(H,H) = 6.9 Hz, 1H), 5.43 (d, ^3J(H,H) = 8.6 Hz, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 2.58 (q, ^3J(H,H) = 7.5 Hz, 2H), 1.18 (d, ^3J(H,H) = 7.4 Hz, 3H); ^{13}C NMR δ 169.6, 158.4, 156.0, 146.4, 109.1, 104.9, 52.9, 52.4, 52.0, 21.2, 11.8; $[\alpha]^{rt}_D = -131$ ($c = 0.5$ in $CHCl_3$) (88% ee); HPLC (Daicel Chiralpak AS, hexane/2-propanol 95/5, 1 mL/min) $t_R = 12.5$ min (minor enantiomer), $t_R = 15.2$ min (major enantiomer); HRMS $C_{11}H_{15}NO_5$ $[M + Na]^+$ calcd 264.0848, found 264.0847.

(5-*tert*-Butylfuran-2-yl)methoxycarbonylaminoacetic acid methyl ester 5j: ^{1}H NMR δ 6.21 (d, ^3J(H,H) = 2.8 Hz, 1H), 5.91 (d, ^3J(H,H) = 5.9 Hz, 1H), 5.59 (bd, ^3J(H,H) = 6.5 Hz, 1H), 5.46 (d, ^3J(H,H) = 7.3 Hz, 1H), 3.77 (s, 3H), 3.71 (s, 3H), 1.24 (s, 9H); ^{13}C NMR δ 169.7, 164.8, 156.1, 146.3, 108.8, 102.9, 52.9, 52.5, 52.1, 32.6, 28.9; $[\alpha]^{rt}_D = -132.0$ ($c = 1$ in $CHCl_3$) (95% ee); GC (Chiraldex B-PM, 70−110 °C (5 °C/min), 110 °C isotherm (10 min), 110−160 (2 °C/min) then 160 °C isotherm: $t_R = 41.00$ min (major enantiomer), $t_R = 41.32$ min (minor enantiomer); HRMS $C_{13}H_{19}NO_5$ $[M + Na]^+$ calcd 292.1161, found 292.1165.

(5-Benzylfuran-2-yl)methoxycarbonylaminoacetic acid methyl ester 5k: ^{1}H NMR δ 7.32−7.19 (m, 5H), 6.25 (d, ^3J(H,H) = 3.2 Hz, 1H), 5.91 (d, ^3J(H,H) = 3.0 Hz, 1H), 5.64 (bd, ^3J(H,H) = 7.5 Hz, 1H), 5.46 (d, ^3J(H,H) = 8.3 Hz, 1H), 3.93 (s, 2H), 3.75 (s, 3H), 3.69 (s, 3H); ^{13}C NMR δ 169.5, 156.0, 155.3, 147.3, 137.5, 128.7, 128.5, 126.6, 109.4, 107.3, 52.9, 52.5, 52.0, 34.4; $[\alpha]^{rt}_D = -132.0$ ($c = 1$ in $CHCl_3$) (95% ee); HPLC (Daicel Chiralpak AS, hexane/2-propanol 95/5, 1 mL/min) $t_R = 18.3$ min (minor enantiomer), $t_R = 25.7$ min (major enantiomer); HRMS $C_{16}H_{17}NO_5$ $[M + Na]^+$ calcd 326.1004, found 326.1005.

Methoxycarbonylamino[5-(4-methoxyphenyl)furan-2-yl]acetic acid methyl ester 5l: ^{1}H NMR δ 7.53 (dt, J(H,H) = 8.7 Hz, 2.5 Hz, 2H), 6.88 (d, ^3J(H,H) = 9.3 Hz, 2H), 6.44 (d, ^3J(H,H) = 3.4 Hz, 1H), 5.40 (d, ^3J(H,H) = 3.0 Hz, 1H), 5.88 (bd, ^3J(H,H) = 7.7 Hz, 1H), 5.55 (d, ^3J(H,H) = 8.1 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.69 (s, 3H); ^{13}C NMR δ 169.4, 159.2, 156.0, 154.3, 147.2, 125.2, 123.2, 114.0, 110.6, 104.1, 55.2, 52.9, 52.4, 52.0; $[\alpha]^{rt}_D = -108$ ($c = 1.0$ in $CHCl_3$) (74% ee); HPLC (Daicel Chiralpak AS, hexane/2-propanol 95/5, 1 mL/min) $t_R = 29.3$ min (minor enantiomer), $t_R = 39.1$ min (major enantiomer); HRMS $C_{16}H_{17}NO_6$ $[M + Na]^+$ calcd 342.0954, found 342.0955.

