

Ring Opening of Methylenecyclopropane Moieties in the Palladium-Catalyzed Cross-Coupling of Methylenecyclopropyl Bromides with Metallated CH-Acidic Compounds

Melanie Brandl, Sergei I. Kozhushkov, Stefan Bräse, and Armin de Meijere*

Institut für Organische Chemie der Georg-August-Universität Göttingen,
Tammannstrasse 2, D-37077 Göttingen, Germany
Fax: (internat.) + 49 (0)551/399475
E-mail: ameijer1@uni-goettingen.de

Received October 21, 1997

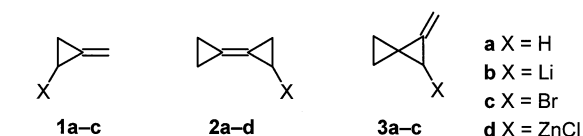
Keywords: Amino acids / Bicyclopropylidene / Methylenecyclopropane / Palladium catalysis / Zinc reagents

Palladium-catalyzed cross-coupling reactions of bromo-(methylenecyclopropanes) **1c**, **2c** with the sodium enolate of dimethyl malonate **4a** and the chlorozinc enolates of the glycine equivalent (diphenylmethyleamino)acetate **4c** and diethyl malonate **4d**, respectively, have been found to proceed with opening of the three-membered ring in each

case, to give the corresponding dienyl-substituted CH-acidic compounds **5–7** in moderate to good yields. On the other hand, coupling of bicyclopropylidenylzinc chloride (**2d**) with diethyl bromomalonate (**4e**) and the electrophilic glycine equivalent ethyl 2-acetoxy-2-(diphenylmethyleamino)acetate (**4f**) gave **7** and **6** in 27 and 29% yield, respectively.

Palladium-catalyzed nucleophilic substitution of allylic substrates with carbon nucleophiles, proceeding via π -allyl-palladium intermediates, has become one of the most important C–C bond forming processes employed in modern organic synthesis^[1]. The range of applicable allylic substrates covers a considerable structural variety, and even includes alkenylcyclopropyl derivatives^[2]. The most commonly used carbon nucleophiles are malonate and other suitably stabilized ester enolates. The enolate of ethyl α -(diphenylmethyleamino)acetate (O'Donnell's glycine equivalent^[3]) has frequently been employed in palladium-catalyzed allylic substitutions to prepare precursors of α -amino acids^[4], including some containing a methylenecyclopropyl fragment^{[2b][2c]}. Due to their wide-ranging biological activities, α - and β -amino acids containing a three-membered ring have attracted ever increasing interest over the last two decades^[5]. In continuation of our investigations in this area^[6] we have now tested the applicability of palladium-catalyzed allylic substitutions with the O'Donnell glycine equivalent in the preparation of amino acids containing a methylenecyclopropane fragment attached directly to the α -position^[7].

The required starting materials, the allylic bromides 2-bromo-1-methylenecyclopropane (**1c**), bromobicyclopropylidene (**2c**), and 2-bromo-1-methylenespiropentane (**3c**) were prepared by deprotonation^[8] of the corresponding hydrocarbons **1a–3a**^[9] with butyllithium and subsequent reaction of the lithio derivatives **1b–3b** with 1,2-dibromoethane^[8] (see Experimental Section).

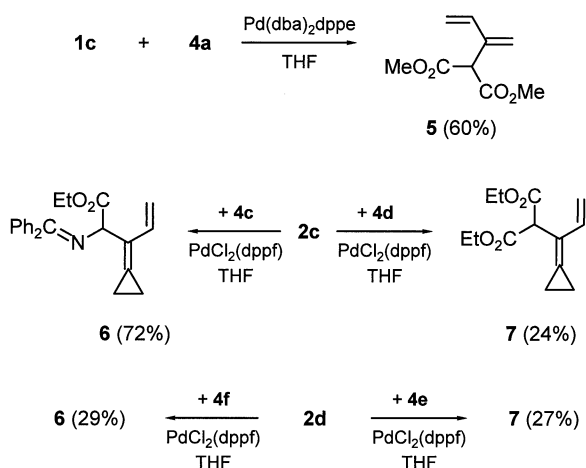


	4	a	b	c	d	e	f
X		CO ₂ Me	CO ₂ Et	CO ₂ Et	CO ₂ Et	CO ₂ Et	CO ₂ Et
Y		CO ₂ Me	N=CPh ₂	N=CPh ₂	CO ₂ Et	CO ₂ Et	N=CPh ₂
M		Na	Li	ZnCl	ZnCl	Br	AcO

