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Palladium Catalyzed Decarboxylative Rearrangement of *N*-Alloc Indoles

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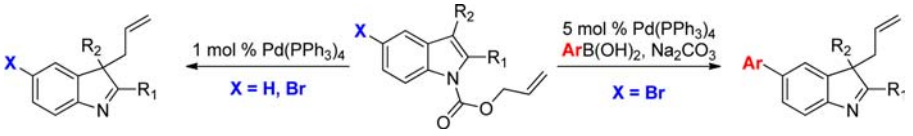
ABSTRACT



A highly efficient palladium catalyzed decarboxylative allylic rearrangement of alloc indoles has been developed. This can also be combined with a Suzuki–Miyaura cross-coupling reaction in a single pot transformation. Substituted alloc groups and benzylic variants have also been demonstrated alongside promising initial results on the enantioselective variant.

Since its inception in the 1950s, π-allyl chemistry has developed into many synthetically useful variants.[1] A large number of these processes have been further developed into enantioselective processes with asymmetric allylic alkylation reactions being particularly widely used.[2]

The use of indoles as nucleophilic partners in π-allyl chemistry has been demonstrated by several groups. Billups first demonstrated the use of indoles in π-allyl chemistry using allylic acetates in 1980.[3] Kimura then modified this with π-allyl species generated from allylic alcohols also reacting with indole to afford C-3 substitution.[4] Trost later developed this into an enantioselective variant whereby C-3 substituited indoles react with allylic alcohol derived π-allyl species to afford products with good enantioselectivity.[5] Rawal demonstrated that 2,3-disubstituted indoles could react with allyl carbonates in the presence of a palladium(0) catalyst.[6] The use of iridium catalysts has also been shown to afford similar reactions, albeit with the opposite regiochemistry.[7]

We speculated that indoles containing carbamate nitrogen-protecting groups could be used as π-allyl precursors. Upon treatment with a palladium(0) catalyst these could decarboxylate to afford a π-allyl intermediate and an indole anion. The two could recombine at the C-3 position affording an allylated indoline imine. This rearrangement would effectively be an aromatic aza-Tsuji allylation reaction.[8] Herein we report the development of the decarboxylative allyl rearrangement of *N*-allyl indoles.

We first began by looking at carbazole **1a** and screened a number of conditions including palladium sources, solvents, and the use of additives (Table 1). Gratifyingly we found that $Pd(PPh_3)_4$ did catalyze the reaction; however, the reaction was slow with a significant amount of simple alloc deprotection being observed. A screen of solvents found that non-polar aprotic solvents such as toluene and methylene chloride resulted in much faster reaction times with less deprotection observed affording the C-3 allylated product **2a** in 90% yield. The mass balance of the reaction was made up of small amounts of deprotected carbazole as a byproduct. Both Kimura and Trost had used BEt_3 as an

(1) Seminal papers: (a) Smidt, J.; Hafner, W. *Angew. Chem.* **1959**, *71*, 284. (b) Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, *6*, 4387. (c) Hata, G.; Takahashi, K.; Miyake, A. *J. Chem. Soc., Chem. Commun.* **1970**, 1392. (d) Trost, B. M.; Dietsch, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 8200.

(2) For reviews of asymmetric allylic alkylations, see: (a) Tsuji, J. *Pure Appl. Chem.* **1999**, *71*, 1539. (b) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258. (c) Trost, B. M.; Lee, C. *Catalytic Asymmetric Synthesis*, 2nd ed; Ojima, I., Ed.;Wiley-VCH: New York, 2000; pp 593–649. (d) Pfaltz, A.; Lautens, M. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; pp 833–886. (e) Trost, B. M. *Org. Process Res. Dev.* **2012**, *16*, 195.

(3) Billups, W. E.; Erkes, R. S.; Reed, L. E. *Synth. Commun.* **1980**, *10*, 147.

(4) Kimura, M.; Futamata, M.; Mukai, R.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 4592.

(5) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314.

