N-Acyl-5,5-Dimethylhydantoins: Mild Acyl-Transfer Reagents for the Synthesis of Ketones using Pd–PEPPSI or Pd/Phosphine Catalysis

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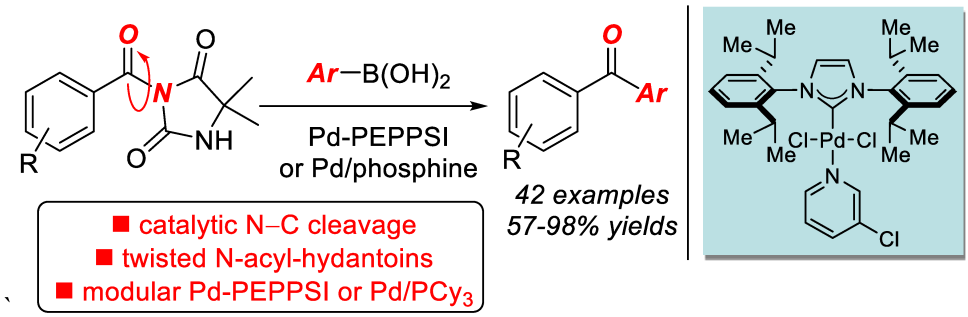


Abstract: *N*-Acyl-hydantoins have emerged as novel acyl transfer reagents for the synthesis of ketones via selective N–C(O) cleavage. Herein, we report two new protocols for the cross-coupling of *N*-acyl-5,5-dimethylhydantoins using versatile and readily accessible Pd–PEPPSI or Pd/phosphine catalysts. The acyl Suzuki reactions afford biaryl ketones in good to excellent yields under operationally-simple conditions using commercially-available, bench- and air-stable twisted *N*-acyl-hydantoins as acyl donors. The method complements and expands on the previous protocol for the cross-coupling of *N*-acyl-hydantoins (*Org. Process Res. Dev.* **2018**, *22*, 1188).

Keywords: *twisted amides, N-acyl-hydantoins, Suzuki coupling, amide cross-coupling, N–C activation*

1. Introduction

Over the past five years, tremendous advances have been made in transition-metal-catalyzed amide bond cross-coupling.[1–3] These reactions are valuable due to the very common presence of amide bonds in pharmaceuticals, biomolecules and functional materials.[4–6] Furthermore, this field has resulted in the development of new acyclic twisted amides as practical, bench-stable precursors for acyl-transfer reactions that could also be translated to decarbonylative processes by CO loss.[7]

In 2018, Zeng and co-workers introduced *N*-acyl-5,5-dimethylhydantoins as new acyl-transfer reagents using [Pd(IPr)(allyl)Cl] precatalyst (*Org. Process Res. Dev.* **2018**, *22*, 1188).[8] Simultaneously, we have reported a mechanistic study on the structures and energetics on N-acyl-hydantoins (*J. Org. Chem.* **2018**, *83*, 14676), finding that the amide bond in *N*-acyl-hydantoins is significantly twisted with the additive Winkler-Dunitz parameter, $\tau+\chi_N = 70°$, for the model compound (Figure 1A).[9]

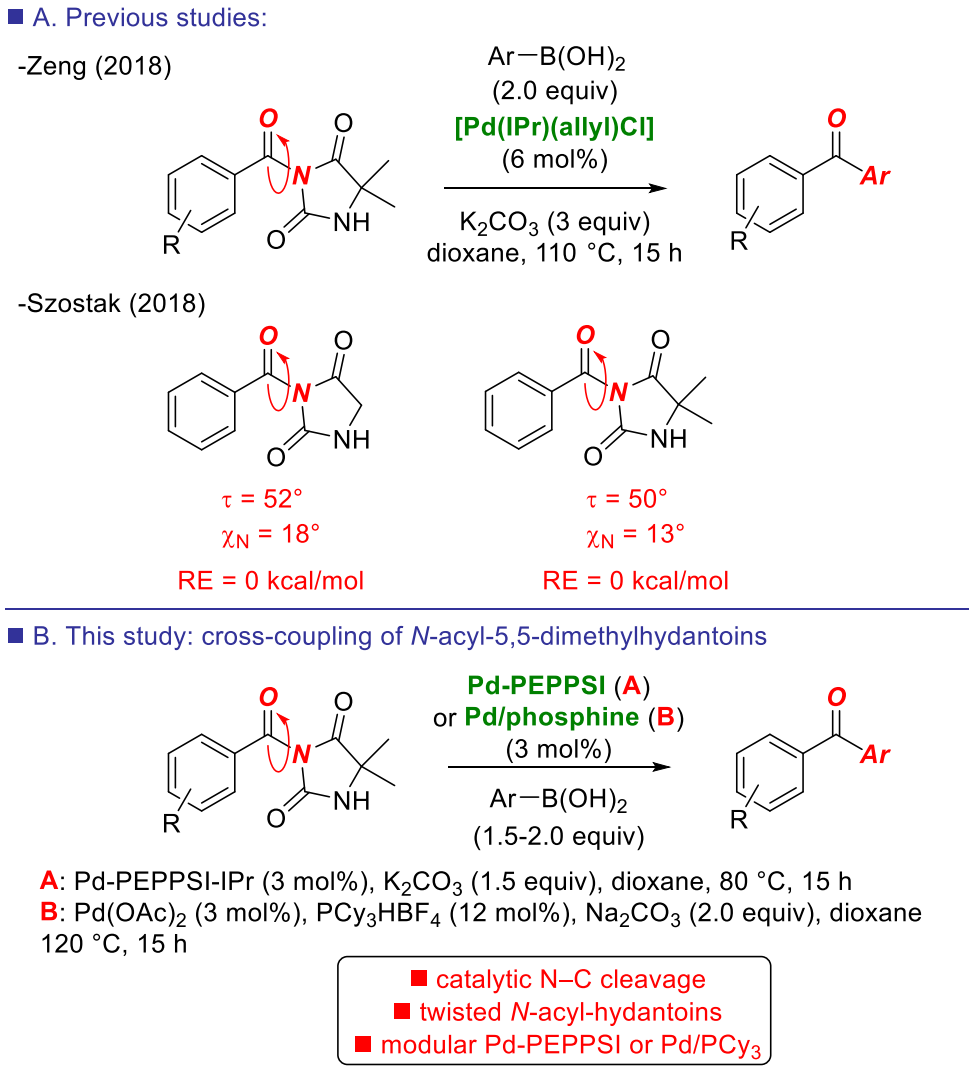


Figure 1. Context of this work: Suzuki cross-coupling of twisted *N*-acyl-5,5-dimethylhydantoins.

