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Highly Selective Palladium-Catalyzed Direct C–H α-Monoarylation of Carbonyl Compounds using Water Containing the Surfactant Polyoxyethylene-α-Tocopheryl Sebacate (PTS) as a Solvent

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Abstract: Highly selective direct C–H α-monoarylation reactions of 4-chromanones, ketones and 2-phenylacetaldehyde with aryl halides have been performed in satisfactory yields by using a tris(dibenzylideneacetone)dipalladium(0)/tri-*tert*-butylphosphine tetrafluoroborate catalyst system, potassium bicarbonate as the base and a solvent consisting of pure water containing a small amount of polyoxyethylene-α-tocopheryl sebacate (PTS). Analogous reaction conditions have been employed in a tandem process leading to phenyl-substituted isocoumarins from carbonyl compounds and methyl 2-bromobenzoate.

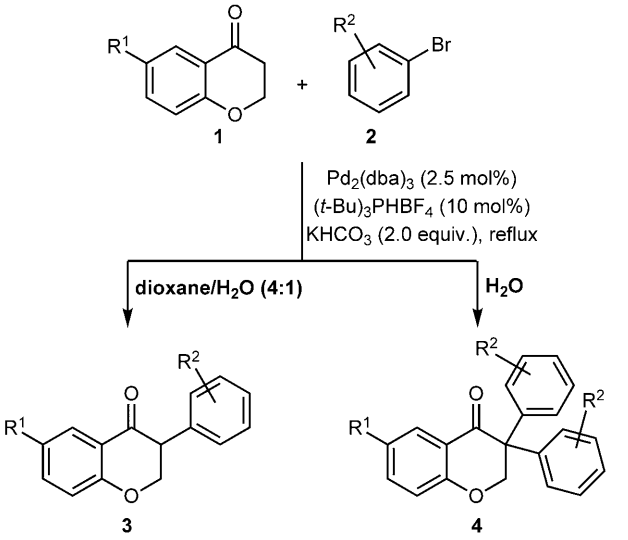
Keywords: C–C coupling; direct arylation; isocoumarins; ketones; palladium; water chemistry

Introduction

A general and effective strategy that emerged over the last three decades to connect inter- and intramolecularly aryl units to sp^3-hybridized C–H bonds in the α-position of carbonyl groups involves the transition metal-catalyzed direct coupling of aryl halides or pseudohalides with enolates obtained *in situ* from the corresponding carbonyl derivatives under basic conditions.[1]

However, the strong basic conditions often required by this process are unsuitable for the direct α-arylation of base-labile substrates, such as aldehydes, which can give aldol condensation by-products, or 4-chromanones, which undergo ring-opening to phenolate anions.[2]

In the context of our studies on palladium-catalyzed selective direct C–H arylation reactions,[3] we recently described the first examples of palladium-catalyzed direct α-arylation reactions[4] of 4-chromanones **1** with aryl bromides **2** (Scheme 1).[5] In particular, we developed procedures involving the use of a $Pd_2(dba)_3/(t\text{-}Bu)_3PHBF_4$ catalyst system and $KHCO_3$ as the base that enabled the selective synthesis of isoflavanones **3** and 3,3-diaryl-4-chromanones **4** in satisfactory yields. Interestingly, the relative amount of compounds **3** versus **4** was found to be dependent on the amount of water into the reaction medium and the **1**:**2** molar ratio. In fact, isoflavanones **3**, which represent an important class of bioactive natural products,[6] were obtained when a 4:1 mixture of diox-



Scheme 1. Pd-catalyzed direct α-arylation of 4-chromanones **1** in dioxane/H_2O or in H_2O.

ane and water was employed as a solvent and the **1**:**2** molar ratio was 2. On the contrary, the use of water as a reaction medium and a large molar excess of **2** led to the formation of compounds **4** as the only reaction products.[5]

Intrigued by the role played by water, we then decided to evaluate the influence of a variety of ionic and non-ionic organic surfactants on the efficiency and selectivity of the α-arylation of **1** with aryl halides **2** in water.[7] On the other hand, it is well known that organic surfactants are able to self-aggregate into aqueous micelles able to accomodate hydrophobic substrates and catalysts, leading to the acceleration of organic reactions performed in water.[8]

