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New Versatile Pd-Catalyzed Alkylation of Indoles via Nucleophilic Allylic Substitution: Controlling the Regioselectivity

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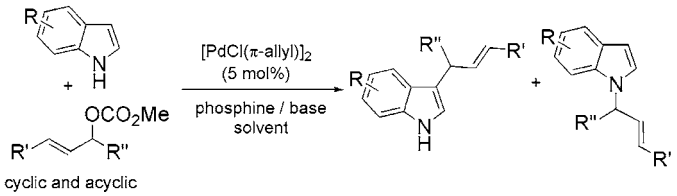
ABSTRACT



A systematic study addressed toward the optimization of the Pd-catalyzed alkylation of indoles by allylic carbonates is presented. The protocol uses a catalytic amount of [PdCl(π-allyl)]$_2$/phosphine as a promoting agent, providing allylindoles in excellent yields. The regioselectivity of the reaction can be controlled by a proper choice of the base and the reaction media. The method proved to be effective also for intramolecular allylic alkylations of indolyl carbonates, providing a flexible route to fused indole alkaloids.

Indole is widely recognized as a key motif in the synthesis of complex molecules with numerous applications in material science, pharmaceuticals, and agrochemicals.[1] For this reason, the functionalization of such a compound via low cost, selective, and ecofriendly strategies has captured the attention of the chemical community over the past decades. Among them, Lewis acid promoted Friedel−Crafts reactions[2] and metal-catalyzed arylation processes[3] proved to be remarkably effective in the alkylation/arylation of indole under homogeneous as well as heterogeneous conditions. In this context, a related straightforward approach could involve the nucleophilic allylic alkylation[4] of the heteroaromatic system via π-allylmetallo intermediates (Tsuji−Trost reaction).[5]

Despite the high potential of this approach, only a few examples of alkylation of indoles via mild allylic substitution have been reported to date, and most of them generally exhibit scarce regioselectivity or require stoichiometric amounts of Lewis acids.[4d] As a matter of fact, the discrimination between the N-alkylated product (kinetic control) and the C3-alkylated product (thermodynamic control) with unsubstituted indoles is usually a challenging task.[6]

In this scenario, Kočovský and co-workers recently reported on the Mo(II)-catalyzed alkylation of electron-rich aromatics, but only a few examples of indole alkylations with unsymmetrical allyl acetates were described.[7]

In this paper, we intend to describe our systematic study in the regioselective alkylation of indoles with cyclic and

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(2) Yamamoto, H. In *Lewis Acids in Organic Synthesis*; Wiley-VCH: Weinheim, 2000.
(3) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684−11688 and references therein.
(4) (a) Billups, W. E.; Erkes, R. S.; Reed, L. E. *Synth. Commun.* **1980**, *10*, 147−151. (b) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc.* **1981**, *103*, 5969−5972. (c) Bourak, M.; Gallo, R. *Heterocycles* **1990**, *31*, 447−457. (d) Zhu, X.; Ganesan, A. *J. Org. Chem.* **2002**, *67*, 2705−2708. (e) Yadav, J. S.; Reddy, B. V. S.; Muralikrishna Reddy, P.; Srinivas, Ch. *Tetrahedron Lett.* **2002**, *43*, 5185−5187. (f) Trost, B. M.; Krische, M. J.; Berl, V.; Grenzer, E. M. *Org. Lett.* **2002**, *4*, 2005−2008.
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(7) Malkov, A. V.; Davis, S. L.; Baxendale, I. R.; Mitchell, W. L.; Kočovský, P. *J. Org. Chem.* **1999**, *64*, 2751−2764.

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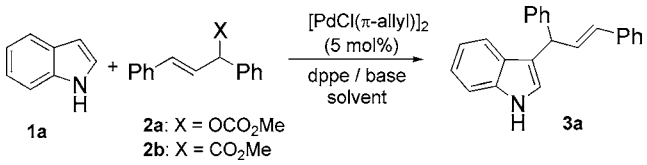
acyclic carbonates in the presence of a catalytic amount of [PdCl(π-allyl)]$_2$/phosphine complexes. The protocol allowed the regioselectivity of the reaction to be effectively controlled.

The allylic substitution between indole **1a** and *rac*-1,3-diphenylprop-2-enyl methyl carbonate (**2a**) was taken into account as the model reaction and a brief screening of reaction conditions were undertaken.

