Synlett S. Parpart et al. Letter

Synthesis of Optically Pure (*S*,*E*)-2-Amino-5-arylpent-4-enoic Acids by Heck Reactions of Nickel Complexes

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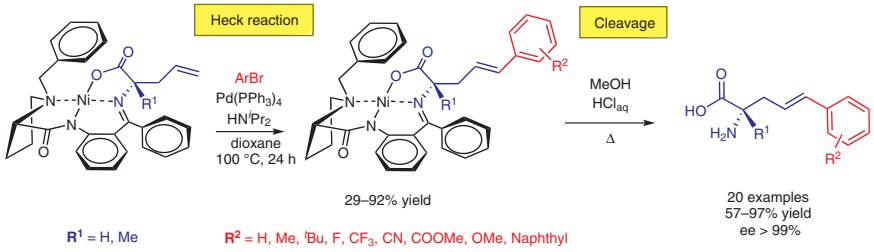

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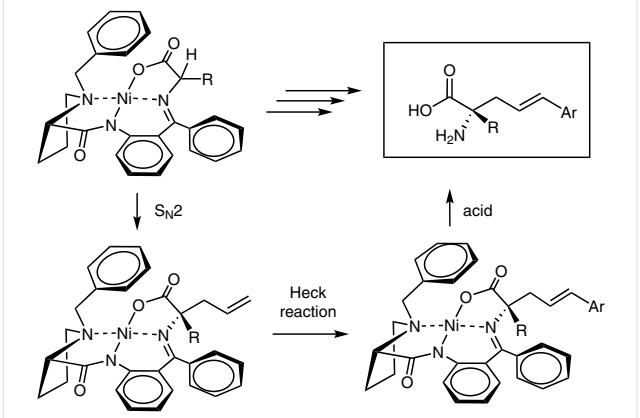
Abstract Starting from commercially available building blocks a variety of enantiomerically pure (*S*)-2-amino-4-enoic acids has been synthesized by the Heck reaction using Ni-(*S*)-BPB [Nickel-*N*-[(*S*)-benzylprolyl]aminobenzophenone] as a chiral auxiliary. The reactions proceeded in very good yields and with high *E*-selectivity.

Key words amino acids, Heck reaction, catalysis, chiral auxiliary, enantioselectivity

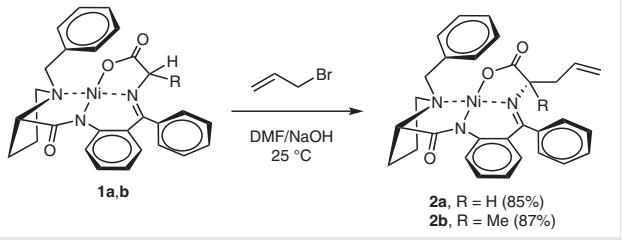
Naturally occurring α-allylglycine[1] and its derivatives have a high level of biological activity. The parent compound is known to have antibiotic[2] as well as GABA and glutamate decarboxylase inhibiting properties;[3] while its derivatives can inhibit nitric oxidase synthase,[4] viral protease,[5] and cathepsin.[6] Thus, synthesis of novel allyl-containing amino acids is an important topic in synthetic chemistry. Racemic allylglycine can be accessed easily by the malonic ester synthesis.[7] To obtain optically pure amino acids, an enzymatic protocol has been used to separate racemic allylglycineamids using a substrate selective aminopeptidase.[8] Nevertheless, the direct synthesis of optically pure amino acids is a topic of ongoing research. This can be achieved by chiral catalysts, chiral substrates, or a chiral environment.[9]

Allylglycine can be enantiomerically enriched by a phase-transfer reaction, using different cinchonidine catalysts.[10] Unfortunately, the published enantiomeric excess (ee) is limited to 75%. Higher ee values, with over 90%, are reported for the application of amino acid–Ni–BPB complexes (Ni-BPB = nickel-*N*-(benzylprolyl)aminobenzophenone).[11] Such Ni–BPB complexes were developed in recent decades with optically active BPB to perform the asymmetric induction and Ni to increase the stability and reactivity of the coordinated amino acid.[12] The complexes are stable to air and are synthesized from readily available building blocks (benzyl chloride, L-proline, 2-aminobenzophenone). In the past, these amino acid–Ni–BPB complexes have been applied to Michael additions,[13] Mannich reactions,[14] aldol reactions,[15] S_N2 reactions,[16] and Sonogashira couplings.[17]

In this work, we present a new and convenient synthesis of optically pure allylglycine derivatives using glycine–Ni–BPB and alanine–Ni–BPB as starting materials. Both compounds undergo substitution with allyl chloride in very good yield and high enantiomeric excess. Further functionalization via Heck[18] reaction yields a great diversity of optically pure allylglycine derivatives (Scheme 1).



