Tetrahedron: *Asymmetry* 21 (2010) 540–543

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Rhodium/olefin-catalyzed reaction of arylboronic acids with an α-acetamido acrylic ester: Mizoroki–Heck-type reaction versus asymmetric conjugate addition

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ARTICLE INFO

Article history:
Received 22 January 2010
Accepted 24 March 2010
Available online 13 April 2010

ABSTRACT

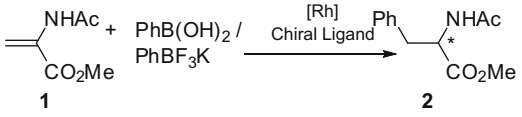
In this paper we present our results concerning the rhodium/olefin-catalyzed reaction of arylboronic acids with an α-acetamido acrylic ester. With a chiral norbornadiene ligand rather low enantioselectivities (up to 21% ee) were obtained. Besides the expected conjugate adduct, we also observed the formation of a significant amount of Mizoroki–Heck-type product. The ratio of the conjugate adduct/Mizoroki–Heck product could be adjusted by a proper choice of the olefin ligand.

1. Introduction

The use of olefin ligands in transition metal chemistry has become very important since the synthesis of Zeise's salt.[1] Olefin ligands are known as labile ligands. Most of the time, they serve as placeholders for vacant coordination sites for ligand exchange reactions with stronger binding ligands, for example, phosphanes and nitrogen ligands. Recently, the use of chiral dienes as spectator ligands in asymmetric catalysis has been explored by various groups.[2] Some of these chiral dienes show very high reactivity and selectivity in several rhodium- and iridium-catalyzed asymmetric reactions.[3,4]

An interesting reaction is the 1,4-addition of $PhB(OH)_2$ to α-acetamido acrylic ester **1** giving phenylalanine derivatives **2** (Scheme 1). The stereochemistry is in this case not determined at the stage of the insertion step but at the hydrolysis step. The use of a bisphosphonite resulted in quantitative yield and a selectivity of 77% ee.[5] A bisphosphite ligand formed the product in 91% yield and a selectivity of 72% ee.[6] The use of a BINAP/rhodium catalyst and $PhBF_3K$ resulted in 100% conversion. However, the product was racemic when water was used as a proton source. The use of guaiacol, a more-hindered proton source, proved to be crucial and a selectivity of 89.5% ee was achieved.[7] With $PhB(OH)_2$, a lower yield and selectivity were obtained (42% yield, 42% ee). This was explained by the fact that boronic acids can act as competitive proton sources.

We wondered whether chiral diene ligands would be effective in the tandem conjugate addition/enantioselective protonation. As we describe in this paper, olefin ligands were tested in the 1,4-addition of $PhB(OH)_2$ to α-acetamido acrylic ester **1**.



1 2

Scheme 1. Rhodium(I)-catalyzed asymmetric tandem conjugate addition/enantioselective protonation.

2. Results and discussion

First, we tried to optimize the reaction conditions with achiral olefin ligands (Table 1). The reaction proceeded well but, to our surprise, we found that besides the conjugate addition product **2**, a Mizoroki–Heck-type product **3** was also formed (Table 1, entry 1). To the best of our knowledge, for this substrate this has not been reported before in the literature.

Heck reactions are typically catalyzed by Pd(0)-complexes.[8] Also, iridium[9]- and ruthenium[10]-catalyzed Heck reactions are described in the literature.

Lautens et al. were the first to describe a rhodium-catalyzed Heck-type coupling with styrenes.[11] It was attributed to the fact that styrenes are incapable of enolization. The same was also observed by Genêt et al.[12] Almost at the same time, Mori et al. reported that it was possible to produce the Heck product with a rhodium catalyst in anhydrous THF.[13] However by a simple solvent-switch to THF/H_2O, the major product became the 1,4-adduct. The reason for this is that the intermediate oxa-π-allylrhodium is readily protonated to form the conjugate adduct. It appeared that the conjugate addition becomes more dominant when the substrate has a more electron-deficient carbonyl. Methyl vinyl ketone gives exclusively the 1,4-adduct, unsaturated amides give a mixture and unsaturated esters give preferentially the Heck product. Lautens et al. observed that the reaction of *t*-butyl acrylate with

