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Strategies for the Synthesis of 2-Substituted Indoles and Indolines Starting from Acyclic α-Phosphoryloxy Enecarbamates

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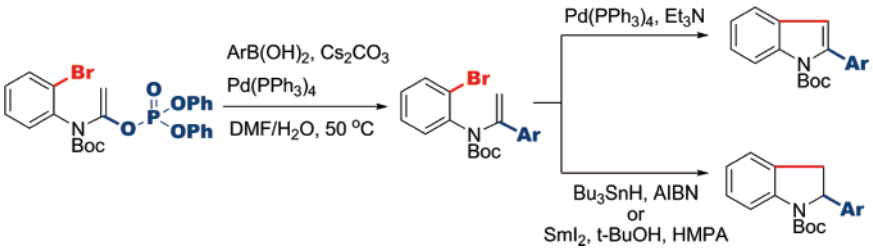
ABSTRACT



Strategies have been developed for the synthesis of 2-substituted indoles and indolines starting from acyclic α-phosphoryloxy enecarbamates. A highly chemoselective cross-coupling of *N*-(*o*-bromophenyl)-α-phosphoryloxyenecarbamates with boron nucleophiles enabled the efficient preparation of various *N*-(*o*-bromophenyl)enecarbamates, which served as useful precursors for subsequent Heck-type cyclization or 5-*endo*-*trig* aryl radical cyclization to furnish 2-substituted indoles or indolines, respectively.

Utilization of alkenyl phosphates in palladium(0)-catalyzed reactions, pioneered by Oshima and co-workers,[1] has recently gained much attention among organic chemists due to their potential as substitutes for triflate counterparts.[2] Alkenyl phosphates are easy to prepare and handle because they are more stable than the corresponding triflates. In addition, reagents for phosphorylation, such as diphenylphosphoryl chloride, are less expensive than conventional triflating agents [e.g., trifluoromethanesulfonic anhydride or *N*-phenyl bis(trifluoromethanesulfonimide)]. However, the reactivity profile of alkenyl phosphates remains largely unexplored despite their potential to expand the scope of palladium(0)-catalyzed processes. An understanding of the reactivity difference between alkenyl phosphates and other functionalities, such as aryl bromides/chlorides, is essential for the successful design of sequential or cascade processes involving palladium(0)-catalyzed reactions.

We reported that Suzuki−Miyaura coupling with cyclic α-phosphoryloxy enol ethers is a powerful process for the convergent synthesis of marine polycyclic ether natural products.[3,4] However, acyclic α-phosphoryloxy enamides/

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(2) (a) Nicolaou, K. C.; Shi, G.-Q.; Gunzner, J. L.; Gärtner, P.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 5467. (b) Nicolaou, K. C.; Shi, G.-Q.; Namoto, K.; Bernal, F. *Chem. Commun.* **1998**, 1757. (c) Buon, C.; Chacun-Lefevre, L.; Rabot, R.; Bouyssou, P.; Coudert, G. *Tetrahedron* **2000**, *56*, 605. (d) Lepifre, F.; Clavier, S.; Bouyssou, P.; Coudert, G. *Tetrahedron* **2001**, *57*, 6969. (e) Lo Galbo, F.; Occhiato, E. G.; Guarna, A.; Faggi, C. *J. Org. Chem.* **2003**, *68*, 6360. (f) Mousset, D.; Gillaizeau, I.; Hassan, J.; Lepifre, F.; Bouyssou, P.; Coudert, G. *Tetrahedron Lett.* **2005**, *46*, 3703. (g) Occhiato, E. G.; Lo Galbo, F.; Guarna, A. *J. Org. Chem.* **2005**, *70*, 7324. (h) Hansen, A. L.; Ebran, J.-P.; Ahlquist, M.; Norrby, P.-O.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3349. (i) Ebran, J.-P.; Hansen, A. L.; Gogsig, T. M.; Skrydstrup, T. *J. Am. Chem. Soc.* **2007**, *129*, 6931.

