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Pd^{II}-Catalyzed Conjugate Addition of Boronic Acids to Ketoglutaconic Esters toward the Synthesis of Functionalized Pyridazin-3(2*H*)-ones with Neuroprotective Activity

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The development of the regioselective conjugate addition of boronic acids to ketoglutaconic esters under transition metal catalysis is reported. Among the different catalysts tested for this transformation, the dicationic Pd^{II} catalysts generated with $Pd(OCOCF_3)_2$, dppben, and HBF_4 performed best in terms of yields, regioselectivities and avoidance of Heck-type by-products. The resulting 4-aryl-2-oxopentadienoates were transformed into pyridazin-3(2*H*)-ones, potentially useful for the therapy of neurodegenerative diseases. These compounds simultaneously exhibited β-secretase activity, inhibition of β-amyloid (βA) aggregation, and disaggregation of pre-formed βA fibrils, and also had a good scavenging profile for intracellular reactive oxygen species (ROS).

Introduction

The conjugate addition reaction constitutes one of the most powerful methods available for the construction of C–C bonds.[1] Among the different approaches reported for the addition of carbon nucleophiles in this type of reaction, the use of boronic acids under transition metal catalysis has become a general method for the introduction of aryl and alkenyl groups. Boronic acids are readily available chemicals, have low toxicity, and do not require manipulation in anhydrous solvents.[2] This gives an advantage over other more conventional reagents.

Rh^I complexes have become the most popular catalysts for this type of reaction since their first introduction in 1997.[3,4] Despite their widespread use, and due to the high price of Rh, alternative transition metal catalysts have been sought. In particular, dicationic Pd^{II} complexes and some palladacycles have proved useful in these reactions, with minor competition from the Mizoroki–Heck reaction, typical of other Pd-based systems.[5] However, the number of examples reported for the Pd-catalyzed conjugate addition reaction of boronic acids remains scarce in comparison with those using Rh^I catalysis.

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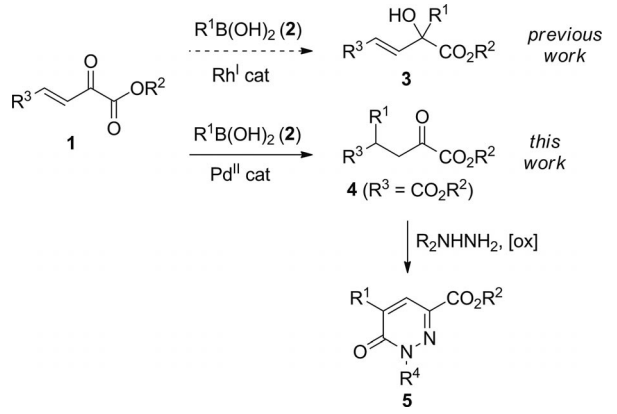
Among the different types of unsaturated carbonyl compounds used as substrates, ene-dicarbonyl compounds have not received much attention. The Rh^I-catalyzed conjugate addition of arylboronic acids to maleimides constitutes one of the more studied examples,[6] but ene-diesters[7] and ene-diketones[8] have been less considered. On the other hand, the Rh^I-catalyzed additions to electronically differentiated 1,4-unsaturated dicarbonyl compounds, such as 4-oxobut-2-enamides[9] and 4-oxobut-2-enoates,[10] have been much less developed. These types of substrates are challenging, due to the possibility of two alternative regiochemistries in the formation of the new C–C bond. Regarding Pd^{II} catalysis, the conjugate addition of arylboronic acids to ene-dicarbonyl compounds has been reported only in the case of maleimides.[11]

In this paper, we have centered our attention (Scheme 1) on the conjugate addition of boronic acids to ketoglutaconic esters **1** ($R^3 = CO_2R^2$) as a simple route for the construction of functionalized pyridazin-3(2*H*)-ones **5**.[12] There are no previous literature reports for the conjugate addition of boronic acids to ketoglutaconic esters **1** ($R^3 = CO_2R^2$). In addition, the Rh^I-catalyzed addition of boronic acids to other α,β-unsaturated α-keto esters is known to take place in a 1,2-fashion to give alcohols **3**,[13] and under Pd^{II} catalysis, boronic acids give 1,2-addition to the keto group of α-keto esters.[14]

Pyridazin-3-(2*H*)-ones **5** were interesting to us due to their potential neuroprotective activities.[15] The inhibition of β-secretase activity,[16] the prevention of β-amyloid (βA) aggregation, and the disaggregation of preformed βA fibrils[17] constitute three major target processes in the devel-



Scheme 1. Conjugate addition of boronic acids to α,β-unsaturated α-keto esters.

opment of small-molecule lipophilic drugs for the treatment of Alzheimer's disease (AD). In addition, several lines of evidence show that mitochondrion-derived reactive oxygen species (ROS) result in enhanced amyloidogenic processing of the amyloid precursor protein (APP), and this process could be partly reduced by antioxidants.[18] Since AD is a complex neurodegenerative disorder resulting from multiple molecular abnormalities, strategies to develop new drugs that simultaneously affect multiple biological targets is highly important.[19]

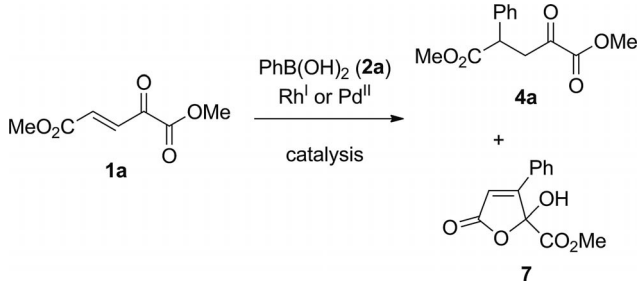
Different pyrazolopyridinepyridazinones have shown to be good phosphodiesterase (PDE) inhibitors;[20] 5-(benzylsulfonyl)-4-bromo-2-methyl-3(2*H*)-pyridazinones have been identified as inhibitors of permeability transition pores (PTP), mitochondrial megachannels involved in neuronal cell-death and neurodegenerative diseases;[21] 6-methyl-2-[4-(naphthylpiperazin-1-yl)-butyl]-3-(2*H*)-pyridazinone has been described as a mixed dopamine D_2-antagonist and 5-HT_{1A}-partial agonist in functional in vitro and in vivo assays;[22] and some 3(2*H*)-pyridazinone derivatives have shown in vitro inhibition of the activity of acetylcholinesterase (AChE), a proposed drug target for the palliative treatment of AD.[23,24]

Due to their reported pharmacological activities in the context of neuroprotection, and in the course of our exploratory research targeting the aggregation or deposition of the βA peptide, we have profiled pyridazinones **5** against the βA aggregation process, β-secretase activity, and the intracellular generation of ROS.

