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Suppression of racemization in the carbonylation of amino acid-derived aryl triflates

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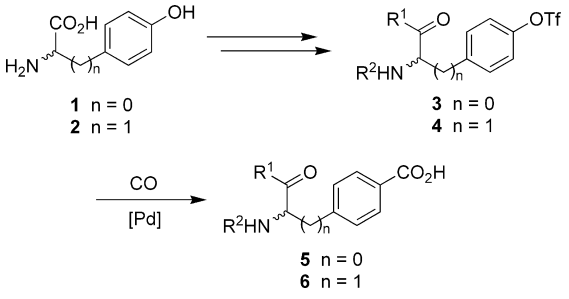
Abstract—The carbonylation of enantiopure phenylglycine-derived aryl triflates was achieved to afford 4-carboxyphenylglycine analogs with high enantiomeric excesses (88 to >99% ee). Amide analogs of phenylglycine were well-tolerated in the hydroxy- and methoxycarbonylation processes, providing efficient access to benzoic acid and ester building blocks. The % ee of the product was dependent on the relative steric bulk of both the amino acid substrate and the requisite amine base, with $^{i}Pr_2NEt$ proving optimal in minimizing product racemization.

The palladium-catalyzed carbonylation of aryl triflates was first published 20 years ago[1] and has since become a common strategy to access benzoate derivatives from phenols. The scope of this reaction includes the carbonylation of triflates derived from tyrosine analogs[2] (Scheme 1), and these conditions can successfully convert an enantiomerically pure tyrosine triflate **4** into the corresponding 4-carboxyphenylalanine derivative **6** with complete retention of enantiopurity. With the accessibility of D- and L-tyrosine ((***R***)-**2** and (***S***)-**2**), this method represents a useful approach to enantiopure 4-carboxyphenylalanines and has been used in the synthesis of molecules with various biological properties[3] as well as for large scale preparation.[4]



Scheme 1. Carbonylation route to 4-carboxyphenylalanine and 4-carboxyphenylglycine derivatives.

During the course of an ongoing medicinal chemistry program, we required access to various 4-carboxyphenylglycine intermediates **5** as single enantiomers. Numerous methods for producing enantiopure phenylglycine derivatives have been reported, including a plethora of biocatalyzed processes[5] and more traditional synthetic organic approaches.[6,7] However, since D- and L-4-hydroxyphenylglycine ((***R***)-**1** and (***S***)-**1**) are readily available commercial products, it was hoped that the target compounds might be accessed via a carbonylation approach employing aryl triflate derivatives (**3**, Scheme 1). This route represents a more direct protocol than existing methods, as it avoids the addition and removal of chiral auxiliaries and reduces the number of protecting group manipulations. It was anticipated that the application of this methodology to phenylglycine analogs might be complicated by racemization resulting from the acidity of the benzylic proton. Nonetheless, the required triflates were synthesized according to Scheme 2 and were obtained in high enantiomeric excess (>99% ee in most cases). Firstly, the amino acids were protected as *N*-Boc intermediates[8] **7** and **8**. Functionalization of the acids to the required amides **9a**–**e** and **10b** was achieved using EDC and HOBt. The enantiomers of methyl ester **9f** were produced by methylation with TMS–diazomethane. Facile conversion of the phenols to the required triflates **11a**–**f** and **12b** using $PhNTf_2$ completed the synthesis.