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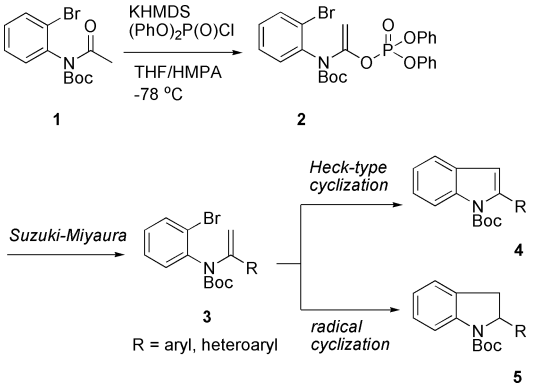
enecarbamates have not been used in palladium(0)-catalyzed processes despite their potential utility in the synthesis of nitrogen heterocycles.[5] We recently reported the first successful application of acyclic α-phosphoryloxy enecarbamates to the synthesis of indole-2,3-quinodimethanes and 2-(*N*-alkoxycarbonylamino)-1,3-dienes and demonstrated their versatility in the Heck reaction.[6] As part of our studies on the exploitation of α-phosphoryloxy enamides/enecarbamates in the palladium(0)-catalyzed synthesis of nitrogen heterocycles,[7] we describe herein strategies for the synthesis of 2-substituted indoles and indolines starting from acyclic α-phosphoryloxy enecarbamates based on a highly chemoselective Suzuki−Miyaura coupling.

Scheme 1. Concept of the Present Work

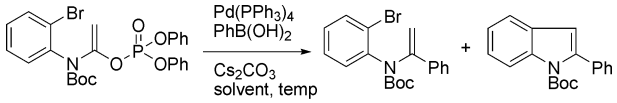


Scheme 1 illustrates our strategies for the synthesis of 2-substituted indoles and indolines starting from acyclic α-phosphoryloxy enecarbamates. Thus, a highly chemoselective cross-coupling of α-phosphoryloxy enecarbamate **2**, readily derived from the corresponding imide **1** by treatment with KHMDS and $(PhO)_2P(O)Cl$, in the presence of an aryl bromide would give *N*-(*o*-bromophenyl)enecarbamate **3**. The Heck-type cyclization of **3** would afford 2-substituted indole derivative **4**. On the other hand, 5-*endo-trig* aryl radical cyclization of **3** would furnish 2-substituted indoline **5**, although this type of cyclization is generally disfavored according to Baldwin's rules.[8]

We first examined a chemoselective cross-coupling of α-phosphoryloxy enecarbamate **2** with 1.1 equiv of phenylboronic acid[9] (Table 1). When the reaction was performed with **2**, phenylboronic acid, $Pd(PPh_3)_4$, and Cs_2CO_3 in dioxane at 60 °C, the desired enecarbamate **6a** was isolated in 47% yield (from **1**) along with a considerable amount of indole **7** (entry 1). To suppress the formation of **7**, we surveyed a series of reaction conditions and found that the addition of H_2O as a cosolvent dramatically increased the yield of **6a**. Thus, employing $Pd(PPh_3)_4$ catalyst and Cs_2CO_3 in 10:1 dioxane/H_2O at 50 °C, the cross-coupling proceeded smoothly and without incident, giving **6a** in 72% overall yield from **1** (entry 2). Further examination revealed that 10:1 DMF/H_2O is the best solvent for the cross-coupling; a remarkable chemoselectivity was attained under these conditions, and **6a** was isolated in 90% yield (entry 4). On the other hand, when the reaction was performed at room temperature, the yield of **6a** declined (entry 5). Thus, under the aqueous Suzuki−Miyaura conditions, the reactivity order α-phosphoryloxy enecarbamate > aryl bromide is established.

We then investigated the Heck-type cyclization of **6a** as summarized in Table 2. Although there are reports on the

Table 1. Chemoselective Cross-Coupling of **2** with Phenylboronic Acid[a]

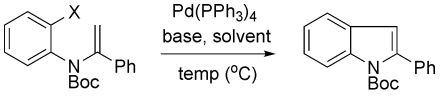


2 **6a** **7**

entry	substrate	solvent	temp (°C)	% yield **6a**	% yield **7**
1	**2**	1,4-dioxane	60	47	24
2	**2**	1,4-dioxane/H_2O (10:1)	50	72	0
3	**2**	THF/H_2O (10:1)	50	85	0
4	**2**	DMF/H_2O (10:1)	50	90	0
5[b]	**2**	DMF/H_2O (10:1)	rt	52	0

[a] All reactions were performed with 10 mol % of $Pd(PPh_3)_4$, 1.1 equiv of $PhB(OH)_2$, and 3 equiv of Cs_2CO_3. Yields are overall from **1**. [b] Na_2CO_3 was used as a base.