In order to find the appropriate conditions for the palladium-catalyzed substitution of **1c–3c** with stabilized enolates, 2-bromo-1-methylenecyclopropane (**1c**) was treated with dimethyl sodiomalonate (**4a**) in the presence of palladium bis(dibenzylideneacetate) [Pd(dba)₂] and bis(diphenylphosphano)ethane (dppe), a commonly used catalyst system for such transformations^{[2][4]}. This reaction proceeded smoothly at 60 °C to give dimethyl (2'-buta-1',3'-dienyl)malonate (**5**) as the only isolated product in 60% yield. Apparently, the substitution of bromine in **1c** had taken place only with complete ring opening of the three-membered ring. However, the lithiated glycine equivalent **4b** did not undergo this type of reaction with **2c** under such conditions. At room temperature, no reaction was observed, whereas upon heating the reaction mixture to 35 °C, complete decomposition of the starting material **4b** was observed.

[○] Part 42: S. I. Kozhushkov, M. Brandl, D. S. Yufit, R. Machinek, A. de Meijere, *Liebigs Ann.* **1997**, 2197–2204.

Scheme 1

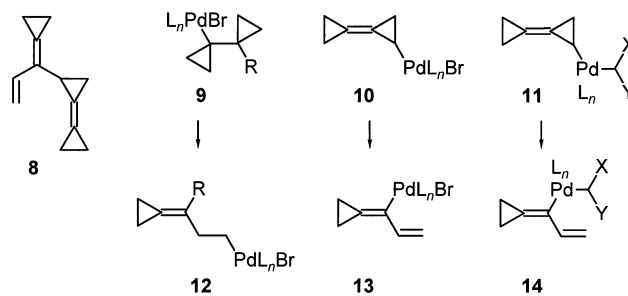


Among the great number of palladium catalysts available, dichloro[1,1'-bis(diphenylphosphano)ferrocene]palladium(II) [$\text{PdCl}_2(\text{dppf})$] has been reported to be by far the most active and selective in the coupling reactions of *n*-, *sec*-, and *tert*-alkylzinc and -magnesium halides, leading to high yields without any side reactions (β -elimination, etc.).^[10] Under the action of this catalyst, the coupling of 2-bromobicyclopentylidene (**2c**) with the chlorozinc derivative **4c** of the glycine equivalent (prepared from the lithio derivative **4b** by transmetalation with zinc chloride) proceeded even at room temperature, to give the dienyl-substituted glycine derivative **6** as the only isolated product in 72% yield. The structure of **6** is indicative of the same mode of cyclopropane ring opening as that seen in the reaction of **1c** with sodiummalonate to give **5**. Surprisingly, no reaction of the chlorozinc derivative **4c** with 2-bromo-1-methylenespiropentane (**3c**) could be observed under the same conditions, even after 56 h at room temperature.

In contrast, reaction of **2c** with the chlorozinc derivative of diethyl malonate **4d** in the presence of $\text{PdCl}_2(\text{dppf})$ gave the dienylmalonate **7**, but only in moderate yield (24%), along with some polymeric material. This result can be rationalized by assuming a rapid bromine exchange between the compounds **2c** and **4d**, leading to **2d** and diethyl bromomalonate **4e**. The subsequent palladium-catalyzed coupling of **2c** with **2d** would then presumably produce the triene **8**, which would be prone to polymerization. The ^{13}C -NMR spectrum of an unstable fraction with $R_f = 0.73$, isolated by column chromatography, showed signals consistent with the structure **8**. Thus, essentially the same product distribution was observed in the coupling of a twofold excess of the zinc derivative **2d** with diethyl bromomalonate **4e**, and compound **7** was isolated in 27% yield.

Formally, the structural transformations observed in these reactions are very similar to those reported for the coupling of bicyclopentylidene (**2a**) itself with haloarenes and alkenes under Heck conditions^[11]. Mechanistically, however, there is a difference. Whereas in the Heck reaction of **2a**, ring opening occurs at the stage of the (cyclopropylmethyl)palladium intermediate **9**, in the reactions re-

ported here, cyclopropylpalladium intermediates of the types **10** and/or **11** must be involved.

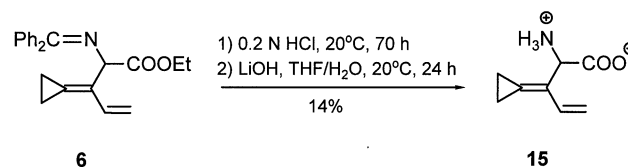


The conversion of **9** to **12** corresponds to the well-known (cyclopropylmethyl)metal to homoallylmetal^[12a] rearrangement, while the conversion of **10** or **11** to **13** and **14**, respectively, is analogous to the cyclopropylmetal (or cyclopropyl carbanion) to allylmetal (or allyl anion) ring opening^[12b].