Keywords: Carbonylation; Carboxyphenylglycine; Aryl triflates; Steric effect; Amino acids.
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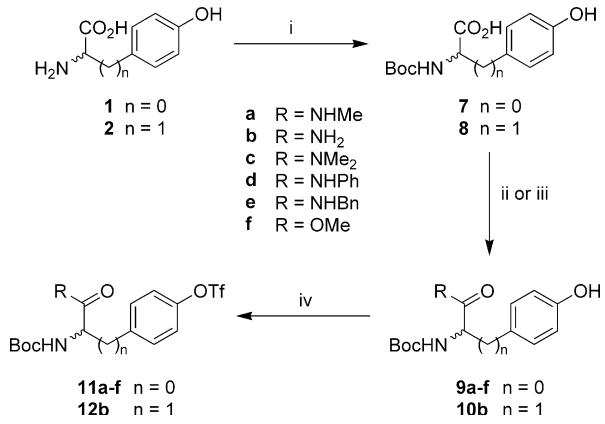
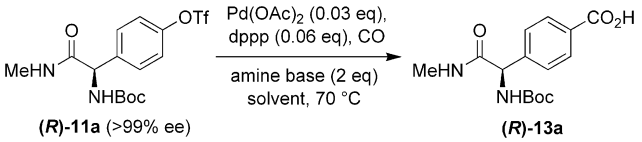


Scheme 2. Reagents and conditions: (i) Boc_2O, 1,4-dioxane, 1 N NaOH, rt; (ii) $R = NR^1R^2$: amine, EDC, HOBt, DMF, rt or amine·HCl, EDC, HOBt, $^iPr_2NEt$, DMF, rt; (iii) R = OMe: TMS–diazomethane, THF, EtOH, rt; (iv) $PhNTf_2$, DCM, rt.

N-Methyl amide (***R***)-**11a** was selected as a model substrate to investigate the carbonylation reaction. Employment of a number of existing literature conditions gave high yields but variable levels of racemization (Table 1). Although the $Pd(OAc)_2$/dppf/KOAc system of Cacchi and Lupi[9] afforded a high yield of acid (***R***)-**13a**, significant racemization occurred during the reaction (entry 1).[10,11] Exclusion of KOAc from the reaction (entry 2) resulted in an increased ee, but a decreased yield. A higher yield and an improved ee resulted from substitution of K_2CO_3 for KOAc and DMF for DMSO (entry 3).[4] Similar results were obtained by using Et_3N with $Pd(OAc)_2$/dppp in DMF/H_2O (entry 4, 90% ee).[2,3d] Given the unacceptable level of racemization still occurring during the carbonylation, we undertook an investigation to minimize racemization and maximize yields for amino acid-derived substrates similar to **11a**.

Using the initial $Pd(OAc)_2$/dppp/Et_3N conditions as a starting point and (***R***)-**11a** as the substrate, we performed a brief screen of solvents, ligand/catalyst ratios, and bases (Table 2). The reactions were performed at 70 °C under a CO balloon until complete (or conversion ceased) by LC/MS. In line with the literature precedent,[2,3,9] dppp was found to be the superior ligand with regards to yield and conversion, though dppf was a comparable substitute. Changes in the ligand:catalyst ratio from the 2:1 ratio shown in Table 2 offered no appreciable advantage in yield, ee, or reaction time. Alteration of the DMF:H_2O solvent ratio had a noticeable effect on the racemization level. A 3:1 ratio (entry 2) was found to be ideal; decreasing or increasing this ratio adversely affected the ee of product **13a** (entries 1 and 3, 80% ee). The use of DMSO (entry 4) in place of DMF had little effect on the yield or ee of the carboxylic acid. Not surprisingly, decreasing the amount of Et_3N from 2 equiv to 1 equiv resulted in an increase in ee from 90% to 96% (entry 5), but the reaction failed to reach completion (77% yield).[12]

Table 2. Screening of hydroxycarbonylation conditions



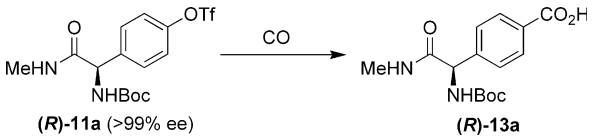
(***R***)-**11a** (>99% ee) (***R***)-**13a**