Within our research program on amide bond cross-coupling and Pd-NHC catalysis,[2,3] we now report two new protocols for the cross-coupling of *N*-acyl-5,5-dimethylhydantoins using versatile and readily accessible Pd–PEPPSI or Pd/phosphine catalysts (Figure 1B). The following features of our study are noteworthy: (1) The reactions complement and expand on the previous protocol for the cross-coupling of *N*-acyl-hydantoins using [Pd(IPr)(allyl)Cl].[8] (2) Pd-PEPPSI represent a completely distinct class of Pd-NHC catalysts that are (i) cheaper and easier to synthesize than the allyl-type precatalysts,[10,11] (ii) undergo activation under complementary mechanism to the allyl-type precursors, and (iii) many Pd-PEPPSI-type catalysts have been reported, which is significant for the future developments in amide bond N–C(O) cross-coupling.[12] (3) We demonstrate that, alternatively, cheap and readily accessible

Pd/phosphine catalysts can also be used for the cross-coupling of *N*-acyl-5,5-dimethylhydantoins in excellent yields. (4) The protocols are also applied to the Suzuki cross-coupling of other classes of twisted amides by selective N–C(O) activation, showing higher reactivity than the use of [Pd(IPr)(allyl)Cl] catalyst.[8,13–15]

The new protocols are compared and contrasted with the [Pd(IPr)(allyl)Cl]-catalyzed cross-coupling of N-acyl-5,5-dimethylhydantoins reported by Zeng and co-workers.[8] More broadly, it should be noted that (i) phosphines and NHCs represent fundamentally different classes of ligands, resulting in a distinct monoligated Pd species,[10b] and (ii) the activation, synthesis and properties of Pd-allyl-type and Pd-PEPPSI-type catalysts are fundamentally distinct as they belong to different classes of throw-away ligands.[10,11]

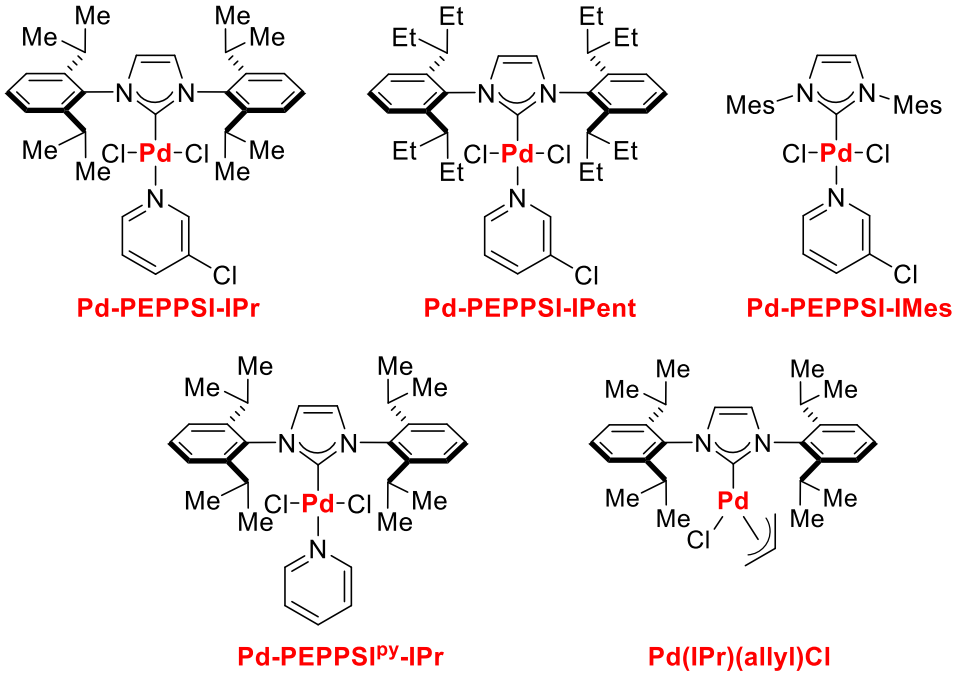
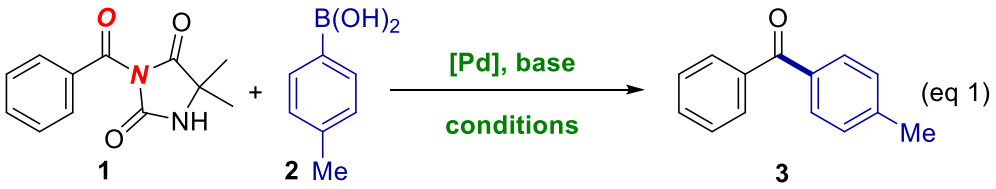


Figure 2. Structures of [Pd–NHC] catalysts.

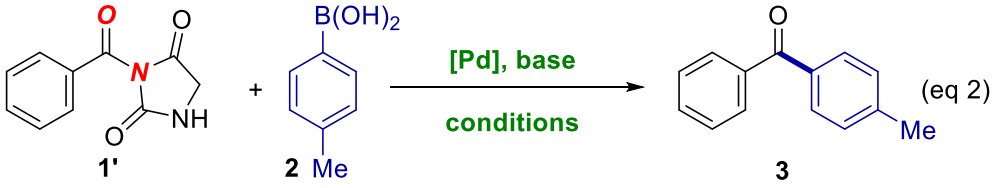
2. Results and Discussion

In 2018, during our structural studies, we performed preliminary catalytic investigations establishing that N-benzoyl-5,5-dimethylhydantoin could undergo the cross-coupling with 4-Tol-B(OH)$_2$ under Pd–PEPPSI and Pd/PCy$_3$ conditions (eq 1). Interestingly, the parent *N*-benzoylhydantoin without the 5,5-

gem-dimethyl substitution resulted in significantly lower yields, likely due to low stability under the reaction conditions (eq. 2).



A: Pd-PEPPSI-IPr (6 mol%), K_2CO_3, 120 °C, 97% yield
B: $Pd(OAc)_2$ (3 mol%), PCy_3HBF_4 (12 mol%), Na_2CO_3, 120 °C, 73% yield

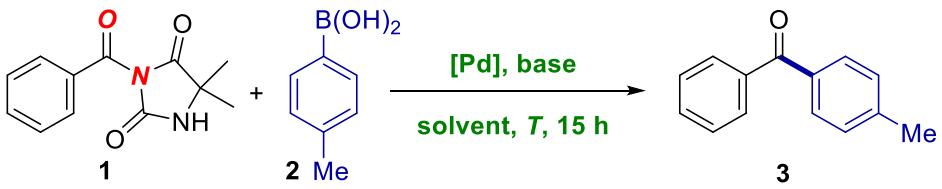


A: Pd-PEPPSI-IPr (6 mol%), K_2CO_3, 120 °C, 56% yield
B: $Pd(OAc)_2$ (3 mol%), PCy_3HBF_4 (12 mol%), Na_2CO_3, 120 °C, <10% yield

Further optimization indicated that the reaction of *N*-benzoyl-5,5-dimethylhydantoin with 4-Tol-$B(OH)_2$ produced the desired ketone product in close to quantitative yield using either Pd–PEPPSI–IPr (Table 1, entry 1, Figure 2) or Pd/PCy_3 catalyst systems (Table 1, entry 2) at 3 mol% of [Pd] loading at 80 °C or 120 °C, respectively, while the previous report required 6 mol% of the [Pd(IPr)(allyl)Cl] catalyst at 110 °C. Optimization studies revealed that for the Pd/PCy_3-catalyzed conditions (Table 1, entries 3-10), the stoichiometry of boronic acid and base are critical parameters (entries 3-6). Importantly, decomposition was observed at higher boronic acid and base loading. Furthermore, the optimum results were obtained with 3 mol% of [Pd] loading (entries 7-8). A base screen revealed that Na_2CO_3 is a superior base to K_2CO_3 (entries 9-10). More interesting is the optimization using Pd–PEPPSI catalysts (entries 11-25). Extensive evaluation of various bases showed that K_2CO_3 is the preferred base under these conditions (entries 11-15). Excess of the boronic acid and the base was tolerated under the Pd–PEPPSI conditions (entry 16), consistent with more facile oxidative addition using Pd-NHC systems. Optimization of stoichiometry and temperature (entries 17-22) revealed that efficient coupling ensued at 80 °C (entry 1 cf. [Pd(IPr)(allyl)Cl] at 110 °C). Cross-coupling was not observed at 23 °C, resulting in recovery of starting material (entry 21). Interestingly, water could also be used as a co-solvent, which could lead to the development of green organic processes using water-

