The Heck Reaction of *N*-Protected Vinylglycines with 4-Iodoanisole

Taisuke ITAYA* and Shigeyuki SHIMIZU

Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan.
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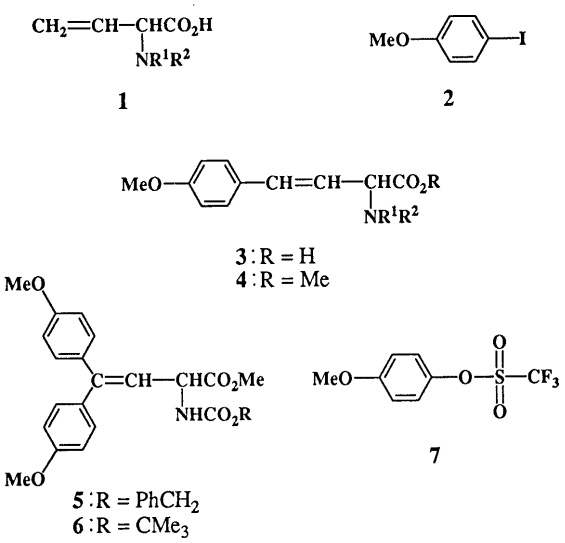
Among *N*-protected and unprotected vinylglycines tested, *N*-(benzyloxycarbonyl)vinylglycine (1c) provided the highest yield of the coupling product 3c in the reaction with 1-iodo-4-methoxybenzene (2) in *N*,*N*-dimethylformamide in the presence of palladium acetate, sodium bicarbonate, and tetrabutylammonium chloride, whereas none of the desired product was obtained in the reaction with 4-methoxyphenyl trifluoromethanesulfonate (7). The stereoselectivity of the reaction was reversed by employing triethylamine instead of sodium bicarbonate to furnish (*Z*)-3c predominantly. In the presence of sodium bicarbonate, replacement of the solvent by water improved not only the chemical yield and stereoselectivity but also the optical purity: geometrically pure (*E*)-3c of 96% ee was formed in a good yield.

Key words (2-arylvinyl)glycine synthesis; palladium-catalyzed arylation; stereoselectivity; solvent effect; base effect

Chiral synthesis of (2-arylvinyl)glycine derivatives is a challenging problem because of their marked tendency to racemization.[1] We have accomplished the synthesis of this class of compounds through the Wittig reaction[1,2] or the Heck reaction[3] as the key step. The latter method, which utilizes vinylglycine as a chiral synthon[4] attracted the attention of Australian chemists: they obtained coupling products of (*S*)-*N*-(benzyloxycarbonyl)vinylglycine [(*S*)-**1c**] with five endocyclic vinyl and two 2-naphthyl trifluoromethanesulfonates.[5] The limited success attained by these authors has prompted us to report our own results obtained in the Heck reaction between vinylglycines (**1**) and 1-iodo-4-methoxybenzene (**2**).

When 1-iodo-4-methoxybenzene (**2**) was treated with (±)-**1c** under the conditions[3] specified in Table I (entry 3), a 92:8 mixture of (*E*)- and (*Z*)-**4c** was obtained in 44% yield after treatment of the products with trimethylsilyldiazomethane. A small amount of (±)-**5** was also obtained. On the other hand, we merely recovered 4-methoxyphenyl trifluoromethanesulfonate (**7**)[6] and (±)-**1c** in 71% and 31% yields, respectively, when **7** was treated under similar conditions. The reaction in the presence of an equimolar amount of lithium chloride,[7] afforded undesired benzyl carbamate (40% yield) together with unchanged **7** (88%).



* To whom correspondence should be addressed.

Using the iodide **2** as the substrate, we next investigated the effect of the *N*-substituent of vinylglycine on the yield of the desired olefins under similar conditions (Table I). Although unprotected vinylglycine [(±)-**1a**] was consumed, **2** (91%) was recovered unchanged (entry 1). *N*-Phthaloylated vinylglycine [(±)-**1g**] afforded no desired product (entry 7), while acylated [(±)-**1e,f**], alkoxycarbonylated [(±)-**1b—d**], and aralkylated vinylglycine [(±)-**1h**] afforded geometrical mixtures of the desired olefins in 13—44% yields (entries 2—6 and 8).

Selecting (±)-**1c** as a partner of **2**, we effected a series of experiments to determine the optimum reaction conditions. The results are summarized in Table II. The use of palladium black or tetrakis(triphenylphosphine)-palladium instead of palladium acetate did not give a better result (entries 2 and 3 *versus* entry 1). We could not find a better base than sodium bicarbonate from the viewpoint of not only the yield of **3c** (isolated as the methyl ester **4c**) but also the reaction rate (entries 4—14). It is interesting to note, however, that the use of aliphatic amines remarkably changed the *E*/*Z* ratio (entries 8, 9, and 11); triethylamine reversed the stereoselectivity (entry 8). Addition of a phosphine ligand (entries 15—17) did not improve the yield of **3c**. Comparison of the results obtained in entries 1 and 29—31 indicates that about 60 °C is the optimum temperature for the reaction in *N*,*N*-di-

