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Palladium-Catalyzed β-Allylation of 2,3-Disubstituted Indoles

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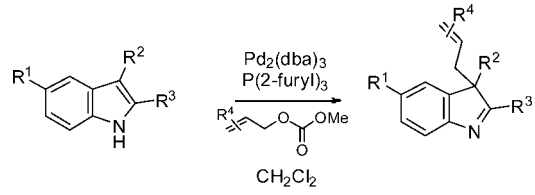
ABSTRACT



20 examples, 63% - 99% yield

Given the prevalence of the indole nucleus in biologically active compounds, the direct C3-functionalization of 2,3-disubstituted indoles represents an important problem. Described is a general, high-yielding method for the palladium-catalyzed β-allylation of carba- and heterocycle fused indoles, including complex natural product substrates.

Indoles and indole-derived heterocycles are prevalent structural motifs in natural products, medicinal compounds, and organic materials.[1] Given their importance, much effort has been directed toward the development of methods for the selective functionalization of the indole nucleus at the N1, C2, and C3 sites.[2] A particularly difficult transformation is the electrophilic attack at C3 on 3-substituted indoles to produce indolenines containing a new carbon−carbon bond and a quaternary stereocenter. Indolenine units are found as the core of many natural products, as biogenetic precursors to indole alkaloids, and as pivotal intermediates in total synthesis.[3,4] Traditional methods for β-functionalization of indoles, which take advantage of the ambident character of indoles or indole anions, have limitations.[5] Not only is alkylation of C3-substituted indoles difficult, but the strong, nucleophilic bases (e.g., Grignard reagents, $NaNH_2$) typically used for such transformations restrict their scope due to functional group incompatibility. In the course of our studies toward the total synthesis of complex alkaloids, we required a mild, functional group tolerant method for the introduction of an allyl group regioselectively on a β-carboline substrate (e.g., **1**, Scheme 1). While the literature records methods for the palladium-catalyzed β-allylation of simple indoles,[6] the direct allylation of hindered, 2,3-disubstituted indoles, such as **1**, remains an unsolved problem.[7] We report here a general, high-yielding method for the palladium-catalyzed

(1) (a) Sundberg, R. J. *Indoles*; Academic Press: London, 1996. (b) Saxton, J. E. E. *Indoles*; John Wiley & Sons: New York, 1983; Vol. 25, Part 4.

(2) (a) Remers, W. E. In *Indoles, Part 1*; Houlihan, W. J., Ed.; John Wiley & Sons: New York, 1983; pp 1−226. (b) Nunomoto, S.; Kawakami, Y.; Yamashita, Y.; Takeuchi, H.; Eguchi, S. *J. Chem. Soc., Perkin Trans. 1* **1990**, 111–114. For reviews, see: (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920. (d) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199–1222.

(3) Julian, J. L.; Meyer, E. W.; Printy, H. C. In *Heterocyclic Compounds*; Elderfield, R. C., Ed.; John Wiley & Sons: New York, 1952; Vol. 3, pp 74−114.

(4) For examples of indolenines used in total synthesis, see: (a) Li, C.; Chan, C.; Heimann, A. C.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1444–1447. (b) Bosch, J.; Bennasar, M.-L.; Amat, M. *Pure Appl. Chem.* **1996**, *68*, 557–560. (c) Sapi, J.; Dridi, S.; Laronze, J.; Sigaut, F.; Patigny, D.; Laronze, J. Y.; Levy, J.; Toupet, L. *Tetrahedron* **1996**, *52*, 8209–8222. (d) Rey, A. W.; Szarek, W. A.; MacLean, D. B. *Can. J. Chem.* **1992**, *70*, 2922–2928. (e) Vercauteren, J.; Massiot, G.; Levy, J. *J. Org. Chem.* **1984**, *49*, 3230–3231. (f) Wenkert, E.; Sliwa, H. *Bioorganic Chem.* **1977**, *6*, 443–452. (g) Bramely, R. K.; Caldwell, J.; Grigg, R. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1913–1921. (h) Barton, J. E. D.; Harley-Mason, J. *Chem. Commun. (London)* **1965**, 298–299. (i) Robinson, R.; Suginome, H. *J. Chem. Soc.* **1932**, 298–304.

