

Palladium-Catalyzed Direct 2-Alkylation of Indoles by Norbornene-Mediated Regioselective Cascade C–H Activation

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Supporting Information

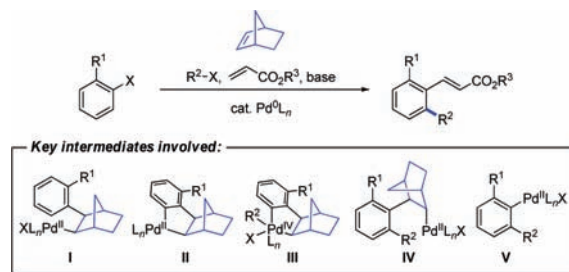
ABSTRACT: A palladium-catalyzed direct 2-alkylation reaction of free *N*-H indoles has been developed. This reaction relies on a norbornene-mediated cascade C–H activation process at the indole ring, which features high regioselectivity and excellent functional group tolerance. The reaction represents the first example for a generally applicable, direct C–H alkylation of indole at the 2-position.

Indole derivatives are important compounds that occur widespread in nature and exhibit significant biological activity.¹ Consequently, there is continuing interest in reactions that allow for a regioselective indole functionalization.² Among them, transition metal-catalyzed direct C–H functionalization reactions³ of indole derivatives are very attractive. To date, the regioselective direct C–H arylation^{4,5} and alkenylation^{6,7} at either the C2- or C3-position of indole have been successfully achieved by using palladium, rhodium, or copper catalysis. However, attempts to perform direct C–H alkylation reactions of indoles have been less successful so far. Although the 3-alkylation of indole can be achieved by catalytic methods such as Friedel–Crafts alkylation, allylic alkylation, and conjugate addition,² a general protocol for the regioselective direct C–H alkylation at the C2-position of free *N*-H indoles has not yet been established.⁸ Given the limited availability of synthetic routes toward 2-alkylindoles,⁹ a straightforward approach is highly demanded. Herein, we report in preliminary form on the first direct 2-alkylation reaction of free *N*-H indole derivatives by a norbornene-mediated cascade C–H activation process under palladium catalysis.

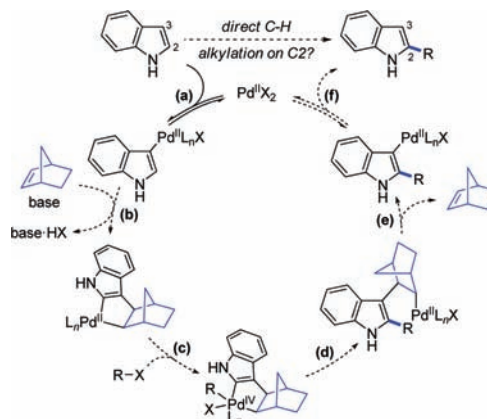
Our design was inspired by the alkylation/alkenylation reaction of aryl halides via a Pd-catalyzed norbornene-mediated tandem C–H activation (the Catellani reaction, Scheme 1).^{10,11} It was reported that, in this reaction, reactive norbornene can insert into the Ar–Pd bond of the previously formed ArPdX species to generate intermediate **I** that then undergoes an intramolecular C–H activation at the proximate aromatic position to form palladacycle **II**.¹⁰

Oxidative addition of an alkyl halide to the Pd(II) center of **II** forms Pd(IV) intermediate **III**, which after reductive elimination (formation of **IV**) and expulsion of norbornene generates an alkylated ArPdX species **V**. Finally, a Heck-type reaction between intermediate **V** and an acrylate generates the alkylation/alkenylation product.¹⁰ This norbornene-mediated process provides an opportunity to activate the C–H bond at the neighboring position of the initially generated Ar–Pd bond and thus enables an aryl–alkyl linkage at this position.

