ORGANIC LETTERS

2013
Vol. 15, No. 24
6262–6265

Regioselective Synthesis of 4-Substituted Indoles via C−H Activation: A Ruthenium Catalyzed Novel Directing Group Strategy

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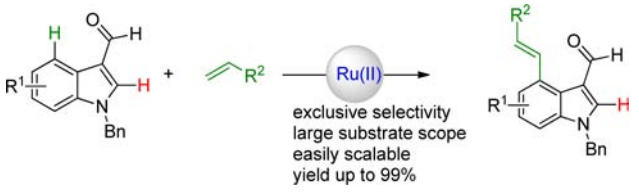
Received October 30, 2013

ABSTRACT



A highly regioselective functionalization of indole at the C-4 position by employing an aldehyde functional group as a directing group, and Ru as a catalyst, under mild reaction conditions (open flask) has been uncovered. This strategy to synthesize 4-substituted indoles is important, as this class of privileged molecules serves as a precursor for ergot alkaloids and related heterocyclic compounds.

Among indoles, 4-substituted indoles are known as *privileged frameworks* that are attractive synthetic targets in organic synthesis.[1,2] This class of compounds are the backbone of ergot alkaloids,[3] which are biologically active and promising drug candidates.[4] Development of a short synthetic route for 4-substituted indoles is a challenging task, as the C-4 position of indole is less reactive and requires a multistep sequence using 4-formylindole derivatives.[5] Synthesis of 4-substituted indoles is crucial in developing synthetic routes to ergot and related alkaloids, as it can be transformed to a variety of natural products (Figure 1).[6] Formation of C−C bonds using unfunctionalized precursors is cumbersome due to the unfavorable reactivity of C−H bonds,[7] and selective functionalization is an even more difficult task.[8] A directing group (DG) strategy for C−H activation is a subject of research as it provides a simple, short, and economical route to the target molecules.[9] In recent times, Ru-catalysts have emerged as highly efficient and useful catalysts for the formation of C−C bonds using a DG strategy.[10] However, there are only limited studies for the alkenylation of indole derivatives by employing Ru catalysts. The C-4 alkenylation of indoles has rarely been addressed, except for a recent report on a Pd catalyzed reaction of tryptophan,[11] which is limited to only tryptophan

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10.1021/ol4031149
Published on Web 11/25/2013

derivatives. Recently, Jeganmohan et al. reported Ru catalyzed *ortho*-alkenylation of aromatic aldehydes.[12e] Based on the literature precedence[12] and in continuation of our quest for the selective functionalization of indoles,[13] we undertook an investigation to functionalize indole at the C-4 position.

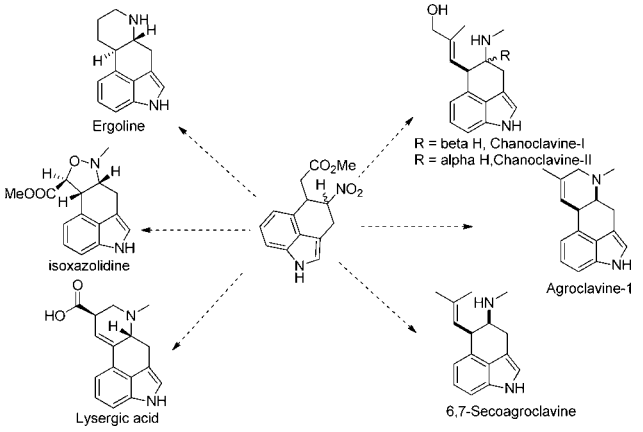
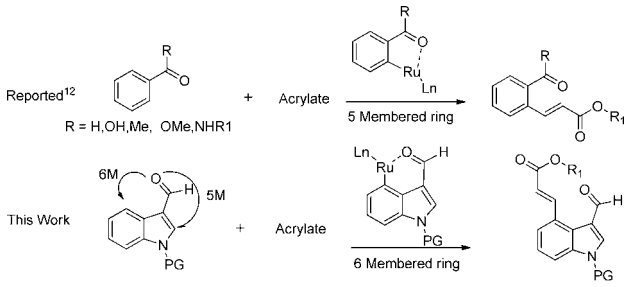


Figure 1. Biologically active compounds derived from C-4 substituted indoles.

