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Synthesis of a Polar Phosphinoferrocene Amidosulfonate Ligand and Its Application in Pd-Catalyzed Cross-Coupling Reactions of Aromatic Boronic Acids and Acyl Chlorides in an Aqueous Medium

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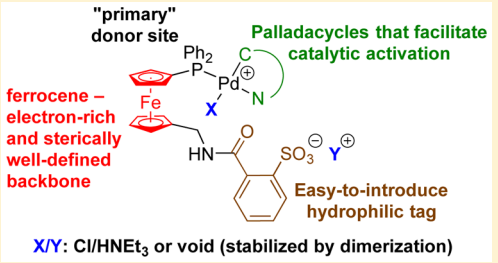
Supporting Information

ABSTRACT: The reaction of [1′-(diphenylphosphino)ferrocenyl]-methylamine (**1**), generated in situ from its hydrochloride and triethylamine, with 2-sulfobenzoic anhydride afforded an anionic phosphino-amide, which was isolated as a triethylammonium salt, $Ph_2PfcCH_2NHCOC_6H_4SO_3$-$(HNEt_3)$ (**2**; fc = ferrocene-1,1′-diyl). A similar reaction of **1** with phthalic anhydride only furnished the salt $(Ph_2PfcCH_2NH_3)[C_6H_4CO_2H(CO_2)]$. When it was reacted with $[PdCl_2(MeCN)_2]$ and $[L^{NC}Pd(\mu\text{-Cl})]_2$ (L^{NC} = 2-[(dimethylamino-κN)methyl]phenyl-κC^1), compound **2** gave rise to the bis-phosphine complex $[PdCl_2(\mathbf{2}\text{-}\kappa P)_2]$ and the bridge-cleavage product $[L^{NC}PdCl(\mathbf{2}\text{-}\kappa P)]$, respectively. An analogue of the latter complex containing 2′-amino-[1,1′-biphenyl]-2-yl-κ^2N,C^2 as the auxiliary chelating ligand, compound **8**, was prepared in a similar manner from **2** and the respective Pd precursor. Finally, the reaction of **2** with $[L^{NC}Pd(acac)]$ proceeded with the replacement of the acetylacetonate ligand (acac), affording a dipalladium complex featuring two phosphinosulfonate anions as the O,P-bridges, $[L^{NC}Pd(\mu(P,O)\text{-}Ph_2PfcCH_2NHCOC_6H_4SO_3)]_2$, which was structurally characterized by single-crystal X-ray diffraction analysis. All of these Pd(II) complexes, especially compound **8**, formed active catalysts for Pd-mediated cross-coupling of aromatic boronic acids with benzoyl chlorides to produce substituted benzophenones in toluene (benzene)−water biphasic mixtures. This particular coupling reaction was employed during the preparation of 4′-chloro-4-hydroxybenzophenone, which was in turn converted to fenofibrate, a generic drug widely used to reduce cholesterol levels in blood.



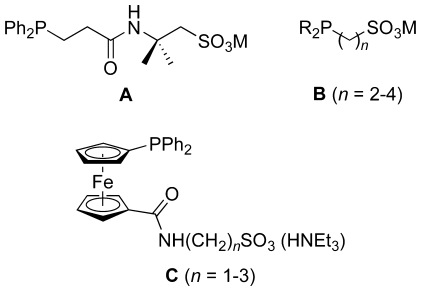
INTRODUCTION

The introduction of sulfonate groups represents one of the most efficient tools for converting conventional phosphine donors into water-soluble species.[1] Sulfonated phosphines (including the archetypal and widely utilized TPPTS[2]) are typically prepared by direct sulfonation and, hence, bear their sulfonate substituents directly on the organic backbone. In contrast, donors whose sulfonate moiety comes from a sulfonated synthon *and* is separated from the phosphine part of the molecule by spacer groups remain rather scarce, even though the use of stable sulfonate building blocks can make ligand synthesis easier and further allows for various structural variations. Examples of ligands resulting from the latter approach include phosphinocarboxylic amide[3] **A** (Chart 1), obtained through the addition of diphenylphosphine or $LiPPh_2$ across the terminal double bond in 2-acrylamido-2-methyl-1-propanesulfonic acid or its salt,[4,5] and sulfonated phosphines **B**, resulting from the alkylation of secondary phosphines and phosphides with $X(CH_2)_nSO_3Na$ (X = halogen)[6] or, similarly, from propane and butane sultones.[7]

We have recently utilized the modular synthetic approach outlined above to prepare a series of phosphinoferrocene amidosulfonates (**C** in Chart 1)[8] by amide coupling between 1′-(diphenylphosphino)ferrocene-1-carboxylic acid (Hdpf)[9] (or its active ester) and ω-aminosulfonic acids.[10] Compounds **C** not only were highly water-soluble, a feature uncommon among phosphinoferrocene donors,[11] but also gave rise to active catalysts for the Pd-catalyzed cyanation of aryl bromides with $K_4[Fe(CN)_6]$.

To expand the family of polar phosphinoferrocene amidosulfonate donors, we have decided to formally invert our synthetic approach and utilize amidation reactions of the recently synthesized [1′-(diphenylphosphino)ferrocenyl]-methylamine (**1**).[12] Already in 1979, Whitesides et al.[13] reported that sulfonated amidophosphine donors can be easily

Chart 1. Examples of Phosphinosulfonate Donors[a]



[a]M is typically H^+ or an alkylammonium or alkali-metal cation.

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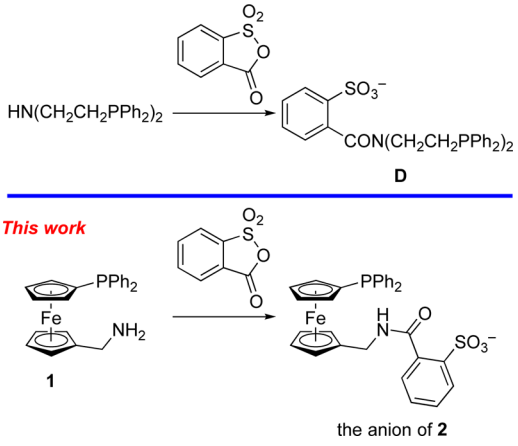
obtained through the reactions of phosphinoamines with 2-sulfobenzoic anhydride (see compound **D** in Chart 2). However, this approach has found *very* little use in the preparation of polar phosphine donors.[14]

Chart 2. Synthesis of Sulfonated Phosphinoamides from Phosphinoamines and 2-Sulfobenzoic Anhydride

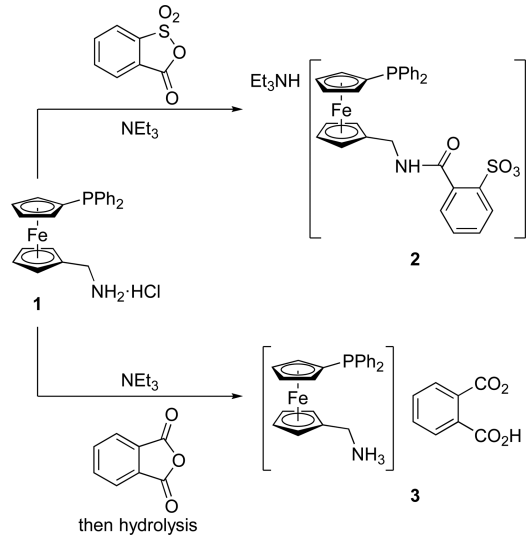


In this contribution, we describe the synthesis of the new phosphinoferrocene amidosulfonate **2** from amine **1** (Chart 2), the results of coordination studies with this donor and various Pd(II) precursors, and the application of the resulting complexes in the Pd-mediated Suzuki−Miyaura-type coupling of arylboronic acids with aromatic acyl chlorides to produce benzophenones.

RESULTS AND DISCUSSION

Synthesis of the Ligands. The reaction of 2-sulfobenzoic anhydride with **1**·HCl in the presence of excess triethylamine, which liberates free **1** from the hydrochloride and also acts as the source of the counterion for the product, led to the anticipated anionic phosphinoferrocene amidosulfonate **2** (Scheme 1). In contrast, an analogous reaction with phthalic anhydride only afforded the salt **3**, which consisted of the cation

Scheme 1. Synthesis of Compounds 2 and 3



$[\mathbf{1H}]^+$ and a hydrogen phthalate anion that resulted from hydrolysis during the workup and chromatography.

The target amide **2** is stable in air but hygroscopic, which somewhat complicates its manipulation. In its NMR spectra, **2** gives rise to characteristic signals due to the phosphinoferrocene unit, its appended polar pendant, and the triethylammonium cation. The ^{31}P NMR resonance observed at δ_P −15.8 indicates the presence of an intact phosphine substituent, whereas the formation of an amide linkage is indicated by the amide bands at 1652 and 1552 cm^{-1} in the IR spectrum and the ^{13}C NMR signal of the amide C═O at δ_C 168.66.

The salt **3** was isolated as a slowly crystallizing, rusty orange oil. Its NMR spectra contain signals for $[\mathbf{1H}]^+$ and the hydrogen phthalate anion, whose NMR signature (e.g., only one C═O resonance in the ^{13}C NMR spectrum at δ_C 173.21) suggests rapid proton exchange (in solution).