To probe this mechanistic assumption, palladium-catalyzed coupling of O'Donnell's electrophilic glycine equivalent, the acetate **4f**^[13], with bicyclopentylidenylzinc chloride (**2d**) was examined. The chlorozinc derivative **2d** was generated by transmetalation of the lithio derivative **2b** with ZnCl_2 . Indeed, only the cyclopropylideneallyl-substituted glycine derivative **6** was isolated from this reaction, albeit in only 29% yield. This result confirms that the ring opening can at least occur in a cyclopropylpalladium intermediate of type **11**.

Deprotection of compound **6** with 0.2 N hydrochloric acid followed by saponification (LiOH , $\text{THF}/\text{H}_2\text{O}$) yielded the amino acid **15**, which represents an interesting example of a highly unsaturated α -amino acid containing a methyl-enecyclopropane moiety (Scheme 2).

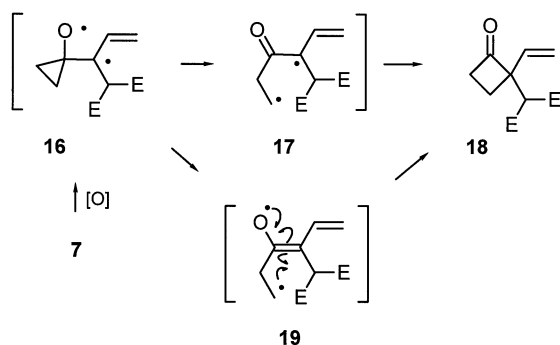
Scheme 2



The diene **7** was found to be rather unstable and polymerized even at -20°C , probably as a result of autooxidation. After a pure sample had been stored in a freezer for 6 months, only 4% of **7** could be recovered after repeated column chromatography, along with the cyclobutanone derivative **18** (9.2%). The ketone **18** can be formed from **7** via the intermediate diradicals **16**, **17**, or **19** (Scheme 3), with a cyclopropylmethyl to homoallyl radical rearrangement as a key step^[14].

In conclusion, palladium-catalyzed reaction of 2-bromo-1-methylenecyclopropane (**1c**) and bromobicyclopentylidene (**2c**) with deprotonated CH-acidic compounds **4a–d** proceeds with an unexpected, yet readily rationalized ring opening of a three-membered ring, to produce dienyl-substituted derivatives **5–7**. Compound **15** represents a new potentially interesting amino acid incorporating a cyclopropylidenepropenyl substituent.

Scheme 3



This work was supported by the *Deutsche Forschungsgemeinschaft* (SFB 416, Projekt A3) and the *Fonds der Chemischen Industrie*. We are grateful to the companies *BASF AG*, *Bayer AG*, *Chemtall GmbH*, *Degussa AG*, and *Hüls AG* for generous gifts of chemicals and to Dr. B. Knieriem for his careful reading of the manuscript.

Experimental Section

¹H- and ¹³C-NMR spectra: at 250 (¹H) and 62.9 MHz [¹³C, additional DEPT (Distortionless Enhancement by Polarization Transfer)] on a Bruker AM 250 instrument in CDCl₃ solution, CHCl₃/CDCl₃ as internal reference. – FT-IR: Bruker IFS 66, measured as KBr pellets, or as oils between NaCl plates. – MS (EI) and MS (HR-EI): Finnigan MAT 95 spectrometer (70 eV). MS (HR-EI): pre-selected ion peak matching at $R >> 10\,000$ to be within ± 2 ppm of the exact masses. – CI-MS: with NH₃. – TLC: Macherey-Nagel precoated sheets, 0.25 mm Sil G/UV₂₅₄. – Column chromatography: Merck silica gel, grade 60, 230–400 mesh.

Starting Materials: Anhydrous diethyl ether and THF were obtained by distillation from sodium benzophenone ketyl. Compounds **2a**^[9a], **3a**^[9c], **2c**^[8], and **4f**^[13] were prepared according to published procedures. All other chemicals were used as commercially available (Merck, BASF, Bayer, Hoechst, Degussa, and Hüls AG). Organic extracts were dried over MgSO₄. All reactions were performed under argon.

