Ruthenium-Catalyzed Oxidative Heck Reactions**

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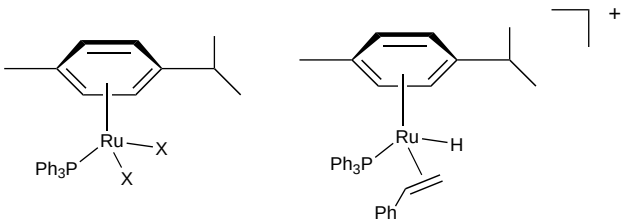
The coupling of organic electrophiles with alkenes is one of the cornerstones of Pd complex catalysis. The basis of the chemistry involved lies in early contributions by Mizoroki[1] and Heck.[2] Many of Heck's examples involve stoichiometric reactions of organomercurials and other potential organic nucleophiles in addition to Pd salts. Since then, but with a notable recent exception (see below),[3] palladium complexes have been used essentially exclusively in Heck catalysis.

Ruthenium complexes are readily accessible, but less widely utilized in the catalysis of C–C coupling reactions.[4] Faller and Chase demonstrated that complex **1b**, prepared from the dichloride **1a** and PhMgBr, reacted with ethene and $AgSbF_6$ to form styrene and the corresponding Ru–H complex **2**.[5] An intramolecular variant through insertion of ethene into the Ru–C bond of complex **3** was reported by Pfeffer and co-workers.[6] These stoichiometric reactions provided the key to catalysis, since reversion from a Ru–H complex to the halide together with a compatible method for the formation of a Ru–C bond would, in principle, complete the cycle.



1a X = Cl
1b X = Ph, Br
1c X = Ph, Cl

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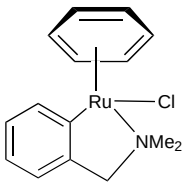

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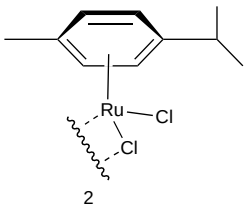

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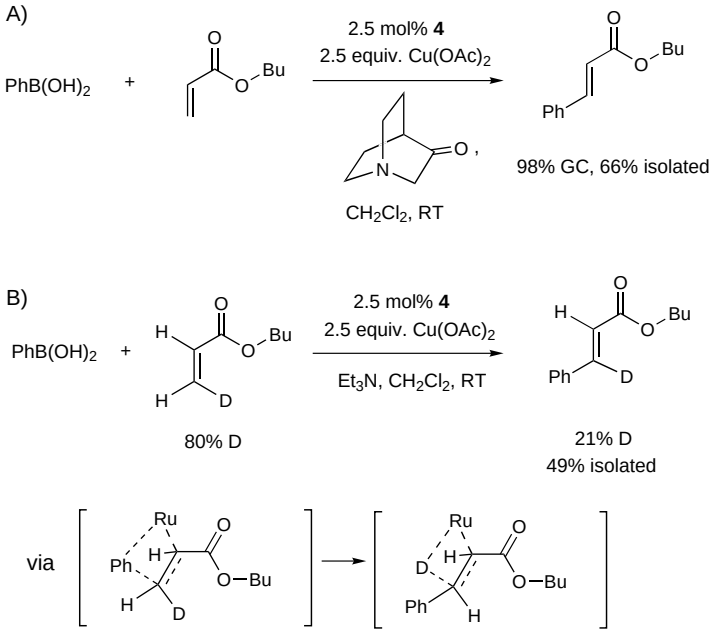
In preliminary experiments it was established that the reaction of **1a** with $PhSnBu_3$ or $PhB(OH)_2$ occurred readily to give **1c** as a stable product.[7] This observation formed the basis of a successful stoichiometric reaction between $PhB(OH)_2$ and methyl propenoate, promoted by complex **1a** in the presence of NEt_3 under mild conditions. The use of more than 2 equivalents of $Cu(OAc)_2$ to reoxidize the expected Ru–H complex led to catalytic turnover; the process was more efficient when PPh_3 was omitted from the initial Ru catalyst (Scheme 1).[8] Optimization experiments



Scheme 1. Ruthenium-catalyzed Heck reactions: A) optimum conditions; B) with stereospecifically labeled butyl propenoate.

demonstrated that other oxidizing agents (e.g. Me_3NO, Fremy's salt) also promoted the reaction, but less effectively than Cu^{II}. Significant improvements in the base component were achieved by this approach: 3-quinuclidone gave the highest turnover (Scheme 1 A). The conditions were successfully applied with *n*-butyl propenoate and other $ArB(OH)_2$ species (Ar = *p*-CHO, OMe, OCF_3).

