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Sequential Suzuki/Asymmetric Aldol and Suzuki/Knoevenagel Reactions Under Aqueous Conditions

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Dedicated to Professor Domenico Spinelli on the occasion of his 80th birthday

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Here we describe for the first time a sequential Suzuki/asymmetric aldol reaction. Such sequential approach was achieved through the combined use of an ionic liquid supported palladium catalyst and the organocatalyst *trans*-4-(2,2-diphenylacetoxy)proline. Suzuki and asymmetric aldol reactions were performed under aqueous conditions. The use of a palladium catalyst under basic conditions allowed also the first example of sequential Suzuki/Knoevenagel reaction. Reactions were carried out under aqueous conditions and products were isolated in good to high yields and, in the case of the Suzuki/aldol reaction, with diastereoselectivities up to 91:9 and enantioselectivities up to at least 99 %.

Introduction

Catalytic palladium-mediated synthesis and organocatalytic reactions have received a paramount interest from the scientific community in the last years. The palladium-catalyzed Suzuki–Miyaura cross-coupling reaction[1] between aryl boronic acids and aryl halides has been proven a very useful method for forming the C–C bond of biaryls, and many studies have been conducted using supported Pd-catalysts under aqueous conditions.[2] Aqueous conditions are also currently employed in organocatalyzed asymmetric reactions.[3] In particular, the combined use of water as the reaction medium together with the proper organocatalyst is very useful in aminocatalysis, allowing the synthesis of aldols with high enantioselectivities.[3,4] The Knoevenagel reaction has also been the subject of many synthetic studies and can be considered as the root of aminocatalysis.[5] The great synthetic utility of such reactions allowed the preparation of many useful building blocks as well as natural and synthetic molecules possessing important biological activities.[6] As well as the Pd-catalyzed and asymmetric aldol reaction, also the Knoevenagel reaction has been widely investigated in water, both in the presence of heterogeneous catalysts and without catalysts.[7] In addition, many other methodologies related to these reactions have been developed, for example use of ionic liquids, supported catalysts and flow systems.[8] From an economical point of view, the replacement of a multistep process with a sequential, tandem, domino or cascade reaction may lead to a rapid increase of molecular complexity with minimized purification and isolation efforts.[9]

Recently, several examples of sequential reactions have been reported, involving Pd-based catalysts[10] or metal catalyzed/organocatalytic asymmetric reaction sequence.[11] We were interested in the feasibility of sequential reactions involving catalytic organometallic/organocatalytic processes. Here we describe for the first time the Suzuki C–C cross-coupling reaction, furnishing biarylaldehydes, coupled with organocatalytic asymmetric aldol reaction under aqueous conditions. In addition, we explored the feasibility of the Suzuki/Knoevenagel sequence under aqueous conditions. Usually, Suzuki/Knoevenagel reactions are not usually carried out in a sequential manner. The two steps Suzuki reaction/Knoevenagel reaction is widely applied for the synthesis of dye-sensitized solar cells.[12]

In order to develop the Suzuki coupling/organocatalytic asymmetric aldol reaction sequence we decided to test two catalytic systems previously reported by us. We recently developed a new supported palladium catalyst (SiO_2-Pd-**1**) for the Suzuki C–C coupling employed in the synthesis of biaryl compounds.[13] Moreover, we found out that *trans*-4-acyloxyproline **2**, synthesized in one step from 4-hydroxyproline, is an excellent catalyst for the asymmetric aldol reaction under aqueous conditions (Figure 1).[4a]

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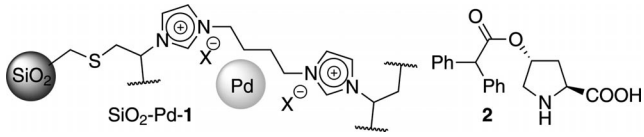
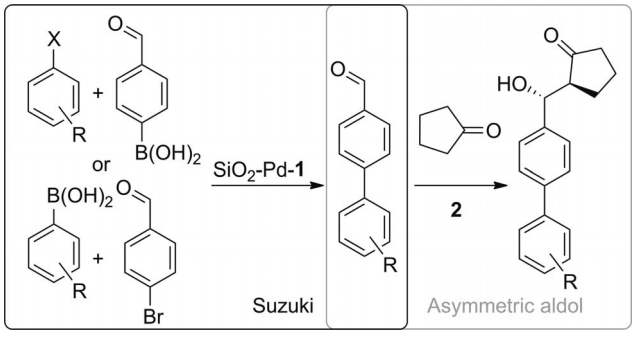


Figure 1. Structure of catalysts SiO_2-Pd-**1** and **2**.

Results and Discussion

The general approach of the synthetic procedure we have followed in the case of the Suzuki C–C cross-coupling reaction, coupled with organocatalytic asymmetric aldol reaction is reported in Scheme 1. The Suzuki step can be carried out starting from 4-bromobenzaldehyde and the proper arylboronic acid or from 4-formyl-phenylboronic acid and the substituted aryl halide. Once the biaryl aldehydes have been generated, such compounds are directly employed for the asymmetric aldol reaction. The SiO_2-Pd-**1** catalyst has been employed in the first step, whereas the proline derivative **2** was used in the second one. Whilst palladium catalyst SiO_2-Pd-**1** has already been tested in the synthesis of several biaryl compounds,[13] *trans*-4-acyloxyproline **2** has never been used with biaryl aldehydes. Before starting with the sequential synthesis of biaryl aldol compounds, we carried out some preliminary asymmetric aldol reactions using catalyst **2** (Table 1).

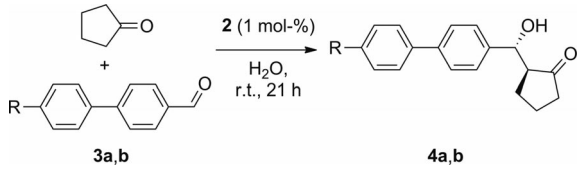


Scheme 1. General scheme for the sequential Suzuki/organocatalytic asymmetric aldol reaction.