General Procedure (GP1) for the Preparation of Bromides 1c and 3c: *n*BuLi (10 mmol, 4.29 ml of a 2.33 M solution in hexane) was added to a solution of the hydrocarbon **1a**, **3a** (10 mmol) in anhydrous THF (20 ml) at -78°C . After stirring the solution at 0°C for 1 h, it was cooled to -78°C once more, whereupon 1,2-dibromoethane (1.08 ml, 12.5 mmol) was added. The mixture was allowed to warm to room temperature, then diluted with pentane (50 ml), and washed with water (10 $\times$ 50 ml) and satd. NaCl solution (100 ml). The organic layer was dried and slowly concentrated under normal (for **1c**) or reduced (for **3c**) pressure. The residue was bulb-to-bulb distilled (20°C , 0.1 Torr) to give **1c**, **3c** as colorless oils.

2-Bromomethylenecyclopropane (1c): From **1a** (0.82 ml, 0.70 g, 13 mmol), 0.94 g (54%) of **1c** was obtained according to GP1; b.p. 92°C . – ¹H NMR: δ = 0.78–1.45 (m, 2 H, Cpr), 3.45 (m, 1 H, CH), 5.65 (br. s, 1 H, =CH₂), 5.80 (br. s, 1 H, =CH₂). – ¹³C NMR: δ = 12.77, 118.43 (CH₂), 35.32 (CH), 107.18 (C). – MS (EI), m/z (%): 134/132 (14/14) [M^{+}], 109/107 (43/41) [$\text{M}^{+} - \text{C}_2\text{H}_2$], 53 (100) [C_4H_5^{+}]. – MS (HR-EI): 131.9574 (C₄H₅⁷⁹Br, calcd. 131.9575).

2-Bromo-1-methylenespiropentane (3c): From **3a** (0.761 g, 9.5 mmol), **3c** was obtained as a 59% solution in pentane (1.495 g,

59%) according to GP1. – ¹H NMR: δ = 1.25–1.35 (m, 2 H, Cpr), 1.36–1.42 (m, 1 H, Cpr), 1.50–1.58 (m, 1 H, Cpr), 3.82 (br. s, 1 H, CH), 5.31 (d, J = 1.5 Hz, 1 H, =CH₂), 5.65 (br. s, 1 H, =CH₂). – ¹³C NMR: δ = 12.72, 14.40, 103.12 (CH₂), 23.40 (CH), 20.28, 136.29 (C). – MS (CI), m/z (%): 161/159 (25/44) [$\text{M}^{+} + \text{H}$], 146/144 (11/16) [$\text{M}^{+} - \text{CH}_2$], 133/131 (8/21) [$\text{M}^{+} - \text{C}_2\text{H}_3$], 121 (100). – C₆H₇Br (159.0): calcd. C 45.32, H 4.44; found C 46.32, H 5.06.

Dimethyl (Buta-1,3-dien-2-yl)malonate (5): To a solution of bis(dibenzylideneacetone)palladium(0) [Pd(dba)₂] (53.4 mg, 92.9 μmol) and 1,2-bis(diphenylphosphano)ethane (dppe) (47.2 mg, 118 μmol) in THF (1 ml), which had been stirred for 5 min at room temp., was added 2-bromo-1-methylenecyclopropane (**1c**) (500 mg, 3.76 mmol). After 5–10 min, the solution turned green, and a solution of dimethyl sodiomalonate, freshly prepared from NaH (100 mg, 3.33 mmol, 80% in mineral oil) and dimethyl malonate (530 mg, 4.01 mmol) in THF (3 ml), was added dropwise. After stirring at 60°C for 24 h and allowing to cool, the solution was poured into diethyl ether (20 ml), and the resulting mixture was washed with 10% NH₄Cl solution (40 ml). The aqueous phase was extracted with diethyl ether (3 $\times$ 20 ml), the combined organic phases were dried, and then concentrated under reduced pressure. Column chromatography of the residue on silica gel (petroleum ether/Et₂O, 20:1) gave 415 mg (60%) of **5** as a colorless oil, which readily polymerized; R_f = 0.31. – ¹H NMR: δ = 3.33 (s, 1 H, CH), 3.79 (s, 6 H, 2 OCH₃), 5.13 (d, J = 11.0 Hz, 1 H, =CH₂), 5.20 (d, J = 17.5 Hz, 1 H, =CH₂), 5.27 (s, 1 H, =CH₂), 5.41 (s, 1 H, =CH₂), 6.39 (dd, J = 11.0, 17.5 Hz, 1 H, =CH). – ¹³C NMR: δ = 52.31 (CH₃), 114.34, 120.18 (CH₂), 41.10, 137.07 (CH), 138.56, 166.91 (C). – MS (EI), m/z (%): 184 (15) [M^{+}], 153 (3) [$\text{M}^{+} - \text{CH}_3\text{O}$], 125 (100) [$\text{M}^{+} - \text{CH}_3\text{CO}_2$], 65 (37) [$\text{M}^{+} - 2 \text{CH}_3\text{CO}_2 - \text{H}$], 59 (55) [$\text{CH}_3\text{CO}_2^{+}$].

