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Sterically Hindered Ketones via Palladium-Catalyzed Suzuki−Miyaura Cross-Coupling of Amides by N−C(O) Activation

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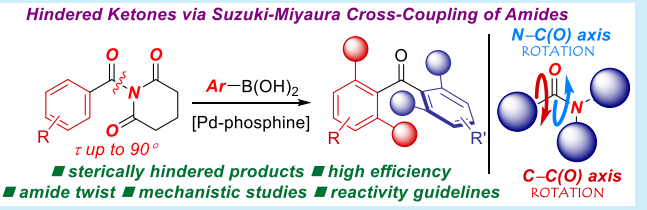
Supporting Information

ABSTRACT: Herein, we report a new protocol for the synthesis of sterically hindered ketones that proceeds via palladium-catalyzed Suzuki−Miyaura cross-coupling of unconventional amide electrophiles by selective N−C(O) activation. Mechanistic studies demonstrate that steric bulk on the amide has a major impact, which is opposite to the traditional Suzuki−Miyaura cross-coupling of sterically hindered aryl halides. Structural and computational studies provide insight into ground-state distortion of sterically hindered amides and show that ortho-substitution alleviates the N−C(O) bond twist.



The development of catalytic methods for the synthesis of sterically hindered ketones is an important objective in synthetic chemistry because bulky ketones are ubiquitous in natural products, bioactive compounds, and advanced materials and can be further exploited to access a myriad of derivatives by the classical *ipso*-carbonyl addition.[1−3] In this context, transition-metal-catalyzed cross-coupling of acyl electrophiles would represent a very attractive method for the synthesis of sterically hindered ketones because it offers the advantages of well-controlled cross-coupling mechanisms, high levels of selectivity, and operational practicality.[4,5] However, in contrast to the synthesis of sterically hindered biaryls by the traditional Suzuki−Miyaura cross-coupling of aryl halides,[6] methods for the construction of sterically hindered ketones by the cross-coupling of acyl electrophiles remain largely underdeveloped.[7,4] In general, very few methods for the synthesis of di-ortho,ortho′-substituted biaryl ketones by the acyl Suzuki−Miyaura cross-coupling have been developed.[4] Mechanistically, a key difference between the two types of cross-coupling is the capacity of the acyl (ArC(O)−X) vs aryl (Ar−X) electrophile to undergo productive metal insertion, which generates the acyl−metal vs aryl−metal complex for the subsequent transmetalation step.[8,9]

We were attracted by the potential of amides[10−15] to serve as electrophiles[16−18] in the synthesis of sterically hindered ketones by a catalytic mechanism involving chemoselective metal insertion into the N−C(O) bond (Figure 1A). Herein, we report the first general method for the synthesis of sterically hindered ketones that proceeds via Pd-catalyzed Suzuki−Miyaura cross-coupling of amides by selective N−C(O) activation (Figure 1B).[4]

Notable features of our findings are as follows: (1) we describe the first general protocol for the synthesis of sterically hindered ketones by the acyl Suzuki−Miyaura cross-coupling using readily available *N*-acylglutarimides as coupling precursors; (2) we present a series of mechanistic, structural, and computational studies that demonstrate that the origin of low reactivity of sterically hindered amides is a result of minimized amide bond distortion. This novel protocol sets the stage for the development of general strategies to sterically hindered ketones by cross-coupling of unconventional amide electrophiles.

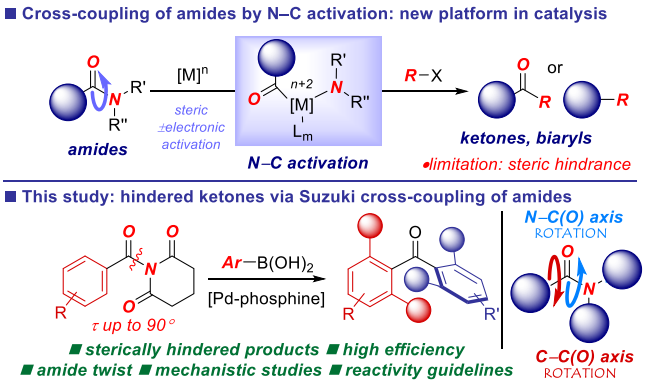


Figure 1. (a) Cross-coupling of amides by N−C activation. (b) This work: hindered ketones via Suzuki−Miyaura cross-coupling of amides.