Repeated crystallization experiments yielded crystals suitable for X-ray diffraction analysis only for **3**. The molecular structure of this compound is depicted in Figure 1. The ferrocene

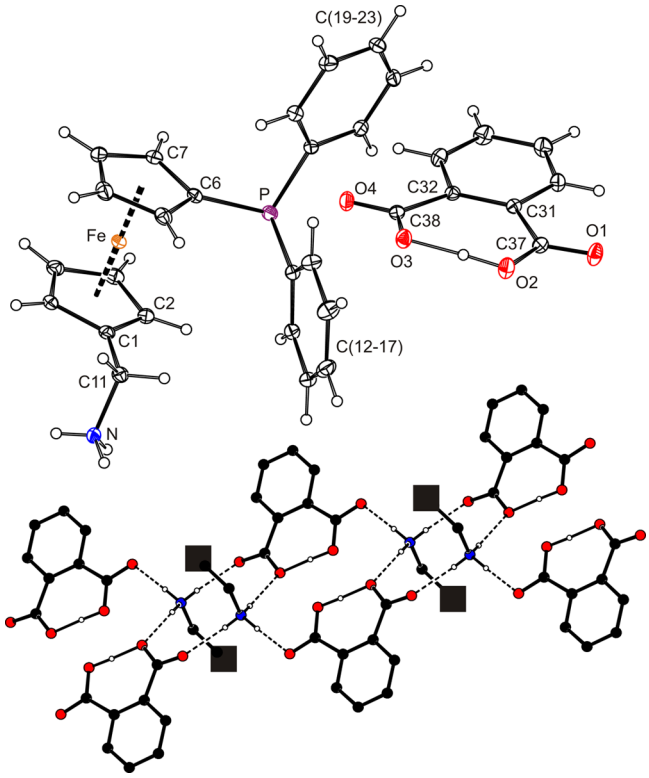


Figure 1. (top) PLATON plot of the molecular structure of **3** showing 30% probability ellipsoids. (bottom) Section of the hydrogen-bonded array in the structure of **3**. For clarity, only the NH and OH hydrogens are shown and the bulky phosphinoferrocenyl moieties are replaced with black squares.

cyclopentadienyls in the cation $[\mathbf{1H}]^+$ are tilted by as little as 1.00(8)°, which in turn corresponds to negligible variation in the Fe−C bond lengths (2.037(1)−2.053(2) Å). As indicated by the torsion angle C1−Cg1−Cg2−C6, in which Cg1 and Cg2 are the centroids of the cyclopentadienyl rings C(1−5) and C(6−10), respectively, of 81.2(1)°, the ferrocene unit in **3** is nearly synclinal eclipsed.[15] The attached CH_2NH_3 arm is directed away from the Fe center so that the C11−N1 bond and the axis of the ferrocene units (Cg1···Cg2) subtend an angle of 21.20(5)°.

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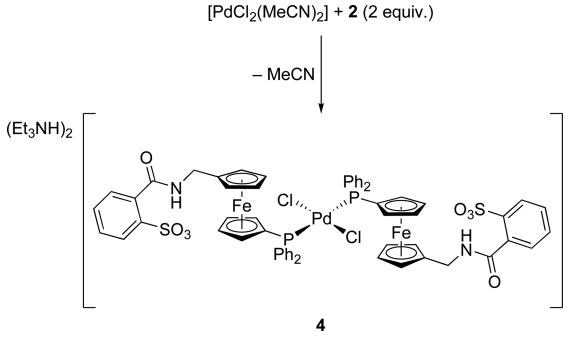
The entire hydrogen phthalate anion in the structure of **3** is planar (within 0.17 Å for the 12 non-hydrogen atoms) and shows alternation of the C−O bond lengths in both carboxyl moieties (ca. 1.23 and 1.29 Å). The distance of the oxygen atoms forming the asymmetric hydrogen bridge, O2 and O3, is 2.400(2) Å. In the solid state, the anion acts as a hydrogen bond acceptor for three different cations, which in turn results in the formation of infinite ribbons oriented along the crystallographic *a* axis (N···O = 2.763(2)−2.859(2) Å; see Figure 1).

Coordination Study. Aiming at its utilization in Pd-catalyzed cross-coupling reactions (see below), we first studied compound **2** as a ligand for the Pd(II) ion bearing various supporting ligands. In an initial experiment, 2 equiv of ligand **2** was reacted with $[PdCl_2(MeCN)_2]$ to afford bis-phosphine complex **4** (Scheme 2). The coordination of the phosphine

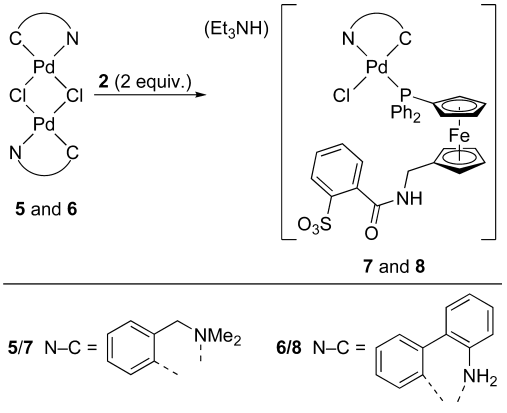
Scheme 2. Synthesis of Bis-Phosphine Complex 4



groups was in this case manifested through a shift of the ^{31}P NMR resonance to a lower field (coordination shift, Δ_P = 32.1 ppm) and by the appearance of virtual triplets for the phosphorus-coupled ^{13}C resonances that arise from virtual coupling in the $^{12}C-^{31}P-Pd-^{31}P-^{13}C$ AA′X spin systems.[16]

Reactions between **2** and dipalladium complexes with ortho-metalated amine ligands **5** and **6** (Scheme 3) provided the

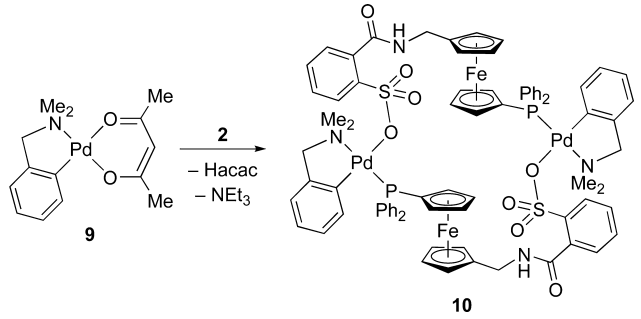
Scheme 3. Synthesis of Pd(II) Complexes with Auxiliary N,C Ligands



respective products of the cleavage of the chloride bridges, compounds **7** and **8**, in practically quantitative yields. The amidosulfonate ligand in these complexes coordinates as a simple P donor (cf. the coordination shifts Δ_P = 48.9 and 46.1 for **7** and **8**, respectively), and correspondingly, the bands due to NH stretching vibrations and amide moieties in their IR spectra are observed at positions similar to those of uncoordinated **2** (and also **4**). The NMR spectra of **7** and **8** combine the signals due to the ferrocene ligand with those of the auxiliary N,C-donors. In their ESI+ mass spectra, these complexes give rise to peaks attributable to species resulting from elimination of chloride ligand and from a simultaneous loss of chloride and NEt_3. The spectra recorded in the negative ion mode display peaks of the ligand's anion ($[\mathbf{2} - HNEt_3]^-$) at *m*/*z* 582. In the case of **7**, there is also observed a signal due to the entire complex anion (i.e., $[\mathbf{7} - HNEt_3]^-$), while for **8**, the spectrum reveals a fragment ion at *m*/*z* 688 attributable to $[Pd^0(\mathbf{2} - HNEt_3)]^-$. The presence of the latter species formally resulting via reductive elimination of the N,C-ligand is in agreement with an easy catalytic activation (Pd(II) → Pd(0)) of palladacycles containing 2′-amino-[1,1′-biphenyl]-2-yl as a C,N-chelating donor.[17]

Notably, the reactions of **2** with analogous Pd(II) precursors containing anionic ligands with a leaving ability better than that of chloride proceeded differently. The addition of **2** to complex **9** (Scheme 4) resulted in replacement of the chelating

Scheme 4. Synthesis of Dipalladium Complex 10



acetylacetonate (acac) ligand (formally an elimination of acetylacetone and NEt_3) and dimerization through P,O-bridging coordination of the phosphinoferrocene amidosulfonate anion. The steric properties of the amidosulfonate donor, e.g., the spatial distribution of the donor moieties included in the coordination and the large size of the potential chelate ring, presumably caused the neutral dipalladium complex **10** with O,P-chelating phosphino-sulfonate anions to form rather than a monopalladium chelate. Similar reactions of **2** with an analogue of **8** possessing an aminobiphenyl N,C-ligand and methanesulfonate groups in place of the chloride bridges (i.e., with $[(C_6H_4NH_2\text{-}C_6H_4\text{-}\kappa^2C,N)Pd(CH_3SO_3)]_2$) and also with $[(C_6H_4NH_2\text{-}C_6H_4\text{-}\kappa^2C,N)Pd(acac)]$ followed a similar course and led to an identical product. Unfortunately, this compound proved to be essentially insoluble in common organic solvents and could not be crystallized. Although this points to a dimeric or even polymeric nature of the formed product, reliable structural information could not be obtained, and the compound was not studied further.

The IR spectrum of dipalladium complex **10** shows one composite band in the region of NH stretching vibrations (ν_{max} ~3330 cm^{-1}) and characteristic amide vibrations at positions similar to those of the free ligand. The ^{31}P NMR signal of **10** is observed as a broad singlet at δ_P 33.8 (Δ_P = 49.6 ppm). Signal broadening is observed also in the ^1H and ^{13}C NMR spectra, presumably due to limited molecular mobility.