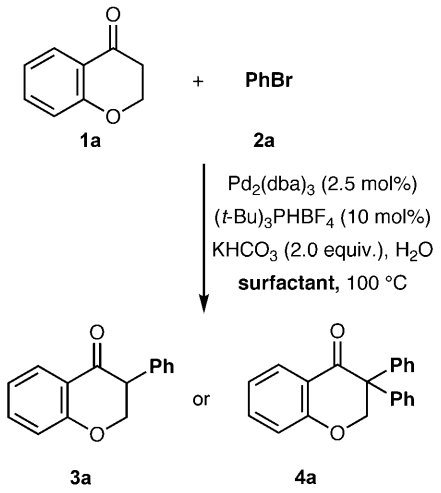
In this update we describe a protocol for the direct Pd-catalyzed α-monoarylation of 4-chromanones **1** with aryl bromides **2** or chlorobenzene **5a**, involving the use of a reaction medium consisting of pure water containing a small amount of an amphiphile, which allowed us to improve the synthesis of isoflavanones **3** in terms of chemical yields and selectivity compared with our previously described procedure.[5] Efficient direct α-monoarylation reactions of ketones bearing a C–H bond in the α-position and 2-phenylacetaldehyde by using reaction conditions similar to those employed for the improved synthesis of compounds **3** are also reported. Finally, a tandem process based on the use of this new α-monoarylation protocol, which allowed us to prepare phenyl-substituted isocoumarins is mentioned.

Results and Discussion

We began our study by examining the outcome of the $Pd_2(dba)_3$/(*t*-Bu)$_3$PHBF$_4$-catalyzed α-arylation of 4-chromanone (**1a**) with bromobenzene (**2a**) at 100 °C in the presence of 2 equivalents of of $KHCO_3$ using pure water containing a surfactant as a solvent (Scheme 2).

The commercially available surfactants selected for this reaction were the non-ionic amphiphiles polyoxyethylene-α-tocopheryl sebacate (PTS) and polyoxyethylene-sorbitan monooleate (Tween 80), the cationic amphiphile cetyl trimethylammonium bromide (CTAB), and the anionic amphiphile sodium dodecyl sulfate (SDS) (Figure 1).

We had previously observed that an increase of the water/dioxane ratio resulted in an increase of the **4a**:**3a** molar ratio in the crude reaction mixtures and that 3,3-diarylated chromanone **4a** was exclusively formed when pure water was used as a solvent.[5] However, we found that the addition of a small amount of an ionic or non-ionic surfactant to water invariably drove the coupling reaction towards the formation of racemic isoflavanone **3a** with selectivity higher than 95% (entries 1–4, Table 1).



Scheme 2. Direct α-arylation of **1a** with **2a** in H_2O containing a surfactant.

Interestingly, the selectivity of the reaction proved to be unrelated to the non-ionic or ionic nature of the surfactant, but its efficiency was deeply influenced by the chemical structure of this additive. Remarkably, a high yield of **3a** was obtained when the reaction was carried out in the presence of 5 wt% PTS in water using a 2:1 molar ratio between **1a** and **2a** (entry 4, Table 1) and **3a** was isolated in the highest yield when water containing 15 wt% PTS was used as a solvent (entry 7, Table 1). On the other hand, **3a** was isolated in lower yields when the molar excess of **1a** was decreased while doubling the reaction time (compare entries 5 and 6 with entry 4, Table 1).[9] A lower yield of **3a** was also obtained when the reaction temperature was lowered to 60 °C (compare entries 7 and 8, Table 1).

Good results were also obtained either by using CTAB or SDS as the surfactant agent, but the chemical yields resulted to be lower than those obtained using PTS (entries 1 and 2, Table 1). On the other hand, the low yield of **3a** obtained by using Tween 80 (entry 3, Table 1) might be ascribed at least in part to protodehalogenation of **2a**.[10]

On the basis of these results, we next examined the outcome of the reaction of 4-chromanones **1a–c** with aryl bromides **2a–e** and chlorobenzene **(5a)** under the optimized reaction conditions of entry 7 of Table 1. As shown in entries 1–7 of Table 2, non-activated, deactivated and activated aryl bromides **2**, including *ortho*- and *para*-substituted derivatives, were used, and the required isoflavanones **3** were obtained after 2–4 h at 100 °C in satisfactory chemical yields and with selectivities higher than 95%. Interestingly, bromide **2d** containing an acidic unprotected OH group also gave the required isoflavanone **3d** in a satisfactory yield (entry 4, Table 2).