soluble NHC ligands (entry 19). Moreover, 2-MeTHF serves as a convenient green solvent in this cross-coupling[12c] (97% yield, Pd-PEPPSI-IPr; 69% yield, $Pd(OAc)_2/PCy_3HBF_4$ conditions, not shown). Furthermore, evaluation of various NHC ancillary ligands (entries 1, 23-24) indicated that IPr is the optimum NHC ligand for the cross-coupling, while significantly lower yields were observed using both the less sterically-demanding IMes (entry 23) and the more sterically-hindered IPent (entry 24). Finally, 3-chloropyridine throw-away ligand was found to be superior to pyridine throw-away ligand in the PEPPSI scaffold (entry 25). *Taken together with previous examples,[2a] the present study decidedly highlights that IPr might be the privileged NHC ligand for amide bond cross-coupling.*

Table 1. Optimization of the Reaction Conditions[a]



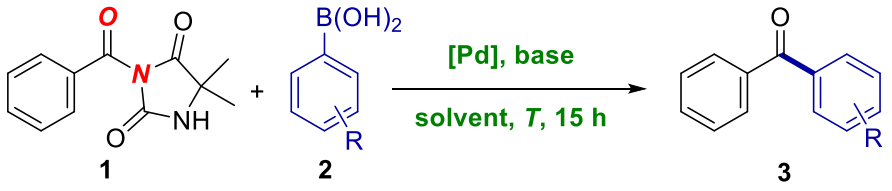
entry	[Pd]	ligand	base	base (eq)	*T* (°C)	yield (%)[b]
1	Pd-PEPPSI-IPr	-	K_2CO_3	1.5	80	96
2[c]	$Pd(OAc)_2$	PCy_3HBF_4	Na_2CO_3	2.0	120	92
3	$Pd(OAc)_2$	PCy_3HBF_4	Na_2CO_3	3.0	120	61
4[d]	$Pd(OAc)_2$	PCy_3HBF_4	Na_2CO_3	3.0	120	28
5[d]	$Pd(OAc)_2$	PCy_3HBF_4	Na_2CO_3	1.5	120	69
6	$Pd(OAc)_2$	PCy_3HBF_4	Na_2CO_3	2.0	120	72
7[c,e]	$Pd(OAc)_2$	PCy_3HBF_4	Na_2CO_3	2.0	120	65
8[c,f]	$Pd(OAc)_2$	PCy_3HBF_4	Na_2CO_3	2.0	120	25
9[c]	$Pd(OAc)_2$	PCy_3HBF_4	K_2CO_3	2.0	120	<5
10[c]	$Pd(OAc)_2$	PCy_3HBF_4	K_2CO_3	2.0	80	53
11	Pd-PEPPSI-IPr	-	K_2CO_3	3.0	120	69
12	Pd-PEPPSI-IPr	-	K_3PO_4	3.0	120	<2
13	Pd-PEPPSI-IPr	-	Na_2CO_3	3.0	120	19

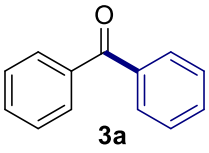
14	Pd-PEPPSI-IPr	-	Cs_2CO_3	3.0	120	<2
15	Pd-PEPPSI-IPr	-	KOH	3.0	120	5
16[g]	Pd-PEPPSI-IPr	-	K_2CO_3	4.5	120	81
17	Pd-PEPPSI-IPr	-	K_2CO_3	2.0	120	80
18[c]	Pd-PEPPSI-IPr	-	K_2CO_3	2.0	120	50
19[h]	Pd-PEPPSI-IPr	-	K_2CO_3	2.0	120	71
20	Pd-PEPPSI-IPr	-	K_2CO_3	1.5	120	93
21	Pd-PEPPSI-IPr	-	K_2CO_3	1.5	23	<2
22	Pd-PEPPSI-IPr	-	K_2CO_3	1.5	60	25
23	Pd-PEPPSI-IMes	-	K_2CO_3	1.5	80	57
24	Pd-PEPPSI-IPent	-	K_2CO_3	1.5	80	79
25	Pd-PEPPSI^{py}-IPr	-	K_2CO_3	1.5	80	82

[a]Conditions: **1** (1.0 equiv), Ar-B(OH)$_2$ (2.0 equiv), [Pd] (3 mol %), PCy_3HBF_4 (12 mol %), base, (1.5-4.5 equiv), dioxane (0.25 M), *T*, 15 h. [b]GC/^{1}H NMR yields. [c]Ar-B(OH)$_2$ (1.5 equiv). [d]Ar-B(OH)$_2$ (1.2 equiv). [e]Pd(OAc)$_2$ (6 mol %), PCy_3HBF_4 (12 mol %). [f]Pd(OAc)$_2$ (1 mol %), PCy_3HBF_4 (4 mol %). [g]Ar-B(OH)$_2$ (3.0 equiv). [h]H_2O (5 equiv).

With the optimized conditions in hand, the scope of these two new protocols was examined (Schemes 1-2). *For comparison, yields obtained by Zeng and co-workers using the [Pd(IPr)(allyl)Cl] catalyst are shown in brackets for all examples.*[8] With respect to the boronic acid scope (Scheme 1), we were pleased to find that the reaction accommodates a broad range of boronic acids, including electronically-neutral (**3a-b**), electron-donating (**3c**) and electron-withdrawing substrates (**3d-g**). Steric hindrance was well-tolerated (**3h**). Furthermore, the scope includes meta-substitution (**3i-j**), polyarenes (**3k**) and heterocycles (**3l**). A noteworthy feature is functional group tolerance to sensitive electrophiles, such as ester (**3d**) and aldehyde (**3g**), which would not be tolerated under classical Weinreb amide conditions. Overall, both of the protocols showed comparable or superior performance to the [Pd(IPr)(allyl)Cl] catalysis at lower catalyst loading. Typically, Pd–PEPPSI gave slightly higher yields than Pd/PCy_3 catalysis.

