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[12] The ^{1}H NMR spectra showed the existence of the 1:1 pseudorotaxane complex **4**(**5**) and uncomplexed **4** under conditions of slow exchange on the ^{1}H NMR time scale. The association constant for the 1:1 complex in chloroform was determined to be $7.9 \times 10^3\,\text{M}^{-1}$ (21.8 °C) from integration of the signals for the protons from complexed and uncomplexed **4** using the expression $K_a = [\mathbf{4}(\mathbf{5})]/[\mathbf{4}][\mathbf{5}]$. The K_a value for the 1:1 complex between the monotopic salt **5** and DB24C8 in [D]chloroform was estimated to be $2.7 \times 10^4\,\text{M}^{-1}$ (25 °C).[10] The lower association constant for 1:1 complex **4**(**5**) may be attributed to the reduced accessibility and flexibility of the macrocyclic moiety of **4** due to the bulky dendritic substituent.
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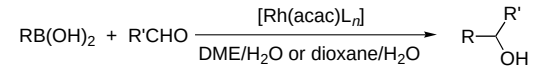
[16] A solution of **4** (3.0×10^{-2} M) was mixed with 1/3 mol equiv of solid **1** for 3 d. The mixture was then filtered and the filtrate was concentrated to afford a white solid, which was submitted for MALDI-MS analysis.
[17] The apparent distribution of the complexes indicate partial dissociation of $\mathbf{1}(\mathbf{4})_3$ into subunits $\mathbf{1}(\mathbf{4})_2$ and **1**(**4**) during ionization. It is also noteworthy that MALDI-MS detectors are nonlinear with respect to molecular mass and thus do not give molar response. For a review on principles, instrumentation, and application of MALDI MS, see: F. Hillenkamp, M. Karas, R. C. Beavis, B. T. Chait, *Anal. Chem.* **1991**, *63*, 1193A – 1203A. ESI-MS has to date given similar results; we are currently investigating the use of low sample cone voltage (V_c) to minimize fragmentation. For reviews on characterization of hydrogen-bonded assemblies by ESI-MS, see: a) K. C. Russell, E. Leize, A. Van Dorsselaer, J.-M. Lehn, *Angew. Chem.* **1995**, *107*, 244 – 248; Angew. *Chem. Int. Ed. Engl.* **1995**, *34*, 209 – 213; b) X. Cheng, Q. Gao, R. D. Smith, E. E. Simanek, M. Mammen, G. M. Whitesides, *J. Org. Chem.* **1996**, *61*, 2204 – 2206.

Rhodium-Catalyzed Addition of Organoboronic Acids to Aldehydes

Masaaki Sakai, Masato Ueda, and Norio Miyaura*

The transmetalation between organo/main group metal reagents and transition metal compounds is of great importance for application in organic synthesis, since it allows the formation of new carbon – carbon bonds between various organometallic units and electrophiles. We previously demonstrated the efficiency of transmetalation between boron and palladium in the cross-coupling reaction of organoboron compounds with organic electrophiles[1] and the transmetalation between boron and rhodium in the catalytic 1,4-addition of aryl- or 1-alkenylboronic acids to enones.[2] An analogous addition reaction of organotin compounds to enones[3] and to aldehydes[4] has recently appeared. Here we report our first attempts to extend the protocol to the addition of aryl- and 1-alkenylboronic acids to aldehydes in an aqueous solution (Scheme 1). The insertion of carbonyl groups into transition metal – carbon bonds has not received much attention, but the use of transition metals as catalysts may allow addition of organometallics that are otherwise inert,[5] asymmetric addition using a chiral phosphane complex,[6] or reaction in an aqueous phase.



Scheme 1. Rhodium-catalyzed addition of organoboronic acids to aldehydes. R = aryl, 1-alkenyl; R′ = alkyl, aryl.

A combination of $[\text{Rh(acac)(CO)}_2]$ (acac = acetylacetonate) and a phosphane ligand in an aqueous solvent, conditions that gave good results for the 1,4-addition of organoboronic acids to enones,[2] was also effective for the addition to aldehydes (Table 1). The reaction was induced by phosphane complexes having a large P-Rh-P angle,[7a] which may affect the rate of carbonyl insertion into the Rh–C bond.[7b–d] Thus, monodentate phosphanes and dppe were totally ineffective ligands (entries 1 – 4), but the complexes derived from dppp, diop, and dppf exhibited high catalytic activity (entries 5, 7, and 8). However, the ligand dppb unexpectedly resulted in a low yield although it has a similar bite angle (entry 6). The reaction smoothly proceeded in aqueous 1,2-dimethoxyethane (DME), dioxane, and propanol at temperatures above 80 °C (entries 9 and 10), but it was very slow in the absence of water or at temperatures below 80 °C.

