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Ligand-free palladium catalysed Heck reaction of methyl 2-acetamido acrylate and aryl bromides as key step in the synthesis of enantiopure substituted phenylalanines

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Dedicated to Jean-Pierre Genêt on the occasion of his 60th birthday

Abstract

A range of substituted aryl bromides were coupled with methyl 2-acetamido acrylate using ligand-free palladium catalysis. Subsequently asymmetric hydrogenation with Rh/MonoPhos yielded substituted phenylalanines in high enantioselectivities (e.e. 92–99%).

Keywords: Ligand-free; Palladium; Heck; Substituted phenylalanines; MonoPhos

1. Introduction

Current methods of drug development are still largely based upon mimicking the natural substrate for an enzyme or a receptor. Since these are mostly peptides, problems arise because of their hydrolytic instability in biological systems. Stabilisation of peptide type structures is often done by the use of non-natural amino acids [1]. The use of non-natural amino acids in drug development is in turn dependent upon their ready availability. As enantiopure substituted phenylalanines are increasingly used in peptidomimetics [2], we decided to investigate scaleable methods for their production. Since we, in close collaboration with the group of Feringa, have recently developed the use of low-cost monodentate phosphoramidites as ligands for rhodium-catalysed asymmetric hydrogenation of olefins [3], we were interested in synthetic methods towards dehydrophenylalanines.

A wide range of methods has been reported for the preparation of aromatic dehydroamino acids [4]. Amongst these the classical Erlenmeyer synthesis with subsequent hydrolysis of the 5(4*H*)-oxazolone is most frequently employed. As the Pd-catalysed Heck reaction tolerates a wide array of functional groups we were particularly attracted by the coupling of dehydroalanine derivatives (**1**) [5] with aryl halides, first reported by the groups of Naso [6] and Hegedus [7]. The combination of this Heck reaction followed by (asymmetric) hydrogenation, disclosing an easy access to unnatural phenylalanines, has been demonstrated by several groups (see Scheme 1) [8].

However, in most cases expensive aryl iodides were used as starting materials. The rare cases where aryl bromides were used, large amounts of palladium, usually in combination with phosphine ligands, were employed as catalyst. In fine chemical processes the presence of phosphine ligands is not desirable, since they often hamper the isolation and purification of the product. We have recently found that it is possible to perform the Heck reaction on aryl bromides with ligand-free palladium, using $Pd(OAc)_2$ only, as long as the amount of palladium is low (usually between 0.01 and

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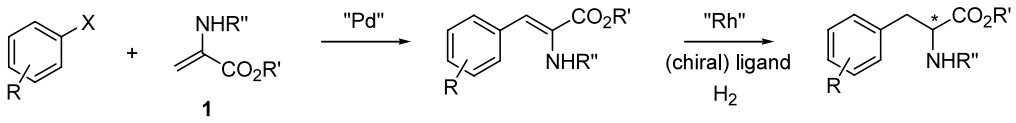


Scheme 1.

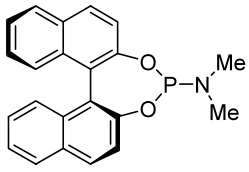
0.1 mol%) [9]. These low palladium concentrations prevent the precipitation of palladium black during the ligand-free Heck reaction.

In this note we describe the synthesis of a range of substituted phenylalanines by using consecutively a ligand-free Heck reaction on aryl bromides followed by an asymmetric hydrogenation reaction catalysed by Rh/MonoPhos (**3**).

2. Results

Initial tests on the Heck reaction between 4-fluorobromobenzene and methyl 2-acetamido acrylate (**1a**) in which we screened several variables of the reaction (32 reactions performed simultaneously in the ASW 2000 of Chemspeed) resulted in the following optimised conditions that could be used: 0.3 mol% of $Pd(OAc)_2$ in combination with $C_6H_5CH_2NEt_3Br$ and *i*-$PrNEt_3$ or NaOAc as base. All reactions were performed in NMP at 125 °C. The products were purified by crystallisation from EtOAc. Table 1 shows that the method works well for electron-poor and electron-rich aryl bromides. The Heck reaction gave moderate isolated yields of **2**, but these are comparable with the yields reported by others using more expensive aryl iodides, and/or higher palladium loadings and/or a phosphine ligand [6–8]. Possible reasons for the moderate yields are the presence of the electron donating nitrogen substituent on the olefin, which retards the reaction. Secondly, it is likely that the NaBr, which is present in the dipolar aprotic solvent, reacts with the methyl ester **2** to form MeBr and the sodium salt of the acetamido-cinnamate. Indeed, we have found the acid upon closer inspection of the aqueous phase during work-up. Although reported by others [6], our attempts to perform the Heck reaction on 2-acetamido acrylic acid were unsuccessful. The reactions led to the formation of gels, presumably caused by polymerisation of the 2-acetamido acrylic acid.