Recrystallization from methanol−diethyl ether afforded crystals of the mixed solvate **10**·2MeOH·Et_2O that were used

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for a structural determination. A simplified view of the molecular structure of the complex is presented in Figure 2, and the pertinent structural parameters are given in Table 1 (for a complete structural diagram, see the Supporting Information).

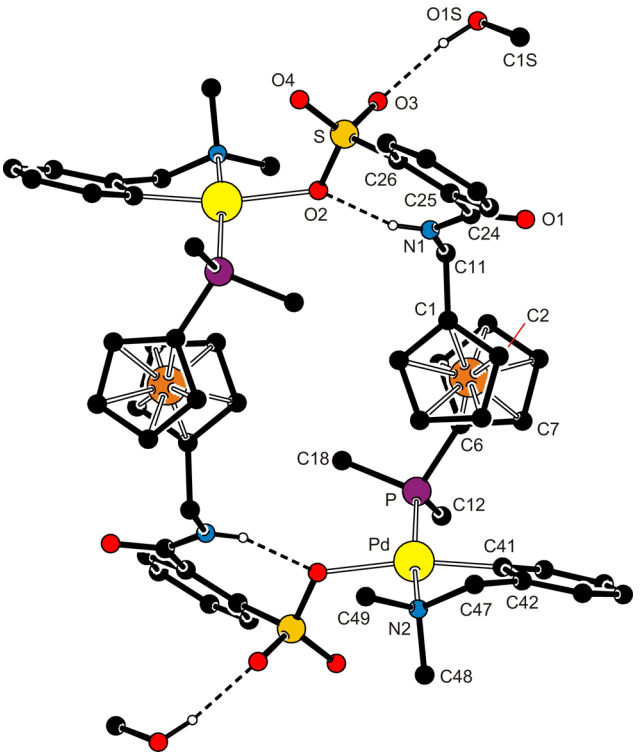


Figure 2. View of the complex molecule in the structure of **10**·2MeOH·Et_2O and its H-bond interactions with solvating methanol. For clarity, only the pivotal atoms from the phosphine phenyl groups and the NH/OH hydrogens are shown.

Table 1. Selected Geometric Data for 10·2MeOH·Et_2O (in Å and deg)[a]

Pd–P	2.2584(4)	P–Pd–O2^i	94.44(3)
Pd–O2^i	2.161(1)	P–Pd–C41	94.00(5)
Pd–N2	2.159(2)	N2–Pd–O2^i	91.18(5)
Pd–C41	1.974(2)	N2–Pd–C41	82.16(6)
C11–N1	1.462(2)	C1–C11–N1	111.0(1)
C24–N1	1.321(2)	C11–N1–C24	123.2(2)
C24–O1	1.239(2)	N1–C24–O1	121.6(2)
C26–S	1.785(2)	C25–C26–S	124.1(1)
S–O2	1.494(1)	O2–S–O3	110.56(7)
S–O3	1.448(1)	O2–S–O4	111.43(7)
S–O4	1.440(1)	O3–S–O4	115.20(7)
Fe–C[b]	2.035(2)–2.053(2)	tilt[c]	1.0(1)

[a]Symmetry operation: (i) $1-z, 2-y, 1-z$. [b]Range of Fe–C(1–10) bonds. [c]Dihedral angle of the least-squares cyclopentadienyl planes.

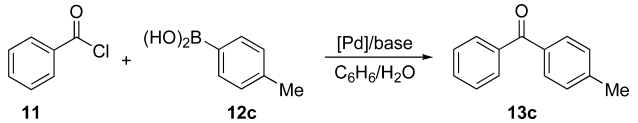
Complex **10** crystallizes as a centrosymmetric dimer comprising two equivalent Pd(II) centers bridged by the amidosulfonate anion coordinated through its phosphine moiety and sulfonate oxygen O2. The Pd atom is further coordinated by a chelating [2-(dimethylamino-κN)methyl]-phenyl-κC^1 ligand, which forms a relatively small chelate ring and thus results in distortion of the coordination sphere (cf. the interligand angles in Table 1). The twisting of the coordination sphere around the Pd(II) ion can be demonstrated by the angle of 15.93(8)° subtended by the coordination half-planes {Pd, P, O2} and {Pd, N2, C41}.

As indicated by the C1–Cg1–Cg2–C6 torsion angle of −144.6(1)°, the ferrocene unit in the amidosulfonate ligand adopts an opened anticlinal eclipsed conformation. Its polar pendant is thus directed opposite the phosphine unit, presumably to avoid spatial contact within the dimeric structure. The amide plane {C24, N1, O1} is rotated with respect to its parent benzene ring C(25–30) by as much as 31.34(6)°, but the substituents assuming ortho positions on the latter ring bind without any significant torsion (S–C26–C27–C28 = −177.9(2)°). The molecular conformation of **10** in the solid state is stabilized by intramolecular N–H···O_3S hydrogen bonds (N1···O2 = 2.756(2) Å), and the charged sulfonate groups further form hydrogen bridges toward the solvating methanol (O1S···O3 = 2.850(2) Å). Another notable feature in the structure of **10** can be found among the S–O distances, which decrease from O4 to O2, reflecting the involvement of O2 and O3 in the coordination and the type of H-bond interactions, respectively.

Catalytic Evaluation. The catalytic properties of the newly prepared polar donor **2** were assessed in the Pd-catalyzed cross-coupling reaction of arylboronic acids with benzoyl chlorides to produce substituted benzophenones. This variant[18] of the widely applied Suzuki–Miyaura reaction[19] offers an efficient alternative route to specifically substituted benzophenones, which are valuable building blocks for the synthesis of fine chemicals.[20] Given the nature of the starting materials (viz. boronic acid and acyl chloride), the reaction can be advantageously performed in aqueous reaction media, which we recently demonstrated for palladium complexes with other polar phosphinoferrocene donors.[21]

In view of the rather complicated coordination behavior of the amidosulfonate ligand **2**, however, only defined (and fully characterized) complexes were employed in the catalytic evaluation. As a model testing reaction, we chose the coupling of benzoyl chloride (**11**) with 4-methylphenylboronic acid (**12c**) to give 4-methylbenzophenone (**13c**; Scheme 5), which

Scheme 5. Coupling Reaction Used for the Screening Experiments



11 **12c** **13c**

allows for easy monitoring by ^{1}H NMR spectroscopy. All reactions were performed with a slight excess of the acyl chloride (1.2 equiv) with respect to the boronic acid to ensure complete consumption of the latter material even if some of the acyl chloride becomes hydrolyzed. Any unreacted acyl chloride or carboxylate salt formed by its hydrolysis are easily removed during the aqueous workup (extraction) and chromatography and do not therefore contaminate the desired reaction product.

Inspection of the results summarized in Table 2 indicates a generally very good catalytic performance of complexes containing compound **2** or its anion as the ligands. At a palladium loading of 0.2 mol %, the yields of the coupling product **13c** attained at 50 °C within 1 h were 80% or higher in a benzene–water mixture with Na_2CO_3 as the base. The best yield of 90% was achieved with complex **8** (note: when just 1

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Table 2. Catalytic Evaluation of the Pd(II) Complexes with the Amidosulfonate Ligand[a]

entry	catalyst	loading (mol %)	yield of **13c** (%)
1	**4**	0.2	82
2	**7**	0.2	80
3	**8**	0.2	90 (81)[b]
4	**10**	0.2	88
5	**3**/**6**[c]	0.2	17
6	$FcPPh_2$/**6**[c]	0.2	10
7	$[PdCl_2(MeCN)_2]$	0.2	34
8	**5**	0.2	11
9	**6**	0.2	41
10	none		0
11	**8**	0.2	<5[d]
12	**8**	0.2	18[e]
13	**8**	0.1	88[f]
14	**8**	0.1	87[f,g]

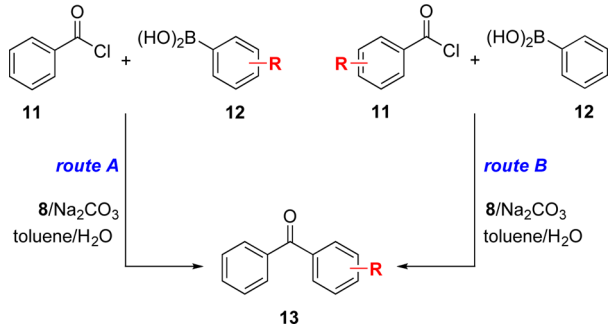
[a]Conditions unless specified otherwise: boronic acid **12c** (1.25 mmol), benzoyl chloride (1.5 mmol), sodium carbonate (1.5 mmol), and the catalyst were reacted under argon in a benzene−water mixture (3 mL each) at 50 °C for 1 h. The yield was determined by ^{1}H NMR spectroscopy after extraction of the reaction mixture and addition of anisole. An average of two independent runs is given. [b]Reaction with 1.25 mmol (1 equiv) of benzoyl chloride. [c]The catalyst was generated in the reaction vessel by mixing the phosphine with the Pd source in dichloromethane or dichloromethane/methanol. The mixture was stirred for 5 min and then evaporated. [d]Reaction in pure water. [e]Reaction in benzene. [f]Reaction on a double scale. [g]Reaction performed in commercial reagent-grade solvent and without an inert atmosphere.

equiv of **11** was used, the yield of **13c** decreased to 81%). In contrast, a catalyst formally analogous to **8**, generated in situ from **7** and the hydrogen phthalate salt **3**, performed markedly worse (entry 5), and an even poorer result was obtained with a similar catalyst resulting from (diphenylphosphino)ferrocene ($FcPPh_2$; entry 6). Even so, the yields achieved with palladium precursors **5**, **6**, and $[PdCl_2(MeCN)_2]$ without any additional ligand were considerably lower than those with the corresponding catalysts comprising **2** as a supporting donor (entries 7−9; the most pronounced difference was observed for the pair of **5** and **7**) and, finally, no coupling product was detected in the reaction mixture when the coupling was performed in the absence of a palladium salt (entry 10).