TABLE I. Palladium-Catalyzed Arylation of (±)-**1a—h** with **2**[a]

Entry	Olefin	R^1	R^2	Reaction time (h)	(±)-**4** Yield (%)	(±)-**4** *E*:*Z*[b]
1	(±)-**1a**·HCl[c]	H	H	168	0	—
2	(±)-**1b**	H	CO_2Me	24	43	95:5
3	(±)-**1c**	H	CO_2CH_2Ph	24	44	92:8
4	(±)-**1d**	H	CO_2CMe_3	24	29	96:4[d]
5	(±)-**1e**	H	Ac	24	25	91:9
6	(±)-**1f**	H	$COCF_3$	24	13	93:7[d]
7	(±)-**1g**	Phthaloyl		48	0	—
8	(±)-**1h**	H	Phfl[e]	168	24	91:9

a) A mixture of **2** (1 mmol), (±)-**1** (1.1 mmol), palladium acetate (0.03 mmol), tetrabutylammonium chloride (1.01 mmol), sodium bicarbonate (3 mmol), and DMF (16.7 ml) was stirred at 45°C. *b*) Determined by means of ^{1}H-NMR spectroscopy on the basis of relative areas of the C(γ)H signals. *c*) Four mmol of sodium bicarbonate was used. *d*) Determined on the basis of relative areas of the C(β)H signals. *e*) Phfl stands for a 9-phenylfluoren-9-yl group.

TABLE II. Palladium-Catalyzed Arylation of (±)-**1c** with **2** under Various Conditions[a]

Entry	Solvent	Base	Additive (mol %)	Temp. (°C)	Time (h)	(±)-**4c**		Recovery (%)	
						Yield (%)	$E:Z$[b]	(±)-**1c**[c]	**2**
1	DMF	$NaHCO_3$	None	45	24	44	92:8	—[d]	—[d]
2[e]	DMF	$NaHCO_3$	None	45	240	0	—	63[f]	84
3[g]	DMF	$NaHCO_3$	None	45	24	18	93:7	0	29
4	DMF	K_2CO_3	None	45	144	43	92:8	4	0
5	DMF	Tl_2CO_3	None	45	168	10	90:10	36	56
6	DMF	TlOAc	None	45	72	2	—[d]	17	74
7	DMF	NaOAc	None	45	72	6	83:17	4	57
8	DMF	Et_3N	None	45	48	21	18:82	0	53
9	DMF	$(Me_2CH)_2NEt$	None	45	120	9	67:33	7	59
10	DMF	Et_2NH	None	45	48	—[h]	—	10	74
11	DMF	$(Me_2CH)_2NH$	None	45	48	29	50:50	6	35
12	DMF	Morpholine	None	45	48	—[h]	—	0	76
13	DMF	$BuNH_2$	None	45	120	—[h]	—	0	83
14	DMF	Pyridine	None	45	168	—[h]	—	20	82
15	DMF	$NaHCO_3$	Ph_3P (6)	45	24	22	95:5	0	15
16	DMF	$NaHCO_3$	$(Tol)_3P$[i] (6)	45	24	15	91:9	0	47
17	DMF	$NaHCO_3$	DPPF[j] (3)	45	24	30	88:12	0	31
18	DMF	$NaHCO_3$	H_2O (5600)	45	264	59	100:0	—[h]	—[h]
19	Toluene[k]	$NaHCO_3$	None	45	72	38	94:6	0	19
20	MeCN	$NaHCO_3$	None	45	168	24	94:6	28	28
21	Me_2CHOH	$NaHCO_3$	None	45	70	4.5	100:0	79	—[d]
22	EtOH	$NaHCO_3$	None	45	70	11	100:0	73	—[d]
23	EtOH	$NaHCO_3$	None	45	336	47	100:0	36	32
24	MeOH	$NaHCO_3$	None	45	70	22	100:0	61	—[d]
25	H_2O	$NaHCO_3$	None	45	24	79	100:0	<11	—[h]
26	None	$NaHCO_3$	None	45	72	7	—[d]	0	44
27	DMF	$NaHCO_3$	None	60	1	20	91:9	47	—[d]
28	DMF	$NaHCO_3$	None	60	4	51	94:6	—[h]	—[h]
29	DMF	$NaHCO_3$	None	60	5	54	95:5	0	—[h]
30	DMF	$NaHCO_3$	None	80	0.5	49	>97:<3	0	3
31	DMF	$NaHCO_3$	None	100	0.5	38	>97:<3	0	15
32	H_2O	$NaHCO_3$	None	60	56	73	100:0	0	—[h]

a) The reactions were carried out employing **2** (1 mmol), (±)-**1c** (1.1 mmol), palladium acetate (0.03 mmol), tetrabutylammonium chloride (1.01 mmol), the base (3 mmol), and the solvent (*ca.* 16 ml). *b*) Determined by means of ^{1}H-NMR spectroscopy on the basis of relative areas of the C(γ)H signals. *c*) Isolated as the methyl ester. *d*) Not determined. *e*) Palladium black was used instead of palladium acetate. *f*) Isolated in the form of **1c**. *g*) Tetrakis(triphenylphosphine)palladium was used instead of palladium acetate. *h*) A trace, if any. *i*) Tris(2-methylphenyl)phosphine. *j*) 1,1′-Bis(diphenylphosphino)ferrocene. *k*) A mixture of toluene and DMF (60:40, v/v).

