Palladium-Catalyzed Highly Regio- and Stereoselective Addition of Organoboronic Acids to Allenes in the Presence of AcOH

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Abstract: The Pd⁰-catalyzed regio- and stereoselective addition of organoboronic acids to allenes leads to stereodefined tri- or tetrasubstituted alkenes. Furthermore, this method shows high substituent-loading capability and tolerance of various substituents. A hydropalladation–Suzuki coupling mechanism, which may account for the regio- and stereoselectivity, is proposed.

Introduction

Organoboronic acids enjoy high prestige as reagents in metal-catalyzed C–C bond-formation reactions. The most notable progress is in rhodium- and nickel-catalyzed conjugate additions to unsaturated C–C bonds⁰–³ aldehydes,⁴ and N-sulfonylimines⁵ reported by Miyaura, Hayashi, and Shirakawa. Although organoboronic acids are widely used in palladium-catalyzed Suzuki cross-coupling reactions,⁶ transition-metal-catalyzed addition reactions of organoboronic acids to electron-rich unsaturated compounds are rare.⁷

However, palladium-catalyzed reactions of allenes⁸ especially addition reactions with different nucleophiles to form a carbon–carbon or carbon–heteroatom bond,⁹–¹¹ have become an important area of study in synthetic organic chemistry.⁹,¹⁰ In principle six different products¹² can be obtained by addition of allenes to HZ (Scheme 1), owing to regio- and stereoselectivity: this problem must be addressed in order to make this addition synthetically attractive. Here, we report the first highly regio- and stereoselective palladium-catalyzed hydroarylation or hydroalkenylation of allenes forming tri- or tetrasubstituted alkenes.

Results and Discussion

Synthesis of 2-(2',3'-dienyl)malonates 1: Compounds 1a–1e were prepared from the alkylation of malonates with the corresponding 2,3-dienyl bromides in THF with NaH as the base.¹³,¹⁴ 2,3-Dienyl bromides were prepared from 2,3-dien-1-ols¹⁵ and PBr₃ (Scheme 2).¹³,¹⁶ Allenic compound 1f was prepared by Pd⁰-catalyzed 2,3-allylation of malonate, and 1g was synthesized by methylation of 1a (Scheme 3). 2,3-Allenato 2a–f were synthesized according to the Wittig-type reactions shown in Scheme 4.¹³,¹⁷,¹⁸

Scheme 1. Regioselectivity in addition of allenes.

Scheme 2. Synthesis of 2-(2',3'-dienyl)malonates.

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The palladium-catalyzed addition reaction of organoboronic acid with allenes: During our recent research on the chemistry of 2,3-allenylmalonates, we observed that the Pd(OAc)\(_2\)-catalyzed reaction of dimethyl 2-(2-benzyl-2,3-butadienyl)malonate (1a) with 4-methoxyphenylboronic acid (3a) did not give addition products in decent yields (Scheme 5). Fortunately, after some screening, we found that the reaction of 1a with 3a afforded an unexpected 67:33 mixture of hydroarylation products 4aa and 5aa in a 66% combined yield in the presence of 10 mol% \([\text{Pd}(\text{PPh}_3)_4]\) (Scheme 5). Interestingly, we found that the reaction occurred in the presence of AcOH (40 mol%), demonstrating a high regioselectivity, giving tetrasubstituted 5aa as the major product in 75% yield (5aa/4aa = 95:5, t-5aa/c-5aa (Z/E) = 87:13) (entry 1, Table 1). The effects of different acids and temperature on the reaction are summarized in Table 1.

Based on these results, conditions A (10 mol% \([\text{Pd}(\text{PPh}_3)_4]\), 20% AcOH, RT) were applied for the highly regio- and stereo-selective formation of tri- or tetrasubstituted alkenes 5. The results of the reaction of different 2,3-allenoates with aryloboronic acid under conditions A are summarized in Table 2. The configurations of the C=C bond in 5 were determined by the \(^1\)H–\(^1\)H NOESY spectra. In order to expand the scope of the Pd-catalyzed hydroarylation, we also studied the reaction of 2,3-allenoates bearing different substituents with arylboronic acid; the results are summarized in Table 3.

To establish the stereochemistry of this reaction further, the structure of the (E)-7ac was determined by X-ray single-crystal X-ray analysis (Figure 1). The reactions of ethyl 2-benzylbuta-2,3-dienoate (2a) with different aryloboronic acids are summarized in Table 4. The corresponding reaction with 1-alkenylmalonates with aryloboronic acid under conditions A are summarized in Table 5.
nlyboronic acid also afforded conjugated diene highly regio- and stereoselectively [Eq. (1)].