Results and Discussion

We began our work with substrates **1a** and **2a** (Table 1) by screening several catalytic systems which have proved to be of general use in conjugate addition reactions of arylboronic acids. We did not observe any reaction when using either neutral or cationic Rh^I catalysts (Table 1, entries 1–3), and with the exception of the $Pd_2(dba)_3CHCl_3$ / Ph_3P / Cs_2CO_3 (dba = dibenzylideneacetone) system[25] (Table 1, entry 4), the addition of **2a** in the presence of different types of Pd^{II} catalysts (Table 1, entries 5–11) took place with low regioselectivity to give variable yields of conjugate addition product **4a** together with furanone **7**.[26] Direct addition of the nucleophile to the keto group of compound **1a** (1,2-addition, resulting in the formation of alcohols **3**) was not observed in any case. In particular, di-

Table 1. Conjugate addition of **1a** with phenylboronic acid (**2a**).[a]

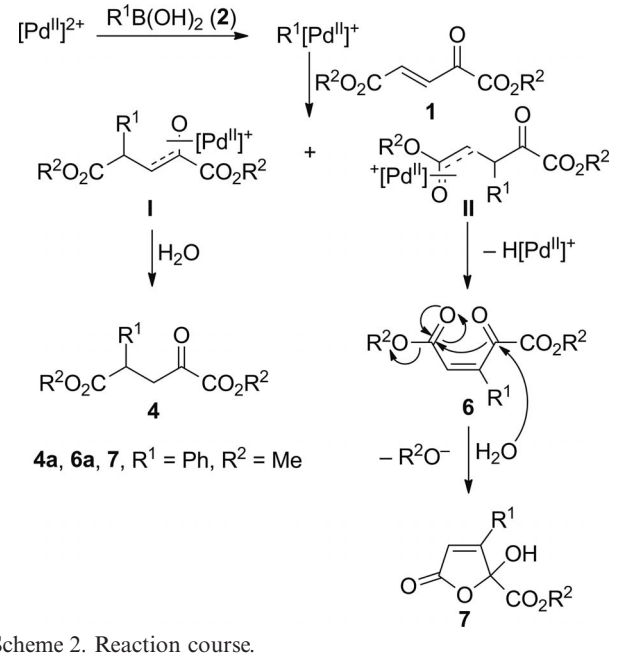


Entry	Catalyst[b]	Additives [equiv.][b]	Solvent	**4a** [%][c]	**7** [%][c]
1	$[Rh(cod)Cl]_2$	K_3PO_4 [1.0]	dioxane/H_2O [10:1]	–	–
2	$[Rh(cod)Cl]_2$	Et_3N [1.0]	dioxane/H_2O [10:1]	–	–
3	$[Rh(cod)_2]BF_4$	Et_3N [1.0]	dioxane/H_2O [10:1]	–	–
4	$Pd_2(dba)_3CHCl_3$	PPh_3 [0.05] Cs_2CO_3 [1.0]	toluene	–	–
5	$Pd(OAc)_2$	2,2′-bpy [0.2]	AcOH/THF/H_2O [1.0:0.5:0.1]	16	28
6	$Pd(OAc)_2$	2,2′-bpy [0.2]	CH_3NO_2	5	8
7	$Pd(OCOCF_3)_2$	dppben [0.055] HBF_4 [1.0]	dioxane/H_2O [8:2]	18	35
8	$Pd(acac)_2$	dppben [0.05] $Cu(BF_4)_2$ [0.2]	dioxane/H_2O [8:2]	40	60
9	$Pd(acac)_2$	dppben [0.05] $Cu(BF_4)_2$ [0.2]	Dioxane/H_2O [10:1]	38	52
10	$Pd(acac)_2$	dppben [0.05] $Cu(BF_4)_2$ [0.2]	THF/H_2O [8:2]	16	29
11	$Pd(acac)_2$	dppethy [0.05] $Cu(BF_4)_2$ [0.2]	dioxane/H_2O [10:1]	10	26

[a] Reactions carried out at room temp. for 18 h. [b] Dppben = 1,2-bis(diphenylphosphanyl)benzene; dppethy = 1,2-bis(diphenylphosphanyl)ethylene; cod = 1,5-cyclooctadiene; 2,2′-bpy = 2,2′-bipyridine. [c] Isolated yields after purification by column chromatography.

cationic Pd^{II} catalysts generated either with $Pd(OCOCF_3)_2$, 1,2-bis(diphenylphosphanyl)benzene (dppben), and HBF_4 (Table 1, entry 7),[27] or $Pd(acac)_2$ (acac = acetylacetone), $Cu(BF_4)_2$, and dppben,[28] resulted in good conversions of the starting materials (Table 1, entries 8–10).[29] The best results were obtained for the $Pd(acac)_2$, $Cu(BF_4)_2$, dppben system when working in dioxane/H_2O (8:2) as solvent (Table 1, entry 8). This can be compared with the results obtained using other solvent mixtures (Table 1, entries 9 and 10) or other bisphosphane ligands (Table 1, entry 11).

The formation of compound **4a** (Scheme 2) can be understood by the addition of the Ph-$[Pd^{II}]^+$ species, generated by transmetallation of **2a**, to the β position with respect to the ketone group, followed by protonation of the corresponding oxa-π-allyl-species **I**. The formation of furanone **7** can be explained by the addition of the Ph-$[Pd^{II}]^+$ species with the alternative regiochemistry, i.e., at the β position with respect to the 4-ester moiety, in a Heck-type reaction via intermediate **II**. Compound **6a** (R^1 = Ph, R^2 = Me) was not detected, but rather it cyclized in the reaction medium to give **7** directly.[26]

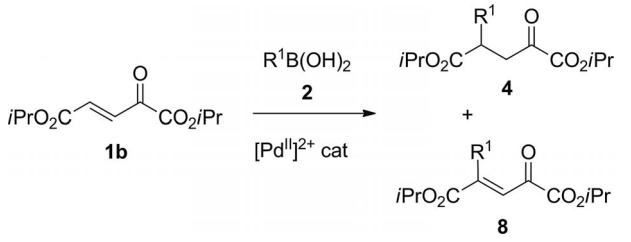


Scheme 2. Reaction course.

We found that switching to α,ω-diisopropyl ester **1b** as starting material (Table 2) allowed us to improve the regioselectivity of the reaction, which was the major flaw observed in the previous reactions with α,ω-dimethyl ester **1a**.

The best results for the conjugate addition of **2a** to **1b** were observed (Table 2, entries 1–3) when using the dicationic Pd^{II} complex formed with $Pd(OCOCF_3)_2$ (5 mol-%), dppben (5 mol-%), and HBF_4 (1.0 equiv.) in dioxane/H_2O (8:2) (Conditions A). These conditions were used for the reaction of **1b** with other arylboronic acids substituted either with electron-donating or electron-withdrawing substituents (Table 2, entries 2–7), and the formation of alcohols **3** was not observed. The use of the catalytic system formed with $Pd(acac)_2$ (5 mol-%), dppben (5 mol-%), and

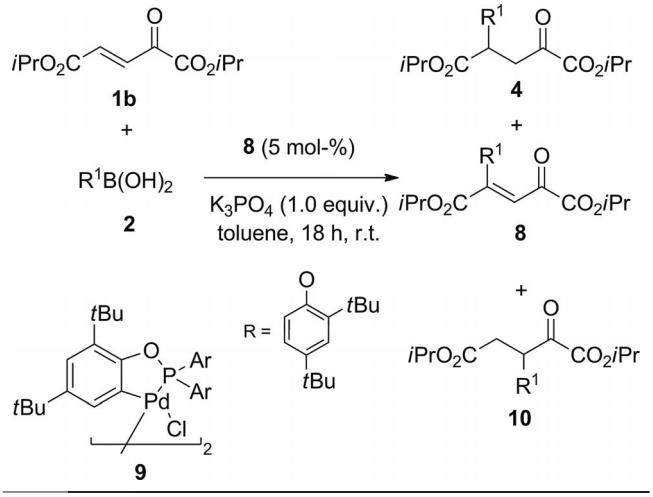
Table 2. $[Pd^{II}]^{2+}$-catalyzed conjugate addition of **1b** with boronic acids **2**.[a]



Entry	2	R^1	Conditions[b]	4/8 (ratio,[c] yield [%][d])
1	**2a**	Ph	A	**4b/8a** (90:10, 65)
2	**2b**	4-F-C_6H_4	A	**4c/8b** (95:05, 63)
3	**2c**	4-CF_3-C_6H_4	A	**4d/8c** (95:05, 53)
4	**2d**	4-MeO-C_6H_4	B	**4e/8d** (65:35, 74[e])
5	**2e**	3,4-(O-CH_2-O-)C_6H_3	A	**4f/8e** (90:10, 64)
6	**2f**	4-Br-C_6H_4	A	**4g** (100:0, 61)
7	**2g**	3,4-di-Cl-C_6H_3	A	**4h** (100:0, 48)
8	**2a**	Ph	B	**4b/8a** (75:25, 86)
9	**2b**	4-F-C_6H_4	B	**4c/8b** (75:25, 80)