Scheme 1



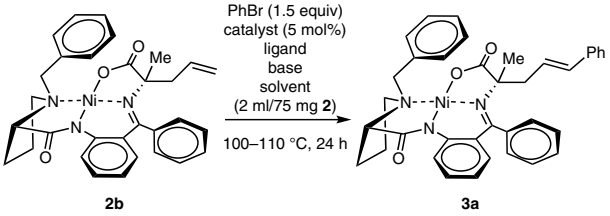
Scheme 2

Initially, starting compounds glycine–Ni–(*S*)-BPB (**1a**) and alanine–Ni–(*S*)-BPB (**1b**) were synthesized according to a published procedure.[19] Compounds **1a**,**b** were functionalized with allyl bromide promoted by NaOH in DMF to obtain starting materials **2a**,**b** in 85% and 87% yields, respectively (Scheme 2). These S_N2 reactions proceeded stereoselectively due to kinetic as well as thermodynamic control and yielded (*S*)-allylglycine–Ni–(*S*)-BPB (**2a**) and (*S*)-allylalanine–Ni–(*S*)-BPB (**2b**) in high enantiomeric excess.[20]

To find the optimal conditions for the Heck reaction we started with $Pd(PPh_3)_4$ as catalyst and examined different bases (Table 1). It was found that K_3PO_4 resulted in lower yields compared to NEt_3 and HN^iPr_2. The best yield was obtained with HN^iPr_2 as a 1:1 mixture with the solvent (Table 1, entry 8). Different ratios led to diminished yields of **3a**. Dioxane was the optimal solvent, while DMF gave similar results at higher temperature (Table 1, entries 1–5). Nonpolar solvents such toluene or heptane did not dissolve **2b** completely and resulted in poor yields (Table 1, entries 6 and 7). Although we examined different catalysts, the readily available $Pd(PPh_3)_4$ gave the highest yield.[21]

With optimized reaction conditions in hand we synthesized a range of derivatives to investigate the scope of this reaction. Electron-rich as well as electron-poor aryl bromides were tested and both achieved good to very good yields (Table 2). *ortho*-Substituted aryl bromides such as 2-bromotoluene **3f** led to slightly lower yields (Table 2, entry 6). The alkyl group of the starting material **2b** did not affect the yield. For example, **3a** (Ar = Ph, R = H) and **3j** (Ar = Ph, R = Me) resulted in 88% and 91% yields, respective-

Table 1 Optimization of the Heck Reaction[a]