Furthermore, the reactions performed with the most active catalyst **8** in pure solvents, especially water, afforded markedly lower yields in comparison to those in the benzene−water mixture (cf. entries 3, 11, and 12 in Table 2), which can be explained by an insufficient solubility of some of the reaction partners (*e.g.*, the inorganic base in C_6H_6 and the organic components in water). When the amount of **8** was lowered to only 0.1 mol %, the model coupling reaction still proceeded with nearly a 90% NMR yield, which did not decrease significantly when the reaction was performed in air and with unpurified commercial solvents (entries 13 and 14). Finally, when $NaHCO_3$ was employed as the base (instead of Na_2CO_3), the reaction with the otherwise highly active catalyst **8** provided only traces (<5%) of the coupling product **13c** (result not tabulated).

In view of our recent results[21] showing that the reaction outcome can change significantly upon transposing the substituents between the reaction partners, benzoyl chloride and boronic acid, further reaction tests were focused on a comparison of complementary reactions that lead to the same monosubstituted benzophenones (Scheme 6). All of these

Scheme 6. Reaction Scope Tests[a]



[a]For conditions and results, see Table 3.

experiments were performed using only 0.1 mol % of complex **8** as the catalyst and Na_2CO_3 as the base. The reactions were carried out in toluene−water at 50 °C for 1 h, and the products were isolated by column chromatography.

The results presented in Table 3 corroborate our previous findings, revealing often significant differences in the yields

Table 3. Reactions with Various Substrates[a]

			yield (%)	
entry	R	product	route A	route B
1	2-Me	**13a**	80	22
2	3-Me	**13b**	72	0
3	4-Me	**13c**	86	34
4	4-MeO	**13d**	81	0
5	4-F	**13e**	95	96
6	4-Cl	**13f**	75	99
7	4-Br	**13g**	17	8[b]
8	4-CF_3	**13h**	52	98
9	4-CN	**13i**	<5	17
10	4-NO_2	**13j**	<5	73

[a]Conditions: boronic acid (2.0 mmol), benzoyl chloride (3.0 mmol), sodium carbonate (2.5 mmol), and catalyst **8** (0.1 mol %) were reacted under argon in a toluene−water mixture (3 mL each) at 50 °C for 1 h. Isolated yields are given as the average of two independent runs. [b]4-(4-Bromophenyl)benzophenone (**14**) was also isolated (ca. 5−10%).

achieved through the complementary routes. For instance, the synthesis of methyl-substituted benzophenones **13a−c** is better performed with substituted boronic acids and benzoyl chloride (route A) than in the inverted manner. The difference is particularly pronounced in the case of 3-methylbenzophenone (**13b**), for which route B failed entirely. Conversely, route B appears more appropriate for the preparation of benzophenones bearing electron-withdrawing substituents (4-F, 4-Cl, 4-CF_3, and 4-NO_2).

The effects of the substituents can partially explain these observations. Electron-donating substituents at the benzene ring of benzoyl chloride increase the electron density at the carbonyl group and thus facilitate the attack of water (or OH^- anion) during the hydrolysis, which can be expected as an unwanted parallel reaction that consumes one of the reagents and, consequently, diminishes the reaction yield. Nonetheless, the reaction course is further affected by solubility phenomena, which mainly affect the preparation of **13i,j** in the present case

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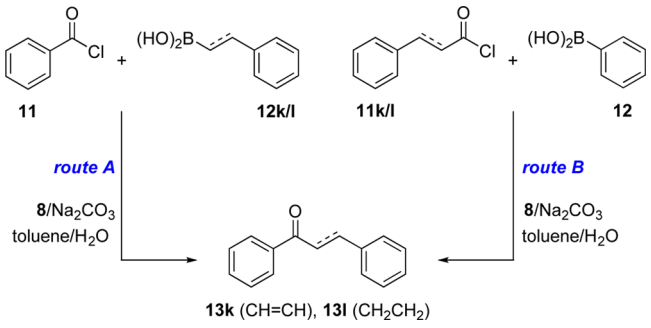
because 4-nitro- and 4-cyanophenylboronic acids are poorly soluble in the reaction mixture, which in turn strongly disfavors route A.

It is also noteworthy that, whereas the reactions with substrates possessing less reactive C–halogen bonds proceeded with very good to practically quantitative yields (especially via route B), the reaction of 4-Br-substituted substrates (either route) were complicated by consecutive steps leading to insoluble polyaromatic compounds by Suzuki–Miyaura biaryl coupling. As a result, the yields of **13g** were considerably lower than those for other halogen-substituted benzophenones.

As an extension of the catalytic study, we have focused also on the reactions of model *aliphatic* substrates (Scheme 7 and Table 4) which further corroborated that the choice of starting materials is essential for obtaining good yields of the coupling products, particularly in the case of less reactive substrates. Thus, while the reaction of (*E*)-styrylboronic acid (**12k**) with benzoyl chloride provided *trans*-chalcone (**13k**) in a good 82% isolated yield (route A), the cross-coupling of cinnamoyl chloride (**11k**) and phenylboronic acid (**12**) produced the same product in a 55% yield (route B). An even more significant difference between the alternative routes was noted in the case of reactions leading to the analogous product 1,3-diphenyl-1-propanone (**13l**), which require a coupling of an sp^3 carbon substrate. In this case, the reaction of phenethylboronic acid (**12l**) with benzoyl chloride gave no coupling product at all, whereas the coupling between 3-phenylpropanoic chloride (**11l**) and phenylboronic acid (**12**) led to **13l** in a modest 23% yield.

Scheme 7. Preparation of 13k and 13l[a]



[a]Reaction same conditions were the same as for the synthesis of **13a**-**13j**.

Table 4. Synthesis of Aliphatic Ketones 13k and 13l[a]

product	yield (%) route A	yield (%) route B
trans-chalcone (**13k**)	82	55
1,3-diphenyl-1-propanone (**13l**)	0	23

[a]For reaction conditions, see footnote *a* in Table 3. Isolated yields are given as an average of two independent runs.

In subsequent work, we applied the developed catalytic procedure to the synthesis of fenofibrate (**15**), a generic drug widely used for the treatment of hypercholesterolemia and dyslipidemia.[22] The synthesis (Scheme 8) was pursued along several directions sharing 4-chloro-4′-hydroxybenzophenone (**13fm**) as the common key intermediate. Unfortunately, this compound could not be prepared directly by the coupling of 4-hydroxyphenylboronic acid (**12m**) with 4-chlorobenzoyl chloride (**11f**, route 1 in Scheme 8), presumably due to the low solubility of the boronic acid in the reaction mixture. However, when boronic acid **12m** was replaced by its O-silylated analogue **12n**, the coupling reaction proceeded smoothly to afford benzophenone **13fn** in 90% isolated yield (route 2). The subsequent deprotection with Bu_4NF led to the desired ketone **13fm**, which was in turn alkylated[23] with isopropyl 2-bromo-2-methylpropanoate (**16**) to give the target compound **15** in 71% yield.

As an alternative, a more atom economical synthesis of ketone **13fm** was devised (see Scheme 8), making use of the selective replacement of the fluoride substituent in 4-chloro-4′-fluorobenzophenone (**13ef**) upon action of NaOH in aqueous dimethyl sulfoxide.[24] Nonetheless, even the synthesis of ketone **13ef** required proper selection of the reaction partners, because the coupling between 4-chlorobenzoyl chloride (**11f**) and 4-fluorophenylboronic acid (**12e**; route 3) provided a significantly better yield than the reaction exploiting reagents with transposed functional groups (compare routes 3 and 4 in Scheme 8). The subsequent conversion of **13ef** to **13fk** proceeded smoothly with a good yield.

CONCLUSION

Compound **2**, directly accessible from the reaction of 2-sulfobenzoic anhydride with amine **1**, combines a phosphinoferrocene moiety as a primary coordination site for soft transition metals and a polar anionic amidosulfonate tag, which increases its affinity toward water and can further serve as the source of additional (potentially stabilizing) donor atoms in its structure. As such, the compound appears to be suitable for applications in catalysis at the organic–water interphase, which was demonstrated for the preparation of benzophenones by the palladium-catalyzed cross-coupling reaction of arylboronic acids with benzoyl chlorides.

The best catalytic results were obtained with complex **8**, which typically afforded the coupling products in very good to excellent yields at a Pd loading of only 0.1 mol % when the starting materials were selected appropriately. The high efficiency of the (pre)catalyst **8** can be ascribed to the particular coordination of the Pd(II) ions, namely the presence of the chelating 2′-amino-[1,1′-biphenyl]-2-yl donor that is easily reductively eliminated and thus facilitates catalytic activation [Pd(II) → Pd(0)],[17] and also to the P,O-coordinated hybrid[25] amidosulfonate anion, whose hemilabile coordination can further aid in catalytic activation through opening of the Pd–O bond.

Catalyst **8** was successfully employed in the synthesis of 4-chloro-4′-hydroxybenzophenone, which is the key precursor of fenofibrate **15**, one of the top-selling drugs. Although perhaps not suitable for large-scale preparations, the reported method represents a convenient alternative for laboratory synthesis of fenofibrate itself as well as its derivatives and congeners.