methylformamide (DMF) in the presence of sodium bicarbonate[8] and that the stereoselectivity increased with increasing reaction temperature. The stereoselectivity is also enhanced by prolonged reaction (entries 27—29). We supposed that the good result obtained in the reaction in the presence of sodium bicarbonate or potassium carbonate was partly due to water formed *in situ*. Further addition of water indeed increased the yield of (*E*)-**3c** in a perfectly stereoselective manner, although the reaction was markedly retarded (entry 18).

Being encouraged by these results and recent reports on palladium-catalyzed coupling reactions using hydroxylic solvents,[9,10] we investigated the solvent effect (entries 19—26). The desired olefin **3c** formed in the reaction in a hydroxylic solvent (entries 21—25) was exclusively the (*E*)-isomer. The reaction in water (entry 25) proceeded at a rate much faster than that in an alcohol; a change of the solvent from a higher alcohol to a lower alcohol caused an increase in rate (entries 21, 22, and 24). In the reaction in water, higher temperature afforded no advantage (entry 32).

Having achieved the completely stereoselective synthesis of (*E*)-**3c** in an acceptable yield, we finally tested this method for a chiral synthesis. Table III shows that the use of water affords [*S*-(*E*)]-**3c** of high optical purity. Thus, it has become evident that water is an excellent solvent for the Heck reaction between **2** and **1c**. Syntheses of optically active (*E*)-vinylglycines bearing different aryl groups at the 4-position by the present method are in progress.

TABLE III. Palladium-Catalyzed Arylation of (*S*)-**1c** with **2**[a]

Entry	Solvent	**4c**		Optical purity of **3c** (% ee)[c]	Recovery (%)	
		Yield (%)	$E:Z$[b]		**1c**[d]	**2**
1	DMF	42	93:7	70	0	23
2	H_2O	57	100:0	96	10	8

a) A mixture of **2** (0.5 mmol), (*S*)-**1c** (0.55 mmol), palladium acetate (0.015 mmol), tetrabutylammonium chloride (0.5 mmol), and sodium bicarbonate (1.5 mmol) in DMF or water (8 ml) was stirred at 45 °C for 24 h. *b*) Determined by means of ^{1}H-NMR spectroscopy on the basis of relative areas of the C(γ)H signals. *c*) Determined by HPLC on a chiral column after conversion of **3c** into methyl 2-[(methoxycarbonyl)amino]-4-(4-methoxyphenyl)butanoate. *d*) Isolated as the methyl ester.

Experimental

General Notes All melting points were determined by using a Yamato MP-1 or Büchi 530 capillary melting point apparatus and are corrected. MS were recorded on a Hitachi M-80 mass spectrometer. NMR spectra

were measured with a JEOL JNM-EX-270 NMR spectrometer; unless otherwise stated, they were recorded in $CDCl_3$ with tetramethylsilane as an internal standard. The HPLC system was a Waters model 204 ALC, which included a 6000A pump, a U6K injector, and a model 440 absorbance detector operating at 254 nm. Elemental analyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. Flash chromatography was performed according to the reported procedure.[11] The following abbreviations are used: br = broad, d = doublet, dd = doublet-of-doublets, ddd = doublet-of-doublets-of-doublets, m = multiplet, q = quartet, s = singlet.

(±)-2-[(Methoxycarbonyl)amino]-3-butenoic Acid [(±)-1b] Crude (±)-**1b** (452 mg, 71%), mp 78—79.5 °C, was obtained from (±)-**1a**·HCl[12] (550 mg, 4 mmol) according to the reported procedure for the preparation of (*S*)-**1b**.[3b,13] Recrystallization of this product from benzene afforded an analytical sample of (±)-**1b** as colorless scales, mp 88—90 °C; MS *m/z*: 159 (M^+). *Anal.* Calcd for $C_6H_9NO_4$: C, 45.28; H, 5.70; N, 8.80. Found: C, 45.22; H, 5.68; N, 8.90. The ^{1}H-NMR spectrum [$(CD_3)_2SO$] of this sample was identical with that of (*S*)-**1b**.[3b]

(±)-2-[(Benzyloxycarbonyl)amino]-3-butenoic Acid [(±)-1c] Benzyl chloroformate (4.09 g, 24 mmol) was added to a solution of (±)-**1a**·HCl[12] (2.75 g, 20 mmol) and sodium bicarbonate (8.40 g, 0.1 mol) in water (100 ml) under cooling with ice. The mixture was stirred at room temperature for 4 h, washed with benzene, brought to pH 1 by addition of 10% hydrochloric acid, and extracted with ethyl acetate (3 × 50 ml). The organic phases were separated, dried ($MgSO_4$), and concentrated to leave (±)-**1c** (3.24 g, 69%), mp 98—100 °C. Recrystallization of this material from hexane–ethyl acetate (1 : 1, v/v) afforded an analytical sample of (±)-**1c** as colorless scales, mp 106.5—107.5 °C. *Anal.* Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.25; H, 5.55; N, 5.93. The ^{1}H-NMR spectrum of this sample was identical with that of (*S*)-**1c**.[13]

