C–H Activation

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Rhodium-Catalyzed Regioselective C7-Functionalization of *N*-Pivaloylindoles

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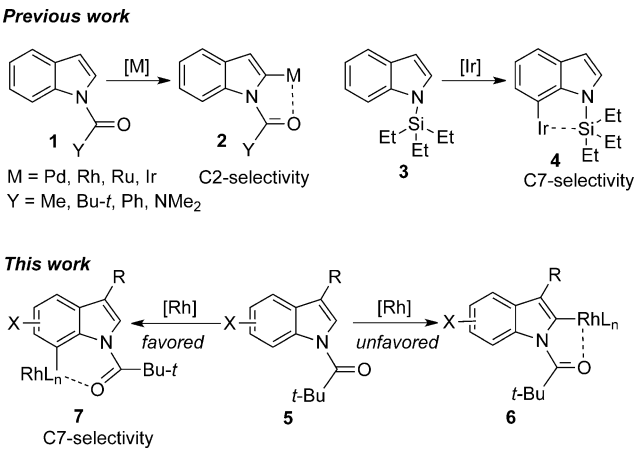
Abstract: *An efficient rhodium-catalyzed method for direct C–H functionalization at the C7 position of a wide range of indoles has been developed. Good to excellent yields of alkenylation products were observed with acrylates, styrenes, and vinyl phenyl sulfones, whereas the saturated alkylation products were obtained in good yield with α,β-unsaturated ketones. Both the N-pivaloyl directing group and the rhodium catalyst proved to be crucial for high regioselectivity and conversion.*

The indole ring system is one of the most ubiquitous heterocycles in nature and plays an essential role in medicinal chemistry.[1] Numerous studies have shown that diverse substituent patterns around the indole nucleus impart a wide range of interesting biological properties to these compounds,[2] and as a result, great effort has been made to develop synthetic methods for the direct functionalization of indoles over the past decades. To date, a number of approaches have been reported for the regioselective introduction of a functional group at the 2-, 3-, 5-, or 6-position of indoles.[3] However, selective direct functionalization at the 7-position remains challenging, owing to the inherently poor reactivity of this carbon center. Solutions to this problem are highly desirable as they would enable access to an important range of natural and unnatural products containing a 7-substituted indole moiety.[4]

In the last decade, substantial progress has been made in the field of transition-metal-catalyzed C–H bond functionalization, which has provided a general and straightforward approach for the assembly of substituted indoles.[5–8] On account of the higher electron density at the 2- and 3-positions, direct metal-catalyzed functionalization is possible at these positions even without the assistance of a directing group.[5b,9] When a directing group is introduced at the indole 1-position, C–H bond cleavage has been demonstrated to take place exclusively at the 2-position through the formation of a five-membered metallocycle **2** (Scheme 1).[5c,e,6k–m] For direct functionalization at the 7-position, two methods have been frequently used. One is to protect or block the indole 2-position,[8a,c,10] and the other is the use of indoline derivatives as alternative substrates.[11] Hartwig and co-workers described the first regioselective C7-functionalization, in which C–H bond cleavage gave a five-membered metallocycle **4** from *N*-silylindole **3**.[8b] During our studies on the synthesis of unnatural amino acid derivatives through direct C–H bond functionalization,[12] we discovered that regioselective 7-olefination of indoles could be promoted by tuning metal catalysts and using *N*-pivaloyl as a directing group. This unprecedented observation could be rationalized by a preference for the formation of a six-membered intermediate **7** over a five-membered intermediate **6** owing to the bulkiness of the *tert*-butyl group.



Scheme 1. Regioselectivity in the metal-catalyzed direct functionalization of N-protected indoles.