The data collected in Table 1 clearly proved that, in the presence of 5 mol % of [PdCl(π-allyl)]$_2$/dppe[8] as the catalytic

Table 1. Pd-Catalyzed Alkylation of Indole **1a** by Allylic Substitution[a]



entry	solvent/base	allylic compd	convn[b] (%)	yield[c] (%)
1	DMF/Cs_2CO_3	**2a**	62	55 (7)
2	THF/K_2CO_3	**2a**	75	61 (19)
3	THF/Li_2CO_3	**2a**	25	19 (−)
4	CH_2Cl_2/Li_2CO_3	**2a**	70	65 (8)
5	CH_2Cl_2/Li_2CO_3	**2b**	<10	
6	CH_2Cl_2/Li_2CO_3	**2a**	58	52 (31)[d]

[a] All the reactions were carried out under nitrogen atmosphere in CH_2Cl_2 at reflux unless otherwise specified. Reaction time 24 h. Indole/carbonate/[Pd]/dppe/base ratio: 1/2/0.05/0.11/2. [b] Determined by HPLC analysis of the crude material and related to the **3a** formation. [c] Isolated yields. Isolated yields of the N/C-dialkylated product are given in parentheses. [d] The reaction was carried out without base.

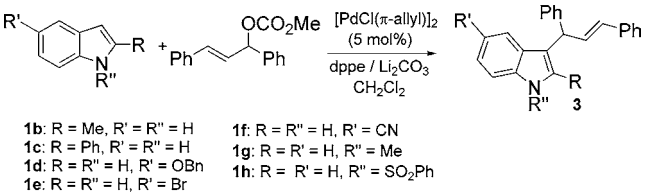
system, indole **1a** (1 equiv) coupled smoothly with allyl carbonate **2a**[9] (2 equiv), and the combined use of a low-coordinating solvent (DCM) and Li_2CO_3 as the base drove the reaction course toward the exclusive formation of the thermodynamic C-attack (70%) with the double-alkylated adduct being the only side product (8%, entry 4). Interestingly, no kinetic N-allylic indole was observed under these conditions. On the other hand, the use of strongest bases (i.e., Cs_2CO_3, K_2CO_3) and more coordinating solvents (i.e., DMF, THF) also promotes the alkylation of **1a** in satisfactory yields (entries 1 and 2). However, the reaction conversion as well as the regioselectivity of the process were inferior respect to the use of Li_2CO_3 in DMC.

Allyl carbonates as alkylating precursors as well as the base proved to be essential in order to guarantee optimal chemical outcomes. In fact, while the use of allylic acetate (**2b**) afforded **3a** just in traces (<10%, entry 5), the absence of base drops the regioselection by enhancing the formation of the side N/C-dialkylated product (entry 6).[10]

(8) Several commercially available Pd complexes were tested in the model reaction, however the use of [PdCl(π-allyl)]$_2$ provided the highest yields and selectivity. For instance, by using [Pd_2dba_3]·$CHCl_3$, a significant amount of 1,4-addition of indole to the dba (dibenzylidenacetone) was detected. For a related case, see: Bandini, M.; Cozzi, P. G.; Giacomini, M.; Melchiorre, P.; Selva, S.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 3700−3704.

Then the generality of the reaction was taken into account; excellent tolerance toward sterically demanding indoles (**1b** and **1c**), which smoothly reacted with **2a** to give **3b** and **3c** in high yields (78%, 92% respectively) and in excellent regioselectivity (Table 2). Moreover, in the presence of both

Table 2. Screening of Indoles in the Pd-catalyzed Allylic Alkylation with **2a**[a]



entry	indole	product	yield[b] (%)
1	**1b**	**3b**	78 (72)
2	**1c**	**3c**	92 (87)
3	**1d**	**3d**	62 (60)
4	**1e**	**3e**	87 (82)
5	**1f**	**3f**	68 (62)
6	**1g**	**3g**	15 (8)
7	**1h**	**3h**	

[a] All the reactions were carried out under nitrogen atmosphere in CH_2Cl_2 at reflux. Reaction time 24 h. Indole/carbonate/[Pd]/dppe/Li_2CO_3 ratio: 1/2/0.05/0.11/2. [b] Determined by HPLC analysis of the crude material. Isolated yields are given in parentheses.

indoles bearing electron-releasing (**1d**) and electron-withdrawing groups (**1e**,**f**) the reaction with **2a** proceeded effectively yielding the C-alkylated adduct (62−87%) in high regioselectivity (entries 3−5). Finally, the disappointing results obtained with *N*-Me- (**1g**) and *N*-SO_2Ph-indole (**1h**) (entries 6 and 7, Table 2) suggest the pivotal role played by *N*-metalloindole species as active nucleophiles in the present allylic alkylation.