General Procedure (GP2) for the Palladium(0)-Catalyzed Substitution of the Allyl Bromide 2c: To a stirred solution of lithium diisopropylamide (LDA), prepared from *n*BuLi (9 mmol, 3.86 ml of a 2.33 M solution in hexane) and diisopropylamine (1.33 ml, 9.5 mmol) in THF (50 ml), a solution of ethyl *N*-(diphenylmethylene)glycinate (2.406 g, 9 mmol) or diethyl malonate (1.442 g, 9 mmol) in THF (10 ml) was added dropwise at -75°C over a period of 1 h. After stirring for a further 1 h at this temperature, a solution of anhydrous ZnCl₂·THF complex^[15] (2.085 g, 10 mmol) in THF (10 ml) was added to the suspension of lithio compound over a period of 15 min, with the temperature maintained at -75°C . The mixture was stirred for 0.5 h at 0°C and then for 1 h at 20°C , before being cannulated into a solution of bromobicyclopropylidene (**2c**) (1.590 g, 10 mmol) and PdCl₂(dppf) (365 mg, 5 mol%) in THF (40 ml) at 0°C . After stirring for 24 h at 20°C , the solution was poured into a cold, satd. NH₄Cl solution (40 ml), the resulting mixture was diluted with diethyl ether (20 ml), and the organic layer was separated. It was washed with satd. NH₄Cl solution, dried, and concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel deactivated with ammonia.

Ethyl *N*-(Diphenylmethylene)(1-cyclopropylideneprop-2-enyl)glycinate (6): By reaction of **2c** (1.431 g, 9.0 mmol) and **4b** [prepared from ethyl *N*-(diphenylmethylene)glycinate (2.388 g, 9 mmol), *n*BuLi (9.4 mmol, 4.03 ml of a 2.33 M solution in hexane), diisopropylamine (1.33 ml, 9.5 mmol) and anhydrous ZnCl₂·THF (2.126 g, 10.2 mmol) in THF (50 ml)] according to GP2, 2.232 g (72%) of **6** was obtained after column chromatography (100 g of deactivated silica gel, 40 $\times$ 4 cm, hexane/EtOAc, 3:1); R_f = 0.49, m.p. $32\text{--}34^{\circ}\text{C}$ (H₂O/MeOH). – ¹H NMR: δ = 0.84–1.05 (m, 2 H, Cpr), 1.03–1.35 (m, 2 H, Cpr), 1.22 (t, J = 7.1 Hz, 3 H, CH₃),

4.19 (q, $J = 7.1$ Hz, 2 H, OCH₃), 5.09 (s, 1 H, CH), 5.12 (d, $J = 11.3$ Hz, 1 H, =CH₂), 5.52 (d, $J = 17.8$ Hz, 1 H, =CH₂), 6.55 (dd, $J = 11.3, 17.8$ Hz, 1 H, =CH), 7.09–7.88 (m, 10 H, Ph-H). – ¹³C NMR: $\delta = 14.17$ (CH₃), 2.67, 3.02, 60.95, 114.0 (CH₂), 127.94, 128.30, 128.42, 128.87 (2 CH), 68.12, 128.54, 130.25, 134.70 (CH), 125.63, 128.11, 136.30, 139.50, 169.89, 171.60 (C). – MS (EI), m/z (%): 345 (18) [M⁺], 272 (50) [M⁺ – CO₂C₂H₅], 182 (70) [NH₂C-Ph₂⁺], 165 (16) [M⁺ – NCPH₂], 105 (100) [C₇H₇N⁺], 77 (43) [C₆H₅⁺], 51 (10) [C₄H₃⁺]. – MS (HR-EI): 345.1728 (C₂₃H₂₃NO₂, calcd. 345.1729). – C₂₃H₂₃NO₂ (345.4): calcd. C 79.97, H 6.71; found C 80.02, H 6.47.

To a suspension of **2b**, prepared from **2a** (1.800 g, 22.5 mmol) and *n*BuLi (22.5 mmol, 9.67 ml of a 2.33 M solution in hexane) as described above, a solution of anhydrous ZnCl₂·THF (5.620 g, 27 mmol) in THF (15 ml) was added at –78°C. After stirring at 20°C for 1 h, the solution was cannulated into a mixture of **4f** (4.880 g, 15 mmol) and PdCl₂(dppf) (548 mg, 5 mol%) in THF (100 ml). After stirring this mixture at 20°C for 24 h, the solution was worked-up according to GP2. Yield 1.488 g (29%) of **6** after column chromatography (200 g of deactivated silica gel, 40 × 5 cm, hexane/Et₂O, 7:3).

