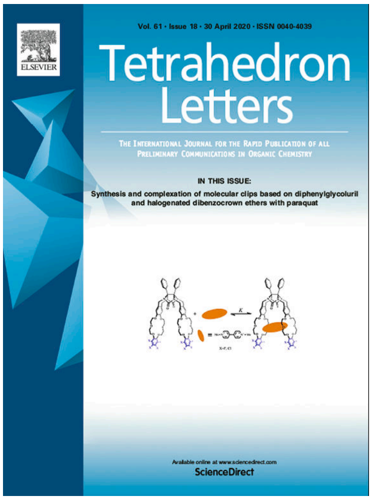

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Graphical Abstract

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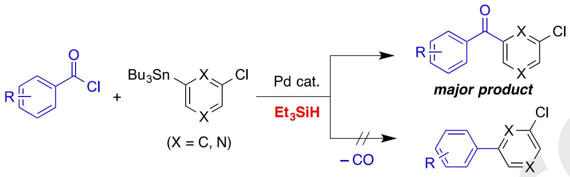

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Palladium-catalyzed Cross-coupling of Aroyl Chlorides with Aryl Stannanes in the Presence of Triethylsilane: Efficient Access to Aromatic Ketones

Shoko Higashi[a], Sota Uno[a], Yui Ohsuga[a], Maiko Noumi[a], and Ryota Saito[a,b] *

[a] Department of Chemistry, Faculty of Science, Toho University, Funabashi, Chiba 274-8510, Japan
[b] Research Center for Materials with Integrated Properties, Toho University, Funabashi, Chiba 274-8510, Japan

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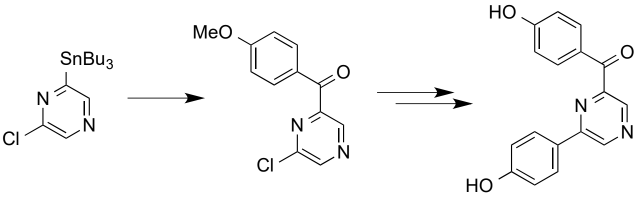
ABSTRACT

Herein, we report the development of a palladium-catalyzed cross-coupling reaction that focuses on the preparation of aromatic ketones. Aroyl chlorides react quickly at 120 °C with aryl stannanes in the presence of $Pd(PPh_3)_4$ and Et_3SiH to efficiently give the corresponding ketones without the formation of significant decarbonylated byproducts. In other words, the decarbonylative side reaction is practically suppressed by simply adding Et_3SiH to the reaction mixture, which reduces the amount of biaryl impurities in the products.

Introduction

Among a number methods for the syntheses of targeted compounds, four general popular strategies exist for preparing aromatic ketones: (i) the reactions of aroyl halides with organometallics such as organolithiums[1] or Grignard reagents,[2] which are well-known classical methods; (ii) the Friedel–Crafts acylation of aromatic compounds activated by aluminum chloride;[3] (iii) CO insertion into aryl halides or their equivalents catalyzed by organometallic complexes,[4, 5] which is an efficient process with high atom economy that has remarkably advanced in recent years; and (iv) the Stille and Suzuki–Miyaura cross-coupling reactions of aroyl halides with aryl partners (aryl stannanes and aryl boronic acids, respectively) promoted by palladium catalysts.[6-15] Compared with the other three methods, the Stille and Suzuki–Miyaura cross-coupling strategies are advantageous for the fine syntheses of asymmetric aromatic ketones with diverse structures. These cross-coupling reactions are mostly very chemoselective and can be applied to a range of substrates.[7-15] Moreover, methods for the synthesis of aryl stannanes and aryl boronic acids have already been developed through the pioneering efforts of a number of researchers,[16-19] and has provided a large number of substrates to choose from. In addition, aroyl halides are also readily prepared from benzoic acids; hence, CO gas or CO-metal complexes are not required in subsequent ketone-forming coupling reactions. Furthermore, the oxidative additions of palladium catalysts to aroyl halides are faster than those involving aryl halides, which enables the use of molecules that possess both aroyl halide and aryl halide functionalities as starting materials.[11, 14] Based on this background, we used the Stille coupling strategy with aroyl chlorides and heteroaryl stannanes to synthesize botryllazine B analogs that are expected to be drug candidates for diabetic complications (Scheme 1).[20, 21]