(6) Kagawa, N.; Malerich, J. P.; Rawal, V. *Org. Lett.* **2008**, *10*, 2381.

(7) Lui, W.-B.; He, H.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2008**, *10*, 1815.

(8) For a review of Tsuji reaction, see: Mohr, J. T.; Stoltz, B. M. *Chem.—Asian J.* **2007**, *2*, 1476.

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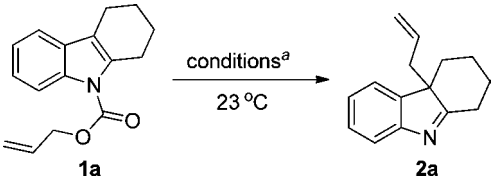
additive in their reports, and the use of this was explored. When BEt_3 was used there was no observed deprotection; however the reaction proceeded more slowly. This could be circumvented by increasing the temperature to 50 °C which restored the reaction to a yield of 90% with no observed deprotection. We screened various other palladium/ligand combinations, including those used by Rawal and found that these were inferior for this particular reaction.

Table 1. Optimization Studies



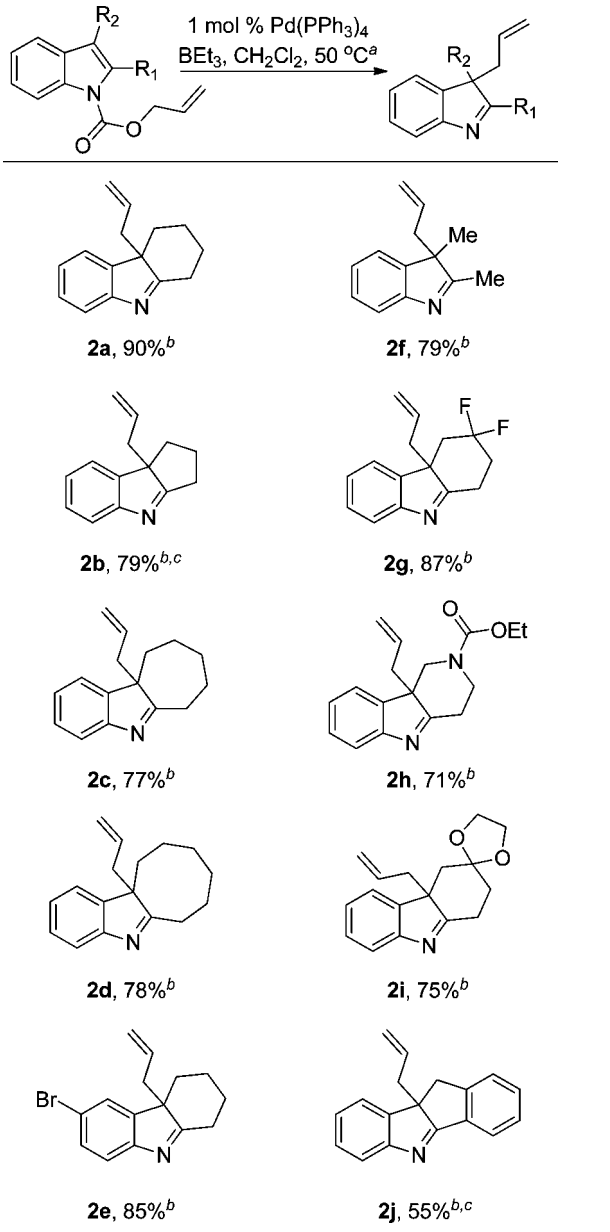
entry	catalyst	solvent	additive	yield (%)[b]
1	$Pd(PPh_3)_4$	THF	none	12
2	$Pd(PPh_3)_4$	toluene	none	80
3	$Pd(PPh_3)_4$	CH_2Cl_2	none	90
4	$Pd(PPh_3)_4$	CH_2Cl_2	BEt_3	45
5	$Pd(PPh_3)_4$	CH_2Cl_2	BEt_3	90[c]
6	$Pd_2dba_3/P(2\text{-Fur})_3$	CH_2Cl_2	BEt_3	38
7	$Pd(OAc)_2/PPh_3$	CH_2Cl_2	BEt_3	n.r.