Diethyl (1-Cyclopropylideneprop-2-enyl)malonate (7): By reaction of **2c** (1.590 g, 10.0 mmol) and **4d** [prepared from *n*BuLi (10.5 mmol, 4.51 ml of a 2.33 M solution in hexane), diisopropylamine (1.47 ml, 10.5 mmol), diethyl malonate (1.52 ml, 10.0 mmol), and a solution of anhydrous ZnCl₂·THF (2.50 g, 12 mmol) in THF (15 ml) as described above] according to GP2, **7** (0.563 g, 24%) was obtained after column chromatography on deactivated silica gel (hexane/diethyl ether, 5:2); $R_f = 0.40$. – IR (film): $\tilde{\nu} = 2982$ cm^{–1}, 1734, 1446, 1368, 1311, 1247, 1153, 1035. – ¹H NMR: $\delta = 1.20$ – 1.29 (m, 10 H, 2 Cpr, 2 CH₃), 4.14–4.25 (m, 4 H, 2 OCH₂), 4.49 (br. s, 1 H, CH), 5.04 (d, $J = 12.8$ Hz, 1 H, =CH₂), 5.10 (d, $J = 19.2$ Hz, 1 H, =CH₂), 6.59 (dd, $J = 12.8, 19.2$ Hz, 1 H, =CH). – ¹³C NMR: $\delta = 13.96$ (2 CH₃), 61.41 (2 CH₂), 2.27, 3.55, 111.62 (CH₂), 53.94, 136.29 (CH), 120.57, 129.84, 168.01 (C). – MS (EI), m/z (%): 238 (3) [M⁺], 209 (7) [M⁺ – C₂H₅], 165 (100) [M⁺ – CO₂C₂H₅], 137 (5), 119 (17), 91 (27). – MS (HR-EI): 238.1205 (C₁₃H₁₈O₄, calcd. 238.1205). – C₁₃H₁₈O₄ (238.3): calcd. C 65.53, H 7.61; found C 65.27, H 7.81.

The solution of **2d**, prepared as described above from **2a** (1.593 g, 19.9 mmol), *n*BuLi (19.9 mmol, 8.54 ml of a 2.33 M solution in hexane) in THF (35 ml) and anhydrous ZnCl₂·THF (4.585 g, 22 mmol) in THF (10 ml), was cannulated into a mixture of diethyl bromomalonate (**4e**) (2.391 g, 1.71 ml, 10 mmol) and PdCl₂(dppf) (366 mg, 5 mol%) in THF (50 ml). After stirring at 20°C for 24 h, the solution was worked-up according to GP2. Yield 0.641 g (27%) of **7** after column chromatography (150 g of deactivated silica gel, 40 × 4 cm, hexane/Et₂O, 5:2).

[3-(Cyclopropylidene)prop-1-en-3-yl]glycine (15): Compound **6** (2.304 g, 6.67 mmol) was stirred in 0.2 N HCl solution (200 ml) for 70 h at 20°C, completely protected from light. The reaction mixture was adjusted to pH 8 with conc. NH₄OH solution and then extracted with Et₂O. After concentration under reduced pressure, the ethereal extract was diluted with a 3:1 mixture of THF and H₂O (120 ml) and stirred with LiOH (156 mg, 6.5 mmol) for 24 h at 20°C. The reaction mixture was then concentrated under reduced pressure and brought to pH 2 with 0.2 N HCl solution. Subsequent concentration of the solution, filtration through Dowex-50 (3 × 20 cm column, eluent 0.9 N NH₄OH), followed by repeated concentration and recrystallization from acetone/H₂O gave 139 mg (14%) of **15**, m.p. 148–150°C (decomp.). – IR (KBr): $\tilde{\nu} = 2978$ cm^{–1}, 1735, 1617, 1576, 1446, 1284, 1181, 1030, 911, 732, 696. – ¹H

NMR (D₂O): $\delta = 1.05$ (br. s, 4 H, Cpr), 4.47 (s, 1 H, CH), 5.00 (d, $J = 11.0$ Hz, 1 H, =CH₂), 5.15 (d, $J = 18.4$ Hz, 1 H, =CH₂), 6.36 (dd, $J = 11.0, 18.4$ Hz, 1 H, =CH). – ¹³C NMR (D₂O): $\delta = 3.23, 4.09, 114.38$ (CH₂), 55.40, 135.81 (CH), 122.69, 134.63, 174.56 (C). – MS (CI), m/z (%): 187 (100) [M⁺ + 2 NH₃], – C₈H₁₁NO₂ (153.2): calcd. C 62.72, H 7.24; found C 62.58, H 7.11.

Diethyl (2-Vinylcyclobutan-1-one-2-yl)malonate (18): Compound **7** (500 mg, 2.1 mmol) was stored at –20°C for 6 months. Thereafter, repeated column chromatography on deactivated silica gel (50 g, column 25 × 3.2 cm, hexane/Et₂O, 5:2) gave **7** (21 mg, 4.2%) and **18** (49 mg, 9.2%); $R_f = 0.32$. – ¹H NMR: $\delta = 1.22$ (t, $J = 7.1$ Hz, 3 H, CH₃), 1.24 (t, $J = 7.1$ Hz, 3 H, CH₃), 2.17 (dt, $J = 12.1, 7.7$ Hz, 1 H, CH₂), 2.57 (dt, $J = 12.1, 9.0$ Hz, 1 H, CH₂), 3.08 (dd, $J = 7.7, 9.0$ Hz, 2 H, CH₂), 4.16 (q, $J = 7.1$ Hz, 2 H, OCH₂), 4.17 (s, 1 H, CH), 4.18 (q, $J = 7.1$ Hz, 2 H, OCH₂), 5.23 (d, $J = 10.3$ Hz, 1 H, =CH₂), 5.29 (d, $J = 16.7$ Hz, 1 H, =CH₂), 5.81 (dd, $J = 10.3, 16.7$ Hz, 1 H, =CH). – ¹³C NMR: $\delta = 13.86, 13.97$ (CH₃), 19.95, 43.61, 61.43, 61.86, 116.72 (CH₂), 56.44, 134.68 (CH), 68.67, 166.80, 167.28, 207.51 (C). – MS (EI), m/z (%): 254 (4) [M⁺], 180 (8) [M⁺ – H – CO₂C₂H₅], 160 (8) [M⁺ – C₆H₆O], 133 (61) [M⁺ – C₆H₇O – C₂H₂], 115 (100) [M⁺ – C₆H₇O – C₂H₂ – H₂O], 111 (5), 88 (32). – MS (HR-EI): 254.1154 (C₁₃H₁₈O₅, calcd. 254.1154). – C₁₃H₁₈O₅ (254.3): calcd. C 61.41, H 7.14; found C 61.72, H 7.35.

- [1] For reviews see: [1a] B. M. Trost, *Tetrahedron* **1977**, *33*, 2615–2649. – [1b] B. M. Trost, *Acc. Chem. Res.* **1980**, *13*, 385–393. – [1c] J. Tsuji, *Organic Synthesis with Palladium Compounds*, Springer, Berlin **1980**. – [1d] J. Tsuji, *Tetrahedron* **1986**, *42*, 4361–4401. – [1e] J. Tsuji, I. Minami, *Acc. Chem. Res.* **1987**, *20*, 140–145. – [1f] G. Consiglio, R. M. Waymouth, *Chem. Rev.* **1989**, *89*, 257–276. – [1g] B. M. Trost, *Angew. Chem.* **1989**, *101*, 1199–1219; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1173–1192. – [1h] C. G. Frost, J. Howarth, J. M. J. Williams, *Tetrahedron Asymmetry* **1992**, *3*, 1089–1122. – [1i] S. Bräse, A. de Meijere in *Metal-Catalyzed Cross Coupling Reactions* (Eds.: P. J. Stang, F. Diederich), Wiley-VCH, Weinheim, **1997**.
- [2] [2a] A. Stolle, J. Salaün, A. de Meijere, *Synlett* **1991**, 327–330. – [2b] A. Stolle, J. Ollivier, P. P. Piras, J. Salaün, A. de Meijere, *J. Am. Chem. Soc.* **1992**, *114*, 4051–4067. – [2c] K. Voigt, A. Stolle, J. Salaün, A. de Meijere, *Synlett* **1995**, 226–228.
- [3] M. J. O'Donnell, R. L. Polt, *J. Org. Chem.* **1982**, *47*, 2663–2666.
- [4] [4a] D. Ferroud, J.-P. Genet, R. Kiolle, *Tetrahedron Lett.* **1986**, *27*, 23–26. – [4b] J.-P. Genet, S. Juge, S. Achi, S. Mallart, J. Ruiz-Montes, G. Levif, *Tetrahedron* **1988**, *44*, 5263–5273. – [4c] B. Cazes, D. Djahanbini, J. Gore, J.-P. Genet, J.-M. Gaudin, *Synthesis* **1988**, 983–985. – [4d] J.-P. Genet, N. Kopola, S. Juge, J. Ruiz-Montes, O. A. C. Antunes, S. Tanier, *Tetrahedron Lett.* **1990**, *31*, 3133–3136.
- [5] [5a] J. Salaün, M. S. Baird, *Curr. Med. Chem.* **1995**, *2*, 511–542. – [5b] C. H. Stammer, *Tetrahedron* **1990**, *46*, 2231–2254. – [5c] H. C. Pirrung, J. Cao, J. Chen, *J. Org. Chem.* **1995**, *60*, 5790–5794. – [5d] K. Burgess, D. Lim, K.-K. Ho, C.-Y. Ke, *J. Org. Chem.* **1994**, *59*, 2179–2185.
- [6] [6a] M. Es-Sayed, C. Gratkowski, N. Krass, A. I. Meyers, A. de Meijere, *Synlett* **1992**, 962–964. – [6b] P. Aufranc, J. Ollivier, A. Stolle, C. Bremer, M. Es-Sayed, A. de Meijere, J. Salaün, *Tetrahedron Lett.* **1993**, *34*, 4193–4196. – [6c] M. Es-Sayed, T. Heiner, A. de Meijere, *Synlett* **1993**, 57–58. – [6d] J. Zindel, A. Zeeck, W. A. König, A. de Meijere, *Tetrahedron Lett.* **1993**, *34*, 1917–1920. – [6e] J. Zindel, A. de Meijere, *Synthesis* **1994**, 190–194. – [6f] M. Es-Sayed, P. Devine, L. E. Burgess, A. de Meijere, A. I. Meyers, *J. Chem. Soc., Chem. Commun.* **1995**, 141–142. – [6g] J. Zindel, A. de Meijere, *J. Org. Chem.* **1995**, *60*, 2968–2973.
- [7] [7a] D. O. Gray, L. Fowden, *Biochem. J.* **1962**, *82*, 385–389. – [7b] L. Fowden, H. M. Pratt, A. Smith, *Phytochemistry* **1972**, *11*, 3521–3523.
- [8] A. de Meijere, S. I. Kozhushkov, N. S. Zefirov, *Synthesis* **1993**, 681–683.