Scheme 1. A Pathway for the Synthesis of Botryllazine B

During this study, we encountered a serious problem: the Stille-coupling products from the reactions of some substituted aryl chlorides contained considerable amounts of byproducts that had lost their carbonyl moieties. While decarbonylative cross-coupling reactions using aroyl halides instead of aryl halides have been studied intensively in recent years,[22-24] we needed to suppress this side reaction in order to obtain our target ketones. Herein, we report the unprecedented and surprising ability of triethylsilane to suppress decarbonylation.

Results and Discussion

4-Methoxybenzoyl chloride (**1a**) was coupled with aryl stannane **2a** in the presence of 3 mol% $Pd(PPh)_3$ at 120 °C for 3 h to afford the botryllazine B building block **3aa** in good yield without the decarbonylated byproduct **4aa** (Table 1, entry 1). In contrast, 3-methoxybenzoyl chloride (**1b**) gave a non-negligible amount of **4ba** under the same reaction conditions (entry 2). Decreasing the reaction temperature to 60 °C led to the formation of less **4ba**; however, significantly long reaction times were required for reaction completion (entry 5). For us, the reaction

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* Corresponding author. Tel.: +81-47-472-1926; fax: +81-47-472-1926; e-mail: saito@chem.sci.toho-u.ac.jp

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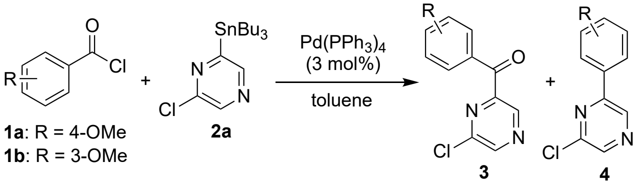
inconvenient because we wanted to synthesize as many botrillazine B analogs as possible in order to create a chemical library for thorough structure-activity relationship studies. For that reason, we explored more-efficient and versatile reaction conditions that are applicable to aroyl chlorides in general and that do not generate decarbonylated byproducts. We first explored the use of CO-rich conditions to suppress decarbonylation, since this process involves an equilibrium between CO migration and insertion at the palladium-acyl intermediate stage of the catalytic reaction cycle. Hence, we chose reactions that use the safe and readily available CO sources reported by Manabe *et al.*[25] for the acylation of aryl halides to avoid the direct use of toxic CO gas (Table 2).

Table 1. Coupling Reactions of Benzoyl chlorides with **2a**[a]



entry	substrate	temp. (°C)	time (h)	Product (yield/%)[b]	
1	**1a**	120	2.5	**3aa** (81)	**4aa** (0)
2	**1b**	120	2.5	**3ba** (76)	**4ba** (20)
3	**1b**	90	2.5	**3ba** (84)	**4ba** (9)
4	**1b**	60	2.5	**3ba** (19)	**4ba** (0)
5	**1b**	60	48	**3ba** (89)	**4ba** (2)

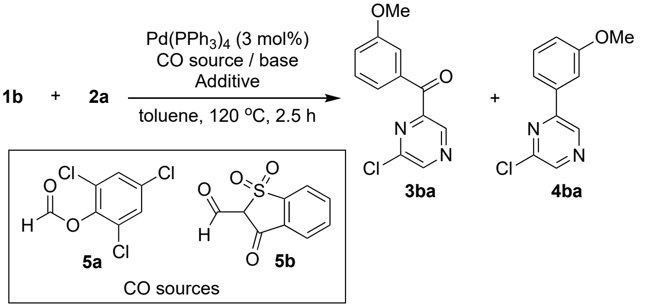
[a]Reaction conditions: **1** (3.0 mmol), **2a** (1.0 mmol), $Pd(PPh_3)_4$ (0.03 mmol), and toluene (20 mL) at 60–120 °C for 2.5 h. [b]Determined by ^1H NMR spectroscopy of a mixture of **3** and **4** obtained after silica-gel column chromatography.