To compare the pathway with the more familiar Pd case, the addition of $PhB(OH)_2$ to butyl (*Z*)-3-D-propenoate[9] was effected (Scheme 1 B). The label was largely, but not completely, absent in the product. This is in accord with partial stereoselectivity in the catalytic process, most probably through stereospecific *cis* addition of Ru–Ph[10] to the alkene followed by some randomization (Ru keto-enol equilibria?)[11] prior to stereospecific Ru-H/D *cis* elimination. Electrospray mass spectrometry revealed intermediates in the catalytic cycle, best observed with $4\text{-}BrC_6H_4B(OH)_2$ in a CH_3CN matrix (Scheme 2). Before the addition of the alkene, three monomeric complexes **5a–c** and one dimeric cationic complex **5d** can be characterized on the basis of the typical

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Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

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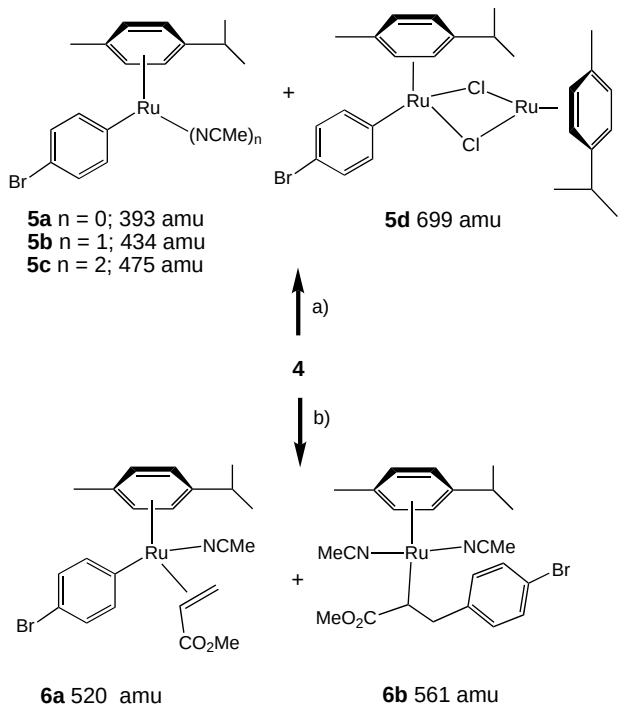
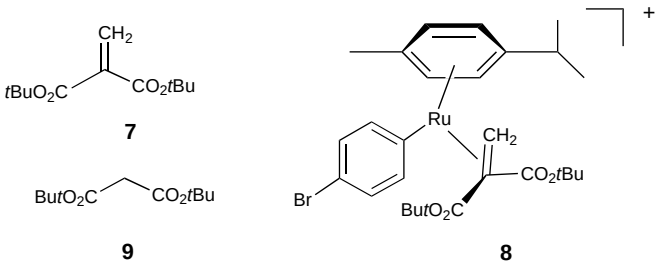


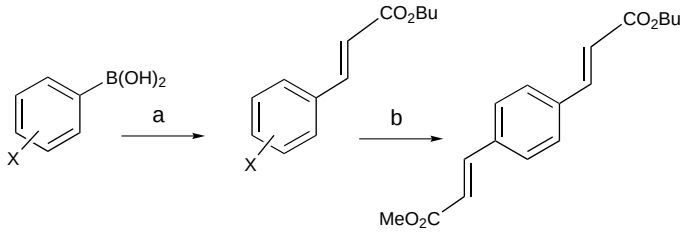
Scheme 2. Cationic species observed by electrospray mass spectrometry recorded on a Micromass BioQ II-ZS at a cone voltage of +20 V, Ru-102, Br-81, Cl-35 ion specified. Reagents and conditions: a) $[Ru(p\text{-cymene})Cl_2]_2$ (3.26×10^{-5} mol), *p*-bromobenzeneboronic acid (3.26×10^{-5} mol), NEt_3 (3.26×10^{-5} mol), MeCN (20 mL), 30 min, room temperature; b) same conditions as (a), but allowed to stand with a tenfold excess of methyl propenoate for 15 h at −20 °C before assay.

isotope distributions in the parent molecular ion. In the presence of methyl propenoate, the same set of monomeric ions are observed together with two distinct new halide-free species, corresponding to monoalkene complexes with one or two coordinated acetonitrile ligands. The simplest representation in which these preserve an 18 e configuration at the ruthenium center is as the aryl and alkyl complexes **6a** before, and **6b** after the expected migration step; ring slippage is an alternative possibility.[12] The nature of propenoate binding



was explored through the use of methylene malonate **7**, which gave rise to a strong acetonitrile-free molecular ion **8** for the coordinated alkene complex, under conditions in which the parent malonate **9** remains passive.