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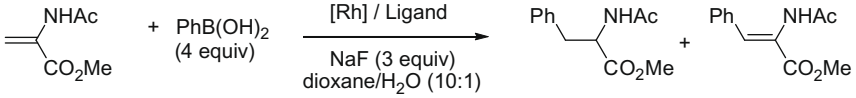
0957-4166/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2010.03.021

phenylboronic acids gave preferentially the Heck product.[14] Remarkable was the fact that the solvent was toluene/H_2O. With bulky boronic acids, the conjugate product was selectively formed. The boronic acid was probably bulky enough to interfere in the Rh–H elimination. In the presence of α- or β-substituents on the acrylate, the formation of the 1,4-adduct was selective. A possible explanation is that through σ-bond inductive electron-donation, the oxa-π-allylrhodium intermediate is more basic which results in a faster protonation. Recently, a base-free rhodium-catalyzed Mizoroki–Heck reaction was discovered. Again, the presence of water resulted in the formation of the conjugate adduct as a single product.[15]

Several reaction parameters were adjusted in order to optimize the reaction outcome (Table 1, entries 2–8). A lower temperature resulted in a lower yield and also a lower selectivity for the conjugate addition product (Table 1, entry 2). Addition of KOH gave a similar result (Table 1, entry 3). $Rh(COD)(CH_3CN)_2{\cdot}BF_4$ as a catalyst resulted in a similar selectivity as the first experiment but a somewhat lower yield (Table 1, entry 4). With OH^- as counterion, both a lower yield and a lower selectivity for the 1,4-adduct were obtained (Table 1, entry 5). A remarkable result was observed with norbornadiene and ethene as ligands: the selectivity was clearly in favour of the Heck product (Table 1, entries 6–8). So, by a proper choice of the ligand the selectivity could clearly be altered. Zou et al. have already demonstrated that Heck-coupling was obtained selectively in the presence of triphenylphosphane, while conjugate addition was favoured in the presence of bisphosphanes.[16]

Although the selectivity for the conjugate addition was low in the presence of norbornadiene (22% of 1,4-adduct), we decided to perform the reaction in the presence of the chiral Hayashi ligand **4** (Table 2).[3a,4] First, we carried out the reaction in analogy with the experiment with the achiral norbornadiene ligand (Table 1, entry 6), resulting in a slightly higher total yield (Table 2, entry 1). Moreover, a higher selectivity for the conjugate adduct was observed, but no chiral induction. The use of aq KOH as a cosolvent resulted in both a lower yield of a 1,4-adduct and a lower total yield. A noticeable enantioselectivity was observed in this case however, albeit very low (Table 2, entry 2). Again, lowering the reaction

Table 1
Rhodium(I)-catalyzed conjugate addition versus Mizoroki–Heck reaction[a]

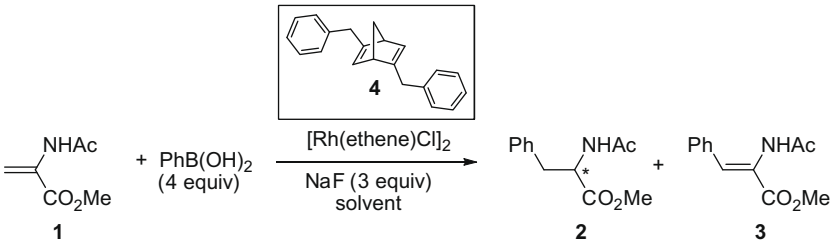


1 **2** **3**

Entry	Rhodium catalyst [Rh]	Additive	Temperature (°C)	Time (h)	Total yield[b] (%)	% Conjugate adduct **2**[c]	% Mizoroki–Heck product **3**[c]
1	$[Rh(COD)Cl]_2$	/	100	24	77	82	18
2	$[Rh(COD)Cl]_2$	/	50	24	21[d]	67	33
3	$[Rh(COD)Cl]_2$	1.5 M aq KOH	50	24	23[d]	64	36
4	$Rh(COD)(CH_3CN)_2{\cdot}BF_4$	/	100	48	54[d]	83	17
5	$[Rh(COD)OH]_2$	/	100	24	56[d]	74	26
6	$[Rh(nbd)Cl]_2$	/	100	24	36[d]	22	78
7	$[Rh(ethene)Cl]_2$	/	100	48	39[d]	25	75
8	$Rh(acac)(ethene)_2$	/	100	48	34[d]	21	79