To the best of our knowledge, very few methods for the synthesis of sterically hindered ketones by the acyl Suzuki−Miyaura cross-coupling have been reported.[4,7,11,12] Our initial studies focused on the cross-coupling of electronically

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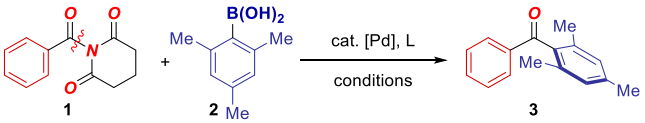
unbiased *N*-benzoylglutarimide with 2,4,6-trimethylphenylboronic acid (Table 1). Upon investigating reaction parameters,

Table 1. Optimization of Reaction Conditions[a]



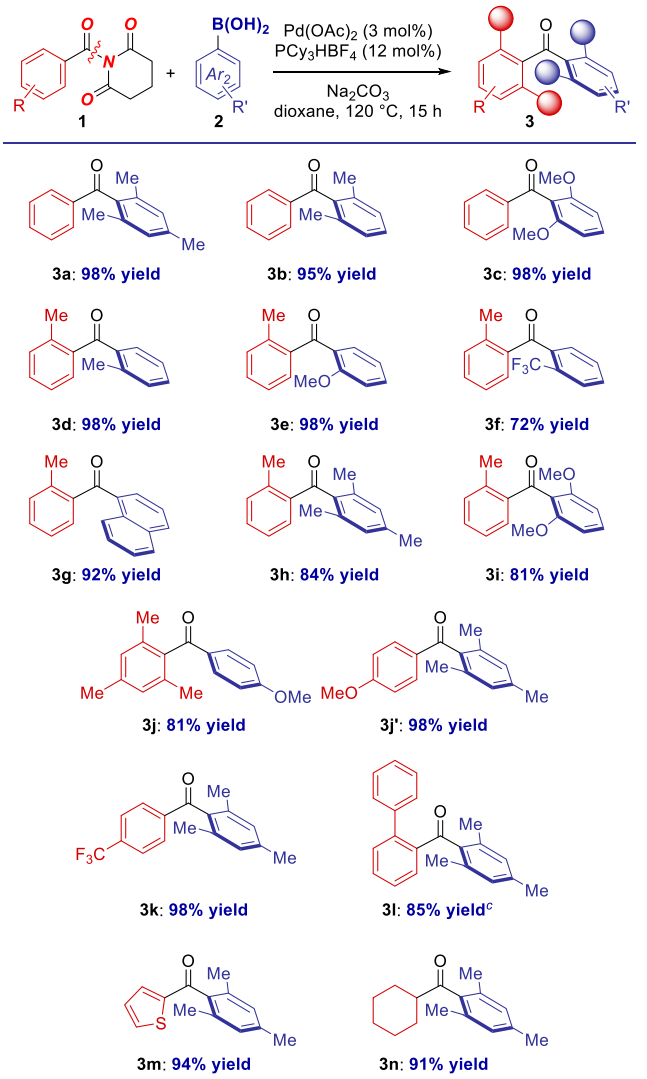
entry	catalyst	ligand	base	yield (%)
1	$Pd(OAc)_2$	PCy_3HBF_4	Na_2CO_3	97
2[b]	$Pd(OAc)_2$	PCy_3HBF_4	Na_2CO_3	<2
3[c]	$Pd(OAc)_2$	PCy_3HBF_4	Na_2CO_3	<2
4[d]	$Pd(OAc)_2$	PCy_3HBF_4	Na_2CO_3	95
5[e]	$Pd(OAc)_2$	PCy_3HBF_4	Na_2CO_3	>98
6[f]	$Pd(OAc)_2$	PCy_3HBF_4	Na_2CO_3	>98
7[g]	$Pd(OAc)_2$	PCy_3HBF_4	Na_2CO_3	32
8	$Pd_2(dba)_3$	PCy_3HBF_4	Na_2CO_3	68
9	$Pd(OAc)_2$	PCy_3HBF_4	K_2CO_3	92
10	$Pd(OAc)_2$	PCy_3HBF_4	K_3PO_4	19
11	$Pd(OAc)_2$	PCy_3HBF_4	Cs_2CO_3	<2
12[h]	$Pd(OAc)_2$	PCy_3HBF_4	K_2CO_3	91
13[h]	$Pd(OAc)_2$	PCy_3HBF_4	Na_2CO_3	93
14	$Pd(OAc)_2$	PCy_2Ph	Na_2CO_3	47
15	$Pd(OAc)_2$	$PCyPh_2$	Na_2CO_3	24
16	$Pd(OAc)_2$	PPh_3	Na_2CO_3	10
17	$Pd(OAc)_2$	$P(o\text{-Tol})_3$	Na_2CO_3	<2
18	$Pd(OAc)_2$	PEt_3HBF_4	Na_2CO_3	<2
19	$Pd(OAc)_2$	$P(n\text{-Bu})_3HBF_4$	Na_2CO_3	45
20	$Pd(OAc)_2$	$PMe(t\text{-Bu})_2HBF_4$	Na_2CO_3	19
21	$Pd(OAc)_2$	$P(t\text{-Bu})_3HBF_4$	Na_2CO_3	<2
22	$Pd(OAc)_2$	Dppb	Na_2CO_3	<2