It should also be noted that the use of the water/PTS solvent system allowed the synthesis of com-

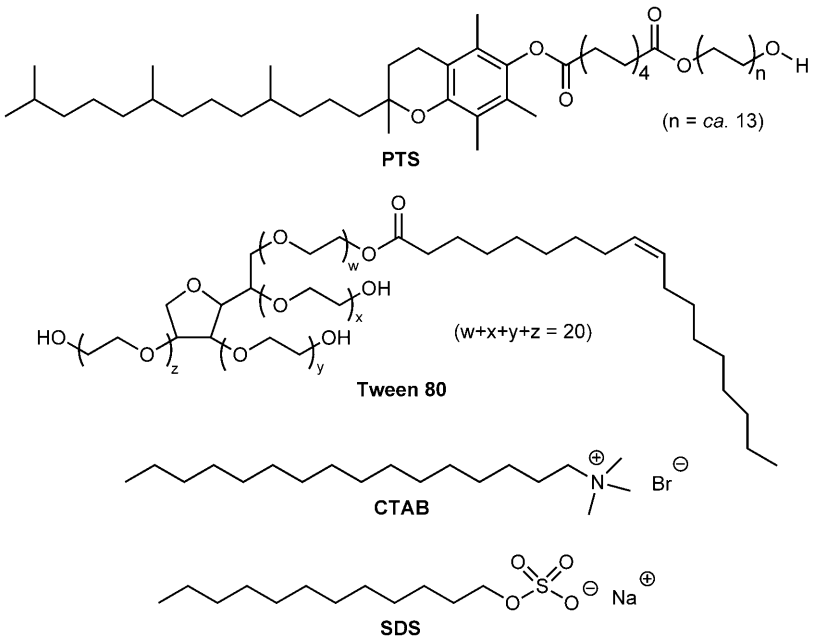


Figure 1. Chemical structures of PTS, Tween-80, CTAB and SDS.

Table 1. Effect of the surfactant on the direct α-arylation of **1a** with **2a** in H_2O.

Entry[a]	**1a**:**2a** ratio	$KHCO_3$ [equiv.]	Surfactant [wt%]	Reaction time [h][b]	Yield [%] of **3a**[c]
1	2:1	2.0	CTAB (5)	4	67
2	2:1	2.0	SDS (5)	2.5	61
3	2:1	2.0	Tween 80 (5)	3.5	20
4	2:1	2.0	PTS (5)	2	70
5	1.2:1	1.2	PTS (5)	2	56
6	1.2.1	1.2	PTS (5)	4	59
7	2:1	2.0	PTS (15)	2	83
8[d]	2:1	2.0	PTS (15)	7	67

[a] Unless otherwise stated, the reactions were performed at 100 °C (oil bath) by treatment of **2a** (1.0 mmol) with **1a** (1.2 or 2.0 mmol) in the presence of 2.5 mol% $Pd_2(dba)_3$, 10 mol% $(t\text{-Bu})_3PHBF_4$ in water (5 mL).
[b] The reactions were stopped when the amount of **2a** in the reaction mixture was less than 5% (GLC).
[c] Isolated yield.
[d] The reaction was performed at 60 °C (oil bath).

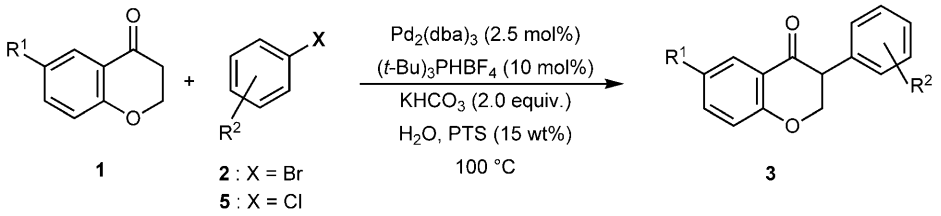
pounds **3** in higher yields than those previously obtained by using a mixture of dioxane and water as the reaction solvent[5] (see entries 1–6 of Table 2). Moreover, this protocol proved suitable for the synthesis of **3a** from **1a** and chlorobenzene (**5a**), although a reaction time (24 h) longer than that employed in the synthesis involving bromide **2a** was necessary to complete the reaction (entry 8, Table 2) and the yield was significantly lower than that obtained in entry 1 of Table 2.