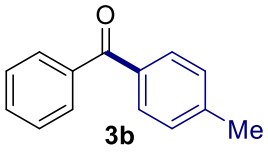
Scheme 1. Suzuki Cross-Coupling of *N*-Acyl-5,5-dimethylhydantoin: Scope of Boronic Acids[a]





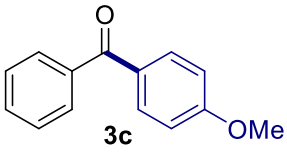
3a

Pd-PEPPSI: **96% yield**
Pd/PCy$_3$: **82% yield**
(Pd(IPr)(allyl)Cl: 90% yield)



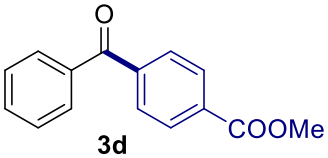
3b

Pd-PEPPSI: **96% yield**
Pd/PCy$_3$: **92% yield**
(Pd(IPr)(allyl)Cl: 92% yield)



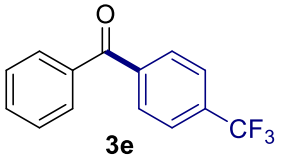
3c

Pd-PEPPSI: **91% yield**
Pd/PCy$_3$: **86% yield**
(Pd(IPr)(allyl)Cl: 95% yield)



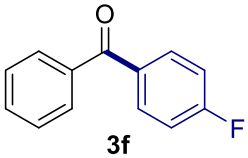
3d

Pd-PEPPSI: **79% yield**
Pd/PCy$_3$: **88% yield**
(Pd(IPr)(allyl)Cl: 81% yield)



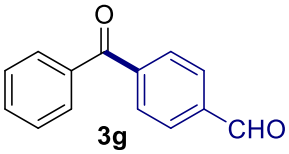
3e

Pd-PEPPSI: **72% yield**
Pd/PCy$_3$: **63% yield**
(Pd(IPr)(allyl)Cl: 56% yield)



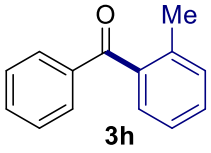
3f

Pd-PEPPSI: **95% yield**
Pd/PCy$_3$: **55% yield**[b]
(Pd(IPr)(allyl)Cl: 86% yield)



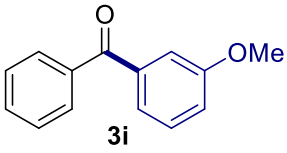
3g

Pd-PEPPSI: **71% yield**
Pd/PCy$_3$: **58% yield**
(Pd(IPr)(allyl)Cl: 57% yield)



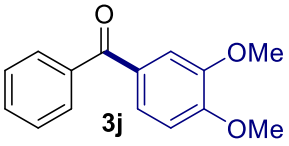
3h

Pd-PEPPSI: **88% yield**
Pd/PCy$_3$: **65% yield**
(Pd(IPr)(allyl)Cl: 88% yield)



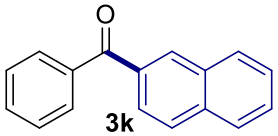
3i

Pd-PEPPSI: **88% yield**
Pd/PCy$_3$: **66% yield**
(Pd(IPr)(allyl)Cl: 80% yield)



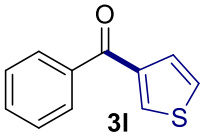
3j

Pd-PEPPSI: **82% yield**
Pd/PCy$_3$: **72% yield**
(Pd(IPr)(allyl)Cl: 61% yield)



3k

Pd-PEPPSI: **98% yield**
Pd/PCy$_3$: **59% yield**
(Pd(IPr)(allyl)Cl: 82% yield)



3l

Pd-PEPPSI: **72% yield**
Pd/PCy$_3$: **79% yield**
(Pd(IPr)(allyl)Cl: 80% yield)

[a]Conditions: **A: Pd–PEPPSI–IPr:** amide (1.0 equiv), Ar-B(OH)$_2$ (2.0 equiv), Pd–PEPPSI–IPr (3 mol%), K_2CO_3 (1.5 equiv), dioxane (0.25 M), 80 °C, 15 h. **B: Pd/PCy$_3$:** amide (1.0 equiv), Ar-B(OH)$_2$ (1.5 equiv), Pd(OAc)$_2$ (3 mol%), PCy$_3$HBF$_4$ (12 mol%), Na_2CO_3 (2.0 equiv), dioxane (0.25 M), 120 °C, 15 h. **C: [Pd(IPr)(allyl)Cl] (Ref. 8):** amide (1.0 equiv), Ar-B(OH)$_2$ (2.0 equiv), [Pd(IPr)(allyl)Cl] (6 mol%), K_2CO_3 (3.0 equiv), dioxane (2.0 M), 110 °C, 15 h. [b]Pd(OAc)$_2$ (6 mol%), PCy$_3$HBF$_4$ (24 mol%).

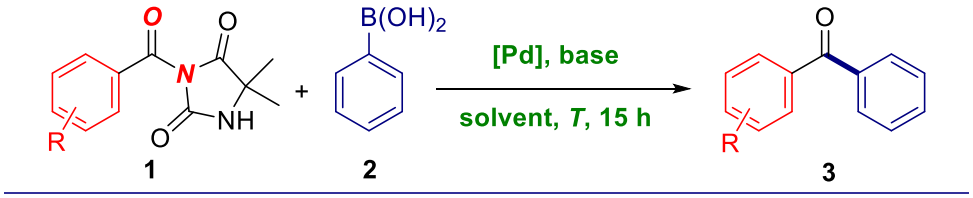
Note: Conditions C: [Pd(IPr)(allyl)Cl] correspond to the yields obtained in ref. 8.

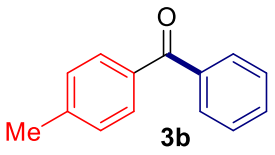
Scheme 2 summarizes the scope of the reaction with respect to the *N*-acyl-5,5-dimethylhydantoin component. As mentioned (eq 1-2), 5,5-gem-dimethyl-subsitution is preferred over the unsubstituted variant. Regarding the amide scope, we were pleased to find that neutral (**3b**), electron-rich (**3c**) and electron-deficient (**3d-e**) amides underwent coupling in high to excellent yields under both reaction conditions. Moreover, sterically-hindered (**3h**) and heterocyclic amides (**3m**) afforded the desired ketone products catalyzed by both systems. The results obtained with *N*-acyl-5,5-dimethylhydantoins using Pd–PEPPSI and Pd/PCy_3 compare favorably with the [Pd(IPr)(allyl)Cl] catalysis.

To demonstrate scalability, a gram scale reaction was performed (**1a**, 1.0 g, 4.31 mmol), Ph-$B(OH)_2$ (1.5 equiv, 6.46 mmol, 0.79 g), $Pd(OAc)_2$ (3 mol%, 29 mg), PCy_3HBF_4 (12 mol%, 190 mg), Na_2CO_3 (2.0 equiv, 8.62 mmol, 0.91 g), dioxane (0.25 M), 120 °C, 15 h, resulting in 87% isolated yield (0.685 g), attesting to the scalability of the cross-coupling (not shown).

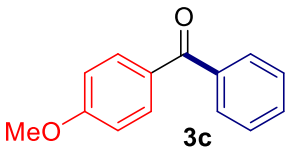
We were further interested to test the generality of the catalyst systems and applied the reaction conditions to the Suzuki cross-coupling of other classes of twisted amides (Scheme 3). For comparison, the yields obtained using the [Pd(IPr)(allyl)Cl] catalyst by Zeng and co-workers for the same amide substrate combinations are presented in brackets.[8] Thus, the Suzuki cross-coupling of *N*-benzoyl-5,5-dimethylhydantoin (**1a**), *N*-benzoylsuccinimide (**1h**),[16,13g] *N*-benzoylsaccharin (**1i**)[17,13i] and *N*-Ts-*N*-phenylbenzamide (**1j**)[2a] all occurred in high to excellent yields, comparing favorably with the [Pd(IPr)(allyl)Cl] conditions.