In Table 1 are reported the results of the asymmetric aldol reaction between two biaryl aldehydes (**3a**,**b**) and cyclopentanone catalyzed by proline derivative **2**. We have chosen to employ cyclopentanone as a more challenging substrate, since aldol reactions carried out with this ketone usually afford aldols with poorer stereoselectivities as compared, for instance, to cyclohexanone. Our previous work demonstrated that catalyst **2** shows excellent activity and stereoselectivity when used with cyclopentanone. Then, we were interested to see if performances of catalyst **2** can be maintained under the new reaction conditions.

Reactions were carried out on 1 mmol scale, using catalyst **2** in 1 mol-% loading,[14] under aqueous conditions, and with 5 or 10 equiv. of ketone. In a first attempt, we used

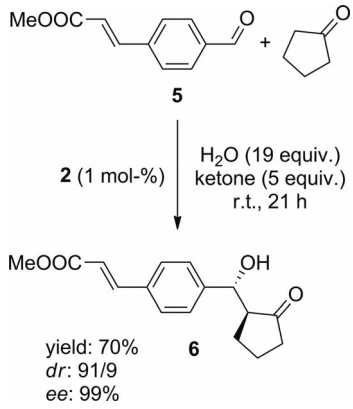
Table 1. Direct asymmetric aldol reaction between cyclopentanone and biarylaldehydes.[a]



Entry	R	4	H_2O [mL]	Ketone [mL]	Yield[b] [%]	*anti*/*syn*[c]	*ee*[d] [%]
1	H	**a**	0.35	0.44	84	94:6	82
2	H	**a**	0.70	0.88	74	93:7	87
3	Me	**b**	0.70	0.88	43[e]	87:13	98

[a] Reaction conditions: aldehyde (1 mmol), water (19 or 39 equiv.), cyclopentanone (5 or 10 equiv.), catalyst (0.01 mmol), room temperature, 21 h. [b] Isolated yield. [c] Determined by ^1H NMR of the crude product. [d] *anti* Diastereoisomer, determined by HPLC using a chiral column. [e] Recovered aldehyde 48%.

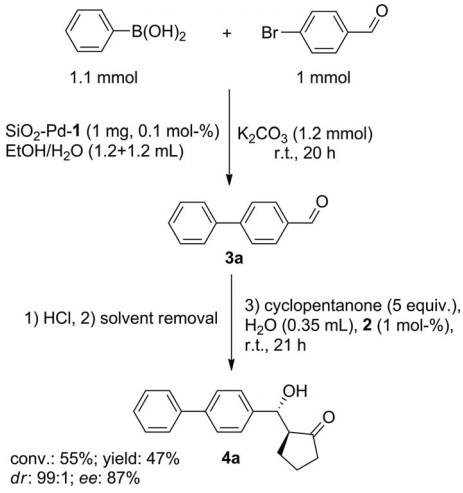
5 equiv. of ketone and a large amount of water (19 equiv., 0.35 mL). This particular choice is justified by the fact that a suitable amount of solvent is required in the second step of the sequential procedure (vide infra). Under such conditions, aldehyde **3a** afforded the aldol product in high yield and diastereoselectivity, as well as with a good *ee* value (Table 1, entry 1). A small increase in enantioselectivity was observed when the amounts of water and ketone were doubled (entry 2). The use of the same condition with aldehyde **3b** gave excellent enantioselectivity, although lower conversion was observed (entry 3). In addition to these two biaryl aldehydes, we also tested catalyst **2** with aldehyde **5** (Scheme 2), which can be obtained in situ by a Heck reaction. The aldol product was again isolated in good yield and high stereoselectivity. The good to high stereoselectivities observed were encouraging, because they demonstrated the efficiency of catalyst **2** even with cyclopentanone.



Scheme 2. Asymmetric aldol reaction catalyzed by **2**.

After these preliminary screening reactions, we undertook the Suzuki/asymmetric aldol reaction sequential procedure. As a first attempt we carried out the Suzuki reaction, catalyzed by SiO_2-Pd-**1** in 0.1 mol-% loading, between

phenylboronic acid and 4-bromobenzaldehyde (Scheme 3). After the reaction was complete (TLC), we carried out the second step. However, the basic conditions used in the first step are not suitable for the second one. As a matter of fact, such conditions are able to catalyze the aldol reaction (giving a racemic mixture of aldols) and cause the deprotonation of proline **2** (making it no more a bifunctional catalyst). In order to overcome these problems, the reaction mixture was neutralized with concentrated HCl before the second step. In this way, the solvent mixture for the aldol step was formed by water, ethanol and cyclopentanone. The presence of ethanol caused a low stereoselectivity. Thus, after HCl neutralization, solvents (water and ethanol) were removed under reduced pressure, and then cyclopentanone, water and catalyst **2** were added. The reaction was quenched after 21 h and the aldol product **4a** was isolated in 47% yield (55% conversion), excellent diastereoselectivity and good enantioselectivity (Scheme 3). Interestingly, stereoselectivity was even better with respect to the asymmetric aldol reaction carried out in a single step (Table 1, entry 1). The lower conversion may be ascribed to the occurrence of a more complex reaction mixture.

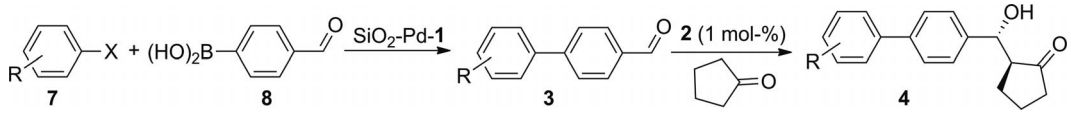


Scheme 3. Sequential Suzuki/asymmetric aldol reaction.

In order to apply this synthetic approach to the synthesis of several substituted biphenyl aldols **4**, we carried out some experiments starting from substituted aryl bromides or iodides **7** and (4-formylphenyl)boronic acid **8** (Table 2). The 2-cyano derivative **4c** was obtained in good yield, but moderate stereoselectivity (entry 1) whereas the 4-cyano derivative **4d** was obtained in high enantioselectivity and good diastereoselectivity, although yield was moderate (entry 2).