Table 1. Effect of ligand and solvent on the addition of phenylboronic acid to 4-methoxybenzaldehyde in the presence of $[\text{Rh(acac)(CO)}_2]$.[a]

Entry	Ligand	Solvent	Yield [%][b]
1	$3\,\text{Ph}_3\text{P}$	DME/H_2O	0
2	$3\,\text{Ph}_3\text{As}$	DME/H_2O	< 1
3	$3\,\text{Cy}_3\text{P}$	DME/H_2O	5
4	dppe[c]	DME/H_2O	0
5	dppp[d]	DME/H_2O	82 (79)
6	dppb[e]	DME/H_2O	17
7	diop[f]	DME/H_2O	66
8	dppf[g]	DME/H_2O	99 (83)
9	dppf[g]	dioxane/H_2O	72
10	dppf[g]	*n*PrOH/H_2O	84

[a] A mixture of $4\text{-MeOC}_6\text{H}_4\text{CHO}$ (1 mmol), PhB(OH)_2 (2 mmol) and $[\text{Rh(acac)(CO)}_2]$/ligand (3 mol %) was stirred at 80 °C for 16 h in solvent/H_2O (1/1) (6 mL). [b] GC yields based on the aldehyde and yields of the isolated product are given in the parentheses. [c] 1,2-Bis(diphenylphosphanyl)ethane. [d] 1,3-Bis(diphenylphosphanyl)propane. [e] 1,4-Bis(diphenylphosphanyl)butane. [f] 2,3-*O*-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphanyl)butane. [g] 1,1′-Bis(diphenylphosphanyl)ferrocene.

Representative results are summarized in Table 2. The reaction is rather sensitive to electronic effects both in aldehydes and arylboronic acids, suggesting that the mechanism proceeds through the nucleophilic attack of the aryl group to the carbonyl. Thus, the reaction was facilitated in the

[*] Prof. Dr. N. Miyaura, M. Sakai, M. Ueda
Division of Molecular Chemistry
Graduate School of Engineering
Hokkaido University
Sapporo 060-8628 (Japan)
Fax: (+81) 11-706-6561 or 11-706-7882
E-mail: miyaura@org-mc.eng.hokudai.ac.jp

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Table 2. Addition of arylboronic acids to aldehydes.[a]

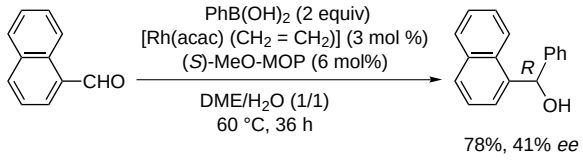
Entry	$ArB(OH)_2$	Aldehyde	Yield [%][b]
1	$PhB(OH)_2$	PhCHO	92
2	$PhB(OH)_2$	$4\text{-}CF_3C_6H_4CHO$	97
3	$PhB(OH)_2$	$4\text{-}NCC_6H_4CHO$	97
4	$PhB(OH)_2$	$4\text{-}MeCOC_6H_4CHO$	93
5	$PhB(OH)_2$	$4\text{-}NO_2C_6H_4CHO$	< 1[c]
6	$PhB(OH)_2$	$4\text{-}BrC_6H_4CHO$	88
7	$PhB(OH)_2$	$4\text{-}MeC_6H_4CHO$	48 (76)[d]
8	$4\text{-}MeOC_6H_4B(OH)_2$	$4\text{-}NCC_6H_4CHO$	84
9	$4\text{-}MeC_6H_4B(OH)_2$	$4\text{-}NCC_6H_4CHO$	99
10	$4\text{-}FC_6H_4B(OH)_2$	$4\text{-}NCC_6H_4CHO$	52
11	$4\text{-}MeCOC_6H_4B(OH)_2$	$4\text{-}NCC_6H_4CHO$	< 1[c]
12	$2\text{-}MeC_6H_4B(OH)_2$	$4\text{-}MeOC_6H_4CHO$	80 (86)[d]
13	$2,4,6\text{-}Me_3C_6H_2B(OH)_2$	$4\text{-}MeOC_6H_4CHO$	31 (43)[d]
14	$PhB(OH)_2$	2-furaldehyde	78
15	$PhB(OH)_2$	1-naphthaldehyde	91
16	$PhB(OH)_2$	$C_5H_{11}CHO$	69
17	$PhB(OH)_2$	$C_6H_{11}CHO$	45 (95)[d]
18	$(E)\text{-}C_4H_9CH{=}CHB(OH)_2$	$4\text{-}NCC_6H_4CHO$	76