Initially, we used 1-acyl indoles **1a** as the substrate. The treatment of **1a** with methyl acrylate in the presence of $[\{Cp^*RhCl_2\}_2]$, $AgSbF_6$, and $Cu(OAc)_2{\cdot}H_2O$ gave the 2-olefination product **11a** and the 7-olefination product **9a** in 12 and 7% yield, respectively (Table 1, entry 1). This result prompted us to explore the possible determining factors for regioselectivity. We speculated that the size of the directing group might play an important role. To our delight, with larger acyl groups, higher selectivity for the 7-position and conversion were observed (Table 1, entries 1–4). With 1-pivaloylindole, **10a** and **12a** were obtained in 60% combined yield with 9:1 regioselectivity favoring C7-olefination (Table 1, entry 4). These results clearly demonstrated that the introduction of a bulky acyl group on the indole nitrogen

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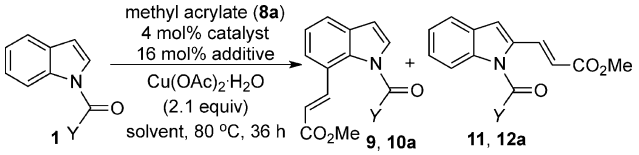
Table 1: Alkenylation of *N*-acyl indoles with methyl acrylate.[a]