In this study, we describe our recent finding on the highly regioselective functionalization of indole at the C-4 position by employing the aldehyde functional group as a directing group, and Ru as a catalyst under mild reaction conditions (open flask). An interesting observation is that, unlike other known methods,[12] in the present study it was found that the reaction involves a six membered transition state[14] that leads to the expected product (Scheme 1). A selective functionalization of indole at the C-4 position using an aldehyde as a directing group provides advantages of either removing the aldehyde group[6a] or further functionalization.

Scheme 1



The preliminary reaction of 1-benzyl-1*H*-indole-3-carbaldehyde (**1a**) with methyl acrylate (**2a**) in the presence of Ru(II) (5 mol %), $AgSbF_6$ (20 mol %), and $Cu(OAc)_2 \cdot H_2O$ (1.0 equiv) in $ClCH_2CH_2Cl$ at 100 °C resulted in the formation of C-4-substituted product **3aa** in a major amount (47%) along with a mixture of C-2 alkenylated product **4aa** (12%), **5aa** (at C-2 and C-4 positions, 5%), and **1a** (34%, entry 1, Table 1). In the absence of either Ru or Ag, no reaction was observed, whereas the absence of copper acetate resulted in the formation of C-4 substituted indole **3aa** in trace amounts (entries 2−4, Table 1). Further, enhancing the amount of Ru(II) to 10 mol % resulted in the formation of a mixture of products **3aa**, **4aa**, **5aa**, and **1a** (45:20:13:22 ratio, entry 5, Table 1). Decreasing the amount of the Cu catalyst to 0.5 equiv resulted in the formation of the expected C-4 alkenylated product **3aa** in low yields (18%) along with unreacted aldehyde **1a** (82%, entry 6). Temperature control experiments revealed the formation of **3aa** in 17% yield when the reaction was performed at 60 °C (entry 7). Increasing the temperature to 120 °C resulted in the formation of a mixture of **3aa**, **4aa**, **5aa**, and starting material **1a** in a ratio of 45:19:7:29, respectively (entry 8, Table 1). Based on these observations (entries 5−8), we performed the reaction using Ru (10 mol %), Cu (0.5 equiv) at 120 °C to find the formation of **3aa** as a major product (58% yield) along with **4aa**, **5aa**, and aldehyde **1a** (4%, 2%, 36% yields, entry 9). Further screening studies revealed that $AgSbF_6$ is a suitable activator, as the noncoordinating counterion SbF_6^- keeps the Ru coordination site empty so that Ru can bind to the substrate. It was also found that $Cu(OAc)_2 \cdot H_2O$ is the most appropriate oxidant for the reaction (entries 10−14). Increasing the stoichiometry of methyl acrylate (**2a**) to 2.5 and 4 equiv in the presence of 10 mol % Ru(II) and 0.5 equiv of Cu(II) has enhanced the yield of C-4 alkenylated product **3aa** to 63% and 82% respectively (entries 15−16). Based on these screening studies, we arrived at the optimal conditions for this reaction, i.e., **1a** (1 equiv), **2a** (4 equiv), $[Ru(p\text{-cymene})Cl_2]_2$ (10 mol %), Ag salt (20 mol %), and $Cu(OAc)_2 \cdot H_2O$ (0.5 equiv) in $ClCH_2CH_2Cl$ at 120 °C in the presence of air.

Next, we continued to explore the scope of the reaction, and the results are presented in Schemes 2 and 3. A variety of 1-benzyl-1*H*-indole-3-carbaldehyde derivatives **1a**−**1e** reacted with methyl acrylate **2a** to furnish C-4 alkenylated products **3aa**, **3ba**, **3ca**, **3da**, and **3ea** in good yields (80−95%).