[a] Reactions carried out at room temp. for 18 h. [b] Conditions A: **2** (2.5 equiv.), $Pd(OCOCF_3)_2$ (5 mol-%), dppben (5 mol-%), HBF_4 (1.0 equiv.), dioxane/H_2O (8:2); Conditions B: **2** (1.5 equiv.), $Pd(acac)_2$ (5 mol-%), dppben (5 mol-%), $CuBF_4$ (0.2 equiv.), dioxane/H_2O (8:2). [c] Determined by integration of the ^1H NMR ($CDCl_3$, 300 MHz) spectra of the crude reaction mixtures. [d] Isolated yields of **4b–4h** after purification by column chromatography. [e] Combined isolated yield of the mixture **4e/8d**, not separated.

Table 3. Conjugate addition of **1b** with boronic acids **2** catalyzed by Pd^{II}-palladacycle **9**.[a]



Entry	2	R^1	4/8/10 (ratio,[b] yield [%][c])
1	**2a**	Ph	**4b/8a/10a** (75:10:15, 70)
2	**2b**	4-F-C_6H_4	**4c/8b/10b** (75:10:15, 68)
3	**2c**	4-CF_3-C_6H_4	**4d/8c/10c** (75:10:15, 60)
4	**2e**	3,4-(O-CH_2-O-)C_6H_3	**4f/8e/10d** (70:10:20, 59)
5	**2f**	4-Br-C_6H_4	**4g/8f/10e** (75:15:10, 68)
6	**2g**	3,4-di-Cl-C_6H_3	**4h/8g/10f** (70:15:15, 64)

[a] Reaction conditions: **2** (2.0 equiv.), palladacycle **9** (5 mol-%), K_3PO_4 (1.0 equiv.), toluene, room temp., 18 h. [b] Determined by integration of the ^1H NMR ($CDCl_3$, 300 MHz) spectra of the crude reaction mixtures. [c] Isolated yields of **4b–4h** after purification by column chromatography.

Table 4. Activities of pyridazinones in the pharmacological assays.

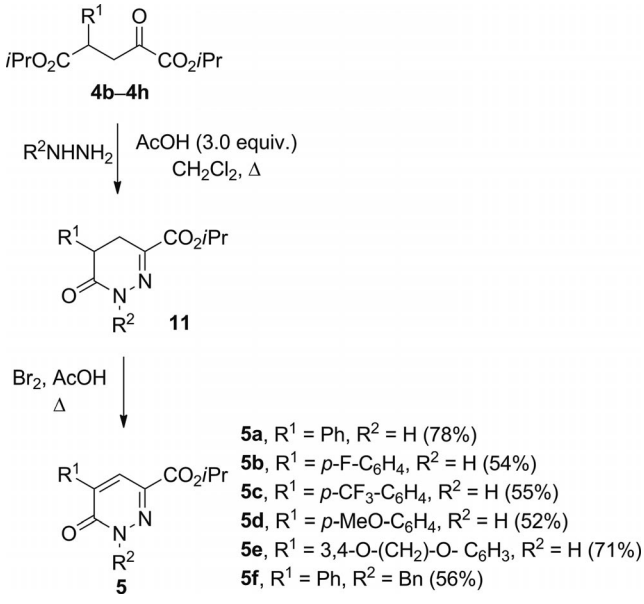
5, 11	βA aggregation inhibition[a]	βA fibril disaggregation[b]	β-secretase inhibition[c]	ROS inhibition[d]
5a	8.302 ± 0.422	8.345 ± 0.593	38.89 ± 1.704	1.508 ± 0.326
5b	6.888 ± 0.197	8.200 ± 0.255	27.62 ± 0.831	0.444 ± 0.135
5c	7.132 ± 0.390	7.153 ± 0.505	22.81 ± 2.638	6.116 ± 0.161
5e	6.307 ± 0.388	7.759 ± 0.569	20.49 ± 0.816	2.415 ± 0.391
11a	6.909 ± 0.239	7.482 ± 0.141	–	3.035 ± 0.190
11c	6.215 ± 0.155	7.885 ± 0.777	25.83 ± 1.952	1.879 ± 0.508

[a] Inhibition of βA aggregation, IC_{50} [μM]. [b] Disaggregation of βA fibrils, IC_{50} [μM]. [c] Inhibition of β-secretase activity at 10 μM concentration [%]. [d] Inhibition of ROS generation, IC_{50} [μM]. Treatment of APPswe cells with pyridazinones **5a**–**11c** for 24 h did not show any significant toxicity up to 20 μM in comparison with untreated cells.

$CuBF_4$ (0.2 equiv.) (Conditions B) gave higher ratios of compounds **8** (Table 2, entries 8 and 9).

In the search for other Pd^{II} catalysts active in this type of transformation, we also tested the reaction between **1b** and boronic acids **2** using palladacycle **9** (Table 3).[30] In this case, we observed good overall conversions and the formation of compounds **4** as major products, but we detected the formation of minor amounts of Heck-type products **8**, together with conjugate addition products **10**.

The conversion of compounds **4** into pyridazin-3(2*H*)-ones **5** was carried out by reaction with hydrazines, followed by aromatization of the corresponding dihydro intermediates (i.e., **11**)[31] (Scheme 3).



Scheme 3. Synthesis of pyridazin-3(2*H*)-ones **5**.

Table 4 summarizes our results on the inhibition of βA aggregation, the disaggregation ability towards pre-formed βA fibrils, the inhibition of β-secretase activity, and the inhibition of intracellular ROS for pyridazinones **5a**–**c**,**e**,**f** and dihydropiridazinones **11a**–**c**. We observed that the two *N*-benzylated derivatives **5f** and **11b** showed cytotoxicity on the neuroblastoma APPswe cells up to 20 μM, and so they were discarded for the in vitro assays undertaken.

With respect to inhibition of βA aggregation (IC_{50} = 8.3–6.2 μM), disaggregation activity of preformed βA fibrils (IC_{50} = 8.3–7.1 μM), and β-secretase inhibition (39–20% at 10 μM), all the compounds tested were active in the μM range. In addition, they also exhibited good inhibition of intracellular ROS (IC_{50} = 3.0–0.4 μM). Compound **5b** (IC_{50} = 0.444 ± 0.135 μM) was particularly good in this respect.

Conclusions

In summary, we have developed the synthesis of the new pyridazin-3(2*H*)-ones **5** using the conjugate addition reaction of arylboronic acids to ketoglutaconic esters as a key step. Among the different catalysts tested for this transformation, the dicationic Pd^{II} catalysts generated with $Pd(OCOCF_3)_2$, dppben, and HBF_4 performed best in terms of yields, regioselectivities, and avoidance of Heck-type byproducts. These pyridazin-3(2*H*)-ones are presented as promising candidates in the development of small-molecule lipophilic drugs for the treatment of neurodegenerative diseases simultaneously targeting the βA peptide aggregation process and β-secretase activity, while also having a good intracellular ROS scavenging profile.