Methoxycarbonylamino(5-methoxyfuran-2-yl)acetic acid methyl ester 5m: ^{1}H NMR δ 6.21 (d, ^3J(H,H) = 3.1 Hz, 1H), 5.69 (bd, ^3J(H,H) = 8.2 Hz, 1H), 5.34 (d, ^3J(H,H) = 8.2 Hz, 1H), 5.07 (d, ^3J(H,H) = 3.44 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.66 (s, 3H); ^{13}C NMR δ 169.3, 161.5, 156.0, 138.3, 110.2, 80.2, 57.7, 52.9, 52.4, 51.9; $[\alpha]^{rt}_D = -114$ ($c = 1$ in $CHCl_3$) (96% ee); HPLC (Daicel Chiralpak AS, hexane/2-propanol 90/10, 1 mL/min) $t_R = 23.9$ min (minor enantiomer), $t_R = 28.7$ min (major enantiomer); HRMS $C_{10}H_{13}NO_6$ $[M + Na]^+$ calcd 266.0641, found 266.0633.

Methoxycarbonylamino(4-methylfuran-2-yl)acetic acid methyl ester 5n: ^{1}H NMR δ 7.24 (s, 1H), 6.20 (s, 1H) 5.78 (bd, ^3J(H,H) = 7.4 Hz, 1H), 5.48 (d, ^3J(H,H) = 8.3 Hz, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 2.08 (s, 3H); ^{13}C NMR δ 169.6, 156.1, 143.8, 141.8, 118.4, 113.3, 52.9, 52.4, 49.8, 9.5; $[\alpha]^{rt}_D = -124.0$ ($c = 1.0$ in $CHCl_3$) (72% ee); HPLC (Daicel Chiralpak AD, hexane/2-propanol 95/5, 1 mL/min) $t_R = 12.4$ min (major enantiomer); $t_R = 14.9$ min (minor enantiomer); HRMS $C_{11}H_{15}NO_5$ $[M + Na]^+$ calcd 250.0691, found 250.0690.

(4,5-Dimethylfuran-2-yl)methoxycarbonylaminoacetic acid methyl ester 5o: ^{1}H NMR δ 6.11 (s, 1H), 5.68 (bd, ^3J(H,H) = 7.2 Hz, 1H), 5.37 (d, ^3J(H,H) = 8.2 Hz, 1H), 3.75 (s, 3H), 3.67 (s, 3H), 2.14 (s, 3H), 1.88 (s, 3H); ^{13}C NMR δ 169.6, 156.0, 148.0, 145.3, 114.9, 111.7, 52.9, 52.4, 51.9, 11.2, 9.9; $[\alpha]^{rt}_D = -130.0$ ($c = 1$ in $CHCl_3$) (84% ee); GC (Chiraldex B-PM, 70−110 °C (5 °C/min), 110−160 °C (2 °C/min) then 160 °C isotherm) $t_R = 40.73$ min (minor enantiomer), $t_R = 40.92$ min (major enantiomer); HRMS $C_{11}H_{15}NO_5$ $[M + Na]^+$ calcd 264.0848, found 264.0845.

