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Highly Regioselective C2-Alkenylation of Indoles Using the *N*-Benzoyl Directing Group: An Efficient Ru-Catalyzed Coupling Reaction

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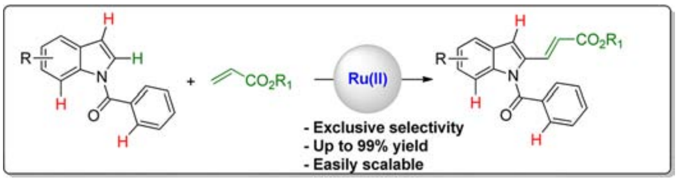
ABSTRACT



A highly regioselective alkenylation of indole at the C2-position has been achieved using the Ru(II) catalyst by employing a directing group strategy. This strategy offers rare selectivity for the alkenylation *N*-benzoylindole at the C-2 position in the presence of the more active C3- and C7-position of indole and the *ortho*-positions of the benzoyl protecting group. A simple deprotection of the benzoyl group has also been exemplified, and the resulting product serves as a useful synthon for natural product syntheses.

Formation of C–C bonds using nonfunctionalized precursors is a challenging task due to the unfavorable reactivity of C–H bonds.[1–4] To achieve such a distinction, it is important to understand the relative reactivity of various centers of the molecule.[5] The idea of employing directing groups (DGs) for the activation of C–H bonds has been conceived by de Vries and van Leeuwen for coupling anilides with olefins.[6] In designing a directing group strategy, it is important to employ a suitable group which can be readily installed and removed/transformed, and the substitution itself should not occur on the directing group.[7] In this regard, Pd catalyzed C–H functionalization reactions are well explored.[1a,7a,8,9] Indole is an integral feature of several biologically active compounds and natural products and an important constituent in pharmaceutical applications.[10] Alkenylation of indole at the C2-position is a challenging task due to the electrophilic nature of the reaction;[11] thus functionalization of indole at

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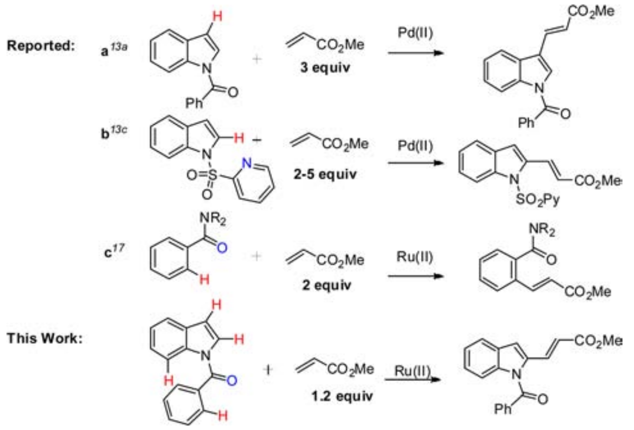
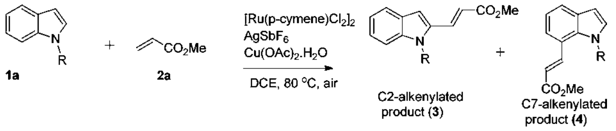
Scheme 1. Selective Alkenylation Using Directing Groups



the C2-position is less addressed.[12,13] Alkenylation of 1-acylindoles has been explored as early as 1983 by Itahara and co-workers[13a] by using Pd(II), which led to substitution at the C3-position (Scheme 1a). Furthermore, Gaunt et al. reported C2-alkenylation of indoles using Pd catalysts by altering the solvent to obtain C2- or C3-alkenylated products in low to moderate yields.[13b] Recently, Arrayás, Carretero and co-workers[13c] employed *N*-pyridylsulfonyl as a directing group to functionalize indole at the C2-position using an excess of alkenes in the presence of a Pd(II) catalyst (Scheme 1b). The concept was based on the ability of Pd to form six-membered palladacycles.[14] Other than the *N*-pyridylsulfonyl group, there have been no attempts to use other directing groups to alkenylate indole at the C2-position. With this background and previous reports on Ru-based catalysts,[15] we hypothesized that the Ru(II) catalyst could perform a selective C2-alkenylation of indole using a carbonyl oxygen as a directing group. Moreover, a C2-directing ability of Ru(II) would be favorable, as there are a number of reports on Ru(II) forming five-membered cyclic intermediates.[16]