Good results were observed with the methoxy derivative **4e**. With the latter derivative the Suzuki step was also quenched after 4 h (entry 4), in order to verify the outcome of the aldol reaction in the presence of an excess of the reagents of the first step. Although aldol yield was almost the same, stereoselectivity was highly affected, being much lower with respect to the previous case (entry 3). Therefore, the yield of the Suzuki step must be as high as possible. In the case of 4-nitro derivative **4f** aldol product was isolated in excellent stereoselectivity and high yield (entry 5). In this case we employed 2 mol-% of catalyst **2**. Because of the excellent results observed in the latter case, we investigated the use of only 3 equiv. of cyclopentanone and 1 mol-% of catalyst **2**. Although the use of a lesser amount of ketone did not allow the reaction mixture to be adequately stirred, the result was indeed excellent (entry 6). Finally, we investigated the synthesis of aldol **4b**. In this case we disclosed the importance of the fine modification of reaction conditions for the best result. As a matter of fact, under the usual reaction conditions, yield was high, but stereoselectivity was only moderate (entry 7). By changing the reaction conditions we improved stereoselectivity although yield was moderate (entries 8 and 9). However, product **4b** was obtained

Table 2. Sequential Suzuki/asymmetric aldol reactions.[a]

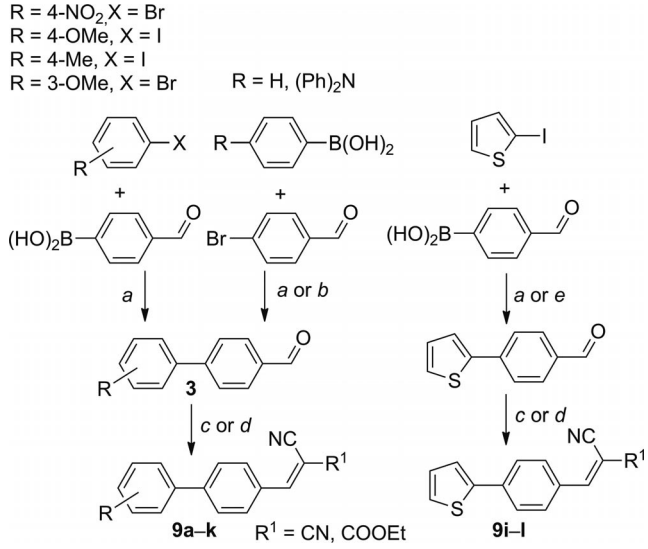


Entry	R	X	Step 1 *t* [h]	Step 2 *t* [h]	**4**	Aldol yield [%]	RCHO yield[b] [%]	*dr* [*anti*/*syn*]	*ee*[*anti*] [%]
1	2-CN	Br	20	23	**c**	73	23	66:34	76
2	4-CN	I	20	22	**d**	42	34	85:15	93
3[c]	4-CH_3O	I	20	19	**e**	61	37	84:16	88
4[c]	4-CH_3O	I	4	15	**e**	59	3[d]	53:47	56
5[e]	4-NO_2	Br	6	38	**f**	86	–	91:9	>99
6[f]	4-NO_2	Br	6	16	**f**	84	8	91:9	>99
7[c]	4-CH_3	I	24	20	**b**	92	8	63:37	60
8[c,g,h]	4-CH_3	I	24	20	**b**	60	40	73:27	76
9[c,g,h,i]	4-CH_3	I	24	20	**b**	39	61	84:16	88
10[c,j]	4-CH_3	I	24	20	**b**	–	100	–	–

[a] Reaction conditions: 1st step: aryl halide (1 mmol), (4-formylphenyl)boronic acid (1.1 mmol), ethanol (1.2 mL), water (1.2 mL), K_2CO_3 (1.2 mmol), SiO_2-Pd-**1** (1 mg, 0.1 mol-% or 4 mg, 0.4 mol-%); 2nd step: *a*) HCl neutralization, *b*) solvent removal, *c*) water (0.7 mL), cyclopentanone (0.88 mL, 10 equiv.), **2** (1 mol-%). [b] Recovered aldehyde **3**. [c] SiO_2-Pd-**1** (0.4 mol-%). [d] Recovered unreacted 4-iodoanisole (21%). [e] Proline catalyst **2** (2 mol-%) (1 mol-% + 1 mol-% after 14 h). [f] Cyclopentanone (3 equiv.). [g] Aryl iodide (1.1 mmol). [h] Proline catalyst **2** (0.5 mol-%). [i] Solvent removal, then neutralization with HCl. [j] Without proline catalyst.

with lower enantioselectivity (88%) with respect to the single-step aldol reaction (Table 1, entry 3). The actual role of the proline catalyst **2** was confirmed observing that in the absence of it no aldol reaction occurs (entry 10).

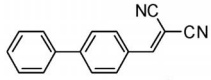
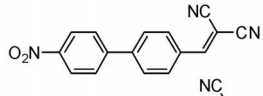
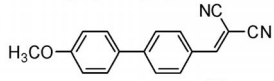
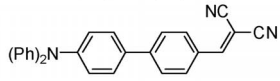
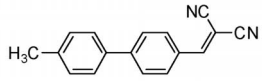
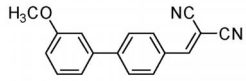
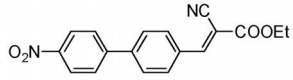
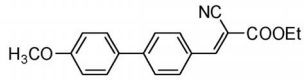
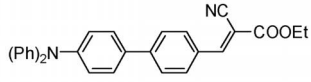
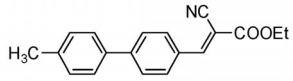
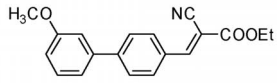
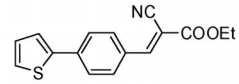
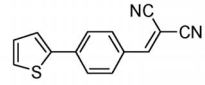
The Suzuki reaction catalyzed by SiO_2-Pd-**1** was also coupled with the Knoevenagel reaction (Scheme 4). Knoevenagel reaction has been widely used in sequential reactions.[9,15] Recently, it was reported the Suzuki/Knoevenagel-Doebner sequence in the presence of Pd-$(OAc)_2/K_2CO_3$ and malonic acid/piperidine in glycerol as solvent.[16] To the best of our knowledge, this is the first report of this kind of approach, in which the basic condition of the Suzuki reaction operates in the Knoevenagel reaction under aqueous condition without the use of amine catalyst.