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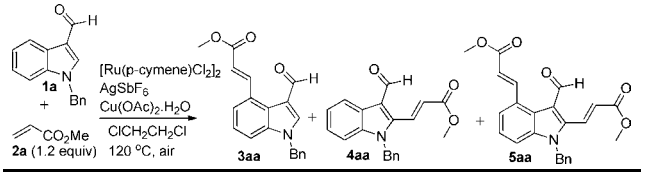
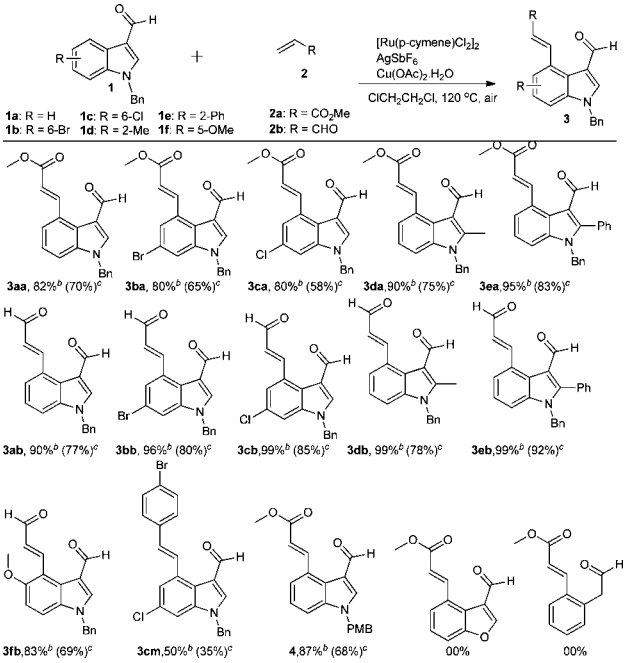
Table 1. Screening Studies for Optimization



entry	Ru (mol %)	additive (mol %)	oxidant (equiv)	NMR conversion[a] 3aa	4aa	5aa	sm
1[b]	5	$AgSbF_6$ (20)	Cu(II) (1)	47	12	5	34
2[b]	none	$AgSbF_6$ (20)	Cu(II) (1)	nd	nd	nd	100
3[b]	5	none	Cu(II) (1)	nd	nd	nd	100
4[b]	5	$AgSbF_6$ (20)	none	<10	nd	nd	90
5[b]	10	$AgSbF_6$ (20)	Cu(II) (1)	45	20	13	22
6[b]	5	$AgSbF_6$ (20)	Cu(II) (0.5)	18	nd	nd	82
7[c]	5	$AgSbF_6$ (20)	Cu(II) (1)	17	nd	nd	83
8	5	$AgSbF_6$ (20)	Cu(II) (1)	45	19	7	29
9	10	$AgSbF_6$ (20)	Cu(II) (0.5)	58	4	2	36
10	10	KPF_6 (20)	Cu(II) (0.5)	6	nd	nd	94
11	10	NH_4PF_6 (20)	Cu(II) (0.5)	42	nd	nd	43
12	10	$AgSbF_6$ (20)	PIDA	nd	nd	nd	100
13	10	$AgSbF_6$ (20)	AgOAc	nd	nd	nd	100
14	10	$AgSbF_6$ (20)	NaOAc	nd	nd	nd	100
15[d]	10	$AgSbF_6$ (20)	Cu(II) (0.5)	63	7	5	25
16[e]	**10**	**$AgSbF_6$ (20)**	**Cu(II) (0.5)**	**82**	**5**	**2**	**11**

[a] Based on ^{1}H NMR data. [b] Reaction performed at 100 °C. [c] Reaction performed at 60 °C. [d] 2.5 equiv of **2a**. [e] 4.0 equiv of **2a**. PIDA = phenyliodine(III) diacetate.

Scheme 2. Substrate Scope with Indole Derivatives[a]



[a] Reaction conditions: 1-benzyl-1*H*-indole-3-carbaldehyde (1 equiv), $[Ru(p\text{-cymene})Cl_2]_2$ (10 mol %), $AgSbF_6$ (20 mol %), acrylate (**2a**) (4 equiv), $ClCH_2CH_2Cl$ (2 mL), 120 °C, 8−24 h. In the case of **2b**, $Cu(OAc)_2 \cdot H_2O$ (1 equiv) was used. [b] Conversion based on ^{1}H NMR data. [c] Isolated pure yields.