Experimental Section

General Methods: All starting materials were commercially available research-grade chemicals, and were used without further purification. The catalysts were commercially available. All solvents were dried by standard methods and distilled under argon. Silica gel 60 F254 was used for TLC, and the spots were detected with UV light or vanillin solution. Flash column chromatography was carried out on silica gel 60. ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz, both in $CDCl_3$ solution, unless otherwise stated. Compound **1a** was prepared following a previously reported procedure.[32]

(*E*)-Diisopropyl 4-Oxopent-2-enedioate (1b): 2-Ketoglutaric acid (2.1 g, 14.6 mmol) and 2-propanol (3.4 mL, 43.9 mmol) were heated at reflux in toluene (44 mL) with *p*-toluenesulfonic acid (140 mg, 0.7 mmol) as a catalyst in a Dean Stark apparatus for 18 h. After cooling to room temp., H_2O (10 mL) was added. The organic layer was separated, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (73 mL) and a solution of bromine (1.1 mL, 22.0 mmol) in CH_2Cl_2 (0.5 mL) was added. The solution was stirred at reflux for 3 h. After cooling to room temp., the solvent and residual HBr were evaporated under vacuum to yield diisopropyl bromoglutarate as an orange oil. The diisopropyl bromoglutarate was dissolved in diethyl ether (88 mL), and triethylamine

(2.3 mL, 16.1 mmol) was added. After stirring at room temp. for 30 min, the mixture was filtered twice through a pad of silica gel. The ether solution was evaporated to give an oil, which was purified by column chromatography (hexane/EtOAc = 9:1). Yellow oil (2.3 g, 70%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.33 (d, ^3J = 6.3 Hz, 6 H, CH_3 *i*Pr), 1.39 (d, ^3J = 6.3 Hz, 6 H, CH_3 *i*Pr), 5.14 (q, ^3J = 6.3 Hz, 1 H, CH *i*Pr), 5.22 (q, ^3J = 6.3 Hz, 1 H, CH *i*Pr), 6.92 (d, $^3J_{trans}$ = 16.1 Hz, 1 H, CH), 7.57 (d, $^3J_{trans}$ = 16.1 Hz, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 21.5 (CH_3 *i*Pr), 21.6 (CH_3 *i*Pr), 69.3 (CH *i*Pr), 71.2 (CH *i*Pr), 133.9 (C-3), 136.1 (C-4), 160.3 (CO), 164.1 (C-5), 183.1 (CO) ppm. $C_{11}H_{16}O_5$ (228.24): calcd. C 57.88, H 7.07; found C 57.99, H 7.14.

General Reaction Conditions for the Conjugate Addition of 1a with Phenylboronic Acid 2a (Table 1)

Entries 1, 2: The base (K_3PO_4 or Et_3N, 0.175 mmol) was added to a mixture of $[RhCl(cod)]_2$ (7 mg, 15×10^{-3} mmol), **2a** (42 mg, 0.35 mmol), and **1a** (50 mg, 0.29 mmol) in dioxane/H_2O 10:1 (1 mL). The mixture was stirred at room temp. for 40 h and then filtered through a silica gel pad covered with $MgSO_4$. Filtration and evaporation under vacuum gave the crude reaction products.

Entry 3: Et_3N (25 μL, 0.175 mmol) was added to a mixture of $Rh(cod)_2BF_4 \cdot H_2O$ (4 mg, 8.7×10^{-3} mmol), **2a** (42 mg, 0.35 mmol), and **1a** (31 mg, 0.175 mmol) in dioxane/H_2O 10:1 (1 mL). The mixture was stirred at room temp. for 30 h and then filtered through a silica gel pad covered with $MgSO_4$. Filtration and evaporation under vacuum gave the crude reaction products.

Entry 4: A mixture of $Pd(dba)_3CHCl_3$ (5 mg, 4.3×10^{-3} mmol), PPh_3 (2 mg, 0.009 mmol), Cs_2CO_3 (57 mg, 0.174 mmol), **2a** (42.5 mg, 0.40 mmol), and **1a** (31 mg, 0.175 mmol) in toluene (0.5 mL) was stirred at room temp. for 18 h. Evaporation under vacuum gave the crude reaction products.

Entry 5: A solution of **1a** (30 mg, 0.175 mmol) in AcOH/THF/H_2O (1:0.5:0.1, 1.5 mL) was added to a mixture of $Pd(OAc)_2$ (2 mg, 8.7×10^{-3} mmol), 2,2′-bipyridine (5 mg, 0.035 mmol), and **2a** (64 mg, 0.52 mmol). After stirring for 3 d, a saturated solution of $NaHCO_3$ was added. The organic products were extracted with Et_2O (3×5 mL). The combined organic extracts were washed with brine, dried with $MgSO_4$, filtrered, and concentrated in vacuo. The crude product was purified by chromatography on silica gel (hexane/EtOAc = 8:2).

Entry 6: A solution of **1a** (30 mg, 0.175 mmol) in CH_3NO_2 (1 mL) was added to a mixture of $Pd(OAc)_2$ (2 mg, 8.7×10^{-3} mmol), 2,2′-bipyridine (5 mg, 0.035 mmol), and **2a** (42 mg, 0.35 mmol). The resulting mixture was stirred at room temp. for 18 h. Evaporation under vacuum gave the crude reaction products, which were purified by column chromatography (hexane/EtOAc = 8:2).

Dimethyl 2-Oxo-4-phenylpentanedioate (4a): 37 mg, 18% yield. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.14 (dd, ^2J = 19.2, ^3J = 4.3 Hz, 1 H, 3-H), 3.67 (s, 3 H, OMe), 3.79 (dd, ^2J = 19.2, ^3J = 10.2 Hz, 1 H, 3-H), 3.88 (s, 3 H, OMe), 4.15 (dd, ^3J = 10.2, ^3J = 4.3 Hz, 1 H, 4-H), 7.19–7.38 (m, 5 H, 2′-H, 3′-H, 4′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 43.1 (C-3), 46.0 (C-4), 52.6 (OMe), 53.2 (OMe), 127.8 (2 C-2′), 127.9 (C-4′), 129.1 (2 C-3′), 137.5 (C-1′), 160.9 (C-1), 173.3 (C-5), 191.8 (C-2) ppm. $C_{13}H_{14}O_5$ (250.25): calcd. C 62.39, H 5.64; found C 62.28, H 5.71.

Methyl 2-Hydroxy-5-oxo-3-phenyl-2,5-dihydrofuran-2-carboxylate (7): 68 mg, 35% yield. IR (CH_2Cl_2): $\tilde{\nu}$ = 1756, 3317 cm^{-1}. ^{1}H NMR (300 MHz $CDCl_3$, 25 °C): δ = 3.82 (s, 3 H, OMe), 5.35 (br. s, 1 H, OH), 6.53 (s, 1 H, 4-H), 7.53–7.39 (m, 3 H, 2′-H, 4′-H), 7.63–7.55 (m, 2 H, 3′-H) ppm. ^{13}C NMR (75 MHz $CDCl_3$, 25 °C): δ = 54.8 (OMe), 100.6 (C-2), 116.6 (C-4), 127.8 (2 C-2′), 128.4 (C-1′), 129.4 (2 C-3′), 132.0 (C-4′), 160.8 (C-3), 168.6 (C-1), 169.4 (C-5) ppm. MS (70 eV, EI): *m*/*z* (%) = 235 (10) [M + 1], 234 (48) [M], 202 (72), 176 (84), 175 (100), 148 (73), 147 (99), 105 (80), 102 (99), 90 (41). $C_{12}H_{10}O_5$ (234.21): calcd. C 61.54, H 4.30; found C 61.62, H 4.25.