Scheme 4. Sequential Suzuki/Knoevenagel. Reaction conditions: *a*) Arylboronic acid (1.1 mmol), aryl halide (1 mmol), SiO_2-Pd-**1** (2 mg, 0.2 mol-%), EtOH/H_2O, K_2CO_3, 50 °C, 6–23 h; *b*) Pd-$(OAc)_2$ (0.5 mol-%), *i*PrOH/H_2O, K_3PO_4, room temp., 10 min; *c*) $CH_2(CN)_2$ (1.1 mmol), H_2O (3 mL), room temp., overnight; *d*) $CNCH_2COOEt$ (1.1 mmol), 50 °C, 2 h; *e*) $Pd(OAc)_2$ (0.2 mol-%), EtOH/H_2O, K_2CO_3, 50 °C, 2 h.

Aldehydes **3** (R = H, 4-NO_2, 4-CH_3O, 3-CH_3O, 4-CH_3) were synthesized according to our procedure using 0.2 mol-% of catalyst SiO_2-Pd-**1** under aqueous condition (EtOH/H_2O).[13] Under such conditions, the phenylboronic acid bearing the 4-$N(Ph)_2$ group did not react. The latter aldehyde was obtained by applying a known procedure [$Pd(OAc)_2$ 0.5 mol-%, *i*PrOH/H_2O, K_3PO_4, room temp.].[17] Aldehydes were not isolated. We reasoned that the basic conditions due to the Suzuki reaction should be suitable for the Knoevenagel step under aqueous condition. Then, we investigated the sequential procedure by using two methylene active compounds, namely malononitrile and ethyl cyanoacetate. After the Suzuki step was almost complete (TLC) the reaction mixture was cooled to room temperature, then water and a slight excess of malononitrile were added. In a few minutes a yellow precipitate was formed. The reaction mixture was stirred at room temperature overnight. Compounds **9a**–**e** were isolated in good to excellent yields (Table 3).

Table 3. Sequential Suzuki/Knoevenagel.

Entry	Compound **9**		Isolated yield [%]	Recovered aldehyde [%]
1		**a**	99	–
2		**b**	88	7
3		**c**	93	<5
4		**d**	65	20
5		**e**	61	21
6		**f**	35 (74)[a]	12
7		**g**	65	33
8		**h**	80	16
9		**i**	81	19
10		**j**	64	38
11		**k**	47	48
12		**l**	87(84)[b]	8 (<5)[b]
13		**m**	75	<5

[a] Suzuki step: 3-iodoanisole; Knoevenagel step: 50 °C, 2 h, no additional water. [b] Using SiO_2-Pd-**1**.

Reactions were clean, indeed, in the reaction mixture were present the final compounds, unreacted aldehydes and, in some cases, starting unreacted aryl halide. Under these conditions compound **9f** was obtained in low yield (35%). The reaction was repeated starting from 3-iodoanisole, then the Knoevenagel step was carried out by adding malononitrile without additional water, and stirring the reaction

mixture at the same temperature of the Suzuki step (50 °C) for 2 h. Under these conditions a higher yield was achieved (74%). The latter approach worked well also with ethyl cyanoacetate (Table 3, entries 7–11). Compounds **9g**–**k** were isolated in good yields together with unreacted aldehydes in several cases. Suzuki reaction was also carried out starting from 2-iodothiophene. In this case, $Pd(OAc)_2$ or SiO_2-Pd-**1** were employed in 0.2 mol-% at 50 °C, followed by sequential reaction with ethyl cyanoacetate or malononitrile to give compounds **9l**–**m** (Table 3, entries 12–13). The use of supported palladium catalyst SiO_2-Pd-**1** gave a comparable result with $Pd(OAc)_2$.

Finally, we checked the feasibility of the Heck/Baylis–Hillman sequential reaction. Our idea was to apply the reaction conditions previously developed by us for the Baylis–Hillman reaction (proline/$NaHCO_3$ in DMF/water)[18] to the reaction conditions for the Heck reaction catalyzed by SiO_2-Pd-**1**. Following this approach, we carried out the Heck reaction between 4-iodobenzaldehyde and methyl acrylate in DMF/water (9:1) in the presence of SiO_2-Pd-**1** in 0.1 mol-% loading, followed by addition of proline and methyl vinyl ketone. Results are reported in the Supporting Information section.

Conclusions

In conclusion we have demonstrated the feasibility of sequential Suzuki/asymmetric aldol and Suzuki/Knoevenagel reactions under aqueous conditions. In particular, we would like to stress the very interesting results observed when the organocatalytic asymmetric aldol reaction was coupled with the Suzuki reaction employing the proline catalyst **2** in low loading. The isolation of aldols in useful levels of stereoselectivities in the presence of a complex reaction mixture highlights the high catalytic performances of the simple organic catalyst **2**. An improvement of the latter methodology will consist in the development of the proper combination of Pd-catalyst/organocatalyst working in the same solvent. The good results obtained in the case of Suzuki/Knoevenagel sequential reaction further demonstrated the synthetic utility of this approach. Additional applications, such as a Heck/Baylis–Hillman sequence may be developed.

Experimental Section

General: Chemicals and solvents were purchased from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates (Merck 60 F_{254}) were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution $KMnO_4$. Flash chromatography was carried out using Macherey–Nagel silica gel (0.04–0.063 mm). Light petroleum refers to the fraction with the boiling range 40–60 °C. ^1H and ^{13}C NMR spectra were recorded with a Bruker 300 MHz spectrometer. FTIR spectra were registered with a Shimadzu FTIR 8300 infrared spectrophotometer. Melting points were determined by using a Kofler hot plate. Chiral HPLC analyses for *ee* determinations were performed using a Shimadzu LC-10AD apparatus equipped with a SPD-M10A UV detector and Daicel columns (AD-H, AS-H), using hexane/2-propanol as the eluent. Carbon and nitrogen contents were determined by combustion analysis with a Fisons EA 1108 elemental analyzer. All optical rotations were measured in dichloromethane at the same concentration (c = 1) with a Jasco P1010 polarimeter. The absolute configurations of the products were assigned by comparison with literature data. Configurations of new products were assigned by analogy. Compounds **4a**[19] and **9a**[20] have been already reported.

Typical Procedure for the Sequential Suzuki/Asymmetric Aldol Reaction: In a round-bottomed flask the aryl halide (1 mmol), 4-formylphenylboronic acid (164.8 mg, 1.1 mmol), ethanol (1.2 mL), water (1.2 mL), K_2CO_3 (165.8 mg, 1.2 mmol) and SiO_2-Pd-**1** (1 mg, 0.1 mol-% or 4 mg, 0.4 mol-%, see Table 2) were placed. The reaction mixture was stirred at 50 °C for the time indicated. After completion of the reaction, the reaction mixture was cooled to room temperature, then neutralized with conc. HCl (32%, 90 μL) and the solvents removed under reduced pressure. Then, water (0.7 mL), cyclopentanone (0.88 mL, 10 equiv.) and catalyst **2** (1 mol-%) were added to the residue and the mixture stirred at room temperature for the time indicated in Table 2. After this time the reaction mixture was extracted with dichloromethane. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was checked by ^1H NMR to calculate the conversion and *dr* and then purified by column chromatography.

4′-{(*R*)-Hydroxy[(*S*)-2-oxocyclopentyl]methyl}-1,1′-biphenyl-2-carbonitrile (4c): Oil. $[\alpha]_D^{26} = -58$ (c = 0.74, $CHCl_3$); yield 213 mg (73%). ^1H NMR $CDCl_3$: δ = (mixture of diastereoisomers) 1.50–2.56 (m, 7 H), 4.67 (s, 1 H, OH), 4.80 (d, J = 9.0 Hz, 1 H, *anti*), 5.38–5.40 (m, 1 H, *syn*), 7.42–7.70 (m, 7 H), 7.78 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8, 23.1, 27.5, 39.1, 39.5, 55.6, 56.5, 75.3, 111.6, 119.1, 123.9, 126.3, 127.3, 128.0, 129.2, 129.3, 130.4, 130.5, 133.3, 134.2, 137.5, 138.2, 142.4, 143.8, 145.5, 220.6, 223.4 ppm. IR (nujol): $\tilde{\nu}_{max}$ = 3455, 2222, 1722 cm^{-1}. $C_{19}H_{17}NO_2$ (291.13): calcd. C 78.33, H 5.88, N 4.81; found C 78.31, H 5.90, N 4.84.

4′-{(*R*)-Hydroxy[(*S*)-2-oxocyclopentyl]methyl}-1,1′-biphenyl-4-carbonitrile (4d): M.p. 109–112 °C. $[\alpha]_D^{27} = -106 \pm 1$; yield 122 mg (42%). ^1H NMR $CDCl_3$: δ = (mixture of diastereoisomers) 1.50–1.85 (m, 3 H), 2.00–2.05 (m, 1 H), 2.21–2.34 (m, 1 H), 2.42–2.52 (m, 2 H), 4.65 (s, 1 H, OH), 4.79 (d, J = 9.3 Hz, 1 H, *anti*), 5.35 (m, 1 H, *syn*), 7.46 (d, J = 8.4 Hz, 2 H), 7.58 (d, J = 8.4 Hz, 2 H), 7.66–7.76 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.5, 27.0, 38.7, 55.2, 74.8, 111.0, 118.9, 123.7, 127.3, 127.4, 128.7, 132.7, 138.8, 142.1, 145.3, 222.8 ppm. IR (nujol): $\tilde{\nu}_{max}$ = 3449, 2225, 1715 cm^{-1}. $C_{19}H_{17}NO_2$ (291.13): calcd. C 78.33, H 5.88, N 4.81; found C 78.35, H 5.91, N 4.79.

(*S*)-2-{(*R*)-Hydroxy[4′-methoxy-1,1′-biphenyl-4-yl]methyl}cyclopentanone (4e): M.p. 130–133 °C. $[\alpha]_D^{31} = -70 \pm 1$; yield 179 mg (61%). ^1H NMR $CDCl_3$: δ = (mixture of diastereoisomers) 1.50–2.53 (m, 7 H), 3.85 (s, 3 H), 4.58 (s, 1 H, OH), 4.76 (d, J = 9.0 Hz, 1 H, *anti*), 5.33–5.35 (m, 1 H, *syn*), 6.99 (d, J = 9.0 Hz, 2 H), 7.39 (d, J = 9.0 Hz, 2 H), 7.55 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3, 27.0, 38.7, 55.2, 74.9, 114.1, 126.0, 126.6, 126.9, 128.0, 133.2, 139.8, 140.4, 159.1, 223.0 ppm. IR (nujol): $\tilde{\nu}_{max}$ = 3500, 1717 cm^{-1}. $C_{19}H_{20}O_3$ (294.14): calcd. C 77.00, H 6.80; found C 77.05, H 6.86.

(*S*)-2-{(*R*)-Hydroxy[4′-nitro-1,1′-biphenyl-4-yl]methyl}cyclopentanone (4f): M.p. 110–113 °C. $[\alpha]_D^{25} = -108 \pm 1$; yield 268 mg (86%). ^1H NMR $CDCl_3$: δ = (mixture of diastereoisomers) 1.5–1.9 (m, 3 H), 1.95–2.06 (m, 1 H), 2.21–2.34 (m, 1 H), 2.42–2.52 (m, 2 H), 4.66 (s, 1 H, OH), 4.80 (d, J = 9.0 Hz, 1 H, *anti*), 5.36 (s, 1 H, *syn*),

7.48 (d, *J* = 8.1 Hz, 2 H), 7.61 (d, *J* = 8.1 Hz, 2 H), 7.73 (d, *J* = 9.0 Hz, 2 H), 8.29 (d, *J* = 9.0 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8, 27.4, 39.1, 55.6, 75.2, 124.5, 127.8, 127.9, 128.0, 128.1, 138.7, 142.8, 147.5, 147.6, 223.3 ppm. IR (nujol): $\tilde{\nu}_{max}$ = 3450, 1712 cm^{-1}. $C_{18}H_{17}NO_4$ (311.12): calcd. C 69.44, H 5.50, N 4.50; found C 69.39, H 5.48, N 4.53.