(±)-2-[[(1,1-Dimethylethoxy)carbonyl]amino]-3-butenoic Acid [(±)-1d] This compound (95 mg, 94%) was obtained as a colorless oil from (±)-**1a**·HCl[12] (69 mg, 0.5 mmol) according to the reported procedure for the preparation of (*S*)-**1d**,[14] except that the reaction was carried out at room temperature for 3.5 h. ^{1}H-NMR δ: 1.45 (9H, s, Me_3), 4.71 (0.4H) and 4.91 (0.6H) [br each, C(α)H], 5.16 (0.6H) and 7.02 (0.4H) (br each, NH), 5.31 (1H, d, J = 9.9 Hz) and 5.40 (1H, d, J = 17.5 Hz) (CH_2), 5.93 [1H, m, C(β)H].

(±)-2-[(Trifluoroacetyl)amino]-3-butenoic Acid [(±)-1f] A mixture of (±)-**1a**·HCl[12] (138 mg, 1 mmol), trifluoroacetic anhydride (0.28 ml, 2 mmol), and trifluoroacetic acid (1.16 ml) was stirred at room temperature for 5 h and then concentrated. The residue was dissolved in water (10 ml). The solution was extracted with dichloromethane using a continuous extractor after adjusting the pH to 1 by addition of 10% hydrochloric acid. The organic layer was dried ($MgSO_4$) and concentrated to leave (±)-**1f** (163 mg, 82%) as a yellowish oil, ^{1}H-NMR δ: 5.20 [1H, m, C(α)H], 5.44 (1H, dd, J = 1.7, 10.2 Hz) and 5.45 (1H, dd, J = 1.7, 17.2 Hz) (CH_2), 5.95 [1H, ddd, J = 5.9, 10.2, 17.2 Hz, C(β)H], 6.95 (1H, br, NH).

(±)-2-(1,3-Dioxo-2-azaindan-2-yl)-3-butenoic Acid [(±)-1g] Sodium bicarbonate (336 mg, 4 mmol) and *N*-ethoxycarbonylphthalimide (460 mg, 2.1 mmol) were added to a solution of (±)-**1a**·HCl[12] (137 mg, 1 mmol) in water (2 ml). The whole was stirred at room temperature for 6 h. The resulting precipitate was filtered off and washed with water (1 ml). The filtrate and washings were combined and brought to pH 1 by addition of 20% hydrochloric acid. The resulting precipitate was collected by filtration and dried to give (±)-**1g** (139 mg, 60%) as a colorless solid, mp 118—123 °C. Recrystallization of crude (±)-**1g** from hexane–ethyl acetate (2 : 1, v/v) afforded an analytical sample of (±)-**1g** as colorless needles, mp 129—130 °C; MS *m/z*: 231 (M^+); ^{1}H-NMR δ: 5.36 (1H, dd, J = 1.3, 17.5 Hz) and 5.39 (1H, br d, J = 10.2 Hz) (CH_2), 5.48 [1H, m, C(α)H], 6.38 [1H, ddd, J = 6.9, 10.2, 17.5 Hz, C(β)H], 7.73—7.81 and 7.84—7.92 (2H each, m, C_6H_4). *Anal.* Calcd for $C_{12}H_9NO_4$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.40; H, 3.84; N, 6.05.

(±)-2-[(9-Phenylfluoren-9-yl)amino]-3-butenoic Acid [(±)-1h] This compound was prepared as a colorless glass from (±)-homoserine in 39% overall yield according to the reported procedure for the synthesis of (*S*)-**1h**[13] through the following compounds; ^{1}H-NMR δ: 3.21 [1H, ddd, J = 6.6, 1.3, 1.3 Hz, C(α)H], 5.02 (1H, dd, J = 1.3, 17.2 Hz) and 5.08 (1H, dd, J = 1.3, 10.2 Hz) (CH_2), 5.64 [1H, ddd, J = 6.6, 10.2, 17.2 Hz, C(β)H], 7.19—7.44 (11H) and 7.64—7.75 (2H) (m each, aromatic protons).

(±)-4-Hydroxy-2-[(9-phenylfluoren-9-yl)amino]butanoic Acid: 66% yield; colorless pillars from ethanol–water (1 : 2, v/v); mp 168—169.5 °C. *Anal.* Calcd for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.90. Found: C, 76.88; H, 5.88; N, 3.83.