[a]Conditions: **1** (1.0 equiv), Ar-B$(OH)_2$ (2.0 equiv), catalyst (3 mol %), ligand (12 mol %), base (2.5 equiv), dioxane (0.125 M), 120 °C, 15 h. [b]60 °C. [c]80 °C. [d]100 °C. [e]Ar-B$(OH)_2$ (3.0 equiv), base (4.5 equiv). [f]Ar-B$(OH)_2$ (4.5 equiv), base (7.5 equiv). [g]Ar-B$(OH)_2$ (1.2 equiv), base (1.2 equiv). [h]H_3BO_3 (2.0 equiv). See the SI for details.

we found that the desired cross-coupling proceeds in excellent 97% yield in the presence of Mes-B$(OH)_2$ (2.0 equiv) and Na_2CO_3 (2.5 equiv) in dioxane at 120 °C (Table 1, entry 1). No cross-coupling is observed at lower temperatures (entries 2 and 3); however, 100 °C suffices for efficient coupling (entry 4), consistent with challenging insertion and/or transmetalation steps.[8,9] Further improvement can be realized by increasing the stoichiometry of boronic acid and base (entries 5−7). $Pd_2(dba)_3$ was identified as another promising Pd source, although it resulted in lower yield (entry 8). Interestingly, K_2CO_3 is also an effective base (entry 9), while K_3PO_4 and Cs_2CO_3 are not effective for this cross-coupling (entries 10 and 11). It should be noted that H_3BO_3 is not required (entries 12 and 13), suggesting that amide bond activation by O-protonation of the glutarimide fragment is not particularly important for this cross-coupling.[18d,19] A ligand screen revealed that PCy_3 is the preferred phosphine ligand for this cross-coupling (entries 14−22).[20] The best results are obtained using 3−4 equiv of the phosphine ligand with respect to Pd, while a lower ratio is insufficient for the reaction. Decreasing the electron richness in a series of PCy_3, PCy_2Ph, $PCyPh_2$, and PPh_3 leads to a gradual decrease in catalytic activity (entries 14−17) due to more challenging oxidative insertion with less σ-donating phosphine ligands. Furthermore, in the series of trialkylphosphines, PCy_3 is vastly preferred (entries 18−21) because the steric bulk in oxidative addition of the acyl electrophile to Pd(0) is accommodated.[9a,b]

Having developed suitable conditions, the substrate scope of this process was next investigated (Scheme 1). As shown, we

Scheme 1. Synthesis of Hindered Ketones by Pd-Catalyzed Suzuki−Miyaura Cross-Coupling of Amides[a,b]