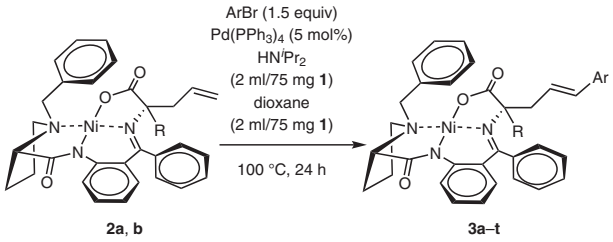


Entry	Catalyst	Ligand (mol%)	Solvent	Base (mL)	Temp (°C)	Yield (%)[b]
1	$Pd(PPh_3)_4$	–	DMF	K_3PO_4[c]	110	36
2	$Pd(PPh_3)_4$	–	DMF	Et_3N (2.0)	110	63
3	$Pd(PPh_3)_4$	–	DMF	HN^iPr_2 (2.0)	110	77
4	$Pd(PPh_3)_4$	–	DMF	HN^iPr_2 (4.0)	110	48
5	$Pd(PPh_3)_4$	–	DMF	HN^iPr_2 (0.7)	110	36
6	$Pd(PPh_3)_4$	–	toluene	HN^iPr_2 (2)	100	22
7	$Pd(PPh_3)_4$	–	heptane	HN^iPr_2 (2)	100	0
8	$Pd(PPh_3)_4$	–	dioxane	HN^iPr_2 (2)	100	88
9	$PdCl_2(PPh_3)_2$	–	dioxane	HN^iPr_2 (2)	100	38
10	$Pd(OAc)_2$	PCy_3 (10)	dioxane	HN^iPr_2 (2)	100	30
11	$Pd(dba)_2$	XPhos (10)	dioxane	HN^iPr_2 (2)	100	41
12	$Pd(dba)_2$	$HP^tBu_3BF_4$ (10)	dioxane	HN^iPr_2 (2)	100	64
13	$Pd(dba)_2$	$MeP(^tBu)_2$(10)	dioxane	HN^iPr_2 (2)	100	20
14	$Pd(dba)_2$	dppe (5)	dioxane	HN^iPr_2 (2)	100	24
15	$Pd(dba)_2$	dppf (5)	dioxane	HN^iPr_2 (2)	100	27

[a] Reaction of 75 mg **2b** in 2 mL solvent.
[b] Isolated yields.
[c] 5 equiv base in 2 mL DMF.

ly (Table 2, entries 1 and 10). Based on the ^{1}H NMR spectra it was found that the double bond was exclusively *E*-configurated.

Table 2 Synthesis of Compounds **3a–t**[a]



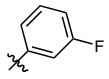
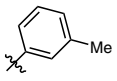
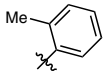
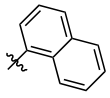
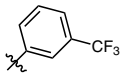
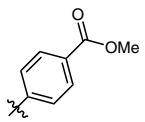
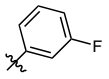
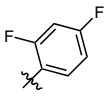
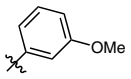
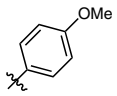
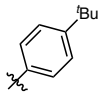
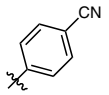
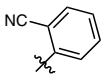
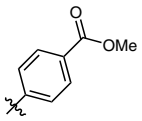
Entry		R	Ar	Yield (%)
1	**3a**	Me		88
2	**3b**	Me		51
3	**3c**	Me		92
4	**3d**	Me		89
5	**3e**	Me		80
6	**3f**	Me		72
7	**3g**	Me		58
8	**3h**	Me		77
9	**3i**	Me		81
10	**3j**	H		91

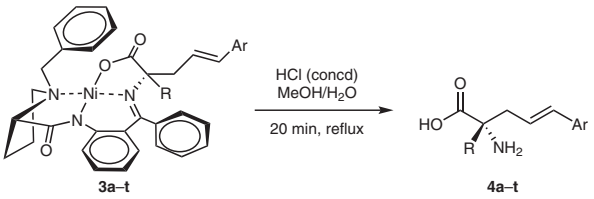
Table 2 (continued)

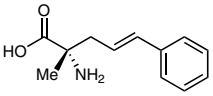
Entry		R	Ar	Yield (%)
11	**3k**	H		46
12	**3l**	H		85
13	**3m**	H		83
14	**3n**	H		67
15	**3o**	H		63
16	**3p**	H		29
17	**3q**	H		75
18	**3r**	H		87
19	**3s**	H		88
20	**3t**	H		87

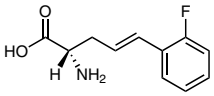
[a] Isolated yields.

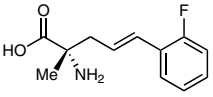
The Ni complexes **3a–t** were cleaved following a known procedure, in order to obtain the free amino acids **4a–t** (Table 3).[17,22] Afterwards the free amino acids were purified using a cation-exchange column. The procedure worked well for most of the synthesized derivatives. From the ^{1}H NMR spectra of the amino acids the *E*/*Z*-selectivity was analyzed and it was found that the Heck reaction gave exclusively the *E*-isomer of amino acids **4a–t**.