The inertness of the aryl bromide residue towards ruthenium (i.e. dominance of nucleophilic attack by the boronic acid) indicated valuable synthetic potential. Several haloaryl boronic acids were subjected to our best conditions of catalytic turnover, with *n*-butyl propenoate as the alkene component. The results are recorded in Scheme 3, and



Scheme 3. Ru-catalyzed reactions of haloaryl boronic acids. Reagents and conditions: a) boronic acid (0.4 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (6.2 mg, 0.02 mmol), $Cu(OAc)_2$ (201 mg, 1 mmol), quinuclidin-3-one (126 mg, 1 mmol), and butyl propenoate (155 mg, 1.2 mmol), toluene, 24 h, room temperature, X = *m*-Cl (77 %), X = *p*-Cl (93 %), X = *p*-Br (63 %),[13] X = *m*-Br (96 %), X = *m*-I (76 %), X = *p*-I (77 %); b) butyl *p*-iodocinnamate (50 mg, 0.15 mmol), tris(*o*-tolyl)phosphane (4.56 mg, 0.015 mmol), $Pd_2(dba)_3$ (7.8 mg, 0.0076 mmol), methyl propenoate (65 mg, 0.76 mmol), triethylamine (76 mg, 0.76 mmol), DMF, 24 h, room temperature, **10** (90 %); dba = *trans*,*trans*-dibenzylideneacetone, DMF = *N*,*N*-dimethylformamide. For product characterization, see Supporting Information.

demonstrate the generality of the selective C–B activation and transfer. Good yields are maintained over a range of boronic acids substituted with Cl, Br, or I. In one case, a tandem Pd- and Ru-catalyzed coupling reaction in which C–B is activated first, followed by C–X, gave the unsymmetrical phenylene-bis-propenoate **10**.[14]

In related work, it was demonstrated that aryl stannanes,[15] aryl silanols,[16] and aryl boronic acids[17] can be coupled with electrophilic alkenes under $Pd(OAc)_2$ catalysis (5–10 mol %). In the first two cases Cu^{II} is present as a reoxidant. In the last case, the authors favor, but do not prove, an oxidative addition of $ArB(OH)_2$ as the initial step; the reaction works only in AcOH. Very recently, Lautens and co-workers observed the coupling of styrenes with an excess of functionally diverse boronic acids in aqueous solution, to form *E* stilbenes in the absence of a formal oxidant.[3] The relationship of these procedures to ours is intriguing, but as yet unclear.

The synthetic potential of the ruthenium Heck reaction is being actively investigated further.[18]

Experimental Section

Butyl (*E*)-3-bromocinnamate: 3-bromobenzeneboronic acid (81 mg, 0.4 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (6.2 mg, 0.02 mmol), $Cu(OAc)_2$ (201 mg, 1 mmol), and 3-quinuclidinone (126 mg, 1 mmol) were combined in a dry Schlenk tube, which was sealed and placed under vacuum for 30 min. The Schlenk tube was flushed with argon, and butyl propenoate (155 mg, 1.2 mmol) and freshly distilled toluene (10 mL) were added through a syringe. The reaction mixture was stirred for 24 h at ambient temperature. The volatile components were removed in vacuo, and the product was purified by flash column chromatography on silica gel (diethyl ether) to give butyl (*E*)-3-bromocinnamate (112 mg, 96 %). M.p. 36 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.96$ (3 H, t, $J = 7.3$ Hz; CH_3), 1.44 (2 H, m; CH_2), 1.70 (2 H, m; CH_2), 4.22 (2 H, t, $J = 6.7$ Hz; OCH_2), 6.46 (1 H, d, $J = 16$ Hz; H1), 7.26 (1 H, dd, $J = 8$ Hz and 7.95 Hz; H5′), 7.46 (1 H, d, $J = 8$ Hz; H4′), 7.52 (1 H, d, $J = 7.95$ Hz; H6′), 7.61 (1 H, d, $J = 16$ Hz; H3), 7.68 (1 H, s; H2′); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 13.6$ (CH_3), 19.1 (CH_2), 30.6 (CH_2), 64.5 (OCH_2), 119.7 (C2), 122.9, 126.5, 130.3, 130.6, 132.9, 136.4, (C1′, C2′, C3′, C4′, C5′, C6′), 142.7 (C3) 166.5 (C1); IR (Nujol): $\tilde{\nu}_{max} = 2920.9$, 1727.3 (C=O), 1641.7 cm^{-1} (C=C); HR-MS: calcd for $C_{13}H_{16}O_2Br$: 283.0335, found: 283.0335; MS (atmospheric pressure chemical ionisation; APCI+): *m*/*z* (%): 284 [*M*H+], 226 [*M* − Bu].