(*S*)-2-{(*R*)-Hydroxy[4′-methyl-1,1′-biphenyl-4-yl]methyl}cyclopentanone (4b): M.p. 85–88 °C. $[\alpha]_D^{31}$ = –103 ± 2; yield 121 mg (43%). ^{1}H NMR $CDCl_3$: δ = (mixture of diastereoisomers) 1.50–2.60 (m, 7 H), 2.44 (s, 3 H), 4.60 (s, 1 H, OH), 4.77 (d, *J* = 9.0 Hz, 1 H, *anti*), 5.35 (s, 1 H, *syn*), 7.26 (d, *J* = 8.1 Hz, 2 H), 7.40 (d, *J* = 8.1 Hz, 2 H), 7.50 (d, *J* = 8.1 Hz, 2 H), 7.58 (d, *J* = 8.1 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8, 21.5, 27.4, 39.2, 55.7, 75.4, 127.3, 127.4, 129.9, 137.5, 138.3, 140.6, 141.2, 223.5 ppm. IR (nujol): $\tilde{\nu}_{max}$ = 3480, 1717 cm^{-1}. $C_{19}H_{20}O_2$ (280.15): calcd. C 81.40, H 7.19; found C 81.46, H 7.22.

(*E*)-Methyl 3-(4-{(*R*)-Hydroxy[(*S*)-2-oxocyclopentyl]methyl}phenyl)-acrylate (6): M.p. 83–86 °C. $[\alpha]_D^{27}$ = –113 ± 1; yield 192 mg (70%). ^{1}H NMR $CDCl_3$: δ = (mixture of diastereoisomers) 1.45–1.55 (m, 1 H), 1.65–1.78 (m, 2 H), 1.90–2.02 (m, 1 H), 2.16–2.30 (m, 1 H), 2.36–2.47 (m, 2 H), 3.79 (s, 3 H), 4.61 (s, 1 H, OH), 4.73 (d, *J* = 9.0 Hz, 1 H, *anti*), 5.28 (s, 1 H, *syn*), 6.42 (d, *J* = 15.9 Hz, 1 H), 7.35 (d, *J* = 8.1 Hz, 2 H), 7.49 (d, *J* = 8.1 Hz, 2 H), 7.67 (d, *J* = 15.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4, 26.9, 38.7, 51.7, 55.2, 74.8, 117.9, 127.1, 128.2, 134.1, 143.8, 144.4, 167.4, 222.6 ppm. IR (nujol): $\tilde{\nu}_{max}$ = 3450, 1715, 1705 cm^{-1}. $C_{16}H_{18}O_4$ (274.12): calcd. C 70.06, H 6.61; found C 70.10, H 6.66.

Typical Procedure for the Sequential Suzuki/Knoevenagel Reaction: In a round-bottomed flask the aryl halide (1 mmol), the arylboronic acid (1.1 mmol), ethanol (1.2 mL), water (1.2 mL), K_2CO_3 (165.8 mg, 1.2 mmol) and SiO_2-Pd-**1** (2 mg, 0.2 mol-%) were placed. The reaction mixture was stirred at 50 °C for 6 h (R = NO_2, OCH_3) or 23 h (R = H). After completion of the reaction two procedures were followed: *a*) the reaction mixture was cooled to room temperature, then water (3 mL) and malononitrile (1.1 mmol) were added and the mixture was stirred for further 23 h or *b*) ethyl cyanoacetate (1.1 mmol) was added and the reaction mixture was stirred for further 2 h at 50 °C. After this time the reaction mixture was extracted with dichloromethane. The organic phase was dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (petroleum ether/ethyl acetate, 5:1). Compound **9d** was prepared following the Suzuki procedure reported in the literature.[15] After completion of the reaction, water (3 mL) and malononitrile (1.1 mmol) were added and the mixture stirred for 23 h. Work-up and purification were carried out as described above.

2-{[4′-Nitro-1,1′-biphenyl-4-yl]methylene}malononitrile (9b): M.p. 200–203 °C; yield 242 mg (88%). ^{1}H NMR ($CDCl_3$): δ = 7.79–7.84 (m, 5 H, ArH + CH), 8.06 (d, *J* = 8.5 Hz, 2 H), 8.37 (d, *J* = 9.0 Hz, 2 H) ppm. ^{13}C NMR (75 MHz), ($CDCl_3$): δ = 84.0, 112.9, 113.9, 124.8, 128.5, 128.9, 131.5, 131.8, 144.9, 145.5, 148.4, 159.1 ppm. IR (nujol): $\tilde{\nu}_{max}$ = 2224, 1583 cm^{-1}. $C_{16}H_9N_3O_2$ (275.07): calcd. C 69.81, H 3.30, N 15.27; found C 69.92, H 3.38, N 15.21.

2-{[4′-Methoxy-1,1′-biphenyl-4-yl]methylene}malononitrile (9c): M.p. 155–156 °C; yield 242 mg (93%). ^{1}H NMR $(CD_3)_2CO$: δ = 3.86 (s, 3 H), 7.07 (d, *J* = 9.0 Hz, 2 H), 7.75 (d, *J* = 9.0 Hz, 2 H), 7.87 (d, *J* = 9.0 Hz, 2 H), 8.08 (d, *J* = 9.0 Hz, 2 H), 8.26 (s, 1 H) ppm. ^{13}C NMR [75 MHz, $(CD_3)_2CO$]: δ = 56.2, 81.9, 114.6, 115.5, 115.9, 128.2, 129.7, 131.1, 132.3, 132.8, 147.5, 161.2, 162.0 ppm. IR (nujol): $\tilde{\nu}_{max}$ = 2224, 1571 cm^{-1}. $C_{17}H_{12}N_2O$ (260.09): calcd. C 78.44, H 4.65, N 10.76; found C 78.48, H 4.68, N 10.80.

