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Pd-catalyzed asymmetric conjugate addition of arylboronic acids to 2-nitroacrylates: a facile route to β²-homophenylglycines

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ABSTRACT

Asymmetric conjugate addition of arylboronic acids to 2-nitroacrylamide in the presence of cationic palladium–Chiraphos complex proceeds with high yield and enantioselectivity (73–89% ee) using as low as 0.05–0.25 mol % of the catalyst. The adducts can be smoothly transformed into the corresponding β²-homophenylglycines in two simple steps.

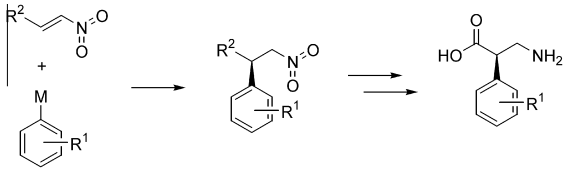
Introduction

The preparation of enantiopure β²-amino acids has gained increasing attention in recent years due to the fact that they are components of numerous natural products and precursors of active pharmaceutical ingredients, β-lactams, and β-peptides. Syntheses and applications of β²-amino acids have already been the subject of extensive reviews.[1]

As a part of an ongoing project concerning the synthesis of β²-amino acids,[2] we set a goal to develop a general catalytic, enantioselective approach to β²-homophenylglycines implementing nitroacrylate strategy, an addition of metalated aryl species to nitroacrylate esters, and derivatives followed by uncomplicated transformation into target compounds (Scheme 1).

Discussion

For practical reasons the source of structurally diverse aryl groups should be readily available commercially, environmentally benign, cheap, easy to handle, and stable. Arylboronic acids meet all the requirements and can be used in combination with those transition metal catalysts (Rh, Pd) which allow facile B-Rh/Pd transmetalation and aryl group transfer to Michael acceptors.



Scheme 1. From nitroacrylates to β²-homophenylglycines.

Numerous Rh-catalyzed enantioselective addition reactions of arylboronic acids to nitroalkenes were reported so far,[3] some publications demonstrated utility of the obtained nitro compounds for transformation into other functional groups and molecular systems.

Enantioselective Pd-catalyzed addition of arylboronic acids to common Michael acceptors like enones was first discovered and later extensively studied by Miyaura and co-workers.[4] They showed that cationic $[Pd(Chiraphos)(PhCN)_2](SbF_6)_2$ complex exhibits the highest activity: TONs up to 9900 with 0.01 mol % of catalyst loading at >98% yield and >89% ee. Minnaard and co-workers successfully applied Me-DuPHOS/$Pd(O_2CCF_3)_2$ based catalysts.[5] In spite of this fact only few examples of Pd-catalyzed additions of aryl species to nitroalkenes have been known, all of them racemic.[6]

It should be noted that application of rhodium catalysis to the studied reaction is hampered by high costs of corresponding precatalysts (1–3 mol % amounts are usually required), and by the fact that basic reaction conditions used for the addition of organoboronic acids are not generally compatible with active nitroalkene

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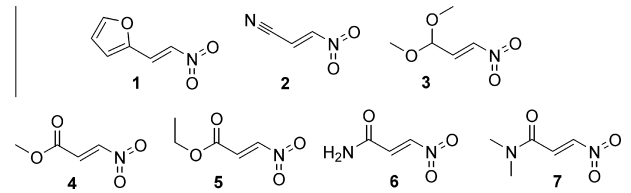


Figure 1. Nitroalkene substrates.

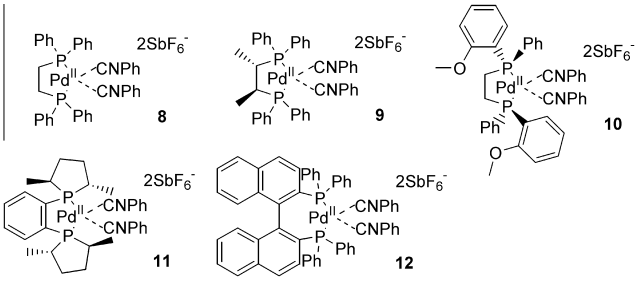


Figure 2. Pd-catalysts employed.

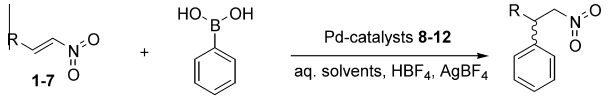
substrates, especially 2-nitroacrylates, leading to their reasonable decomposition. Therefore we decided to explore a more favorable combination of readily available 2-nitroacrylate derivatives and their precursors (Fig. 1)[7] with $ArB(OH)_2$ and phosphine–Pd catalysts (Fig. 2).

Furyl derivative **1** appeared to be too unreactive under the reaction conditions, and nitrile **2** underwent complete decomposition. Dimethylacetal **3** was more promising showing up to 67% yield and 85% ee (Table 1, entries 8–11), however reasonable amounts of hydrate $(CH_3O)_2CH(OH)CH_2NO_2$ (up to 20%) were isolated together with the desired product. The conjugated addition of water to the C=C bond could be mostly suppressed by addition of HBF_4, but this led in its turn to partial hydrolysis of the acetal group thus reducing the yield. Nitroacrylates **4** and **5** exhibited high reactivity but the reaction was accompanied by numerous side reactions: diphenyl formation and formation of cinnamic acid esters, which could result from inverted addition to the C=C bond followed by NO_2-group elimination. The latter substrates brought generally low yields and moderate ee values (entries 12–14). 2-Nitroacrylamides **6** and **7** (entries 15–23) showed most clean reactions almost without substrate decomposition and substrate derived side products (<5%, GC). Chiraphos catalyst **9** exhibited better activity and enantioselectivity than that derived from DIPAMP **10**. Other catalysts revealed less promising or even no activity. The 2-nitroacrylamide **6** was chosen for further optimizations for best stability and ease of handle.

Extensive solvent screening showed that all tested solvents can be divided into two parts (Table 2). The first group comprises mainly of polar aprotic DMF, DMA, tetramethylurea, NMP, DMSO, acetonitrile, sulfolane, and PEG-400 which caused relatively slow main reaction, but also very slow protodeboronation of $PhB(OH)_2$. The second group (acetone, MeOH, EtOH, dioxane, THF, and nitromethane) facilitated both reactions. However, as appeared, an important requirement for organic co-solvents is their miscibility with water. Solvents which do not form binary aqueous solutions with high water content (e.g., TBME, toluene) proved to be an inappropriate medium for very slow reaction rates.

A minor influence of solvent on enantioselectivity should be also noted. Finally we chose to use THF as a compromise solution of several practical factors (protodeboronation, reaction rate, and toxicity). The ratio THF–H_2O 2:1 and substrate concentration ~1.7 M appeared to be optimal, as the reaction became sluggish

Table 1
Initial screening of substrates, catalysts, and conditions



Entry[a]	Alkene	Solvent	Catalyst	Yield[b] (%)	ee[c] (%)
1	1	aq acetone	8	~5 (GC)[d]	—
2	2	aq DMA	8	0 (GC)[e]	—
3[f]	3	aq acetone	8	51	—
4	4	aq acetone	8	33	—
5	5	aq DMA	8	36	—
6	6	aq DMA	8	78	—
7	7	aq DMA	8	94	—
8[f]	3	aq DMA	9	67	83
9[f]	3	aq acetone	9	47	85
10[f]	3	aq DMA	10	42	51
11[f]	3	aq DMA	11	17	38
12	4	aq DMA	9	9	22
13	4	aq DMA	10	15	49
14	5	aq DMA	10	16	58
15	6	aq DMA	9	86	81
16	6	aq DMA	10	36	75
17	6	aq acetone	10	72	70
18	6	aq DMA	11	49	41
19	6	aq acetone	12	0	—
20	7	aq DMA	9	81	84
21	7	aq acetone	9	76	85
22	7	aq DMA	10	68	61
23	7	aq DMA	11	56	64