The reaction of ethyl 3,4-pentadienoate 8 with 3a behaved similarly [Eq. (2)].
Furthermore, the reaction of a simple allene, e.g., 1,2-decadiene (11), with 4-methoxyphenylboronic acid (3a) under the standard conditions afforded a mixture 12 and 13 (13/12 = 89:11, E-13/Z-13 > 96:4) in 71% yield [Eq. (3)].

Mechanism: From these results it should be noted that:

1) The regioselectivity is controlled by the relative steric hindrance of the two C=C bonds of the allenes, with the hydroarylation or hydroalkenylation occurring highly regioselectively with the terminal C=C bond.

2) The stereoselectivity may be determined by the relative steric hindrance of R1 and R2 (Scheme 1) (compare entries 1, 2, 6, and 8 with entries 3–5, 7, and 9, Table 2.) These results were further supported by the reaction of 1e. It was due to introduction of the n-hexyl group to the terminal position that the regioselectivity dropped dramatically while the stereoselectivity was still excellent [Eq. (4)].

3) A Pd0 complex is required, since none of the expected products was formed in the reaction with 10 mol% Pd(OAc)2 as the catalyst (Scheme 5).

4) The interconversion between 4aa and 5aa under conditions A was not observed, indicating that the regioselectivity is not controlled thermodynamically (Scheme 6).

Scheme 6. The possibility of interconversion between 4aa and 5aa under the standard conditions A.

Based on these results we have proposed a rationale for the reaction of allenes with organoboronic acids under the standard conditions A or B. Firstly, a highly regioselective oxidative addition reaction occurs between the HX and Pd0 to afford palladium hydride species 14, which may undergo hydropalladation with the less sterically hindered terminal C=C bond in the allene moiety to afford an alkényl palladium intermediate 15.[21] Suzuki coupling of 15 with aryl 1-alkenyloboronic acid affords the tri- or tetrasubstituted alkenes 5 (Scheme 7).[22]

Conclusion

We have demonstrated the highly selective palladium-catalyzed addition of organoboronic acids to allenes in the presence of AcOH. The advantages of this method are easy availability and diversity of the starting compounds, and high regio- and stereoselectivity leading to stereodefined tri- or tetrasubstituted alkenes. Although the mechanism needs further attention, the current reaction may open a new area for the control of regio- and stereoselectivity in the transition metal-catalyzed addition of allenes. Further studies on details of the mechanism, the scope, and the synthetic applications of this reaction are being carried out in our laboratory.

Experimental Section

The starting 2-(2,3-dienyl)malonates 1a,[13] 1b,[13] and 1e[13] were prepared according to literature procedures.

Typical preparation of 1c–1d

Methyl 2-(2-benzyl-2,3-butenyl)malononitrile (1c): The reaction of 3-bromomethyl-4-phenyl-1,2-butaadiene (2.65 g, 12 mmol),[13] malononitrile (1.1 g, 16.8 mmol), and NaNH (60% dispersion in mineral oil, 0.528 g, 13.2 mmol) afforded 1c (1.50 g, 60%) by means of the reported procedures.[23] Liquid; IR(neat): ν = 2912, 2258, 1961, 1602, 1496, 1455, 702 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 7.18–7.37 (m, 5H), 5.03–5.12 (m, 2H), 3.72 (t, J = 7.30 Hz, 1H), 3.38–3.43 (m, 2H), 2.49–2.60 ppm (m, 2H); ¹³C NMR (CDCl₃), 75.4 MHz: δ = 205.41, 137.39, 128.67, 126.66, 126.97, 112.42, 97.52, 80.45, 37.07, 28.43, 13.87 ppm; MS: m/z (%): 208 (87.2) [M⁺], 91 (100); HRMS: m/z (EI): calcd for C₁₄H₁₂N₂: 208.10005; found: 208.09895.