Methyl (±)-4-Hydroxy-2-[(9-phenylfluoren-9-yl)amino]butanoate: 95% yield; colorless prisms from hexane–benzene (20 : 1, v/v); mp 98.5—100 °C; ^{1}H-NMR δ: 1.47—1.60 and 1.67—1.80 [1H each, m, C(β)H_2], 2.78 [1H, dd, J = 9.9, 4.0 Hz, C(α)H], 3.28 (3H, s, Me), 3.52—3.61 and 3.69—3.77 [1H each, m, C(γ)H_2], 3.0—4.4 (2H, br, OH and NH), 7.14—7.46 (11H) and 7.69—7.73 (2H) (m each, aromatic protons). *Anal.* Calcd for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 77.41; H, 6.23; N, 3.77.

Methyl (±)-2-[(9-Phenylfluoren-9-yl)amino]-3-butenoate: 81% yield; colorless prisms from hexane; mp 73—74.5 °C. *Anal.* Calcd for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.94. Found: C, 81.01; H, 5.88; N, 3.97. The ^{1}H-NMR spectrum of this sample was identical with that of the (*S*)-isomer.[13]

The Heck Reaction of (±)-1 with 2 The reaction of (±)-**1c** (Table I, entry 3 or Table II, entry 1) will be described below in detail as a typical example of the experiments summarized in Table I.

Reaction of (±)-1c Compound **2** (234 mg, 1 mmol), sodium bicarbonate (252 mg, 3 mmol), and a 0.15 M tetrabutylammonium chloride solution in DMF (6.7 ml, 1.01 mmol) were added to a solution of palladium acetate (6.8 mg, 0.03 mmol) in DMF (10 ml). The mixture was stirred at 45 °C for 10 min, then (±)-**1c** (259 mg, 1.1 mmol) was added and the whole was stirred at 45 °C for 24 h. The resulting mixture was brought to pH 3—4 by addition of 10% aqueous phosphoric acid and extracted with ethyl acetate (6 × 10 ml). The organic layers were combined, washed with 10% aqueous phosphoric acid (3 × 20 ml), dried ($MgSO_4$), and concentrated under reduced pressure to leave a brown oil (429 mg). This was submitted to flash chromatography [chloroform–methanol–water (40 : 12 : 1, v/v)]. The fractions containing (±)-**3c** were collected and concentrated. The residue was partitioned between chloroform (10 ml) and 10% aqueous phosphoric acid (10 ml). The aqueous layer was extracted with chloroform (5 × 10 ml). The organic layers were combined, dried ($MgSO_4$), and concentrated to afford crude (±)-**3c** (228 mg) as a brown semi-solid. This was dissolved in a mixture of benzene (4.6 ml) and methanol (1.3 ml), and then trimethylsilyldiazomethane (*ca.* 10% solution in hexane) was added until the yellow color persisted. The solution was concentrated and the residue was purified by flash chromatography [hexane–ethyl acetate (2 : 1, v/v)] to afford a mixture of (*E*)- and (*Z*)-**4c** (156 mg, 44%), and (±)-**5** (4 mg, 0.9%) as colorless oils. Compound (±)-**5**: MS *m/z*: 461 (M^+); ^{1}H-NMR δ: 3.74 (3H, s, CO_2Me), 3.79 and 3.83 (3H each, s, two C_6H_4OMe's), 4.94 [1H, m, C(α)H], 5.07 (2H, s, PhCH_2), 5.40 (1H, br, NH), 5.76 [1H, d, J = 9.9 Hz, C(β)H], 6.80 and 7.14 (2H each, d, J = 8.9 Hz), and 6.91 and 7.23 (2H each, br d, J = 6.9 Hz) (two C_6H_4OMe's), 7.32 (5H, br s, Ph).

Reaction of (±)-1b Crude (±)-**3b** (129 mg) obtained by flash chromatography [chloroform–methanol–water (40 : 14 : 1, v/v)] was treated with trimethylsilyldiazomethane, followed by flash chromatography [benzene–ethyl acetate (5 : 1, v/v)] to afford (±)-**4b** (119 mg, 43%) as a colorless oil. ^{1}H-NMR for (*E*)-**4b** δ: 3.71 (s, $NHCO_2$Me), 3.79 (s, $CHCO_2$Me), 3.81 (s, C_6H_4OMe), 5.03 [m, C(α)H], 5.42 (br, NH), 6.04 [dd, J = 6, 16 Hz, C(β)H], 6.62 [d, J = 16 Hz, C(γ)H], 6.85 and 7.31 (d each, J = 8.6 Hz, C_6H_4). A signal due to the C(γ)H of (*Z*)-**4b** appeared at 6.70 ppm (d, J = 11 Hz).

Reaction of (±)-1d Methylation of crude (±)-**3d** (149 mg), which had been obtained by flash chromatography [chloroform–methanol–water (40 : 10 : 1, v/v)], followed by flash chromatography [hexane–ethyl acetate (2 : 1, v/v)], afforded (±)-**4d** (93 mg, 29%) as a colorless oil. ^{1}H-NMR for (*E*)-**4d** δ: 1.46 (s, Me_3), 3.78 (s, CO_2Me), 3.81 (s, C_6H_4OMe), 4.98 [m, C(α)H], 5.25 (br, NH), 6.03 [dd, J = 6.6, 15.8 Hz, C(β)H], 6.61 [d, J = 15.8 Hz, C(γ)H], 6.85 and 7.30 (d each, J = 9 Hz, C_6H_4). A small signal due to the C(β)H of (*Z*)-**4d** was observed at 5.41 ppm (dd, J = 10, 11 Hz).