Encouraged by the results obtained in the direct α-arylation of the base-labile 4-chromanone moiety, we subsequently tested the $Pd_2(dba)_3/(t\text{-Bu})_3PHBF_4/KHCO_3$/PTS/$H_2O$ system for the direct α-arylation of carbonyl derivatives different from **1** that included an aldehyde and some ketones bearing a C–H bond in the α-position.

The results reported in Table 3 concerning α-arylation reactions of ketones **6** with aryl bromides deserve some comments. The reaction of acetophenone (**6a)** with PhBr (**2a**) (entry 1, Table 3), unexpectedly gave a mixture of benzyl phenyl ketone (**7a**) and the α,α-diarylated derivative **8a** in which the latter compound was the main component. However, the use of *ortho*-substituted bromides **2e–g** resulted in the selective formation of the required α-monoarylated ketones **7b–d** (entries 2–4, Table 3).[11] Selective monoarylation reactions were found also to occur when two typical α-substituted ketones, 1- and 2-tetralone (**6b**, **6c**), were used (entries 5 and 6, Table 3).

The α-arylation protocol involving the use of the $Pd_2(dba)_3/(t\text{-Bu})_3PH/KHCO_3$/PTS/$H_2O$ system was next tested for the α-monoarylation of aldehydes, a class of challenging substrates that can give rise to

Table 2. Pd-catalyzed α-arylation of 4-chromanones **1** with aryl halides **2** or **5a** in PTS/H_2O.

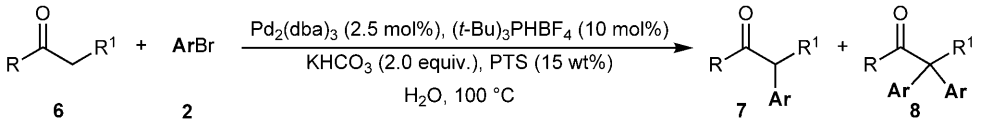


1 2 : X = Br 5 : X = Cl 3

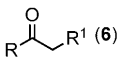
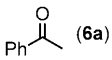
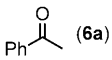
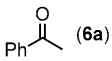
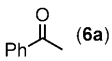
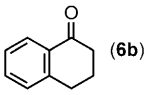
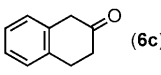
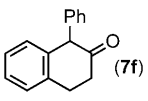
Entry[a]	Reagents				Reaction time [h][b]	Product[c]	
	1	R^1	**2**, **5**	R^2		**3**	Yield [%][d]
1	**1a**	H	**2a**	H	2	**3a**	83 (71)
2	**1a**	H	**2b**	4-OMe	4	**3b**	79 (55)
3	**1a**	H	**2c**	4-CF_3	2	**3c**	67 (40)
4	**1a**	H	**2d**	4-OH	4	**3d**	66 (44)
5	**1b**	Cl	**2a**	H	3	**3e**	65 (58)
6	**1c**	Me	**2a**	H	3	**3f**	86 (81)
7	**1a**	H	**2e**	2-Me	3	**3g**	68
8	**1a**	H	**5a**	H	24	**3a**	47

[a] All reactions were performed at 100 °C (oil bath) with **1** (2.0 mmol) and **2** or **5a** (1.0 mmol) in the presence of 2.5 mol% $Pd_2(dba)_3$, 10 mol% $(t\text{-Bu})_3PHBF_4$, 2.0 equiv. of $KHCO_3$ in water (5 mL) containing 15 wt% PTS.
[b] The reactions were stopped when the amount of **2** or **5a** in the reaction mixture was less than 5% (GLC).
[c] The amount of 3,3-diaryl-4-chromanone **4** in the crude reaction mixture was less than 5% (GLC).
[d] Isolated yields. The yields reported in parenthesis were obtained by using a 4:1 mixture of dioxane and H_2O as a solvent.[5]

Table 3. Pd-catalyzed α-arylation of ketones **6** with aryl halides **2** in PTS/H_2O.