Methoxycarbonylamino(5-methoxythiophen-2-yl)acetic acid methyl ester 5p: ^{1}H NMR δ 6.65 (d, ^3J(H,H) = 3.7 Hz, 1H), 5.07 (d, ^3J(H,H) = 4.3 Hz, 1H), 5.71 (bd, ^3J(H,H) = 7.1 Hz, 1H), 5.43 (d, ^3J(H,H) = 7.7 Hz, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 3.67 (s, 3H); ^{13}C NMR δ 170.5, 166.5, 155.8, 124.1, 124.0, 103.2, 60.1, 53.9, 52.9, 52.4; $[\alpha]^{rt}_D = -131$ ($c = 1$ in $CHCl_3$) (94% ee); HPLC (Daicel Chiralpak AS, hexane/2-propanol 90/10, 1 mL/min) $t_R = 21.8$ min (minor enantiomer), $t_R = 43.1$ min (major enantiomer); HRMS $C_{10}H_{13}NO_5S$ $[M + Na]^+$ calcd 282.0412, found 282.0416.

[5-(4-Dimethylaminophenyl)thiophen-2-yl]methoxycarbonylaminoacetic acid methyl ester 5q: ^{1}H NMR δ 7.42 (d, ^3J(H,H) = 8.5 Hz, 2H), 6.99−6.96 (m, 2H), 6.70 (d, ^3J(H,H) = 8.8 Hz, 2H), 5.76 (bd, ^3J(H,H) = 7.6 Hz, 1H), 5.61 (d, ^3J(H,H) = 7.8 Hz, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 2.98 (s, 6H); ^{13}C NMR δ 170.6, 155.9, 150.0, 146.0, 135.3, 127.1, 126.7, 122.1, 120.4,

112.3, 53.6, 53.0, 52.5, 40.3; $[\alpha]^{rt}_D = -144$ ($c = 1.0$ in $CHCl_3$) (94% ee); HPLC (Daicel Chiralpak AS, hexane/2-propanol 90/10, 1 mL/min) $t_R = 23.0$ min (minor enantiomer), $t_R = 29.7$ min (major enantiomer); mp 141−144 °C; HRMS $C_{17}H_{20}N_2O_4S$ $[M + Na]^+$ calcd 371.1041, found 371.1037.

Methoxycarbonylamino(1-methyl-1*H*-pyrrol-2-yl)acetic acid methyl ester 5r: ^{1}H NMR δ 6.60 (t, ^3J(H,H) = 2.3 Hz, 1H), 6.06−6.02 (m, 2H), 5.50−5.44 (m, 2H), 3.75 (s, 3H), 3.68 (s, 3H), 3.66 (s, 3H); ^{13}C NMR δ 170.8, 156.1, 126.9, 123.6, 107.6, 107.3, 52.7, 52.4, 50.3, 33.9; $[\alpha]^{rt}_D = -82$ ($c = 1.0$ in $CHCl_3$) (59% ee); HPLC (Daicel Chiralpak AS, hexane/2-propanol 90/10, 1 mL/min) $t_R = 16.4$ min (minor enantiomer), $t_R = 23.9$ min (major enantiomer); HRMS $C_{10}H_{14}N_2O_4$ $[M + Na]^+$ calcd 249.0851, found 249.0817.

(4-Dimethylaminophenyl)methoxycarbonylaminoacetic acid methyl ester 7a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, ^3J(H,H) = 8.6 Hz, 2H), 6.65 (d, ^3J(H,H) = 8.6 Hz, 2H), 5.61 (bd, ^3J(H,H) = 5.8 Hz, 1H), 5.22 (d, ^3J(H,H) = 7.0 Hz, 1H), 3.68 (s, 3H), 3.64 (s, 3H), 2.91 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 155.9, 150.4, 127.9, 123.6, 112.3, 57.3, 52.5, 52.2, 40.3; $[\alpha]^{rt}_D = -146.3$ ($c = 0.8$ in $CHCl_3$) (98% ee); HPLC (Daciel Chiralcel OD, hexane/2-propanol 90/10, 1 mL/min) $t_R = 17.2$ min (minor enantiomer), $t_R = 22.8$ min (major enantiomer); HRMS $C_{13}H_{18}N_2O_4$ $[M + Na]^+$ calcd 289.1164, found 289.1168.