[a] Reactions carried out using 1 mol % of catalyst and 1 equiv of additive (when used) at 0.2 M concentration. [b] Isolated yields. [c] Reaction carried out at 50 °C.

With the optimized conditions in hand, we next explored the substrate scope (Scheme 1). A variety of carbocyclic variants were used, and the reaction was tolerant of differing ring sizes from five to eight affording 77−90% yields. It was necessary to reduce the five-membered indole product **2b** with $NaBH_3CN$ prior to purification, as this was not stable to silica gel chromatography. We examined whether an aryl bromide could be tolerated, and gratifyingly, the use of bromo carbazole **1e** afforded the corresponding rearranged product **2e** in 85% yield with no sign of insertion into the carbon−bromine bond. Noncyclic dimethyl derivative **1f** could also be rearranged with **2f** being formed in 79% yield.

We next began to examine installing substitution and in particular the installation of heteroatom substituents. We discovered that the reaction was indeed tolerant of a variety of groups and difluoro-substrate **2g** is well tolerated giving a yield similar to that of the nonfluorinated analog. A piperidine can also be used with little effect on the yields, as can ketal **2i** and the tetracyclic substrate **2j**. Once again the five-membered substrate was unstable to silica gel and therefore had to be reduced prior to purification. It is important to mention that the functionalized substrates required the use of BEt_3 as an additive to obtain good

Scheme 1. Substrate Scope[a]



[a] Reaction conditions: 1 mol % $Pd(PPh_3)_4$, 1 equiv of BEt_3 (1 M in hexane), CH_2Cl_2 (0.2 M), 50 °C, 16 h. [b] Isolated yield. [c] Reduced with $NaBH_3CN$ for isolation.

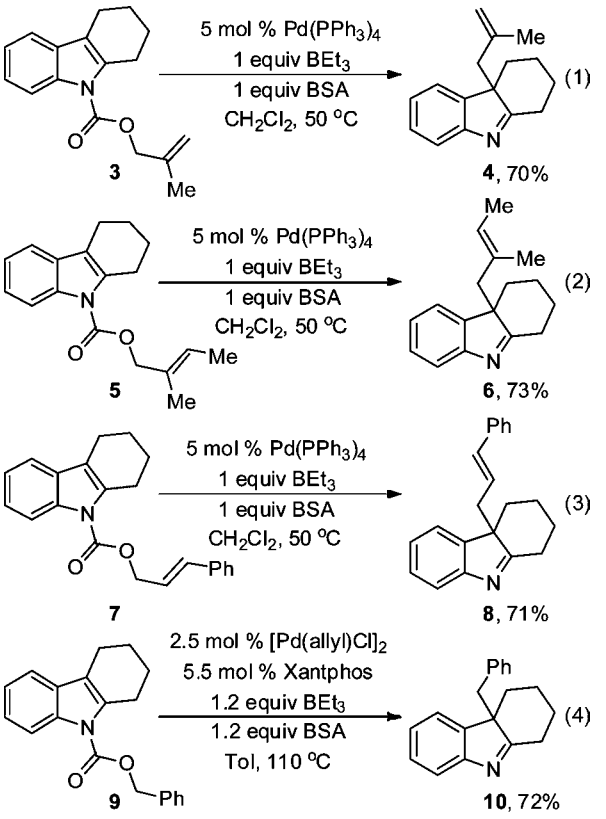
yields. In the absence of this additive a very slow reaction is observed.

We next examined the use of substituted alloc groups. These could be easily prepared using Sarpong's protocol without the need for phosgene based reagents.[9] 2-Methyl substrate **3** rearranged under slightly modified conditions to provide good yields of product **4** (eq 1). A higher catalyst loading was required (5 mol % $Pd(PPh_3)_4$), and the addition of BSA[10] as an additional additive gave optimal results. Under the modified conditions, the reaction of 2,3-dimethyl alloc substrate **5** also proceeded well to give

(9) Heller, S. T.; Schultz, E. E.; Sarpong, R. *Angew. Chem., Int. Ed.* **2012**, *51*, 8304.

(10) BSA = N,O-Bis(trimethylsilyl)acetamide.

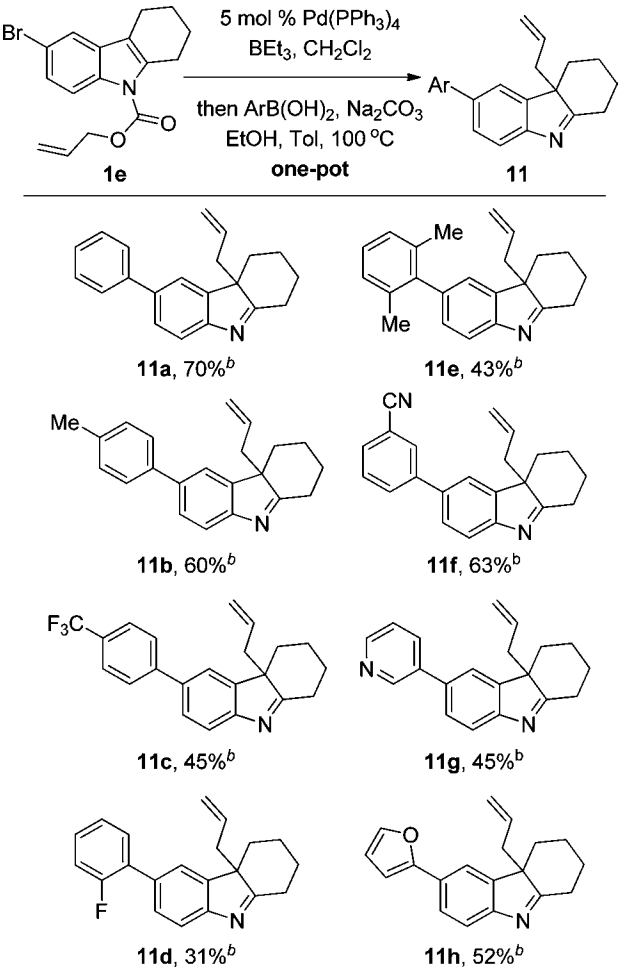
the linear substitution product **6** (eq 2). Likewise, cinnamyl derivative **7** also rearranged in good yield to afford the linear product **8** (eq 3). As Rawal had recently reported the use of benzyl carbonates in a π-allyl substitution reaction with 2,3-substituted indoles,[11] we investigated whether Cbz indoles could undergo a similar transformation. With the conditions used for the substituted alloc groups, no reaction was observed, and utilizing Rawal's conditions, a moderate 45% yield of benzyl migrated product **10** was obtained. The combination of $[Pd(allyl)Cl]_2$ and Xantphos provided the optimal conditions for this rearrangement with **10** being produced in 72% yield (eq 4) .



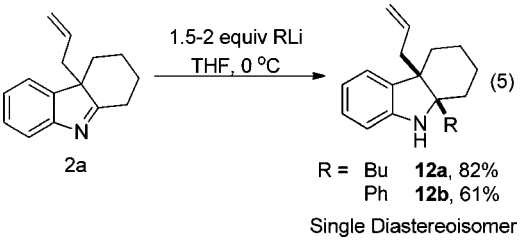
As the decarboxylative rearrangement process was tolerant of the aromatic bromide present in **2e**, we examined whether a second cross-coupling step could be performed in the same reaction vessel. We decided to examine the Suzuki–Miyaura reaction due to the wide availability of aryl boronic acids. Indeed this was possible with the addition of a boronic acid, base, and ethanol following the rearrangement step (scheme 2). This allowed for the formation of C-3 allylated biaryl indolines in good to moderate yields. Alongside the phenyl substituent **11a**, a range of electronically differentiated 4-substituted boronic acids could be used including methyl **11b** and trifluoromethyl **11c**. The 2-position could be substituted with fluoro **11d** and 2,6-dimethyl groups **11e** being incorporated. Other tolerated groups were 3-cyano **11f** and heterocycles including pyridine **11g** and furan **11h**.