[a]Conditions: amide (1.0 equiv), Ar-B$(OH)_2$ (2.0 equiv), $Pd(OAc)_2$ (3 mol %), PCy_3HBF_4 (12 mol %), Na_2CO_3 (2.5 equiv), dioxane (0.125 M), 120 °C, 15 h. [b]Isolated yields. [c]Ar−B$(OH)_2$ (5.0 equiv), base (7.2 equiv).

found that the developed conditions can be applied to the synthesis of a range of sterically hindered biaryl ketones. In addition to mesitylboronic acid (**3a**), the reaction can tolerate both 2,6-dimethylphenyl (**3b**) and 2,6-dimethoxyphenylboronic acids (**3c**), furnishing ortho-disubstituted biaryl ketones in excellent yields. Products containing electronically varied ortho,ortho′-disubstitution can be synthesized in good yields (**3d**−**3f**). Note that this includes the challenging electronically deactivated 2-trifluoromethylphenylboronic acid (**3f**). Furthermore, the cross-coupling with 1-naphthylboronic acid is possible (**3g**). Moreover, tri-ortho-substituted biaryl ketones were synthesized in excellent yields (**3h**−**3i**), thus testing the steric limits of the cross-coupling. The use of steric hindrance

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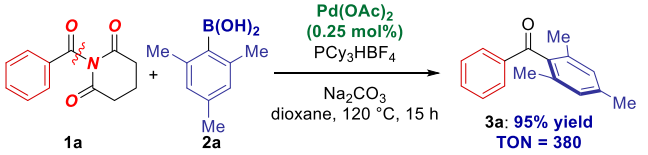
on the amide fragment is also feasible as illustrated by the synthesis of **3j**. Note, however, that reactions with di-ortho-substituted sterically hindered amides were in general more difficult (vide infra). Pleasingly, the reaction seems to be insensitive to the electronic properties of the amide electrophile, furnishing the ketone products in excellent yields (**3j′**, **3k**). The highly hindered 2-Ph-amide substrate underwent the cross-coupling in high yield (**3l**). In this instance, increasing the boronic acid and base stoichiometry significantly improved the yield, consistent with slow transmetalation. Finally, the reaction conditions could be applied to the synthesis of sterically hindered heterocyclic (**3m**) and alkyl ketones (**3n**). Thus, the scope of the reaction is broad and supersedes related methods utilizing unstable aroyl chlorides.[4,7] At the present stage, the synthesis of tetra-ortho-substituted ketones is not feasible (vide infra). Unactivated alkenyl and aliphatic boronic acids are not suitable reaction partners. It is worthwhile to note that high reactivity of *N*-acylglutarimides results from a combination of minimized amidic resonance (ER = −1.40 kcal/mol)[18d] and high stability under the reaction conditions.[11e] Other amides, such as *N*- or *O*-heteroaryl-activated amides, are not suitable coupling partners.

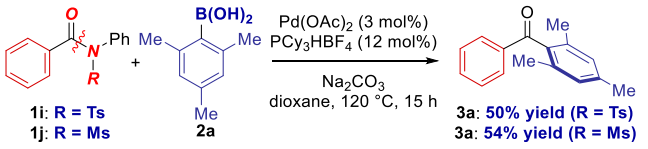
To test the cross-coupling efficiency, we determined TON (Scheme 2). Pleasingly, under the optimized conditions, the cross-coupling is feasible at 0.25 mol % [Pd] loading, consistent with highly efficient coupling.

Scheme 2. Determination of TON



Furthermore, we found that the reaction also proceeds with other amide electrophiles (Scheme 3). In particular, the use of

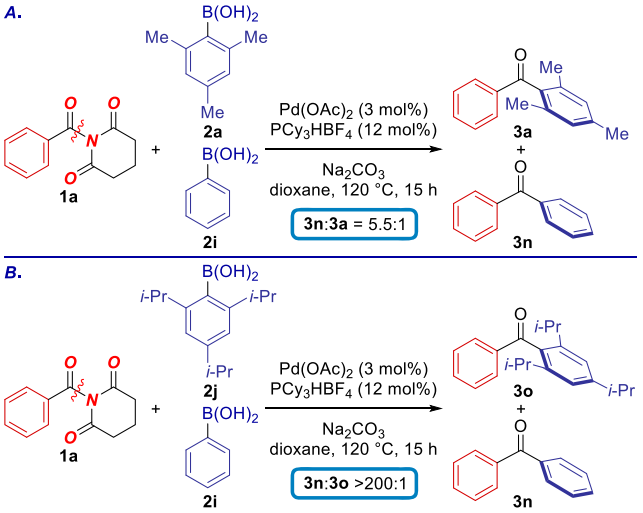
Scheme 3. Cross-Coupling of Secondary Amides



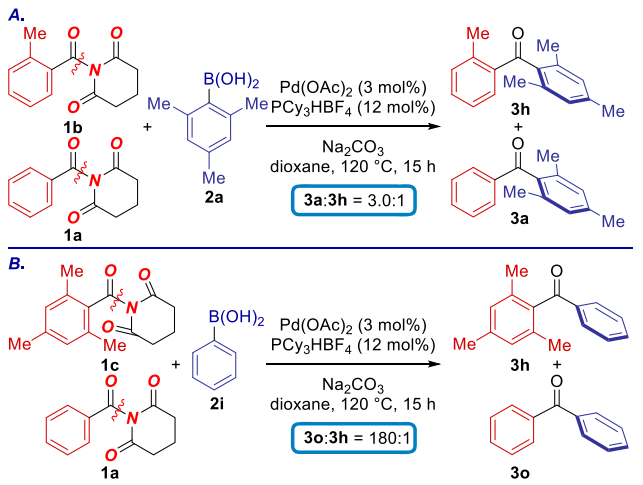
N-Ts and *N*-Ms amides allows one to engage secondary amides as cross-coupling electrophiles in this reaction manifold. The cross-coupling using benzoyl chloride was unsuccessful under these conditions, highlighting the robust nature of amide electrophiles in the cross-coupling.

In order to gain insight into the reaction mechanism, we conducted competition experiments (Schemes 4 and 5). The cross-coupling of **1a** using phenylboronic acid is slightly preferred compared to 2,4,6-trimethylphenylboronic acid (Ph/3,4,6-$Me_3C_6H_2$ = 5.5:1) (Scheme 4A). The ratio dramatically increases when more hindered 2,4,6-triisopropylphenylboronic acid (Ph/3,4,6-*i*-$Pr_3C_6H_4$ > 200:1) is used (Scheme 4B). Competition between 2-Me-*N*-benzoylglutarimide (**1b**) and the unsubstituted **1a** revealed that although the latter is inherently more reactive (2-MeC_6H_4/Ph = 1:3.0), the difference in reactivity is very small (Scheme 5A). This sharply contrasts with the reactivity of (**1c**), which is dramatically less

Scheme 4. Competition Experiments



Scheme 5. Competition Experiments



reactive than its unsubstituted counterpart (2,4,6-$Me_3C_6H_2$/Ph = 1:180) (Scheme 5B). Thus, our studies quantify that (1) steric bulk on the amide has a significantly greater impact on the coupling than on the boronic acid. This is opposite to the traditional Suzuki−Miyaura cross-coupling of aryl halides and consistent with a difficult metal insertion into the N−C(O) bond.[6,8,9] (2) The results show that cross-coupling of mono-ortho-substituted amides and di-ortho-substituted arylboronic acids is feasible, and this is further supported by our findings with respect to the reaction scope.

To gain insight into the origin of the high reactivity of *N*-benzoylglutarimides, we determined the X-ray structures of 2-Me-*N*-benzoylglutarimide **1b** and its di-ortho-substituted counterpart **1c** (Figure 2 and SI). *An even higher amide bond twist, τ = 89.2°, in **1b** than in **1a**[21] places this amide at the extreme geometry range of the amide bond*[22,23] (χ_N = 5.0°; N−C(O), 1.476 Å; C═O, 1.195 Å; C−C(O), 1.482 Å; the C−C(O) bond is still planar, τ = 1.5°, Figure 2B). This dramatically changes in the di-ortho-substituted **1c** (Figure 2C). The amide bond twist of τ = 63.3° in **1c** reveals a major drop in amide bond distortion of nearly 50% compared with **1b** (Figure 2D, top). The second most striking feature in **1c** is half-twisted C−C(O) bond, τ = 50.7° (Figure 2D, bottom), which can be contrasted with fully planar C−C(O) bond in **1b**

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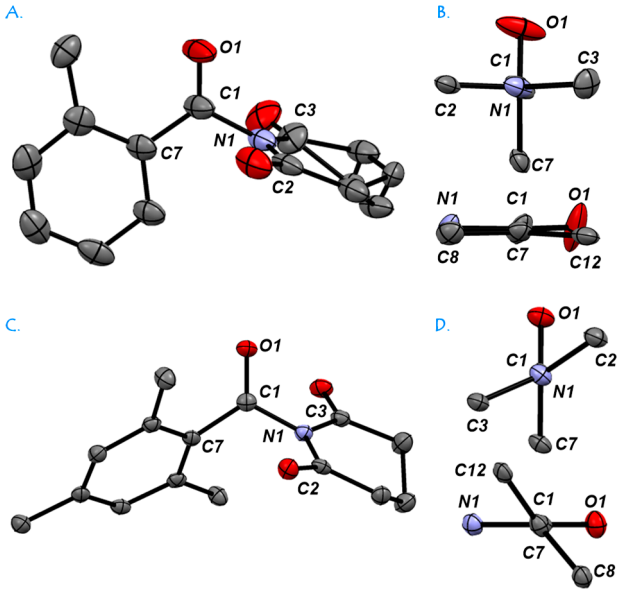

Figure 2. (a) Crystal structure of **1b**. (b) Newman projection along the N−C(O) bond (top) and C−C(O) bond (bottom). (c) Crystal structure of **1c**. (d) Newman projection along the N−C(O) bond (top) and C−C(O) bond (bottom). Crystallographic data have been deposited under CCDC Nos. 1940215 (**1b**) and 1940216 (**1c**).

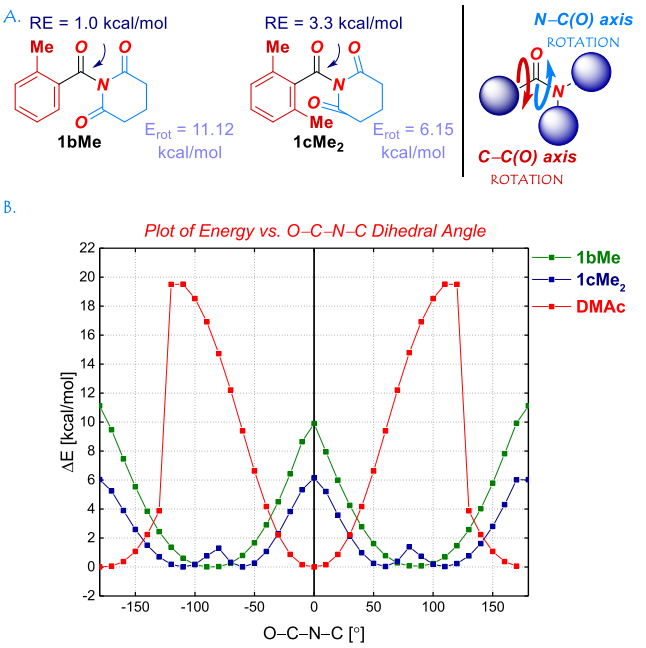

Figure 3. (a) Amides employed in computational studies. (b) Rotational profile of **1bMe** and **1cMe$_2$** (ΔE, kcal/mol, vs O−C−N−C (deg)). Rotational profile of DMAc (*N*,*N*-dimethylacetamide, ΔE = 19.51 kcal/mol) is shown for comparison.

and **1a** or fully perpendicular C−C(O) in di-ortho-substituted planar benzamides.[21b] Collectively, the structural features in **1b** and **1c** demonstrate that *di-ortho-substitution in acyclic twisted amides leads to a decrease of amide bond distortion as a result of nonbonding interactions between the N-substituents and the aromatic ring; however, monosubstitution is well-compatible with accommodating the extreme amide bond twist.*

Next, computational studies were performed to determine the effect of substitution on amide bond destabilization in **1b** and **1c** (Figure 3 and SI). 2,6-Dimethyl-*N*-benzoylglutarimide (**1cMe$_2$**) was used as a model amide for **1c**.

(1) Resonance energy (RE) of the amide bond in **1b** and **1cMe$_2$** showed that amidic resonance in **1b** (RE = 0.95 kcal/mol) is practically nonexistent, while in **1cMe$_2$** (RE = 3.34 kcal/mol) it is consistent with a reduced amide twist.
(2) Rotational profiles determined by systematic rotation along the O−C−N−C angle showed that the energy minimum in **1b** is located at a 90° O−C−N−C angle (τ = 86.31°; χ_N = 7.34°). In contrast, the energy minimum of **1cMe$_2$** is at a 60° O−C−N−C angle (τ = 64.52°; χ_N = 11.18°).
(3) Calculation of N-/O-protonation affinities (ΔPA) in amides **1b** and **1cMe$_2$** revealed that both amides strongly favor protonation at the amide oxygen atom (**1b**, ΔPA = 19.9 kcal/mol; **1cMe$_2$**, ΔPA = 20.6 kcal/mol).[9,24]

Thus, energetic parameters in amides **1b** and **1cMe$_2$** provide strong support for chemoselective N−C(O) bond activation and explain the lower reactivity of the di-ortho-substituted amide, cf. mono-ortho-substituted amide.

In summary, we have reported the first general method for the synthesis of sterically hindered ketones via Pd-catalyzed acyl Suzuki−Miyaura cross-coupling. The reaction proceeds via selective N−C(O) activation in sterically hindered twisted amides and delivers the desired hindered ketones in good to excellent yields. Mechanistic studies quantified a major impact of the steric bulk on the amide electrophile. Another key aspect involved determination of steric and electronic factors of the amide bond that govern ground-state destabilization of sterically hindered twisted amides. Expanding the substrate scope to tetra-ortho-substituted biaryl ketones and the development of new sterically hindered twisted amide cross-coupling partners is underway and will be reported shortly.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, CIF files for amides **1b** and **1c**, computational details. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02961.

Experimental details, characterization data, X-ray data for amides **1b** and **1c**, computational details (PDF)

Accession Codes

CCDC 1940215−1940216 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(4) Very few methods for the synthesis of ortho,ortho′-disubstituted ketones have been reported (Scifinder search, Aug 19, 2019): (1) Pd(II)-NHC-catalyzed cross-coupling of amides, introduced by our group.[11a] Pd(II)-NHC catalysis is not suitable for the synthesis of triortho-substituted ketones and not suitable for the synthesis of bis-ortho,ortho-substituted ketones. (2) Pd(0) phosphine catalyzed cross-coupling of not easily available N-Ts amides in which the other N-substituent is a highly electron-deficient aniline (e.g., 3,5-$(CF_3)_2$-C_6H_3).[11] This method is not suitable for the synthesis of triortho-substituted ketones and not suitable for the synthesis of bis-ortho,ortho-substituted ketones. (3) The Suzuki cross-coupling of acyl chlorides is generally not suitable for the synthesis of sterically hindered ketones due to facile decomposition.[7a,b] Typically, bis-ortho,ortho′-ketones are obtained from acyl halides after conversion to toxic stannanes. (4) The only examples of the synthesis of bis-ortho,ortho-substituted ketones from acyl chlorides (but not amides) via Suzuki cross-coupling are as follows: boronic acids (50% yield), organotrifluoroborates (38%), and boronic acids using designer phosphinoferrocene ligands with extended urea-amide substituents (55%).[7a,b] Thus, at present, there are no general methods for the assembly of sterically hindered ketones by the Suzuki−Miyaura cross-coupling of acyl electrophiles.

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