General Procedure for the Dicationic Pd^{II}/dppben-Catalyzed Conjugate Addition of Boronic Acids 2 to Ketoglutaconic Ester 1b (Table2)

Conditions A: 1,2-diphenylphosphanyl benzene (dppben, 21 mg, 0.04 mmol) and $Pd(OCOCF_3)_2$ (14 mg, 0.04 mmol) were dissolved in THF (5 mL). The resulting solution was stirred at room temp. for 20 min. After this time, **1b** (190 mg, 0.83 mmol), $ArB(OH)_2$ **2** (2.5 mmol), HBF_4 (50% aqueous solution, 0.06 mL, 0.83 mmol), and H_2O (0.5 mL) were added. After stirring at room temp. for 18 h, a saturated solution of $NaHCO_3$ was added. The organic products were extracted with Et_2O (3×10 mL). The organic phase was dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude products were purified by chromatography on silica gel (hexane/EtOAc = 8:2).

Conditions B: A solution of **1b** (230 mg, 1.00 mmol) in dioxane/H_2O (8:2, 3 mL) was added to a mixture of $Pd(acac)_2$ (15 mg, 0.05 mmol), 1,2-diphenylphosphanyl benzene (dppben, 22 mg, 0.05 mmol), $Cu(BF_4)_2$ (48 mg, 0.202 mmol), and $ArB(OH)_2$ **2** (1.51 mmol). The mixture was stirred at room temp. for 18 h, and then filtered through a silica gel pad covered with $MgSO_4$. Filtration and evaporation under vacuum gave the crude reaction products, which were purified by column chromatography (hexane/EtOAc = 8:2).

Conjugate Addition Boronic Acids 2 to 1b Catalyzed by Pd^{II}-Palladacycle 9 (Table 3): Compound **1b** (40 mg, 0.175 mmol), K_3PO_4 (37 mg, 0.175 mmol), and Pd^{II}-palladacycle **9** (14 mg, 9×10^{-3} mmol) were added to a stirred solution of $ArB(OH)_2$ **2** (0.35 mmol) in toluene (0.7 mL). The resulting mixture was stirred at room temp. for 18 h, then quenched with water, extracted with CH_2Cl_2 (3×5 mL), and dried with $MgSO_4$. The filtrate was concentrated under reduced pressure. The crude products were purified by chromatography on silica gel (hexane/EtOAc = 8:2).

Diisopropyl 2-Oxo-4-phenylpentanedioate (4b): 165 mg, 65% yield. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.08 (d, ^3J = 6.3 Hz, 3 H, CH_3*i*Pr), 1.24 (d, ^3J = 6.3 Hz, 3 H, CH_3*i*Pr), 1.33 (d, ^3J = 6.3 Hz, 6 H, CH_3*i*Pr), 3.11 (dd, ^2J = 19.1, ^3J = 4.2 Hz, 1 H, 3-H), 3.75 (dd, ^2J = 19.1, ^3J = 10.5 Hz, 1 H, 3-H), 4.06 (dd, ^3J = 10.5, ^3J = 4.2 Hz, 1 H, 4-H), 4.98 (q, ^3J = 6.3 Hz, 1 H, CH*i*Pr), 5.13 (q, ^3J = 6.3 Hz, 1 H, CH*i*Pr), 7.23–7.37 (m, 5 H, 2′-H, 3′-H, 4′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 21.5 (CH_3*i*Pr), 21.7 (2 CH_3*i*Pr), 21.8 (CH_3*i*Pr), 43.3 (C-3), 46.4 (C-4), 68.9 (CH*i*Pr), 71.0 (CH*i*Pr), 127.7 (C-4′), 127.9 (2 C-2′), 129.0 (2 C-3′), 137.9 (C-1′), 160.2 (C-1), 172.4 (C-5), 192.6 (C-2) ppm. $C_{17}H_{22}O_5$ (306.36): calcd. C 66.65, H 7.24; found C 66.78, H 7.20.

Diisopropyl 2-(4-Fluorophenyl)-4-oxopentanedioate (4c): 175 mg, 65% yield. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.13 (d, ^3J = 6.3 Hz, 3 H, CH_3*i*Pr), 1.30 (d, ^3J = 6.3 Hz, 3 H, CH_3*i*Pr), 1.38 (d, ^3J = 6.3 Hz, 6 H, CH_3*i*Pr), 3.16 (dd, ^2J = 19.1, ^3J = 4.6 Hz, 1 H, 3-H), 3.76 (dd, ^2J = 19.1, ^3J = 10.2 Hz, 1 H, 3-H), 4.10 (dd, ^3J = 10.2, ^3J = 4.6 Hz, 1 H, 4-H), 5.03 (q, ^3J = 6.3 Hz, 1 H, CH*i*Pr), 5.18 (q, ^3J = 6.3 Hz, 1 H, CH*i*Pr), 7.10–7.10 (m, 2 H, 3′-H), 7.26–7.34 (m, 2 H, 2′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 21.4 (CH_3*i*Pr), 21.6 (2 CH_3*i*Pr), 21.7 (CH_3*i*Pr), 43.1 (C-3), 45.6 (C-4), 68.9 (CH*i*Pr), 71.1 (CH*i*Pr), 115.6 (C-3′), 115.9 (C-3′), 129.4 (C-2′), 129.5 (C-2′), 133.5 (C-1′), 133.6 (C-1′), 160.0 (C-1), 163.9 (C-4′), 165.9 (C-4′), 172.1 (C-5), 192.3 (C-2) ppm. $C_{17}H_{21}FO_5$ (324.35): calcd. C 62.95, H 6.53; found C 62.79, H 6.61.

Diisopropyl 2-Oxo-4-[4-(trifluoromethyl)phenyl]pentanedioate (4d): 165 mg, 53% yield. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.10 (d, ^3J = 6.3 Hz, 3 H, CH_3*i*Pr), 1.25 (d, ^3J = 6.3 Hz, 3 H, CH_3*i*Pr), 1.34 (d, ^3J = 6.3 Hz, 6 H, CH_3*i*Pr), 3.14 (dd, ^2J = 19.1, ^3J = 4.6 Hz, 1 H, 3-H), 3.75 (dd, ^2J = 19.1, ^3J = 9.9 Hz, 1 H, 3-H), 4.14 (dd, ^3J = 9.9, ^3J = 4.6 Hz, 1 H, 4-H), 5.00 (q, ^3J = 6.3 Hz, 1 H, CH*i*Pr), 5.14 (q, ^3J = 6.3 Hz, 1 H, CH*i*Pr), 7.41 (d, ^3J = 8.1 Hz, 2 H, 3′-H), 7.59 (d, ^3J = 8.1 Hz, 2 H, 2′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 21.5 (CH_3*i*Pr), 21.7 (2 CH_3*i*Pr), 21.8 (CH_3*i*Pr), 42.8 (C-3), 46.2 (C-4), 69.4 (CH*i*Pr), 71.3 (CH*i*Pr), 125.9 (C-3′), 126.0 (C-3′), 127.2 (C-2′), 127.3 (C-2′), 141.8 (C-1′), 160.0 (C-1), 171.6 (C-5), 192.2 (C-2) ppm. $C_{18}H_{21}F_3O_5$ (374.35): calcd. C 57.75, H 5.65; found C 57.59, H 5.58.