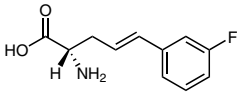
Table 3 Synthesis of Compounds **4a–t**[a]

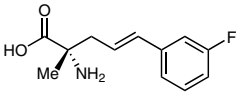


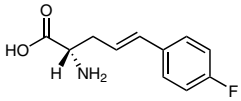

4a (85%)

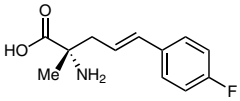

4k (96%)

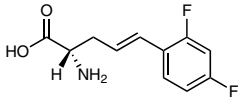

4b (91%)

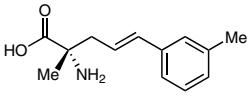

4l (97%)

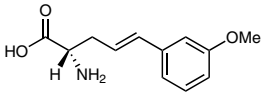

4c (91%)

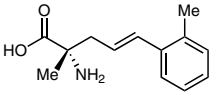

4m (83%)

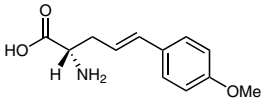

4d (93%)

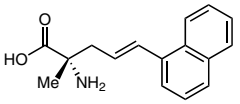

4n (80%)

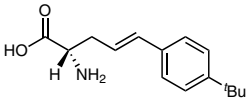

4e (57%)

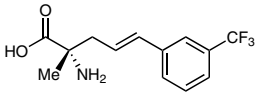

4o (85%)

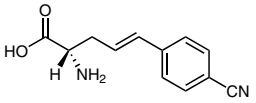

4f (93%)

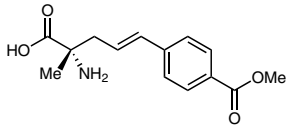

4p (83%)

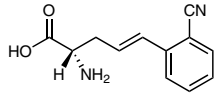

4g (88%)

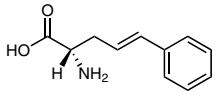

4q (91%)

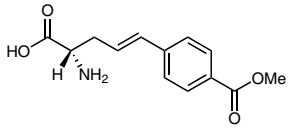

4h (90%)


4r (87%)


4i (83%)


4s (88%)


4j (91%)


4t (87%)

[a] Isolated yields.

In addition, compound **4l** was selected to check the enantiomeric purity of the synthesized amino acids via HPLC on a chiral-phase column. The enantiomeric purity from starting material **2a** (ee >99%) was maintained during the Heck reaction and subsequent cleavage gave **4l** with ee >99% (see Supporting Information).

In conclusion, we have demonstrated a straightforward strategy to synthesize a range of 2-amino-4-pentenoic acids. The reaction proceeds enantioselectively as well as showing *E*-selectivity. Overall 20 different amino acids were prepared in good to excellent yields with ee >99%.

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Supporting Information

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(21) **(*S*,*E*)-2-Amino-2-methyl-5-[phenyl]pent-4-enoic acid–Ni–(*S*)-BPB (3a)**

Compound **2b** (221 mg, 1.0 equiv), $Pd(PPh_3)_4$(23 mg, 0.05 equiv), and bromobenzene (72 µl, 1.7 equiv) were added to a pressure tube and dissolved in 1,4-dioxane (6 ml, 15 l/mol **2b**) and HN^iPr_2 (6 mL, 15 l/mol **2b**). The mixture was stirred at 101 °C for 24 h. After cooling to room temperature it was diluted with ethyl acetate and washed with water. The organic layer was dried with Na_2SO_4 and filtered. The solvent was removed under reduced pressure, and the residue was purified by silica column chromatography (ethyl acetate/heptanes, 2:1 >> 1:0) to yield **3a** as a red solid; yield 88%, mp 112–113 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.27 (s, 3 H, CH_3), 1.35–1.74 (m, 1 H, CH_2), 1.82–1.99 (m, 1 H, CH_2), 2.01–2.25 (m, 2 H, CH_2), 2.48–2.73 (m, 3 H, CH_2), 3.27 (dd, ^3J = 9.8 Hz, ^3J = 7.1, 1 H, CH), 3.42–3.55 (m, 1 H, CH_2), 3.61 (d, ^2J = 12.7 Hz, 1 H, CH_2Ph), 4.40 (d, ^2J = 12.7 Hz, 1 H, CH_2Ph), 6.58–6.74 (m, 3 H, CH), 6.85–7.00 (m, 1 H, CH), 7.03–7.19 (m, 2 H, CH), 7.21–7.57 (m, 11 H, CH), 7.61–7.74 (m, 1 H, CH), 7.96–8.10 (m, 3 H, CH). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 23.1 (CH_3), 29.7, 30.7, 43.9, 63.6 (CH_2), 70.2 (CH), 78.7 (C), 120.9, 124.0, 124.2, 126.8, 127.2, 127.7, 128.0, 128.3 (CH), 128.7 (C) 128.8, 129.0, 129.1, 129.7, 130.8, 131.9 (CH), 133.5 (C), 133.7, 134.7 (CH), 136.8, 137.3, 142.0 (C), 172.8 (C=N), 180.7 (C=O), 181.9 (C=O). IR (ATR): ν = 3057 (w), 3025 (w), 2922 (br, w), 2867 (w), 1668 (m), 1634 (s), 1594 (w), 1574 (w), 1534 (w), 1495 (w), 1469 (w), 1436 (m), 1355 (s), 1331 (m), 1312 (w), 1287 (w), 1250 (s), 1163 (m), 1118 (w), 1062 (w), 1000 (w), 964 (m), 927 (w), 885 (w), 824 (w), 748 (s), 695 (s), 618 (w), 563 (w), 540 (m) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 627 (5) [M^+], 585 (15), 584 (13), 583 (32), 510, (7), 492 (4), 440 (4), 439 (4), 425 (4), 347 (1), 328 (2), 280 (2), 278 (2), 161 (9), 160 (89). ESI-HRMS: *m/z* calcd for $C_{37}H_{36}N_3NiO_3$ [M + H^+]: 628.21047; found: 628.20997; *m/z* calcd for $C_{37}H_{36}N_3{}^{60}NiO_3$ [M + H^+]: 630.20798; found: 630.20805; *m/z* calcd for $C_{37}H_{35}N_3NiNaO_3$ [M + Na^+]: 650.19241; found: 650.19232; *m/z* calcd for $C_{37}H_{35}N_3Na^{60}NiO_3$ [M + Na^+]: 652.18992; found: 652.18952.