Improved ratios of ketone **3ba** to biaryl **4ba** were obtained in the presence of **5a** or **5b,** Na_2CO_3, and Et_3SiH (entries 1 and 2). The results were quite satisfactory; the CO sources were apparently effective at suppressing decarbonylation. At this point, we considered that Et_3SiH, which was used as a hydride source in the original reaction to afford aldehydes, was unnecessary in the present reaction; hence the same reaction was carried out in the absence of Et_3SiH (entry 3). However, contrary to expectation, the yields of **3ba** and **4ba** were almost the same as those from the reaction in the absence of the CO source (Table 1, entry 2). The same reaction was then performed in the absence of the CO source but in the presence of Et_3SiH (entry 4). Surprisingly, an unexpected and desirable effect, which gave the required ketone in excellent yield, was observed, clearly demonstrating that the addition of only Et_3SiH to the reaction mixture effectively suppressed decarbonylation.

We next explored the silane scope of this reaction (Table 3). Increasing or decreasing of the equivalents of aroyl chloride **1b** did not improve the yield of **3ba** (entries 1, 2), while the generation of **4ba** was clearly suppressed in the presence of Et_3SiH (entries 3, 4). Using 0.5 or 2.6 equivalents of Et_3SiH was less effective than 1.0 or 1.3 equivalents (entries 5-7). Bulky silanes, such as triisopropyl, triphenyl, and triethoxysilane, were less effective than Et_3SiH (entries 8-10). Meanwhile, compact silanes, such as diphenyl, phenyl, and diethylmethyl silane, were effective at reducing decarbonylation rates (entries 11-14). Chlorotriethylsilane and tributylstannane were inactive in this reaction (entries 15-16). Et_3GeH proved to be most effective among the tested additives, completely suppressing

1.3 equivalents of Et_3SiH because of its availability and low cost.

Table 2. Reactions using CO sources and Et_3SiH[a]



entry	CO source	base (equiv.)	Additive (equiv.)	yield (%)[b]	
				3ba	**4ba**
1	**5a**	Na_2CO_3 (1.6)	Et_3SiH (1.3)	85	3
2	**5b**	Na_2CO_3 (1.6)	Et_3SiH (1.3)	69	2
3	**5a**	Na_2CO_3 (1.6)	–	77	29
4	–	–	Et_3SiH (1.3)	94	3

[a]Reaction conditions: **1b** (3.0 mmol), **2a** (1.0 mmol), $Pd(PPh_3)_4$ (0.03 mmol), CO source (1.5 mmol), Na_2CO_3 (1.6 mmol), Et_3SiH (1.3 mmol), and toluene (20 mL) at 120 °C for 2.5 h under Ar. [b]Determined by ^1H NMR spectroscopy of a mixture of **3** and **4** obtained after silica-gel column chromatography.

Table 3. Optimizing the Reaction Conditions[a]

$$\mathbf{1b} + \mathbf{2a} \xrightarrow[\text{toluene, 120 °C, 2.5 h}]{\text{Pd(PPh}_3)_4\text{ (3 mol\%), Additive}} \mathbf{3ba} + \mathbf{4ba}$$