Table 2. Screening of Conditions[a]



6a: X = Br
6b: X = H

7

entry	base (equiv)	solvent	temp (°C)	% yield
1	K_2CO_3 (3)	DMF	100	48
2[b,c]	K_2CO_3 (3)	CH_3CN	80	71
3[b,c]	Et_3N (10)	DMF	100	76
4[b]	Et_3N (10)	DMF	100	94
5[b]	*i*-Pr_2NEt (10)	DMF	100	38
6	PMP (5)	DMF	100	18

[a] All reactions were carried out for 20−24 h unless otherwise noted. Yields are overall from **1**. [b] Reactions performed in a sealed tube. [c] *n*-Bu_4NCl (1 equiv) was used as an additive.

(4) (a) Fuwa, H.; Sasaki, M.; Satake, M.; Tachibana, K. *Org. Lett.* **2002**, *4*, 2891. (b) Fuwa, H.; Kainuma, N.; Tachibana, K.; Sasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14983. (c) Tsukano, C.; Sasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 14294. (d) Tsukano, C.; Ebine, M.; Sasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4326. (e) Fuwa, H.; Ebine, M.; Sasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 9648. (f) Fuwa, H.; Ebine, M.; Bourdelais, A. J.; Baden, D. G.; Sasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 16989.

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(6) Fuwa, H.; Sasaki, M. *Chem. Commun.* **2007**, 2876.

(7) (a) Fuwa, H.; Kaneko, A.; Sugimoto, Y.; Tomita, T.; Iwatsubo, T.; Sasaki, M. *Heterocycles* **2006**, *70*, 101. (b) Fuwa, H.; Sasaki, M. *Org. Biomol. Chem.* **2007**, *5*, 1849.

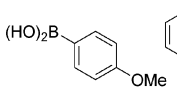
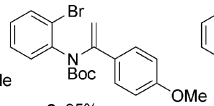
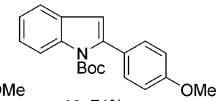
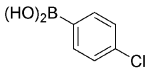
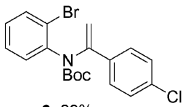
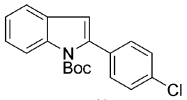
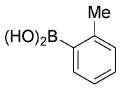
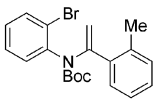
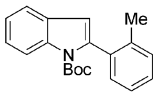
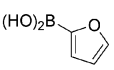
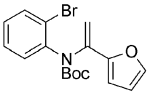
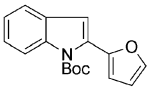
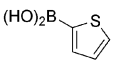
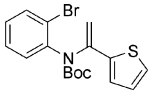
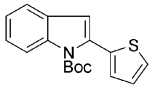
(8) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(9) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

Heck-type cyclization of related enamines and enaminones,[10,11] its application to the synthesis of 2-substituted indoles has been less explored and, to the best of our knowledge, the use of *N*-alkoxycarbonyl derivatives in such reactions has not been reported. We initially performed the cyclization of **6a** using 10 mol % of $Pd(PPh_3)_4$ and K_2CO_3 as a base in DMF at 100 °C (Table 2, entry 1). The desired *N*-Boc-2-phenylindole **7** was isolated in 48% yield, and the major byproduct was the dehalogenated **6b** (22%). On the other hand, under the Jeffery conditions,[12] the desired product **7** was cleanly obtained in an improved 71% yield, and the formation of **6b** was completely suppressed (entry 2). Employing Et_3N as a base, further enhancement of the yield was attained (entries 3 and 4). Thus, exposure of **6a** to catalytic $Pd(PPh_3)_4$ and Et_3N in DMF at 100 °C afforded **7** in 94% yield. Changing the base to *i*-Pr_2NEt or 1,2,2,6,6-pentamethylpiperidine (PMP) was found to be detrimental due to the significant dehalogenation as a side reaction (entries 5 and 6).

