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Rhodium-Catalyzed Asymmetric Hydroarylation of 3-Pyrrolines Giving 3-Arylpyrrolidines: Protonation as a Key Step

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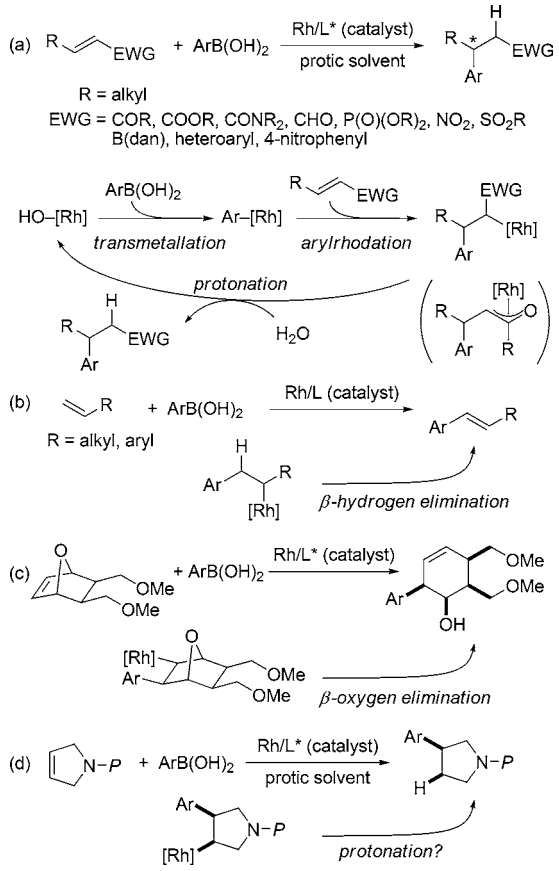
Supporting Information

ABSTRACT: A hydroxorhodium complex coordinated with (*R*)-segphos was found to catalyze the hydroarylation of 3-pyrrolines with arylboroxines under neutral conditions to give 3-arylpyrrolidines with high enantioselectivity in high yields.

The Rh-catalyzed asymmetric arylation of alkenes with arylboronic acids has offered one of the most convenient and reliable methods of creating benzylic stereocenters with high enantioselectivity.[1] The reaction has been performed in protic solvents, typically water or alcohols, to give hydroarylation products. The alkenes successfully used for the hydroarylation have been so far limited mainly to those activated by electron-withdrawing substituents represented by carbonyl groups[2−8] (Scheme 1a). In the hydroarylation of electron-deficient alkenes, the catalytic cycle consists of (1) transmetalation of aryl group from B to Rh to generate an arylrhodium species, (2) insertion of the alkene into the aryl−Rh bond to form an alkylrhodium species, and (3) protonation of the rhodium enolate-type alkylrhodium intermediate in the reaction of carbonyl compounds, to release the hydroarylation product.[9] Kinetic studies on the reaction of an *α*,*β*-unsaturated ketone demonstrated that the protonation step is a fast step,[10] and hence, the protonation step does not compete against unfavorable reactions such as *β*-hydrogen elimination in the Rh-catalyzed asymmetric reactions. On the other hand, the asymmetric hydroarylation of alkenes has not been successfully applied to those which lack the electron-withdrawing groups, where the alkylrhodium intermediates are reluctant to undergo the protonation to result in *β*-hydrogen elimination to lead to olefinic products (Scheme 1b).[11,12] In the reactions of oxa- or azabicyclo[2.2.1]heptenes reported by Murakami[13] and Lautens,[14] alkylrhodium intermediates, generated by arylrhodation, do not have syn *β*-hydrogens for *β*-hydrogen elimination, and they undergo *β*-oxygen or *β*-nitrogen elimination to form ring-opened olefinic products (Scheme 1c).[15,16] In this context, we have been interested in the asymmetric hydroarylation of 3-pyrrolines, which is challenging because of the high possibility of side reactions such as *β*-hydrogen and *β*-nitrogen eliminations (Scheme 1d). Another reason for studying the addition to 3-pyrrolines is that the enantiomerically enriched hydroarylation products, 3-arylpyrrolidines, are known to constitute an important subgroup of compounds with pharmacologic acitvities.[17,18]

