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Palladium-Catalyzed Decarboxylative Allylation and Benzylation of *N*-Alloc and *N*-Cbz Indoles

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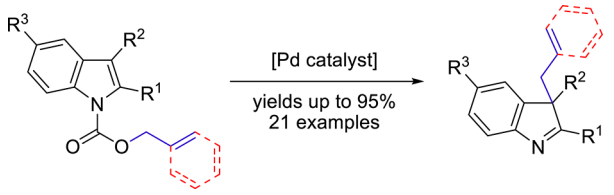
ABSTRACT



A set of general methods for the palladium-catalyzed decarboxylative C3-allylation and C3-benzylation of indoles, starting from the corresponding *N*-alloc and *N*-Cbz indoles, respectively, is reported. This chemistry provides ready access to a wide range of functionalized indolenines in good to excellent yields. A tandem process, wherein the palladium catalyzed allylation chemistry is coupled with a Mizoroki–Heck reaction, offers a simple route to cinnamylated products.

The selective functionalization of indoles continues to be the focus of numerous studies, due in no small part to the prevalence of this fundamental heterocycle in bioactive natural products and pharmaceutical agents.[1,2] The C3 functionalization of 3-substituted indoles, in particular, presents a significant challenge, as standard alkylation protocols necessitate the use of strong bases and are further complicated by the formation of a mixture of C1- and C3-alkylated products.[3] To overcome these limitations, a number of groups have demonstrated the use of palladium catalysis for the C3-allylation of C3-unsubstituted indoles.[4,5] The allylation of C3-substituted indoles, while more challenging, as it also generates a quaternary center, can also be accomplished through transition metal catalysis.[6,7] The scope of this methodology has recently been extended to the benzylation of C3-substituted indoles.[8] The reported functionalization methods generally involve the reaction of the two partners, an indole substrate having a free NH and an allyl or benzyl carbonate, alcohol or acetate (Scheme 1). Given the ready availability of *N*-alloc and *N*-Cbz indoles,[9] we considered the possibility of using such simple precursors for the direct

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(2) Indole functionalization: (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920. Update 1: *Chem. Rev.* **2011**, *111*, PR215. (b) Joucla, L.; Djakovitch, L. *Adv. Synth. Catal.* **2009**, *351*, 673–714. (c) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608–9644. (d) Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Chem. Soc. Rev.* **2010**, *39*, 4449–4465.

(3) For examples of alkylation of indolyl anion using alkyl halide: (a) Hoshino, T. *Liebigs Ann. Chem.* **1933**, *500*, 35–42. (b) Nakazaki, M. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 838–840. Reactions between indoles and *o*-halomethyl phenol/aniline: (c) Spande, T. F.; Wilchek, M.; Witkop, B. *J. Am. Chem. Soc.* **1968**, *90*, 3256–3258. (d) May, J. A.; Zeidan, R. K.; Stoltz, B. M. *Tetrahedron Lett.* **2003**, *44*, 1203–1205.

(4) Reviews on Pd-catalyzed allylation and related processes: (a) Tsuji, J.; Minami, R. *Acc. Chem. Res.* **1987**, *20*, 140–145. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422. (c) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2943.

(5) (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) Cheung, H.-L.; Yu, W.-Y.; Lam, F. L.; Au-Yeung, T. T.-L.; Zhou, Z.; Chan, T. H.; Chan, A. S. C. *Org. Lett.* **2007**, *9*, 4295–4298. (f) Usui, I.; Schmidt, S.; Keller, M.; Breit, B. *Org. Lett.* **2008**, *10*, 1207–1210. (g) Kimura, M.; Tohyama, K.; Yamaguchi, Y.; Kohono, T. *Heterocycles* **2010**, *80*, 787–797. (h) Cao, Z.; Liu, Y.; Liu, Z.; Feng, X.; Zhuang, M.; Du, H. *Org. Lett.* **2011**, *13*, 2164–2167. (i) Hoshi, T.; Sasaki, K.; Sato, S.; Ishii, Y.; Suzuki, T.; Hagiwara, H. *Org. Lett.* **2011**, *13*, 932–935. (j) Yuan, F.-Q.; Gao, L.-X.; Han, F.-S. *Chem. Commun.* **2011**, *47*, 5289–5291.