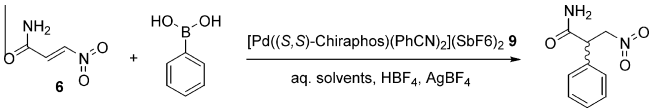
[a] The reaction was carried out on a 2 mmol scale with $PhB(OH)_2$ (4 mmol), catalyst (0.04 mmol), $AgBF_4$ (0.2 mmol), 50% aq HBF_4 (6 mmol) in 12 ml of solvent–H_2O 2:1 mixture at 20 °C for 18 h.
[b] Yield of isolated product if not indicated otherwise.
[c] Determined by chiral HPLC analysis.
[d] Marginal conversion of substrate.
[e] Substrate decomposition.
[f] Without HBF_4 and $AgBF_4$.

under different conditions. Last but not the least, the conditions allowed to reduce the amount of $PhB(OH)_2$ to 1.5 equiv.

In order to screen more chiral ligands and to check a possibility to generate the catalysts in situ we tested 4 precatalysts: $(Pd(acac)_2$, $PdCl_2$, $Pd(OAc)_2$, and $Pd(cod)Cl_2)$. It appeared that only $Pd(cod)Cl_2$ is inactive to catalyze the racemic background reaction without support of a phosphine ligand. Corresponding in situ generated catalysts were than tested in the reaction of 2-nitroacrylamide **6** and $PhB(OH)_2$ (Table 3).

All precatalysts in combination with Chiraphos demonstrated comparable results (entries 1–3), and $Pd(cod)Cl_2$ being slightly bet-

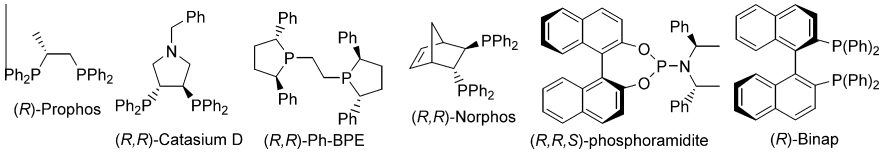
Table 2
Influence of solvents on the reaction of 2-nitroacrylamide **6**



Entry[a]	Solvent	Yield[b] (%)	ee[c] (%)
1	DMA/water	85	81
2	Acetone/water	72	81
3	MeOH/water	76	77
4	EtOH/water	81	81
5	*i*-PrOH/water	84	82
6	*t*-BuOH/water	88	83
7	THF/water	87	84

[a] The reaction was carried out on a 10 mmol scale with $PhB(OH)_2$ (15 mmol), $[Pd((S,S)\text{-Chiraphos})(PhCN)_2](SbF_6)_2$ catalyst (0.02 mmol), $AgBF_4$ (1 mmol), 50% aq HBF_4 (30 mmol) in 60 ml of solvent–H_2O 2:1 mixture at 20 °C for 18 h.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.

Table 3
Reaction of 2-nitroacrylamide **6** and $PhB(OH)_2$ with in situ generated catalysts



Entry[a]	Precatalyst and ligand	T (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	$Pd(acac)_2$ and Chiraphos	20	7	69	83
2	$Pd(OAc)_2$ and Chiraphos	20	7	77	87
3	$Pd(cod)Cl_2$ and Chiraphos	20	7	80	86
4	$Pd(cod)Cl_2$ and (*R,R*)-Norphos	50	65	>2	—
5	$Pd(cod)Cl_2$ and (*R,R*)-Ph-BPE	20	72	19	42
6	$Pd(cod)Cl_2$ and (*R,R*)-Catasium D	20	48	42	87
7	$Pd(cod)Cl_2$ and (*R*)-Prophos	20	8	83	63
8	$Pd(acac)_2$ and (*R*)-BINAP	60	8	51	0
9	$Pd(acac)_2$ and (*R,R,S*)-phosphoramidite[d]	60	4	56	0

[a] The reaction was carried out on a 4 mmol scale with $PhB(OH)_2$ (6 mmol), precatalyst (0.08 mmol), phosphine ligand (0.084 mmol), $AgBF_4$ (0.4 mmol), 50% aq HBF_4 (12 mmol) in 24 ml of THF–H_2O 2:1 mixture.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] 0.17 mmol (2 equiv) of the ligand was taken.

ter. Most of the tested ligands exhibited lower activity and/or enantioselectivity than those of Chiraphos. (*R*)-Binap and (*R,R,S*)-phosphoramidite furnished racemic product. This is in accordance with earlier observations that only P–C–C–P tethered diphosphine ligands are able to form active and enantioselective Pd-catalysts for the conjugate addition.