Scheme 1. Rh-Catalyzed Asymmetric Alkene Hydroarylation



The reaction of *N*-(4-methoxybenzenesulfonyl)-3-pyrroline (**1a**) with $(PhBO)_3$ (**2m**) was carried out in the presence of $[RhCl(cod)]_2$ (5 mol % Rh, cod =1,5-cyclooctadiene) and KOH (2.0 equiv to **1a**) in 1,4-dioxane/H_2O (10/1), which is one of the best conditions in terms of catalytic activity for the Rh-catalyzed conjugate addition of arylboronic acids to electron deficient alkenes.[19] The reaction at 60 °C for 16 h gave only 15% yield of the desired hydrophenylation product **3am**, major product being arylated olefin **4am** in 30% yield together with 15% of isomerized olefin **5a** (entry 1 in Table 1). Thus, the *β*-hydrogen elimination

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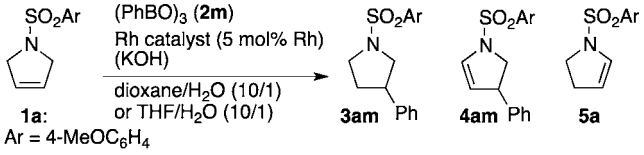
Table 1. Rh-Catalyzed Hydrophenylation of 1a with 2m[a]



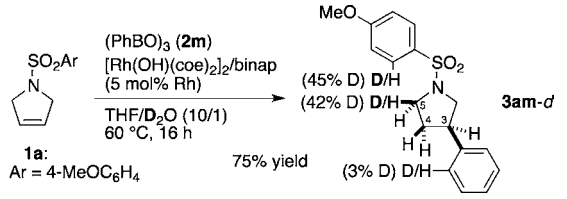
					yield (%)[b]		
entry	ligand	additive (equiv)	solvent	T (°C)	**3am**[c]	**4am**	**5a**
1	cod[d]	KOH (2.0)	dioxane	60	15	30	15
2	binap[e]	KOH (2.0)	dioxane	60	7	0	26
3	binap[e]	KOH (0.1)	dioxane	60	30	0	4
4	binap[f]	—	dioxane	60	79 (84)	0	9
5	cod[g]	—	dioxane	60	5	1	8
6	binap[f]	—	THF	60	81 (84)	0	14
7[h]	binap[f]	—	THF	40	88 (86)	0	7
8[h]	segphos[i]	—	THF	40	95 (91)	0	4
9[h]	segphos[i]	—	THF	23	93 (94)	0	6
10[j]	segphos[i]	—	THF	10	54 (96)	0	2

[a]Reaction conditions: 3-pyrroline **1a** (0.25 mmol), $(PhBO)_3$ **2m** (0.17 mmol for entries 1−2 and 0.42 mmol for other entries), Rh catalyst (5 mol % of Rh), dioxane/H_2O or THF/H_2O (1.0/0.1 mL) for 16 h. [b]Determined by ^1H NMR of the reaction mixture. [c]The enantiomeric excess of **3am** (%) is shown in parentheses. [d]$[RhCl(cod)]_2$. [e]$[RhCl(C_2H_4)_2]_2$/(*R*)-binap. [f]$[Rh(OH)(coe)_2]_2$/(*R*)-binap. [g]$[Rh(OH)(cod)]_2$. [h]For 24 h. [i]$[Rh(OH)(coe)_2]_2$/(*R*)-segphos. [j]For 36 h.