Coupling of butyl (*Z*)-3-D-propenoate: Benzeneboronic acid (10 mg, 8.2×10^{-5} mol), $[Ru(p\text{-cymene})Cl_2]_2$ (1.25 mg, 4.1×10^{-7} mol), and $Cu(OAc)_2$ (40.9 mg, 0.2 1mmol) were combined in a vial, and THF (0.9 mL) and

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triethylamine (0.1 mL) were added. Butyl (*Z*)-3-D-propenoate was added through a syringe. The vial was sealed, and the reaction mixture was stirred at ambient temperature for 17 h. The solvent was removed in vacuo, and the product was purified by filtration through a short plug of silica gel (diethyl ether) to afford butyl (*E*)-cinnamate (8.2 mg, 49 %). B.p. 280–284 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.99$ (3 H, t, $J = 7.3$ Hz; CH_3), 1.43 (2 H, m; CH_2), 1.72 (2 H, m; CH_2), 4.23 (2 H, t, $J = 6.7$ Hz; OCH_2), 6.48 (1 H, d, $J = 16$ Hz; H2), 7.40 (3 H, m; ArH), 7.53 (2 H, m; ArH), 7.77 (1 H, d, $J = 16$ Hz; H3); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 13.6$ (CH_3), 19.1 (CH_2), 30.6 (CH_2), 64.3 (OCH_2), 118.2 (C2), 127.9, 128.7, 130.1, 134.3, (Ar-C), 144.4 (C3), 167.0 (C1); UV/Vis: $\tilde{\nu}_{max}$ (MeOH) = 276 nm ($\varepsilon = 22\,000$); MS (CI +): *m*/*z* (%): 205 [MH^+].

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Enantiopure Double-Helical Alkynyl Cyclophanes

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Chiral π-conjugated molecules have been the subject of extensive investigation from the standpoints of structural chemistry and material science.[1] Double-helical molecules, in particular, are of great interest on account of their unique structural features as well as potential applications in optics and electronics. Several twisted alkynyl cyclophanes have been reported, but, unfortunately, they were obtained as racemates.[2, 3] To the best of our knowledge, only one nonracemic double-helical molecule has been prepared. Namely, a cyclophane was synthesized by connecting a (+)-2,15-diethynyl[6]helicene auxiliary with *ortho*-phenylene bridges.[4] However, this synthesis was rather lengthy, and only one enantiomer was obtained. Moreover, in the key coupling of the helicene with an *o*-diiodobenzene unit, the target molecule was obtained in less than 3 % yield. We report here on a rational synthesis and full characterization of double-helical alkynyl cyclophanes **1** of both enantiopure forms.[5]

The synthetic route is shown in Scheme 1. Separately (*R*)- and (*S*)-2,2′-diformyl-1,1′-binaphthyl (**2**)[6] underwent carbon–carbon coupling, and the resulting diethynyl compound **3** was converted to the monosilylethynyl derivative **4**. Exposure of this compound to an aryl iodide with the diethyltriazene function **5** afforded **6**. The triazene derivatives **6** were transformed into iodides **7** or desilylated to give **8**.[7] Sonogashira coupling[8] of **7** with **8** furnished **9**. After conversion of **9** to **11** via **10** through successive functional group transformations, intramolecular Sonogashira coupling provided the desired cyclophanes **1** in enantiopure form (Table 1). These compounds formed white needlelike crystals upon recrystallization, but none of them were suitable for X-ray analyses. Then, we prepared racemic **1b** by mixing equimolar amounts of (*R*,*P*)- and (*S*,*M*)-**1b**. Recrystallization of this mixture from CH_2Cl_2/hexane furnished crystals conducive to X-ray crystallographic analysis.[9]

As is evident from the ORTEP view depicted in Figure 1, the cyclophane skeleton is twisted, resulting in the double-helical motif. The C≡C bonds are slightly deformed from linearity. Notably, the two binaphthyl groups differ significantly in the dihedral angle defined by the naphthalene planes (68° and 78°, respectively). The space-filling model (Figure 2) indicates that the symmetrical structure places the inside hydrogen atoms of the phenylene rings very close to each other. The resulting ring strain is passed on unsymmetrically into the binaphthyl termini in the crystal.

In contrast to the solid-state molecular structure, ^{1}H and ^{13}C NMR spectra of **1** (Table 1) are compatible with a single

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