With the rearranged imines in hand we examined whether we could add nucleophiles to these. We had already demonstrated the use of $NaBH_3CN$ to reduce them as other groups had previously;[6] therefore we focused on carbon-based nucleophiles. Initial attempts with Grignard reagents proved unsuccessful; however the use of organolithium reagents proved effective.[12] Both butyl lithium and phenyl lithium gave the addition products **12a** and **12b** respectively as a single diastereoisomer (eq 5). This was tentatively assigned as the *syn*-diastereoisomer based on literature precedent.[12]

Scheme 2. Rearrangement–Suzuki Process[a]



[a] Reaction conditions: 1 mol % $Pd(PPh_3)_4$, 1 equiv of BEt_3 (1 M in hexane), CH_2Cl_2 (0.2 M), 50 °C, 16 h then 1.5 equiv of boronic acid, 2 M Na_2CO_3, EtOH, toluene, 100 °C, 3–8 h. [b] Isolated yield.

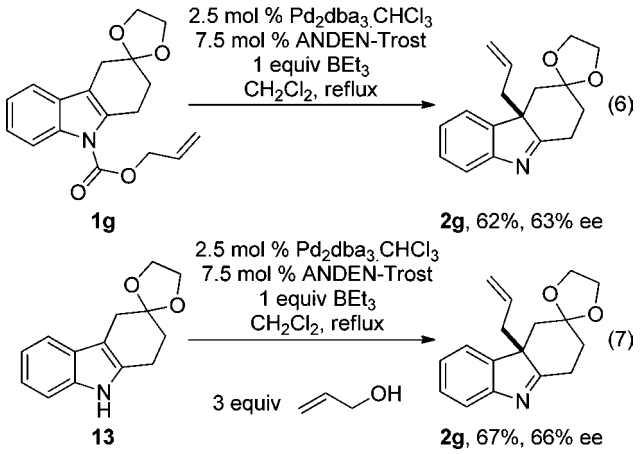


Finally we have briefly examined the enantioselective variant of this reaction. Trost's conditions that were

(11) Zhu, Y.; Rawal, V. *J. Am. Chem. Soc.* **2012**, *134*, 111.

(12) Rodriguez, J. G.; Urrutia, A. *Tetrahedron* **1998**, *54*, 15613.

previously reported used 9-BBN-Hex as an additive in the place of BEt_3 to increase enantioselectivity.[5] Little or no reactivity was observed when 9-BBN-Hex was used as an additive, although Trost reported no examples of 2,3-substituted indoles. Gratifyingly, the use of BEt_3 and Trost's ANDEN ligand with ketalcarbazole **1i** did yield a rearranged product and afforded this product **2l** in 62% yield and 63% ee (eq 6). By contrast, Trost's intermolecular allylic alcohol conditions gave similar results with 66% ee being obtained (eq 7). While far from being optimized these are encouraging initial results suggesting that an enantioselective variant can be developed.



In conclusion, we have developed the first example of a decarboxylative rearrangement of *N*-alloc indoles. This reaction is tolerant of functional groups and can also be used for the rearrangement of substituted alloc groups as well as Cbz protecting groups. A one-pot rearrangement−Suzuki coupling has also been developed, and the use of the products has been explored. Finally we have demonstrated that this reaction can be rendered enantioselective, and our current efforts are focused on improving the enantioselectivity to synthetically useful levels.

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Supporting Information Available. Detailed experimental procedures, full characterization of all compounds reported, and copies of NMR spectra (^1H, ^{13}C, and ^{19}F were applicable) are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.