from an alkylrhodium intermediate is a predominant process over protonation giving **3am** under the conditions with a diene ligand (vide infra for the catalytic pathway in detail). On the other hand, the use of binap[20] in place of cod as a ligand under otherwise the same conditions gave hydrophenylation product **3am** selectively albeit in a low yield (7%) (entry 2). The reaction with a smaller amount (0.1 equiv to **1a**) of KOH (entry 3), which was performed in order to accelerate the protonation of an alkylrhodium intermediate by making the reaction media less basic, increased the reaction rate to give **3am** in 30% yield. A higher yield (79%) of **3am** was obtained in the absence of KOH by use of a hydroxo complex $[Rh(OH)((R)\text{-binap})_2]_2$[9] generated from $[Rh(OH)(coe)_2]_2$[21] and (*R*)-binap (entry 4). Attempts to further improve the yield of **3am** by addition of acidic proton sources such as carboxylic acids or phenol derivatives failed; almost no hydrophenylation product was observed. It is probably due to the deceleration of the transmetalation step in acidic media.[3b] Interestingly, the reaction catalyzed by the cod complex was not improved at all by use of hydroxo rhodium complex, $[Rh(OH)(cod)]_2$ (entry 5), which has been also known to be an active catalyst for the addition to several types of olefins and imines.[10b] The enantioselectivity in giving (*R*)-**3am** was 84% ee with the (*R*)-binap-hydroxo catalyst at the reaction temperature of 60 °C (entry 4), and the reaction in THF/H_2O gave a slightly higher yield of **3am** than in dioxane/H_2O, in which the enantioselectivity was kept the same (entry 6). By lowering the reaction temperature to 23 °C and using segphos[22] as a chiral ligand, the % ee of **3am** was increased to 94% ee (entries 7−9). The selectivity was further increased to 96% ee at 10 °C, but the reaction was too slow to obtain a high yield of the product in an acceptable reaction time (entry 10).

The hydrophenylation of 3-pyrroline **1a** in D_2O in place of H_2O (Scheme 2) gave us a significant insight into the catalytic cycle which involves protonation as a key step. The product **3am** obtained in 75% yield by the reaction in the presence of hydroxo-

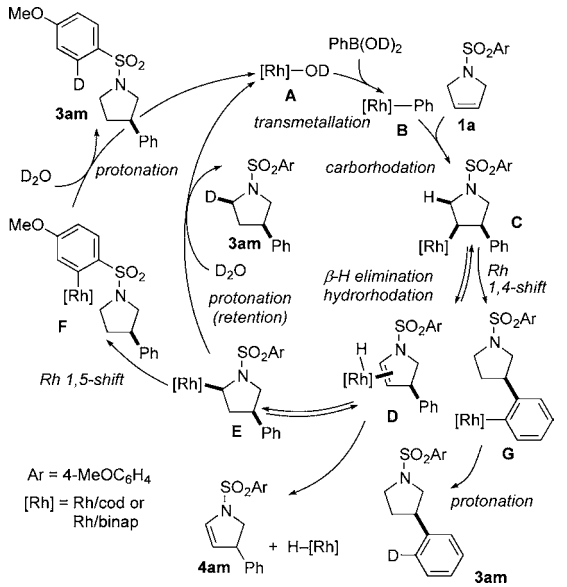
Scheme 2. Rh-Catalyzed Reaction of 1a with 2m in THF/D_2O



binap catalyst in THF/D_2O at 60 °C (corresponding to entry 6 in Table 1) was found to incorporate deuterium mainly (45% D) at the ortho-position of 4-methoxybenzenesulfonyl group. The second highest proportion of deuterium (42% D) was observed at 5-position of the pyrrolidine ring, where the deuterium was all located on the same side as the phenyl group. A minor amount of deuterium (3% D) was also detected at the ortho-position of phenyl group derived from phenylboroxine. It should be noted that the 4-position of **3am** is not substituted with deuterium at all.

On the basis of the deuterium incorporation studies, the catalytic cycle producing **3am** and **4am** is proposed as shown in Scheme 3. Phenylrhodium species **B**, generated by trans-

Scheme 3. Reaction Pathway for 1a



metalation of $PhB(OH)_2$ to hydroxorhodium species **A**, adds to 3-pyrroline **1a** to generate alkylrhodium intermediate **C**, which does not undergo protonation but undergoes β-hydrogen elimination to form hydridorhodium−alkene complex **D**. Dissociation of the olefin from **D** would give phenylated alkene **4am**, which is a main product in the reaction catalyzed by Rh/cod in the presence of KOH (entry 1 in Table 1). The phenylation product **3am** is formed in part (42%) by protonolysis of alkylrhodium intermediate **E** which is generated by hydrorhodation on **D** with the regiochemistry opposite to that returning to **C**. A major pathway (45%) to **3am** is by way of arylrhodium intermediate **F** which is generated by 1,5-shift of Rh[23] from 5-position of the pyrrolidine ring to ortho-position of the arenesulfonyl group. The 1,4-Rh shift[14c,24] from **C** to ortho-phenyl intermediate **G** is not a main route (3%) leading to **3am**. Before the 1,4-shift, the alkylrhodium intermediate **C** immediately undergoes the β-hydrogen elimination to isomerize into **E** which may be stabilized by the vicinal sulfonamide group. It is