2-{[4′-(Diphenylamino)-1,1′-biphenyl-4-yl]methylene}malononitrile (9d): M.p. 53–55 °C; yield 258 mg (65%). ^{1}H NMR ($CDCl_3$): δ = 7.10–7.19 (m, 8 H), 7.30–7.36 (m, 4 H), 7.55 (d, *J* = 8.7 Hz, 2 H), 7.73–7.76 (m, 2 H, overlapped with 7.76 s, 1 H), 7.98 (d, *J* = 8.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz), ($CDCl_3$): δ = 81.3, 113.5, 114.6, 123.0, 124.2, 125.5, 127.5, 128.4, 129.6, 129.8, 129.9, 131.9, 132.0, 147.2, 147.5, 149.4, 159.6 ppm. IR (nujol): $\tilde{\nu}_{max}$ = 2225, 1576 cm^{-1}. $C_{28}H_{19}N_3$ (397.16): calcd. C 84.61, H 4.82, N 10.57; found C 84.66, H 4.78, N 10.62.

2-{[4′-Methyl-1,1′-biphenyl-4-yl]methylene}malononitrile (9e): M.p. 168–170 °C; yield 149 mg (61%). ^{1}H NMR ($CDCl_3$): δ = 2.44 (s, 3 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 7.57 (d, *J* = 8.4 Hz, 2 H), 7.75 (d, *J* = 8.4 Hz, 2 H), 7.77 (s, 1 H), 7.98 (d, *J* = 8.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz), ($CDCl_3$): δ = 21.7, 82.0, 113.3, 114.4, 127.5, 128.1, 129.9, 130.3, 131.9, 136.3, 140.0, 147.7, 159.7 ppm. IR (nujol): $\tilde{\nu}_{max}$ = 2226, 1583 cm^{-1}. $C_{17}H_{12}N_2$ (244.29): calcd. C 83.58, H 4.95, N 11.47; found C 83.65, H 5.03, N 11.51.

2-{[3′-Methoxy-1,1′-biphenyl-4-yl]methylene}malononitrile (9f): M.p. 124–126 °C; yield 192 mg (74%). ^{1}H NMR ($CDCl_3$): δ = 3.89 (s, 3 H), 7.00 (d, *J* = 8.1 Hz, 1 H), 7.16 (s, 1 H), 7.23 (d, *J* = 8.1 Hz, 1 H), 7.42 (dd, *J* = 8.1 and 8.1 Hz, 1 H), 7.74 (d, *J* = 8.1 Hz, 2 H), 7.77 (s, 1 H), 7.97 (d, *J* = 8.1 Hz, 2 H) ppm. ^{13}C NMR (75 MHz), ($CDCl_3$): δ = 55.8, 82.3, 113.3, 113.5, 114.4, 114.7, 120.1, 128.5, 130.3, 130.7, 131.8, 140.7, 147.5, 159.7, 160.6 ppm. IR (nujol): $\tilde{\nu}_{max}$ = 2228, 1579 cm^{-1}. $C_{17}H_{12}N_2O$ (260.09): calcd. C 78.44, H 4.65, N 10.76; found C 78.50, H 4.61, N 10.70.

(*E*)-Ethyl 2-Cyano-3-(4′-nitro-1,1′-biphenyl-4-yl)acrylate (9g): M.p. 181–183 °C; yield 210 mg (65%). ^{1}H NMR ($CDCl_3$): δ = 1.42 (t, *J* = 7.2 Hz, 3 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 7.74–7.82 (m, 4 H), 8.12 (d, *J* = 8.1 Hz, 2 H), 8.29–8.35 (m, 3 H) ppm. ^{13}C NMR (75 MHz), ($CDCl_3$): δ = 14.6, 21.6, 63.3, 104.2, 115.8, 124.7, 128.5, 128.6, 132.2, 143.5, 146.1, 148.1, 154.2, 162.7 ppm. IR (nujol): $\tilde{\nu}_{max}$ = 2226, 1729, 1593 cm^{-1}. $C_{18}H_{14}N_2O_4$ (322.31): calcd. C 67.07, H 4.38, N 8.69; found C 67.14, H 4.43, N 8.71.

(*E*)-Ethyl 2-Cyano-3-(4′-methoxy-1,1′-biphenyl-4-yl)acrylate (9h): M.p. 104–106 °C; yield 246 mg (80%). ^{1}H NMR ($CDCl_3$): δ = 1.40 (t, *J* = 7.2 Hz, 3 H), 3.86 (s, 3 H), 4.38 (q, *J* = 7.2 Hz, 2 H), 7.00 (d, *J* = 8.7 Hz, 2 H), 7.58 (d, *J* = 8.7 Hz, 2 H), 7.67 (d, *J* = 8.4 Hz, 2 H), 8.03 (d, *J* = 8.4 Hz, 2 H), 8.23 (s, 1 H) ppm. ^{13}C NMR (75 MHz), ($CDCl_3$): δ = 14.6, 55.8, 63.0, 102.1, 114.9, 116.3, 127.4, 128.7, 130.1, 132.0, 132.2, 145.9, 154.9, 160.2, 163.1 ppm. IR (nujol): $\tilde{\nu}_{max}$ = 2225, 1720, 1590 cm^{-1}. $C_{19}H_{17}NO_3$ (307.12): calcd. C 74.25, H 5.58, N 4.56; found C 74.30, H 5.60, N 4.51.