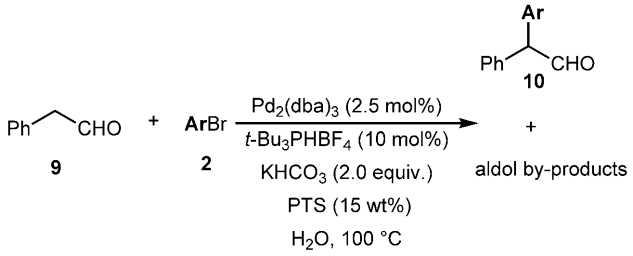


6 2 7 8

Entry[a]	Reagents		Reaction time [h][b]	**7**:**8**	Product	
		ArBr (**2**)		GLC ratio	**7**, **8**	Yield [%][c]
1	 (**6a**)	C_6H_5Br (**2a**)	2	38:62	**7a**, **8a**	19, 40
2	 (**6a**)	2-MeC_6H_4Br (**2e**)	2	90:10	**7b**	46
3	 (**6a**)	2-bromobiphenyl (**2f**)	2	98:2	**7c**	43
4	 (**6a**)	2-$MeOC_6H_4Br$ (**2g**)	2	90:10	**7d**	68
5	 (**6b**)	C_6H_5Br (**2a**)	4	100:0	**7e**	74
6	 (**6c**)	C_6H_5Br (**2a**)	24	100:0	 (**7f**)	54

[a] All reactions were performed at 100 °C (oil bath) with 1 mmol ArBr **2**, 2.0 mmol of ketone **6** in the presence of 2.5 mol% $Pd_2(dba)_3$, 10 mol% $(t\text{-Bu})_3PHBF_4$, 2.0 equiv. of $KHCO_3$ in water (5 mL) containing 15 wt% PTS.
[b] The reactions were stopped when the amount of **2** in the reaction mixture was less than 5% (GLC).
[c] Isolated yields.

Table 4. Pd-catalyzed α-arylation of 2-phenylacetaldehyde **9** with aryl bromides **2** in PTS/H_2O.



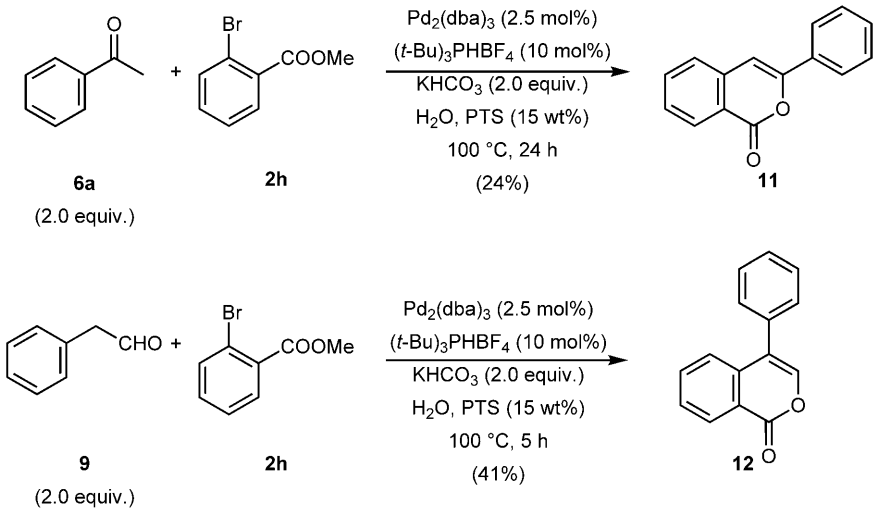
Entry[a]	ArBr (**2**)	**10**:aldol by-products (GLC ratio)	Product **10**	Yield [%][b]
1[c]	C_6H_5Br (**2a**)	60:40	**10a**	48
2	C_6H_5Br (**2a**)	83:17	**10a**	51
3	4-$MeOC_6H_4Br$ (**2g**)	80:20	**10b**	42
4	2-MeC_6H_4Br (**2e**)	87:13	**10c**	59
5	4-$F_3CC_6H_4$ (**2c**)	53:47	**10d**	24

