OL Organic Letters

pubs.acs.org/OrgLett Letter

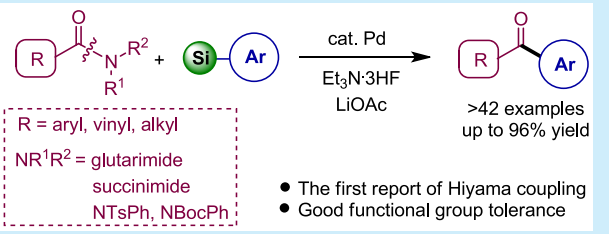
Palladium-Catalyzed Amide N–C Hiyama Cross-Coupling: Synthesis of Ketones

Muhammad Aliyu Idris and Sunwoo Lee*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c03260 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: *N*-Acylglutarimides and arylsiloxanes reacted in the presence of $Pd(OAc)_2/PCy_3$, $Et_3N{\cdot}3HF$, and LiOAc to provide the corresponding arylketones in good yields. Aryl-, vinyl-, and alkyl-substituted *N*-acylglutarimides showed good activity in the coupling reactions of arylsiloxanes. The reaction had a broad substrate scope and showed good functional group tolerance. *N*-Benzoylsuccinimide and *N*-protected *N*-phenylbenzamides showed good activities in coupling reactions with phenylsiloxane. The employment of CuF_2 as an activor afforded the decarbonylative products at 160 °C.



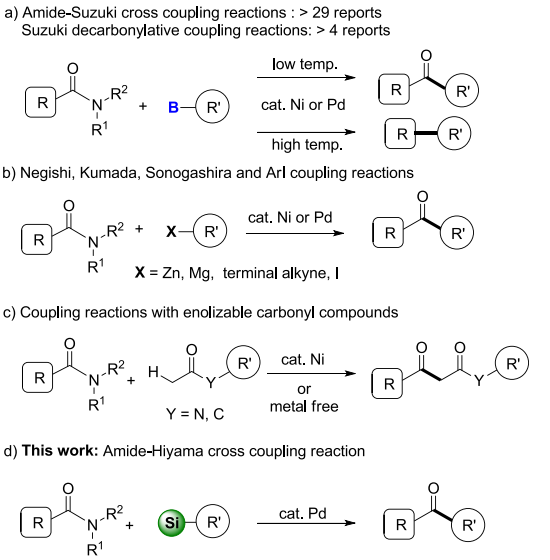
The amide functionality is one of the most important structures in nature because peptides, the key components of proteins and enzymes, consist of an amide backbone.[1] In addition, amide moieties have been widely utilized as building blocks for various materials owing to the robust nature of the amide C–N bond. In recent years, amide C–N bond cleavage has received considerable attention for the transformation of amides to carbonyl compounds, including other amides.

Transamidation, which is the transformation of one amide to another, has been reported by numerous groups. Stahl reported that amides reacted with amines in the presence of Lewis acids such as Zr, Al, and Sc to provide thermodynamic equilibrium mixtures.[2] The use of palladium or nickel catalysts afforded the desired transamidated products as the major products in reactions between amides and amines.[3] Transition-metal-catalyst-free transamidations were also reported by several groups.[4] Very recently, the Szostak group demonstrated that a variety of unactivated tertiary amides could be transformed to other amides in the presence of LiHMDS.[5]

Amide C–N activation has likewise been employed for reactions with oxygen and carbon nucleophiles. Amide to ester transformations employing transition-metal catalysts such as nickel and zinc, as well those proceeding under metal-free conditions, have been reported by several groups.[6]

The reaction of amides and carbon nucleophiles in the presence of transition-metal catalysts provides ketones. Various carbon nucleophiles can be employed for this purpose. Suzuki cross-coupling between amides and arylboron compounds has been independently reported by Garg, Huang, Jian, Rueping, Szostak, Zeng, and Zou (Scheme 1a).[7] It has been reported that Suzuki decarbonylative coupling products were formed when the reaction was conducted at high temperature.[8] Arylzinc compounds, which are coupling partners in Nigeshi cross-coupling, have also been employed in reactions with

Scheme 1. Coupling of Amides and Carbon Nucleophiles



amides for the synthesis of ketones, as reported by Garg and Szostak.[9] Grignard reagents have been utilized for coupling reactions with amides by the Kandasamy group to generate ketones. Very recently, the Szostak group also reported the coupling with amide and Grignard reagents.[10] Zheng reported that palladium-catalyzed Sonogashira coupling of amides

Received: September 28, 2020

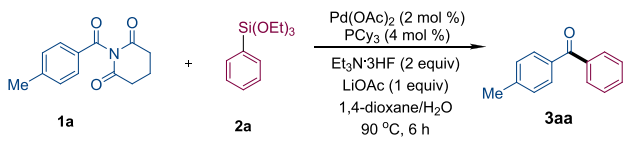
https://dx.doi.org/10.1021/acs.orglett.0c03260
Org. Lett. XXXX, XXX, XXX–XXX

provided alkynyl ketones.[11] Han reported that nickel-catalyzed reductive N−C coupling of amides and aryl iodides provides diarylketones[12] (Scheme 1b). Recently, we reported a nickel-catalyzed Claisen condensation-type coupling reaction between two different amides for the construction of new C−C bonds.[13] In addition, we demonstrated that an enolizable ketone functions as a carbon nucleophile, reacting with amides under transition-metal-free conditions to provide 1,3-diketones in good yields[14] (Scheme 1c).

However, to the best of our knowledge, there are no reports on the use of arylsilanes as nucleophiles in coupling reactions with amides. Numerous methods for the synthesis of arylsilanes have recently been developed.[15] Therefore, arylsilanes would be favorable coupling partners for the formation of ketones via C−N activation of amides. Herein, we report palladium-catalyzed Hiyama-type amide coupling reactions for the synthesis of the corresponding ketones (Scheme 1d).