Methyl (±)-2-[(1,1-dimethylethoxy)amino]-4,4-bis(4-methoxyphenyl)-3-butenoate [(±)-**6**] (18 mg, 4.2%) was obtained from the more polar fractions as a colorless oil, ^{1}H-NMR δ: 1.41 (9H, s, Me_3), 3.74 (3H, s, CO_2Me), 3.79 and 3.84 (3H each, s, two C_6H_4OMe's), 4.84 [1H, dd, J = 7.3, 9.9 Hz, C(α)H], 5.09 (1H, br, NH), 5.76 [1H, d, J = 9.9 Hz, C(β)H], 6.80 and 7.15 (2H each, m, C_6H_4), 6.92 and 7.22 (2H each, m, C_6H_4).

Reaction of (±)-1e Flash chromatography [chloroform–methanol–water (20 : 7 : 1, v/v)] of the products obtained from the reaction of **2** and (±)-**1e**[13] afforded (±)-**3e** (66 mg) as a yellow solid. Methylation

of this material, followed by layer chromatography on silica gel [hexane–ethyl acetate (1 : 2, v/v)] afforded (±)-**4e** (66 mg, 25%) as a colorless oil. ^{1}H-NMR for (*E*)-**4e** δ: 2.08 (s, Ac), 3.79 and 3.80 (s each, two OMe's), 5.26 [m, C(α)H], 6.03 [dd, J=6.6, 15.8 Hz, C(β)H], 6.29 (d, J=7.3 Hz, NH), 6.59 [d, J=15.8 Hz, C(γ)H], 6.84 and 7.30 (m each, C_6H_4). The C(γ)H of (*Z*)-**4e** resonated at 6.69 ppm (d, J=10.2 Hz).

Reaction of (±)-1f Crude (±)-**3f** (54 mg), mp 150.5—159 °C, was obtained by flash chromatography [chloroform–methanol–water (20 : 7 : 1, v/v)] of the crude products. Methylation of this material with trimethylsilyldiazomethane, followed by layer chromatography on silica gel [hexane–ethyl acetate (2 : 1, v/v)] afforded (±)-**4f** (42 mg, 13%) as a colorless glass. ^{1}H-NMR for (*E*)-**4f** δ: 3.81 and 3.83 (s each, two Me's), 5.23 [dd, J=7.3 Hz each, C(α)H], 5.98 [dd, J=7.3, 15.8 Hz, C(β)H], 6.65 [d, J=15.8 Hz, C(γ)H], 7.13 (br, NH), 6.86 and 7.31 (m each, C_6H_4). The C(β)H of (*Z*)-**4f** resonated at 5.42 ppm (dd, J=9.9, 10.9 Hz).

Reaction of (±)-1g Flash chromatography [chloroform–methanol–water (20 : 7 : 1, v/v)] of the crude products afforded crude **2** [159 mg, 68% after further purification by flash chromatography (hexane)] and fractions containing a carboxylic acid. These fractions were combined and concentrated. The residue was suspended in 10% aqueous phosphoric acid (5 ml) and then extracted with dichloromethane (4 × 10 ml). The organic layers were combined, dried ($MgSO_4$), and concentrated to afford (*Z*)-(±)-2-(1,3-dioxo-2-azaindan-2-yl)-2-butenoic acid (155 mg, 61%), mp 133—145 °C; ^{1}H-NMR δ: 1.87 (3H, d, J=7.3 Hz, Me), 7.51 [1H, q, J=7.3 Hz, C(β)H], 7.74—7.80 and 7.89—7.95 (2H each, m, aromatic protons). This compound was treated with trimethylsilyldiazomethane, followed by flash chromatography [hexane–ethyl acetate (3 : 1, v/v)], to afford methyl (*Z*)-(±)-2-(1,3-dioxo-2-azaindan-2-yl)-2-butenoate[15] as a colorless oil, ^{1}H-NMR δ: 1.84 (3H, d, J=7.3 Hz, CMe), 3.77 (3H, s, OMe), 7.41 [1H, q, J=7.3 Hz, C(β)H], 7.71—7.84 and 7.84—7.97 (2H each, m, aromatic protons). Compound (±)-**1g** was found to be unstable under basic conditions: after stirring it (127 mg, 0.55 mmol) in DMF (5 ml) in the presence of sodium bicarbonate (126 mg) at 45 °C for 48 h, (*Z*)-(±)-2-(1,3-dioxo-2-azaindan-2-yl)-2-butenoic acid was isolated as the methyl ester (98 mg, 73%).