Scheme 1. Pd(0)-Catalyzed Tandem Alkylation/Alkenylation Reaction Mediated by Norbornene



Scheme 2. Postulated Catalytic Cycle for a Direct 2-Alkylation of Indole by a Norbornene-Mediated Cascade C–H Activation



We envisioned that a similar mechanism might also operate in a designed palladium-catalyzed cascade C–H activation process to achieve the 2-alkylation of indole (Scheme 2): direct palladation of indole with a Pd(II) complex should occur preferentially at the C3-position⁷ (the first C–H activation, step a), and the generated 3-palladated indole may interact with norbornene to undergo insertion and the second intramolecular C–H activation (step b); after oxidative addition with an alkyl halide R–X (step c), reductive elimination (step d), and a norbornene expulsion step (step e), a 2-alkyl-indol-3-yl palladium species may form, which

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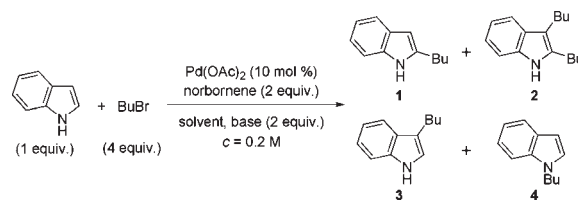
can release the 2-alkyl indole product and regenerate the Pd(II) species for the next catalytic cycle (step f). Different from the previous oxidative-addition-triggered norbornene-mediated cascade reactions,^{10,11} we hoped to initiate the catalytic cycle by a C–H activation reaction and to complete it by a proto-depalladation. If these postulated steps proceeded smoothly, a direct 2-alkylation reaction of indole could be achieved by combining indole, an alkyl halide, norbornene, and a base in one flask.

To test the described hypothesis, the reaction of indole with butyl bromide was attempted in the presence of norbornene and Pd(OAc)₂ under different conditions (Table 1). The first runs were conducted at room temperature to 50 °C employing KOAc as a mild base^{11a} in acetonitrile, *N,N*-dimethylformamide (DMF), or *N,N*-dimethylacetamide (DMA) as the solvents (entries 1–3). In all solvents tested the desired 2-butylandole (**1**) could be detected, and the possible uncatalyzed alkylation byproducts, *N*- and 3-butylandole, were not formed. Although the desired 2-butylandole was only generated in low yields, these results indicated that the postulated catalytic cycle could indeed operate. Since DMA proved to be better suited than the other two solvents, it was selected as the solvent in the following tests. A screen of base showed that Cs₂CO₃ resulted in the formation of *N*-butylandole (entry 4) as the major product, while K₂CO₃ turned out to be optimal (entry 5). Raising the reaction temperature from rt to 50 °C promoted the reaction to afford a reasonable yield after 14 h (entry 6). However, the use of freshly distilled DMA instead of the previous reagent grade DMA resulted in a decreased reaction rate (entry 7). Therefore, we probed the effect of residual water on this reaction.

It was found that the presence of water accelerates the reaction,¹² and a water concentration of [H₂O] = 0.5 M was ideal in a range of 0.1–1 M (entries 8–11). Elevated temperature (70 °C) resulted in a faster reaction (entry 12). Finally, a brief screen of Pd(II) sources showed that commonly used Pd(II) salts exhibit no obvious difference in promoting this reaction (entries 13–15). PdCl₂(MeCN)₂ was chosen as the preferred catalyst because it provided higher conversion than the other catalysts and could avoid undesired nucleophilic attack of the catalyst anion at an alkyl bromide. Thus, DMA with H₂O (0.5 M) as the solvent, K₂CO₃ as the base, a reaction temperature of 70 °C, and a reaction time of 14 h were selected as the optimal conditions. A synthetic-scale run (1 mmol) under these conditions afforded isolated product **1** in 67% yield (entry 16). It is noteworthy that in most of the reactions, 2,3-dibutylandole (**2**) was observed as the byproduct due to overalkylation. Control experiments showed that no trace of 2-butylandole or 2,3-dibutylandole could be detected in a reaction without either norbornene or a Pd(II) source, supporting the catalytic cycle proposed in Scheme 2.