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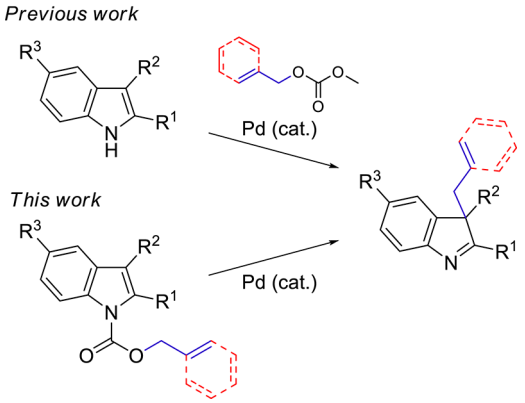
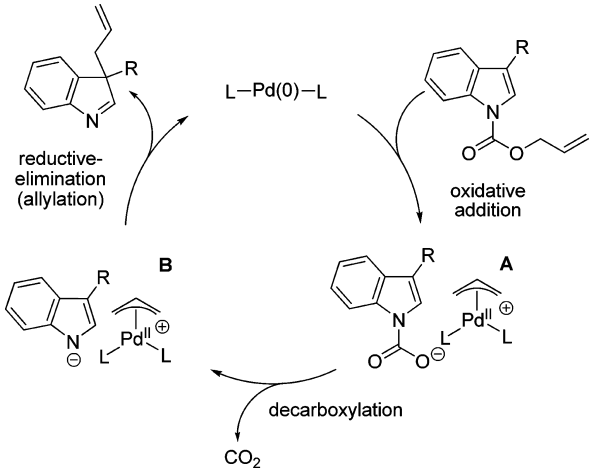
introduction of allyl and benzyl groups on indoles. For *N*-alloc indole, for example, treatment with a palladium catalyst was expected to produce π-allyl palladium and an indole carboxylate (**A**), which upon CO_2 loss would generate indoyl-π-allyl palladium (**B**), the penultimate intermediate in our earlier reported method (Scheme 2).[6c] We

Scheme 1. Decarboxylative Allylation of Indole



Scheme 2. Catalytic Cycle for Decarboxylative Allylation



describe below the realization of this concept of palladium-catalyzed decarboxylative allylation and benzylation of indoles.

We began these studies by examining a range of conditions for the decarboxylative allylation of *N*-alloc 2,3-dimethylindole (**1a**).[10] Among the palladium sources evaluated, $Pd_2(dba)_3$•$CHCl_3$ was found to give the best yield. An investigation of mono- and bidentate ligands revealed that electron-deficient monodentate phosphines gave superior results, with trifuryl phosphine[11] affording the highest yields. Optimal conditions involved the use of a 1:1 molar ratio of phosphine to palladium. The reaction conditions determined by this study proved to be applicable to a variety of alloc-protected derivatives of substituted indoles, including tetrahydrocarbazoles and β-and γ-tetrahydrocarbolines (Table 1).

Alloc derivatives of indole and tetrahydrocarbazole were successfully converted to the desired allylated products in high yields under low catalyst loadings (**2a**–**b**). Electron-donating and -withdrawing groups at the C5 position were tolerated (**2c**–**d**). Both β- and γ-tetrahydrocarbolines were successfully converted to the allylated products (**2e**–**h**), albeit under slightly higher catalyst loadings (2–5%). For reasons that are unclear, the Boc-protected carboline, **1f**, consistently gave lower yields than did other carbolines. The alloc derivatives of indole and 2-methyl indole produced a mixture of the respective mono- and bis-allylated compounds (**2i**–**2l**). Formation of the bis-allylated products is noteworthy: it demonstrates that the decarboxylative allylation does not involve an intramolecular transfer of the allyl group.[12] Finally, more substituted allylic groups can be incorporated by starting with the corresponding indole precursor. Thus, the crotylated indole substrate afforded the crotylated product **(2m)** in 84% yield, completely as the *trans*-diastereomer.

