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Rhodium(III)-Catalyzed Direct Regioselective Synthesis of 7-Substituted Indoles

Zengqiang Song,[†,‡] Rajarshi Samanta,[§,†] and Andrey P. Antonchick*[,†,‡]

Max-Planck-Institut für Molekulare Physiologie, Abteilung Chemische Biologie, Otto-Hahn-Strasse 11, 44227 Dortmund, Germany, and Technische Universität Dortmund, Fakultät Chemie und Chemische Biologie, Chemische Biologie, Otto-Hahn-Strasse 6, 44227 Dortmund, Germany

andrey.antonchick@mpi-dortmund.mpg.de

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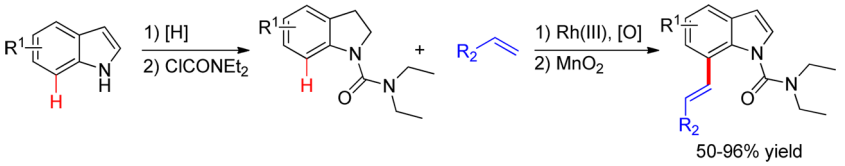
ABSTRACT



An efficient, atom-economic one-pot method was developed for the preparation of 7-substituted indoles via rhodium(III)-catalyzed oxidative cross-coupling. Regioselective olefination of indoline derivatives followed by one-pot subsequent oxidation provided the desired products in good to excellent yields.

Many natural products with a broad spectrum of bioactivity are based on indole. Moreover, indole has been identified as a privileged scaffold for the design of biological probes and medicinal drugs.[1] The synthesis of substituted indole derivatives has received considerable attention in organic chemistry. Many practical and efficient methods have been developed for the construction of an indole core in recent decades.[2] Nevertheless, efficient protocols for direct regioselective functionalization of indole derivatives in order to get fast access to a variety of indole derivatives are in high demand.[3] Extensive studies have been carried out over the past decades targeting transition-metal-catalyzed C−H bond activations at the C-2 and C-3 positions of indole (Scheme 1).[4] It has been shown that 2- or 3-alkenylated indole derivatives can be obtained via intermolecular oxidative coupling with corresponding nonfunctionalized coupling partners using transition-metal catalysis.[4−6] Recently, an elegant method for preparation of 4-substituted tryptophans has been reported (Scheme 1).[7] 7-Substituted indole derivatives are very important due to their ubiquitous presence in numerous natural products and pharmaceutically important compounds (Figure 1).[8] Regioselective oxidative C−H functionalization of indole derivatives at the C-7 position has limited reports.[9]

[†] Max-Planck-Institut für Molekulare Physiologie.
[‡] Technische Universität Dortmund.
[§] Indian Institute of Technology Kharagpur, 721302 Kharagpur, India.

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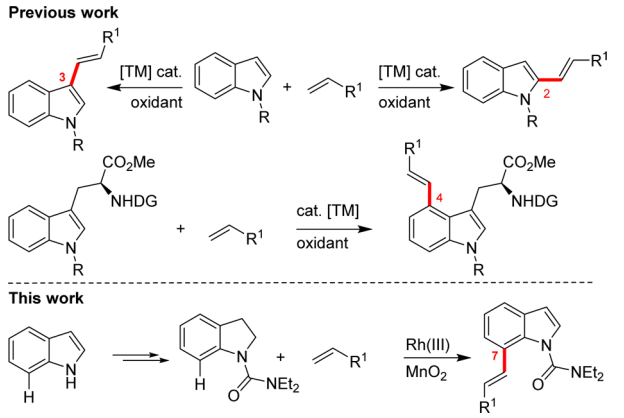
Scheme 1. Regioselective Functionalization of Indoles



As part of our studies on the direct functionalization of unactivated C−H bonds,[10] we were interested in the development of a transition-metal-catalyzed regioselective method for 7-substituted indoles (Scheme 1). Here we report an one-pot general approach for functionalization of indole derivatives at the C-7 position.

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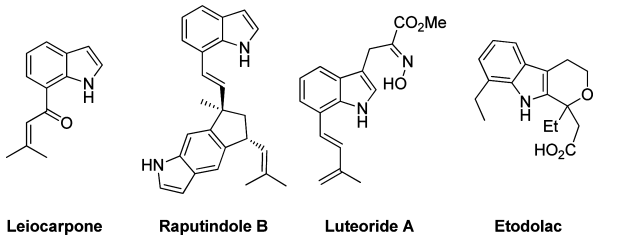
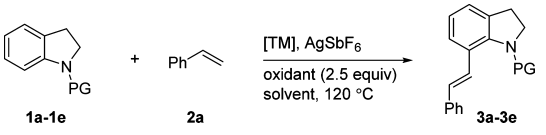


Figure 1. Bioactive compounds based on 7-substituted indoles.

Our proposal is based on the functionalization of indoline derivatives, which are widely available from corresponding indoles by reduction and following protection (Scheme 1). In the initial study, we first examined the coupling reaction between *N*-acetylindoline (**1a**) and styrene (**2a**) using $[Ru(SbF_6)_2(p\text{-cymene})]_2$ as catalyst and anhydrous $Cu(OAc)_2$ as oxidant in DCE at 120 °C (Table 1, entry 1). We obtained the desired product **3a** in 24% isolated yield. Further screening of solvents with DMF, *t*-AmOH, CH_3CN, or 1,4-dioxane did not improve the yield of our desired product (Table 1, entries 2−5). Several oxidants such as AgOAc or benzoquinone were

Table 1. Optimization of Reaction Conditions[a]

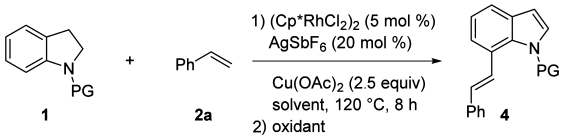


entry	PG	solvent	oxidant	time (h)	yield[c] (%)
1	Ac (**1a**)	DCE	$Cu(OAc)_2$	24	24
2	Ac (**1a**)	DMF	$Cu(OAc)_2$	24	20
3	Ac (**1a**)	*t*-AmOH	$Cu(OAc)_2$	24	14
4	Ac (**1a**)	CH_3CN	$Cu(OAc)_2$	24	<14
5	Ac (**1a**)	dioxane	$Cu(OAc)_2$	24	<14
6	Ac (**1a**)	DCE	AgOAc	24	trace
7	Ac (**1a**)	DCE	BQ	24	trace
8	Piv (**1b**)	DCE	$Cu(OAc)_2$	24	n.d.[d]
9	CO-2Py (**1c**)	DCE	$Cu(OAc)_2$	24	n.d.[d]
10	$CONEt_2$ (**1d**)	DCE	$Cu(OAc)_2$	24	53
11	SO_2-2Py (**1e**)	DCE	$Cu(OAc)_2$	24	n.d.[d]
12[b]	**$CONEt_2$ (1d)**	**DCE**	**$Cu(OAc)_2$**	**36**	**96**
13[b]	$CONEt_2$ (**1d**)	dioxane	$Cu(OAc)_2$	16	51
14[b]	$CONEt_2$ (**1d**)	toluene	$Cu(OAc)_2$	48	31
15[b]	**Ac (1a)**	**DCE**	**$Cu(OAc)_2$**	**36**	**99**
16[b]	**$CONEt_2$ (1d)**	***t*-AmOH**	**$Cu(OAc)_2$**	**8**	**90**
17[b]	$CONEt_2$ (**1d**)	*t*-AmOH	Ag_2CO_3	20	45
18[b]	$CONEt_2$ (**1d**)	*t*-AmOH	Ag_2O	36	58
19[b]	$CONEt_2$ (**1d**)	*t*-AmOH	$PhI(OAc)_2$	36	trace
20[b]	$CONEt_2$ (**1d**)	*t*-AmOH	NFSI	36	trace

[a] Reaction conditions: **1** (0.2 mmol), **2a** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), $AgSbF_6$ (40 mol %), oxidant (2.5 equiv), 0.2 M at 120 °C (the internal temperature of vial was 105 °C). [b] Reaction conditions: **1** (0.1 mmol), **2a** (0.5 mmol), $[Cp^*Rh(III)Cl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), oxidant (2.5 equiv), 0.1 M at 120 °C. [c] Isolated yield. [d] The formation of product was not detected.

tested to improve the yield of the desired product. Unfortunately, only formation of trace amount of **3a** was detected (Table 1, entries 6 and 7). Various directing groups were tested to improve the yield of the product. We found that *N,N*-diethylcarbamoyl-protected indoline provided the desired alkenylated product **3d** with 53% yield (Table 1, entry 10). Other protecting groups like pivolyl, 2-pyridylcarbonyl, or 2-pyridylsulfonyl did not work (Table 1, entries 8, 9, and 11). After various experiments with $[Ru(SbF_6)_2(p\text{-cymene})]_2$ we decided to switch to $[RhCp^*(SbF_6)_2]_2$ as catalyst. Our initial attempt for coupling of styrene with *N,N*-diethylcarbamoyl-protected indoline in 1,2-dicholoroethane provided a very impressive 96% yield of the product (Table 1, entry 12) in 36 h when 5 mol % of rhodium(III) catalyst was used. Others solvents such as 1,4-dioxane or toluene did not provide better yields (Table 1, entries 13 and 14). When *t*-AmOH was used as solvent, the desired product was obtained in excellent yield and shorter reaction time (Table 1, entry 16). Other oxidants like Ag_2CO_3 or Ag_2O provided moderate yields, whereas $PhI(OAc)_2$ or NFSI gave almost no conversion (Table 1, entries 17−20). In control experiment, the coupling of styrene with the *N,N*-diethylcarbamoyl-protected indole was tested and resulted in a mixture of products. On the other hand, the coupling of styrene with *N,N*-diethylcarbamoyl-protected 2-methylindole or *N,N*-diethylcarbamoyl 2,3,4,9-tetrahydro-1*H*-carbazole under rhodium(III)-catalyzed conditions did not give any desired product, and only starting material was remained (see the Supporting Information for details).

Table 2. Optimization of One-Pot Reaction Conditions[a]

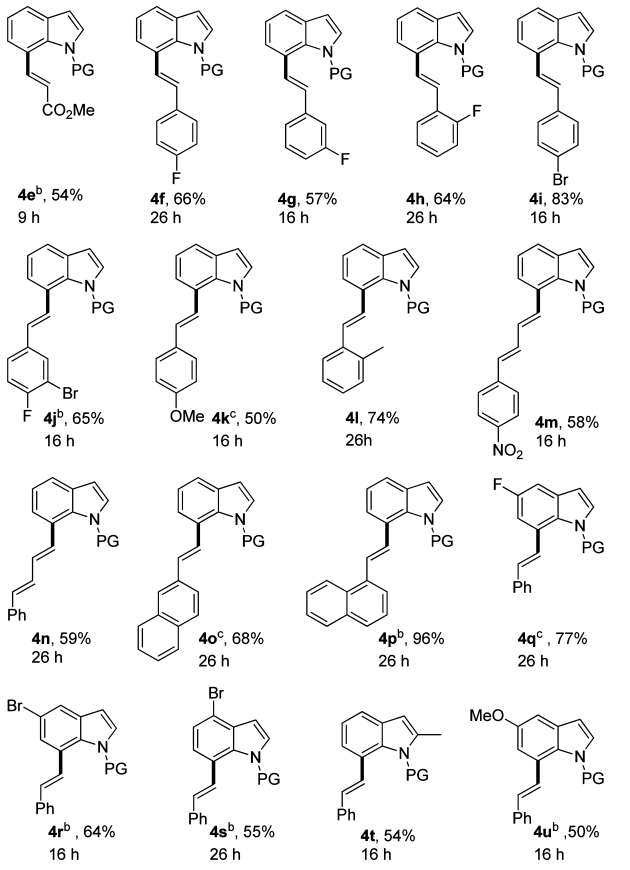


entry	PG	solvent	oxidant (equiv)	time (h)	yield[b] (%)
1[c]	Ac (**1a**)	DCE	MnO_2 (20)	24	38
2[c]	Ac (**1a**)	DCE	DDQ (3)	24	11
3[c,d]	Ac (**1a**)	DCE	TBHP (4)	24	trace
4[c]	$CONEt_2$ (**1d**)	DCE	MnO_2 (20)	24	76
5	**$CONEt_2$ (1d)**	***t*-AmOH**	**MnO_2 (20)**	**8**	**80**
6	$CONEt_2$ (**1d**)	*t*-AmOH	DDQ (3)	4	57
7	$CONEt_2$ (**1d**)	*t*-AmOH	$Mn(OAc)_3 \cdot 2H_2O$ (1.5)	24	22
8[d]	$CONEt_2$ (**1d**)	*t*-AmOH	TBHP (4)	24	trace
9	$CONEt_2$ (**1d**)	*t*-AmOH	chloranil (3)	24	36

[a] Reaction conditions: **1** (0.1 mmol), **2a** (0.5 mmol), $(Cp^*RhCl_2)_2$ (5 mol %), $AgSbF_6$ (20 mol %), and anhydrous $Cu(OAc)_2$ (2.5 equiv), *t*-AmOH (0.1M) at 120 °C (the internal temperature of vial is 105 °C), after **1** completely disappeared (8 h), oxidant was added to the reaction system, continued stirring at 120 °C. [b] Isolated yield. [c] After 36 h, **1** completely diasppeared. [d] TBHP 5.5 M in decane.

Afterward, we explored the one-pot reaction conditions for selective 7-functionalized indole synthesis, which is based on the coupling of an indoline derivative with a styrene, followed by oxidation. In initial trials, acetyl-protected indoline was used for olefination followed by oxidation. Although the first step finished efficiently, the oxidation of 7-alkenylated indoline to its indole derivative did not provide a good yield (Table 2, entries 1−3) under different oxidation conditions.[11] However, changing of the acetyl protection group to the *N,N*-diethylcarbamoyl group led to **4d** in satisfactory yield (80% for two steps) using oxidation with MnO_2 (Table 2, entry 5). Furthermore, product **4d** was obtained with 86% yield from **1d** performing the reaction at 1 mmol scale. Other oxidants such as DDQ, $Mn(OAc)_3 \cdot 2H_2O$ or TBHP did not provide improvement of yield.

Scheme 2. Scope of 7-Substituted Indoles[a]



[a] Reaction conditions: indoline (0.1 mmol), alkene (0.5 mmol), $(Cp^*RhCl_2)_2$ (5 mol %), $AgSbF_6$ (20 mol %), and anhydrous $Cu(OAc)_2$ (2.5 equiv) with *t*-AmOH (0.1 M) at 120 °C (the internal temperature of vial is 105 °C), after indolines completely disappeared, MnO_2 was added (30 equiv) to the reaction system, continue stirring at 120 °C for 8 h, total reaction times are given in Scheme 2. [b] 40 equiv MnO_2 used. [c] 20 equiv of MnO_2 used. PG = $CONEt_2$.

Having the optimized conditions in hand, we explored the scope and generality of this transformation. Initially, we checked the generality of alkenes. Coupling with methyl

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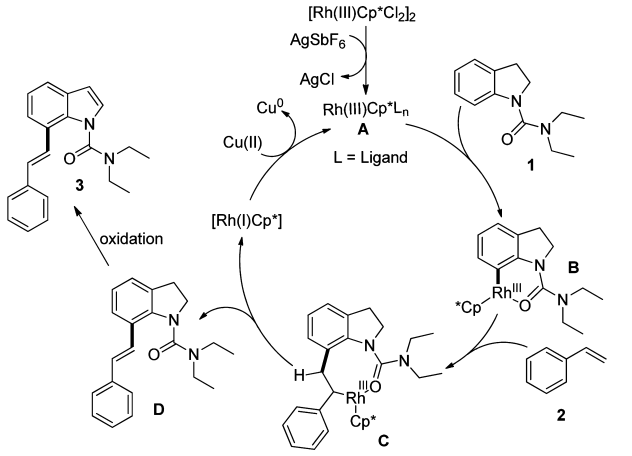
Scheme 3. Proposed Mechanism



acrylate (Scheme 2, **4e**) proceeds quickly under the developed reaction conditions and the desired indole was isolated with 54% yield. Then we examined the effect of substituents in different positions of the styrene. Halogen-containing styrenes provided the products in moderate to good yield (Scheme 2, **4f**–**j**). Electron-rich methoxystyrene provided the product in moderate yield (Scheme 2, **4k**). Coupling with *o*-methyl-substituted styrene gave the desired product with satisfactory yield (Scheme 2, **4l**). For phenyl-1,3-butadiene derivatives (Scheme 2, **4m**,**n**) we obtained the products with excellent regioselectivity and yield. Investigation on vinyl-substituted naphthalene provided excellent yield from 1-vinylnaphthalene (Scheme 2, **4p**), compared to the yield of 2-vinylnaphthalene (Scheme 2, **4o**). The scope of the reaction with respect to the indoline reactant has been also explored. Both electron-rich and -poor indoline substrates bearing various groups at different positions of the indoline ring participated well in the reaction, providing the corresponding 7-substituted indoles (Scheme 2, **4q**–**u**) with moderate to good yield.

A plausible mechanistic pathway for the synthesis of 7-substituted indoles was proposed via catalytic dehydrogenative cross-coupling and its subsequent oxidation (see Scheme 3). It has been postulated that $[Rh(III)Cp^*Cl_2]_2$ reacts with $AgSbF_6$ to generate a more active cationic species **A**. This active rhodium species could contain ligands such as acetate or solvent in addition to pentamethylcyclopentadienyl (Cp*) ligands. Rhodium species coordinate to the carbonyl oxygen of the diethyl carbamoyl group, and subsequent C(sp^2)–H bond activation via concerted metalation/deprotonation provided the five membered rhodacycle **B**. Insertion of olefin to the carbon–rhodium bond of **B** generated the seven-membered rhodacycle **C**. β-Hydride elimination of the intermediate **C** provided the desired product **D** with a rhodium(I) complex which could be further oxidized to the rhodium(III) complex by $Cu(OAc)_2$ to continue the catalytic cycle. Moreover, copper acetate could be the source of an acetate ligand for the active rhodium species.[12] In situ oxidation of **D** via addition of external oxidant afforded the crucial 7-substituted indoles.

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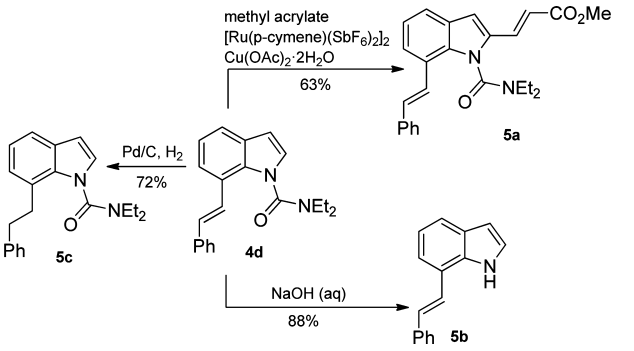
Scheme 4. Application of 7-Substituted Indoles



After developing the synthetic approach for synthesis of 7-substituted indoles, we tried to modify our product to demonstrate its further synthetic utility. Using a known method,[5j] we were able to alkenylate at the C-2 position of **4d** with a different olefin in 63% isolated yield (Scheme 4, **5a**). Hydrolysis of the directing group provided the 7-substituted indole **5b** in 88% isolated yield. After the hydrogenation of **4d** over palladium on charcoal, we obtained the 7-alkylated indole with 72% yield (Scheme 4, **5c**).

In summary, a novel, rhodium(III)-catalyzed, versatile regioselective olefination and its subsequent MnO_2-mediated one-pot oxidation strategy to access 7-substituted indoles has been developed. The desired products were formed in a highly regioselective manner. This methodology provides a broad substrate scope for 7-substituted indole scaffolds with good to excellent yield.

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Supporting Information Available. Experimental procedures, full characterization of new compounds, and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.