Having secured reliable conditions for the cross-coupling and cyclization processes, application of the present strategy to a variety of substrates was investigated, and the results are summarized in Table 3. Suzuki−Miyaura cross-coupling

Table 3. Application to a Variety of Substrates[a]

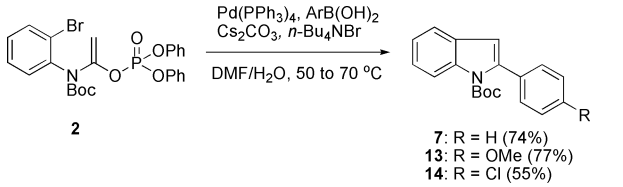
entry	boronic acid	enecarbamate	indole
1		 **8**: 95%	 **13**: 71%
2		 **9**: 89%	 **14**: 59%
3		 **10**: 86%	 **15**: 91%
4		 **11**: 100%	 **16**: 54% (44%)[b]
5		 **12**: 97%	 **17**: 63% (31%)[b]

[a] Cross-coupling reactions: $Pd(PPh_3)_4$ (0.1 equiv), Cs_2CO_3 (3 equiv), boron nucleophile (1.1 equiv) in 10:1 DMF/H_2O at 50 °C. Cyclization reactions: $Pd(PPh_3)_4$ (0.1 equiv), Et_3N (10 equiv) in DMF at 100 °C. [b] Yields in parentheses are the corresponding *N*-deprotected indole.

of **2** with a range of arylboronic acids proceeded without incident to give enecarbamates **8**−**12** without touching the aryl bromide. Under the established conditions, cyclization reactions of **8**−**12** were efficiently achieved, affording 2-aryl and 2-heteroaryl indoles **13**−**17** in good to excellent yields.[13]

We next investigated a cross-coupling/cyclization cascade starting from α-phosphoryloxy enecarbamate **2**, exploiting its unique reactivity profile (Scheme 2). In the previous

Scheme 2. Suzuki−Miyaura Coupling/Heck-Type Cyclization Cascade



experiment, we unexpectedly isolated indole **7** as a byproduct in 24% yield when cross-coupling of **2** with phenylboronic acid was performed in anhydrous dioxane at 60 °C (see Table 1, entry 1). Under these conditions, however, further conversion of enecarbamate **2** to indole **7** stalled after ca. 24 h. Elevation of temperature (100 °C) and/or prolonged reaction time proved to be ineffective. After several attempts, we found that consecutive cross-coupling/cyclization could be realized using 10 mol % of $Pd(PPh_3)_4$, Cs_2CO_3 (3 equiv), arylboronic acid (1.1 equiv), and *n*-Bu_4NBr (1 equiv)[12] in 10:1 DMF/H_2O at 50−70 °C. Under these conditions, we isolated *N*-Boc-2-substituted indole derivatives **7**, **13**, and **14** in good yields.

Finally, 5-*endo-trig* aryl radical cyclization of enecarbamates **6a** and **8**−**11** was examined. It is well-known that 5-*exo-trig* radical cyclization is a powerful strategy for the construction of 3-substituted indoline derivatives.[14] To the best of our knowledge, however, there has been no report of the application of 5-*endo-trig* radical cyclization for the synthesis of an indoline system.[15,16] To our delight, treatment

(10) For early examples see: (a) Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Org. Chem.* **1980**, *45*, 2938. (b) Kasahara, A.; Izumi, T.; Murakami, S.; Yanai, H.; Takatori, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 927. (b) Sakamoto, T.; Nagano, T.; Kondo, Y.; Yamanaka, H. *Synthesis* **1990**, 215.

(11) (a) Michael, J. P.; Chang, S.-F.; Wilson, C. *Tetrahedron Lett.* **1993**, *34*, 8365. (b) Koerber-Plé, K.; Massiot, G. *Synlett* **1994**, 759. (c) Chen, L.-C.; Yang, S.-C.; Wang, H.-M. *Synthesis* **1995**, 385. (d) Latham, E. J.; Stanforth, S. P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2059. (e) Edmondson, S. D.; Mastracchio, A.; Parmee, E. R. *Org. Lett.* **2000**, *2*, 1109. (f) Yamazaki, K.; Nakamura, Y.; Kondo, Y. *J. Org. Chem.* **2003**, *68*, 6011. (g) Watanabe, T.; Arai, S.; Nishida, A. *Synlett* **2004**, 907. (h) Nazaré, M.; Schneider, C.; Lindenschmidt, A.; Will, D. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 452. (i) Lachnace, N.; April, M.; Joly, M.-A. *Synthesis* **2005**, 2571. (j) Barluenga, J.; Fernandez, M. A.; Aznar, F.; Valdes, C. *Chem. Eur. J.* **2005**, *11*, 2276. (k) Baran, P. S.; Hafensteiner, B. D.; Ambhaikar, N. B.; Guerrero, C. A.; Gallagher, J. D. *J. Am. Chem. Soc.* **2006**, *128*, 8678. (l) Jia, J.; Zhu, J. *J. Org. Chem.* **2006**, *71*, 7826.