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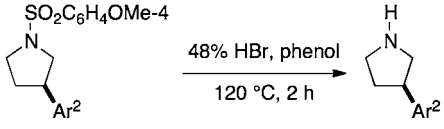
remarkable that the protonation of alkylrhodium complex **E** was demonstrated to take place with retention of configuration at the sp^3 carbon under the present conditions.[25] The difference between Rh/cod and Rh/binap catalyst systems is that the olefinic product **4am** is readily released from intermediate **D** in the Rh/cod system while **D** is stable against its dissociation in the Rh/binap system. As a result, the Rh intermediates are isomerized into **E** and finally into aryl−rhodium species **F** in part. They undergo the protonolysis under less basic conditions to give a high yield of **3am**.

The reaction in D_2O shown in Scheme 2 was significantly slower than the reaction in H_2O. Thus, the relative reaction rate k_{H2O}/k_{D2O} obtained by the reactions in two separate reaction vessels was not smaller than 1.8.[26] A competition reaction carried out in the presence of a 1: 1 mixture of D_2O and H_2O gave the product **3am** where the deuterium incorporation is 11% at both 5 position of pyrrolidine and the ortho-position of the sulfonyl group, indicating that the relative reactivity at the protonolysis is k_H/k_D = 3. These deuterium kinetic isotope effects may well demonstrate that the protonolysis step is a turnover-limiting step.[27]

Under the optimized conditions found for the reaction of 3-pyrroline **1a** with phenylboroxine **2m** (entry 9 in Table 1), the $[Rh(OH)(coe)_2]_2$/(*R*)-segphos catalyst system was examined for its scope in the asymmetric hydroarylation producing several 3-arylpyrrolidines **3**. The results are summarized in Table 2. Pyrrolines protected with sulfonamides substituted with *p*-tolyl (**1b**), phenyl (**1c**), and 2-naphthyl (**1d**) groups gave the corresponding hydrophenylation products with similar chemical yield and enantioselectivity (entries 2−4) to the *p*-methoxyphenyl-substituted one **1a** (entry 1). Because of the easier deprotection[28] of 4-methoxybenzenesulfonyl group from nitrogen, the pyrrolidine **1a** was used for the introduction of different aryl groups (entries 5−18). In general, electronic effects of arylboroxines are minimal in the present asymmetric hydroarylation. Electron neutral (**2n**−**2q** and **2y**), electron rich (**2r**, **2s**, and **2z**), and electron poor (**2t**−**2x**) aryl groups were successfully introduced onto the pyrrolidine ring in high yields. The enantioselectivity was kept high for all the substituted phenyl groups.

The absolute configuration of hydrophenylation product **3bm** was determined to be *R* by comparison of its specific rotation with that reported.[17f] In accordance with the highly skewed structure known for segphos and binap complexes,[2b,20,22] (*R*)-segphos-Rh complex should have an open space at the lower part of the olefin coordination site while the upper part is blocked by one of the phenyl rings of segphos (Scheme 4). The arylrhodation of the 3-pyrroline **1** at its coordination shown in **H**, where the steric repulsions are minimized, gives the product **3** of *R*-configuration by way of the alkylrhodium intermediate **I**.

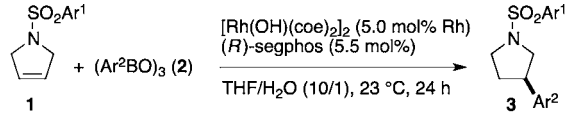
The 4-methoxybenzenesulfonyl group in **3am**, **3at**, and **3as** was readily removed without loss of their enantiomeric purities by treatment with 48% hydrobromic acid and phenol[28] (eq 1).