[4-(2,5-Dihydropyrrol-1-yl)phenyl]methoxycarbonylaminoacetic acid methyl ester 7b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, ^3J(H,H) = 8 Hz, 2H), 6.46 (d, ^3J(H,H) = 8 Hz, 2H), 5.19 (s, 2H), 5.60 (bd, ^3J(H,H) = 6.6 Hz, 1H), 5.21 (d, ^3J(H,H) = 7.0 Hz, 1H), 4.07 (s, 4H), 3.69 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1; 156.0, 147.1, 128.3, 126.2, 122.9, 111.3, 57.5, 54.3, 52.6, 52.3; $[\alpha]^{rt}_D = -112.6$ ($c = 1.0$ in $CHCl_3$) (88% ee); HPLC (Daciel Chiralpak AD, hexane/2-propanol 95/5, 1 mL/min) $t_R = 31.8$ min (minor enantiomer), $t_R = 38.8$ min (major enantiomer); mp = 112−114 °C; HRMS $C_{15}H_{18}N_2O_4$[M + Na]$^+$ calcd 313.1164, found 313.1161.

(4-Dimethylamino-2-methoxyphenyl)methoxycarbonylaminoacetic acid methyl ester 7c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, ^3J(H,H) = 8.5 Hz, 1H), 6.23 (dd, ^3J(H,H) = 8.5, 2.3 Hz, 1H), 6.17 (d, ^3J(H,H) = 2.3 Hz, 1H) 5.76 (bd, ^3J(H,H) = 8.5 Hz, 1H), 5.36 (d, ^3J(H,H) = 8.5 Hz, 1H), 3.78 (s, 3H), 3.65 (s, 3H), 3.63 (s, 3H), 2.93 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 169.8, 157.7, 156.4, 152.0, 130.6, 113.2, 104.3, 95.6, 55.2, 54.4, 53.1, 52.5, 40.4; $[\alpha]^{rt}_D = -131.0$ ($c = 1$ in $CHCl_3$) (96% ee); HPLC (Daciel Chiralcel OD, hexane/2-propanol 85/15, 1 mL/min) $t_R = 14.5$ min (minor enantiomer), $t_R = 34.1$ min (major enantiomer); mp = 124−126 °C; HRMS $C_{14}H_{20}N_2O_5$ $[M + Na]^+$ calcd 319.1270, found 319.1266.

Ethoxycarbonylamino(1-methyl-2,3-dihydro-1*H*-indol-5-yl)acetic acid Methyl Ester 7d. See ref 11.

Methoxycarbonylamino(1-methyl-1,2,3,4-tetrahydroquinolin-6-yl)acetic acid methyl ester 7e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, ^3J(H,H) = 8.6 Hz, 1H), 6.89 (s, 1H), 6.49 (d, ^3J(H,H) = 8.6 Hz, 1H), 5.58 (bd, ^3J(H,H) = 7.0 Hz, 1H), 5.16 (d, ^3J(H,H) = 7.0 Hz, 1H), 3.69 (s, 3H), 3.64 (s, 3H), 3.19 (t, ^3J(H,H) = 5.6 Hz, 2H), 2.84 (s, 3H), 2.71 (t, ^3J(H,H) = 6.2 Hz, 2H), 1.95−1.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 155.9, 146.8, 127.5, 125.9, 123.7, 122.9, 110.7, 57.4, 52.5, 52.2, 51.0, 38.8, 27.6, 22.0; $[\alpha]^{rt}_D = -130.1$ ($c = 1$ in $CHCl_3$) (92% ee); HPLC (Daciel Chiralcel OD, hexane/2-propanol 85/15, 1 mL/min) $t_R = 11.4$ min (minor enantiomer), $t_R = 17.2$ min (major enantiomer); HRMS $C_{15}H_{20}N_2O_4$ $[M + Na]^+$ calcd 315.1321, found 315.1326.