Ethyl 2-cyanohexa-4,5-dienoate (1d): The reaction of 4-bromo-1,2-butaadiene[13] (1.06 g, 8 mmol), ethyl cyanoacetate (1.27 g, 11.2 mmol), and NaNH (60% dispersion in mineral oil, 0.352 g, 8.8 mmol) afforded 1d (0.35 g, 26%) by means of the reported procedures.[13,14] Liquid; IR(neat): ν = 2989, 2252, 1958, 1745, 1260 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 5.14–5.23 (m, 1H), 4.81–4.92 (m, 2H), 4.27 (q, J = 7.09 Hz, 2H), 3.60 (dd, J = 7.65, 6.05 Hz, 1H), 2.56–2.68 (m, 2H), 1.32 ppm (t, J = 7.09 Hz, 3H); ¹³C NMR (CDCl₃), 75.4 MHz: δ = 208.93, 165.38, 116.05, 84.84, 77.26, 62.81, 37.07, 28.43, 13.87 ppm; MS: m/z (%): 165 (0.72) [M⁺], 53 (100); HRMS: m/z (EI): calcd for C₉H₁₁NO₂: 165.07898; found: 165.07414.
Preparation of 2-methyl-2-(2-benzyl-2,3-butenadienyl)malonate (1f)

Synthesis of 3-benzylpertric-3,4-dienyl acetate: 3-Benzylpertric-3,4-dienyl-2-ol (3.48 g, 18.4 mmol) and Et$_2$N (3.8 mL) was added to a mixture of Pd(PPh$_3$)$_4$ (0.754 g, 0.65 mmol; 5 mol%) and NaH (60% dispersion in mineral oil, 0.572 g, 14.3 mmol) in dry 1,2-dichloroethane (104 mL); this was followed by the addition of 3-benzylpertric-3,4-dien-2-yl acetate (2.63 g, 13 mmol) under nitrogen. The resulting mixture was stirred at RT for 18 h, while being monitored by TLC. The solution was quenched with an aqueous saturated solution of NaCl (10 mL) and extracted with diethyl ether (200 mL). The organic layer was dried over anhydrous sodium sulfate. After evaporation to dryness, the residue was purified by flash chromatography on silica gel (eluent: petroleum ether/diethyl ether, 20:1) to afford 1f, 3-benzylpertric-3,4-dienyl acetate (3.62 g, 91%)

Synthesis of 2-(2-benzyl-2,3-butenadienyl)malonate (1j): Dimethyl malonate (4.66 mL, 39.0 mmol) was added dropwise to a mixture of Pd(PPh$_3$)$_4$ (0.754 g, 0.65 mmol; 5 mol%) and NaH (60% dispersion in mineral oil, 0.572 g, 14.3 mmol) in dry 1,2-dichloroethane (104 mL); this was followed by the addition of 3-benzylpertric-3,4-dien-2-yl acetate (2.63 g, 13 mmol) under nitrogen. The resulting mixture was stirred at RT for 18 h, while being monitored by TLC. The solution was quenched with an aqueous saturated solution of NaCl (10 mL) and extracted with diethyl ether (200 mL). The organic layer was dried over anhydrous sodium sulfate. After evaporation to dryness, the residue was purified by flash chromatography on silica gel (eluent: petroleum ether/diethyl ether, 20:1) to afford 1j, 2-(2-benzyl-2,3-butenadienyl)malonate (4.02 g, 81%)

Typical procedure for preparation of 1-methyl-2-(2-benzyl-2,3-butenadienyl)malonate (1g): Compound 1a (272 mg, 1.0 mmol) was added dropwise to a mixture of NaH (60% dispersion in mineral oil, 46 mg, 1.2 mmol) in THF (3 mL); then Me$_2$C(213 mg, 1.5 mmol) was added and the mixture was heated under nitrogen. The resulting mixture was stirred at RT for 5 h, while being monitored by TLC. The solution was quenched with an aqueous saturated solution of NaCl (2 mL) and extracted with diethyl ether (20 mL). The organic layer was dried over anhydrous sodium sulfate. After evaporation to dryness, the residue was purified by flash chromatography on silica gel (eluent: petroleum ether/diethyl ether, 10:1, 3 mL) to afford 1g (171 mg, 61%).

Viscosid liquid; IR (neat): $\nu = 2952, 2957, 1735, 1604, 1495, 1259$ cm$^{-1}$. 1H NMR (300 MHz, CDCl$_3$): $\delta = 7.31-7.18$ (m, 5H), 4.73-4.68 (m, 2H), 3.71 (s, 3H), 3.66 (s, 3H), 3.48 (d, $J = 10.26$ Hz, 1H), 3.37-3.35 (m, 2H), 2.80-2.68 (m, 1H), 1.00 ppm (m, 3H, $J = 6.75$ Hz). $1^3$C NMR (CDCl$_3$, 75.4 MHz): $\delta = 204.50, 167.76, 167.50, 137.80, 128.02, 120.07, 125.18, 105.21, 77.20, 55.04, 51.92, 51.34, 37.42, 34.36, 16.74 ppm; MS: $m/z$: 288 (4.01) $^{15}$O $^{16}$C$_{18}$H$_{22}$O$_2$, 100% (elemental analysis calcd. (%) for C$_{18}$H$_{22}$O$_2$: 70.83, H 6.49, found: C 70.90, H 7.00).