Diisopropyl 2-(4-Methoxyphenyl)-4-oxopentanedioate (4e) and (*E*)-Diisopropyl 2-(4-methoxyphenyl)-4-oxopent-2-enedioate (8d): Mixture **4e**:**8d** = 65:35. 249 mg, 74% combined yield. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.08 (d, ^3J = 6.2 Hz, 3 H, CH_3*i*Pr), 1.23 (d, ^3J = 6.2 Hz, 3 H, CH_3*i*Pr), 1.25 (d, ^3J = 6.4 Hz, 6 H, CH_3*i*Pr), 1.32 (d, ^3J = 6.4 Hz, 12 H, CH_3*i*Pr), 3.09 (dd, ^2J = 19.1, ^3J = 4.4 Hz, 1 H, 3-H **4e**), 3.70 (dd, ^2J = 19.1, ^3J = 10.3 Hz, 1 H, 3-H **4e**), 3.78 (s, 3 H, OMe **4e**), 3.81 (s, 3 H, OMe **8d**), 4.00 (dd, ^3J = 10.3, ^3J = 4.4 Hz, 1 H, 4-H **4e**), 4.90–5.19 (m, 4 H, CH*i*Pr), 6.31 (s, 1 H, 3-H **8d**), 6.84 (d, ^3J = 8.9 Hz, 2 H, 3′-H **4e**), 6.88 (d, ^3J = 8.9 Hz, 2 H, 3′-H **8d**), 7.19 (d, ^3J = 8.9 Hz, 2 H, 2′-H **4e**), 7.36 (d, ^3J = 8.9 Hz, 2 H, 3′-H **8d**) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 21.5 (CH_3*i*Pr), 21.6 (CH_3*i*Pr), 21.7 (2 CH_3*i*Pr), 21.8 (CH_3*i*Pr), 21.9 (CH_3*i*Pr), 43.3 (C-3, **4e**), 45.5 (C-4, **4e**), 55.3 (OMe, **4e**), 55.5 (OMe, **8d**), 68.7 (CH*i*Pr), 69.3 (CH*i*Pr), 70.9 (CH*i*Pr), 71.0 (CH*i*Pr), 114.3 (2 C-3′, **4e**), 114.6 (2 C-3′, **8d**), 117.8 (C-3, **8d**), 125.5 (C-4, **8d**), 128.7 (2 C-2′, **8d**), 128.9 (2 C-2′, **4e**), 129.9 (C-4′, **4e**), 154.3 (C-1′, **8d**), 159.0 (C-1′, **4e**), 159.1 (C-4′, **4e**), 160.1 (C-1, **4e**), 161.7 (C-1, **8d**), 166.3 (C-5, **8d**), 172.5 (C-5, **4e**), 189.2 (C-2, **8d**), 192.7 (C-2, **4e**) ppm.

Diisopropyl 2-(Benzo[*d*][1,3]dioxol-5-yl)-4-oxopentanedioate (4f): 186 mg, 64% yield. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.11 (d, ^3J = 6.2 Hz, 3 H, CH_3*i*Pr), 1.25 (d, ^3J = 6.2 Hz, 3 H, CH_3*i*Pr), 1.34 (d, ^3J = 6.3 Hz, 6 H, CH_3*i*Pr), 3.09 (dd, ^2J = 19.2, ^3J = 4.4 Hz, 1 H, 3-H), 3.68 (dd, ^2J = 19.2, ^3J = 10.0 Hz, 1 H, 3-H), 3.97 (dd, ^3J = 10.0, ^3J = 4.4 Hz, 1 H, 4-H), 4.98 (q, ^3J = 6.2 Hz, 1 H, CH*i*Pr), 5.14 (q, ^3J = 6.2 Hz, 1 H, CH*i*Pr), 5.95 (s, 2 H, O-CH_2-O), 5.75–6.80 (m, 3 H, 2′-H, 5-H, 6′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 21.6 (CH_3*i*Pr), 21.7 (2 CH_3*i*Pr), 21.8 (CH_3*i*Pr), 43.5 (C-3), 46.0 (C-4), 68.9 (CH*i*Pr), 71.0 (CH*i*Pr), 101.3 (O-CH_2-O), 108.2 (C-2′), 108.7 (C-5′), 121.2 (C-6′), 131.6 (C-1′), 147.2 (C-4′), 148.2 (C-3′), 160.1 (C-1), 172.2 (C-5), 192.4 (C-2) ppm. $C_{18}H_{22}O_7$ (350.37): calcd. C 61.71, H 6.33; found C 61.92, H 6.41.

Diisopropyl 2-(4-Bromophenyl)-4-oxopentanedioate (4g): 195 mg, 61% yield. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.09 (d, ^3J = 6.3 Hz, 3 H, CH_3*i*Pr), 1.25 (d, ^3J = 6.3 Hz, 3 H, CH_3*i*Pr), 1.33 (d, ^3J = 6.3 Hz, 6 H, CH_3*i*Pr), 3.10 (dd, ^2J = 19.1, ^3J = 4.6 Hz, 1 H, 3-H), 3.70 (dd, ^2J = 19.1, ^3J = 9.9 Hz, 1 H, 3-H), 4.03 (dd, ^3J = 9.9, ^3J = 4.6 Hz, 1 H, 4-H), 4.98 (q, ^3J = 6.3 Hz, 1 H, CH_3*i*Pr), 5.00 (q, ^3J = 6.3 Hz, 1 H, CH_3*i*Pr), 7.16 (d, ^3J = 8.4 Hz, 2 H, 2′-H), 7.46 (d, ^3J = 8.4 Hz, 2 H, 3′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 21.5 (CH_3*i*Pr), 21.7 (2 CH_3*i*Pr), 21.8 (CH_3*i*Pr), 42.9 (C-3), 45.8 (C-4), 69.2 (CH*i*Pr), 71.2 (CH*i*Pr), 121.8 (C-4′), 129.7 (2 C-2′), 132.2 (2 C-3′), 136.8 (C-1′), 160.1 (C-1), 171.9 (C-5), 192.3 (C-2) ppm. $C_{17}H_{21}BrO_5$ (385.25): calcd. C 53.00, H 5.49; found C 53.17, H 5.39.

Diisopropyl 2-(3,4-Dichlorophenyl)-4-oxopentanedioate (4h): 150 mg, 48% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (d, ^3J = 6.2 Hz, 3 H, CH_3*i*Pr), 1.25 (d, ^3J = 6.2 Hz, 3 H, CH_3*i*Pr), 1.34 (d, ^3J = 6.2 Hz, 6 H, CH_3*i*Pr), 3.12 (dd, ^2J = 18.8, ^3J = 4.8 Hz, 1 H, 3-H), 3.69 (dd, ^2J = 18.8, ^3J = 10.0 Hz, 1 H, 3-H), 4.02 (dd, ^3J = 10.0, ^3J = 4.8 Hz, 1 H, 4-H), 4.99 (q, ^3J = 6.2 Hz, 1 H, CH*i*Pr), 5.14 (q, ^3J = 6.2 Hz, 1 H, CH*i*Pr), 7.14 (dd, ^3J = 8.3, ^4J = 2.1 Hz, 1 H, 6′-H), 7.39 (d, ^4J = 2.1 Hz, 1 H, 1′-H), 7.40 (d, ^3J = 8.3 Hz, 1 H, 5′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 21.6 (CH_3*i*Pr), 21.7 (2 CH_3*i*Pr), 21.8 (CH_3*i*Pr), 42.8 (C-3), 45.5 (C-4), 69.4 (CH*i*Pr), 71.3 (CH*i*Pr), 127.3 (C-6′), 130.0 (C-1′), 130.9 (C-5′), 132.0 (C-4′), 133.1 (C-3′), 138.0 (C-1′), 160.0 (C-1), 171.3 (C-5), 192.0 (C-2) ppm. $C_{17}H_{20}Cl_2O_5$ (375.25): calcd. C 54.41, H 5.37; found C 54.62, H 5.42.

General Procedure for the Synthesis of 4,5-Dihydropyridazin-3-(2*H*)-ones 11: The corresponding hydrazine (2.0 mmol) and acetic acid (0.07 mL, 1.2 mmol) were added to a solution of **4** (0.41 mmol) in CH_2Cl_2 (5 mL). The solution was heated at refulx for 18 h. After cooling to room temp., the volatiles were removed in vacuo, and the resultant residue was purified by column chromatography (hexane/EtOAc = 1:1).