In order to further expand the scope of the allylation reaction to give the cinnamylated product, we considered additional pathways to these compounds. One option was to start with a cinnamyl carbamate precursor (**1n**), analogous to the crotyl precursor (**1m**). Indeed, decarboxylative rearrangement of **1n** under the standard conditions gave the expected cinnamyl product in 80% yield (Scheme 3, **I**). However, as the preparation of the required starting material for the cinnamyl product was neither as trivial nor as efficient as for the alloc-protected indole derivatives, we envisioned a tandem sequence in which a decarboxylative

(6) (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. (c) Kagawa, N.; Malerich, J. P.; Rawal, V. H. *Org. Lett.* **2008**, *10*, 2381–2384. (d) Xu, Q.-L; Dai, L.-X.; You, S.-L. *Chem. Sci.* **2013**, *4*, 97–102.

(7) Alylation using other transition metals; see, inter alia: (a) Dieter, J. W.; Li, Z.; Nicholas, K. M. *Tetrahedron Lett.* **1987**, *28*, 5415–5418. (b) Prajapati, D.; Gohain, M.; Gogoi, B. J. *Tetrahedron Lett.* **2006**, *47*, 3535–3539. (c) Yadav, J. S.; Reddy, B. V. S.; Aravind, S.; Kumar, G. G. K. S. N.; Reddy, A. S. *Tetrahedron Lett.* **2007**, *48*, 6117–6120. (d) Zaitsev, A. B.; Gruber, S.; Pregosin, P. S. *Chem. Commun.* **2007**, 4692–4693. (e) Liu, W.-B.; He, H.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2008**, *10*, 1815–1818. (f) Sundararaju, B.; Achard, M.; Demerseman, B.; Bruneau, C.; Toupet, L.; Sharma, G. V. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2782–2785.

(8) For the C3-benzylation of indoles, see: Zhu, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2012**, *134*, 111–114.

(9) *N*-alloc and *N*-Cbz indoles can be easily accessed by several methods: (a) Shingarova, I. D.; Sizova, O. S.; Preobrazhenskaya, M. N. *Chem. Hetercycl. Compd. (N.Y.)* **1983**, *19*, 1188–1191. (b) Weedon, A. C.; Zhang, B. *Synthesis* **1992**, 95–100. (c) Macor, J. E.; Cuff, A.; Cornelius, L. *Terahedron Lett.* **1999**, *40*, 2733–2736. (d) Jacquemard, U.; Bénéteau, V.; Lefoix, M.; Routier, S.; Mérour, J.-Y.; Coudert, G. *Tetrahedron* **2004**, *60*, 10039–10047.

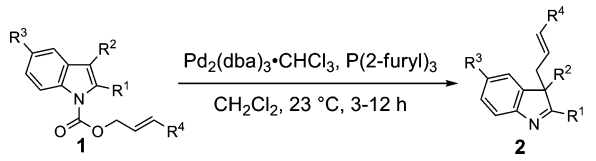
(10) Please see Supporting Information for a table of some of the conditions examined.

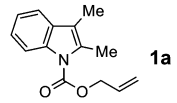
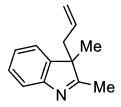
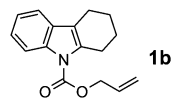
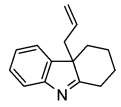
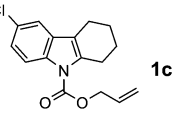
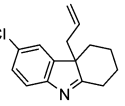
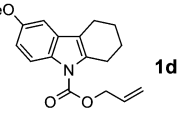
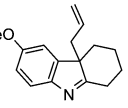
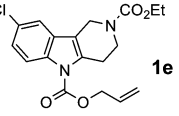
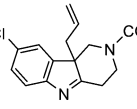
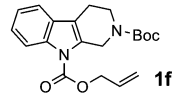
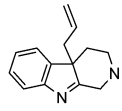
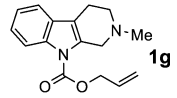
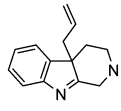
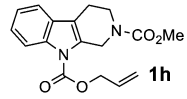
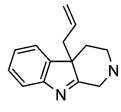
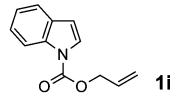
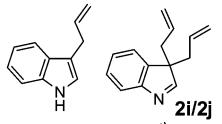
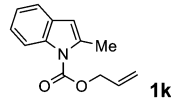
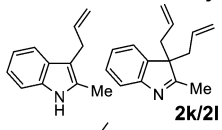
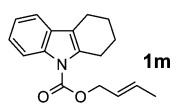
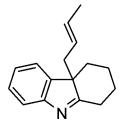
(11) Andersen, N. G.; Keay, B. A. *Chem. Rev.* **2001**, *101*, 997–1030.