[a] Unless otherwise stated, the reactions were performed at 100 °C (oil bath) for 2 h with 1 mmol ArBr **2** and 1.2 mmol **9** in the presence of 2.5 mol% $Pd_2(dba)_3$, 10 mol% $(t\text{-Bu})_3PHBF_4$, 2.0 equiv. of $KHCO_3$ in water (5 mL) containing 15 wt% PTS.
[b] Isolated yields.
[c] The reaction was performed by using 2.0 mmol **9**.

aldol-type products under the basic conditions usually employed for Pd-catalyzed α-arylation reactions.[12] We found that the reaction of 2-phenylacetaldehyde (**9**) with 2 equivalents of **2a** gave 2,2-diphenylacetaldehyde (**10a**) in 48% yield (entry 1, Table 4).

On the other hand, GLC and GC-MS analyses showed the presence of significant amounts of by-products derived from aldol-type reactions in the crude reaction mixture. Nevertheless, we found that the amount of these undesired by-products could be decreased by reducing the molar excess of aldehyde from 2.0 to 1.2 equiv. and **10a** could be isolated in 51% yield (entry 2, Table 4). The reaction conditions used in this entry were then employed for the synthesis of compounds **10b**, **10c** and **10d** in 42, 59 and 24% yield, respectively (entries 3–5, Table 4). It should be noted that, in order to avoid the slow oxidative cleavage of aldehydes **10** in open air,[13] the work-up of the crude reaction mixtures of these syntheses was performed under a nitrogen atmosphere.

Finally, we found that when 0.5 equivalents of methyl 2-bromobenzoate (**2h**) were used for the arylation of acetophenone (**6a**) or 2-phenylacetaldehyde (**9**), isocoumarins **11** and **12**, derived from a base-



Scheme 3. Pd-catalyzed synthesis of isocoumarins **11** and **12**.

mediated α-arylation–spontaneous lactonization sequence, were obtained in 24 and 41% yield, respectively (Scheme 3).[14]

Conclusions

In summary, we have demonstrated that the use of water containing a small amount of PTS as the reaction solvent and $KHCO_3$ as the base allows for direct highly selective $Pd_2(dba)_3$/(t-Bu)$_3$PHBF$_4$-catalyzed α-monoarylation reactions of carbonyl derivatives, including base-labile 4-chromanones, ketones and aldehydes bearing a C–H bond in the α-position, with aryl halides. Due to the use of a very mild base this method represents an important alternative to other established procedures for the direct α-monoarylation of carbonyl derivatives that, requiring strong bases such as KHMDS,[4b,d] t-BuOK,[4p] or MeONa,[4d,m] suffer a reduced chemoselectivity. This protocol, which provides better results in terms of selectivity and yields than those obtained by using our previously reported procedure for the α-arylation of 4-chromanones,[5] may be a useful tool for the synthesis of relevant synthetic targets.

Experimental Section

General Procedure for the Pd-Catalyzed α-Monoarylation of 4-Chromanones 1, Ketones 6 or 2-Phenylacetaldehyde (9) with Aryl Bromides 2 or Chlorobenzene (5a)

$Pd_2(dba)_3$ (22.9 mg, 0.025 mmol), (t-Bu)$_3$PHBF$_4$ (29.0 mg, 0.1 mmol), and $KHCO_3$ (200 mg, 2.0 mmol) were placed in a reaction vessel containing a magnetic stir bar under an argon atmosphere. The reaction vessel was fitted with a silicon septum, evacuated and back-filled with argon, and this sequence was repeated thrice. A deaerated solution of 15 wt% PTS in H_2O (5 mL), a 4-chromanone **1** (2.0 mmol), a ketone **6** (2.0 mmol) or 2-phenylacetaldehyde (**9**) (1.2 mmol), and an aryl halide **2** (1.0 mmol) or **5a** (1.0 mmol) were then sequentially added under argon. The reaction vessel was placed in an oil bath heated to 100 °C and after a few minutes at this temperature the color of the reaction mixture changed from dark brown to pale green. The mixture was then maintained at 100 °C for the period of time reported in Table 2, Table 3 and Table 4 and periodically monitored by GLC, GLC-MS and TLC analyses of its samples extracted with AcOEt. It was then allowed to cool to room temperature and diluted with AcOEt (25 mL). The reaction mixtures derived from reactions involving 4-chromanones **1** or ketones **6** were filtered over silica gel, concentrated under reduced pressure, and the resulting residues were purified by flash chromatography on silica gel. This procedure was employed to prepare isoflavanones **3a–g** and ketones **7a–f**. On the other hand, the crude reaction mixtures of the couplings involving 2-phenylacetaldehyde (**9**) were filtered over silica gel and quickly concentrated under reduced pressure in a nitrogen atmosphere. The resulting residues were purified by flash chromatography on silica gel. This procedure was employed to prepare aldehydes **10a–d**.