Entry	Amine base	Solvent system	Yield[a] (%)	ee[b] (%)
1	Et_3N	1:1 DMF:H_2O	87	80
2	Et_3N	3:1 DMF:H_2O	99	90
3	Et_3N	10:1 DMF:H_2O	98	80
4	Et_3N	3:1 DMSO:H_2O	96	88
5	Et_3N[c]	3:1 DMF:H_2O	77	96
6	DABCO	3:1 DMF:H_2O	99	28
7	*N*-Methylpiperidine	3:1 DMF:H_2O	98	66
8	*N*-Methylmorpholine	3:1 DMF:H_2O	73	84
9	$^iPr_2NH$	3:1 DMF:H_2O	99	90
10	$^iPr_2NEt$	3:1 DMF:H_2O	97	>99
11	2,6-Lutidine	3:1 DMF:H_2O	35	98
12	DBU	3:1 DMF:H_2O	<5	N/A

[a] Reactions stirred at 70 °C until complete (or progression ceased) by LC/MS (12–18 h).
[b] Determined by chiral HPLC after conversion of the acids to the methyl esters with trimethylsilyldiazomethane in THF/MeOH.
[c] Using only 1 equiv of base.

The most significant effect on the racemization levels was seen upon changing the base (Table 2, entries 6–12). In our screening of selected amines, DABCO, *N*-methylpiperidine, and *N*-methylmorpholine (entries 6–8) all resulted in lower enantiomeric excesses than Et_3N. While $^iPr_2NH$ was comparable to Et_3N in yield and ee (entry 9), $^iPr_2NEt$ was vastly superior, affording (***R***)-**13a** in >99% ee (entry 10). The employment of

Table 1. Hydroxycarbonylation of triflate (***R***)-**11a**



(***R***)-**11a** (>99% ee) (***R***)-**13a**

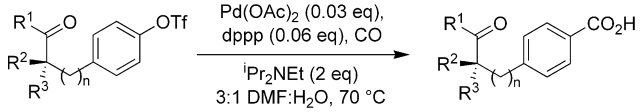
Entry	Conditions[a]	Yield (%)	ee[b] (%)
1	$Pd(OAc)_2$ (0.05 equiv), dppf (0.20 equiv), KOAc (3 equiv), DMSO, 60 °C	93	40
2	$Pd(OAc)_2$ (0.05 equiv), dppf (0.20 equiv), DMSO, 60 °C	26	98
3	$Pd(OAc)_2$ (0.10 equiv), dppf (0.20 equiv), K_2CO_3 (5 equiv), DMF, 60 °C	98	90
4	$Pd(OAc)_2$ (0.03 equiv), dppp (0.06 equiv), Et_3N (2 equiv), DMF/H_2O, 70 °C	99	90

[a] Reactions stirred at indicated temperature until complete by LC/MS (16–24 h).
[b] Determined by chiral HPLC after conversion of the acids to the methyl esters with trimethylsilyldiazomethane in THF/MeOH.

2,6-lutidine (entry 11) or DBU (entry 12) resulted in poor conversion, with the latter yielding only trace product. Examination of the relative amine basicities indicated that there was essentially no correlation between amine pK_a and erosion of product enantiopurity. For example, *N*-methylpiperidine and DABCO are both less basic than Et_3N, yet both racemized the product to a greater extent than Et_3N.[13] This suggested that the degree of racemization was largely determined by the steric bulk surrounding the amine nitrogen. This notion was supported by the excellent result obtained with the bulky $^iPr_2NEt$, as well as the poor enantiopurities achieved with less hindered amines, for example, *N*-methylpiperidine and DABCO.