[a] A mixture of $ArB(OH)_2$ (2 mmol), aldehyde (1 mmol), $[Rh(acac)(CO)_2]$ (3 mol %), and dppf (3 mol %) in DME/H_2O (1/1, 6 mL) was stirred at 80 °C for 16 h, unless otherwise noted. [b] Yields of products isolated by chromatography over silica gel. [c] The aldehyde were recovered unchanged. [d] The reactions were carried out at 95 °C for 16 h in dioxane/H_2O (1/1, 6 mL).

presence of an electron-withdrawing group in aromatic aldehydes (entries 1–7) and a donating group in arylboronic acids (entries 8–11). On the other hand, the addition to electron-rich aldehydes (entry 7) and the arylation with electron-deficient arylboronic acids (entries 10 and 11) were slow at 80 °C. In the one exceptional case 4-nitrobenzaldehyde remained intact during the reaction (entry 5).

The reaction is specific for aldehydes. Aromatic ketones, esters, nitriles, halides (Cl, Br) were unreactive, as evidenced by the recovery of these substrates. Steric hindrance around the boron atom retarded the reaction (entry 13), but the reactions of *ortho*-monosubstituted arylboronic acids proceeded smoothly at 80 °C (entry 12). The additions to aliphatic aldehydes such as hexanal and cyclohexanecarbaldehyde were very slow at 80 °C because their electrophilicity is lower than that of aromatic aldehydes, but the reaction at 95 °C in dioxane/H_2O gave the tertiary alcohols in high yields (entries 16 and 17). (*E*)-1-Hexenylboronic acid also participated in the catalytic reaction, and its stereochemistry was retained in the product (entry 18).

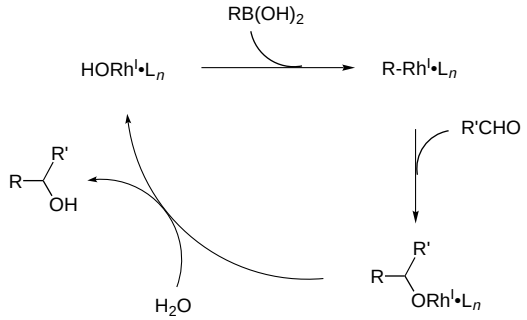
The facile addition of arylboronic acids to aldehydes encouraged us to examine the asymmetric version of this protocol (Scheme 2). The monodentate ligand 2-(diphenylphosphanyl)-2′-methoxy-1,1′-binaphthyl ((*S*)-MeO-MOP)[8] gave rise to a moderate asymmetric induction: (*R*)-(+)-(1-naphthyl)(phenyl)methanol was formed preferentially ($[\alpha]_D^{20} = +9.3$ ($c = 0.01$, EtOH), 41 % *ee*), though the chiral



Scheme 2. Asymmetric addition.

bidentate ligands such as diop and binap unfortunately resulted in the formation of racemic alcohols.

The reaction may involve the transmetalation between arylboronic acid and the RO–Rh species (RO = acac or OH) to give an $Ar{-}Rh^I$ complex and the insertion of an aldehyde into the Ar–Rh bond (Scheme 3).[4] The arylrhodium(I) complexes are unstable such as to preclude isolation in pure



Scheme 3. Proposed catalytic cycle.

form, but they have been reasonably speculated to be the key intermediates in various coupling reactions with organic halides[9] and the addition to alkenes and alkynes.[10] However, the insertion of aldehydes into the carbon–metal bond is very rare in transition metals except the allylic derivatives.[5, 11]

Experimental Section

Procedure for the reactions presented in Tables 1 and 2: $[Rh(acac)(CO)_2]$ (8 mg, 0.03 mmol, 3 mol %) and dppf (17 mg, 0.03 mmol, 3 mol %), $PhB(OH)_2$ (0.244 g, 2 mmol), and naphthaldehyde (0.156 g, 1.0 mmol) were dissolved in DME (3 mL) and water (3 mL) under nitrogen. After the mixture was stirred at 80 °C for 16 h, the product was extracted with benzene, dried over $MgSO_4$, and finally purified by chromatography on silica gel with hexane/ethyl acetate (20/1) to give (1-naphthyl)(phenyl)-methanol (0.213 g, 0.91 mmol, 91 %).