Methoxycarbonylamino(4-methyl-3,4-dihydro-2*H*-benzo[1,4]oxazin-7-yl)acetic acid methyl ester 7f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (d, ^3J(H,H) = 8.2 Hz, 1H), 6.72 (d, ^3J(H,H) = 2.0 Hz, 1H), 6.58 (d, ^3J(H,H) = 8.2 Hz, 1H), 5.58 (bd, ^3J(H,H) = 7.0 Hz, 1H), 5.17 (d, ^3J(H,H) = 7.0 Hz, 1H), 4.25 (t, ^3J(H,H) = 4.3 Hz, 2H) 3.70 (s, 3H), 3.64 (s, 3H), 3.23 (t, ^3J(H,H) = 4.7 Hz, 2H), 2.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 160.0, 144.2, 136.8, 125.7, 120.4, 114.4, 112.4, 64.8, 57.3, 52.6, 52.3, 48.8, 38.8; $[\alpha]^{rt}_D = -49.0$ ($c = 1$ in $CHCl_3$) (67% ee); HPLC (Daciel Chiralcel OD, hexane/2-propanol 90/10, 1 mL/min) $t_R = 43.8$ min (minor enantiomer), $t_R = 54.2$ min (major enantiomer); HRMS $C_{14}H_{18}N_2O_5$ $[M + Na]^+$ calcd 317.1113, found 317.1118.

(4-Dimethylaminonaphthalen-1-yl)ethoxycarbonylaminoacetic Acid Methyl Ester 7g. See ref 11.

(4-Dimethylaminoanthracen-1-yl)ethoxycarbonylaminoacetic Acid Methyl Ester 7h. See ref 11.

(4-Aminophenyl)methoxycarbonylaminoacetic Acid Methyl Ester 8. To a flame-dried flask was added iodosobenzene (435 mg, 1.98 mmol) and the mixture stirred under vacuum for 1 h at room temperature before CH_2Cl_2 (6.6 mL) was added and the suspension cooled to −40 °C. Compound **7a** (132 mg, 0.5 mmol) and azidotrimethylsilane (0.26 mL, 1.98 mmol) were added, and the resulting mixture was stirred vigorously for 3 h, poured directly into ice−water (50 mL), and subsequently extracted with CH_2Cl_2 (3 × 15 mL). The organic extract was concentrated in vacuo to half the volume, THF (22.5 mL) and saturated aqueous $NaHCO_3$ (22.5 mL) were added, and the mixture was stirred for 48 h before being neutralized by 1 M aqueous HCl. The organic solvents were removed in vacuo, and the aqueous fraction was extracted with CH_2Cl_2 (3 × 15 mL). Drying of the organic extracts over Na_2SO_4 afforded the crude product, which was purified by FC (EtOAc/pentane 1:1) to give **8** in 78% isolated yield as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, ^3J(H,H) = 7.8 Hz, 2H), 6.54 (d, ^3J(H,H) = 7.8 Hz, 2H), 5.65 (bd, ^3J(H,H) = 6.2 Hz, 1H), 5.14 (d, ^3J(H,H) = 7.0 Hz, 1H), 3.62 (s, 3H), 3.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 156.0, 146.7, 128.2, 125.9, 115.1, 57.3, 52.5, 52.2. $[\alpha]^{rt}_D = -96.2$ ($c = 1$ in $CHCl_3$); HRMS $C_{11}H_{14}N_2O_4$ $[M + Na]^+$ calcd 261.0851, found 261.0851.

Methoxycarbonylaminophenylacetic Acid Methyl Ester 9. A dry flask under argon atmosphere was charged with $NOBF_4$ (24 mg, 0.20 mmol) and CH_2Cl_2 (10 mL). Compound **8** (45 mg, 0.19 mmol) dissolved in CH_2Cl_2 (4 mL) was added dropwise at 0 °C and stirred for 35 min. The diazonium salt was treated with saturated aqueous H_3PO_2 (0.16 mL) and a catalytic amount of Cu_2O (4 mg). Saturated aqueous $NaHCO_3$ was added until basic pH and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic phases were dried over $MgSO_4$, and the solvent was removed in vacuo. Purification by FC (EtOAc/hexane 1:2) gave the title compound as a crystalline solid in 83% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.30 (m, 5H), 5.74 (bd, ^3J(H,H) = 6.6 Hz, 1H), 5.34 (d, ^3J(H,H) = 7.4 Hz, 1H), 3.70 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 155.9, 136.5, 126.8, 128.5, 127.1, 57.8, 52.7, 52.3; $[\alpha]^{rt}_D = -46.8$ ($c = 1$ in $CHCl_3$) (88% ee); HPLC (Daciel Chiralcel OD, hexane/2-propanol 90/10, 1 mL/min) $t_R = 26.4$ min (minor enantiomer), $t_R = 32.1$ min (major enantiomer); mp = 88−88.5 °C; HRMS $C_{11}H_{13}NO_4$ $[M + Na]^+$ calcd 246.0742, found 246.0741.