With these results in mind, the optimized hydroxycarbonylation conditions were applied to a variety of phenylglycine- and phenylalanine-derived aryl triflates (Table 3).[14] For the amide-containing phenylglycine triflates (entries 1–11), the corresponding acids were uniformly obtained in nearly quantitative yields and consistently high enantiopurities when $^iPr_2NEt$ was employed as the base. Tertiary, secondary, and primary amides were well-tolerated in the reaction. Notably, the primary amide (***R***)-**11b** displayed an enhanced disparity in enantiopurity between the Et_3N (entry 3, only 28%) and $^iPr_2$-NEt (entry 4, 92%) runs. Phenylalanine analogs (***R***)- and (***S***)-**12b** (entries 12–13) were also smoothly converted to carboxylic acids with excellent results (>90% yield, >99% ee). The reaction was also found to be highly scalable, as demonstrated by the example performed on a 5 g scale with no appreciable decrease in yield or ee (entry 2). Furthermore, the carboxylic acid products were universally isolated in high purity without chromatography through an aqueous base extraction and acidification protocol. In contrast to the amide analogs, the acid products afforded by carbonylation of phenylglycine ester substrates were obtained as racemic mixtures (e.g., entries 14 and 15). It was not clear whether this resulted from the lower pK_a of the ester α-proton or from the small size of the methyl ester moiety. A future experiment involving larger ester groups (e.g., $CO_2{}^tBu$) in place of the methyl ester could provide more insight into the precise source of this effect.

Table 3. Hydroxycarbonylation of amino acid-derived aryl triflates



11a-f n = 0
12b n = 1 (>99% ee)

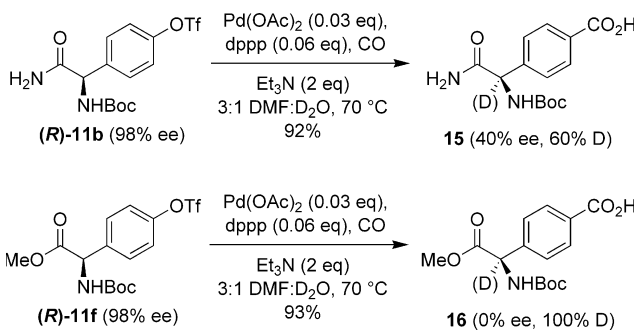
13a-f n = 0
14b n = 1

Entry	R^1	R^2	R^3	*n*	Yield[a] (%)	ee[b] (%)
1	NHMe	NHBoc	H	0	97	>99
2	NHMe	H	NHBoc	0	95[c]	>99
3	NH_2	NHBoc	H	0	93	40[d,e]
4	NH_2	NHBoc	H	0	99	92[d]
5	NH_2	H	NHBoc	0	99	95[d]
6	NMe_2	NHBoc	H	0	97	>99
7	NMe_2	H	NHBoc	0	98	>99
8	NHPh	NHBoc	H	0	99	93
9	NHPh	H	NHBoc	0	99	92
10	NHBn	NHBoc	H	0	98	>99
11	NHBn	H	NHBoc	0	94	>99
12	NH_2	NHBoc	H	1	90	>99
13	NH_2	H	NHBoc	1	92	>99
14	OMe	NHBoc	H	0	98	0
15	OMe	H	NHBoc	0	99	0

[a] Reactions stirred at indicated temperature until complete by LC/MS (12–18 h).
[b] Determined by chiral HPLC after conversion of the acids to the methyl esters with trimethylsilyldiazomethane in THF/MeOH.
[c] Performed on a 5 g scale.
[d] Aryltriflate starting material ee = 98%.
[e] Reaction performed with Et_3N instead of $^iPr_2NEt$.

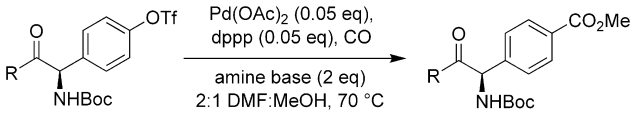
In a preliminary effort to understand the mechanism of racemization, hydroxycarbonylations of selected substrates were performed in the presence of D_2O. Carbonylation of triflate (***R***)-**11b** with Et_3N and D_2O (Scheme 3) gave acid **15** (40% ee) with 60% deuterium incorporation at the benzylic position. This suggested that the transient enolate intermediate was reprotonated by solvent and not immediately quenched by an associated ammonium species (i.e., the protonated base). Likewise, D_2O hydroxycarbonylation of (***R***)-**11f** afforded **16** as a racemate with complete deuterium incorporation.