- [9] [9a] A. de Meijere, S. I. Kozhushkov, T. Spaeth, N. S. Zefirov, *J. Org. Chem.* **1993**, *58*, 502–505. – [9b] P. Binger, H. M. Büch, *Top. Curr. Chem.* **1987**, *135*, 77–151. – [9c] S. Arora, P. Binger, *Synthesis* **1974**, 801–803. – [9d] P. Binger, T. Schmidt in *Houben-Weyl, Vol. E 17c* (Ed.: A. de Meijere), Thieme, Stuttgart, **1997**, pp. 2217–2294.
- [10] T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi, K. Hirotsu, *J. Am. Chem. Soc.* **1984**, *106*, 158–163.
- [11] S. Bräse, A. de Meijere, *Angew. Chem.* **1995**, *107*, 2741–2743; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2545–2547.
- [12] [12a] D. Wendisch in *Houben-Weyl, Vol. 4/3*, Thieme, Stuttgart, **1971**, pp. 399–405. For (cyclopropylcarbonyl)palladium intermediates see also: G. Dyker, *Angew. Chem.* **1995**, *107*, 2407–2408; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2223–2224. – [12b] G. Boche, H. M. Walborsky, *Cyclopropane-Derived Reactive Intermediates* (Eds.: S. Patai, Z. Rappoport), Wiley, Chichester, **1990**, and references cited therein.
- [13] [13a] M. J. O'Donnell, W. D. Bennett, R. L. Polt, *Tetrahedron Lett.* **1985**, *26*, 695–698. – [13b] M. J. O'Donnell, C. Zhou, A. Mi, N. Chen, J. A. Kyle, *Tetrahedron Lett.* **1995**, *36*, 4205–4208. – [13c] M. J. O'Donnell, X. Yang, M. Li, *Tetrahedron Lett.* **1990**, *31*, 5135–5138.
- [14] J. C. Walton in *Houben-Weyl, Vol. E 17c* (Ed.: A. de Meijere), Thieme, Stuttgart, **1997**, p. 2438–2525.
- [15] Commercial ZnCl_2 was twice melted in vacuo (0.1 Torr), recrystallized from anhydrous THF, and dried at 20°C/0.1 Torr for 4 h. $^1\text{H-NMR}$ spectroscopic analysis (D_2O , DMSO as internal reference) of a precisely weighed sample of the product showed it to be a 1:1 $\text{ZnCl}_2\cdot\text{THF}$ complex. This complex shows much better solubility in THF than pure ZnCl_2 and was used in the described coupling experiments.

[97316]