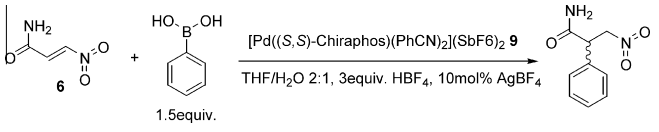
The catalyst loading was then stepwise reduced and the results are summarized in Table 4.

As low as 0.05 mol % of the catalyst was able to bring the reaction to full conversion albeit very slowly after 7 days. The amount of 0.25 mol % was chosen as optimal for further experiments.

The conditions were further optimized and the amount of $AgBF_4$ was reduced from 10 to 0.4 mol % relative to substrate without having influence on the reaction rate and enantioselectivity.

Attempts to replace HBF_4 with other strong non-nucleophilic acids ($HSbF_6$, HPF_6) did not bring any improvement. Apart from acceleration of protonolysis of intermediate C-bound palladium enolates, the addition of acid strongly increases the stability of 2-nitroacrylamide **6** against polymerization and formation of hydrate $NH_2COCH(OH)CH_2NO_2$.

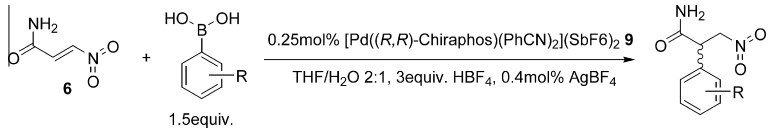
Table 4
Influence of catalyst loading



Entry[a]	Catalyst loading (mol %)	Time[b] (h)	Yield[c] (%)	ee[d] (%)
1	1.5	8	81	87
2	1	25	89	86
3	0.5	25	83	86
4	0.25	72	79	86
5	0.2	72	72	85
6	0.15	72	66	87
7	0.1	120	61	84
8	0.05	168	56	86

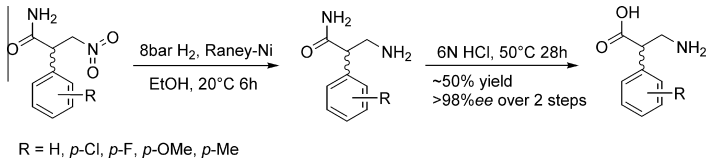
[a] The reaction was carried out on a 10 mmol scale with $PhB(OH)_2$ (15 mmol), $[Pd((S,S)\text{-Chiraphos})(PhCN)_2](SbF_6)_2$ catalyst, $AgBF_4$ (1 mmol), 50% aq HBF_4 (30 mmol) in 60 ml of THF–H_2O 2:1 mixture at 20 °C.
[b] The reaction was carried out until full conversion was achieved.
[c] Isolated yield.
[d] Determined by chiral HPLC analysis.

Table 5
Addition of substituted arylboronic acids



Entry[a]	Ar	Time	Yield[b] (%)	ee[c] (%)
1	*p*-ClPh	48	88	88, (*R*)-(+)
2	*p*-FPh	64	67	87, (*R*)-(+)
3	*p*-OMePh	24	44	73, (*R*)-(+)
4	*p*-MePh	64	71	82, (*R*)-(+)
5	*m*-MePh	48	79	86, (*R*)-(+)
6	*m*-ClPh	48	85	88, (*R*)-(+)
7	*m*-OMePh	24	65	82, (*R*)-(+)
8	*p*-BrPh	48	84[d]	89, (*R*)-(+)

[a] The reaction was carried out on a 20 mmol scale with $ArB(OH)_2$ (30 mmol), $[Pd((R,R)\text{-}(+)\text{-Chiraphos})(PhCN)_2](SbF_6)_2$ catalyst (0.05 mmol, 0.25 mol %), $AgBF_4$ (0.08 mmol, 0.4 mol %), 50% aq HBF_4 (60 mmol) in 130 ml of THF–H_2O 2:1 mixture at 20 °C.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] No Suzuki coupling products were determined.