One of the many benefits of the palladium-catalyzed carbonylation of aryl triflates is the ability to conduct the reaction in the presence of an alcohol (instead of water) to directly form a benzoate ester.[2] Not surprisingly, the same base-dependent racemization effect existed in the methoxycarbonylation of the phenylglycine-derived aryl triflates to form methyl benzoates. Methoxycarbonylation of these substrates with $^iPr_2NEt$ gave, upon flash chromatography, the desired methyl esters in excellent yields and good to excellent enantiomeric excesses (Table 4).[15] For the sake of comparison, methoxycarbonylations of three of the substrates were also performed with the less hindered Et_3N. For the primary amide (***R***)-**11b** (entry 1) and methyl amide (***R***)-**11a** (entry 3), high levels of racemization were seen with Et_3N (18% and 34% ee, respectively). However, methoxycarbonylation of the more hindered dimethylamide triflate (***R***)-**11c** with Et_3N gave a result (>99% ee, entry 5) nearly identical to that obtained with $^iPr_2NEt$ (entry 6). This outcome lended credence to the notion that the steric bulk of both the amine base and the substrate determined the level of racemization in the product. Also of interest was the observation that unlike the



Scheme 3. Hydroxycarbonylations in the presence of D_2O.

Table 4. Methoxycarbonylation of amino acid-derived aryl triflates



(*R*)-**11a-e** (>99% ee) (*R*)-**17a-e**

Entry	R	Amine base	Yield[a] (%)	ee[b] (%)
1	NH_2	Et_3N	72	18[c]
2	NH_2	$^iPr_2NEt$	93	88[c]
3	NHMe	Et_3N	86	34
4	NHMe	$^iPr_2NEt$	97	98
5	NMe_2	Et_3N	92	>99
6	NMe_2	$^iPr_2NEt$	96	>99
7	NHPh	$^iPr_2NEt$	99	93
8	NHBn	$^iPr_2NEt$	88	>99

[a] Reactions stirred at indicated temperature until complete by LC/MS (2–8 h).
[b] Determined by chiral HPLC.
[c] Aryl triflate starting material ee = 98%.

hydroxycarbonylation, the methoxycarbonylation was highly sensitive to the ligand:catalyst ratio. A 1:1 ratio proved to be optimal; higher ligand loadings resulted in sluggish reactions and poor levels of conversion.

In summary, we have developed a convenient and efficient protocol for the synthesis of enantiopure 4-carboxy derivatives of phenylglycine. These useful building blocks can be prepared from the corresponding aryl triflates through a palladium-catalyzed carbonylation. The enantiopurity of the carboxylate products was found to be highly dependent on the steric environment of both the benzylic stereocenter and the amine base. Excellent retention of ee was achieved when the bulky amine $^iPr_2NEt$ was employed in the reaction. This method proved to be effective for a range of substrates and could be performed on multi-gram scale without diminishing yield or chiral purity.