(5) (a) Hoshino, T. *Ann.* **1933**, *500*, 35–42. (b) Nakazaki, M. *Bull. Chem. Soc. Jpn.* **1961**, *34*, 334–337.

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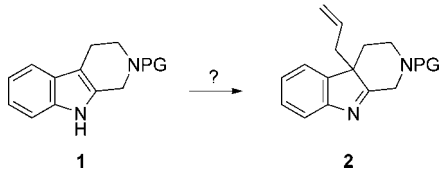
Scheme 1

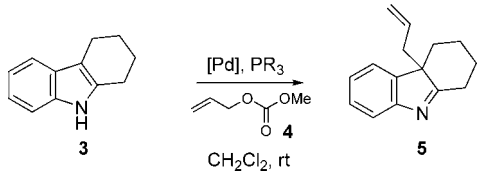


1 2

allylation of carba- and heterocycle fused indoles, including highly functionalized complex natural product substrates.[8]

In initial studies, we examined the effectiveness of published methods for the palladium-catalyzed indole allylation using 1,2,3,4-tetrahydrocarbazole (**3**) as a challenging substrate and allyl methyl carbonate (**4**) as the allyl source (Table 1, entries 1−4).[6,7,9] The modest yields obtained using

Table 1. Optimization of Allylation Reaction



3 5

	[Pd] (mol %)	PR_3 (mol %)	time (h)	yield (%)
1[a]	$Pd(acac)_2$ (2.0)	PPh_3 (2.0)	20	17
2[b]	$Pd(PPh_3)_4$ (5.0)		20	20
3[c]	$Pd_2(dba)_3$ (2.5)	Trost's ligand (7.5)	20	52
4[d]	$[PdCl(\pi\text{-allyl})]_2$ (5.0)	dppe (11)	20	90
5	$Pd_2(dba)_3$ (2.5)	PPh_3 (15)	20	91
6	$Pd_2(dba)_3$ (2.5)	*t*-Bu_3P (15)	20	trace
7[e]	$Pd_2(dba)_3$ (2.5)	P(*t*Bu)$_2$(biphenyl) (15)	20	85
8[e]	$Pd_2(dba)_3$ (2.0)	*rac*-BINAP (6.0)	20	45
9	$Pd_2(dba)_3$ (2.5)	dppp (2.5)	20	NR
10	$Pd_2(dba)_3$ (2.5)	$P(OMe)_3$ (5.0)	20	trace
11	$Pd_2(dba)_3$ (2.5)	P(2-furyl)$_3$ (15)	2	99
12	$Pd_2(dba)_3$ (2.5)	P(2-furyl)$_3$ (5.0)	2	99
13	$Pd_2(dba)_3$ (1.0)	P(2-furyl)$_3$ (2.0)	20	92
14	$Pd_2(dba)_3$ (0.05)	P(2-furyl)$_3$ (1.0)	48	66
15[f]	$Pd_2(dba)_3$ (2.5)	P(2-furyl)$_3$ (15)	20	20

[a] Run in AcOH at 70 °C with allyl acetate in place of **4**. [b] Allyl alcohol and Et_3B were used in place of **4**. [c] Allyl alcohol and *n*-hexyl-9-BBN were used in place of **4**; Trost's phosphine ligand is described in ref 7. [d] Run at 40 °C in the presence of Li_2CO_3. [e] Run in PhMe. [f] Allyl acetate was used in place of **4**.

these protocols prompted us to explore other catalyst systems for this transformation.[10] Some of the many conditions examined during this optimization process are shown in Table 1. $Pd_2(dba)_3$ was quickly determined to be a suitable source of the catalytically active palladium species (entries 5−11). With regard to phosphine ligands, hindered alkylphosphines gave the allylated product in fair to good yields, whereas triphenylphosphine (entry 5) and trifurylphosphine (entry 11) gave the best yields of **5**. Significantly, the rate of the reaction was found to considerably faster with trifurylphosphine than with triphenylphosphine.[11] Additionally, under these conditions, none of the *N*-allylated product was observed. Reduction in the amount of P(2-furyl)$_3$ used to a 1:1 ratio with palladium did not appreciably affect the yield or rate of the reaction (entry 12). Given the faster rate, lower catalyst loadings were examined. When the reaction was carried out using 1 mol % of $Pd_2(dba)_3$ (entry 13), the product was obtained in high yield, but required longer for the reaction to go to completion. Further reduction of $Pd_2(dba)_3$ to 0.5 mol % proved less satisfactory, giving **5** in 66% yield, even after 2 days (entry 14). Allyl acetate (entry 15) was found to be an ineffective allylation precursor, giving the desired product in a reduced yield and accompanied with the *N*-allylation product (19%). This survey defined convenient and mild conditions for the β-allylation of hindered indoles in high yield (entry 12).

The reaction conditions developed above were found to be broadly applicable to a wide variety of carba- and heterocycle fused indoles (Table 2). Substitution the 6-position of tetrahydrocarbazole is well tolerated (entries 1−3), although chloride **6c** required 20 h for complete conversion. Cycloheptane- and cyclooctane-fused indoles **6d** and **6e** participate in the reaction and give high yields of the corresponding allyl indolenine products (entries 4−5). Tetrahydro-γ-carbolines are competent substrates as well but generally require longer reaction times than their all carbon counterparts. Electron-rich γ-carbolines (**6f**−**h**) were allylated in greater than 90% yield, whereas the more electron-deficient chlorocarboline **6i** reacted more sluggishly, generating the allylation product **7i** in 76% yield after 48 h. Tetrahydro-β-carbolines were evaluated also. Boc-protected β-carbolines **6j** and **6k** provided the allylated products in high yield and exhibited similar rates of reaction as the γ-carbolines. Even the more electron-deficient dihydro-β-carboline **6l** was allylated at room temperature, albeit more slowly and in lower yield (63%). Allylation of simpler, monosubstituted indoles gave the expected allyl-indolenines in good yields (entries 13 and 14). Finally, substituted tetrahydro-β-carboline **6o** gave the corresponding allylation product in 73% yield as a 1.2:1 ratio of diastereomers.

(6) For examples of the 3-allylation of 3-unsubstituted indoles, see: (a) Billups, W. E.; Erkes, R. S.; Reed, L. E. *Synth. Commun.* **1980**, *10*, 147–154. (b) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Org. Lett.* **2004**, *6*, 3199–3202. (c) Bandini, M.; Melloni, A.; Piccinelli, F.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **2006**, *128*, 1424–1425. (d) Liu, Z.; Liu, L.; Shafiq, Z.; Wu, Y. C.; Wang, D.; Chen, Y. J. *Tetrahedron Lett.* **2007**, *48*, 3963–3967. (e) Zaitsev, A. B.; Gruber, S.; Pregosin, P. S. *Chem. Commun.* **2007**, 4692–4693. (f) Yadav, J. S.; Reddy, B. V. S.; Aravind, S.; Kumar, G.; Reddy, A. S. *Tetrahedron Lett.* **2007**, *48*, 6117–6120.

(7) For examples of the 3-allylation of 3-substituted indoles, see: (a) Kimura, M.; Futamata, M.; Mukai, R.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 4592–4593. (b) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314–6315.

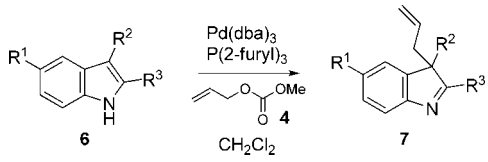
(8) For reviews of π-allyl palladium chemistry, see: (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2943. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422. (c) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140–145.

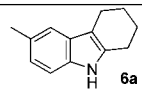
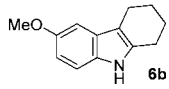
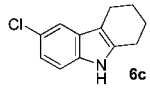
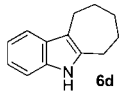
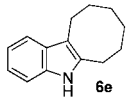
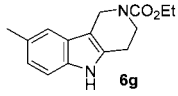
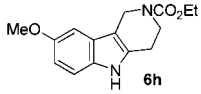
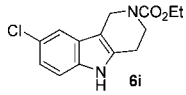
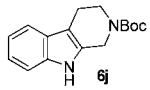
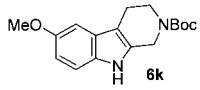
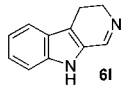
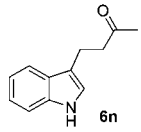
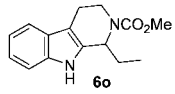
(9) When **3** was subjected to MeMgBr and allyl iodide, **5** was obtained in 94% yield. However, significantly lower yields were observed for carboline substrates.