Isopropyl 6-Oxo-5-phenyl-1,4,5,6-tetrahydropyridazine-3-carboxylate (11a): 94 mg, 88% yield. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.36 (d, ^3J = 6.3 Hz, 6 H, CH_3*i*Pr), 3.11 (dd, ^2J = 18.0, ^3J = 10.5 Hz, 1 H, 3-H), 3.28 (dd, ^2J = 18.0, ^3J = 7.3 Hz, 1 H, 3-H), 3.77 (dd, ^2J = 10.5, ^2J = 7.3 Hz, 1 H, 4-H), 5.21 (q, ^3J = 6.3 Hz, 1 H, CH*i*Pr), 7.19–7.27 (m, 2 H, 3′-H), 7.31–7.41 (m, 3 H, 2′-H, 4′-H), 8.79 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 21.9 (2 CH_3*i*Pr), 29.0 (C-3), 42.2 (C-4), 70.4 (CH *i*Pr), 127.9 (2 C-2′), 128.1 (C-4′), 129.2 (2 C-3′), 136.3 (C-1′), 143.9 (C-2), 162.6 (CO), 168.2 (CO) ppm. $C_{14}H_{16}N_2O_3$ (260.29): calcd. C 64.60, H 6.20; found C 64.73, H 6.29.

Isopropyl 1-Benzyl-6-oxo-5-phenyl-1,4,5,6-tetrahydropyridazine-3-carboxylate (11b): 144 mg, 83% yield. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.33 (d, ^3J = 6.2 Hz, 6 H, CH_3*i*Pr), 3.15 (dd, ^2J = 7.7, ^3J = 1.8 Hz, 2 H, 3-H), 3.76 (t, ^3J = 8.4 Hz, 1 H, 4-H), 5.06 (s, 2 H, CH_2Ph), 5.15 (q, ^3J = 6.2 Hz, 1 H, CH*i*Pr), 7.13–7.19 (m, 2 H, 3′-H), 7.24–7.41 (m, 10 H, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 21.9 (2 CH_3*i*Pr), 29.2 (C-3), 42.5 (C-4), 53.8 (CH_2Ph), 70.1 (CH*i*Pr), 127.7 (2 C-2′′), 127.8 (C-4′), 127.9 (C-4′′), 128.6 (2 C-3′′), 128.7 (2 C′-2′), 129.0 (2 C-3′), 136.7 (C-1′′), 137.1 (C-1′), 143.1 (C-2), 162.6 (CO), 166.8 (CO) ppm. $C_{21}H_{22}N_2O_3$ (350.42): calcd. C 71.98, H 6.33; found C 72.14, H 6.24.

Isopropyl 1-Methyl-6-oxo-5-phenyl-1,4,5,6-tetrahydropyridazine-3-carboxylate (11c): 84 mg, 75% yield. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.34 (d, ^2J = 6.3 Hz, 6 H, CH_3*i*Pr), 3.16 (dd, ^2J = 7.7, ^3J = 3.4 Hz, 2 H, 3-H), 3.53 (s, 3 H, NMe), 3.76 (t, ^3J = 8.6 Hz, 1 H, 4-H), 5.18 (q, ^3J = 6.3 Hz, 1 H, CH*i*Pr), 7.17–7.23 (m, 2 H, 3′-H), 7.28–7.38 (m, 3 H, 2′-H, 4′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 21.9 (2 CH_3*i*Pr), 29.2 (C-3), 38.0 (NMe), 42.4 (C-4), 70.2 (CH*i*Pr), 127.8 (2 C-2′), 128.0 (C-4′), 129.1 (2 C-3′), 136.8 (C-1′), 143.0 (C-2), 162.6 (CO), 167.2 (CO) ppm. $C_{15}H_{18}N_2O_3$ (274.32): calcd. C 65.68, H 6.61; found C 65.91, H 6.70.

General Procedure for the Transformation of Compounds 11 into Pyridazin-3-(2*H*)-ones 5: Br_2 (10 μL, 0.21 mmol) was added to 4,5-dihydropyridazin-3-(2*H*)-ones **11** (0.14 mmol) dissolved in AcOH (0.8 mL). After stirring at room temp. for 18 h, a saturated solution of $NaHCO_3$ was added. The organic products were extracted with Et_2O (3 × 5 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude products were purified by chromatography on silica gel (hexane/EtOAc = 6:4).

General Procedure for the One-Pot Synthesis of Pyridazin-3-(2*H*)-ones 5 from 4b: The corresponding hydrazine (2.0 mmol) and acetic

acid (0.07 mL, 1.2 mmol) were added to a solution of **4** (0.41 mmol) in CH_2Cl_2 (5 mL). The solution was heated at reflux for 18 h. After cooling to room temp., the volatiles were removed in vacuo. The residue was dissolved in AcOH (2 mL), and Br_2 (0.03 mL, 0.60 mmol) was added. After stirring for 18 h at room temp., a saturated solution of $NaHCO_3$ was added. The organic products were extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by chromatography on silica gel (hexane/EtOAc = 6:4).

Isopropyl 5-Oxo-4-phenyl-5,6-dihydropyridine-2-carboxylate (5a): 32 mg, 89% yield. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.42 (d, ^3J = 6.2 Hz, 6 H, CH_3*i*Pr), 5.33 (q, ^3J = 6.2 Hz, 1 H, CH*i*Pr), 7.44–7.54 (m, 3 H), 7.85–7.93 (m, 2 H, 3′-H), 8.06 (s, 1 H, 3-H, 2′-H, 4′-H), 12.2 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 21.9 (2 CH_3*i*Pr), 70.6 (CH*i*Pr), 128.4 (C-3), 128.7 (2 C-2′), 128.8 (2 C-3′), 130.4 (C-4′), 132.8 (C-1′), 138.6 (C-4), 140.0 (C-2), 161.3 (CO), 162.2 (CO) ppm. $C_{14}H_{14}N_2O_3$ (258.28): calcd. C 65.11, H 5.46; found C 65.29, H 5.56.

Isopropyl 4-(4-Fluorophenyl)-5-oxo-5,6-dihydropyridine-2-carboxylate (5b): 61 mg, 54% yield. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.43 (d, ^3J = 6.3 Hz, 6 H, CH_3*i*Pr), 5.34 (q, ^3J = 6.3 Hz, 1 H, CH*i*Pr), 7.18 (t, J = 8.7 Hz, 2 H, 3′-H), 7.88–7.97 (m, 2 H, 2′-H), 8.04 (s, 1 H, 3-H), 12.1 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.9 (2 CH_3 *i*Pr), 70.6 (CH *i*Pr), 115.7 (C-3′), 116.0 (C-3′), 128.1 (C-3), 128.8 (C-1′), 128.9 (C-1′), 130.9 (C-2′), 131.0 (C-2′), 138.6 (C-4), 138.7 (C-2), 162.4 (CO), 162.1 (CO), 162.3 (C-4′), 165.7 (C-4′) ppm. $C_{14}H_{13}FN_2O_3$ (276.27): calcd. C 60.87, H 4.74; found C 60.99, H 4.83.

Isopropyl 5-Oxo-4-[4-(trifluoromethyl)phenyl]-5,6-dihydropyridine-2-carboxylate (5c): 74 mg, 55% yield. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.43 (d, ^3J = 6.3 Hz, 6 H, CH_3*i*Pr), 5.34 (q, ^3J = 6.3 Hz, 1 H, CH_3*i*Pr), 7.75 (d, J = 8.2 Hz, 2 H, 3′-H), 7.99 (d, J = 8.2 Hz, 2 H, 2′-H), 8.09 (s, 1 H, 3-H), 11.3 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 22.0 (2 CH_3 *i*Pr), 70.9 (CH *i*Pr), 125.7 (C-3′), 128.8 (C-3), 129.1 (C-2′), 129.2 (C-2′), 138.5 (C-4), 138.8 (C-2), 160.2 (CO), 161.9 (CO) ppm. $C_{15}H_{13}F_3N_2O_3$ (326.27): calcd. C 55.22, H 4.02; found C 55.44, H 4.13.