Preparation of 1-methyl-2-(2-benzyl-2,3-butenadienyl)malonate (1g): Compound 1a (272 mg, 1.0 mmol) was added dropwise to a mixture of NaH (60% dispersion in mineral oil, 46 mg, 1.2 mmol) in THF (3 mL); then Me$_2$C(213 mg, 1.5 mmol) was added and the mixture was heated under nitrogen. The resulting mixture was stirred at RT for 5 h, while being monitored by TLC. The solution was quenched with an aqueous saturated solution of NaCl (2 mL) and extracted with diethyl ether (20 mL). The organic layer was dried over anhydrous sodium sulfate. After evaporation to dryness, the residue was purified by flash chromatography on silica gel (eluent: petroleum ether/diethyl ether, 10:1, 3 mL) to afford 1g (171 mg, 61%).

Viscosid liquid; IR (neat): $\nu = 2952, 2957, 1735, 1604, 1495, 1259$ cm$^{-1}$. 1H NMR (300 MHz, CDCl$_3$): $\delta = 7.08-7.31$ (m, 5H), 4.54-4.63 (m, 2H), 3.62 (s, 6H), 3.20 (t, $J = 2.63$ Hz, 2H), 2.49 (t, $J = 2.63$ Hz, 2H), 1.41 ppm (s, 3H). $1^3$C NMR (CDCl$_3$, 75.4 MHz): $\delta = 207.50, 216.72, 138.85, 128.88, 128.19, 126.29, 97.84, 76.29, 53.47, 53.52, 46.01, 36.25, 19.82 ppm; MS: $m/z$: 288 (63.7) $^{15}$O $^{16}$C$_{18}$H$_{22}$O$_2$, 100%; HRMS: $m/z$: (Ei) calcd. for C$_{18}$H$_{22}$O$_2$: 288.1356, found: 288.1392.

Synthesis of 2,3-allenoates (2): These were prepared according to literature procedures.$[$15, 17-18$]

The palladium-catalyzed addition reaction

Typical procedure under conditions A: Compound 1a (68 mg, 0.25 mmol) and Ac$_2$O (2.9 mL, 20 mol%) were added under nitrogen to a mixture of Pd(PPh$_3$)$_4$ (29 mg, 0.025 mmol; 10 mol%) and DMAP (242.5 mg, 2.0 mmol) in Et$_2$O (70 mL). The resulting mixture was stirred at RT for 1 h, while being monitored by TLC. After evaporation to dryness, the residue was purified by flash chromatography on silica gel (eluent: petroleum ether/diethyl ether, 20:1) to afford 4aa and 5aa (77 mg, 81%, $^{5aa} = 97.5, ^{15}O$ C$_{18}$H$_{24}$O$_2$, 100%)

Typical procedure under conditions B: Compound 2a (51 mg, 0.25 mmol) and Ac$_2$O (15 mL, 100 mol%) were added under nitrogen to a mixture of Pd(PPh$_3$)$_4$ (29 mg, 0.025 mmol, 10 mol%) and 4-methoxyphenylboronic acid 3a (76 mg, 0.50 mmol) in THF (3 mL). The resulting mixture was stirred at RT for 2 h, while being monitored by TLC. After evaporation to dryness, the residue was purified by flash chromatography on silica gel (eluent: petroleum ether/diethyl ether, 20:1) to afford 4ab and 5ab (77 mg, 81%, $^{5ab} = 97.5, ^{15}O$ C$_{18}$H$_{24}$O$_2$, 100%)

The reaction of 1d (38 mg, 0.23 mmol) and 3a (76 mg, 0.50 mmol) afforded 5a (85 mg, 84%), 5-da/c-5-a = 100) under conditions A. Compound 5-da:

The reaction of 1f (72 mg, 0.25 mmol) and 3a (76 mg, 0.50 mmol) afforded 5a (85 mg, 84%), 5-e/c-5-a = 90:10) under conditions A. Compound 5-e:

The reaction of 1g (72 mg, 0.25 mmol) and 3a (76 mg, 0.50 mmol) afforded 4a and 5g (87 mg, 92%, 5-g/a-g=99:1, 5-t-g-a = 95:5) under conditions A. Compound 5-t-g-a:

The reaction of 1h (72 mg, 0.25 mmol) and 3a (76 mg, 0.50 mmol) afforded 6a and 7aa (85 mg, 73%, 7a-c/a-c-6-a-7-a = 99:1, 7-b-c/a-b-c = 99:1, 7-c-c = 99:1) under conditions B. Compound (7-c-c): viscous liquid; IR (neat): δ = 3093, 1710, 1626, 1513, 1247 cm−1; 1H NMR (300 MHz, CDCl3): δ = 7.33 (d, J = 7.5 Hz, 2H), 7.27 (d, J = 7.0 Hz, 2H), 3.72 (s, 3H), 1.37 ppm (t, J = 7.4 Hz, 3H); MS: m/z (%): 310 (26%), 260 (100%); HRMS: m/z (%): 260 (100%); EI: calcd for C20H22O3: 310.15690; found 310.15213.

The reaction of 2b (28 mg, 0.25 mmol) and 3b (61 mg, 0.50 mmol) afforded 7bb (85 mg, 73%, 7b-c/a-c-7-a-7-b = 99:1, 7-c-c = 99:1) under conditions B. Compound (7-b-c): viscous liquid; IR (neat): δ = 2963, 1716, 1629, 1262 cm−1; 1H NMR (300 MHz, CDCl3): δ = 7.39 (d, J = 8.2 Hz, 2H), 7.18 (d, J = 8.2 Hz, 2H), 6.14 (q, J = 1.2 Hz, 2H), 4.21 (q, J = 0.9 Hz, 2H), 2.57 (d, J = 1.2 Hz, 2H), 2.37 (s, 3H), 1.32 ppm (t, J = 7.0 Hz, 3H); 13C NMR (75.4 MHz, CDCl3): δ = 166.67, 155.51, 142.14, 129.44, 128.45, 117.09, 59.81, 17.89, 14.29 ppm; MS: m/z (%): 200 (100%); 175 (61.69), 149 (21.44); elemental analysis calcd (%) for C12H14O2: C 74.64, H 7.10; found: C 74.06, H 7.05. Compound (7-b-c): viscous liquid; IR (neat): δ = 2963, 1716, 1629, 1262 cm−1; 1H NMR (300 MHz, CDCl3): δ = 7.39 (d, J = 8.2 Hz, 2H), 7.18 (d, J = 8.2 Hz, 2H), 6.14 (q, J = 1.2 Hz, 2H), 4.21 (q, J = 0.9 Hz, 2H), 2.57 (d, J = 1.2 Hz, 2H), 2.37 (s, 3H), 1.32 ppm (t, J = 7.0 Hz, 3H); 13C NMR (75.4 MHz, CDCl3): δ = 166.67, 155.51, 142.14, 129.44, 128.45, 117.09, 59.81, 17.89, 14.29 ppm; MS: m/z (%): 200 (100%); 175 (61.69), 149 (21.44); elemental analysis calcd (%) for C12H14O2: C 74.64, H 7.10; found: C 74.06, H 7.05.
Pd-Catalyzed Addition to Allenes

(86.35) [M]+, 129 (100); HRMS: m/z (EI): calcd for C21H22O5: 324.14633; found: 324.14620.

Ethyl 2-benzyl-3-(4-methoxyphenyl)butenoate (7ae): The reaction of 2a (51 mg, 0.25 mmol) and 6a (56 mg, 0.50 mmol) afforded 6aa and 7ab (42 mg, 68% and 64% yield, respectively).

Ethyl 2-benzyl-3-(4-methoxyphenyl)butenoate (7ae): The reaction of 2a (51 mg, 0.25 mmol) and 3 (64 mg, 0.50 mmol) afforded 6aa and 7ab (42 mg, 68% and 64% yield, respectively).

Ethyl 2-benzyl-3-(4-methoxyphenyl)butenoate (7ae): The reaction of 2a (51 mg, 0.25 mmol) and 3 (64 mg, 0.50 mmol) afforded 6aa and 7ab (42 mg, 68% and 64% yield, respectively).

Ethyl 2-benzyl-3-(4-methoxyphenyl)butenoate (7ae): The reaction of 2a (51 mg, 0.25 mmol) and 3 (64 mg, 0.50 mmol) afforded 6aa and 7ab (42 mg, 68% and 64% yield, respectively).

Ethyl 2-benzyl-3-(4-methoxyphenyl)butenoate (7ae): The reaction of 2a (51 mg, 0.25 mmol) and 3 (64 mg, 0.50 mmol) afforded 6aa and 7ab (42 mg, 68% and 64% yield, respectively).

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[a] For a review, see: T. Hayashi, Synlett 2001, 879.