(10) Although the conditions in entry 4 were successful for **3**, significantly lower yields (<30%) were observed for carboline substrates.

(11) For a review of the applications of tri(2-furyl)phosphine, see: Andersen, N. G.; Keay, B. A. *Chem. Rev.* **2001**, *101*, 997–1030.

Table 2. Scope of Pd-Catalyzed β-Allylation of Indoles[a]

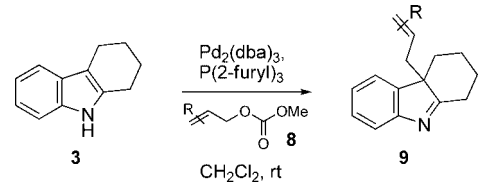


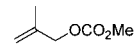
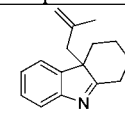
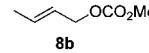
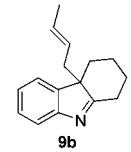
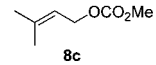
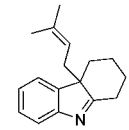
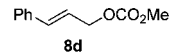
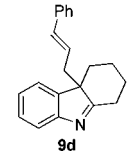
	substrate	product	time	yield
1	 6a	**7a**	2 h	98%
2	 6b	**7b**	4 h	88%
3	 6c	**7c**	20 h	87%
4	 6d	**7d**	4 h	89%
5	 6e	**7e**	4 h	91%
6	 6f	**7f**	20 h	91%
7	 6g	**7g**	20 h	94%
8	 6h	**7h**	20 h	91%
9	 6i	**7i**	48 h	76%
10[b]	 6j	**7j**	20 h	94%
11[b]	 6k	**7k**	20 h	89%
12[b]	 6l	**7l**	120 h	63%
13	 6m	**7m**	48 h	88%
14	 6n	**7n**	20 h	84%
15	 6o	**7o**	20 h	73%

[a] Reactions were carried out on 0.250 mmol of indole substrate with 0.025 equiv of $Pd_2(dba)_3$, 0.050 equiv of P(2-furyl)$_3$, and 2.0 equiv of allyl methyl carbonate (**4**) in 2.5 mL of CH_2Cl_2 at rt. [b] 0.300 equiv of P(2-furyl)$_3$ was used.

The high efficiency of the allylation reactions described above prompted us to extend the reaction to substituted allyl carbonates. The results of these studies are summarized in Table 3. Methallyl carbonate **8a** reacted with carbazole **3** to give **9a** in 98% yield (entry 1). The corresponding reaction with crotyl carbonate **8b**proceeded cleanly to afford indolenine **9b** in high yield (entry 2). Notably, the regio- and geometric alkene isomer products were observed in only trace amounts. The prenylation of **3** with prenyl carbonate **8c** was much slower than analogous allylation reactions but did provide the prenylated indolenine **9c** in 45% yield (entry 3). Lastly, the reaction of carbazole **3** with cinnamyl carbonate **8d** afforded **9d** in 92% yield as the sole observed isomer (entry 4).

Table 3. Allylation with Substituted Allyl Carbonates[a]