Asymmetric arylation (Scheme 2): $[Rh(acac)(CH_2{=}CH_2)_2]$ (8 mg, 0.03 mmol, 3 mol %) and (*S*)-MeO-MOP (28 mg, 0.06 mmol, 6 mol %), $PhB(OH)_2$ (0.243 g, 2 mmol), and naphthaldehyde (0.156 g, 1.0 mmol) were dissolved in DME (3 mL) and water (3 mL) under nitrogen. The mixture was stirred at 60 °C for 36 h and worked up. Chromatography on silica gel with hexane/ethyl acetate (10/1) gave the tertiary alcohol (0.181 g, 0.77 mmol, 77 %). The enantiomeric purity (41 % *ee*) and the absolute configuration (*R*) were established by high-pressure liquid chromatography (Daicel Chiracel OD-H, hexane/2-propanol 4/1) and by comparison with the reported optical rotation.[12]

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Highly Efficient Synthesis of Covalently Cross-Linked Peptide Helices by Ring-Closing Metathesis**

Helen E. Blackwell and Robert H. Grubbs*

Due to the frequency of helical secondary structures in peptides and proteins,[1] considerable effort has been directed toward the design of small-molecule helix mimetics and stabilized helix structures. Designed organic template molecules that initiate α-helix formation in peptide sequences have been reported.[2] Short α-helical peptides have also been stabilized by incorporation of naturally occurring capping motifs[3] and by stabilization of the intrinsic helix dipole.[4] Notably, significant progress has been made toward stabilizing synthetic α-helical peptides through the incorporation of covalent or noncovalent linkages between constituent amino acid side chains. Examples include salt bridges,[5] lactams,[6] disulfide bridges,[7] hydrophobic interactions,[8] and metal ligation between natural[9] and unnatural amino acids.[10] In several of these cases, it was found that substantial helix stabilization was achieved when the linkage was placed between the i and $i+4$ residues in the peptide backbone. Such a linkage encompasses approximately one turn of the helical peptide backbone and places the tethered side chains on the same side of the helix. Recently, the extraordinary functional group tolerance of olefin metathesis catalyst $[(PCy_3)_2Cl_2Ru{=}CHPh]$ (**1**)[11] has enabled the synthesis of cyclic amino acids[12] and peptides exhibiting β-turn[13] and β-sheet[14] secondary structure by ring-closing olefin metathesis (RCM).[15] This transformation effectively introduces non-native carbon – carbon bond constraints which may afford enhanced biostability. Here we present a concise synthesis and structural analysis of a series of cyclic helical peptides wherein RCM is used to incorporate a carbon – carbon tether between amino acid side chains.

We chose to study hydrophobic peptide model systems from the outset, because the use of apolar sequences permits characterization of conformation in poorly solvating organic solvents where folding is mainly controlled by intramolecular hydrogen bonding, nonbonding interactions, and electrostatic effects.[16] We became interested in a hydrophobic peptide (**2**) studied by Karle and Balaram et al.,[17] whose solubility in organic solvents would be compatible with alkylidene **1**.[18] Heptapeptide **2** contains two repeat units of valine – alanine – leucine (Val-Ala-Leu) separated by one α-aminoisobutyric acid residue (Aib), as shown schematically in Figure 1. The Aib residue is known to stabilize 3_{10}- and/or α-helical

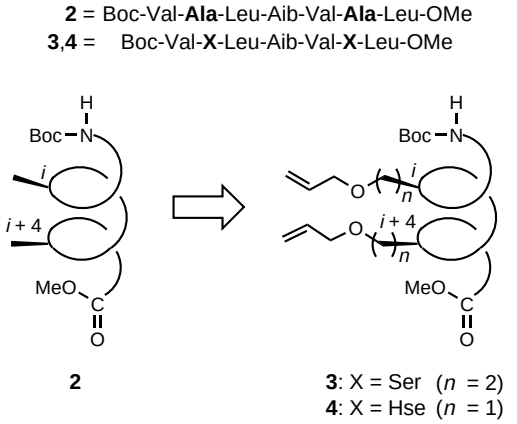

Figure 1. Karle and Balaram's heptapeptide **2**, and two dienic analogues **3** and **4**. Boc = *tert*-butoxycarbonyl.

conformations in apolar oligopeptides and is frequently found in peptides produced by microbial sources.[19] Examples of such Aib-rich peptides include the antibiotics alamethicin, zervamicin, and trichogin A IV, which are purported to adopt helical conformations within lipid bilayer membranes and aggregate therein to form ion channels. Heptapeptide **2** was shown to adopt an α-helical conformation in the solid state by X-ray crystallography and was found to adopt a similar helical conformation in $CDCl_3$ by solution-phase 2D NMR analyses.

[*] Prof. R. H. Grubbs, H. E. Blackwell
Arnold and Mabel Beckman Laboratories of Chemical Synthesis
Division of Chemistry and Chemical Engineering
California Institute of Technology
Pasadena, CA 91125 (USA)
Fax: (+1) 626-564-9297
E-mail: rhg@its.caltech.edu

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