Similarly, the reaction of acrolein **2b** with **1a**−**1e** resulted in the formation of products **3ab**, **3bb**, **3cb**, **3db**, and **3eb** in excellent yields (90−99%). As demonstrated by these examples, substrates with halogen substitution on the indole ring at the C-6 (Cl and Br) position are well tolerated under the reaction conditions to furnish the corresponding alkenylated products (**3ba**, **3ca**, **3bb**, and **3cb**), which are useful precursors for further functionalization.[15]

Further, it was found that the alkenylation of 1-benzyl-5-methoxy-1*H*-indole-3-carbaldehyde (**1f**) proceeds smoothly with acrolein **2b** to furnish the product **3fb** in 83% yield. Alkenylation of **1c** with 4-bromostyrene resulted in the formation of the product **3cm** in moderate yield. Reaction of 1-(4-methoxybenzyl)-1*H*-indole-3-carbaldehyde, which is an *N*-protected PMB derivative of indole-3-carbaldehyde, with **2a** furnished the alkenylated product **4** in good yield. Similarly, a reaction of *N*-benzoyl protected indole-3-carbaldehyde with methyl acrylate (**2a**) under optimal conditions yielded the product **6** in good yield. However, the reactions to alkenylate benzofuran-3-carbaldehyde and 2-phenylacetaldehyde with acrolein were not successful.[16]

The scope of this highly regioselective coupling reaction was further expanded by reacting **1a** with a variety of acrylates. Thus acrylates **2c**−**2i** underwent a facile reaction with **1a** to afford the corresponding 4-substituted indole derivatives **3ac**, **3ad**, **3ae**, **3af**, **3ag**, **3ah**, and **3ai**, in excellent yields (70−87%, Scheme 3). This coupling reaction was a versatile reaction, as the reaction of **1a** with a variety of α,β-unsaturated systems such as **2j**−**2o** furnished the expected coupled products **3aj**, **3ak**, **3al**, **3am**, **3an**, and **3ao** in moderate yields (Scheme 3).[16]

Earlier, we demonstrated that using *N*-benzoyl as a directing group on indole derivatives under a Ru catalyzed reaction can lead to 2-alkenylated products **9**.[13] In light of the present study, it would be appropriate to study the regioselectivity and directing group abilities of formyl and benzoyl directing groups, if they are present in the indole moiety, as in compound **5** (Scheme 4). Therefore, when **5** was subjected to the present reaction conditions, the reaction furnished a mixture of 4-alkenylated product **6** in a major amount (68%) along with 2-alkenylated product **7** in a minor amount (7%, eq 1, Scheme 4). However, the reaction of **1a** (*N*-benzyl indole) with **2a** under the optimal reaction conditions furnished **3aa** in 82% yield (Scheme 2). To evaluate the steric factor involved in the above reaction due to the presence of a formyl group at the third position of indole, an independent reaction using a mixture of 3-formyl-*N*-benzyl indole (**1a**) and *N*-benzoyl indole (**8**) was performed under the optimal conditions. This reaction yielded a mixture of C-4 alkenylated product **3aa** (46%) and C-2 alkenylated product **9** (12%) in an 8:2 ratio along with

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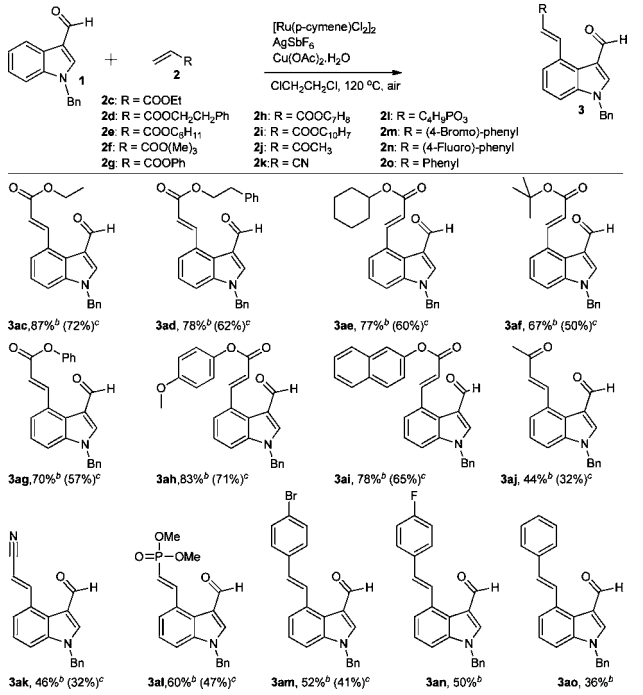
(16) C-2 Alkenylated products were not observed with acrolein, whereas in the remaining olefins, C-2 alkynylated products were obtained in < 7% yield (based on ^{1}H NMR data).