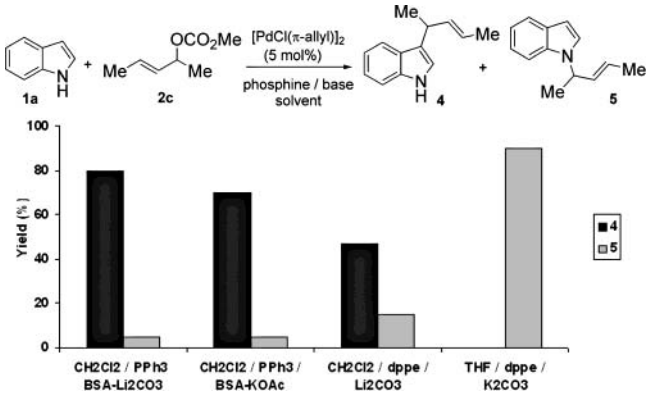
Then, we turned our attention to the alkylation of **1a** (1 equiv) in the presence of less reactive pent-2-enyl methyl carbonate **2c** (2 equiv). However, under the previously utilized conditions (CH_2Cl_2, dppe, Li_2CO_3), a mixture of C-alkylated **4** and N-alkylated product **5** (3.7:1) was isolated in moderate yield (62%, Scheme 1). In accord with our intention to optimize a metallo-catalyzed allylic alkylation protocol that allows allylindoles to be prepared regioselectively,[11] we investigated the influence of the reaction

(9) Trost, B. M.; Fraisse, P. L.; Ball, Z. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1059−1061.

(10) As a peculiarity of carbonate **2a**, we observed that mild acidic conditions (solvent, silica, etc.) also significantly promote the allylic alkylation of **1a** predominantly at the C3 position (i.e., CH_2Cl_2 in the presence of silica, reflux 24 h, convn >90%). On the other hand, carbonates **2c**−**e** and **12** (vide infra), less prone to originate carbocationic species respect to **2a**, did not undergo the present indole alkylation in any extent under the above-mentioned conditions. For a related study, see: Bisaro, F.; Prestat, G.; Vitale M.; Poli, G. *Synlett* **2002**, 1823−1826.

(11) For a related study concerning the synthesis of 3-allylindoles by Pd-catalyzed cyclization of alkynyltrifluoroacetanilidenes, see: Cacchi, S.; Fabrizi, G.; Pace, P. *J. Org. Chem.* **1998**, *63*, 1001−1011.

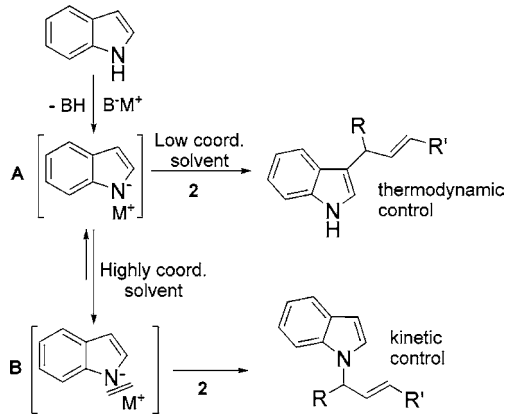
Scheme 1. Effect of Base and Solvent in Controlling the Regioselectivity of the Pd-Catalyzed Coupling of **1a** with **2c**[a]



[a] Reagents and conditions: **1a**/**2c**/[PdCl(π-allyl)]$_2$/phosphine/base, 1/2/0.05/0.22(0.11)/2.

parameters on the outcome of the process.[12] In particular, we supposed that while low coordinating solvents (i.e., CH_2Cl_2) would favor the formation in solution of a contact indolyl−metal ion pair **A** (predominant thermodynamic alkylation), the use of highly coordinating solvents in combination with bases bearing larger cationic radius (K_2CO_3, Cs_2CO_3) would drive the regiochemistry toward the formation of the kinetic N-product through the intermediate solvent-separated ion pair **B** (Scheme 2).

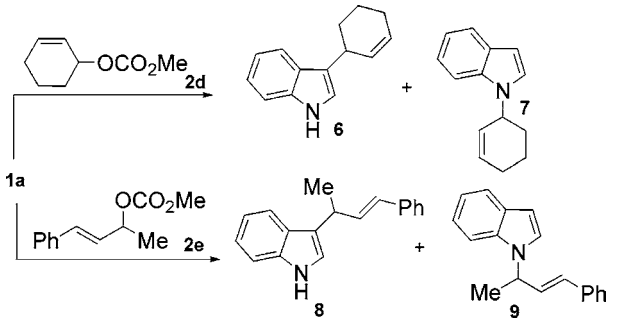
Scheme 2. Influence of the Solvent and Base in the Regioselective Alkylation of Indoles



In fact, while the combined use of low-coordinating solvent (CH_2Cl_2, reflux, PPh_3) and BSA/Li_2CO_3 as the base system provided the desired C-alkylated product in 80% yield after flash chromatography (**4**/**5** 16:1), by running the allylic substitution in THF with a catalytic amount of dppe (11 mol %) and K_2CO_3 (2 equiv), the regiochemistry was completely switched toward the formation of the N-alkylated compound **5** (90% yield, **4**/**5** > 1:50).[13] Interestingly, monitoring the reaction course of the present protocol by gas chromatography revealed that, when the BSA/Li_2CO_3 base system was utilized, N-TMS-indole was initially formed in situ followed by subsequent C-alkylation. Therefore, the initial fast silylation of the indole might be responsible for preventing the formation of the charged species via the equilibrium depicted in Scheme 2.

This strategy has also proven successful for controlling the regiochemistry in the indole alkylation with cyclohex-2-enyl methyl carbonate **2d** and more challenging asymmetric 4-phenylbut-3-enyl methyl carbonate **2e** (Table 3).

Table 3. Pd-Catalyzed Alkylation of Indole **1a** by Allylic Substitution with **2d** and **2e**[a]



entry	carbonate	conditions	overall yield[b] (%)	C/N ratio[c]
1	**2d**	CH_2Cl_2 BSA/Li_2CO_3	99	**6**/**7** (8:1)
2	**2d**	DMF/Cs_2CO_3	99	**6**/**7** (1:12)
3	**2e**	CH_2Cl_2 BSA/Li_2CO_3	91	**8**/**9** (10:1)
4	**2e**	DMF/Cs_2CO_3	84	**8**/**9** (1:50)

[a] All the reactions were carried out under nitrogen atmosphere (reflux with CH_2Cl_2 and rt with DMF). Reaction time 12−24 h. Indole/carbonate/[Pd]/PPh_3/base ratio: 1/2/0.05/0.22/2. [b] Combined overall yields of the two isomers after flash chromatography separation. [c] The C/N ratio was determined by ^{1}H NMR analysis of the crude material.

In the case of cyclic carbonate **2d**, the alternative employment of BSA/Li_2CO_3 in CH_2Cl_2 or Cs_2CO_3 in DMF afforded the **6**/**7** mixture in 8:1 (**6**: 89% isolated yield, entry 1) and 1:12 ratios (**7**: 91% isolated yield, entry 2), respectively. Analogously with the asymmetric carbonate **2e**, while the use of Li_2CO_3/BSA as the base system led to the C-3 adduct **8** in 82% isolated yield (**8**/**9** 10:1, entry 3), the reaction between **1a** with **2e** in the presence of Cs_2CO_3 in DMF at actual temperature provided the N-alkylated compound **9** in 84% yield (**8**/**9** 1:50, entry 4). Noteworthy, in both cases only attack at the less hindered position of the asymmetric carbonate **2e** was detected.[14]

Finally, the synthetic utility of the present catalytic strategy was proven by applying a Pd-catalyzed intramolecular

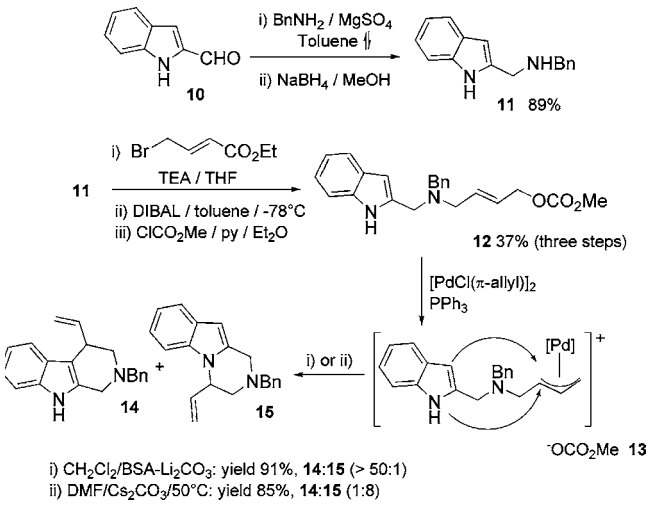
(12) (a) Hogen-Esch, T. E.; Smid, J. *J. Am. Chem. Soc.* **1965**, *87*, 669−670. (b) Zaugg, H. E.; Schaefer, A. D. *J. Am. Chem. Soc.* **1965**, *87*, 1857−1866. (c) Hogen-Esch, T. E.; Smid, J. *J. Am. Chem. Soc.* **1966**, *88*, 307−318. (d) Powers, J. C.; Meyer, W. P.; Parsons, T. G. *J. Am. Chem. Soc.* **1967**, *89*, 5812−5820. (e) Buncel, E.; Menon, B. *J. Org. Chem.* **1979**, *44*, 317−320.

(13) In some cases, with carbonate **2c** the product of N/C-dialkylation was also isolated from the crude mixture (5−10%).

version[15] of the protocol for the synthesis of polycyclic indolyl alkaloids such as 4-substituted 1,2,3,4-tetrahydro-β-carbolines **14**[16a] and pyrazino[1,2-*a*]indoles **15**.[16b]

The synthesis of the key intermediate **12** was readily accomplished starting from 2-carboxy aldehyde **10**[17] in five steps (Scheme 3). In particular, the reductive amination of

Scheme 3



10 with benzylamine afforded the secondary amine **11** in 89% yield. Then, the treatment of **11** with ethyl 4-bromocrotonate in TEA with subsequent reduction of the carboxylic moiety with DIBAL/toluene/−78 °C and derivatization of the primary alcohol obtained with $ClCO_2Me/py/Et_2O$, afforded the desired indolyl precursor **12** in 37% yield (three steps).

Initial attempts of cyclization were performed by treatment of the intermediate **12** (0.1 mM) with $[PdCl(\pi\text{-allyl})]_2/PPh_3$ in the presence of Li_2CO_2/BSA as the base (Scheme 3). Noteworthy, the desired cyclized tetrahydro-β-carboline **14** was isolated, by selective C-alkylation, in 91% yield (99% conversion, **14**/**15** > 50:1) after 4 h at room temperature.[18] Notably, compound **12** underwent Pd-cyclization with exclusive formation of the six-membered ring, stressing the regioselective attack to the internal more hindered position of the η^3-Pd intermediate **13**. One the other hand, by using inorganic bases bearing less covalently coordinating metals (Cs_2CO_3, 2 h) in DMF at 50 °C, the regioselectivity of the reaction was remarkably switched toward the kinetic N-alkylated product **15** (85% yield, **14**:**15** 1:8).

In summary, a general and mild palladium-catalyzed alkylation of indoles through nucleophilic substitution with allylic carbonates is reported. The protocol, besides affording the desired products in excellent yields, provides a rationale to unambiguously predict and control the regioselectivity of the reaction. Moreover, the synthetic usefulness of the method was also demonstrated in the preparation of functionalized polycyclic alkaloids by Pd-catalyzed intramolecular cyclization. Studies addressed toward the development of an asymmetric version of the present strategy are underway in our laboratories.

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Supporting Information Available: Typical experimental procedures for the catalytic allylic substitution and analytical data for the isolated unknown compounds. This material is available free of charge from the Internet at http://pubs.acs.org.

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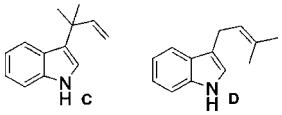
(14) Under thermodynamic conditions (CH_2Cl_2, Li_2CO_3), the reaction between prenyl methyl carbonate and **1a** afforded exclusively (62% yield) the C-alkylated indole as a mixture of the isomers **C**/**D** (5:1). However, kinetic conditions (DMF, Cs_2CO_3) furnished a complex mixture of N- and C-products in low yield and poor regioselectivity.



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(16) (a) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797−1842 (b) Chang-Fong, J.; Tyacke, R. J.; Lau, A.; Westaway, J.; Hudson, A. L.; Glennon, R. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1003−1005.

(17) Suzuki, H.; Unemoto, M.; Hagiwara, M.; Ohyama, T.; Yokoyama, Y.; Murakami, Y. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1717−1724.

(18) For a related Lewis acid mediated cyclization procedure see: Agnusdei, M.; Bandini, M.; Melloni, A.; Umani-Ronchi, A. *J. Org. Chem.* **2003**, *68*, 7126−7129.