Scheme 2. From nitroamides to β^2-homophenylglycines.

Temperature screening showed its little influence on enantioselectivity and big influence on the rate of the reaction (*i*-PrOH/H_2O 2:1, 10 mol % catalyst): 0 °C (48 h, 63%, 84% ee), 10 °C (30 h, 76%, 83% ee), 20 °C (16 h, 84%, 82% ee), 30 °C (3 h, 78%, 80% ee), 40 °C (2.5 h, 86%, 80% ee).

The optimized conditions were then applied to the addition of several substituted arylboronic acids to 2-nitroacrylamide **6** (Table 5).[8]

The results appeared to be similar to those obtained with phenylboronic acid except *p*-OMePhB$(OH)_2$ which underwent rapid protodeboronation, and the reaction resulted in an incomplete conversion and lower ee-value of corresponding nitroamide (entry 3).

Final transformation of substituted nitroamides to homochiral β^2-homophenylglycines proceeded in two straightforward steps (reduction of the nitro-group and amide hydrolysis). Recrystallization of target amino acids either as free bases or suitable salts furnished the products with >98% ee in ~50% yield over two steps (Scheme 2).

Comparison of optical rotation angle of unsubstituted-, *p*-OMe-, and *p*-F-β^2-homophenylglycines prepared using [Pd((*R*,*R*)-(+)-Chiraphos)$(PhCN)_2$]$(SbF_6)_2$ catalyst with previously published values leads to a conclusion that absolute configurations of the products obtained with this catalyst have to be assigned as (*R*).[9] Assuming an analogous reaction mechanism, the absolute configuration of other products obtained was assigned as indicated in Table 5.

In summary, a palladium–diphosphine catalyzed asymmetric conjugate addition of arylboronic acids to 2-nitroacrylate derivatives was developed. The reaction, which can be carried out without inert atmosphere in technical grade THF using up to 0.05% of catalyst, led to enantiomerically enriched 2-aryl-3-nitropropionamides (73–89% ee). The latter were transformed into enantiopure β^2-homophenylglycines on hundred gram scale with high yields in two straightforward steps.

Acknowledgment

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8. *A representative procedure for the asymmetric conjugate addition:* 2-Nitroacrylamide **6** (71.4 g, 615.1 mmol), *p*-chlorophenylboronic acid (125 g, 799.3 mmol), [Pd((*R*,*R*)-(+)-Chiraphos)(PhCN)2](SbF6)$_2$ catalyst (1.861 g, 1.54 mmol), and AgBF4 (0.479 g, 2.46 mmol) were dissolved in a mixture of THF (2.5 L), deionized H_2O (1.25 L), and HBF4 (324 g, 1845.3 mmol, 50% in H_2O). The turbid reaction was stirred at 20 °C for ~50 h under TLC control (ethyl acetate/hexane/MeOH 95:95:10, silica gel) until starting 2-nitroacrylamide **6** disappeared. The reaction was concentrated to remove THF and extracted twice with CH_2Clu (1500 ml and 600 ml). Combined organic phases were dried over Na_2SO_4, filtered, and evaporated to give the crude (+)-2-(4-chlorophenyl)-3-nitropropionamide (133.25 g, 94.7% yield, >90% chemical purity). Chiral HPLC (Daicel Chiralpak AS, Heptane/Isopropanol 30:70, 0.7 ml/min, UV 254 nm, R_t = 8.7 min and 14.3 min) showed 88% ee. The product can be used as is in the next steps. Otherwise twofold recrystallization from ethyl acetate–heptane (200 ml, 1:1) brings 81.4 g of the analytically pure nitroamide (58% yield, 98.7% ee). $_1$H NMR (400 MHz, $CDCl_3$): 7.31 (m, 2H), 7.21 (m, 2H), 5.62 (br s, 1H), 5.47 (br s, 1H), 5.09 (dd, 1H), 4.45 (dd, 1H), 4.25 (dd, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 171.17, 135.06, 132.65, 129.80, 129.38, 75.93, 48.91; mp 109–111 °C; $[\alpha]_D^{20}$ +178.8 (*c* 2.0, CH_2Cl_2, 289 nm, 21 °C).
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