(1)

3am: Ar^2 = Ph (94% ee)
3at: Ar^2 = 4-ClC_6H_4 (89% ee)
3as: Ar^2 = 3-$MeOC_6H_4$ (91% ee)
6m: Ar^2 = Ph (94% ee)
6t: Ar^2 = 4-ClC_6H_4 (89% ee)
6s: Ar^2 = 3-HOC_6H_4 (as HBr salt)

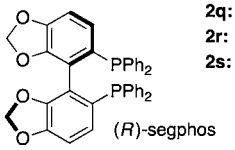
Table 2. Rh-Catalyzed Asymmetric Hydroarylation of 3-Pyrrolines 1 with Arylboroxines 2[a]



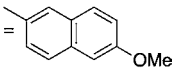
1a: Ar^1 = 4-$MeOC_6H_4$
1b: Ar^1 = 4-MeC_6H_4
1c: Ar^1 = Ph
1d: Ar^1 = 2-naphthyl

2m: Ar^2 = Ph
2n: Ar^2 = 4-MeC_6H_4
2o: Ar^2 = 3-MeC_6H_4
2p: Ar^2 = 4-PhC_6H_4
2q: Ar^2 = 3-PhC_6H_4
2r: Ar^2 = 4-$PhOC_6H_4$
2s: Ar^2 = 3-$MeOC_6H_4$

2t: Ar^2 = 4-ClC_6H_4
2u: Ar^2 = 4-$MeOCOC_6H_4$
2v: Ar^2 = 4-$EtOCOC_6H_4$
2w: Ar^2 = 3-$MeOCOC_6H_4$
2x: Ar^2 = 3-$MeCOC_6H_4$
2y: Ar^2 = 2-naphthyl



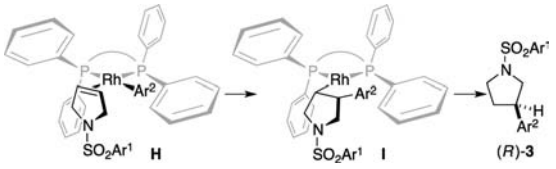
2z: Ar^2 =



entry	1	2	product 3	yield (%)[b]	ee (%)[c]
1	**1a**	**2m**	**3am**	91	94
2	**1b**	**2m**	**3bm**	91	93
3	**1c**	**2m**	**3cm**	90	93
4	**1d**	**2m**	**3dm**	87	93
5	**1a**	**2n**	**3an**	92	93
6	**1a**	**2o**	**3ao**	97	95
7	**1a**	**2p**	**3ap**	96	93
8	**1a**	**2q**	**3aq**	95	93
9[d]	**1a**	**2r**	**3ar**	87	94
10	**1a**	**2s**	**3as**	95	91
11[e]	**1a**	**2t**	**3at**	80	89
12	**1a**	**2u**	**3au**	97	92
13	**1a**	**2v**	**3av**	96	92
14	**1a**	**2w**	**3aw**	82	92
15	**1a**	**2x**	**3ax**	82	85
16	**1a**	**2y**	**3ay**	92	94
17	**1a**	**2z**	**3az**	99	95
18[d]	**1a**	**2z**	**3az**	95	96

[a]Reaction conditions: 3-pyrroline **1** (0.20 mmol), $(Ar^2BO)_3$ **2** (0.42 mmol), $[Rh(OH)(coe)_2]_2$ (5.0 mol % of Rh), (*R*)-segphos (5.5 mol %), THF/H_2O (1.0/0.1 mL) at 23 °C for 24 h. [b]Isolated yield. [c]Determined by HPLC on a chiral stationary phase. [d]At 15 °C. [e]With 10 mol % of the Rh catalyst at 40 °C.

Scheme 4. Stereochemical Path To Form (*R*)-Pyrrolidine 3



The cleavage of methyl ether giving 3-(3-hydroxyphenyl)-pyrrolidine (**6s**) took place for **3as** under the reaction conditions. The deprotected 3-arylpyrrolidines, **6m**, **6t**, and **6s**, are all known[17] to be important compounds in pharmaceutical sciences. Thus, the asymmetric hydroarylation of the 3-pyrrolines provides an easy and efficient method of synthesizing a series of compounds with potentially high biological activity.[29]

■ ASSOCIATED CONTENT

Supporting Information

Procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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