Acknowledgements

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References and notes

1. Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 3931–3934.
2. Dolle, R. E.; Schmidt, S. J.; Kruse, L. I. *J. Chem. Soc., Chem. Commun.* **1987**, 904–905.
3. (a) Wrobel, J.; Dietrich, A. *Tetrahedron Lett.* **1993**, *34*, 3543–3546; (b) Klein, L. L.; Li, L.; Chen, H.-J.; Curty, C. B.; DeGoey, D. A.; Grampovnik, D. J.; Leone, C. L.; Thomas, S. A.; Yeung, C. M.; Funk, K. W.; Kishore, V.; Lundell, E. O.; Wodka, D.; Meulbroek, J. A.; Alder, J. D.; Nilius, A. M.; Lartey, P. A.; Plattner, J. J. *Bioorg. Med. Chem.* **2000**, *8*, 1677–1696; (c) Sundaramoorthi, R.; Siedem, C.; Vu, C. B.; Dalgarno, D. C.; Laird, E. C.; Botfield, M. C.; Combs, A. B.; Adams, S. E.; Yuan, R. W.; Weigele, M.; Narula, S. S. *Biorg. Med. Chem. Lett.* **2001**, *11*, 1665–1669; (d) Chen, L.; Tilley, J.; Trilles, R. V.; Yun, W.; Fry, D.; Cook, C.; Rowan, K.; Schwinge, V.; Campbell, R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 137–140.
4. Cai, C.; Breslin, H. J.; He, W. *Tetrahedron* **2005**, *61*, 6836–6838.
5. Recent examples include, but are by no means limited to: (a) the transamination of phenylglyoxilic acid: Cameron, M.; Cohen, D.; Cottrell, I. F.; Kennedy, D. J.; Roberge, C.; Chartrain, M. *J. Mol. Catal. B: Enzym.* **2001**, *14*, 1–5; (b) the hydration of phenylglycine nitriles: Hensel, M.; Lutz-Wahl, S.; Fischer, L. *Tetrahedron: Asymmetry* **2002**, *13*, 2629–2633; (c) the hydrolysis of phenylglycine trifluoroacetamides: Arnusch, C. J.; Pieters, R. J. *Eur. J. Org. Chem.* **2003**, 3131–3138; (d) the hydrolysis of phenylhydantoins: Wu, S.; Yang, L.; Liu, Y.; Zhao, G.; Wnag, J.; Sun, W. *Enzyme Microb. Technol.* **2005**, *36*, 520–526.
6. For examples of an asymmetric Strecker approach, see: (a) Yet, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 875–877; (b) Prasad, B. A. B.; Bisai, A.; Singh, V. K. *Tetrahedron Lett.* **2004**, *45*, 9565–9567.
7. For examples of an asymmetric reduction approach, see: (a) Versleijen, J. P.; Sanders-Hovens, M. S.; Vanhommerig, S. A.; Vekemans, J. A.; Meijer, E. M. *Tetrahedron* **1993**, *49*, 7793–7802; (b) Micskei, K.; Holczknecht, O.; Hajdu, C.; Patonay, T.; Marchis, V.; Meo, M.; Zucchi, C.; Palyi, G. *J. Organomet. Chem.* **2003**, *682*, 143–148; (c) Kadyrov, R.; Riermeier, T. H.; Dingerdissen, U.; Tararov, V.; Borner, A. *J. Org. Chem.* **2003**, *68*, 4067–4070; (d) Nolin, K. A.; Ahn, R. W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 12462–12463.
8. Hirai, Y.; Yokota, K.; Momose, T. *Heterocycles* **1994**, *39*, 603–612.
9. Cacchi, S.; Lupi, A. *Tetrahedron Lett.* **1992**, *33*, 3939.
10. Because the enantiomers of carboxylic acid products **13a–f** and **14b** were not separable by chiral HPLC, the % ee values correspond to the methyl ester derivatives, obtained by stirring each acid with excess TMS–diazomethane in MeOH/THF for 5 min and subsequent removal of the solvent.
11. *Chiral HPLC conditions:* The following conditions for the *methyl ester* of **13a** (i.e., **17a**) are representative. Chiral column: Chiralpak AD, 4.6 × 250 mm; mobile phase: 40% IPA/60% hexanes, isocratic; flow rate: 0.75 mL/min; UV detector: 254 nm; retention times: 6.02 min (for (***S***) enantiomer), 8.26 min (for (***R***) enantiomer).
12. It was noted that briefly sparging the reaction mixture with CO prior to (rather than after) amine addition gave consistently higher yields. Bubbling the gas through the reaction mixture after addition of the base, even for short periods of time, inevitably resulted in a significant loss of amine.
13. Relevant pK_a values (as reported by the ACD Labs 8.0 pK_a Database from Advanced Chemistry Development): *N*-methylmorpholine 7.4, DABCO 8.1, *N*-methylpiperidine 9.9, Et_3N 10.7, $^iPr_2NEt$ 11.0, $^iPr_2NH$ 11.1.
14. *Hydroxycarbonylation procedure:* The following procedure for (***R***)-**11a** is representative. Triflate (***R***)-**11a** (500 mg, 1.21 mmol), $Pd(OAc)_2$ (8.2 mg, 0.036 mmol), and dppp (30 mg, 0.072 mmol) were taken up in DMF (3 mL), and H_2O (1 mL) was added. After sparging the solution with CO for 10 min, $^iPr_2NEt$ (313 mg, 2.43 mmol) was added. A CO balloon was attached, and the reaction was stirred at 70 °C for 18 h. The mixture was then diluted with EtOAc and extracted with saturated $NaHCO_3$ (2 × 20 mL). The combined aqueous layers were acidified to pH 2 with 1 N HCl and extracted with EtOAc (2 × 40 mL). The combined organic extracts were washed