[a] Reagents and conditions: **1** (0.5 mmol), $PhB(OH)_2$ (2.0 mmol), NaF (1.5 mmol), [Rh] (3 mol % Rh), dioxane/H_2O (10:1).
[b] Isolated as a mixture of conjugate adduct **2** and Mizoroki–Heck product **3**.
[c] The ratio of conjugate adduct **2**/Mizoroki–Heck product **3** was determined via GC on a Chirasil-Val column.
[d] The reaction was not complete after the indicated time. Formation of side products was not observed.

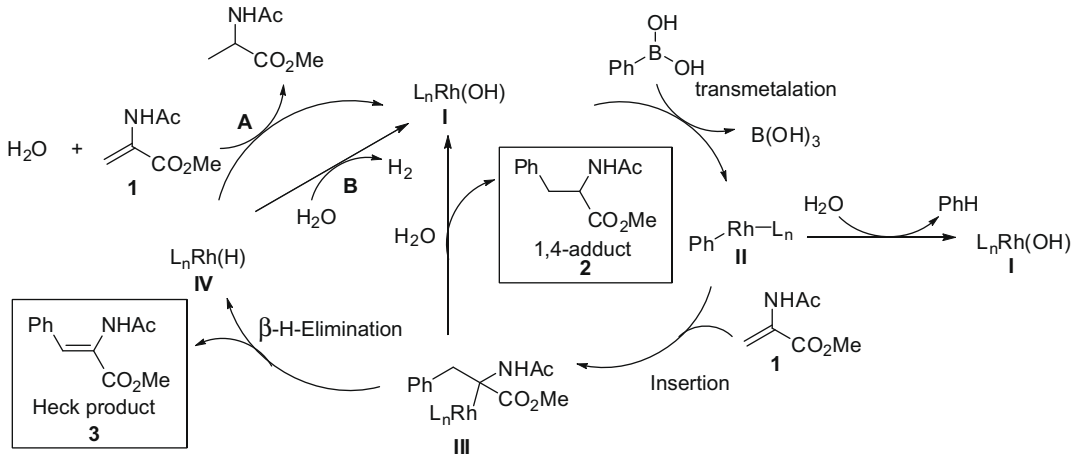
Table 2
Chiral diene/rhodium(I)-catalyzed conjugate addition versus Mizoroki–Heck reaction[a]



1 **2** **3**

Entry	Solvent	Temperature (°C)	Time (h)	Total yield[b,c] (%)	% Conjugate adduct[d,e] (ee [%])	% Heck product[c]
1	Dioxane/H_2O (10:1)	100	24	40	30 (*rac*)	70
2	Dioxane/ 1.5 M aq KOH (10:1)	100	24	27	24 (9)	76
3	Dioxane/H_2O (10:1)	50	48	8	27 (6)	73
4	Toluene/H_2O (10:1)	50	48	12	60 (20)	40
5	EtOH/H_2O (10:1)	50	48	10	46 (21)	54

[a] Reagents and conditions: **1** (0.25 mmol), $PhB(OH)_2$ (1.0 mmol), NaF (0.75 mmol), $[RhCl(C_2H_4)_2]_2$ (3 mol % Rh), chiral diene ligand **4** (**4**/Rh = 1.1/1.0), solvent.
[b] Isolated as a mixture of 1,4-adduct and Heck product.
[c] The reaction was not complete after the indicated time. Formation of side products was not observed.
[d] The ratio of conjugate adduct **2**/Heck product **3** and the enantiomeric excess were determined via GC on a Chirasil-Val column.
[e] The absolute configuration of the major enantiomer was determined to be (*S*).