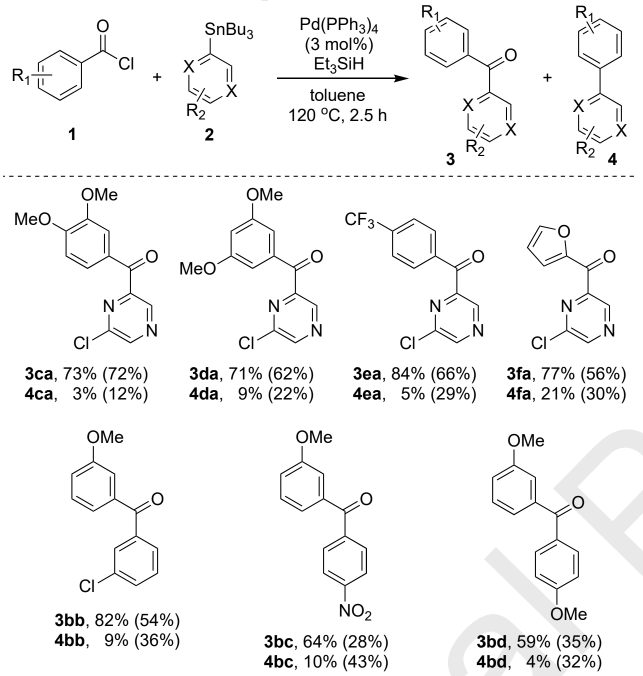
entry	**1b** / **2a** (equiv.)	Additive (equiv.)	yield (%)[b]	
			3ba	**4ba**
1	1 : 1	–	63	16
2	6 : 1	–	66	23
3	1 : 1	Et_3SiH (1.3)	50	1
4	6 : 1	Et_3SiH (1.3)	86	3
5	3 : 1	Et_3SiH (0.5)	82	10
6	3 : 1	Et_3SiH (1.0)	92	4
7	3 : 1	Et_3SiH (2.6)	88	3
8	3 : 1	$^iPr_3SiH$ (1.3)	60	24
9	3 : 1	Ph_3SiH (1.3)	76	20
10	3 : 1	$(EtO)_3SiH$ (1.3)	71	23
11	3 : 1	Ph_2SiH_2 (1.3)	73	1
12	3 : 1	$PhSiH_3$ (1.3)	75	0
13	3 : 1	Et_2MeSiH (1.3)	87	3
14	3 : 1	$EtMe_2SiH$ (1.3)	85	9
15	3 : 1	Et_3SiCl (1.3)	62	23
16	3 : 1	Bu_3SnH (1.3)	75	21
17	3 : 1	Et_3GeH (1.3)	87	0

[a]General Reaction conditions: **1b** (3.0 mmol), **2a** (1.0 mmol), additive (1.3 mmol), $Pd(PPh_3)_4$ (0.03 mmol), and toluene (20 mL) at 120 °C for 2.5 h under Ar. [b]Determined by ^1H NMR spectroscopy of a mixture of **3ba** and **4ba** obtained after silica-gel column chromatography.

With the optimized reaction conditions in hand, we investigated the effect of Et_3SiH on the cross-couplings of vari

Improved yields of ketones (**3ca**, **3da**, **3ea**, and **3fa**) and reduced amounts of decarbonylated byproducts (**4ca**, **4da**, **4ea**, and **4fa**) were observed in all cases when Et$_3$SiH was added to the reaction system; pleasingly, these products are important precursors of botryllazine B analogs. The reaction of **1b** with chlorophenylstannane **2b** also proceeded smoothly under the same conditions to afford the corresponding ketone in 82% yield accompanied by a small amount of **4bb**. Furthermore, when either an electron-donating or -withdrawing substituted phenylstannane (**2c** or **2d)** was used as the starting material, the ratio of the produced ketone dramatically changed to a desired value, which clearly demonstrates that the addition of Et$_3$SiH to the Stille acylation reaction mixture suppresses the decarbonylative side reaction remarkably, irrespective of the substrate.

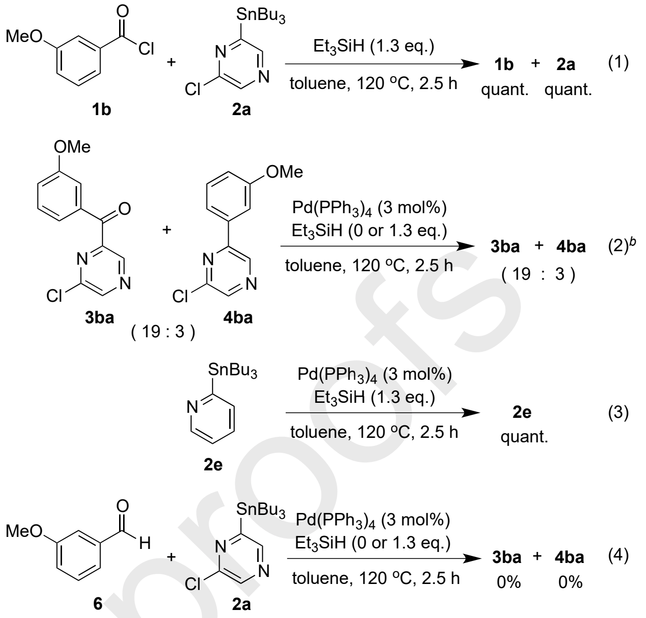
Scheme 2. Substrate scope[a]