N-4-Methylbenzoylglutarimide and triethoxyphenylsilane were chosen as model substrates to determine the optimal cross-coupling conditions (Table 1). After an intensive

Table 1. Optimization of Conditions for the Hiyama Coupling of 1a and 2a[a]



1a 2a 3aa

entry	deviation from the standard conditions	yield[b] (%)
1	none	87
2	no $Pd(OAc)_2/PCy_3$	0
3	PPh_3 instead of PCy_3	30
4	dppb instead of PCy_3	45
5	dppf instead of PCy_3	40
6	Xantphos instead of PCy_3	35
7	$Pd(dba)_2$ instead of $Pd(OAc)_2$	15
8	$Pd(CH_3CN)_2Cl_2$ instead of $Pd(OAc)_2$	68
9	$Pd(PCy_3)_2Cl_2$ instead of $Pd(OAc)_2/PCy_3$	85
10	no H_2O	40
11	THF instead of 1,4-dioxane/H_2O	35
12	toluene instead of 1,4-dioxane/H_2O	50
13	TBAF instead of $Et_3N·3HF$	trace
14	Py·HF instead of $Et_3N·3HF$	20
15	KOAc instead of LiOAc	72
16	NaOAc instead of LiOAc	55
17	1 mol % Pd and L instead of 2 mol %	65
18	50 °C instead of 90 °C	58
19	3 h instead of 6 h	70
20	160 °C instead of 90 °C	84

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), $Pd(OAc)_2$ (0.006 mmol), PCy_3 (0.012 mmol), $Et_3N·3HF$ (0.6 mmol), and LiOAc (0.3 mmol) were reacted in 1,4-dioxane/H_2O (0.5 mL/0.5 mL) at 90 °C for 6 h. [b]Determined by gas chromatography and ^1H NMR spectroscopy with an internal standard.

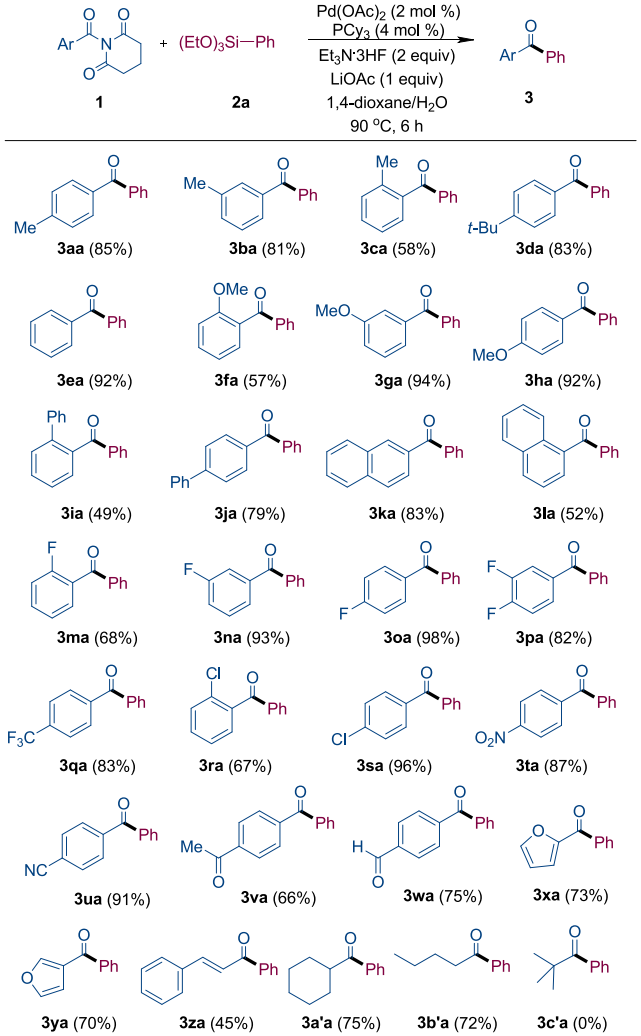
evaluation of various reaction conditions, we established that $Pd(OAc)_2$ and PCy_3 in 1,4-dioxane/H_2O afforded the desired product **3aa** in 87% yield in the presence of $Et_3N·3HF$ and LiOAc (entry 1). When the reaction was performed in the absence of $Pd(OAc)_2$, the coupling product was not obtained (entry 2). Reactions with phosphine ligands such as PPh_3, dppb, dppf, and Xantphos provided **3aa** in 30%, 45%, 40%, and 35% yields, respectively (entries 3−6). When the reactions were conducted with $Pd(dba)_2$ and $Pd(CH_3CN)_2Cl_2$, **3aa** was formed in 15% and 68% yields, respectively (entries 7 and 8). The use of $Pd(PCy_3)_2Cl_2$ resulted in 85% yield, comparable to the result of the $Pd(OAc)_2/PCy_3$ reaction (entry 9). Reactions performed in the absence of H_2O led to a low yield of **3aa** (entry 10). When the reactions were performed in THF and toluene, **3aa** was obtained in 35% and 50% yields, respectively (entries 11 and 12). Reactions carried employing TBAF and Py·HF as activators provided **3aa** in 2% and 20% yields, respectively (entries 13 and 14). Reactions with KOAc or NaOAc delivered lower yields than did the reactions with LiOAc (entries 15 and 16). Reducing the amount of Pd/L to 1 mol %, decreasing the reaction temperature to 50 °C, and shortening the reaction time to 3 h resulted in the formation of **3aa** in 65%, 58%, and 70% yields, respectively (entries 17−19). When the reaction was conducted at 160 °C in the sealed tube reactor, **3aa** was formed in 84%, however, the decarbonylative product was not detected in the reaction mixture (entry 20).