3-Phenylisocoumarin (11): $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol), (t-Bu)$_3$PHBF$_4$ (29.0 mg, 0.1 mmol), and $KHCO_3$ (200 mg, 2.0 mmol) were placed in a reaction vessel containing a magnetic stir bar under an argon atmopshere. The reaction vessel was fitted with a silicon septum, evacuated and back-filled with argon, and this sequence was repeated thrice. A deaerated solution of 15 wt% PTS in H_2O (5 mL), acetophenone **6a** (0.234 mL, 240 mg, 2.0 mmol) and methyl 2-bromobenzoate **2h** (0.140 mL, 215 mg, 1.0 mmol) were sequentially added by syringe and the resulting mixture was stirred at 100 °C under argon for 24 h. The reaction mixture was then allowed to cool to room temperature and diluted with AcOEt (25 mL), filtered over silica gel and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using a mixture of petroleum ether (bp 40–60 °C) and AcOEt (85/15 v/v) as eluant to give **11** as a colorless solid; yield: 52.4 mg (24%); mp 84–87 °C (lit.[15] 88–89 °C); EI-MS: m/z (%) = 223 (17) [M^++1], 222 (100) [M^+], 194 (75), 165 (63), 105 (19), 89 (22); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26 (m, 1H), 7.85 (m, 2H), 7.42 (m, 6H), 6.89 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 162.2, 153.4, 137.4, 134.8, 131.8, 129.9, 129.8 (2C), 128.8, 128.1, 126.0, 125.1 (2C), 120.4, 101.8. GLC analysis showed that **11** was 98% chemically pure. The spectral properties of this compound were in agreement with those previously reported.[15]

4-Phenyl-isocoumarin (12): $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol), (t-Bu)$_3$PHBF$_4$ (29.0 mg, 0.1 mmol), and $KHCO_3$ (200 mg, 2.0 mmol) were placed in a reaction vessel containing a magnetic stir bar under a stream of argon. The reaction vessel was fitted with a silicon septum, evacuated and back-filled with argon, and this sequence was repeated thrice. A deaerated solution of 15 wt% PTS in H_2O (5 mL) was added by syringe, and to the resulting dark brown mixture 2-phenylacetaldehyde **9** (0.234 mL, 240 mg, 2.0 mmol) and methyl 2-bromobenzoate **2h** (0.140 mL, 215 mg, 1.0 mmol) were added by syringe, and the resulting mixture was stirred at 100 °C under argon for 5 h. The reaction mixture was then allowed to cool to room temperature and diluted with AcOEt (25 mL), filtered over silica gel and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using toluene as eluant to give **12** as a colorless solid; yield: 91.2 mg (41%); mp 94–96 °C (lit[16] 94–95 °C); EI-MS: m/z (%) = 223 (12) [M^++1], 222 (73) [M^+], 194 (79), 165 (100), 139 (10), 82 (13); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.36 (m, 1H), 7.52 (m, 8H), 7.20 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 161.9, 142.1, 136.6, 134.6, 132.9, 129.9, 129.7 (2C), 128.8 (2C), 128.5, 128.4, 124.54, 121.2, 120.5; GLC analysis showed that **12** was chemically pure; anal. calcd. for $C_{15}H_{10}O_2$ (222.24): C 81.07, H 4.54; found C 80.96, H 4.57.

Supporting Information

General information and compound characterization data for compounds **3a–g**, **7a–f**, **8a**, and **10a–d** are available as Supporting Information.

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