[a]General reaction conditions: **1** (3.0 mmol), **2** (1.0 mmol), Et$_3$SiH (1.3 mmol), Pd(PPh$_3$)$_4$ (0.03 mmol), and toluene (20 mL) at 120 °C for 2.5 h under Ar. Yields were determined by ^{1}H NMR spectroscopy of a mixture of **3** and **4** obtained after silica-gel column chromatography. Yields in the absence of Et$_3$SiH are shown in parentheses. Isolated yields are shown.

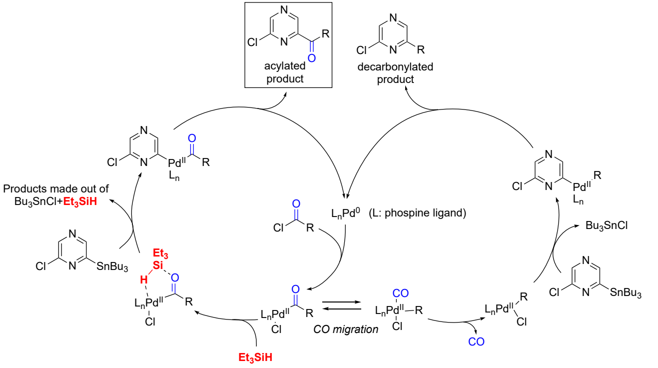
We also studied the behavior of Et$_3$SiH in the reaction pathway (Scheme 3). As might be expected, no coupling products were observed in the presence of Et$_3$SiH but the absence Pd(PPh$_3$)$_4$ (eq. 1). The ketone and biaryl products did not interconvert under the same Pd-catalyzed reaction conditions with/without Et$_3$SiH (eq. 2). In order to examine whether or not the SnBu$_3$ moiety can be replaced by Et$_3$SiH, **2e** was mixed with Et$_3$SiH in the presence of Pd(PPh$_3$)$_4$ (eq. 3), which resulted in the complete recovery of the starting aryl stannane. Aldehyde **6**, which might be generated by Pd-catalyzed reaction of benzoyl halide with Et$_3$SiH, also failed to give **3ba** and **4ba** (eq. 4). Even though further details on the behavior of Et$_3$SiH remain unknown, these observations suggested that the metal-reactive functional groups of the starting materials remain unchanged in the presence of Et$_3$SiH. Although we were unable to determine the critical factors responsible for Et$_3$SiH behavior at this point, based on previous reports that Lewis acids promote CO migratory we considered that Et3SiH behave as a Lewis acid and stabilize the palladium-acyl complexes. And thus ~~w~~e propose the reaction cycle shown in Scheme 4.

Scheme 3. Reaction Pathway Studies[a]



[a] General reaction conditions: **1b** or **6** (3.0 mmol), **2** (1.0 mmol), Pd(PPh$_3$)$_4$ (0.03 mmol), Et$_3$SiH (1.3 mmol), and toluene (20 mL) at 120 °C for 2.5 h under Ar. Yields were determined by ^{1}H NMR spectroscopy. [b]Reaction conditions: **3ba** containing **4ba** (total 62 mg), Pd(PPh$_3$)$_4$ (0.03 mmol), Et$_3$SiH (0 or 1.3 mmol), and toluene (20 mL) at 120 °C for 2.5 h under Ar. Final and initial ratios were determined by ^{1}H NMR spectroscopy against an internal standard (triphenylmethane).

Scheme 4. Proposed reaction mechanism



Conclusion

In summary, we developed a Pd-catalyzed method for cross-coupling aroyl chlorides with aryl stannanes in the presence of Et$_3$SiH to produce aromatic ketones. The addition of Et$_3$SiH to the reaction mixture suppresses decarbonylative side reactions and improves the yields of the desired ketones, irrespective of the substrate. We believe that this discovery will be helpful for the future synthesis of a wide range of aromatic ketones.