Having achieved the desired direct 2-alkylation of indole, we started to explore the substrate scope (Table 2). It was found that the present reaction is compatible with a variety of simple and functionalized alkyl bromides as the alkylation reagent. Generally, the reactions proceeded smoothly at 70 °C, and the yield of 2-alkylated indole varied from 40% to 82% according to the nature of the alkyl bromide employed. In many cases 2,3-dialkylindole was generated as the byproduct (in ca. 10% yield, entries 1, 3, 9, 10 and 11), but for more sterically hindered alkyl bromides, little or no 2,3-dialkylindole was observed (e.g., entries 2, 4, and 7). The reaction delivered an array of 2-substituted indoles with various functional groups, such as tetrahydropyran (entry 5), silyl ether (entries 4 and 6), acetal (entries 7 and 8), carboxylic ester (entries 9 and 10), nitrile (entry 11), and tosylamide (entry 12).

Table 1. Optimization Studies for the 2-Butylation of Indole



entry	solvent	base	T (°C)	t (h)	conv. ^a (%)	yield ^d (%)			
						1	2	3	4
1	MeCN	KOAc	rt–50	64 ^b	29	3	–	–	–
2	DMF	KOAc	rt–50	64 ^b	38	9	–	–	–
3	DMA ^c	KOAc	rt–50	64 ^b	37	11	–	–	–
4	DMA ^c	Cs ₂ CO ₃	rt	48	47	4	3	5	20
5	DMA ^c	K ₂ CO ₃	rt	48	46	19	8	5	–
6	DMA ^c	K ₂ CO ₃	50	14	90	58	17	–	–
7	DMA ^d	K ₂ CO ₃	50	14	56	36	7	–	–
8	DMA ^e	K ₂ CO ₃	50	14	83	46	17	5	–
9	DMA ^f	K ₂ CO ₃	50	14	88	54	18	3	–
10	DMA ^g	K ₂ CO ₃	50	14	84	55	17	2	–
11	DMA ^h	K ₂ CO ₃	50	14	47	29	6	–	–
12	DMA ^g	K ₂ CO ₃	70	8	93	56	19	–	–
13 ⁱ	DMA ^g	K ₂ CO ₃	70	14	97	62	14	–	–
14 ^j	DMA ^g	K ₂ CO ₃	70	14	90	60	12	–	–
15 ^k	DMA ^g	K ₂ CO ₃	70	14	>99	61	13	–	–
16 ^k	DMA ^g	K ₂ CO ₃	70	14	–	67 ^l	11 ^l	–	–

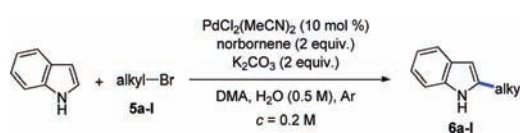
^a Determined by ¹H NMR using an internal standard. ^b Reaction was run under rt for 13 h, and then at 50 °C for 51 h. ^c Reagent grade DMA without purification. ^d Freshly distilled DMA. ^e Freshly distilled DMA with 0.1 M H₂O. ^f Freshly distilled DMA with 0.2 M H₂O. ^g Freshly distilled DMA with 0.5 M H₂O. ^h Freshly distilled DMA with 1 M H₂O. ⁱ Use of 2 equiv BuBr. ^j Pd(OCOCF₃)₂ (10 mol %) as the catalyst, 2 equiv BuBr. ^k PdCl₂(MeCN)₂ (10 mol %) as the catalyst, 2 equiv BuBr. ^l Yield of isolated product after column chromatography.

The reaction was sensitive to steric hindrance of the alkyl group; for the reaction employing an alkyl bromide with a secondary carbon atom adjacent to the bromide methylene group, higher temperature and prolonged reaction times were required (entries 2 and 7); secondary alkyl halides did not react with indole under the optimized conditions.¹³

The scope of the indole component was explored with different alkyl bromides (Scheme 3). Indoles with electron-donating and -withdrawing substituents at the C5, C6, or C7 position participated in the C2-alkylation reaction smoothly. Interestingly, electron-deficient indoles reacted well to give good yields of 2-alkylindole products when a weaker base, KHCO₃ or K₂HPO₄, was employed (**8e–i**), while they reacted poorly under the standard conditions using K₂CO₃ as the base (due to the generation of undesired *N*-alkylated indole as byproduct). Halogen-substituted indoles were proved to be suitable substrates, and the successful synthesis of halogen-substituted 2-alkylindoles **8d–f** enabled further access to more complex compounds by cross-coupling reactions.

It is noteworthy that when 5-iodoindole (**7j**) was employed as the substrate, a 2,5'-bisindole byproduct **8j'** was obtained in 8% yield in addition to the expected 2-alkylation product **8j** (Scheme 4a). This observation indicates that an aryl–iodine bond is reactive toward the palladacycle intermediate,¹⁰ which is

Table 2. Alkylation of Indole at the C2-Position with Different Alkyl Bromides

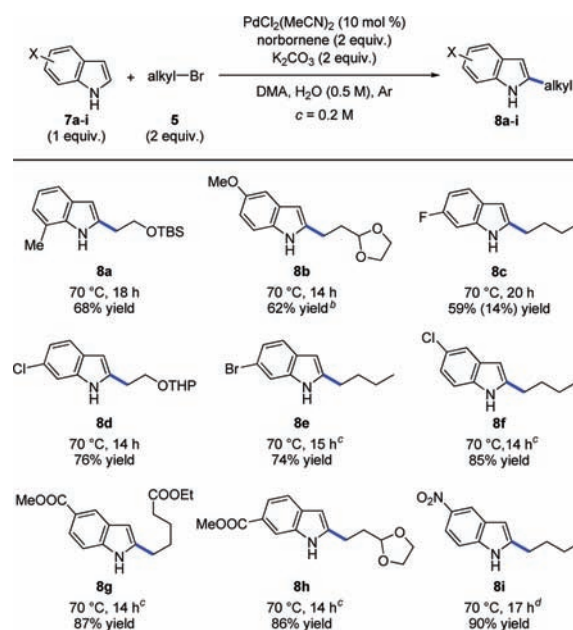


entry	product	method ^a	temp (°C)	time (h)	yield ^b
1		A	70	14	67% (9%)
2		A	90	61	59% (4%)
3		A	70	14	58% (11%)
4		A	70	14	82%
		B	70	17	71%
5		A	70	14	73%
		B ^c	70	14	76%
6		A ^c	70	14	36%
		B ^c	70	14	40%
7		A	90	20	65%
8		A	70	14	72%
		B	70	14	54%
9		A	70	14	61% (12%)
		B	70	14	52% ^d
10		A	70	14	66% (11%)
		B	70	15	69% (12%)
11		A	70	14	56% (19%)
		B	70	14	64%
12		A	90	68	43% ^e

^a Method A: 1 equiv indole and 2 equiv alkyl bromide; method B: 2 equiv indole and 1 equiv alkyl bromide. ^b Yield of isolated product after column chromatography. In parentheses the yield of the corresponding 2,3-dialkylated indole derivative (**6'**) is given if formed in significant amounts. ^c Pd(OCOCF₃)₂ (10 mol %) was used as the catalyst. ^d Intramolecular cyclization byproduct of **6i**, 8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one (**6i'**), was obtained in 10% yield. ^e 50% of indole was recovered. The yield based on recovered starting material was 85%. TBS = *tert*-butyldimethylsilyl, THP = tetrahydropyran-2-yl, Ts = 4-toluenesulfonyl.