(*E*)-Ethyl 2-Cyano-3-[4′-(diphenylamino)-1,1′-biphenyl-4-yl]acrylate (9i): M.p. 154–156 °C; yield 360 mg (81%). ^{1}H NMR ($CDCl_3$): δ = 1.43 (t, *J* = 7.2 Hz, 3 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 7.06–7.18 (m, 8 H), 7.28–7.34 (m, 4 H), 7.54 (d, *J* = 9.0 Hz, 2 H), 7.71 (d, *J* = 8.4 Hz, 2 H), 8.07 (d, *J* = 8.4 Hz, 2 H), 8.27 (s, 1 H) ppm. ^{13}C NMR (75 MHz), ($CDCl_3$): δ = 14.6, 62.7, 101.5, 116.0, 123.0, 123.7, 125.1, 128.0, 129.5, 132.0, 145.6, 147.2, 148.8, 154.6, 162.7 ppm. IR (nujol): $\tilde{\nu}_{max}$ = 2225, 1726, 1589 cm^{-1}. $C_{30}H_{24}N_2O_2$ (444.52): calcd. C 81.06, H 5.44, N 6.30; found C 81.14, H 5.51, N 6.25.

(*E*)-Ethyl 2-Cyano-3-(4′-methyl-1,1′-biphenyl-4-yl)acrylate (9j): M.p. 134–136 °C; yield 186 mg (64%). ^{1}H NMR ($CDCl_3$): δ = 1.41 (t, *J* = 7.2 Hz, 3 H), 2.41 (s, 3 H), 4.38 (q, *J* = 7.2 Hz, 2 H), 7.27 (d, *J* = 8.1 Hz, 2 H), 7.53 (d, *J* = 8.1 Hz, 2 H), 7.68 (d, *J* = 8.4 Hz, 2 H), 8.04 (d, *J* = 8.4 Hz, 2 H), 8.23 (s, 1 H) ppm. ^{13}C NMR (75 MHz), ($CDCl_3$): δ = 14.6, 21.6, 63.1, 102.4, 116.2, 127.4, 127.8, 130.2, 130.4, 132.2, 136.7, 139.1, 146.2, 154.8, 163.0 ppm. IR (nujol): $\tilde{\nu}_{max}$ = 2225, 1714, 1596 cm^{-1}. $C_{19}H_{17}NO_2$ (291.34): calcd. C 78.33, H 5.88, N 4.81; found C 78.23, H 5.86, N 4.71.

(*E*)-Ethyl 2-Cyano-3-(3′-methoxy-1,1′-biphenyl-4-yl)acrylate (9k): M.p. 92–94 °C; yield 144 mg (47%). ^{1}H NMR ($CDCl_3$): δ = 1.30 (t, J = 7.2 Hz, 3 H), 3.77 (s, 3 H), 4.28 (q, J = 7.2 Hz, 2 H), 6.85 (d, J = 8.4 Hz, 1 H), 7.05 (s, 1 H), 7.11 (d, J = 8.4 Hz, 1 H), 7.29 (dd, J = 8.4 and 8.4 Hz, 1 H), 7.60 (d, J = 8.1 Hz, 2 H), 7.95 (d, J = 8.1 Hz, 2 H), 8.15 (s, 1 H) ppm. ^{13}C NMR (75 MHz), ($CDCl_3$): δ = 14.6, 55.8, 63.1, 102.8, 113.3, 114.3, 116.1, 120.1, 128.2, 130.5, 130.9, 132.1, 141.2, 146.2, 154.8, 160.5, 163.0 ppm. IR (nujol): $\tilde{\nu}_{max}$ = 2221, 1723, 1596 cm^{-1}. $C_{19}H_{17}NO_3$ (307.12): calcd. C 74.25, H 5.58, N 4.56; found C 74.33, H 5.63, N 4.60.

(*E*)-Ethyl 2-Cyano-3-[4-(thiophen-2-yl)phenyl]acrylate (9l): M.p. 155–156 °C; yield 247 mg (87%). ^{1}H NMR ($CDCl_3$): δ = 1.41 (t, J = 7.1 Hz, 3 H), 4.39 (q, J = 7.1 Hz, 2 H), 7.14 (dd, J = 5.1 and 3.7 Hz, 1 H), 7.40 (dd, J = 5.1 and 1.1 Hz, 1 H), 7.47 (dd, J = 3.7 and 1.1 Hz, 1 H), 7.74 (d, J = 8.3 Hz, 2 H), 8.01 (d, J = 8.3 Hz, 2 H), 8.22 (s, 1 H) ppm. ^{13}C NMR (75 MHz), ($CDCl_3$): δ = 14.2, 62.7, 102.0, 115.8, 125.1, 126.1, 127.0, 128.5, 130.2, 131.9, 139.0, 142.6, 154.0, 162.6 ppm. IR (nujol): $\tilde{\nu}_{max}$ = 2212, 1721, 1596 cm^{-1}. $C_{16}H_{13}NO_2S$ (283.34): calcd. C 67.82, H 4.62, N 4.94; found C 67.88, H 4.63, N 4.90.

2-[4-(Thiophen-2-yl)benzylidene]malononitrile (9m): M.p. 169–170 °C; yield 177 mg (75%). ^{1}H NMR ($CDCl_3$): δ = 7.16 (dd, J = 5.0 and 3.7 Hz, 1 H), 7.45 (dd, J = 5.0 and 1.0 Hz, 1 H), 7.51 (dd, J = 3.7 and 1.0 Hz, 1 H), 7.71 (s, 1 H), 7.74 (d, J = 8.4 Hz, 2 H), 7.92 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz), ($CDCl_3$): δ = 81.4, 112.9, 114.0, 125.7, 126.2, 127.8, 128.8, 129.6, 131.6, 140.3, 142.1, 158.7 ppm. IR (nujol): $\tilde{\nu}_{max}$ = 2223, 1605, 1576 cm^{-1}. $C_{14}H_8N_2S$ (236.29): calcd. C 71.16, H 3.41, N 11.86; found C 71.22, H 3.43, N 11.80.

Supporting Information (see footnote on the first page of this article): HPLC data for aldol products, IR, ^{1}H- and ^{13}C-NMR spectra of compounds **4a**–**f**, **6**, **9a**–**m**, and example of sequential Heck/Baylis–Hillman reactions are reported.

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