(22) **(*S*,*E*)-2-Amino-2-methyl-5-[phenyl]pent-4-enoic acid (4a)**

Compound **3a** (190 mg, 1.0 equiv) was dissolved in MeOH/H_2O (10 ml/5 ml), and HCl (12 M, 1.5 ml) was added dropwise. The stirred mixture was heated to reflux for 20 min (during which time the color changed from red to green). After cooling to room temperature the mixture was diluted with water and extracted with DCM four times. The aqueous layer was treated with 5% aq NH_3solution to reach pH 2. The solution was further purified by cation exchange column (Dowex 50WX8 H^+, see Supporting Information for details) to yield **4a** as white solid; yield 85%, mp 267–268 °C. ^{1}H NMR (300 MHz, CD_3OD): δ = 1.64 (s, 3 H, CH_3), 2.79 (dd, ^3J = 7.6 Hz, ^2J = 14.5 Hz, 1 H, CH_2), 2.87 (dd, ^3J = 7.6 Hz, ^2J = 14.5 Hz, 1 H, CH_2), 6.21 (dt, ^3J = 7.6 Hz, ^3J = 15.4 Hz, 1 H, C=C),

6.65 (d, ^3J = 15.4 Hz, 1 H, C=C), 7.19–7.34 (m, 3 H, Ph), 7.40–7.45 (m, 2 H, Ph). ^{13}C NMR (75 MHz, CD_3OD): δ = 22.7 (CH_3), 41.8 (CH_2), 61.2 (C), 121.8 (CH), 127.7, 129.1, 129.7, 137.8 (CH), 138.1 (C), 173.5 (COOH). IR (ATR): ν = 3000 (br, m), 1656 (br, w), 1540 (w), 1573 (s), 1494 (w), 1450 (w), 1397 (s), 1366 (m), 1287 (w), 1264 (w), 1239 (w), 1130 (w), 1070 (w), 965 (s), 883 (w), 788 (w), 739 (s), 690 (s), 629 (w), 587 (w), 553 (w) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 206 (4), 205 (2) [M$^+$], 194 (5), 193 (13), 178 (4), 161 (6), 160 (64), 159 (12), 144 (12), 143 (16), 129 (13), 128 (34), 118 (31), 117 (87), 116 (50), 115 (86), 102 (12), 91 (60), 90 (6), 89 (42), 88 (100), 80 (16), 77 (15), 65 (13), 63 (11). HRMS (EI): *m/z* calcd for $C_{12}H_{16}NO_2$ [M + H$^+$]: 206.11756; found: 206.11778.