Scheme 3. Substrate Scope with a Variety of Olefins[a]



[a] Reaction conditions: **1a** (1 equiv), $[Ru(p\text{-cymene})Cl_2]_2$ (10 mol %), $AgSbF_6$ (20 mol %), $Cu(OAc)_2 \cdot H_2O$ (0.5 equiv), acrylate (**2c**−**2i**) (4 equiv), $ClCH_2CH_2Cl$ (2 mL), 120 °C, 8−24 h. In the case of other olefins (**2j**−**2o**), $Cu(OAc)_2 \cdot H_2O$ (1 equiv) was used. [b] Conversion based on ^1H NMR data. [c] Isolated pure yields.

unreacted starting materials (eq 2, Scheme 4). These two reactions indicate that the directing group ability of the formyl group is more pronounced than the *N*-benzoyl group.

Bifunctional molecules such as 4-substituted indoles are attractive synthetic targets, as they serve as precursors for the synthesis of alkaloids that are related to the clavine families and lysergic acid.[2,3] One of the key intermediates for the synthesis of this class of alkaloids is an appropriately substituted 1,3,4,5-tetrahydrobenzo[*cd*] indole moiety, which is generally synthesized using a multiple synthetic sequence.[17] The potential of the present C−H activation strategy using an aldehyde as a directing group has been demonstrated by synthesizing **10** in just two steps by using a suitably substituted 1,3,4,5-tetrahydrobenzo[*cd*] indole moiety with an overall yield of 68% (Scheme 5). The reaction of 1-benzyl-1*H*-indole-3-carbaldehyde **1a** with methyl acrylate **2a** was scaled up to the 750 mg scale under standard reaction conditions to obtain the product **3aa** in 68% isolated yield. Further, a selective reduction of the olefin is also demonstrated using Pd/C at rt to obtain the product **11** in quantitative yield (98%). Interestingly,

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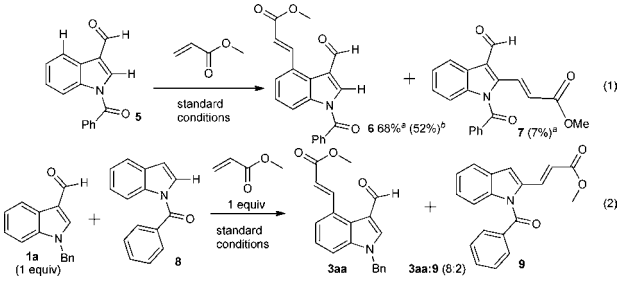
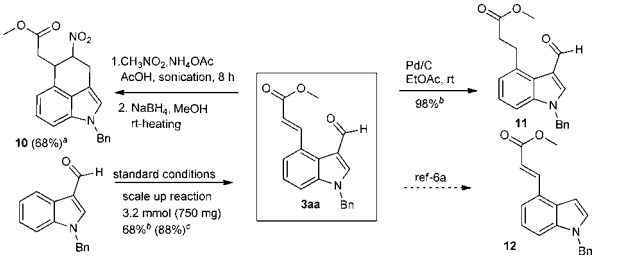
Scheme 4. Selective Alkenylation Reactions



[a] Conversion based on ^1H NMR data. [b] Isolated pure yields.

Scheme 5. Synthetic Applications



[a] Isolated, overall yields from 2 steps. [b] Isolated pure yields. [c] Conversion based on ^1H NMR data.

product **12**[6a] obtained by removing the aldehyde group from **3aa** provides a unique opportunity for functionalization at a third position, and this indole derivative provides potential for the synthesis of a variety of indole heterocyclic compounds.[18]

The C−H functionalization using a directing group strategy approach has been demonstrated for synthesizing 4-substituted indoles using the carbonyl oxygen of an aldehyde as a directing group. This strategy to accomplish 4-substituted indoles is important, as this class of privileged molecules serves as a precursor for ergot alkaloids and related heterocyclic compounds. To the best of our knowledge, this is the first report of C-4 alkenylation of indoles using a Ru catalyst and an aldehyde as a directing group. Further work on the mechanism, reasons for selectivity, and exploration of the synthetic scope of this strategy is in progress.

Acknowledgment. The authors thank IISc and RL Fine Chem for financial support and Dr. A. R. Ramesha (RL Fine Chem) for useful discussions. V.L. thanks CSIR for a fellowship.

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.