In our efforts to simplify the reaction mixture we were delighted to see that the coupling of methyl 2-acetamido acrylate (**1a**) with 4-bromoacetophenone also proceeds smoothly with only 0.05 mol% of $Pd(OAc)_2$ and without any tetraalkylammonium salt (see entry 13).



3 MonoPhos™

All the obtained dehydrophenylalanine derivatives were hydrogenated at 5 bar H_2 using 1 mol% of $[Rh(COD)_2]BF_4$ and 1.1 mol% of enantiomerically pure MonoPhos (**3**) in CH_2Cl_2 [10]. As can be seen from the table the ligand MonoPhos induces excellent e.e. values for all the different substrates tested. The observed turnover frequencies (200–400 h^{-1}, depending on the substrate) are similar as when the substrates are made by the classical Erlenmeyer-hydrolysis sequence [3e], indicating low impurity profiles in the substrates obtained via this Heck coupling. The cyano-substituted analogue did not give a full conversion after 2 h, most likely due to competitive coordination of the cyano-moiety to the rhodium. The asymmetric hydrogenation of the *p*-chloro substituted compound was also carried out with a substrate to catalyst ratio of 1000, yielding pure product with 94% e.e. (80 min, at 5 bar of H_2, room temperature, CH_2Cl_2).

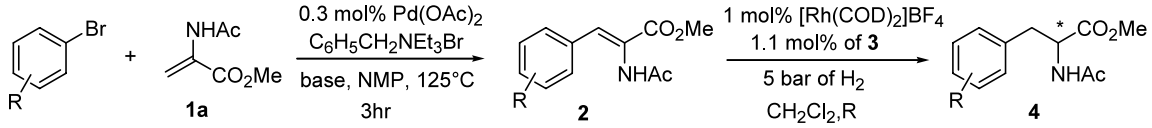
In conclusion, we have shown that a variety of substituted phenylalanines can be produced using a cost-effective sequence of two homogeneously catalysed steps. The ligand-free palladium catalysed arylation of methyl 2-acetamido acrylate using aryl bromides followed by Rh/MonoPhos catalysed hydrogenation of the acetamido-cinnamate ester gave good yields of the various substituted *N*-Acetyl phenylalanine esters in very high enantioselectivities.

3. Experimental

3.1. General procedure for the Heck reaction

A 50 ml Schlenk flask was filled with aryl bromide (13.0 mmol), methyl 2-acetamido acrylate (2.07 g, 14.5 mmol), base (15.0 mmol), $C_6H_5CH_2NEt_3Br$ (163 mg, 0.60 mmol), $Pd(OAc)_2$ (8.8 mg, 0.039 mmol, 0.30 mol% with respect to aryl bromide), and NMP (27 ml). Nitrogen atmosphere was applied, a stirring bar was

Table 1
Methyl *N*-acetyl-phenylalanines by ligand-free Heck reaction on **1a** followed by asymmetric hydrogenation using Rh/MonoPhos [a]



Entry	Base	R	2	Isolated yield of **2** (%)	Completion of hydrogenation (min)	e.e. of **4** [b] (%)
1.	*i*-Pr_2NEt	4-F	**a**	67	25	96
2.	*i*-Pr_2NEt	3-F	**b**	62	30	95
3.	*i*-Pr_2NEt	2-F	**c**	31	15	95
4.	*i*-Pr_2NEt	4-COMe	**d**	71	15	99
5.	*i*-Pr_2NEt	4-OMe	**e**	23	[c]	94
6.	*i*-Pr_2NEt	4-Cl	**f**	62	20	94
7.	*i*-Pr_2NEt	3,4-di-Cl	**g**	55	30	99
8.	*i*-Pr_2NEt	4-CN	**h**	53	[d]	92
9.	NaOAc	4-Ph	**i**	63	25	95
10.	NaOAc	4-NO_2	**j**	44	[c]	95
11.	NaOAc	2-F,4-Ph	**k**	56	25	93
12.	NaOAc	4-COPh	**l**	52	30	94
13. [e]	NaOAc	4-COMe	**d**	55	15	99