Table 1. Screening Studies for Directing Groups



entry	indole	**3** (%)[a] (C2-product)	**4** (%)[b] (C7-product)
1	R = –H	nd	nd
2	R = $-CH_3$	nd	nd
3	R = $-COCH_3$	46	nd
4	R = $-CO(CH_3)_3$	trace	nd
5	R = $-CO(CH_3)_3$	trace	nd
6	R = –COPh	66	12
7	R = $-SO_2C_7H_8$	trace	nd

[a] Conversion based on ^{1}H NMR data. [b] nd = not detected.

To test this hypothesis, we started an investigation to find a suitable directing group, which could promote selective alkenylation of indole at the C2-position. Our preliminary studies indicated the suitability of *N*-acetylindole, as it reacted with methyl acrylate to furnish the C2-coupled product **3ea** in 46% yield (entry 3, Table 1). We anticipated that increasing the electron-donating ability of substrates may increase the reactivity and, therefore, used *N*-*tert*-butoylindole and *N*-*Boc*-indole for the reaction with methyl acrylate (**2a**) under identical reaction conditions. However, these reactions furnished trace amounts of the anticipated C2-alkenylated products (entries 4 and 5, Table 1). Very gratifyingly, when *N*-benzoylindole was treated with methyl acrylate, the expected C2-substituted product **3aa** was obtained in 66% yield (entry 6, Table 1). It is notable that the reaction of anilides with methyl acrylates in similar conditions resulted in the alkenylation of anilides at the *ortho*-position (Scheme 1c),[17] and it is well-known that the reaction of *N*-benzoylindole with methyl acrylate (**2a**) in the presence of Pd catalyst results in the formation of the C3-alkenylated product (Scheme 1a).[13a] Further screening studies revealed that a sulfonyl protecting group and simple indole and *N*-methyl indole were not suitable substrates, as no reaction occurred even after prolonged reaction times (entries 1, 2, and 7, Table 1). We anticipated that Pd also could mimic the role of Ru, and we explored the same reaction with Pd(II) instead of Ru(II). However, this substitution resulted in the mixture of C2- and C3-alkenylated products in low yields (see Supporting Information, SI-Table 1).

With the benzoyl group as a suitable directing group, we continued screening studies to determine the optimal amounts of the catalyst (Ru), activator (Ag), and oxidant (Cu) required for this reaction. *N*-Benzoyl indole (**1a**) and methyl acrylate (**2a**) were used as model substrates in the presence of $[Ru(p\text{-cymene})Cl_2]_2$ as a catalyst, $AgSbF_6$ as an activator, and $Cu(OAc)_2 \cdot H_2O$ as an oxidant in a variety of solvents and different temperatures. The reaction of **1a** with **2a** in the presence of Ru(II) (5 mol %), $AgSbF_6$

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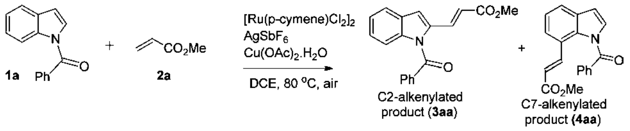
Table 2. Screening Studies for Optimal Conditions