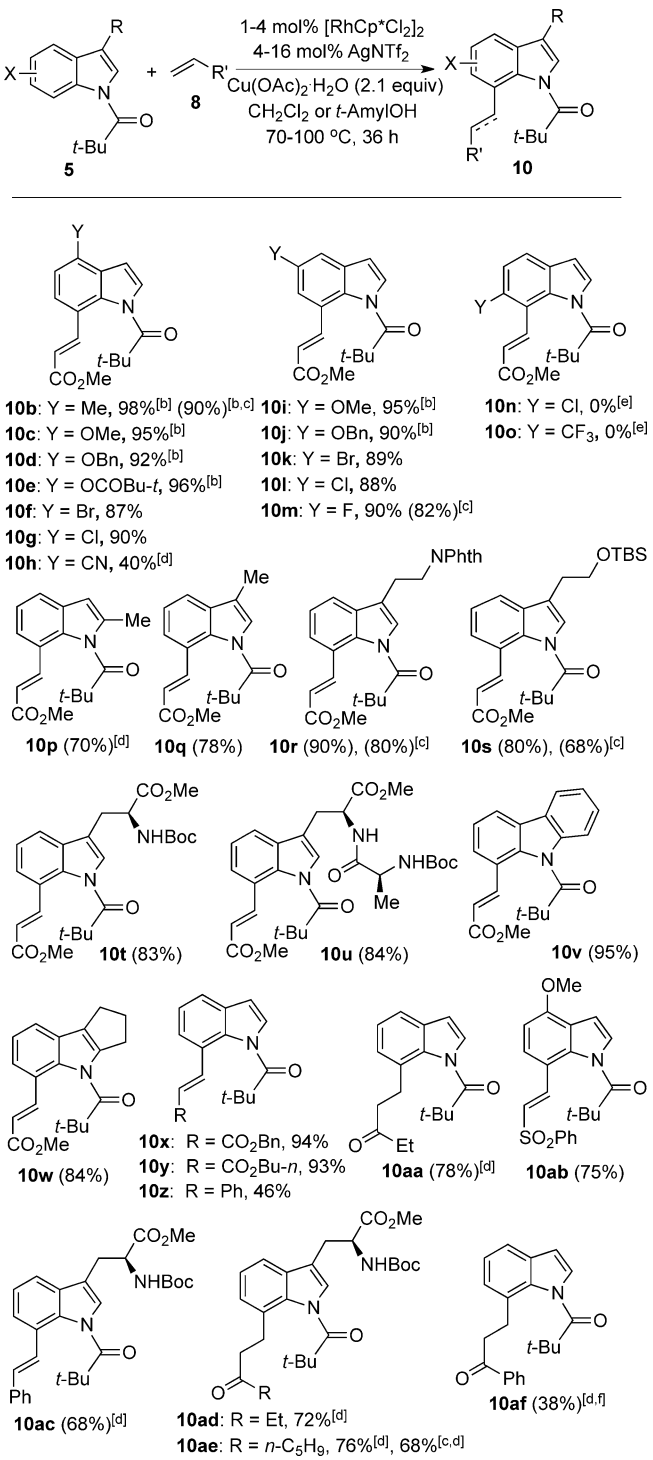


Entry	Y	Catalyst	Solvent	Product (yield [%])[b]
1	Me	[{Cp*RhCl$_2$}$_2$]	CH_2Cl_2	**9a** (7)/**11a** (12)
2	Et	[{Cp*RhCl$_2$}$_2$]	CH_2Cl_2	**9b** (9)/**11b** (14)
3	*i*Pr	[{Cp*RhCl$_2$}$_2$]	CH_2Cl_2	**9c** (15)/**11c** (20)
4	*t*Bu	[{Cp*RhCl$_2$}$_2$]	CH_2Cl_2	**10a** (54)/**12a** (6)
5	*t*Bu	[{Cp*RhCl$_2$}$_2$]	CH_2Cl_2	**10a** (92)/**12a** (3)
6	*t*Bu	[{Cp*IrCl$_2$}$_2$]	CH_2Cl_2	**10a** (28)/**12a** (3)
7	*t*Bu	[{Ru(*p*-cymene)Cl$_2$}$_2$]	CH_2Cl_2	**10a** (16)/**12a** (41)
8	*t*Bu	Pd(OAc)$_2$	CH_2Cl_2	**10a** (0)/**12a** (0)[c]
9	*t*Bu	[{Cp*RhCl$_2$}$_2$]	*t*AmOH	**10a** (94)/**12a** (3)
10	*t*Bu	[{Cp*RhCl$_2$}$_2$]	dioxane	**10a** (80)/**12a** (1)
11	*t*Bu	[{Cp*RhCl$_2$}$_2$]	$Cl(CH_2)_2Cl$	**10a** (64)/**12a** (1)
12	*t*Bu	[{Cp*RhCl$_2$}$_2$]	$C_6H_5CF_3$	**10a** (78)/**12a** (18)
13[d]	*t*Bu	[{Cp*RhCl$_2$}$_2$]	CH_2Cl_2	**10a** (70)/**12a** (7)
14[e]	*t*Bu	[{Cp*RhCl$_2$}$_2$]	CH_2Cl_2	**10a** (25)/**12a** (5)
15[f]	*t*Bu	[{Cp*RhCl$_2$}$_2$]	CH_2Cl_2	**10a** (13)/**12a** (3)

[a] Reaction conditions: **1** (0.2 mmol), **8a** (1.0 mmol), catalyst (4 mol%), $AgSbF_6$ (16 mol%; for entries 1–4) or $AgNTf_2$ (16 mol%; for entries 5–16), $Cu(OAc)_2{\cdot}H_2O$ (0.42 mmol), solvent (1.5 mL), 80°C, 36 h. [b] Yield of the isolated product. [c] The 3-alkenylation product was isolated in 30% yield. [d] AgOAc was used as the oxidant. [e] Ag_2CO_3 was used as the oxidant. [f] No oxidant was added. *t*-AmOH = 2-methyl-2-butanol, Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl.

atom not only facilitated C–H bond functionalization,[13] but also dramatically enhanced the regioselectivity. To improve the conversion, we tried different additives and were pleased to find that complete conversion occurred with 92:3 regioselectivity when $AgNTf_2$ was used in place of $AgSbF_6$ (Table 1, entry 5). Further screening revealed that metal catalysts also had a remarkable influence on both regioselectivity and conversion (Table 1, entries 5–8). When [{Cp*RhCl$_2$}$_2$] was exchanged for [{Cp*IrCl$_2$}$_2$], only slightly lower regioselectivity was observed, but much lower conversion (Table 1, entry 6). By contrast, [{Ru(*p*-cymene)Cl$_2$}$_2$] provided the 2-olefination product **12a** as the major regioisomer (Table 1, entry 7), whereas Pd(OAc)$_2$ delivered the 3-olefination product exclusively (entry 8). Among the solvents examined, 2-methyl-2-butanol gave a similar result (Table 1, entry 9), dioxane and 1,2-dichloroethane gave slightly better selectivity but significantly lower conversion (entry 10 and 11), and trifluoromethylbenzene led to significant decrease in both conversion and regioselectivity (entry 12). Furthermore, the use of $Cu(OAc)_2{\cdot}H_2O$ as an oxidant proved to be important for complete conversion (Table 1, entry 5 vs. entries 13–15).