EXPERIMENTAL SECTION

Materials and Methods. All manipulations were performed under an argon atmosphere using standard Schlenk techniques unless otherwise noted. Compounds **1**,[12] $[(L^{NC})Pd(\mu\text{-}Cl)]_2$ (**5**),[26] $[(L^{NC})$-Pd(acac)] (**9**; L^{NC} = [2-(dimethylamino-κN)methyl]phenyl-κC^1),[27] and $[(C_6H_4NH_2\text{-}C_6H_4\text{-}\kappa^2C,N)Pd(acac)]$[28] were prepared according to the literature methods. Anhydrous dichloromethane and tetrahydrofuran were obtained from an in-house PureSolv MD5 solvent

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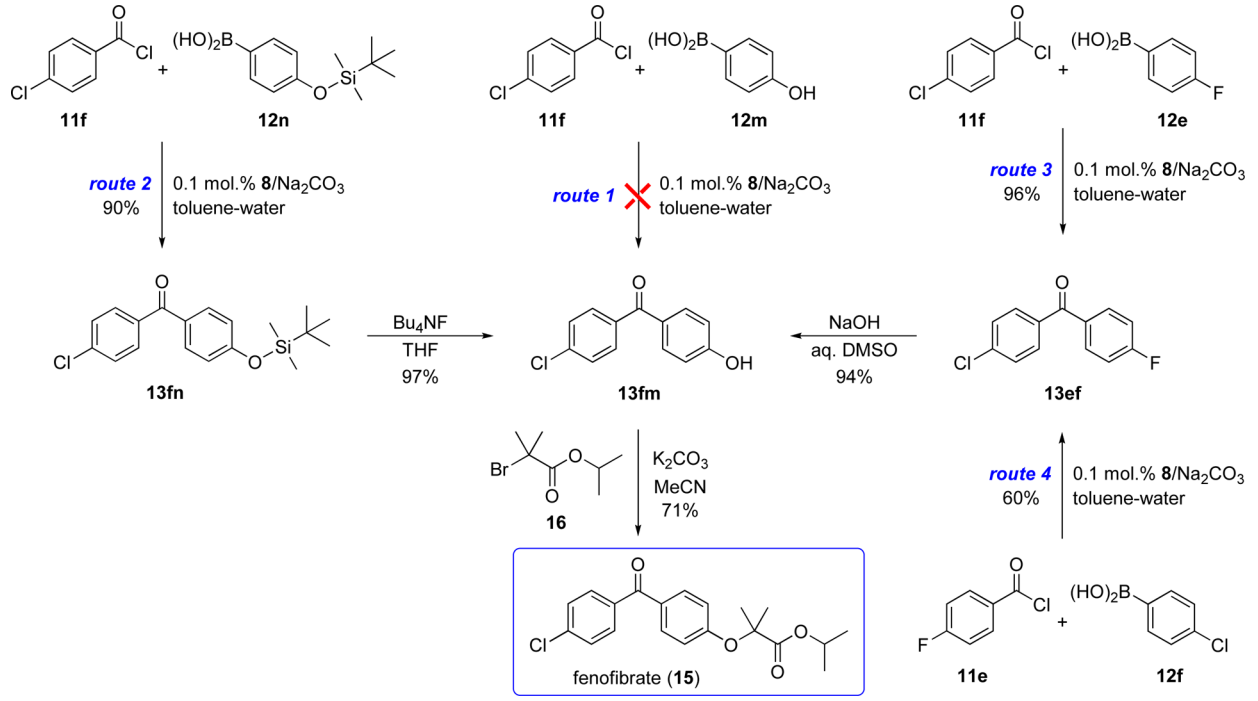
Scheme 8. Synthesis of fenofibrate (15)[a]



[a]The yields are given as the average of two independent runs.

purification system (Innovative Technology, USA). Triethylamine was distilled from sodium metal. Other chemicals as well as the solvents utilized for crystallizations and during chromatography were used without any additional purification.

NMR spectra were recorded at 25 °C on a Varian UNITY Inova 400 or Bruker AVANCE III HD 400 spectrometer. Chemical shifts (δ/ppm) are given relative to internal tetramethylsilane (^{1}H and ^{13}C), external neat $CFCl_3$ (^{19}F), and an external 85% H_3PO_4 standard (^{31}P). In addition to the usual notation of signal multiplicity, vt and vq are used to denote virtual multiplets due to the protons forming the AA′BB′ and AA′BB′X spin systems in the methylene- and PPh_2-substituted cyclopentadienyl rings, respectively (fc = ferrocene-1,1′-diyl). FTIR spectra were measured on a Thermo Nicolet Magna 6700 spectrometer over a range of 400−4000 cm^{-1}. Low-resolution electrospray ionization (ESI) mass spectra were obtained on an Esquire 3000 (Bruker) spectrometer for samples dissolved in HPLC-grade methanol. High-resolution (HR) MS measurements were performed with an LTQ Orbitrap XL spectrometer (Thermo Fisher Scientific). Elemental analyses were determined with a PerkinElmer PE 2400 CHN analyzer. The amount of residual solvent (if any) was confirmed by NMR spectroscopy.

Synthesis of 2. Hydrochloride **1** (871 mg, 2.0 mmol) and 2-sulfobenzoic anhydride (387 mg, 2.1 mmol) were mixed in dry THF (30 mL). Anhydrous triethylamine (1 mL, 7.2 mmol) was introduced with continuous stirring, causing the solid educts to nearly completely dissolve. The resultant mixture was stirred at room temperature for 20 h, filtered, and evaporated. The residue was purified by chromatography over silica gel using a dichloromethane−methanol−triethylamine (100:10:2) mixture as the eluent. Some impurities eluted first, followed by a major orange band due to the product, which was isolated as an orange sticky solid following evaporation under vacuum. Yield of **2**: 1.28 g (93%). Note: the compound is hygroscopic and better stored over potassium hydroxide in a desiccator.

^{1}H NMR ($CDCl_3$): δ 1.21 (t, $^3J_{HH}$ = 7.3 Hz, 9 H, CH_3 of $HNEt_3$), 3.03 (dq, $^3J_{HH}$ = 7.3, 4.7 Hz, 6 H, CH_2 of $HNEt_3$), 3.96 (vt, J' = 1.9 Hz, 2 H, fc), 4.09 (vq, J' = 1.8 Hz, 2 H, fc), 4.22 (d, $^3J_{HH}$ = 5.5 Hz, 2 H, CH_2NH), 4.23 (vt, J' = 1.9 Hz, 2 H, fc), 4.41 (vt, J' = 1.8 Hz, 2 H, fc), 7.26−7.36 (m, 10 H, PPh_2), 7.40−7.44 (m, 2 H, C_6H_4), 7.68 (m, 1 H, C_6H_4), 8.03 (m, 1 H, C_6H_4), 8.32 (br t, $^3J_{HH} \approx$ 5.1 Hz, 1 H, NHCO), 9.64 (br s, 1 H, $HNEt_3$). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 8.56 (CH_3 of $HNEt_3$), 39.35 (CH_2NH), 46.22 (CH_2 of $HNEt_3$), 69.06 (CH of fc), 69.14 (CH of fc), 69.24 (C^{ipso}-P of fc, partially overlapped), 71.88 (d, J_{PC} = 4 Hz, CH of fc), 73.44 (d, J_{PC} = 14 Hz, CH of fc), 85.89 (C^{ipso}-CH_2 of fc), 127.14 (CH of C_6H_4), 128.15 (d, $^3J_{PC}$ = 7 Hz, CH^{meta} of PPh_2), 128.62 (CH of C_6H_4), 129.46 (CH^{para} of PPh_2), 130.07 (CH of C_6H_4), 130.14 (CH of C_6H_4), 133.42 (d, $^2J_{PC}$ = 19 Hz, CH^{ortho} of PPh_2), 134.69 (C^{ipso} of C_6H_4), 138.51 (br s, C^{ipso} of PPh_2), 142.02 (C^{ipso} of C_6H_4), 168.66 (br, CONH). ^{31}P{^{1}H} NMR ($CDCl_3$): δ −15.8 (s). IR (DRIFTS, cm^{-1}): ν_{max} 3466 br m, 3296 br m, 3051 m, 2709 m, 2509 w, 1652 s, 1552 m, 1478 m, 1435 m, 1399 w, 1303 m, 1236 s, 1193, 1139 m, 1082 m, 1019 s, 835 w, 813 w, 792 w, 746 s, 700 s, 616 s, 568 m, 540 w, 489 m, 455 w, 416 w. ESI+ MS: m/z 102 ($HNEt_3^+$), 584 ($[\mathbf{2} - NEt_3 + H]^+$), 606 ($[\mathbf{2} - NEt_3 + Na]^+$), 685 ($[\mathbf{2} + H]^+$); ESI− MS: m/z 582 ($[\mathbf{2} - HNEt_3]^-$). Anal. Calcd for $C_{36}H_{41}FeN_2O_4PS{\cdot}2H_2O$ (720.6): C, 60.00; H, 6.29; N, 3.89. Found: C, 60.28; H, 5.95; N, 3.80.

Synthesis of Compound 3. Hydrochloride **1** (109 mg, 0.25 mmol) and phthalic anhydride (40.7 mg, 0.275 mg) were mixed in THF (10 mL). Dry triethylamine (0.5 mL, 3.6 mmol) was added, and the resulting mixture was stirred at room temperature for 18 h. The reaction was terminated by the addition of dichloromethane (10 mL) and 1 M aqueous HCl (20 mL). The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, and then passed through a silica gel column, with dichloromethane−methanol (5:1) as eluent. The yellow eluate was evaporated, leaving **3** as an orange oil, which gradually solidified. Yield: 98 mg (69%). Crystals suitable for X-ray diffraction analysis were grown by diffusion of diethyl ether into a methanolic solution of **3**.