Isopropyl 4-(4-Methoxyphenyl)-5-oxo-5,6-dihydropyridine-2-carboxylate (5d): 61 mg, 52% yield. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.43 (d, ^3J = 6.3 Hz, 6 H, CH_3*i*Pr), 3.96 (s, 3 H, OMe), 5.33 (q, ^3J = 6.3 Hz, 1 H, CH *i*Pr), 6.99 (d, ^3J = 8.9 Hz, 2 H, 3′-H), 7.98 (d, ^3J = 8.9 Hz, 2 H, 4′-H), 8.07 (s, 1 H, 3-H), 11.6 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 22.0 (2 CH_3 *i*Pr), 56.6 (OMe), 70.9 (CH *i*Pr), 111.7 (2 C-3′), 118.6 (C-1′), 126.3 (C-4), 129.6 (2 C-2′), 133.4 (C-3), 138.7 (C-2), 157.7 (CO), 162.2 (CO) ppm. $C_{15}H_{16}N_2O_4$ (288.30): calcd. C 62.49, H 5.59; found C 62.58, H 5.66.

Isopropyl 4-(Benzo[*d*][1,3]dioxol-5-yl)-5-oxo-5,6-dihydropyridine-2-carboxylate (5e): 87 mg, 71% yield. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.40 (d, ^3J = 6.2 Hz, 6 H, CH_3*i*Pr), 5.32 (q, ^3J = 6.2 Hz, 1 H, CH *i*Pr), 6.06 (s, 2 H, O-CH_2-O), 6.85 (s, 1 H, 5′-H), 6.15 (s, 1 H, 6′-H), 7.92 (s, 1 H, 3-H), 11.1 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 22.1 (2 CH_3 *i*Pr), 71.2 (CH *i*Pr), 102.3 (O-CH_2-O), 110.7 (C-2′), 113.8 (C-5′), 120.4 (C-3), 124.0 (C-6), 126.5 (C-1′), 138.7 (C-4), 143.9 (C-2), 147.9 (C-4′), 149.3 (C-3′), 160.1 (CO), 162.6 (CO) ppm. $C_{15}H_{14}N_2O_5$ (302.29): calcd. C 59.60, H 4.67; found C 59.88, H 4.75.

Isopropyl 1-Benzyl-6-oxo-5-phenyl-1,6-dihydropyridazine-3-carboxylate (5f): 33 mg, 68% yield. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.41 (d, ^3J = 6.3 Hz, 6 H, CH_3 *i*Pr), 5.30 (q, ^3J = 6.2 Hz, 1 H, CH *i*Pr), 5.49 (s, 2 H, CH_2Ph), 7.28–7.29 (m, 3 H, Ar-H), 7.40–7.48 (m, 3 H, Ar-H), 7.50–7.58 (m, 2 H, Ar-H), 7.75–7.86 (m, 2 H, Ar-H) 7.93 (s, 1 H, 3-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 22.0 (2 CH_3 *i*Pr), 57.1 (O-CH_2-O), 70.3 (CH *i*Pr), 127.7 (C-3), 128.2 (C-4′′), 128.6 (2 C-3′′), 128.7 (2 C-2′), 128.8 (2 C-3′), 129.2 (2 C-2′′), 130.0 (C-4′), 133.6 (C-1′), 135.7 (C-4), 136.9 (C-1′′), 139.2 (C-2), 159.7 (CO), 162.1 (CO) ppm. $C_{21}H_{20}N_2O_3$ (348.40): calcd. C 72.40, H 5.79; found C 72.58, H 5.71.

Pharmacological Assays: An overexpressing mutated amyloid precursor protein (APPswe) cell-line (APP695-transfected neuroblastoma SH-SY5Y) was used to select a non-toxic concentration range, and to examine the potential cytoprotective effect of the studied compounds by exposing cells to the hydrogen peroxide insult.

The mitochondrial-dependent reduction of MTT to formazan was used to exclude a cytotoxic effect of the tested compound in APPswe cells. These compounds must be tested at concentrations non-cytotoxic for brain cells, since they would be eventually administered to organisms if active. For that purpose, the compounds were previously tested for cell viability in the APPswe cell-line, which is widely used for studies of neuroprotection and neurotoxicity.

For aggregation inhibition experiments, βA (25–35) peptide was dissolved at 1 mM in PBS, and 10 μL of this solution was mixed with the tested compound and incubated at 37 °C for 4 d. For disaggregating experiments, 10 μM βA (25–35) peptide was incubated at 37 °C for 4 d to generate fibrils. Pre-formed fibrils were mixed with the tested compound for an additional 4 dat 37 °C. The degree of βA aggregation and disaggregation was determined using thioflavin-T (Thio-T) fluorescence analyses. Excitation and emission wavelengths were 448 and 483 nm, respectively. Sample fluorescence was determined by subtracting the fluorescence of a Thio-T blank. Data are shown in Table 4, and are expressed as the 50% inhibitory concentration (IC_{50}).

The assay for β-secretase activity was based on the secretase-dependent cleavage of a specific fluorogenic substrate [H-RE-(EDANS)EVNLDAEFK(DABCYL)R-OH], which results in the release of a fluorescent signal. The level of secretase enzymatic activity is proportional to the fluorimetric reaction. β-secretase assay was carried out at 37 °C using 0.24 U of a human recombinant β-secretase enzyme and 10 μM substrate in 20 mM sodium acetate buffer (pH 4.5) in a final volume of 100 μL. Wavelengths of excitation and emission were 360 and 528 nm, respectively. The enzyme activity assay was performed in the absence (control reaction), and in the presence of compounds **5** or **11**. Before the addition of the substrate, the human recombinant β-secretase enzyme and the tested compound were pre-incubated at 37 °C for 1 h. The inhibition ratio of β-secretase activity exerted by **5** or **11** was calculated as the percentage of the control value after 1 h of incubation, once the substrate was added. Data are shown in Table 4, and are expressed as the percentage inhibition at 10 μM.

The molecular probe dichlorofluorescein diacetate (DCFA-DA) was used to measure intracellular ROS generation in APPswe cells. For this assay, cells were subcultured, and 24 h later they were loaded with 10 μM DCFA-DA, which diffuses through the cell membrane and is hydrolyzed by intracellular esterases to the dichlorofluorescein (DCFH). DCFH reacts with intracellular free radicals to form dichlorofluorescin (DCF), a green fluorescent dye. Compounds **5** or **11** were added to the cells 30 min prior to the treatment with 100 μM H_2O_2, a ROS generator. The fluorescence caused after a 60 min exposure of the cells to H_2O_2 was measured, the wavelengths of excitation and emission being 485 and 520 nm,

respectively. The data are shown in Table 4, and are expressed as the 50% inhibitory concentration (IC_{50}).

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of newly synthesized compounds.

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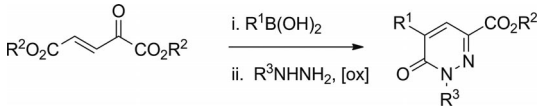

Dicationic Pd^{II} catalysts were found to be efficient for the regioselective conjugate addition of boronic acids to ketoglutaconic esters. The resulting 4-aryl-2-oxopentadienoates were transformed into pyridazin-3(2*H*)-ones, which simultaneously exhibited β-secretase activity, inhibition of βA aggregation, and disaggregation of preformed βA fibrils, and also had an ROS-scavenging profile.

Keywords: Boron / Palladium / Regioselectivity / Homogeneous catalysis / Michael addition / Nitrogen heterocycles / Medicinal chemistry / Neuroprotection