Amino-(4-(dimethylamino)phenyl)acetic acid methyl ester 11. See ref 11.

(5-Benzylidene-2,5-dihydrofuran-2-yl)methoxycarbonylaminoacetic acid methyl ester 14: ^{1}H NMR δ 7.51 (d, ^3J(H,H) = 7.7 Hz, 2H), 7.29 (t, ^3J(H,H) = 7.7 Hz, 2H), 7.13 (t, ^3J(H,H) = 7.5 Hz, 1H), 6.34 (dd, J(H,H) = 5.9 Hz, 2.3 Hz, 1H), 6.24 (dd, J(H,H) = 5.8 Hz, 1.6 Hz, 1H), 5.82 (m, 1H), 5.40 (s, 1H), 5.29 (bd, ^3J(H,H) = 8.7 Hz, 1H), 4.75 (dd, J(H,H) = 9.4 Hz, 2.0 Hz, 1H), 3.89 (s, 3H), 3.65 (s, 3H); ^{13}C NMR δ 169.6, 159.1, 156.7, 135.9, 130.5, 129.6, 128.3, 127.7, 125.5, 99.8, 89.5, 56.3, 53.0, 52.5; $[\alpha]^{rt}_D = -524.8$ ($c = 0.5$ in $CHCl_3$) (99.9% ee); HPLC (Daicel Chiralpak AS, hexane/2-propanol 90/10, 1 mL/min) $t_R = 10.1$ min (minor enantiomer), $t_R = 12.8$ min (major enantiomer); mp 91−93 °C; HRMS $C_{16}H_{17}NO_5$ $[M + Na]^+$ calcd 326.1004, found 326.1006.

X-ray Work. Crystals of **12**, $C_{15}H_{17}NO_5S$, are orthorhombic, $P2_12_12$, with unit cell: $a = 5.116(3)$ Å, $b = 16.909(10)$ Å, $c = 17.746(11)$ Å, $V = 1535(2)$ Å^3, $Z = 4$. Data collected at 120K on a SMART diffractometer with CCD detector. The structure

solved by direct methods[30] and refined by least-squares methods to final $R = 0.083$, $R_w = 0.079$, GOF = 1.33 using 1604 reflections with $I > 2\sigma(I)$, including 547 Bijvoet pairs. The crystals were tiny needles with poor diffracting power, but the absolute configuration was determined by least-squares refinement of the Rogers' factor,[31] which is expected to be 1 for the correct hand, −1 for the wrong hand; the result was 1.9(5), which is (although not ideal) enough to decide the chirality unambiguously.

Crystals of **14**, $C_{16}H_{17}NO_5$, are monoclinic, $P2_1$, with unit cell: $a = 5.767(2)$ Å, $b = 29.913(9)$ Å, $c = 9.307(3)$ Å, $\beta = 108.022(4)$, $V = 1527(1)$ Å^3, $Z = 4$. Data were collected at 120K on a SMART diffractometer with CCD detector. The structure solved by direct methods and refined by least-squares methods to final $R = 0.102$, $R_w = 0.114$, GOF = 1.89 using 3505 reflections with $I > 3\sigma(I)$. Crystals were thin, intergrown, twinned needles. The two molecules in the asymmetric unit are related by a local 2-fold axis, giving rise to pseudo-orthorhombic twinning. The twin ratio was refined to 1.98 for the present crystal. The pseudosymmetry gave rise to correlations making anisotropic refinement impossible.

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Supporting Information Available: Deprotection and assignment of the absolute configuration of **5h**. Complete X-ray data for compounds **12** and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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