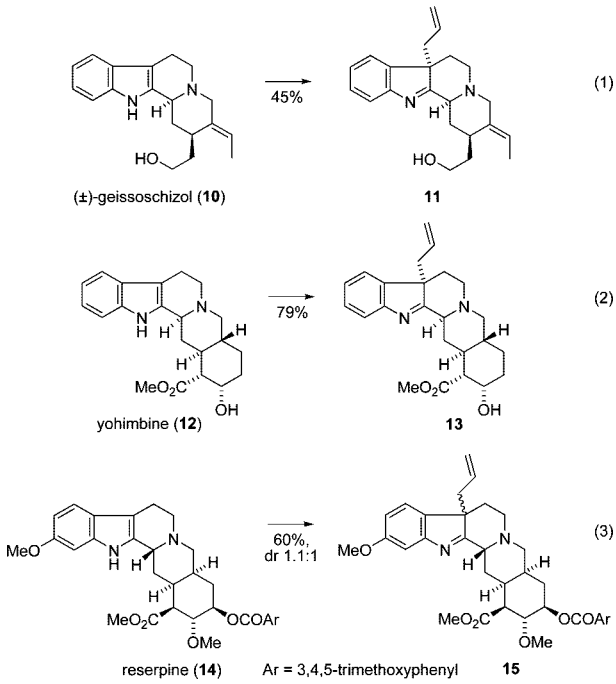


	carbonate	product	time	yield
1	 8a	 9a	20 h	98%
2	 8b	 9b	20 h	90%
3[b]	 8c	 9c	48 h	45%
4	 8d	 9d	20 h	92%

[a] Reactions were carried out on 0.250 mmol of **3** with 2.5 mol % of $Pd_2(dba)_3$, 5.0 mol % of P(2-furyl)$_3$, and 2.0 equiv of **8** in 2.5 mL of CH_2Cl_2 at rt. [b] Reaction was carried out in dichloroethane heated to reflux with 5.0 mol % of $Pd_2(dba)_3$ and 10 mol % of P(2-furyl)$_3$.

The capability of a method is assessed best when it is utilized for complex molecules containing multiple functional groups. With that consideration in mind, we examined the allylation of three different indole alkaloids of varying functional group complexity (Scheme 2). Subjection of synthetic, unprotected (±)-geissoschizol (**10**)[12] to the allylation protocol afforded the corresponding allyl-indolenine (**11**) in high diastereoselectivity in 45% yield (Scheme 2, eq 1).[13,14] The allylation of yohimbine (**12**) was also highly

Scheme 2. Allylation of Complex Natural Products



diastereoselective, providing a single allylation product (**13**) in 79% yield (Scheme 2, eq 2).[15] An even more intricate molecule, reserpine (**14**), underwent allylation under the standard conditions and provided roughly equal amounts of the two diastereomeric allylated products **15** (Scheme 2, eq 3). The relative stereochemistries of the allylation products have been tentatively assigned based on their NMR spectral properties. The dramatic differences in levels of diastereoselection for the three alkaloids are not immediately apparent. The allyl derivatives represent novel analogues of these bioactive indole alkaloids.

In summary, we have described a convenient, high-yielding method for the regioselective allylation of carbazole and carboline substrates, which can be extended to substituted allyl analogs as well as to complex indole alkaloids.[16] Studies directed toward the implementation of an asymmetric variant of the above reaction are underway, and the results will be detailed in due course.

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Supporting Information Available: Characterization data and NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The low isolated yield of **11** is attributed to difficulties in isolation and purification. The conversion of this reaction is estimated to be >60%.

(14) For a study on the diastereoselectivity of chlorination of compounds related to geissoschizol, see: Ito, M.; Clark, C. W.; Mortimore, M.; Goh, J. B.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 8003–8010.

(15) For a review of the oxidation and chlorination of yohimbine, see: Borschberg, H.-J. *Curr. Org. Chem.* **2005**, *9*, 1465–1491. Reaction of yohimbane with $NaNH_2$ and BnBr gave the *N*-benzyl and both epimeric *C*-benzyl products: von Strandtmann, M.; Eilertse, R.; Shavel, J. *J. Org. Chem.* **1966**, *31*, 4202–4204.

(16) **Typical Procedure for Allylation of Indoles.** To a solution of $Pd_2(dba)_3$ (5.7 mg, 0.0063 mmol) and P(2-furyl)$_3$ (2.9 mg, 0.013 mmol) in CH_2Cl_2 (1.3 mL) at rt was added allyl methyl carbonate (57 μL, 0.50 mmol). After 10 min, a solution of the appropriate indole (0.250 mmol) in CH_2Cl_2 (1.3 mL) was added. When indole starting material had disappeared (monitored by TLC), the reaction mixture was concentrated. The residue was purified by flash chromatography to afford the desired 3-allylated products.