with water and brine, dried ($MgSO_4$), and evaporated to afford clean acid (***R***)-**13a** (364 mg, 97%) as a colorless solid. ^{1}H NMR (DMSO-d_6, 600 MHz) δ 12.90 (1H, br s), 8.14 (1H, q, $J = 4.7$ Hz), 7.86 (2H, d, $J = 8.2$ Hz), 7.47 (2H, d, $J = 8.3$ Hz), 7.36 (1H, d, $J = 8.5$ Hz), 5.17 (1H, d, $J = 8.5$ Hz), 2.55 (3H, d, $J = 4.6$ Hz), 1.34 (9H, s); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 170.5, 167.7, 155.5, 144.6, 130.6, 130.0, 128.0, 79.2, 58.2, 28.8, 26.4. MS (ESI) Calcd for $C_{15}H_{20}N_2O_5$ $[M+Na]^+$ 331.1. Found: 331.1.

15. *Methoxycarbonylation procedure:* The following procedure for (***R***)-**11a** is representative. Triflate (***R***)-**11a** (500 mg, 1.21 mmol), $Pd(OAc)_2$ (13.6 mg, 0.061 mmol), and dppp (25 mg, 0.061 mmol) were dissolved in a mixture of DMF (4 mL) and MeOH (2 mL). After bubbling CO through the solution for 5 min, ^{i}Pr$_2$NEt (313 mg, 2.43 mmol) was added. A CO balloon was attached, and the reaction was stirred at 70 °C for 5 h. The mixture was subsequently diluted with saturated NH_4Cl and extracted with EtOAc (2×30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to a brown oil. The residue was purified by silica gel chromatography (15–75% EtOAc/hexanes) to afford methyl ester (***R***)-**17a** (381 mg, 97%) as a colorless solid. ^{1}H NMR (DMSO-d_6, 600 MHz) δ 8.15 (1H, q, $J = 4.5$ Hz), 7.89 (2H, d, $J = 8.1$ Hz), 7.50 (2H, d, $J = 8.1$ Hz), 7.38 (1H, d, $J = 8.6$ Hz), 5.19 (1H, d, $J = 8.4$ Hz), 3.81 (3H, s), 2.55 (3H, d, $J = 4.9$ Hz), 1.34 (9H, s); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 170.4, 166.7, 155.5, 145.0, 129.8, 129.4, 128.2, 79.2, 58.2, 52.8, 28.8, 26.4. MS (ESI) Calcd for $C_{16}H_{22}N_2O_5$ $[M+Na]^+$ 345.1. Found: 345.1.