Having optimized the reaction conditions, we next explored the scope of the reaction with respect to the substrates and functional-group tolerance. A series of indole derivatives with various substituents were subjected to olefination with methyl acrylate, and good to excellent yields were observed in most cases (Scheme 2). Generally, substrates with electron-donating groups at either the 4- or the 5-position gave the 7-olefination products with full



Scheme 2. C7-functionalization of *N*-pivaloylindoles. Reaction conditions: **5** (0.2 mmol), **8** (1.0 mmol), catalyst (4 mol%), $AgNTf_2$ (16 mol%), $Cu(OAc)_2{\cdot}H_2O$ (0.42 mmol), CH_2Cl_2 (1.5 mL), 80°C, 36 h. Yields are for the isolated product. [a] The reaction was conducted at 70°C in 2-methyl-2-butanol. [b] The reaction was conducted on a 1 mmol scale with 1 mol% of the catalyst and 4 mol% of $AgNTf_2$. [c] The reaction was conducted in CH_2Cl_2 at 100°C. [d] The corresponding 2-alkenylation product was isolated in about 50% yield. [e] 1-Pivaloylindole was recovered in 59% yield. Bn = benzyl, Phth = phthaloyl, TBS = *tert*-butyldimethylsilyl.

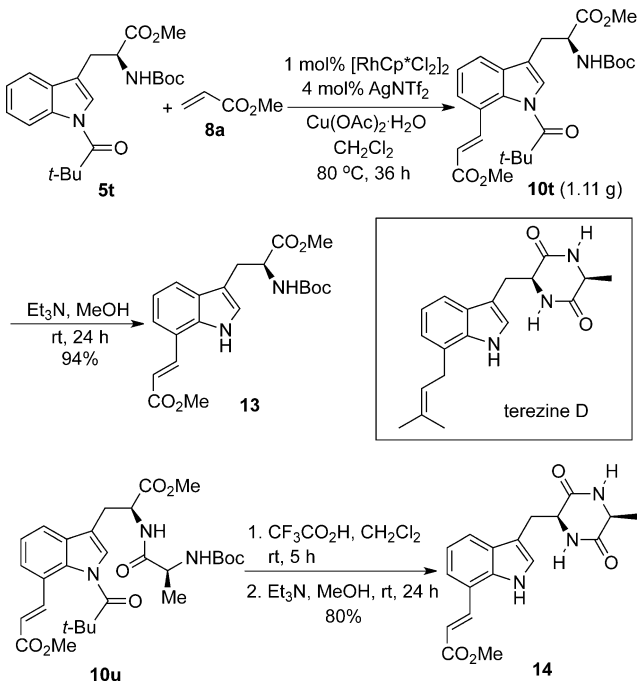
conversion and higher than 90% yield at 70°C in 2-methyl-2-butanol (products **10b–e**, **10i**, and **10j**). Those substrates with a halogen at either the 4- or the 5-position required 80°C in dichloromethane for full conversion, and again the desired products were obtained in excellent yield (products **10f**, **10g** and **10k–m**). In contrast, under similar conditions, substrates with an electron-withdrawing group reacted sluggishly, and the reaction did not proceed to completion. For example, the reaction of 4-cyano-1-pivaloylindole was slow even at 100°C, and the olefination product **10h** was obtained in only 40% yield. When 6-substituted indoles were used, the desired 7-olefination products **10n** and **10o** were not observed, but instead the corresponding 2-olefination products were isolated in about 50% yield. This result provides additional evidence that steric effects are important for the regioselectivity of the reaction.