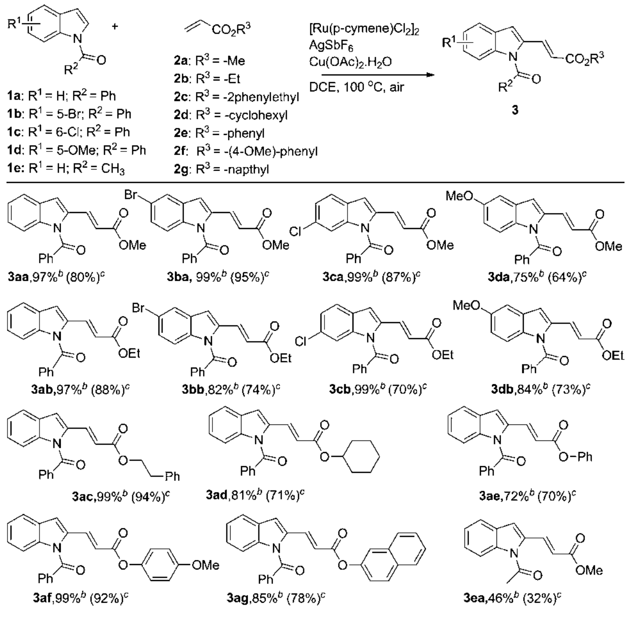
					conversion[a]		
entry	2a	Ru (mol %)	Ag (mol %)	Cu (equiv)	3aa	4aa	SM
1	2	5	20	1.2	66	12	22
2	2	none	20	1.2	nd	nd	100
3	2	5	none	1.2	nd	nd	100
4	2	5	20	none	<10	nd	90
5	2	5	10	0.25	<10	nd	90
6	2	5	20	1	65	5	30
7	3	5	20	1	41	9	50
8	5	5	20	1	13	7	80
9	1.2	5	20	1	66	7	27
10[b]	1.2	5	20	1	6	5	89
11[c]	1.2	5	20	1	17	6	79
12[d]	**1.2**	**5**	**20**	**1**	**97**	**nd**	**nd**
13[e]	1.2	5	100	1	nd	nd	100

[a] Based on ^{1}H NMR data. [b] Reaction at rt. [c] Reaction at 60 °C. [d] Reaction at 100 °C. [e] NaOAc was used instead of $AgSbF_6$.

(20 mol %), and $Cu(OAc)_2 \cdot H_2O$ (1.2 equiv) in DCE at 80 °C resulted in the formation of C2-substituted product **3aa**[18] as the major product (66%) along with C7-alkenylated product **4aa**[19] (12%) and unreacted starting material (22%, entry 1, Table 2). As can be seen, in the absence of either Ru or Ag, no reaction was observed, whereas the absence of copper acetate resulted in the formation of C2-substituted indole **3aa** in trace amounts (entries 2–4, Table 2). Further, it was found that a similar reaction using a catalytic amount of copper forms the C2-alkenylated product **3aa** in trace amounts (entry 5), whereas 1 equiv of copper salt produced the expected C2-alkenylated product **3aa** (65%) along with C7-alkenylated product **4aa** (5%) and **1a** (30%, entry 6). Increasing the stoichiometry of methyl acrylate (**2a**) to 3 or 5 equiv and performing the reaction in the presence of 5 mol % Ru and 1 equiv of Cu resulted in lowering the yield of C2-alkenylated product **3aa** (entries 7–8). Nevertheless, using 1.2 equiv of **2a** and 5 mol % of Ru with 1 equiv of copper acetate resulted in enhancing the yield of C2-alkenylated product **3aa** to 66% along with C7-alkenylated product **4aa** and unreacted *N*-benzoyl indole (**1a**) (7% and 30% respectively, entry 9). The reaction at ambient temperature resulted in the formation of **3aa** and **4aa** in almost equal ratio (58:42) in an overall yield of 10% (entry 10). An increase in the reaction temperate to 60 °C resulted in the formation of a mixture of products **3aa/4aa** (75:25) in 22% overall yield (entry 11). As expected, the reaction at 100 °C resulted in the regioselective formation of the C2-alkenylated product **3aa** as the sole product in almost quantitative yield (97%, entry 12). These reactions (entries 10–12) indicate that the regioselectivity of the reaction is controlled by the temperature of the reaction. As can be seen in entry 13, NaOAc is not useful as an activator in these Ru catalyzed reactions.[20] Solvents screening studies indicated that CH_3CN, toluene, dioxane, and water were not suitable solvents. Based on these studies, we arrived at the optimal conditions for this reaction, i.e. **1a** (1 equiv), **2a** (1.2 equiv), Ru complex (5 mol %), Ag salt (20 mol %), and Cu salt (1 equiv) in DCE at 100 °C in the presence of air.