(12) In support of this suggestion, we have found that subjection of a 1:1 mixture of **1b** and 6-methoxy-1,2,3,4-tetrahydrocarbazole to the standard decarboxylative allylation conditions produced a 1:1.5 mixture of **2b:2d**.

(13) (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (b) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320–2322. For selected reviews, see: (a) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1997**, *33*, 2379–2411. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066.

Table 1. Substrate Scope for Decarboxylative Allylation[a]

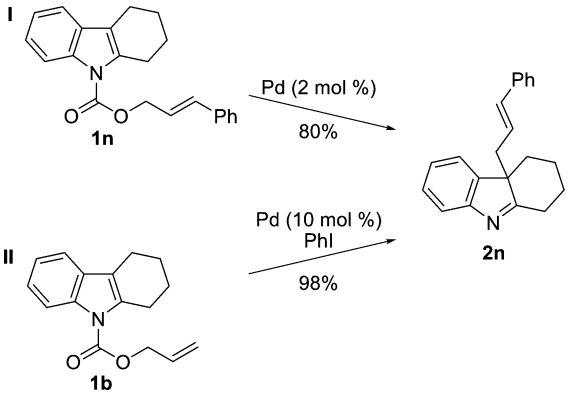


	substrate	Pd (mol %)	product	yield (%)
1[b]	 1a	0.5	 2a	95
2[b]	 1b	0.5	 2b	95
3[b]	 1c	0.5	 2c	95
4[b]	 1d	1.0	 2d	81
5[b]	 1e	1.0	 2e	80
6	 1f	2.0	 2f	36
7	 1g	2.0	 2g	83
8	 1h	5.0	 2h	73
9	 1i	2.0	 2i/2j	48/26
10	 1k	2.0	 2k/2l	48/22
11	 1m	5.0	 2m	84

[a] Reactions performed on 0.5 mmol of substrate at 0.25 M, Pd/P(2-furyl)$_3$ = 1:1, 4 h. [b] Reaction performed on 1.0 mmol of substrate at 3.5 M.

allylation process would be followed by a Mizoroki–Heck reaction.[13] The plan was to use the *N*-alloc precursor and carry out the palladium catalyzed allylation in the presence of an aryl halide (Scheme 3, **II**). Since the decarboxylative allylation takes place at room temperature, this step was expected to take place prior to the Mizoroki–Heck reaction, which typically requires a higher temperature. In the event, heating indole **1a**, iodobenzene, and K_2CO_3 in acetonitrile under the allylation conditions afforded the cinnamylated product in 98% yield.[14,15]

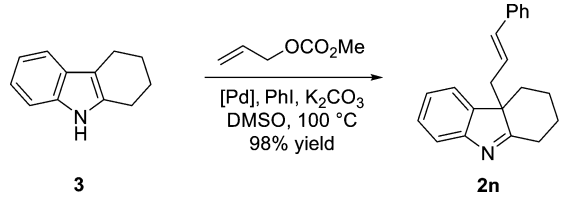
Scheme 3. Formation of Cinnamyl Product[a]



[a] Please see Supporting Information for detailed procedures.

Given the effectiveness of the above sequence, we also examined the possibility of adapting the tandem concept to our prior work on palladium catalyzed intermolecular allylation, thereby providing a three-component coupling route to the cinnamylated products. Under optimized conditions, the reaction of tetrahydrocarbazole **3**, allyl methyl carbonate, and iodobenzene in the presence of $Pd_2(dba)_3$•$CHCl_3$ (5 mol %) and P(2-furyl)$_3$ (10 mol %) afforded the desired cinnamylated product in quantitative yield (Scheme 4).[15]

Scheme 4. Three-Component Cinnamylation Reaction

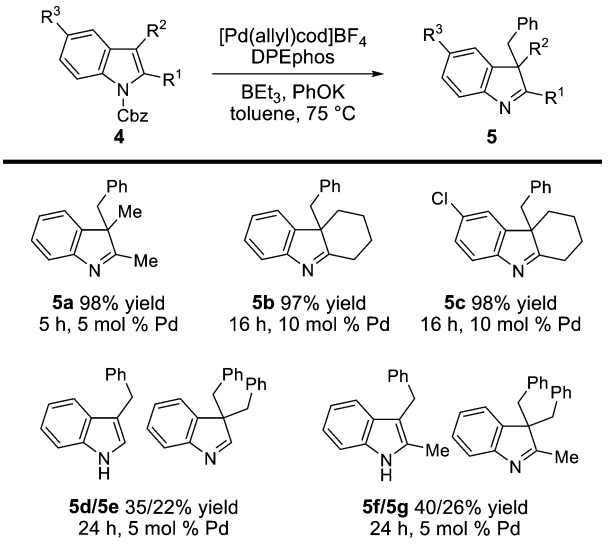


The success of the decarboxylative allylation process encouraged us to apply this strategy to the more challenging C3-benzylation of C3-substituted indoles. Initial studies showed the decarboxylative benzylation reaction to require more forcing conditions than the allylation.

(14) An examination of the reaction mixture by NMR during the course of the reaction showed rapid conversion to an allylated intermediate followed by its gradual transformation to the cinnamylated product.

(15) See the Supporting Information for a table of conditions for the optimization of this reaction.

Scheme 5. Substrate Scope of Benzylation Reaction[a]



[a] Reactions performed on substrate (0.5 mmol), BEt_3 (0.55 mmol), in toluene (0.5 M) at 75 °C.

Optimal reaction conditions called for both higher temperatures (75−80 °C) and longer reaction times.[15] Of the different palladium sources examined, $[Pd(C_3H_5)cod]BF_4$ and $Pd(C_3H_5)Cp$ were found to be the most efficient at catalyzing the reaction. Due to the ease of its preparation and storage requirements $[Pd(C_3H_5)cod]BF_4$ was chosen as the palladium source. Among the phosphine ligands screened, the bidentate ligand DPEphos gave the best yields. Finally, as noted in our earlier work,[8] the addition of boron Lewis acids,[16] namely triethylborane, accelerated the benzylation reaction. The optimized protocol for the decarboxylative benzylation process was utilized with several substrates, and the results are summarized in Scheme 5.

The *N*-Cbz derivatives of 2,3-dimethylindole, tetrahydrocarbazole and 6-chloro-tetrahydrocarbazole (**4a**−**c**), all gave the corresponding C3-benzylated products (**5a**−**c**) in nearly quantitative yields. The C3-unsubstituted precursors, *N*-Cbz-indole (**4d**) and *N*-Cbz-2-methyindole (**4f**), produced a mixture of the corresponding mono- and dibenzylated products.

To conclude, we have developed a set of protocols for the palladium catalyzed decarboxylative C3 allylation and benzylation of indoles, carbazoles, and carbolines, starting from the respective *N*-alloc and *N*-Cbz protected precursors. This chemistry is well suited for sequencing with other transition metal mediated processes, as illustrated through the decarboxylative allylation/Mizoroki−Heck reaction tandem sequence.

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

(16) (a) Tamaru, Y.; Horino, Y.; Araki, M.; Tanaka, S.; Kimura, M. *Tetrahedron Lett*. **2000**, *41*, 5705–5709. (b) Jiang, Y.; Hess, J.; Fox, T.; Berke, H. *J. Am. Chem. Soc*. **2010**, *132*, 18233–18247. Also see reference 6b for borane use in asymmetric allylation.

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