^{1}H NMR ($CDCl_3$): δ 3.46 (br s, 2 H, CH_2), 3.89, 3.98, 4.09, and 4.24 (4× br s, 2 H, CH of fc); 7.25−7.32 (m, 10 H, PPh_2), 7.38 (m, 2 H, C_6H_4), 7.83 (m, 2 H, C_6H_4). The signals due to NH_3^+ and CO_2H could not be identified due to extensive broadening. ^{13}C{^{1}H} NMR ($CDCl_3$): δ 38.92 (CH_2), 70.29 (CH of fc), 70.35 (CH of fc), 71.61 (d, J_{PC} = 4 Hz, CH of fc), 73.49 (d, J_{PC} = 14 Hz, CH of fc), 76.82 (d, $^1J_{PC}$ = 7 Hz, C^{ipso}-P of fc), 79.46 (C^{ipso}-CH_2 of fc), 128.21 (d, $^3J_{PC}$ = 7 Hz, CH^{meta} of PPh_2), 128.63 (CH^{para} of PPh_2), 130.33 (br s, 4× CH of C_6H_4), 133.43 (d, $^2J_{PC}$ = 20 Hz, CH^{ortho} of PPh_2), 134.83 (br s, C^{ipso} of C_6H_4), 138.66 (d, $^1J_{PC}$ = 10 Hz, C^{ipso} of PPh_2), 173.21 (C═O).

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$^{31}P\{^1H\}$ NMR ($CDCl_3$): δ −16.9 (s). IR (Nujol, cm^{-1}): ν_{max} 3055 br m, 2605 w, 2125 w, 1570 w, 1540 s, 1499 w, 1314 w, 1295 w, 1238 m, 1164 s, 1089 s, 1074 s, 1058 s, 1049 s, 1025 s, 956 w, 912 w, 890 m, 879 m, 833 w, 815 m, 790 s, 754 s, 733 s, 702 s, 635 m, 587 m, 501 s, 447 m. ESI+ MS: m/z 383 ($[Ph_2PfcCH_2]^+$); ESI− MS: m/z 165 ($[C_6H_4(CO_2H)CO_2]^-$), 546 ($[\mathbf{3} - H_2O - H]^-$). Anal. Calcd for $C_{31}H_{28}FeNO_4P$ (565.4): C, 65.86; H, 4.99; N, 2.48. Found: C, 65.55; H, 4.89; N, 2.30.

Synthesis of $[PdCl_2(2\text{-}\kappa P)_2]$ (4). Ligand **2** (41.1 mg, 0.060 mmol) and $[PdCl_2(MeCN)_2]$ (7.8 mg, 0.030 mmol) were dissolved in dry dichloromethane (5 mL). After it was stirred for 60 min, the deep red reaction mixture was filtered through a PTFE syringe filter (0.45 μm pore size) and evaporated under vacuum to afford **4** as a gummy red solid in essentially quantitative yield. The compound tends to retain the reaction solvent.

^1H NMR ($CDCl_3$): δ 1.19 (t, $^3J_{HH}$ = 7.3 Hz, 9 H, CH_3 of $HNEt_3$), 2.99 (q, $^3J_{HH}$ = 7.3 Hz, 6 H, CH_2 of $HNEt_3$), 4.32 (d, $^3J_{HH}$ = 5.4 Hz, 2 H, CH_2NHCO), 4.49 (vt, J' = 1.9 Hz, 2 H, fc), 4.50 (vt, J' = 1.9 Hz, 2 H, fc), 4.55 (m, 4 H, fc), 7.34−7.44 (m, 6 H, PPh_2), 7.59−7.65 (m, 4 H, PPh_2), 7.71 (m, 2 H, C_6H_4), 8.02 (m, 2 H, C_6H_4), 8.31 (t, $^3J_{HH}$ = 5.4 Hz, 1 H, NHCO). Signal due to $HNEt_3$ was not observed due to broadening. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 8.68 (CH_3 of $HNEt_3$), 39.42 (CH_2NHCO), 46.24 (CH_2 of $HNEt_3$), 69.69 (CH of fc), 71.10 (CH of fc), 71.41 (apparent t, J = 28 Hz, C^{ipso}-P of fc), 72.95 (apparent t, J = 3 Hz, CH of fc), 75.86 (apparent t, J_{PC} = 6 Hz, CH of fc), 86.56 (C^{ipso}-CH_2 of fc), 127.08 (CH of C_6H_4), 127.69 (apparent t, J_{PC} = 5 Hz, CH of PPh_2), 129.50 (CH of C_6H_4), 130.17 (CH^{para} of PPh_2), 130.29 (CH of C_6H_4), 131.44 (apparent t, J = 25 Hz, C^{ipso} of PPh_2), 134.14 (apparent t, J_{PC} = 6 Hz, CH of PPh_2), 134.54 (CH of C_6H_4), 142.04 (C^{ipso} of C_6H_4), 168.58 (CO). The signal due to one C^{ipso} of C_6H_4 is probably obscured by other, more intense signals. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ +16.3 (s). IR (DRIFTS, cm^{-1}): ν_{max} 3444 br m, 3297 br m, 3055 m, 2984 m, 1648 s, 1552 m, 1481 m, 1436 s, 1303 m, 1235 s, 1193 s, 1098 w, 1082 w, 1019 s, 837 w, 748 m, 696 s, 617 s, 568 m, 541 m, 506 s, 475 m. ESI+ MS: m/z 1271 ($[Pd(Ph_2PfcCH_2NHCOC_6H_4SO_3)_2 + H]^+$); ESI− MS: m/z 1343 ($[\mathbf{4} + H - 2HNEt_3]^+$). Anal. Calcd for $C_{72}H_{82}N_4Cl_2Fe_2O_8PdP_2S_2 \cdot 1.5CH_2Cl_2$ (1673.8): C, 52.74; H, 5.12; N, 3.35. Found: C, 52.99; H, 5.33; N, 3.27.

Synthesis of $[(L^{NC})PdCl(2\text{-}\kappa P)]$ (7). Ligand **2** (68.4 mg, 0.10 mmol) and $[(L^{NC})PdCl]_2$ (27.6 mg, 0.050 mmol) were dissolved in dry dichloromethane (5 mL). The resulting solution was stirred for 60 min and then evaporated under vacuum to afford complex **5** as a yellow-orange foam in virtually quantitative yield.

^1H NMR ($CDCl_3$): δ 1.23 (t, $^3J_{HH}$ = 7.3 Hz, 9 H, CH_3 of $HNEt_3$), 2.83 (d, $^4J_{PH}$ = 2.0 Hz, 6 H, NMe_2), 3.04 (q, $^3J_{HH}$ = 7.3 Hz, 6 H, CH_2 of $HNEt_3$), 4.12 (d, $^4J_{PH}$ = 2.0 Hz, 2 H, CH_2NMe_2), 4.35 (d, J' = 2.0 Hz, 2 H, fc), 4.43 (vtd, J' = 1.9 Hz, 1.0 Hz, 2 H, fc), 4.54 (s, 4 H, fc), 6.27 (m, 1 H, C_6H_4Pd), 6.39 (m, 1 H, C_6H_4Pd), 6.81 (td, J = 7.3 Hz, 1.1 Hz, 1 H, C_6H_4Pd), 7.00 (dd, J = 7.4 Hz, 1.5 Hz, 1 H, C_6H_4Pd), 7.28−7.34 (m, 3 H, PPh_2), 7.37−7.43 (m, 5 H, 2 H of $C_6H_4SO_3$ and 3 H of PPh_2), 7.52−7.58 (m, 4 H, PPh_2), 7.67 (m, 1 H, $C_6H_4SO_3$), 8.03 (m, 1 H, $C_6H_4SO_3$), 8.15 (br s, 1 H, NHCO), 9.66 (br s, $HNEt_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 8.58 (CH_3 of $HNEt_3$), 39.44 (CH_2NHCO), 46.23 (CH_2 of $HNEt_3$), 50.16 (d, $^3J_{PC}$ = 2 Hz, NMe_2), 69.72 (CH of fc), 71.20 (CH of fc), 72.80 (d, J_{PC} = 7 Hz, CH of fc), 72.94 (C^{ipso}-P of fc, partially overlapped), 73.54 (CH_2NMe_2), 75.75 (d, J_{PC} = 10 Hz, CH of fc), 86.36 (C^{ipso}-CH_2 of fc), 122.49 (CH of C_6H_4Pd), 123.69 (CH of C_6H_4Pd), 124.78 (d, J_{PC} = 6 Hz, C_6H_4Pd), 127.10 (CH of $C_6H_4SO_3$), 127.82 (d, J_{PC} = 11 Hz, CH of PPh_2), 129.48 (CH of $C_6H_4SO_3$), 130.12 (C^{ipso} of $C_6H_4SO_3$), 130.17 (CH of $C_6H_4SO_3$), 130.41 (d, $^4J_{PC}$ = 2 Hz, CH^{para} of PPh_2), 131.83 (d, $^1J_{PC}$ = 50 Hz, C^{ipso} of PPh_2), 134.33 (d, J_{PC} = 12 Hz, CH of PPh_2), 134.58 (C^{ipso} of $C_6H_4SO_3$), 138.37 (d, $^3J_{PC}$ = 11 Hz, CH of C_6H_4Pd), 141.93 (CH of $C_6H_4SO_3$), 148.22 (d, $^2J_{PC}$ = 2 Hz, C^{ipso} of C_6H_4Pd), 152.04 (br s, C^{ipso} of C_6H_4Pd), 168.63 (C═O). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ +33.1 (s). IR (Nujol, cm^{-1}): ν_{max} 3462 br m, 3287 br m, 3047 m, 1648 s, 1560 m, 1303 m, 1234 m, 1189 m, 1165 m, 1139 w, 1099 w, 1082 w, 1019 m, 845 m, 745 m, 696 m, 658 w, 616 m, 567 w, 544 w, 524 w, 504 m, 477 m, 439 w. ESI+ MS: m/z 823 ($[7 - Cl - NEt_3]^+$), 924 ($[7 - Cl]^+$); ESI− MS: m/z 582 ($[\mathbf{2} - HNEt_3]^-$), 857 ($[7 - HNEt_3]^-$). Anal. Calcd for $C_{45}H_{53}N_3ClFeO_4PPdS$ (960.7): C, 56.26; H, 5.56; N, 4.37. Found: C, 55.98; H, 5.64; N, 4.19.

Synthesis of Complex 8. This complex was obtained similarly, starting from **2** (68.4 mg, 0.100 mmol) and $[(C_6H_4C_6H_4NH_2)PdCl]_2$ (31.0 mg, 0.050 mmol), and was isolated as an orange solid in quantitative yield.

^1H NMR ($CDCl_3$): δ 1.23 (t, $^3J_{HH}$ = 7.3 Hz, 9 H, CH_3 of $HNEt_3$), 3.05 (q, $^3J_{HH}$ = 7.3 Hz, 6 H, CH_2 of $HNEt_3$), 3.28 (br s, 1 H, fc), 3.89 (br s, 1 H, fc), 3.91 (br s, 1 H, fc), 4.08 (br s, 1 H, fc), 4.14−4.28 (m, 4 H, 2 H of fc and 2 H of CH_2NHCO), 4.50 (br s, 1 H, fc), 4.95 (br s, 1 H, NH_2), 5.01 (br s, 1 H, fc), 5.24 (br s, 1 H, NH_2), 6.45 (t, J = 7.3 Hz, 1 H, C_6H_4Pd), 6.58 (t, J = 6.8 Hz, 1 H, C_6H_4Pd), 6.91 (t, J = 7.3 Hz, 1 H, C_6H_4Pd), 7.01 (m, 2 H, $C_6H_4NH_2$), 7.10 (m, 2 H, $C_6H_4NH_2$), 7.18−7.26 (m, 3 H, 1 H of $C_6H_4SO_3$ and 2 H of PPh_2), 7.29 (d, J_{HH} = 7.4 Hz, 1 H, C_6H_4Pd), 7.38−7.43 (m, 5 H, 1 H of $C_6H_4SO_3$ and 4 H of PPh_2), 7.62 (dd, J = 7.1, 1.8 Hz, 1 H, $C_6H_4SO_3$), 7.62−7.74 (m, 4 H, PPh_2), 7.96 (br s, 1 H, NHCO), 8.03 (m, 1 H, $C_6H_4SO_3$). The signal due to $HNEt_3$ is extremely broadened. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 8.59 (CH_3 of $HNEt_3$), 39.37 (CH_2NHCO), 46.20 (CH_2 of $HNEt_3$), 68.79 (CH of fc), 70.22 (CH of fc), 70.31 (CH of fc), 71.58 (d, $^1J_{PC}$ = 5 Hz, C^{ipso}-P of fc), 72.44 (CH of fc), 73.03 (CH of fc), 73.42 (d, J_{PC} = 8 Hz, CH of fc), 73.76 (d, J_{PC} = 7 Hz, CH of fc), 75.84 (d, J_{PC} = 13 Hz, CH of fc), 86.17 (C^{ipso}-CH_2 of fc), 120.50 (CH of $C_6H_4NH_2$), 124.84 (CH of C_6H_4Pd), 125.67 (CH of C_6H_4Pd), 125.96 (CH of $C_6H_4SO_3$), 127.07 (d, $^3J_{PC}$ = 5 Hz, CH of C_6H_4Pd), 127.18 (CH^{para} of PPh_2), 127.38 (d, J_{PC} = 11 Hz, CH of $C_6H_4NH_2$), 128.15 (CH of $C_6H_4SO_3$), 129.45 (CH of $C_6H_4SO_3$), 129.74 (CH of $C_6H_4SO_3$), 129.86 (d, $^2J_{PC}$ = 18 Hz, CH^{ortho} of PPh_2), 130.70 (CH of $C_6H_4NH_2$), 130.71 (d, $^1J_{PC}$ = 52 Hz, C^{ipso} of PPh_2), 132.21 (d, $^2J_{PC}$ = 47 Hz, C^{ipso} of C_6H_4Pd), 133.41 (d, $^3J_{PC}$ = 10 Hz, C^{ipso} of $C_6H_4NH_2$), 134.57 (d, $^3J_{PC}$ = 13 Hz, CH^{meta} of PPh_2), 135.41 (C^{ipso} of $C_6H_4SO_3$), 138.04 (CH of $C_6H_4NH_2$), 139.71 (d, $^3J_{PC}$ = 10 Hz, CH of C_6H_4Pd), 139.94 (C^{ipso} of $C_6H_4NH_2$), 141.91 (C^{ipso} of $C_6H_4SO_3$), 151.53 (C^{ipso} of C_6H_4Pd), 168.70 (C═O). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ +30.3 (s). IR (Nujol, cm^{-1}): ν_{max} 3435 br w, 3306 br w, 3050 w, 1644 s, 1591 m, 1558 s, 1302 m, 1228 s, 1181 s, 1168 s, 1138 m, 1098 m, 1081 m, 1059 w, 1017 s, 836 w, 792 w, 748 s, 694 s, 658 w, 615 s, 567 m, 523 m, 501 m, 470 m. ESI+ MS: m/z 857 ($[\mathbf{8} - Cl - NEt_3]^+$), 879 ($[\mathbf{8} + Na - HNEt_3 - Cl]^+$), 895 ($[\mathbf{8} + K - HNEt_3 - Cl]^+$), 958 ($[\mathbf{8} - Cl]^+$); ESI− MS: m/z 582 ($[\mathbf{2} - HNEt_3]^-$), 688 ($[Pd(\mathbf{2} - HNEt_3)]^-$). Anal. Calcd for $C_{48}H_{51}N_3ClFeO_4PPdS \cdot 0.5CH_2Cl_2$ (1037.1): C, 56.16; H, 5.05; N, 4.05. Found: C, 56.25; H, 5.19; N, 4.04.

Synthesis of Complex 10. Compound **2** (68.4 mg, 0.10 mmol) and $[(L^{NC})Pd(acac)]$ (33.9 mg, 0.10 mmol) were mixed in dichloromethane (5 mL), and the reaction mixture was stirred for 60 min, during which time all of the solid educts dissolved. The orange solution was filtered through a silica gel column, with dichloromethane−methanol (10:1) as eluent. Subsequent evaporation furnished **10** as a yellow solid (73.5 mg, 89%). The orange crystals used for the structure determination were obtained from methanol−diethyl ether.

^1H NMR ($CDCl_3$): δ 2.56 (br s, 6 H, NMe_2), 3.98 (br s, 2 H) and 4.25−4.57 (br m, 10 H, CH_2 and fc), 6.24 (t, J = 7.2 Hz, 1 H, C_6H_4Pd), 6.32 (br s, 1 H, C_6H_4Pd), 6.78 (br s, 1 H, C_6H_4Pd), 6.89 (br s, 1 H, C_6H_4Pd), 7.28−7.50 (br m, 8 H, PPh_2 and/or $C_6H_4SO_3$), 7.68 (br s, 4 H, PPh_2 and/or $C_6H_4SO_3$), 7.86 (br s, 1 H, $C_6H_4SO_3$), 8.08 (br s, 1 H, $C_6H_4SO_3$), 9.15 (br s, 1 H, CONH). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ +33.8 (br s). ^{13}C NMR spectra could not be recorded for solubility reasons. IR (Nujol, cm^{-1}): ν_{max} 3435 m, 3327 br m, 3052 m, 1649 s, 1580 m, 1564 m, 1546 m, 1301 m, 1248 m, 1182 w, 1162 s, 1135 w, 1099 m, 1076 m, 1019 m, 1004 m, 990 m, 845 m, 812 w, 790 w, 744 s, 697 s, 657 w, 617 s, 564 m, 545 m, 502 m, 487 m, 446 w. ESI− MS: m/z 823 ($[(C_6H_4CH_2NMe_2)Pd(Ph_2PfcCH_2NHCOC_6H_4SO_3 + H]^+$), 845 and 861 (the same as Na/K^+); ESI− MS: m/z 582 ($[\mathbf{2} - HNEt_3]^-$). Anal. Calcd for $C_{39}H_{37}N_2FeO_4PPdS$ (823.0): C, 56.91; H, 4.53; N, 3.40. Found: C, 56.70; H, 4.77; N, 3.58.

Catalytic Experiments: General Procedure. A Schlenk tube was successively charged with a stirring bar, the respective acyl chloride

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(3.0 mmol), boronic acid (2.0 mmol), catalyst (20 μmol, 0.1 mol %), and anhydrous Na_2CO_3 (2.5 mmol), flushed with argon, and finally sealed with a rubber septum. Benzene (or toluene) and water (3 mL each) were introduced, and the reaction vessel was transferred to an oil bath maintained at 50 °C. After it was stirred for 1 h, the reaction mixture was cooled and diluted with diethyl ether (10 mL) or, in the case of products bearing polar groups (NO_2, CN), with ethyl acetate. The organic layer was separated, washed with 1 M NaOH (3× 5 mL) and brine (10 mL), and dried over $MgSO_4$. The product was isolated by column chromatography over silica gel using hexane−ethyl acetate as the eluent (30:1 or 5:1). Characterization data for the coupling products are given in the Supporting Information.

Synthesis of 13fn. 4-Chlorobenzoyl chloride (**11f**; 3.0 mmol) and boronic acid **12n** (2.0 mmol) were reacted according to the general procedure. The standard workup afforded analytically pure **13fn** as a colorless oil in 88 and 92% yields.

^{1}H NMR ($CDCl_3$): δ 0.25 (s, 6 H, $SiMe_2$), 1.00 (s, 9 H, $SiCMe_3$), 6.91 (dm, $J \approx 7$ Hz, 2 H, aromatic CH), 7.45 (dm, $J \approx 8$ Hz, 2 H, aromatic CH), 7.72 (dm, $J \approx 7$ Hz, 4 H, aromatic CH). ^{13}C{^{1}H} NMR ($CDCl_3$): δ −4.33 ($SiMe_2$), 18.26 ($SiCMe_3$), 25.60 (CMe_3), 119.83 (aromatic CH), 128.52 (aromatic CH), 130.35 (aromatic C^{ipso}), 131.18 (aromatic CH), 132.36 (aromatic CH), 136.53 (aromatic C^{ipso}), 138.30 (aromatic CH^{ipso}), 160.18 (aromatic CH^{ipso}), 194.36 (CO). ESI+ MS: m/z 347 ($[M + H]^+$), 369 ($[M + Na]^+$), 385 ($[M + K]^+$), 715 ($[2\ M + Na]^+$); ESI− MS: m/z 231 ($[M - t\text{-}BuSiMe_2]^-$). HR MS: calcd for $C_{19}H_{24}ClO_2Si$ ($[M + H]^+$) 347.1229, found 347.1230.

Preparation of 13ef. The syntheses were carried out as described above. The coupling of **11f** with **12e** provided the coupling product in 87% isolated yield. When the reaction was scaled up 5 times (10 mmol of boronic acid), the isolated yields were 97 and 95% (route 3 in Scheme 8). On the other hand, the reaction between **11e** and **12f** furnished the target ketone in only 58% and 62% NMR yields (on a 2 mmol scale; route 4 in Scheme 8).

Compound **13ef** was isolated as a white microcrystalline solid (flakes). ^{1}H NMR ($CDCl_3$): δ 7.17 (tm, $J \approx 7$ Hz, 2 H, aromatic CH), 7.47 (dm, $J \approx 8$ Hz, 2 H, aromatic CH), 7.72 (dm, $J \approx 7$ Hz, 2 H, aromatic CH), 7.72 (m, 2 H, aromatic CH). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 115.61 (d, $^2J_{FC}$ = 22 Hz, aromatic CH), 128.71 (aromatic CH), 131.27 (aromatic CH), 132.54 (d, $^3J_{FC}$ = 9 Hz, aromatic CH), 133.45 (d, $^4J_{FC}$ = 3 Hz, aromatic C^{ipso}), 135.76 (aromatic C^{ipso}), 138.96 (aromatic C^{ipso}), 165.47 (d, $^1J_{FC}$ = 255 Hz, C^{ipso}), 193.98 (CO). ^{19}F{^{1}H} NMR ($CDCl_3$): δ −105.68 (s). These analytical data are in agreement with those in the literature.[29]

Preparation of 13fm from 13fn. Bu_4NF (1.1 mL of a 1 M solution in THF, 1.1 mmol) was added to a solution of ketone **13fn** (346 mg, 1.0 mmol) in dry THF (5 mL), while it was stirred and cooled on ice (an immediate color change from colorless to yellow was observed). The reaction mixture was stirred at 0 °C for 30 min and then quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL) and ethyl acetate (10 mL). The organic layer was separated, washed with water and brine, and dried over anhydrous $MgSO_4$. The drying agent was filtered off, the filtrate was evaporated with chromatographic silica gel, and the preadsorbed crude product was purified by flash column chromatography (silica gel, 3:1 hexane−ethyl acetate) to afford pure **13fm** after evaporation. Yield: 225 mg (97%), white solid.

^{1}H NMR (dmso-d_6): δ 6.88 (dm, $J \approx 8$ Hz, 2 H aromatic CH), 7.57 (dm, $J \approx 8$ Hz, 2 H aromatic CH), 7.65 (dm, $J \approx 10$ Hz, 4 H, aromatic CH), 10.46 (br s, 1 H, OH). ^{13}C {^{1}H} NMR (dmso-d_6): δ 115.32 (aromatic CH), 127.55 (aromatic C^{ipso}), 128.49 (aromatic CH), 131.02 (aromatic CH), 132.52 (aromatic CH), 136.66 (aromatic C^{ipso}), 136.76 (aromatic C^{ipso}), 162.19 (aromatic C^{ipso}−OH), 193.13 (CO). These data agree with the reported values.[30]

Preparation of 13fm from 13ef. Ketone **13ef** (2.34 g, 10 mmol) and NaOH (1.0 g, 25 mmol) were mixed with reagent-grade DMSO (60 mL) and water (6 mL), and the resulting mixture was stirred at 120 °C for 16 h. After it was cooled to room temperature, the mixture was acidified with 50 mL of 1 M HCl, and the product was extracted with ethyl acetate (100 mL). The organic layer was thoroughly washed with water and brine (three times each) and then passed directly through a short silica gel column (elution with hexane−ethyl acetate, 3:1). Subsequent evaporation gave pure benzophenone **13fm** as a white solid (2.19 g, 94%).

Synthesis of Fenofibrate (15). Ketone **13fm** (1.16 g, 5.0 mmol) and anhydrous K_2CO_3 were mixed in dry acetonitrile (30 mL). Isopropyl 2-bromo-2-methylpropionate (**16**; 1.25 g, 6.0 mmol) (note: the synthesis of this ester is described in the Supporting Information) was introduced to the suspension, and the reaction mixture was heated at reflux temperature for 18 h. After the mixture was cooled to room temperature, the reaction was terminated by addition of 1 M HCl (30 mL) (*caution! gas evolution*), and the product was extracted with ethyl acetate (50 mL). The organic layer was washed with water and brine and dried over $MgSO_4$. The crude product was preadsorbed by evaporation with chromatographic silica gel and purified by flash chromatography (silica gel, 8:1 hexane−ethyl acetate) to afford **15** as a colorless oil, which gradually solidified. Yield: 1.28 g (71%).

^{1}H NMR ($CDCl_3$): δ 1.20 (d, $^3J_{HH}$ = 6 Hz, 6 H, $CHMe_2$), 1.66 (s, 6 H, $CBrMe_2$), 5.09 (sept, $^3J_{HH}$ = 6 Hz, 1 H, $CHMe_2$), 6.87 (dm, $J \approx 9$ Hz, 2 H, aromatic CH), 7.45 (dm, $J \approx 9$ Hz, 2 H, aromatic CH), 7.70 (dm, $J \approx 8$ Hz, 2 H aromatic CH), 7.73 (dm, $J \approx 9$ Hz, 2 H aromatic CH). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 21.53 ($CHMe_2$), 30.68 (C(O)-CMe_2), 69.35 ($CHMe_2$), 79.44 (C(O)CMe_2), 117.26 (aromatic CH), 128.54 (aromatic CH), 130.23 (aromatic C^{ipso}), 131.16 (aromatic CH), 131.95 (aromatic CH), 136.44 (aromatic C^{ipso}), 138.35 (aromatic C^{ipso}), 159.75 (aromatic C^{ipso}), 173.10 (CO, ester), 194.26 (CO, ketone). These analytical data are in accordance with the reported values.[31]

X-ray Crystallography. The diffraction data (±h,±k,±l; θ_{max} = 27.5°, data completeness ≥99.9%) were recorded on a Bruker Apex II CCD diffractometer equipped with a Cryostream cooler (Oxford Cryosystems) using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The data were corrected for absorption by the methods included in the diffractometer software.

The structures were solved by direct methods (SHELXS97[32]) and refined by full-matrix least squares based on F^2 (SHELXL97[32]). Solvating diethyl ether in the structure of **10**·2MeOH·Et_2O was disordered in the structural voids, and hence, its contribution to the overall scattering was modeled by PLATON SQUEEZE.[33] All non-hydrogen atoms were refined with anisotropic displacement parameters. The OH and NH hydrogens were identified on the difference density maps and refined as riding atoms with U_{iso} assigned to $1.2U_{eq}$ of their bonding atom. Hydrogens bonded to carbon atoms (CH_n) were included in their calculated positions and refined similarly. Relevant crystallographic data and structural refinement parameters are given in Table S1 in the Supporting Information.

PLATON[34] was used for the graphical representation of the results and all geometrical calculations. The numerical values are rounded with respect to their estimated deviations (ESDs) and given to one decimal place. The parameters related to atoms in constrained positions are given without ESDs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.6b00600.

Summary of crystallographic data, an additional structural drawing for **10**·2MeOH·Et_2O, the preparation of **16**, characterization data for the coupling products, and NMR spectra (PDF)

X-ray crystallographic data for **2** and **10**·2MeOH·Et_2O (CIF)

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Notes

The authors declare no competing financial interest.

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