(12) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.

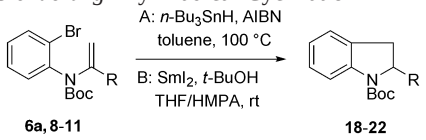
(13) Although the present reaction affords 5-*endo-trig* Heck cyclization-type products, it is believed that it proceeds via a 6-membered palladacycle intermediate. For discussions on the mechanism, see refs 10a and 11d.

(14) (a) Boger, D. L.; Yun, W.; Teegarden, B. R. *J. Org. Chem.* **1992**, *57*, 2873. (b) Boger, D. L.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 1271. (c) Patel, V. F.; Andis, S. L.; Enkema, J. K.; Johnson, D. A.; Kennedy, J. H.; Mohamadi, F.; Schultz, R. M.; Soose, D. J.; Spees, M. M. *J. Org. Chem.* **1997**, *62*, 8868.

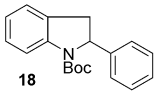
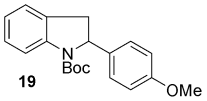
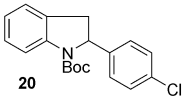
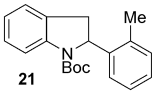
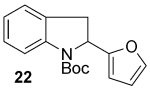
(15) For reviews see: (a) Ishibashi, H.; Sato, T.; Ikeda, M. *Synthesis* **2002**, 695. (b) Ishibashi, H. *Chem. Rec.* **2006**, *6*, 23.

of **6a** and **8**−**11** with Bu_3SnH in the presence of catalytic AIBN in toluene at 100 °C (method A) gave a series of 2-substituted indolines **18**−**22** in moderate to good yields (Table 4). Furthermore, we found that radical cyclization could also be performed under mild conditions using SmI_2 in the presence of *t*-BuOH in THF/HMPA[17] at room temperature (method B). The latter method affords 2-substituted indolines in somewhat better yields and eliminates the need for tedious chromatographic separation of tin byproducts.

Table 4. 5-*endo-trig* Aryl Radical Cyclization



6a, 8-11 **18-22**

entry	enecarbamate	indoline	% yield[a] A	% yield[a] B
1	**6a**	 **18**	82	65[b] 90
2	**8**	 **19**	85	86
3	**9**	 **20**	62	80
4	**10**	 **21**	72	63
5	**11**	 **22**	51	54

[a] Method A: *n*-Bu_3SnH, AIBN, toluene, 100 °C. Method B: SmI_2, *t*-BuOH, HMPA, THF, room temperature. [b] Reaction performed in the absence of *t*-BuOH.

In conclusion, the present study clearly demonstrates the synthetic utility of acyclic α-phosphoryloxy enecarbamates as novel versatile precursors in the synthesis of 2-substituted indoles and indolines. We found that the addition of water as a cosolvent in the Suzuki−Miyaura reaction of α-phosphoryloxy enecarbamates with aryl or heteroaryl boronic acids allowed for a highly chemoselective cross-coupling, giving a series of *N*-(*o*-bromophenyl)enecarbamates in excellent yields. The establishment of the reactivity order α-phosphoryloxy enecarbamate > aryl bromide under aqueous Suzuki−Miyaura conditions is noteworthy. The Heck-type cyclization of *N*-(*o*-bromophenyl)enecarbamates was successfully employed in the synthesis of 2-substituted indole derivatives. Consequently, the Suzuki−Miyaura cross-coupling/Heck-type cyclization cascade was developed based on the established reactivity difference between α-phosphoryloxy enecarbamate and aryl bromide functional groups. We have also succeeded in the 5-*endo-trig* aryl radical cyclization of *N*-(*o*-bromophenyl)enecarbamates, which is an unprecedented example of the successful application of generally disfavored 5-*endo-trig* cyclization to the synthesis of indoline derivatives.[18]

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Supporting Information Available: Representative experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) To expand the scope of the present strategies, we are currently investigating the use of a propionyl imide instead of **1** as the starting material, which would provide 2,3-disubstituted indoles or indolines. The results will be reported in due course.