Both the 2-methyl- and 3-methyl-substituted indoles were good substrates, and **10p** and **10q** were formed in good yield. More importantly, pharmaceutically useful compounds, such as tryptamine, tryptophol, and tryptophan derivatives, also reacted smoothly at the C7 position to provide **10r–u** in 68–90% yield. Direct functionalization of *N*-pivaloylcarbazole and an analogue also successfuly provided products **10v** and **10w** in 95 and 84% yield, respectively.

We also examined the scope of the reaction with respect to the alkene coupling partner. Benzyl and *n*-butyl acrylate reacted just as well as methyl acrylate to give the desired 7-olefination products **10x** and **10y** in 94 and 93% yield, respectively. Vinyl phenyl sulfone and even weakly activated styrene were compatible with this reaction, which delivered the corresponding alkenylation products **10z**, **10ab**, and **10ac** in good yield. Interestingly, the alkylation products **10aa**, **10ad–af** without an alkene double bond were obtained in 38–78% yield when α,β-unsaturated ketones were used. This result indicated that the coupling reaction might involve the protonolysis of an alkyl rhodium species, which might be generated by the insertion of the aryl rhodium intermediate into the C=C double bond. Similar phenomena have been observed in other metal-catalyzed C–H bond-activation studies with α,β-unsaturated ketones as the coupling partner.[7f,14]

Several reactions (to form **10b**, **10m**, **10r**, **10s**, and **10ae**) were scaled up successfully to a 1 mmol scale with only 1 mol% of the catalyst and 4 mol% of the additive. Complete conversion was still observed for all reactions, although the yields were slightly lower. To further demonstrate the robustness and utility of the method, we conducted a gram-scale reaction with the relatively complex tryptophan derivative **5t**. The desired product **10t** was isolated in 76% yield (Scheme 3).

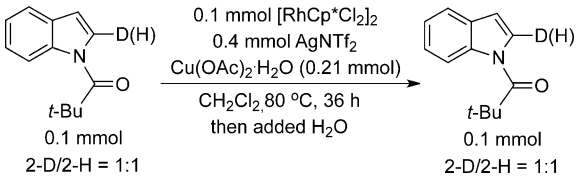
A remarkable aspect of the present method is that the directing group was readily removed under very mild conditions. The treatment of **10t** with triethylamine in methanol left the Boc group and methyl ester intact and provided the 7-functionalized tryptophan derivative **13** in 94% yield (Scheme 3). Compound **13** is potentially useful for the development of peptidomimetics for biological studies. On the other hand, the Boc protecting group in **10u** could be removed selectively with trifluoroacetic acid in the presence



Scheme 3. Deprotection of the alkenylation products.

of the pivaloyl group. The pivaloyl group of the resulting intermediate was then removed by Et_3N-mediated cleavage to afford the fully deprotected compound **14** in 80% overall yield. Compound **14** is a valuable building block for the synthesis of terezine D, an antifungal diketopiperazine alkaloid that was isolated from liquid cultures of the coprophilous fungus *Spwormiella teretispora*.[15]

We used deuterium labeling to gain evidence for the proposed mechanism (Scheme 1). A 1:1 mixture of 1-pivaloylindole and its 2-deuterated derivative was treated with a stoichiometric amount of the catalyst in the absence of an alkene, and then the reaction was quenched with water (Scheme 4). The H/D ratio at the 2-position of the recovered starting material was still 1:1, thus implying that intermediate **7** was produced exclusively during C–H bond activation.



Scheme 4. Deuterium-labeling test.

In conclusion, we have developed a highly efficient method for the rhodium-catalyzed, C7-selective functionalization of *N*-pivaloylindole derivatives. This protocol features low catalyst loading, mild reaction conditions, and compatibility with diverse functional groups, and provides a straightforward strategy for the introduction of a wide variety of side chains at the C7 position of indole derivatives.

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Keywords: alkenylation · C–H activation · homogeneous catalysis · indoles · rhodium

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