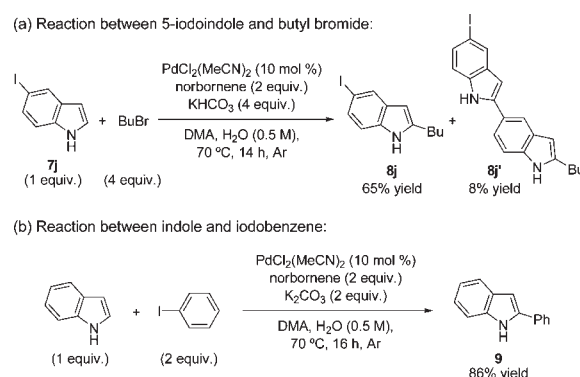
further supported by the generation of 2-phenylindole (**9**) from indole and iodobenzene under the standard C2-alkylation conditions (Scheme 4b). Therefore, the scope of the electrophilic component in the present reaction can be extended to an aryl iodide,¹⁴ which serves as a complement to the well-established Pd(0)-catalyzed indole C2-arylation reaction.^{4,5}

Since the 2-alkylation reaction relies on the interaction of the palladated indole species and norbornene, it was interesting to investigate whether the reaction could proceed normally when an olefin-containing alkyl bromide is employed. It was found that

Scheme 3. C2-Alkylation of Substituted Indole Derivatives^a

^a Yield of isolated product after column chromatography. In parentheses the yield of the corresponding 2,3-dialkylated indole derivative (**8'**) is given if formed in significant amounts. ^b 23% of indole **7b** was recovered. The yield based on recovered starting material was 78%. ^c KHCO₃ (3 equiv) was used as the base instead of K₂CO₃. ^d K₂HPO₄ (3 equiv) was used as the base instead of K₂CO₃.

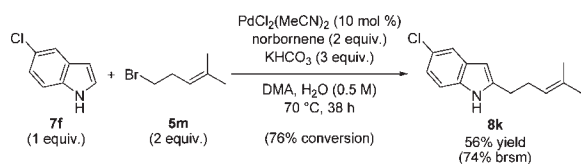
Scheme 4. Reactions of Substrates with an Aryl-Iodine Bond



alkyl bromide **5m** bearing a trisubstituted olefin moiety could participate in the 2-alkylation reaction (Scheme 5), albeit with diminished reactivity. However, the 2-alkylation reaction was completely inhibited when terminal-olefin-containing bromides were used.¹⁵ We suppose that a terminal olefin reacts in competition with norbornene with the indole-palladium species to block the norbornene-mediated catalytic cycle, while a more hindered trisubstituted olefin does not, and thus the 2-alkylation reaction proceeded in the normal way.

In summary, we have developed a straightforward and synthetically useful method for the regioselective alkylation of free *N*-H indoles at the C2-position. This reaction is compatible with a wide range of simple and functionalized primary alkyl bromides, as well as various substituents on indole with different electronic natures. The present method highlights a facile one-step

Scheme 5. Reaction of Indole 7f with Olefin-Containing Alkyl Bromide 5m



transformation from easily available indole and alkyl components to structurally diverse 2-alkylindole derivatives, which are not readily available by conventional synthetic methods. Further studies of this reaction (mechanism and synthetic application) are underway.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, analytical data for all new compounds, and NMR spectra for the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

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■ ACKNOWLEDGMENT

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- (12) Water was also found to have a positive effect on some norbornene-mediated cascade C–H activation reactions, see refs 11b and 11h.
- (13) The reaction between indole and 2-iodopropane was also attempted under the optimized conditions (50–90 °C), but no 2-alkylation product was observed.
- (14) A control experiment showed that without norbornene, the reaction between indole and iodobenzene did not occur under otherwise identical conditions, which excludes the Pd(0)-catalyzed C2-arylation mechanism in this reaction.
- (15) The reactions of indole with 5-bromo-1-pentene and 11-bromo-1-undecene were conducted under the optimized conditions. However, no 2-alkylation product was observed.