Scheme 2. Proposed catalytic cycle for olefin/rhodium-catalyzed conjugate addition versus Mizoroki–Heck-coupling.

temperature resulted in a lower total yield and a lower enantioselectivity for the 1,4-adduct (Table 2, entry 3). Using toluene/H_2O (10:1) as a solvent system gave a higher selectivity in favour of the 1,4-adduct. The enantioselectivity was higher although still unsatisfactory (Table 2, entry 4). The use of EtOH/H_2O resulted in an almost equimolar mixture of the 1,4-adduct **2** and Heck product **3** and a comparable enantioselectivity as for entry 4 (Table 2, entry 5).

A mechanism for the observed transformations is proposed in Scheme 2. The catalytically active hydroxorhodium **I** transmetalates with phenylboronic acid to form the phenylrhodium species **II**. Next, insertion of the alkene **1** causes the formation of a Rh–C bond **III**. Hydrolysis results in the formation of the 1,4-adduct **2** and regenerates the hydroxorhodium **I** catalyst. A second possibility is the β-hydride elimination which results in the formation of the Heck product **3** and a rhodium hydride species **IV**. Subsequently the rhodium hydride **IV** should be converted into the hydroxorhodium **I**. This can be done if we consider that the alkene **1** is used as a hydride acceptor (path **A**). Although we did not immediately discover traces of this product, it would explain the low yields obtained when the Heck product was the major product. It can also explain the lower ee's in the asymmetric reactions when the Heck product **3** is used as a hydride acceptor. A second possibility is the reaction of Rh–H (**IV**) with H_2O to give Rh–OH (path **B**).[17] The excess of boronic acid is partly consumed by reaction of the phenylrhodium species **II** with H_2O.

3. Conclusion

In conclusion, the asymmetric conjugate addition of phenylboronic acid to α-acetamido acrylic ester catalyzed by a rhodium(I)-catalyst in the presence of C_2-symmetrical diene ligand **4** was investigated, but resulted in rather low enantioselectivities. Moreover, we have described for the first time a Mizoroki–Heck-type coupling with an α-acetamido acrylic ester in the presence of an olefin/rhodium(I)-catalyst. The ratio of the conjugate adduct **2**/Mizoroki–Heck product **3** could be adjusted by the proper choice of the ligand.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere in dry solvents under anhydrous conditions, unless otherwise stated. All reagents were purchased and used without purification, unless otherwise noted. Analytical TLC was performed using Macherey-Nagel SIL G-25 UV_{254} plates. Flash chromatography was carried out with Rocc silicagel (0.040–0.063 mm). ^1H NMR and ^{13}C NMR were recorded on a Bruker Avance 300 or on a Bruker AM 500 spectrometer as indicated, with chemical shifts reported in parts per million (ppm) relative to TMS, using the residual solvent signal as a standard. ^{13}C NMR spectra were recorded using the attached proton test (APT). IR-spectra were recorded on a Perkin–Elmer spectrum 1000 FT-IR spectrometer with a Pike Miracle HATR module. EI Mass spectra were recorded with a Hewlett–Packard 5988A mass spectrometer. LC–MS analysis was performed on an Agilent 1100 series HPLC with quaternary pump, DAD and single quadrupole MS detector type VL with an API-ES source, using a Phenomenex Luna C18(2) column (250 × 4.6 mm, particle size 5 μm). Exact molecular masses were measured on a Kratos MS50TC mass spectrometer. Melting points were measured with a Kofler melting point apparatus.