Declaration of Competing Interest

The authors declare no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Ack

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References and notes

1. Park, J. K.; Shin, W. K.; An, D. K., *Tetrahedron Lett.* **2013,** *54*, 3199-3203.
2. Sato, F.; Inoue, M.; Oguro, K.; Sato, M., *Tetrahedron Lett.* **1979**, 4303-4306.
3. Gore, P. H., *Chem. Rev.* **1955,** *55*, 229-281.
4. Bumagin, N. A.; Ponomaryov, A. B.; Beletskaya, I. P., *Tetrahedron Lett.* **1985,** *26*, 4819-4822.
5. Kobayashi, K.; Nishimura, Y.; Gao, F. X.; Gotoh, K.; Nishihara, Y.; Takagi, K., *J. Org. Chem.* **2011,** *76*, 1949-1952.
6. Labadie, J. W.; Stille, J. K., *J. Am. Chem. Soc.* **1983,** *105*, 6129-6137.
7. Milstein, D.; Stille, J. K., *J. Am. Chem. Soc.* **1979,** *101*, 4992-4998.
8. Milstein, D.; Stille, J. K., *J. Org. Chem.* **1979,** *44*, 1613-1618.
9. Jousseaume, B.; Kwon, H.; Verlhac, J. B.; Denat, F.; Dubac, J., *Synlett* **1993**, 117-118.
10. Ishiyama, T.; Kizaki, H.; Miyaura, N.; Suzuki, A., *Tetrahedron Lett.* **1993,** *34*, 7595-7598.

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3112.

12. Couve-Bonnaire, S.; Carpentier, J. F.; Mortreux, A.; Castanet, Y., *Tetrahedron* **2003,** *59*, 2793-2799.
13. Urawa, Y.; Ogura, K., *Tetrahedron Lett.* **2003,** *44*, 271-273.
14. Lerebours, R.; Camacho-Soto, A.; Wolf, C., *J. Org. Chem.* **2005,** *70*, 8601-8604.
15. Bandgar, B. P.; Patil, A. V., *Tetrahedron Lett.* **2005,** *46*, 7627-7630.
16. Miyaura, N.; Suzuki, A., *Chem. Rev.* **1995,** *95*, 2457-2483.
17. Suzuki, A.; Brown, H. C., *Organic Synthesis via Boranes: Volume 3 Suzuki Coupling*. Aldrich Chemical Company, Inc.: Milwaukee, WI, U.S.A., 2003.
18. Hartwig, J. F., *Acc. Chem. Res.* **2012,** *45*, 864-873.
19. Yoshida, H., *Synthesis-Stuttgart* **2016,** *48*, 2540-2552.
20. Buron, F.; Plé, N.; Turck, A.; Queguiner, G., *J. Org. Chem.* **2005,** *70*, 2616-2621.
21. Saito, R.; Tokita, M.; Uda, K.; Ishikawa, C.; Satoh, M., *Tetrahedron* **2009,** *65*, 3019-3026.
22. Zhao, X. D.; Yu, Z. K., *J. Am. Chem. Soc.* **2008,** *130*, 8136-8137.
23. Malapit, C. A.; Ichiishi, N.; Sanford, M. S., *Org. Lett.* **2017,** *19*, 4142-4145.
24. Ogiwara, Y.; Sakai, N., *Angew. Chem. Int. Ed.* **2020,** *59*, 574-594.
25. Konishi, H.; Manabe, K., *Synlett* **2014,** *25*, 1971-1986.
26. Butts, S. B.; Strauss, S. H.; Holt, E. M.; Stimson, R. E.; Alcock, N. W.; Shriver, D. F., *J. Am. Chem. Soc.* **1980,** *102*, 5093-5100.
27. Richmond, T. G.; Basolo, F.; Shriver, D. F., *Inorg Chem* **1982,** *21*, 1272-1273.

Supplementary Material

Supplementary data to this article can be found online athttps://doi.org/10.1016/j.tetlet.xxxx.xxxxxx.