With the optimized conditions in hand, as shown in Scheme 2, we evaluated a variety of substituted *N*-benzoylglutarimides in the coupling reaction with phenyltriethoxysilane. *N*-Benzoylglutarimides bearing alkyl groups such as methyl and *tert*-butyl afforded the corresponding ketones **3aa**, **3ba**, and **3da** in good yields. However, *o*-methyl-substituted *N*-benzoylglutarimide **1c** gave a relatively low product yield due to increased steric hindrance in the substrate. *N*-Benzoylglutarimide provided benzophenone in 92% yield. Methoxy-substituted *N*-benzoylglutarimides provided the corresponding ketones **3fa**, **3ga**, and **3ha** in 57%, 94%, and 92% yields, respectively. *N*-Acylglutarimides bearing biphenyl and naphthyl groups provided the desired ketones, with *ortho*-substituted products (**3ia** and **3la**) being formed in lower yields than their counterparts. Monofluoro- and difluoro-substituted *N*-benzoylglutarimides afforded the corresponding fluorinated benzophenones in moderate to good yields. 4-Trifluoromethyl-, 4-chloro-, and 2-chloro-*N*-benzoylglutarimides provided **3qa**, **3ra**, and **3sa** in 83%, 67%, and 96% yields, respectively. *N*-Benzoylglutarimides bearing electron-withdrawing substituents such as nitro, cyano, ketone, and aldehyde afforded the corresponding ketones in moderate to good yields. 2- and 3-furanyl-substituted *N*-acylglutarimides furnished **3xa** and **3ya** in 73% and 70% yields, respectively. *N*-Acylglutarimides with α,β-unsaturated, cyclic, and straight-chain alkyl groups provided the corresponding ketones **3za**, **3a′a**, and **3b′a** in 45%, 75%, and 72% yields, respectively. However, *N*-acylglutarimide having a sterically bulky alkyl group such as *tert*-butyl did not give the desired coupling product **3c′a**.

Next, 4-methylphenyl-, 4-methoxyphenyl-, 4-chlorophenyl-, and 2-thiophene-yltriethoxysilanes (**2b**, **2c**, **2d**, and **2e**) were evaluated in the coupling reaction with *N*-4-methylbenzoylglutarimide, *N*-benzoylglutarimide, *N*-4-methoxybenzoylglutarimide, and *N*-4-fluorobenzoylglutarimide (**1a**, **1e**, **1h**, and **1o**) under the optimized conditions. In addition, the synthesis and the late-stage modification of biologically active compounds were conducted by using this methodology. The results are summarized in Scheme 3. All reactions afforded the corresponding ketones in good yields. When alkyl-substituted triethoxysilanes such as *n*-octyltriethoxysilane (**2f**) and cyclopentyltriethoxysilane (**2g**) were allowed to react with *N*-4-nitrobenzoylglutarimide (**1t**), no coupled products were found.

https://dx.doi.org/10.1021/acs.orglett.0c03260
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Hiyama Coupling of Various Substituted *N*-Acylglutarimides and 2a[a]



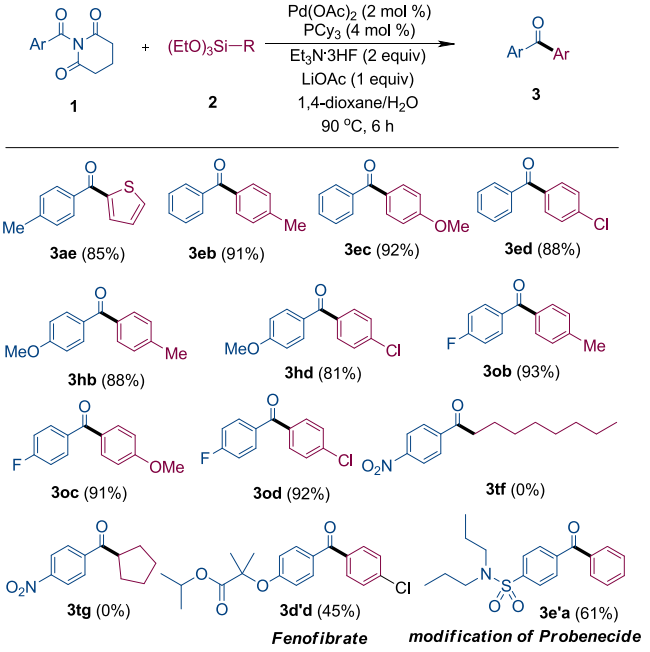
[a]Reaction conditions: **1** (1.0 mmol), **2a** (1.5 mmol), $Pd(OAc)_2$ (0.02 mmol), PCy_3 (0.04 mmol), $Et_3N{\cdot}3HF$ (2.0 mmol), and LiOAc (1.0 mmol) were reacted in 1,4-dioxane/H_2O (1.5 mL/1.5 mL) at 90 °C for 6 h. The numbers in parentheses represent isolated yields.

Fenofibrate (**3d′d**),[16] which is used to treat primary hypercholesterolemia, was formed in 45% yield. In addition, probenecide was employed for the last-stage modification.[17] It was converted to the corresponding 4-*N*,*N*-dipropylsulfonamidobenzoylglutarimide and coupled with **1a** to give the **3e′a** in 61% yield.

To study the influence of the amide structural properties on the reaction, various benzamides were reacted with phenyltriethoxysilane under the optimized conditions (Scheme 4). *N*-Benzoylsuccinimide reacted with **2a** smoothly to give **3ea** in 85% yield. However, *N*-benzoylsaccharin did not produce the desired product. *N*-Tosyl- and *N*-Boc-protected *N*-phenylbenzamides provided **3ea** in 91% and 43% yields, respectively. Unfortunately, unactivated tertiary amides such as *N*-methyl-*N*-phenylbenzamide were not active in this coupling reaction. It was found that **1**−**2** and **1**−**5** did not give the desired product even at 150 °C with 10 mol % catalyst.

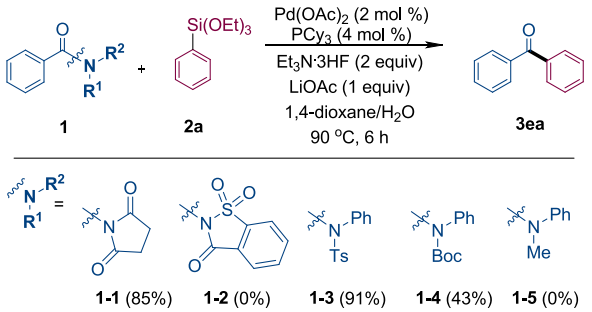
It was noteworthy that we found that the Hiyama decarbonylative coupling products were formed when CuF_2 was employed at 160 °C. However, as shown in eq 1, the maximum yield was 30%.