Next, we continued to explore the scope of the reaction (Schemes 2 and 3). As can be seen in Scheme 2, **1a** reacted with methyl acrylate **2a** to furnish the oxidative coupled product **3aa** in excellent yield as the sole product (97%, Scheme 2). Similarly, *N*-benzoylated derivatives of 5-bromoindole (**1b**), 6-chloroindole (**1c**), and 5-methoxyindole (**1d**) underwent a smooth reaction with **2a** to provide the Heck type coupled products **3ba**, **3ca**, and **3da** in good to excellent yields. Similarly, ethyl acrylate (**2b**) reacted well with indole derivatives **1a**, **1b**, **1c**, and **1d** to furnish the coupled products **3ab**, **3bb**, **3cb**, and **3db** in good to excellent yields.

Scheme 2. Scope of the Reaction[a]



[a] Reaction conditions: *N*-Benzoylindole (1 equiv), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), $Cu(OAc)_2 \cdot H_2O$ (1 equiv), acrylate (1.2 equiv), DCE (2 mL), 100 °C, 3 h. [b] Conversion based on ^{1}H NMR data. [c] Isolated pure yields.

Further studies revealed that other alkyl acrylates such as 2-phenylethylacrylate (**2c**) and cyclohexyl acrylate (**2d**) also underwent smooth coupling to furnish the C2-coupled products **3ac** and **3ad** in good yields (99% and 81% respectively). This coupling reaction turned out to be a

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(18) The C2-alkenylated *N*-benzoylindole derivatives were characterized by spectral data and single crystal structural analysis of **3ba** (see SI).

(19) C7-Alkenylated *N*-benzoylindole **4** is characterized by spectral data, and the structure was resolved by COSY and j-resolved NMR experiments (see SI for details).

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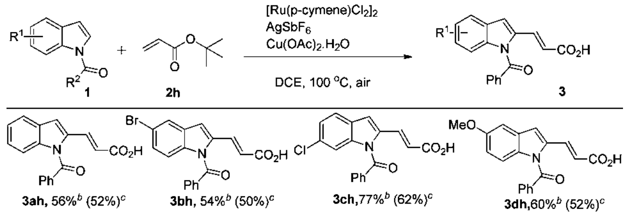
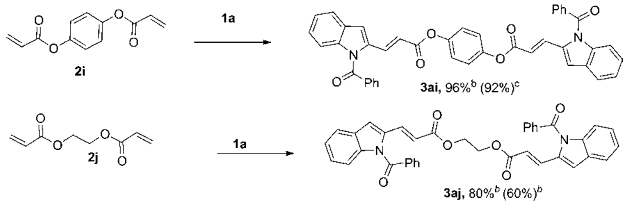
Scheme 3. Reaction with *tert*-Butyl Acrylate[a]



[a] Reaction conditions: *N*-Benzoylindole derivative (1 equiv), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), $AgSbF_6$ (20 mol %), $Cu(OAc)_2 \cdot H_2O$ (1 equiv), acrylate (1.2 equiv), DCE (2 mL), 100 °C, 6 h. [b] Conversion based on ^{1}H NMR data. [c] Isolated pure yields.