Scheme 2. Suzuki Cross-Coupling of *N*-Acyl-5,5-dimethylhydantoin: Scope of Amides

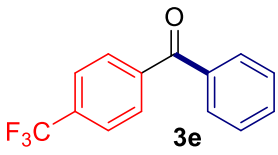




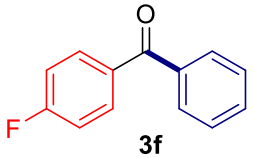
Pd-PEPPSI: 98% yield
Pd/PCy$_3$: 85% yield
(Pd(IPr)(allyl)Cl: 85% yield)



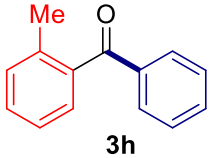
Pd-PEPPSI: 91% yield
Pd/PCy$_3$: 68% yield[b]
(Pd(IPr)(allyl)Cl: 87% yield)



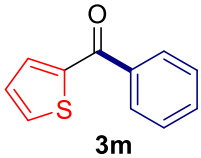
Pd-PEPPSI: 98% yield
Pd/PCy$_3$: 95% yield[c]
(Pd(IPr)(allyl)Cl: 61% yield)



Pd-PEPPSI: 98% yield
Pd/PCy$_3$: 61% yield
(Pd(IPr)(allyl)Cl: 81% yield)



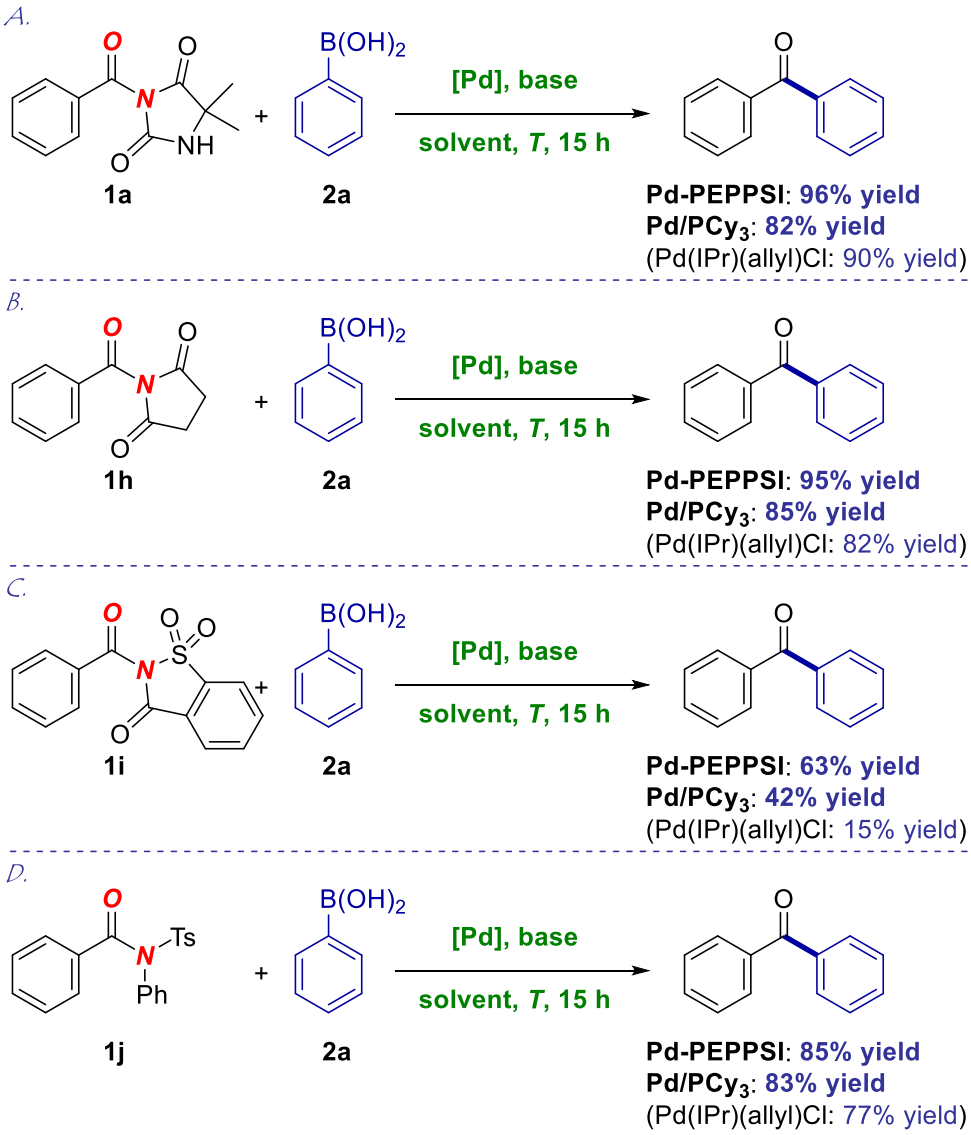
Pd-PEPPSI: 72% yield[d]
Pd/PCy$_3$: 70% yield
(Pd(IPr)(allyl)Cl: 74% yield)



Pd-PEPPSI: 88% yield
Pd/PCy$_3$: 57% yield
(Pd(IPr)(allyl)Cl: 78% yield)

[a]Conditions: **A: Pd–PEPPSI–IPr:** amide (1.0 equiv), Ar-B(OH)$_2$ (2.0 equiv), Pd–PEPPSI–IPr (3 mol%), K_2CO_3 (1.5 equiv), dioxane (0.25 M), 80 °C, 15 h. **B: Pd/PCy$_3$:** amide (1.0 equiv), Ar-B(OH)$_2$ (1.5 equiv), Pd(OAc)$_2$ (3 mol%), PCy$_3$HBF$_4$ (12 mol%), Na_2CO_3 (2.0 equiv), dioxane (0.25 M), 120 °C, 15 h. **C: [Pd(IPr)(allyl)Cl] (Ref. 8):** amide (1.0 equiv), Ar-B(OH)$_2$ (2.0 equiv), [Pd(IPr)(allyl)Cl] (6 mol%), K_2CO_3 (3.0 equiv), dioxane (2.0 M), 110 °C, 15 h. [b]Ar-B(OH)$_2$ (3.0 equiv), Na_2CO_3 (4.5 equiv). [c]Pd(OAc)$_2$ (6 mol%), PCy$_3$HBF$_4$ (24 mol%). [d]Pd–PEPPSI–IPr (6 mol%). Note: Conditions C: [Pd(IPr)(allyl)Cl] correspond to the yields obtained in ref. 8.

Scheme 3. Suzuki Cross-Coupling of *N*-Acyl-5,5-dimethylhydantoin: Various Amides[a]



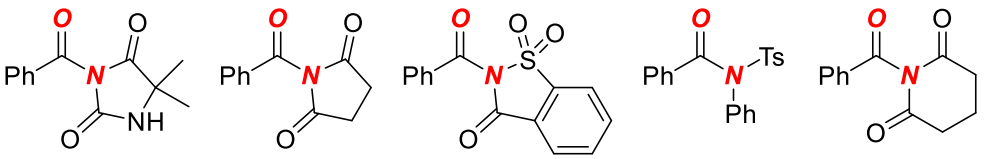
[a]See Scheme 1.

At this stage, electronic and structural parameters of all of amides shown in Scheme 3 have been determined by our group (Table 2).[6] It is absolutely critical to point out that the reactivity of twisted amides in N–C(O) cross-coupling correlates with amide bond resonance (cf. twist), and is significantly influenced by the stability of the N–C(O) amide bond and/or N-activating group to the reaction conditions. There is no doubt that the most reactive amides as determined by resonance and/or twist, a leading example of which are perfectly perpendicular *N*-acyl-glutarimides (RE = 0 kcal/mol, **1k**),[3a] are

not always preferred substrates for select cross-couplings due to the stability of the amide bond under a given set of reaction conditions. All future design should be based on consideration of amidic resonance and amide bond twist of precursors.[18,19]

Table 2. Steric and Energetic Properties of Amides[a,b]

A. Structures of twisted amides



1a **1h** **1i** **1j** **1k**

B. Structural and energetic parameters

entry	**1a** hydantoin	**1h** succinimide	**1i** saccharin	**1j** Ts	**1k** glutarimide
τ	49.5	46.1	23.0	18.8	87.5
χN	13.3	9.5	12.5	19.9	5.6
Σ(τ+χN)[5g]	62.8	55.6	35.5	38.7	93.1
RE	0.0	-0.3	2.0	9.7	-1.4

[a]Winker-Dunitz parameters, τ, χN [deg]. Additive Winkler-Dunitz parameter, Σ(τ+χN) [deg]. See ref. 5,6. [b]RE, resonance energy (kcal/mol) calculated at B3LYP/6-311++G(d,p). See ref. 5d,6.

3. Conclusions

In summary, we have developed conditions for the cross-coupling of *N*-acyl-5,5-dimethylhydantoins using versatile Pd–PEPPSI and Pd/phosphine catalysts. The acyl Suzuki reactions occur in high yields to afford biaryl ketone products under operationally-simple conditions. The reactions feature twisted *N*-acyl-hydantoins as mild, commercially-available, bench- and air-stable acyl donors. The protocols expand the previous study on the use of [Pd(IPr)(allyl)Cl] catalyst. Another important feature involved the finding that IPr is the preferred NHC ancillary ligand for the cross-coupling of *N*-acyl-5,5-dimethylhydantoins in terms of steric demand in lieu of less bulky IMes and more sterically-demanding

IPent, while 3-chloropyridine throw-away ligand is preferred over pyridine throw-away ligand. More generally, the study provides further evidence that the optimum results in amide bond cross-coupling are obtained by using Pd-NHC catalysts with different classes of throw-away ligands, including PEPPSI-type and allyl-type, as well as Pd/phosphine catalysts. Studies directed on application of amide bond cross-coupling in the synthesis of bioactive molecules are ongoing and will be reported in due course. We anticipate that further progress in amide bond cross-coupling will be achieved by studies on ligand design and the development of new twisted amide precursors for cross-coupling.

Experimental Section

General Methods. All starting materials reported in the manuscript have been previously described in literature.[8] All products reported in the manuscript have been previously described.[8] All experiments were performed using standard Schlenk techniques under argon or nitrogen atmosphere. All solvents were purchased at the highest commercial grade and used as received or after purification by passing through activated alumina columns or distillation from sodium/benzophenone under nitrogen. All other chemicals were purchased at the highest commercial grade and used as received. All other general methods have been published.[3a] ^{1}H NMR and ^{13}C NMR data are given for all compounds in the Supporting Experimental for characterization purposes. ^{1}H NMR, ^{13}C NMR and HRMS data are reported for all new compounds.

General Procedure for Suzuki-Miyaura Cross-Coupling of Amides. Pd–PEPPSI: An oven-dried vial equipped with a stir bar was charged with an amide substrate (neat, 1.0 equiv), K_2CO_3 (typically, 1.5 equiv), boronic acid (typically, 2.0 equiv), Pd–NHC catalyst (typically, 3.0 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Dioxane (typically, 0.25 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 80 °C and stirred for the indicated time. After the indicated time, the reaction mixture was cooled down to room temperature, diluted with CH_2Cl_2 (10 mL), filtered, and

concentrated. A sample was analyzed by ^{1}H NMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (EtOAc/hexanes = 20/1) afforded the tile product.

General Procedure for Suzuki-Miyaura Cross-Coupling of Amides. Pd/PCy$_3$: An oven-dried vial equipped with a stir bar was charged with an amide substrate (neat, 1.0 equiv), Na_2CO_3 (typically, 2.0 equiv), boronic acid (typically, 1.5 equiv), $Pd(OAc)_2$ (typically, 3.0 mol%), PCy_3HBF_4 (typically, 12 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Dioxane (typically, 0.25 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 120 °C, and stirred for the indicated time. After the indicated time, the reaction mixture was cooled down to room temperature, diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. The sample was analyzed by ^{1}H NMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, yield and selectivity using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (hexanes/ethyl acetate = 20/1) afforded the title product.

Representative Procedure for Suzuki-Miyaura Cross-Coupling of Amides. Pd–PEPPSI. 1.0 Mmol Scale. An oven dried vial equipped with a stir bar was charged with 3-benzoyl-5,5,-dimethylhydantoin (neat, 232.2 mg, 1.0 mmol), K_2CO_3 (1.5 mmol, 207.3 mg, 1.5 equiv), 4-tolylboronic acid (2.0 mmol, 272.1 mg, 2.0 equiv), Pd–PEPPSI–IPr (20.4 mg, 3 mol%) placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Dioxane (0.25 M) was added with vigorous stirring at room temperature, and the reaction mixture was stirred for 15 h at 80 °C. After the indicated time, the reaction mixture was cooled down to room temperature, diluted with CH_2Cl_2 (20 mL), filtered, and concentrated. Purification by chromatography on silica gel (EtOAc/hexanes = 20/1) afforded the title product. White solid. Yield 82% (160.9 mg). Characterization data are included in the section below.

Representative Procedure for Suzuki-Miyaura Cross-Coupling of Amides. Pd/PCy_3. 1.0 Mmol Scale. An oven dried vial equipped with a stir bar was charged with 3-benzoyl-5,5,-dimethylhydantoin (neat, 232.2 mg, 1.0 mmol), Na_2CO_3 (2.0 mmol, 212.0 mg, 2.0 equiv), 4-tolylboronic acid (1.5 mmol, 204.1 mg, 1.5 equiv), $Pd(OAc)_2$ (6.7 mg, 3 mol%), PCy_3HBF_4 (44.2 mg, 12 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Dioxane (0.25 M) was added with vigorous stirring at room temperature, and the reaction mixture was stirred for 15 h at 120 °C. After the indicated time, the reaction mixture was cooled down to room temperature, diluted with CH_2Cl_2 (20 mL), filtered, and concentrated. Purification by chromatography on silica gel (EtOAc/hexanes = 20/1) afforded the title product. White solid. Yield 95% (186.4 mg). Characterization data are included in the section below.

Characterization Data of Products. All products reported in the manuscript have been previously reported.[8] Spectroscopic data match those reported in the literature.

Benzophenone (3a). According to the general procedure, the reaction of 3-benzoyl-5,5-dimethylhydantoin (0.10 mmol), phenylboronic acid (2.0 equiv), K_2CO_3 (1.5 equiv) and Pd–PEPPSI–IPr (3.0 mol%) in dioxane (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography (hexanes/ethyl acetate = 20/1) the title product in 96% yield (17.5 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90-7.77 (m, 4H), 7.61 (dd, *J* = 10.6, 4.2 Hz, 2H), 7.50 (t, *J* = 7.6 Hz, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.63, 137.54, 132.33, 129.97, 128.20. Pd/PCy_3: 82% yield (14.9 mg).

Phenyl(*p*-tolyl)methanone (3b). According to the general procedure, the reaction of 3-benzoyl-5,5-dimethylhydantoin (0.10 mmol), *p*-tolylboronic acid (2.0 equiv), K_2CO_3 (1.5 equiv) and Pd–PEPPSI–IPr (3.0 mol%) in dioxane (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography (hexanes/ethyl acetate = 20/1) the title product in 96% yield (18.8 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85-7.78 (m, 2H), 7.75 (d, *J* = 8.1 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.51, 143.26, 137.98, 134.91, 132.18, 130.33, 129.95, 129.00, 128.23, 21.68. Pd/PCy_3: 92% yield (18.0 mg).

(4-Methoxyphenyl)(phenyl)methanone (3c). According to the general procedure, the reaction of 3-benzoyl-5,5-dimethylhydantoin (0.10 mmol), *p*-methoxyphenylboronic acid (2.0 equiv), K_2CO_3 (1.5 equiv) and Pd–PEPPSI–IPr (3.0 mol%) in dioxane (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography (hexanes/ethyl acetate = 20/1) the title product in 91% yield (19.3 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88-7.83 (m, 2H), 7.80-7.75 (m, 2H), 7.58 (dd, *J* = 10.6, 4.3 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.01-6.95 (m, 2H), 3.91 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.55, 163.24, 138.32, 132.57, 131.89, 130.20, 129.74, 128.19, 113.57, 55.51. Pd/PCy_3: 86% yield (18.2 mg).

Methyl 4-benzoylbenzoate (3d). According to the general procedure, the reaction of 3-benzoyl-5,5-dimethylhydantoin (0.10 mmol), 4-(methoxycarbonyl)phenylboronic acid (2.0 equiv), K_2CO_3 (1.5 equiv) and Pd–PEPPSI–IPr (3.0 mol%) in dioxane (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography (hexanes/ethyl acetate = 20/1) the title product in 79% yield (18.9 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.5 Hz, 2H), 7.86 (d, *J* = 8.5 Hz, 2H), 7.84-7.80 (m, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 2H), 3.99 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.03, 166.33, 141.35, 136.98, 133.24, 132.95, 130.11, 129.78, 129.51, 128.47, 52.47. Pd/PCy_3: 88% yield (21.1 mg).

Phenyl(4-(trifluoromethyl)phenyl)methanone (3e). According to the general procedure, the reaction of 3-benzoyl-5,5-dimethylhydantoin (0.10 mmol), 4-(methoxycarbonyl)phenylboronic acid (2.0 equiv), K_2CO_3 (1.5 equiv) and Pd–PEPPSI–IPr (3.0 mol%) in dioxane (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography (hexanes/ethyl acetate = 20/1) the title product in 72% yield (18.0 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.0 Hz, 2H), 7.85-7.80 (m, 2H), 7.78 (d, *J* = 8.1 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.52, 140.74, 136.74, 133.86, 133.84 (q, J^F = 32.7 Hz), 130.13, 130.10, 128.53, 125.47 (q, *J* = 3.7 Hz), 123.80 (q, J^F = 272.6 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -63.00. Pd/PCy_3: 63% yield (15.8 mg).

(4-Fluorophenyl)(phenyl)methanone (3f). According to the general procedure, the reaction of 3-benzoyl-5,5-dimethylhydantoin (0.10 mmol), 4-(methoxycarbonyl)phenylboronic acid (2.0 equiv),

K_2CO_3 (1.5 equiv) and Pd–PEPPSI–IPr (3.0 mol%) in dioxane (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography (hexanes/ethyl acetate = 20/1) the title product in 95% yield (19.0 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93-7.84 (m, 2H), 7.82-7.75 (m, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.18 (dd, *J* = 12.1, 5.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.30, 165.41 (d, J^F = 252.5 Hz), 137.52, 133.82 (d, J^F = 2.9 Hz), 132.69 (d, J^F = 9.1 Hz), 132.49, 129.90, 128.38, 115.48 (d, J^F = 21.7 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -105.98. Pd/PCy_3: 55% yield (11.0 mg).

4-Benzoylbenzaldehyde (3g). According to the general procedure, the reaction of 3-benzoyl-5,5-dimethylhydantoin (0.10 mmol), 4-formylphenylboronic acid (2.0 equiv), K_2CO_3 (1.5 equiv) and Pd–PEPPSI–IPr (3.0 mol%) in dioxane (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography (hexanes/ethyl acetate = 20/1) the title product in 71% yield (14.9 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.16 (s, 1H), 8.03 (d, *J* = 8.3 Hz, 2H), 7.95 (d, *J* = 8.1 Hz, 2H), 7.86-7.79 (m, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.82, 191.61, 142.60, 138.51, 136.77, 133.14, 130.34, 130.13, 129.51, 128.55. Pd/PCy_3: 58% yield (12.2 mg).

Phenyl(*o*-tolyl)methanone (3h). According to the general procedure, the reaction of 3-benzoyl-5,5-dimethylhydantoin (0.10 mmol), 3-methoxyphenylboronic acid (2.0 equiv), K_2CO_3 (1.5 equiv) and Pd–PEPPSI–IPr (3.0 mol%) in dioxane (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography (hexanes/ethyl acetate = 20/1) the title product in 88% yield (17.2 mg). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76-7.70 (m, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.31 (td, *J* = 7.6, 1.2 Hz, 1H), 7.23 (dd, *J* = 11.5, 7.3 Hz, 1H), 7.17 (dd, *J* = 9.9, 5.0 Hz, 1H), 2.26 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.61, 138.59, 137.72, 136.72, 133.10, 130.97, 130.21, 130.10, 128.49, 128.43, 125.16, 19.95. Pd/PCy_3: 65% yield (12.7 mg).

(3-Methoxyphenyl)(phenyl)methanone (3i). According to the general procedure, the reaction of 3-benzoyl-5,5-dimethylhydantoin (0.10 mmol), 3-methoxyphenylboronic acid (2.0 equiv), K_2CO_3 (1.5 equiv) and Pd–PEPPSI–IPr (3.0 mol%) in dioxane (0.25 M) for 15 h at 80 °C, afforded after filtration

and chromatography (hexanes/ethyl acetate = 20/1) the title product in 88% yield (18.7 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92-7.79 (m, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.44-7.32 (m, 3H), 7.16 (ddd, *J* = 7.9, 2.6, 1.1 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.52, 159.60, 138.93, 137.65, 132.42, 130.05, 129.22, 128.26, 122.88, 118.87, 114.34, 55.49. Pd/PCy_3: 66% yield (13.9 mg).

(3,4-Dimethoxyphenyl)(phenyl)methanone (3j). According to the general procedure, the reaction of 3-benzoyl-5,5-dimethylhydantoin (0.10 mmol), 3,4-dimethoxyphenylboronic acid (2.0 equiv), K_2CO_3 (1.5 equiv) and Pd–PEPPSI–IPr (3.0 mol%) in dioxane (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography (hexanes/ethyl acetate = 20/1) the title product in 82% yield (19.8 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82-7.74 (m, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.54-7.47 (m, 31H), 7.40 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.93-6.90 (m, 1H), 3.98 (s, 3H), 3.97 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.58, 153.05, 149.04, 138.32, 131.88, 130.26, 129.73, 128.18, 125.51, 112.16, 109.76, 56.11, 56.07. Pd/PCy_3: 72% yield (17.4 mg).

Naphthalen-2-yl(phenyl)methanone (3k). According to the general procedure, the reaction of 3-benzoyl-5,5-dimethylhydantoin (0.10 mmol), naphthalen-2-ylboronic acid (2.0 equiv), K_2CO_3 (1.5 equiv) and Pd–PEPPSI–IPr (3.0 mol%) in dioxane (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography (hexanes/ethyl acetate = 20/1) the title product in 98% yield (22.7 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.97 (s, 2H), 7.96-7.92 (m, 2H), 7.91-7.87 (m, 2H), 7.68-7.62 (m, 2H), 7.57 (ddd, *J* = 17.4, 11.7, 4.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.72, 137.91, 135.26, 134.83, 132.35, 132.25, 131.84, 130.08, 129.40, 128.32, 128.30, 128.28, 127.80, 126.78, 125.77. Pd/PCy_3: 59% yield (13.7 mg).

Phenyl(thiophen-3-yl)methanone (3l). According to the general procedure, the reaction of 3-benzoyl-5,5-dimethylhydantoin (0.10 mmol), thiophen-3-ylboronic acid (2.0 equiv), K_2CO_3 (1.5 equiv) and Pd–PEPPSI–IPr (3.0 mol%) in dioxane (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography (hexanes/ethyl acetate = 20/1) the title product in 72% yield (22.7 mg). White solid. ^{1}H

NMR (500 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 2.9, 1.1 Hz, 1H), 7.89-7.84 (m, 2H), 7.64-7.57 (m, 2H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.39 (dd, *J* = 5.1, 2.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.88, 141.22, 138.56, 133.82, 132.22, 129.28, 128.52, 128.30, 126.13. Pd/PCy_3: 79% yield (14.9 mg).

Phenyl(*p*-tolyl)methanone (3b). According to the general procedure, the reaction of 3-(4-methylbenzoyl)-5,5-dimethylhydantoin (0.10 mmol), phenylboronic acid (2.0 equiv), K_2CO_3 (1.5 equiv) and Pd–PEPPSI–IPr (3.0 mol%) in dioxane (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography (hexanes/ethyl acetate = 20/1) the title product in 98% yield (19.2 mg). White solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.85-7.78 (m, 2H), 7.75 (d, *J* = 8.1 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.51, 143.26, 137.98, 134.91, 132.18, 130.33, 129.95, 129.00, 128.23, 21.68. Pd/PCy_3: 85% yield (16.7 mg).

(4-Methoxyphenyl)(phenyl)methanone (3c). According to the general procedure, the reaction of 3-(4-methoxybenzoyl)-5,5-dimethylhydantoin (0.10 mmol), phenylboronic acid (2.0 equiv), K_2CO_3 (1.5 equiv) and Pd–PEPPSI–IPr (3.0 mol%) in dioxane (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography (hexanes/ethyl acetate = 20/1) the title product in 91% yield (19.3 mg). White solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.88-7.83 (m, 2H), 7.80-7.75 (m, 2H), 7.58 (dd, *J* = 10.6, 4.3 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.01-6.95 (m, 2H), 3.91 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.55, 163.24, 138.32, 132.57, 131.89, 130.20, 129.74, 128.19, 113.57, 55.51. Pd/PCy_3: 68% yield (14.4 mg).

Phenyl(4-(trifluoromethyl)phenyl)methanone (3e). According to the general procedure, the reaction of 3-(4-(trifluoromethyl)benzoyl)-5,5-dimethylhydantoin (0.10 mmol), phenylboronic acid (2.0 equiv), K_2CO_3 (1.5 equiv) and Pd–PEPPSI–IPr (3.0 mol%) in dioxane (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography (hexanes/ethyl acetate = 20/1) the title product in 98% yield (24.5 mg). White solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.0 Hz, 2H), 7.85-7.80 (m, 2H), 7.78 (d, *J* = 8.1 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.52, 140.74, 136.74, 133.86, 133.84 (q, J^F = 32.7 Hz), 130.13, 130.10, 128.53, 125.47 (q, *J* = 3.7 Hz), 123.80 (q, J^F = 272.6 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -63.00. Pd/PCy_3: 95% yield (23.8 mg).

(4-Fluorophenyl)(phenyl)methanone (3f). According to the general procedure, the reaction of 3-(4-fluorobenzoyl)-5,5-dimethylhydantoin (0.10 mmol), phenylboronic acid (2.0 equiv), K_2CO_3 (1.5 equiv) and Pd–PEPPSI–IPr (3.0 mol%) in dioxane (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography (hexanes/ethyl acetate = 20/1) the title product in 98% yield (24.5 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93-7.84 (m, 2H), 7.82-7.75 (m, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.7 Hz, 2H), 7.18 (dd, J = 12.1, 5.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.30, 165.41 (d, J^F = 252.5 Hz), 137.52, 133.82 (d, J^F = 2.9 Hz), 132.69 (d, J^F = 9.1 Hz), 132.49, 129.90, 128.38, 115.48 (d, J^F = 21.7 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -105.98. Pd/PCy_3: 61% yield (12.2 mg).

Phenyl(*o*-tolyl)methanone (3h). According to the general procedure, the reaction of 3-(2-methylbenzoyl)-5,5-dimethylhydantoin (0.10 mmol), phenylboronic acid (2.0 equiv), K_2CO_3 (1.5 equiv) and Pd–PEPPSI–IPr (6.0 mol%) in dioxane (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography (hexanes/ethyl acetate = 20/1) the title product in 72% yield (14.1 mg). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76-7.70 (m, 1H), 7.50 (t, J = 7.4 Hz, 1H), 7.38 (t, J = 7.7 Hz, 1H), 7.31 (td, J = 7.6, 1.2 Hz, 1H), 7.23 (dd, J = 11.5, 7.3 Hz, 1H), 7.17 (dd, J = 9.9, 5.0 Hz, 1H), 2.26 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.61, 138.59, 137.72, 136.72, 133.10, 130.97, 130.21, 130.10, 128.49, 128.43, 125.16, 19.95. Pd/PCy_3: 70% yield (13.7 mg).

Phenyl(thiophen-2-yl)methanone (3m). According to the general procedure, the reaction of 3-(2-methylbenzoyl)-5,5-dimethylhydantoin (0.10 mmol), phenylboronic acid (2.0 equiv), K_2CO_3 (1.5 equiv) and Pd–PEPPSI–IPr (3.0 mol%) in dioxane (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography (hexanes/ethyl acetate = 20/1) the title product in 88% yield (16.5 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 7.4 Hz, 2H), 7.75 (d, J = 4.9 Hz, 1H), 7.67 (d, J = 3.7 Hz, 1H), 7.62 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.7 Hz, 2H), 7.22-7.16 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.24, 143.68, 138.19, 134.83, 134.19, 132.27, 129.19, 128.43, 127.95. Pd/PCy_3: 57% yield (10.7 mg).

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Supporting Information. Copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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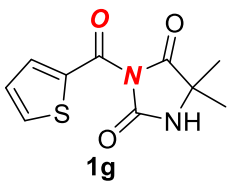

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