Reaction of (±)-1h The reaction mixture was diluted with water (10 ml), brought to pH 4 by addition of 10% aqueous phosphoric acid, and extracted with ethyl acetate (5 × 25 ml). The organic layers were combined, washed with 10% aqueous phosphoric acid (3 × 50 ml), dried ($MgSO_4$), and concentrated to leave a brown oil (350 mg). This was treated with trimethylsilyldiazomethane in the usual manner. The products were separated by flash chromatography [hexane–ethyl acetate (6 : 1, v/v)] to afford **2** (68 mg, 29%) and (±)-**4h** (112 mg, 24%) as a colorless glass, MS m/z: 461 (M^+); ^{1}H-NMR for (*E*)-**4h** δ: 3.12 (br, NH), 3.39 (s, CO_2Me), 3.45 [dd, J=1, 6.9 Hz, C(α)H], 3.79 (s, $C_6H_4O\underline{Me}$), 5.83 [dd, J=6.9, 15.8 Hz, C(β)H], 6.30 [d, J=15.8 Hz, C(γ)H], 6.80 and 7.17 (m each, $C_6\underline{H}_4OMe$), 7.12—7.39, 7.46, and 7.68 (m each, phenylfluorenyl protons). The C(γ)H of (*Z*)-**4h** resonated at 6.20 ppm (d, J=11.6 Hz).

(*E*)-(±)-2-[(Benzyloxycarbonyl)amino]-4-(4-methoxyphenyl)-2-butenoic Acid [(*E*)-3c] and Methyl (*E*)-(±)-2-[(Benzyloxycarbonyl)amino]-4-(4-methoxyphenyl)-2-butenoate [(*E*)-4c] When the reaction was carried out in a mixture of DMF (15 ml) and water (1 ml) (Table II, entry 18), crude (*E*)-**3c** (310 mg) was obtained as a brown semi-solid. A portion (25 mg) of this material was treated with trimethylsilyldiazomethane, followed by layer chromatography on silica gel [hexane–ethyl acetate (2 : 1, v/v)] to afford (*E*)-**4c** (17 mg; 59% yield based on **2**) as a colorless oil, ^{1}H-NMR δ: 3.78 (3H, s, CO_2Me), 3.81 (3H, s, $C_6H_4O\underline{Me}$), 5.05 [1H, m, C(α)H], 5.14 (2H, s, CH_2), 5.35 (0.2H, br) and 5.52 (0.8H, br d, J=7 Hz) (NH), 6.03 [1H, dd, J=15.8, 6.6 Hz, C(β)H], 6.61 [1H, d, J=15.8 Hz, C(γ)H], 6.84 and 7.29 (2H each, d, J=9 Hz, $C_6\underline{H}_4OMe$), 7.36 (5H, br s, Ph).

The rest (285 mg) of the crude (*E*)-**3c** was recrystallized from hexane–ethyl acetate (1 : 1, v/v) to afford (*E*)-**3c** (136 mg, 43%) as colorless scales, mp 137—138.5 °C. Further recrystallization of this material afforded an analytical sample of (*E*)-**3c** as colorless scales, mp 140—141 °C; MS m/z: 341 (M^+); ^{1}H-NMR [$(CD_3)_2SO$] δ: 3.75 (3H, s, Me), 4.72 [1H, m, C(α)H], 5.06 (2H, s, CH_2), 6.13 [1H, dd, J=7, 16 Hz, C(β)H], 6.61 [1H, d, J=16 Hz, C(γ)H], 6.91 and 7.35 (2H each, d, J=8.9 Hz, $C_6\underline{H}_4OMe$), 7.37 (5H, s, Ph), 7.65 (0.2H, br) and 7.89 (0.8H, d, J=7.6 Hz) (NH), 12.80 (1H, br s, CO_2H). *Anal.* Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.78; H, 5.65; N, 3.95.

(*Z*)-(±)-2-[(Benzyloxycarbonyl)amino]-4-(4-methoxyphenyl)-2-butenoic Acid [(*Z*)-3c] and Methyl (*Z*)-(±)-2-[(Benzyloxycarbonyl)amino]-4-(4-methoxyphenyl)-2-butenoate [(*Z*)-4c] A portion (318 mg) of crude (±)-**3c** (368 mg), which had been obtained from the reaction of **2** (585 mg, 2.5 mmol) in the presence of triethylamine, was recrystallized from hexane–ethyl acetate (1 : 1, v/v) to afford (*Z*)-**3c** (87 mg, 12%) as colorless needles, mp 166—170.5 °C. Further recrystallization of this sample from hexane–ethyl acetate (1 : 2, v/v) afforded an analytical sample of (*Z*)-**3c** as colorless needles, mp 175—177 °C; ^{1}H-NMR [$(CD_3)_2SO$] δ: 3.77 (3H, s, Me), 4.94 [1H, m, C(α)H], 5.02 (2H, s, CH_2), 5.52 [1H, dd, J=10, 11.2 Hz, C(β)H], 6.64 [1H, d, J=11.2 Hz, C(γ)H], 6.96 and 7.41 (2H each, d, J=8.6 Hz, $C_6\underline{H}_4OMe$), 7.34 (5H, s, Ph), 7.53 (0.15H, br) and 7.91 (0.85H, d, J=7.3 Hz) (NH), 12.90 (1H, br s, CO_2H). *Anal.* Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.65; H, 5.59; N, 4.04.