[a] General method of Heck coupling: aryl bromide (13.0 mmol), **1a** (14.5 mmol), base (15.0 mmol), $C_6H_5CH_2NEt_3Br$ (0.60 mmol), $Pd(OAc)_2$ (0.039 mmol, 0.30 mol% with respect to aryl bromide), NMP (27 ml), at 125 °C during 3 h. General method of asymmetric hydrogenation: Dehydrophenylalanine **2** (1.0 mmol), $[Rh(COD)_2]BF_4$ (0.010 mmol), MonoPhos (0.011 mmol), CH_2Cl_2 (5 ml), H_2 (5 bar), room temperature, full conversions were obtained in all cases unless stated otherwise.

[b] E.e. values were determined by chiral HPLC.

[c] Not determined.

[d] Conversion is only 70% (2 h reaction time).

[e] Conditions of Heck reaction: 4-bromoacetophenone (26.4 mmol), **1a** (31.7 mmol), NaOAc (31.3 mmol), $Pd(OAc)_2$ (0.013 mmol, 0.049 mol% with respect to aryl bromide), NMP (34 ml) at 130 °C during 3 h.

added and the vessel was closed with a septum. The mixture was stirred and heated to 125 °C. After 3 h reaction time, the mixture was cooled and poured into water (50 ml) and extracted with EtOAc (four times 50 ml). The collected organic layers were washed with water (three times 50 ml), brine (50 ml), dried with Na_2SO_4, filtered and the filtrate was concentrated. The crude product was recrystallised with EtOAc. Yields are given in Table 1. Most products were characterised by ^{1}H- and ^{13}C-NMR, m.p. and exact mass determination.

2a: ^{1}H-NMR ($CDCl_3$) δ 7.37 (m, 3H), 6.97 (m, 3H), 3.79 (s, 3H), 2.09 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 169.22, 166.12, 130.37, 123.95 (C), 132.03, 131.78, 116.19, 115.90 (CH), 53.12, 23.81 (CH_3); M.p. 140.6–142.3; Calculated mass: 237.0801; Observed mass: 237.0788.

2b: ^{1}H-NMR ($CDCl_3$) δ 7.33 (m, 2H), 7.20 (m, 2H), 7.04 (m, 2H), 3.87 (s, 3H), 2.16 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ169.04, 165.92, 164.04, 152.98 (C), 130.96, 130.41, 116.83, 116.56, 116.12 (CH), 53.22, 23.84 (CH_3); M.p. 104.2–104.8; Calculated mass: 237.0801; Observed mass: 237.0775.

2c: ^{1}H-NMR ($CDCl_3$) δ 7.45 (s, 2H), 7.34 (m, 1H), 7.12 (s, 3H), 3.88 (s, 3H), 2.12 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 174.18, 168.34, 164.56, 163.20, 159.94 (C), 134.82, 129.77, 129.01, 124.70, 115.06 (CH), 51.71, 22.15 (CH_3); M.p. 149.7–150.0; Calculated mass: 237.0801; Observed mass: 237.0798.

2d: ^{1}H-NMR ($CDCl_3$) δ 7.95 (d, $J = 8.4$ Hz, 2H), 7.52 (d, $J = 8.4$ Hz, 2H), 7.42 (s, 1H), 7.16 (s, 1H), 3.89 (s, 3H), 2.61 (s, 3H), 2.15 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 197.75, 196.77, 165.75, 138.37, 136.96, 128.82 (C), 130.18, 129.36, 128.69 (CH), 52.65, 27.12, 22.80 (CH_3); M.p. 168.9–170.0; Calculated mass: 261.1001; Observed mass: 261.0984.

2e: ^{1}H-NMR ($CDCl_3$) δ 9.56 (s, 1H), 7.63 (d, $J = 8.8$ Hz, 2H), 7.21 (s, 1H), 7.00 (d, $J = 8.8$ Hz, 2H), 3.34 (s, 3H), 2.51 (s, 3H), 2.10 (s, 3H).