Scheme 3. Hiyama Coupling of Substituted *N*-Acylglutarimides and Arylsiloxanes[a]

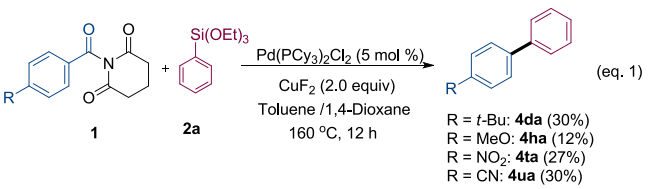


[a]Reaction conditions: **1** (1.0 mmol), **2** (1.5 mmol), $Pd(OAc)_2$ (0.02 mmol), PCy_3 (0.04 mmol), $Et_3N{\cdot}3HF$ (2.0 mmol), and LiOAc (1.0 mmol) were reacted in 1,4-dioxane/H_2O (1.5 mL/1.5 mL) at 90 °C for 6 h. Numbers in parentheses represent isolated yields.

Scheme 4. Hiyama Coupling of Various Amides and 2a[a]



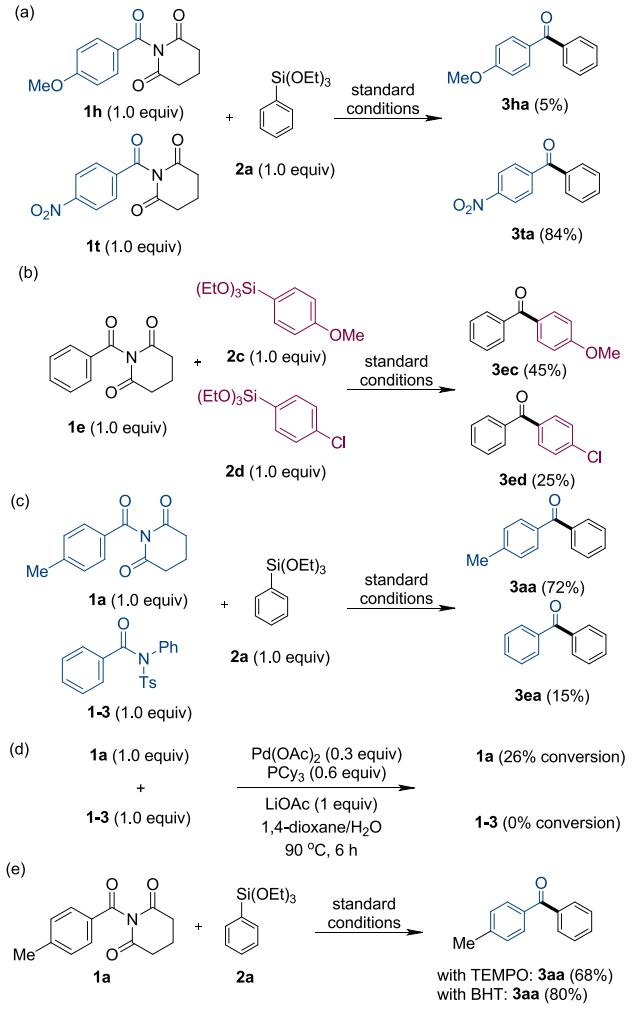
[a]Reaction conditions: **1** (1.0 mmol), **2a** (1.5 mmol), $Pd(OAc)_2$ (0.02 mmol), PCy_3 (0.04 mmol), $Et_3N{\cdot}3HF$ (2.0 mmol), and LiOAc (1.0 mmol) were reacted in 1,4-dioxane/H_2O (1.5 mL/1.5 mL) at 90 °C for 6 h. Numbers in parentheses represent isolated yields.



To elucidate the electronic effects of the substituents and reaction pathways, several control experiments were conducted (Scheme 5). When equal amounts of **1h** and **1t** were reacted with **2a** under standard conditions, the corresponding ketones **3ha** and **3ta** were formed in 5% and 84% yields, respectively. Equal amounts of **2c** and **2d** were treated with **1e** under standard conditions to deliver **3ec** and **3ed** in 45% and 25%

https://dx.doi.org/10.1021/acs.orglett.0c03260
Org. Lett. XXXX, XXX, XXX−XXX

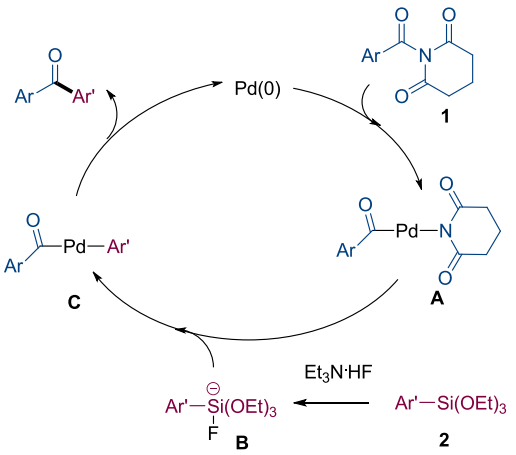
Scheme 5. Control Experiments



yields, respectively. These results imply that *N*-benzoylglutarimides with electron-withdrawing substituents provided higher activities than those with electron-donating substituents. In contrast, electron-donating substituents in triethoxylphenyl silanes led to higher yields than those obtained with electron-withdrawing substituents. The competitive reaction between **1a** and **1−3** provided **3aa** and **3ea** in 72% and 15% yields, respectively. This result implies that *N*-benzoylglutarimide is higher reactive than *N*-phenyl-*N*-tosylbenzamide. When two amides **1a** and **1−3** were treated with $Pd(OAc)_2/PCy_3$ and LiOAc in the absence of $Et_3N{\cdot}3HF$ and $PhSi(OEt)_3$, only **1a** was converted to the palladium complex. This result supports that the oxidative addition step of **1a** might be faster than that of **1−3**. When the reaction of **1e** and **2a** was conducted in the presence of 2 equiv of BHT or TEMPO, the desired product was formed in 68% and 80% yields, respectively. These results indicate that the reaction proceeds via an ionic mechanism.

Based on our experimental results and previous reports on amide coupling reactions, we propose a plausible reaction mechanism, as shown in Scheme 6. Pd(0) is oxidatively added to the amide C−N bond to provide palladium complex **A**. Arylsiloxane is activated by the fluoride anion of $Et_3N{\cdot}3HF$ to give activated arylsiloxane **B**, followed by the exchange of aryl and glutarimide to afford palladium complex **C**. Reductive elimination of **C** finally produces the desired ketone and regenerates Pd(0).

Scheme 6. Proposed Mechanism



In summary, *N*-acylglutarimides reacted with arylsiloxanes to provide the corresponding arylketones via amide C−N bond cleavage. It was established that $Pd(OAc)_2/PCy_3$ showed the highest activity in the presence of $Et_3N{\cdot}3HF$ and LiOAc. The reaction featured broad functional group tolerance, with a variety of substituted *N*-benzoylglutarimides and *N*-alkylacylglutarimides providing the corresponding ketones in good yields. *N*-Benzoylsuccinimide and *N*-protected *N*-phenylbenzamides reacted with phenylsiloxane to give arylketone products in good yields. This is the first example of a Hiyama-type coupling reaction involving amides, which proceeds via an ionic reaction pathway. Further studies to elucidate the detailed reaction mechanisms are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03260.

Experimental procedures and spectral data for the products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Sunwoo Lee − *Department of Chemistry, Chonnam National University, Gwangju 61186, Republic of Korea;* orcid.org/0000-0001-5079-3860; Email: sunwoo@chonnam.ac.kr

Author

Muhammad Aliyu Idris − *Department of Chemistry, Chonnam National University, Gwangju 61186, Republic of Korea*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c03260

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIP) (NRF-2017R1A2B2002929). The spectral and HRMS data were obtained from the Korea Basic Science Institute, Gwangju Center and Daegu Center.

https://dx.doi.org/10.1021/acs.orglett.0c03260
Org. Lett. XXXX, XXX, XXX−XXX

REFERENCES

(1) (a) Hughes, A. B. *Amino Acids, Peptides and Proteins in Organic Chemistry*; Wiley, Weinheim, 2011. (b) Greenberg, A.; Breneman, C. M.; Liebman, J. F. *The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science*; Wiley-VCH: New York, 2003.

(2) (a) Eldred, S. E.; Stone, D. A.; Gellman, S. H.; Stahl, S. S. Catalytic Transamidation under Moderate Conditions. *J. Am. Chem. Soc.* **2003**, *125*, 3422−3423. (b) Stephenson, N. A.; Zhu, J.; Gellman, S. H.; Stahl, S. S. Catalytic Transamidation Reactions Compatible with Tertiary Amide Metathesis under Ambient Conditions. *J. Am. Chem. Soc.* **2009**, *131*, 10003−10008.

(3) (a) Lanigan, R. M.; Sheppard, T. D. Recent Developments in Amide Synthesis: Direct Amidation of Carboxylic Acids and Transamidation Reactions. *Eur. J. Org. Chem.* **2013**, *2013*, 7453−7456. (b) Ouyang, K.; Hao, W.; Zhang, W.-X.; Xi, Z. Transition-Metal-Catalyzed Cleavage of C−N Single Bonds. *Chem. Rev.* **2015**, *115*, 12045−12090. (c) Baker, E. L.; Yamano, M. M.; Zhou, Y.; Anthony, S. M.; Garg, N. K. A two-step approach to achieve secondary amide transamidation enabled by nickel catalysis. *Nat. Commun.* **2016**, *7*, 11554−11558. (d) Adachi, S.; Kumagai, N.; Shibasaki, M. Conquering amide planarity: Structural distortion and its hidden reactivity. *Tetrahedron Lett.* **2018**, *59*, 1147−1158.

(4) (a) Sergeeva, M.; Mozhaev, V. V.; Rich, J. O.; Khmelnitsky, Y. L. Lipase-catalyzed transamidation of non-activated amides in organic solvent. *Biotechnol. Lett.* **2000**, *22*, 1419−1422. (b) Liu, Y.; Shi, S.; Achtenhagen, M.; Liu, R.; Szostak, M. Metal-Free Transamidation of Secondary Amides via Selective N−C Cleavage under Mild Conditions. *Org. Lett.* **2017**, *19*, 1614−1617. (c) Tang, L.; Li, X.-M.; Matuska, J. H.; He, Y.-H.; Guan, Z. Intramolecular Transamidation of Secondary Amides via Visible-Light-Induced Tandem Reaction. *Org. Lett.* **2018**, *20*, 5618−5621. (d) Verho, O.; Lati, M. P.; Oschmann, M. A Two-Step Procedure for the Overall Transamidation of 8-Aminoquinoline Amides Proceeding via the Intermediate N-Acyl-Boc-Carbamates. *J. Org. Chem.* **2018**, *83*, 4464−4476. (e) Liu, Y.; Achtenhagen, M.; Liu, R.; Szostak, M. Transamidation of N-acylglutarimides with amines. *Org. Biomol. Chem.* **2018**, *16*, 1322−1329. (f) Li, G.; Szostak, M. Highly selective transition-metal-free transamidation of amides and amidation of esters at room temperature. *Nat. Commun.* **2018**, *9*, 4165. (g) Sureshbabu, P.; Azeez, S.; Chaudhary, P.; Kandasamy, J. tert-Butyl nitrite promoted transamidation of secondary amides under metal and catalyst free conditions. *Org. Biomol. Chem.* **2019**, *17*, 845−850. (h) Subramani, M.; Rajendran, S. K. 2-piperidones to Amino Acids, Amino Alcohols and Aliphatic Amines and Esterification of N-Acyl-2-piperidones. *Eur. J. Org. Chem.* **2019**, *2019*, 3677−3686. (i) Fiore, V. A.; Maas, G. N-triflyl-propiolamides: Preparation and transamidation reactions. *Tetrahedron* **2019**, *75*, 3586−3595. (j) Rahman, M. M.; Li, G.; Szostak, M. Metal-Free Transamidation of Secondary Amides by N−C Cleavage. *J. Org. Chem.* **2019**, *84*, 12091−12100.

(5) Li, G.; Ji, C.-L.; Hong, X.; Szostak, M. Highly Chemoselective, Transition-Metal-Free Transamidation of Unactivated Amides and Direct Amidation of Alkyl Esters by N−C/O−C Cleavage. *J. Am. Chem. Soc.* **2019**, *141*, 11161−11172.

(6) (a) Hie, L.; Fine Nathel, N. F.; Shah, T. K.; Baker, E. L.; Hong, X.; Yang, Y.-F.; Liu, P.; Houk, K. N.; Garg, N. K. Conversion of amides to esters by the nickel-catalysed activation of amide C−N bonds. *Nature* **2015**, *524*, 79−83. (b) Dander, J. E.; Weires, N. A.; Garg, N. K. Benchtop Delivery of Ni(cod)2 using Paraffin Capsules. *Org. Lett.* **2016**, *18*, 3934−3936. (c) Hie, L.; Baker, E. L.; Anthony, S. M.; Desrosiers, J.-H.; Senanayake, C.; Garg, N. K. Nickel-Catalyzed Esterification of Aliphatic Amides. *Angew. Chem., Int. Ed.* **2016**, *55*, 15129−15132. (d) Weires, N. A.; Caspi, D. D.; Garg, N. K. Kinetic Modeling of the Nickel-Catalyzed Esterification of Amides. *ACS Catal.* **2017**, *7*, 4381−4385. (e) Bourne-Branchu, Y.; Gosmini, C.; Danoun, G. Cobalt-Catalyzed Esterification of Amides. *Chem. - Eur. J.* **2017**, *23*, 10043−10047. (f) Chen, X.; Hu, S.; Chen, R.; Wang, J.; Wu, M.; Guo, H.; Sun, S. Fe-catalyzed esterification of amides via C−N bond activation. *RSC Adv.* **2018**, *8*, 4571−4576. (g) Li, G.; Lei, P.; Szostak, M. Transition-Metal-Free Esterification of Amides via Selective N−C Cleavage under Mild Conditions. *Org. Lett.* **2018**, *20*, 5622−5625. (h) Wu, H.; Guo, W.; Daniel, S.; Li, Y.; Liu, C.; Zeng, Z. Fluoride-Catalyzed Esterification of Amides. *Chem. - Eur. J.* **2018**, *24*, 3444−3447. (i) Rashed, M. N.; Hakim Siddiki, S. M. A.; Tocuchy, A. Su.; Jamil, M. A. R.; Poly, S. S.; Maeno, Z.; Shimizu, K.-i. Direct Phenolysis Reactions of Unactivated Amides into Phenolic Esters Promoted by a Heterogeneous CeO2 Catalyst. *Chem. - Eur. J.* **2019**, *25*, 10594−10605. (j) Ye, D.; Liu, Z.; Chen, H.; Sessler, J. L.; Lei, C. Cesium Carbonate Catalyzed Esterification of N-Benzyl-N-Boc-amides under Ambient Conditions. *Org. Lett.* **2019**, *21*, 6888−6892. (k) Fang, W.-Y.; Zha, G.-F.; Qin, H.-L. Making Carbonyls of Amides Nucleophilic and Hydroxyls of Alcohols Electrophilic Mediated by SO2F2 for Synthesis of Esters from Amides. *Org. Lett.* **2019**, *21*, 8657−8661. (l) Hirai, T.; Kato, D.; Mai, B. K.; Katayama, S.; Akiyama, S.; Nagae, H.; Himo, F.; Mashima, K. Esterification of Tertiary Amides: Remarkable Additive Effects of Potassium Alkoxides for Generating Hetero Manganese−Potassium Dinuclear Active Species. *Chem. - Eur. J.* **2020**, *26*, 10643.

(7) (a) Boit, T. B.; Weires, N. A.; Kim, J.; Garg, N. K. Nickel-Catalyzed Suzuki−Miyaura Coupling of Aliphatic Amides. *ACS Catal.* **2018**, *8*, 1003−1008. (b) Weires, N. A.; Baker, E. L.; Garg, N. K. Nickel-catalysed Suzuki−Miyaura coupling of amides. *Nat. Chem.* **2016**, *8*, 75. (c) Mehta, M. M.; Boit, T. B.; Dander, J. E.; Garg, N. K. Ni-Catalyzed Suzuki−Miyaura Cross-Coupling of Aliphatic Amides on the Benchtop. *Org. Lett.* **2020**, *22*, 1−5. (d) Huang, P.-Q.; Chen, H. Ni-Catalyzed cross-coupling reactions of N-acylpyrrole-type amides with organoboron reagents. *Chem. Commun.* **2017**, *53*, 12584−12587. (e) Liu, X.; Hsiao, C.-C.; Guo, L.; Rueping, M. Cross-Coupling of Amides with Alkylboranes via Nickel-Catalyzed C−N Bond Cleavage. *Org. Lett.* **2018**, *20*, 2976−2979. (f) Meng, G.; Szostak, M. *Org. Lett.* **2015**, *17*, 4364−4367. (g) Liu, C.; Meng, G.; Liu, Y.; Liu, R.; Lalancette, R.; Szostak, R.; Szostak, M. N-Acylsaccharins: Stable Electrophilic Amide-Based Acyl Transfer Reagents in Pd-Catalyzed Suzuki−Miyaura Coupling via N−C Cleavage. *Org. Lett.* **2016**, *18*, 4194−4197. (h) Meng, G.; Szostak, M. Palladium-catalyzed Suzuki−Miyaura coupling of amides by carbon−nitrogen cleavage: general strategy for amide N−C bond activation. *Org. Biomol. Chem.* **2016**, *14*, 5690−5707. (i) Meng, G.; Shi, S.; Szostak. Palladium-Catalyzed Suzuki−Miyaura Cross-Coupling of Amides via Site-Selective N−C Bond Cleavage by Cooperative Catalysis. *ACS Catal.* **2016**, *6*, 7335−7339. (j) Lei, P.; Meng, G.; Ling, Y.; An, J.; Szostak, M. Pd-PEPPSI: Pd-NHC Precatalyst for Suzuki−Miyaura Cross-Coupling Reactions of Amides. *J. Org. Chem.* **2017**, *82*, 6638−6646. (k) Lei, P.; Meng, G.; Szostak, M. General Method for the Suzuki−Miyaura Cross-Coupling of Amides Using Commercially Available, Air- and Moisture-Stable Palladium/NHC (NHC = N-Heterocyclic Carbene) Complexes. *ACS Catal.* **2017**, *7*, 1960−1965. (l) Lei, P.; Meng, G.; Shi, S.; Ling, Y.; An, J.; Szostak, R.; Szostak, M. Suzuki−Miyaura cross-coupling of amides and esters at room temperature: correlation with barriers to rotation around C−N and C−O bonds. *Chem. Sci.* **2017**, *8*, 6525−6530. (m) Osumi, Y.; Liu, C.; Szostak, M. N-Acylsuccinimides: twist-controlled, acyl-transfer reagents in Suzuki−Miyaura cross-coupling by N-C amide bond activation. *Org. Biomol. Chem.* **2017**, *15*, 8867−8871. (n) Liu, C.; Liu, Y.; Liu, R.; Lalancette, R.; Szostak, R.; Szostak, M. Palladium-Catalyzed Suzuki−Miyaura Cross-Coupling of N-Mesylamides by N−C Cleavage: Electronic Effect of the Mesyl Group. *Org. Lett.* **2017**, *19*, 1434−1437. (o) Meng, G.; Lalancette, R.; Szostak, R.; Szostak, M. N-Methylamino Pyrimidyl Amides (MAPA): Highly Reactive, Electronically-Activated Amides in Catalytic N−C(O) Cleavage. *Org. Lett.* **2017**, *19*, 4656−4659. (p) Lei, P.; Meng, G.; Ling, Y.; An, J.; Nolan, S. P.; Szostak, M. General Method for the Suzuki−Miyaura Cross-Coupling of Primary Amide-Derived Electrophiles Enabled by [Pd(NHC)(cin)Cl] at Room Temperature. *Org. Lett.* **2017**, *19*, 6510−6513. (q) Meng, G.; Szostak, R.; Szostak, M. Suzuki−Miyaura Cross-Coupling of N-Acylpyrroles and Pyrazoles: Planar, Electronically Activated Amides in Catalytic N−C Cleavage. *Org. Lett.* **2017**, *19*, 3596−3599. (r) Meng, G.; Szostak, M.

https://dx.doi.org/10.1021/acs.orglett.0c03260
Org. Lett. XXXX, XXX, XXX−XXX

Palladium/NHC (NHC = N-Heterocyclic Carbene)-Catalyzed B-Alkyl Suzuki Cross-Coupling of Amides by Selective N−C Bond Cleavage. *Org. Lett.* **2018**, *20*, 6789−6793. (s) Liu, C.; Li, G.; Shi, S.; Meng, G.; Lalancette, R.; Szostak, R.; Szostak, M. Acyl and Decarbonylative Suzuki Coupling of N-Acetyl Amides: Electronic Tuning of Twisted, Acyclic Amides in Catalytic Carbon−Nitrogen Bond Cleavage. *ACS Catal.* **2018**, *8*, 9131−9139. (t) Lei, P.; Ling, Y.; An, J.; Nolan, S. P.; Szostak, M. 2-Methyltetrahydrofuran (2-MeTHF): A Green Solvent for Pd−NHC-Catalyzed Amide and Ester Suzuki-Miyaura Cross-Coupling by N−C/O−C Cleavage. *Adv. Synth. Catal.* **2019**, *361*, 5654−5660. (u) Rahman, M. M.; Buchespies, J.; Szostak, M. N-Acylphthalimides: Efficient Acyl Coupling Reagents in Suzuki−Miyaura Cross-Coupling by N−C Cleavage Catalyzed by Pd−PEPPSI Precatalysts. *Catalysts* **2019**, *9*, 129−139. (v) Shi, S.; Lalancette, R.; Szostak, R.; Szostak, M. Triflamides: Highly Reactive, Electronically Activated N-Sulfonyl Amides in Catalytic N−C(O) Amide Cross-Coupling. *Org. Lett.* **2019**, *21*, 1253−1257. (w) Zhou, T.; Li, G.; Nolan, S. P.; Szostak, M. [Pd(NHC)(acac)Cl]: Well-Defined, Air-Stable, and Readily Available Precatalysts for Suzuki and Buchwald−Hartwig Cross-coupling (Transamidation) of Amides and Esters by N−C/O−C Activation. *Org. Lett.* **2019**, *21*, 3304−3309. (x) Liu, C.; Lalancette, R.; Szostak, R.; Szostak, M. Sterically Hindered Ketones via Palladium-Catalyzed Suzuki−Miyaura Cross-Coupling of Amides by N−C(O) Activation. *Org. Lett.* **2019**, *21*, 7976−7981. (y) Buchspies, J.; Rahman, M. M.; Szostak, R.; Szostak, M. N-Acylcarbazoles and N-Acylindoles: Electronically Activated Amides for N−C(O) Cross-Coupling by N_{lp} to Ar Conjugation Switch. *Org. Lett.* **2020**, *22*, 4703−4709. (z) Wang, C.-A.; Liu, C.; Szostak, M. N-Acyl-5,5-Dimethylhydantoins: Mild Acyl-Transfer Reagents for the Synthesis of Ketones Using Pd−PEPPSI or Pd/Phosphine Catalysts. *Org. Process Res. Dev.* **2020**, *24*, 1043−1051. (aa) Wu, H.; Li, Y.; Cui, M.; Jian, J.; Zeng, Z. Suzuki Coupling of Amides via Palladium-Catalyzed C−N Cleavage of N-Acylsaccharins. *Adv. Synth. Catal.* **2016**, *358*, 3876−3880. (ab) Zhang, Y.; Wang, Z.; Tang, Z.; Luo, Z.; Wu, H.; Liu, T.; Zhu, Y.; Zeng, Z. Water Phase, Room Temperature, Ligand-Free Suzuki−Miyaura Cross-Coupling: A Green Gateway to Aryl Ketones by C−N Bond Cleavage. *Eur. J. Org. Chem.* **2020**, *2020*, 1620−1628. (ac) Li, X.; Zou, G. Acylative Suzuki coupling of amides: acyl-nitrogen activation via synergy of independently modifiable activating groups. *Chem. Commun.* **2015**, *51*, 5089−5092.

(8) (a) Shi, S.; Meng, G.; Szostak, M. Synthesis of Biaryls through Nickel-Catalyzed Suzuki-Miyaura Coupling of Amides by Carbon-Nitrogen Bond Cleavage. *Angew. Chem., Int. Ed.* **2016**, *55*, 6959−6963. (b) Ji, C.-L.; Hong, X. Factors Controlling the Reactivity and Chemoselectivity of Resonance Destabilized Amides in Ni-Catalyzed Decarbonylative and Nondecarbonylative Suzuki-Miyaura Coupling. *J. Am. Chem. Soc.* **2017**, *139*, 15522−15529. (c) Luo, Z.; Xiong, L.; Liu, T.; Zhang, Y.; Lu, S.; Chen, Y.; Guo, W.; Zhu, Y.; Zeng, Z. Palladium-Catalyzed Decarbonylative Suzuki-Miyaura Coupling of Amides To Achieve Biaryls via C-N Bond Cleavage. *J. Org. Chem.* **2019**, *84*, 10559−10568. (d) Zhou, T.; Ji, C.-L.; Hong, S.; Szostak, M. Palladium-catalyzed decarbonylative Suzuki-Miyaura cross-coupling of amides by carbon-nitrogen bond activation. *Chem. Sci.* **2019**, *10*, 9865−9871.

(9) (a) Simmons, B. J.; Weires, N. A.; Dander, J. E.; Garg, N. K. Nickel-Catalyzed Alkylation of Amide Derivatives. *ACS Catal.* **2016**, *6*, 3176−3179. (b) Shi, S.; Szostak, M. Efficient Synthesis of Diaryl Ketones by Nickel-Catalyzed Negishi Cross-Coupling of Amides by Carbon−Nitrogen Bond Cleavage at Room Temperature Accelerated by a Solvent Effect. *Chem. - Eur. J.* **2016**, *22*, 10420−10424. (c) Shi, S.; Szostak, M. Nickel-Catalyzed Diaryl Ketone Synthesis by N−C Cleavage: Direct Negishi Cross-Coupling of Primary Amides by Site-Selective N,N-Di-Boc Activation. *Org. Lett.* **2016**, *18*, 5872−5875. (d) Shi, S.; Szostak, M. Nickel-Catalyzed Negishi Cross-Coupling of N-Acylsuccinimides: Stable, Amide-Based, Twist-Controlled Acyl-Transfer Reagents via N−C Activation. *Synthesis* **2017**, *49*, 3602−3608.

(10) (a) Sureshbabu, P.; Azeez, S.; Muniyappan, N.; Sabiah, S.; Kandasamy, J. Chemoselective Synthesis of Aryl Ketones from Amides and Grignard Reagents via C(O)−N Bond Cleavage under Catalyst-Free Conditions. *J. Org. Chem.* **2019**, *84*, 11823−11838. (b) Li, G.; Szostak, M. Kinetically Controlled, Highly Chemoselective Acylation of Functionalized Grignard Reagents with Amides by N−C Cleavage. *Chem. - Eur. J.* **2020**, *26*, 611−615.

(11) Cui, M.; Wu, H.; Jian, J.; Wang, H.; Liu, C.; Daniel, S.; Zeng, Z. Palladium-catalyzed Sonogashira coupling of amides: access to ynones via C−N bond cleavage. *Chem. Commun.* **2016**, *52*, 12076−12079.

(12) Ni, S.; Zhang, W.; Mei, H.; Han, J.; Pan, Y. Ni-Catalyzed Reductive Cross-Coupling of Amides with Aryl Iodide Electrophiles via C−N Bond Activation. *Org. Lett.* **2017**, *19*, 2536−2539.

(13) Chen, J.; Xu, M.; Yu, S.; Xia, Y.; Lee, S. Nickel-Catalyzed Claisen Condensation Reaction between Two Different Amides. *Org. Lett.* **2020**, *22*, 2287−2292.

(14) Chen, J.; Xia, Y.; Lee, S. *Org. Chem. Front.* **2020**, *7*, 2931−2937.

(15) (a) Cheng, C.; Hartwig, J. F. Catalytic Silylation of Unactivated C−H Bonds. *Chem. Rev.* **2015**, *115*, 8946−8975. (b) Fukumoto, Y.; Hirano, M.; Chatani, N. Iridium-Catalyzed Regioselective C(sp3)−H Silylation of 4-Alkylpyridines at the Benzylic Position with Hydrosilanes Leading to 4-(1-Silylalkyl)pyridines. *ACS Catal.* **2017**, *7*, 3152−3156. (c) Liu, X.-W.; Zarate, C.; Martin, R. Base-Mediated Defluorosilylation of C(sp2)−F and C(sp3)−F Bonds. *Angew. Chem., Int. Ed.* **2019**, *58*, 2064−2068. (d) Liu, S.; Zhang, S.; Lin, Q.; Huang, Y.; Li, B. Ruthenium(II) Acetate Catalyzed Synthesis of Silylated Oxazoles via C−H Silylation and Dehalogenation. *Org. Lett.* **2019**, *21*, 1134−1138. (e) Jia, J.; Zeng, X.; Liu, Z.; Zhao, L.; He, C.-Y.; Li, X.-F.; Feng, Z. Iron-Catalyzed Silylation of (Hetero)aryl Chlorides with Et3SiBpin. *Org. Lett.* **2020**, *22*, 2816−2821.

(16) Wong, T. Y.; Simó, R.; Mitchell, P. Fenofibrate − A Potential Systemic Treatment for Diabetic Retinopathy? *Am. J. Ophthalmol.* **2012**, *154*, 6−12.

(17) (a) Silverman, W.; Locovei, S.; Dahl, G. Probenecid, a gout remedy, inhibits pannexin 1 channels. *Am. J. Physiol. Cell Physiol.* **2008**, *295*, 761−767. (b) Kayumov, M.; Zhao, J.-N.; Mirzaakhmedov, S.; Wang, D.-Y.; Zhang, A. Synthesis of Arylstannanes via Palladium-Catalyzed Decarbonylative Coupling of Aroyl Fluorides. *Adv. Synth. Catal.* **2020**, *362*, 776−781.

https://dx.doi.org/10.1021/acs.orglett.0c03260
Org. Lett. XXXX, XXX, XXX−XXX