4.2. Synthesis of (*S,S*)-Bn-nbd* 4

A solution of bis-triflate[4] (104.7 mg, 269.7 μmol) and $PdCl_2$(dppf). CH_2Cl_2 (4.7 mg, 5.79 μmol) in Et_2O (1.0 mL) was cooled in an ice bath. To the resulting red suspension was added BnMgCl (1.35 mL, 1.77 mmol, 20 w/w% in THF) under argon. The reaction mixture was stirred for 1 h at room temperature; the reaction was quenched with brine (25 mL) and the mixture was extracted with EtOAc (4 × 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography over silicagel (isooctane/$CHCl_3$, 96/4) resulting in a white solid which contained a significant amount of 1,2-diphenylethane which was removed under reduced pressure (<1 mm Hg, 1 night) resulting in pure (*S,S*)-Bn-nbd* **4** as a white solid, 53.0 mg (72%). ^1H NMR (500 MHz, $CDCl_3$): δ 1.94 (t, *J* = 1.7 Hz, 2H), 3.14 (dt, *J* = 3.8, 1.7 Hz, 2H), 3.49 (s, 4H), 6.02 (dt, *J* = 3.8, 1.6 Hz, 2H), 7.09 (d, *J* = 7.2 Hz, 4H), 7.18 (tt, *J* = 7.2, 1.2 Hz, 2H), 7.26 (t, *J* = 7.2 Hz, 4H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 38.0 (CH_2), 53.1 (CH), 71.4 (CH_2), 125.9 (CH), 128.1 (CH), 129.0 (CH), 134.3 (CH), 139.1 (C), 156.9 (C) ppm. IR (HATR): 2970, 2950, 2929, 2878, 1600, 1492, 1451, 1306, 1183, 1069, 1026, 948, 856, 780, 752, 737, 708 cm^{-1}. EI-MS *m*/*z* (rel. intensity%): 272 (M^+, 9), 181 (34), 165 (21), 156 (34), 141 (17), 128 (22), 115 (39), 103 (8), 91 (88), 84 (29), 65 (30), 49 (71), 40 (100). ES-MS: 273 $[M+H]^+$. $[\alpha]_D^{20} = -180$ (*c* 1.07, $CHCl_3$). Mp: 67 °C. HRMS (EI) calcd for $C_{21}H_{20}$: 272.1565; found 272.1569.

4.3. Typical procedure for the racemic conjugate addition of phenylboronic acid to α-acetamido acrylic ester

Methyl 2-acetamidoacrylate **1** (71.6 mg, 0.5 mmol), $[Rh(COD)Cl]_2$ (7.4 mg, 0.015 mmol), phenylboronic acid (243.9 mg, 2 mmol) and NaF (63.0 mg, 1.5 mmol) were dissolved in dioxane (1.5 mL) and stirred for 30 min at room temperature. Then H_2O (150 μL) was added and the resulting reaction mixture was heated to 100 °C under argon in a sealed tube. After 26 h, full conversion was observed via TLC. The reaction mixture was passed through a short pad of silicagel and eluted with EtOAc. Evaporation in vacuo and purification by flash chromatography over silicagel (hexane/EtOAc, 50/50) resulted in a mixture of **2** and **3**, 84.5 mg (77%; 82% of **2** and 18% of **3**).

4.4. Typical procedure for the asymmetric conjugate addition of phenylboronic acid to α-acetamido acrylic ester

At first, $[Rh(C_2H_4)_2Cl]_2$ (2.9 mg, 7.5 μmol) and (*S*,*S*)-Bn-nbd* **4** (4.5 mg, 16.5 μmol) were dissolved in a mixture of degassed dioxane (0.75 mL) and degassed H_2O (75 μL) and stirred for 30 min at room temperature. After the addition of methyl 2-acetamidoacrylate **1** (35.8 mg, 0.25 mmol), phenylboronic acid (122 mg, 1 mmol) and NaF (31.5 mg, 0.75 mmol), the resulting reaction mixture was stirred for 24 h at 100 °C in a sealed tube. The reaction mixture was passed through a short pad of silicagel and eluted with EtOAc. Evaporation in vacuo and purification by flash chromatography over silicagel (hexane/EtOAc, 50/50) resulted in a mixture of **2** and **3**, 22.0 mg (40%; 30% of **2** (*rac*) and 70% of **3**).

The adducts were fully characterized by making a comparison of their spectral data with those reported in the literature. The enantiomeric excess of the product is determined by GC analysis with a chiral stationary phase column: Chirasil-Val column (30 m × 0.25 mm × 0.25 μm); temperature programme: 150 °C for 11 min, increasing to 190 °C (40 °C/min); retention times: 9.11 min for (*R*)-**2**, 9.38 min for (*S*)-**2** and 14.60 min for **3**.

Acknowledgements

T.N., Y.G. and J.V.D.E. wish to thank Ghent University and COST-Chemistry (Action D.40—'Innovative Catalysis') for financial support.

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