2f: ^{1}H-NMR ($CDCl_3$) δ 7.37 (m, 5H), 7.05 (s, 1H), 3.87 (s, 3H), 2.15 (s, 3H) ^{13}C-NMR ($CDCl_3$) δ 169.12, 166.00, 135.56, 132.72, 124.64 (C), 131.26, 129.14 (CH), 53.17, 23.80 (CH_3); M.p. 168.9–170.2; Calculated mass: 253.0506; Observed mass: 253.0510.

2g: ^{1}H-NMR ($CDCl_3$) δ 7.53 (s, 1H), 7.43 (d, $J = 8.1$ Hz, 1H), 7.31 (s, 1H), 7.27 (m, 1H), 7.18 (s, 1H), 3.88 (s, 1H), 2.16 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 169.71, 165.59, 134.60, 128.12 (C), 131.62, 131.05, 129.97, 128.59 (CH), 52.67, 22.78 (CH_3); M.p. 167.6–168.3; Calculated mass: 287.0116; Observed mass: 287.0108.

2h: ^{1}H-NMR ($CDCl_3$) δ 7.64 (d, $J = 7.6$ Hz, 2H), 7.50 (d, $J = 7.6$ Hz, 2H), 7.37 (s, 1H), 3.90 (s, 3H), 2.15 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 169.79, 166.40, 165.61, 138.65, 118.99, 111.15, (C), 132.72, 130.60, 128.28 (CH), 52.72, 22.81 (CH_3); M.p. 208.0–209.2; Calculated mass: 244.0848; Observed mass: 244.0866.

2i: ^{1}H-NMR ($CDCl_3$) δ 7.52 (m, 5H), 7.85 (d, $J = 6.9$ Hz, 2H), 7.38 (s, 1H), 7.31 (d, $J = 6.9$ Hz, 2H), 3.80 (s, 3H), 2.11 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 169.41, 166.21, 145.07, 142.49, 140.52 (C), 133.03, 132.56, 132.24, 130.68, 129.28, 128.18, 127.55, 127.42, 124.45 (CH), 53.09, 23.78 (CH_3); M.p. 159.0–159.3; Calculated mass: 295.1208; Observed mass: 295.1200.

2j: ^{1}H-NMR ($CDCl_3$) δ 9.88 (s, 1H), 8.26 (d, $J = 8.8$ Hz, 2H), 7.86 (d, $J = 8.8$ Hz, 2H), 7.20 (s, 1H), 3.75 (s, 1H), 2.03 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 169.79, 165.58, 147.27, 140.73, 130.03 (C), 131.00, 127.52, 123.96 (CH), 52.78, 22.86 (CH_3); M.p. 166.9–167.6.

2k: ^{1}H-NMR ($CDCl_3$) δ 7.57 (m, 2H), 7.44 (m, 6H), 7.31 (s, 1H), 7.11 (s, 1H), 3.87 (s, 3H), 2.20 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 165.98, 131.04, 130.81, 124.87 (C), 129.35, 129.30, 128.91, 128.45, 126.43 (CH), 53.26, 23.98 (CH_3); M.p. 157.5–158.2.

2l: ^{1}H-NMR ($CDCl_3$) δ 9.84 (s, 1H), 7.74 (m, 7H), 7.59 (m, 2H), 7.22 (s, 1H), 3.74 (s, 3H), 2.04 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 195.66, 170.02, 165.94, 138.10, 137.46, 137.38, 129.10 (C), 133.32, 130.34, 130.27, 130.09, 129.43, 129.16 (CH), 52.83, 22.99 (CH_3); M.p. 172.7–174.0; Calculated mass: 323.1158; Observed mass: 323.1121.

3.2. Asymmetric hydrogenation

Glass tubes, suitable for a parallel reactor were individually filled with 1 mmol of substrate, 0.01 mmol (1 mol%) of $Rh(COD)_2BF_4$ and 0.011 mmol of ligand **3**. The glass tubes were placed in the reactor and 5 ml of CH_2Cl_2 was added. The reactors were then purged for with N_2 (10 cycles) before applying a hydrogen atmosphere of 5 bars. The pressure was kept constant during the reaction and the hydrogen uptake was monitored. After completion of the reaction, the reactors were opened and samples were taken which were filtered over a short silica column and subjected to e.e. determination by chiral HPLC. Conversions were determined by means of ^{1}H-NMR. Results are depicted in Table 1.

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