A small portion of (*Z*)-**3c** was treated with trimethylsilyldiazomethane, followed by purification by layer chromatography on silica gel [hexane–ethyl acetate (3 : 1, v/v)], to afford (*Z*)-**4c** as a colorless oil, ^{1}H-NMR δ: 3.77 (3H, s, CO_2Me), 3.82 (3H, s, $C_6H_4O\underline{Me}$), 5.09 (2H, s, CH_2), 5.25—5.50 [3H, m, C(α)H, C(β)H, and NH], 6.70 [1H, d, J=10.9 Hz, C(γ)H], 6.90 and 7.40 (2H each, br d, J=8.3 Hz, $C_6\underline{H}_4OMe$), 7.33 (5H, br s, Ph).

The Heck Reaction of (*S*)-1c with 2 The results summarized in Table III were obtained as will be described below for entry 2 as an example. A solution of tetrabutylammonium chloride (139 mg, 0.5 mmol) in water (3 ml) and (*S*)-**1c** (99% ee[13]; 129 mg, 0.55 mmol) were added successively to a mixture of palladium acetate (3.4 mg, 0.015 mmol), **2** (117 mg, 0.5 mmol), sodium bicarbonate (126 mg, 1.5 mmol), and water (5 ml). The whole was stirred at 45 °C for 24 h. The resulting mixture was diluted with water (5 ml), brought to pH 3 by addition of 10% aqueous phosphoric acid, and extracted with ethyl acetate (5 × 10 ml). The organic layers were combined, washed with 10% aqueous phosphoric acid (3 × 20 ml), dried ($MgSO_4$), and concentrated. The residue was treated in a manner similar to that described for the reaction of (±)-**1c** after separation by flash chromatography [chloroform–methanol (3 : 1, v/v)] to afford crude [*S*-(*E*)]-**3c** (157 mg) as a brown solid. Compound **2** (9 mg, 7.7%) was recovered from the faster-eluting fractions after further purification by layer chromatography on silica gel (hexane).

A portion (79 mg) of crude [*S*-(*E*)]-**3c** was treated with trimethylsilyldiazomethane in the usual manner and the products were separated by layer chromatography on silica gel [hexane–ethyl acetate (3 : 1, v/v)] to afford (*S*)-**5** (2 mg, 1.7%), [*S*-(*E*)]-**4c** (51 mg, 57%) and methyl (*S*)-2-[(benzyloxycarbonyl)amino]-3-butenoate[13] (7 mg, 10%).

In order to avoid racemization during HPLC analysis the rest of the crude [*S*-(*E*)]-**3c** was hydrogenated over 10% palladium on carbon in methanol at room temperature. Crude (*S*)-2-amino-4-(4-methoxyphenyl)butanoic acid thus obtained was treated with methyl chloroformate in a mixture of dioxane and water (1 : 1, v/v) in the presence of sodium bicarbonate, followed successively by methylation with trimethylsilyldiazomethane and separation by layer chromatography on silica gel [hexane–ethyl acetate (2 : 1, v/v)], to afford methyl (*S*)-2-[(methoxycarbonyl)amino]-4-(4-methoxyphenyl)butanoate as a colorless oil. This sample showed an identical ^{1}H-NMR spectrum with that of the racemic sample described below and was 96% ee on the basis of chiral HPLC analysis (see below; the peak areas of the components were determined by using a Takeda Riken TR-2217 automatic integrator).

Methyl (±)-2-[(Methoxycarbonyl)amino]-4-(4-methoxyphenyl)butanoate The mixture of geometrical isomers of (±)-**4b** (29 mg) described above was hydrogenated over 10% palladium on carbon (29 mg) in methanol (5 ml) at room temperature for 1 h. The catalyst was filtered off and washed with hot methanol (50 ml). The filtrate and washings were combined and concentrated. The residue was purified by layer chromatography on silica gel [hexane–ethyl acetate (2 : 1, v/v)] to afford the title compound (27 mg, 93%) as a colorless oil, ^{1}H-NMR δ: 1.94 and 2.13 [1H each, m, C(β)H_2], 2.61 [2H, m, C(γ)H_2], 3.70, 3.72, and 3.78 (3H each, s, three Me's), 4.39 [a total of 1H with a small broad signal at 4.25 ppm, m, C(α)H], 5.20 (a total of 1H with a small broad signal at 4.98 ppm, br d, J=6.9 Hz, NH), 6.83 and 7.08 (2H each, d, J=8.6 Hz, aromatic protons). This compound was cleanly resolved to the (*R*)-isomer (retention time, 32.1 min) and the (*S*)-isomer (35.2 min) by HPLC on a Sumichiral OA-3200 column (4.6 × 250 mm) [hexane–ethanol (99 : 1, v/v); 1 ml/min] at room temperature.

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