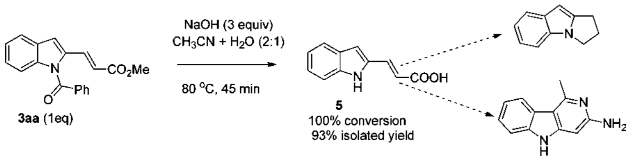
Scheme 4. Reaction of Diacrylates[a]



[a] Reaction conditions: *N*-Benzoylindole (2.5 equiv), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), $AgSbF_6$ (20 mol %), $Cu(OAc)_2 \cdot H_2O$ (1 equiv), acrylate (1 equiv), DCE (2 mL), 100 °C, 6 h. [b] Conversion based on ^{1}H NMR data. [c] Isolated pure yields.

versatile reaction, as the reaction of **1a** with aryl acrylate such as phenyl acrylate (**2e**), 4-methoxy-phenyl acrylate (**2f**) and naphthyl acrylate (**2g**) in a reaction with indole **1a** furnished the expected coupled products **3ae**, **3af**, and **3ag** in good to excellent yields (72%, 99%, and 85% respectively). However, the reaction of *N*-acetylindole (**1e**) with methyl acrylate (**2a**) resulted in a moderate yield of the coupled product **3ea** (46%). The reaction of indole derivatives with *tert*-butylacrylate (**2h**) was interesting. As can be seen in Scheme 3, *N*-benzoyl indole (**1a**) reacted with *tert*-butylacrylate (**2h**) to furnish the product **3ah** in which the *tert*-butyl group was deprotected under the reaction conditions. The generality of this reaction was further established by reacting *tert*-butylacrylate (**2h**) with a few more indole derivatives. Thus, the reaction of *tert*-butylacrylate (**2h**) with *N*-benzoylated derivatives of 5-bromoindole (**1b**), 6-chloroindole (**1c**), and 5-methoxyindole (**1d**) furnished the corresponding alkenylated acids **3bh**, **3ch**, and **3dh** in moderate yields.

Scheme 5. Deprotection and Hydrolysis



The scope of this highly regioselective coupling reaction was further explored by reacting *N*-benzoylindole (**1a**) with diacrylates (Scheme 4) and found that the two indole moieties can couple with diacrylate. Hence, *N*-benzoylindole (**1a**) reacted with 1,4-phenylene diacrylate (**2i**) under optimal reaction conditions.

As expected, diacrylate **2i** coupled with 2.5 equiv of indole **1a** to furnish the coupled product (**3ai**) in excellent isolated yield (92%). Under identical conditions, ethane-1,2-diyl diacrylate (**2j**) also reacted well with **1a** to furnish the coupled product (**3aj**) in 60% yield (Scheme 4).

Due to its importance for further functionalization of the indole moiety, we attempted the facile deprotection of the benzoyl group.

As can be seen from Scheme 5, the deprotection was readily achieved by heating **3aa** with NaOH in H_2O/CH_3CN solution for 45 min to furnish the debenzoylated indole derivative of acrylic acid (**5**) in almost quantitative yield.[21] This product **5** is a very useful intermediate, which can be transformed into a variety of natural products.[22] Further, the utility of the alkenylation of *N*-benzoyl indole has been demonstrated by performing the reaction at 4 mmol scale.[23]

A novel Ru catalyzed versatile regioselective alkenylation strategy for indole derivatives at the C2-position has been demonstrated using the benzoyl group as a directing group. To the best of our knowledge, this is the first report of C2-alkenylation of *N*-benzoylindoles. Although Ru catalysts are well-known catalysts for direct alkenylation of benzamides at the *ortho*-poistion, such functionalization is not observed in the present strategy. The deprotection of the benzoyl group is also very facile thereby making the methodology more useful. Further work to establish the mechanistic reasons for selectivity and to further explore the synthetic scope of this mode of catalytic activation is in progress.

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

The authors declare no competing financial interest.

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(23) Scaling up experiment: