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Coupling Reactions

Ruthenium-Catalyzed Selective C–C Coupling of Allylic Alcohols with Free Indoles: Influence of the Metal Catalyst

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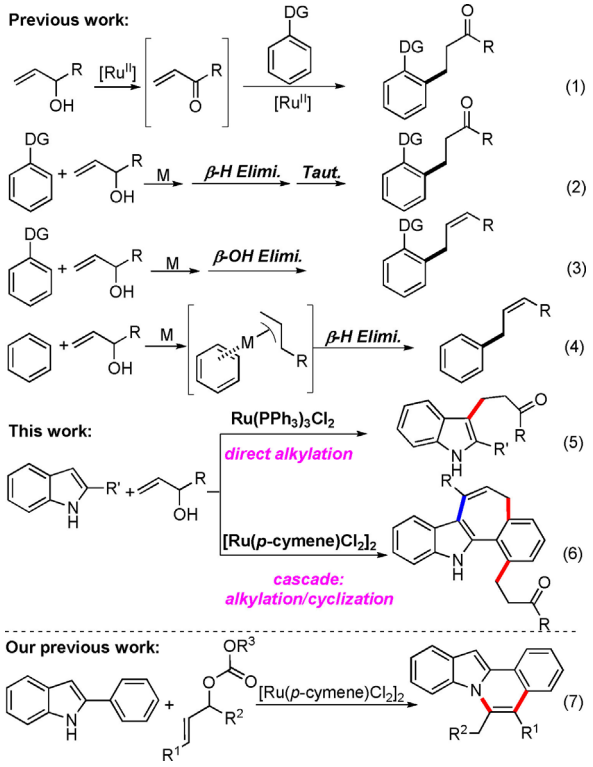
Abstract: Versatile reactive activities of allyl alcohols with free indoles in C–H functionalization reactions were investigated. Direct alkylation or cascade cyclization reactions could be selectively controlled based on the catalyst system: $Ru(PPh_3)_3Cl_2$ provided C3-substituted β-ketone indoles whereas $[Ru(p\text{-cymene})Cl_2]_2$ yielded cyclized indoles.

Indole and many indole derivatives are currently explored as privileged structures present in a large number of pharmaceuticals and biologically active compounds.[1] Among them, C3-substituted indoles as important precursors have drawn the most attention.[2] With the rapid development of transition-metal-catalyzed C–H activation in the past decade,[3] many groups made significant contributions to functionalize the 3-position of the indole structures through C–H alkenylation, arylation, and alkylation reactions.[4] Owing to the continuing increased interest in this field, the development of simple, efficient, selective synthetic approaches for the preparation of C3-substituted indole derivatives are still highly desirable.

In recent years, allyl alcohols have been widely employed as coupling partners in C–H functionalization reactions.[5–10] For example, complex alkylation compounds could be obtained via the oxidation of allylic alcohols to enones by transition metal catalysts at the first step [Scheme 1, Eq. (1)].[6,7] Glorius, Jiang, and others independently developed C–H bond oxidative alkylation with allylic alcohols to afford the functional β-aryl ketones through the β-hydride elimination and keto–enol tautomerism pathway [Scheme 1, Eq. (2)].[8] Recently, metal-catalyzed direct dehydrative C–H allylation with allyl alcohols via β-hydroxide elimination providing allylic alkylation products were reported [Scheme 1, Eq. (3)].[8e,9] Allylic alkylation products could also be obtained through η^3-allyl dication pathway without the chelation assistance [Scheme 1, Eq. (4)].[10] However, to our knowledge, non-activated free-allyl alcohols have rarely been applied to the ruthenium-catalyzed selective C–H functionalization of free indoles. Herein we describe a catalyst-controlled strategy to access various C3-selective substituted indoles from free indoles and allylic alcohols, in which the selectivity of direct C3 alkylation [Scheme 1, Eq. (5)] or cascade cyclization [Scheme 1, Eq. (6)] is dependent on the particular catalyst. These products were different from the C–N cyclization products (annulation of 2-phenyl indoles with allyl carbonates) shown in our previous work [Scheme 1, Eq. (7)].[11]



Scheme 1. Transition-metal-catalyzed C–H activation with allylic alcohol coupling partners.

Our investigation was initiated by examining the selective coupling reactions between 2-phenyl indole **1a** and but-3-en-2-ol **2a** (Table 1). To our delight, C3-substituted β-ketone indole **3aa** could be isolated in 43% yield by using $Ru(PPh_3)_3Cl_2$ as the catalyst in the presence of $Cu(OAc)_2{\cdot}H_2O$ as oxidant (entry 1). In addition, we obtained a reasonable yield of **3aa** when AgOAc was employed (entries 2–5). Other oxidants such as $Cu(OAc)_2$, $Cu(acac)_2$ and CuOAc led to detrimental effects (entries 6–8). Notably, DCE is a suitable solvent in the oxidative alkylation reaction (entries 9–12). Satisfyingly, the yield of **3aa** could be dramatically improved by adding base to the reaction system (entries 13–15). To our surprise, when

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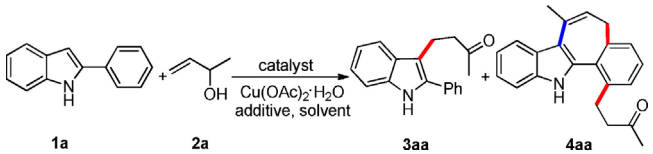
Table 1. Reaction optimization.[a]



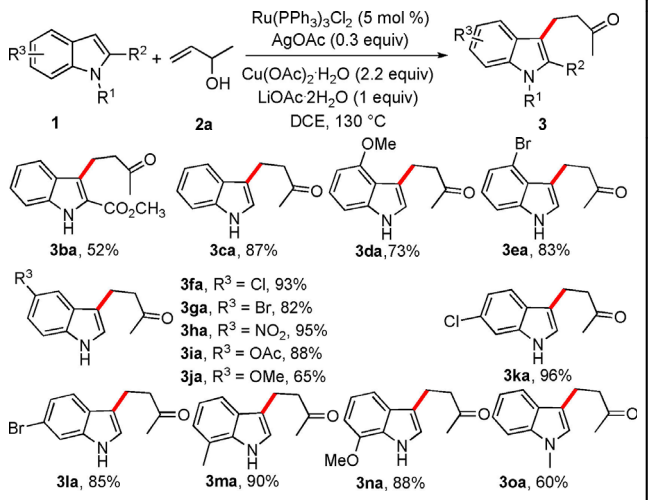
Entry	Catalyst	Additive (equiv)	Solvent	Yield [%][b] 3aa	4aa
1	$Ru(PPh_3)_3Cl_2$	–	DCE	43	–
2	$Ru(PPh_3)_3Cl_2$	AgOAc	DCE	65	–
3	$Ru(PPh_3)_3Cl_2$	$AgSbF_6$	DCE	20	–
4	$Ru(PPh_3)_3Cl_2$	$AgBF_4$	DCE	27	–
5	$Ru(PPh_3)_3Cl_2$	$AgNTf_2$	DCE	17	–
6[c]	$Ru(PPh_3)_3Cl_2$	AgOAc	DCE	60	–
7[d]	$Ru(PPh_3)_3Cl_2$	AgOAc	DCE	–	–
8[e]	$Ru(PPh_3)_3Cl_2$	AgOAc	DCE	–	–
9	$Ru(PPh_3)_3Cl_2$	AgOAc	toluene	36	–
10	$Ru(PPh_3)_3Cl_2$	AgOAc	dioxane	10	–
11	$Ru(PPh_3)_3Cl_2$	AgOAc	CH_3CN	15	–
12	$Ru(PPh_3)_3Cl_2$	AgOAc	CH_3OH	13	–
13	$Ru(PPh_3)_3Cl_2$	AgOAc + AcOH (1)	DCE	57	–
14	$Ru(PPh_3)_3Cl_2$	AgOAc + NaOAc (1)	DCE	76	–
15	$Ru(PPh_3)_3Cl_2$	AgOAc + $LiOAc{\cdot}2H_2O$ (1)	DCE	92	–
16	$[Ru(p\text{-cymene})Cl_2]_2$	–	DCE	–	32
17	$[Ru(p\text{-cymene})Cl_2]_2$	AgOAc	DCE	–	43
18	$[Ru(p\text{-cymene})Cl_2]_2$	$AgSbF_6$	DCE	–	20
19	$[Ru(p\text{-cymene})Cl_2]_2$	$AgBF_4$	DCE	–	–
20	$[Ru(p\text{-cymene})Cl_2]_2$	$AgNTf_2$	DCE	–	17
21	$[Ru(p\text{-cymene})Cl_2]_2$	AgOAc	toluene	–	36
22	$[Ru(p\text{-cymene})Cl_2]_2$	AgOAc	dioxane	–	24
23	$[Ru(p\text{-cymene})Cl_2]_2$	AgOAc	CH_3CN	–	15
24	$[Ru(p\text{-cymene})Cl_2]_2$	AgOAc	TFE	–	0
25	$[Ru(p\text{-cymene})Cl_2]_2$	AgOAc + AcOH (1)	DCE	–	36
26	$[Ru(p\text{-cymene})Cl_2]_2$	AgOAc + NaOAc (1)	DCE	–	44
27[f]	$[Ru(p\text{-cymene})Cl_2]_2$	AgOAc	DCE	–	58
28[g,f]	$[Ru(p\text{-cymene})Cl_2]_2$	AgOAc	DCE		60
29[h]	$Ru(PPh_3)_3Cl_2$	AgOAc + $LiOAc{\cdot}2H_2O$ (1)	DCE	90	–
30[f,g,h]	$[Ru(p\text{-cymene})Cl_2]_2$	AgOAc	DCE	–	55

[a] Reaction conditions: unless otherwise specified, 0.05 mmol of **1a**, 5.0 equiv **2a**, 2.2 equiv $Cu(OAc)_2{\cdot}H_2O$, 5 mol% of catalyst,0.3 equiv silver salt, 0.5 mL of solvent, 130 °C, 48 h, Ar atmosphere. [b] Isolated yield. [c] $Cu(OAc)_2$ (2.2 equiv). [d] $Cu(acac)_2$ (2.2 equiv). [e] CuOAc (2.2 equiv). [f] $Cu(OAc)_2{\cdot}H_2O$ (3.2 equiv). [g] 100 °C. [h] 0.5 mmol of **1a**.

$[Ru(p\text{-cymene})Cl_2]_2$ was used as the catalyst, cascade cyclization product **4aa** was detected as the sole product. In contrast, we only obtained single C–N cyclization products by using allyl carbonates as coupling partners (entry 16).[11] Additives screening revealed that AgOAc could still promote the cyclization reaction (entries 17–20). However, other solvents gave poorer results (entries 21–24). AcOH or NaOAc had a crucial effect on the efficiency of this cascade reaction (entries 25 and 26). Increasing loading of $Cu(OAc)_2{\cdot}H_2O$ improved the catalytic activity to afford the desired seven-membered-ring product **4aa** in moderate yield (entry 27). Decreasing the temperature to 100 °C could slightly increase the yield of **4aa** (entry 28). The reaction could be performed smoothly on a large scale to generate corresponding products in satisfying yields (entries 29 and 30). Significantly, the conditions are controllable in all cases, in which C3 alkylation or cyclization products can be selectively obtained. However, lowering the loading of **2a**, further decreasing the reaction temperature, or reducing the reaction time could slightly decrease the yield of **3aa** and **4aa**. Compounds **3aa** or **4aa** could not be detected in the absence of $Cu(OAc)_2{\cdot}H_2O$.[12]

With the optimized reaction conditions in hand, we first explored the scope of indoles **1** with allylic alcohols **2a** in direct C3 alkylations (Table 2). C2-ester substituted indole **1b** was a suitable substrate but furnished **3ba** in only 52% yield, probably owing to electronic effects. Free indole **1c** could also react well with **2a**. Satisfactory, indoles with various electron-withdrawing or electron-donating groups on the phenyl ring proceeded smoothly to give corresponding alkylation products (**3da**–**3na**) in good-to-excellent yields. It is worth noting that the catalytic systems have good tolerance to strong electron-withdrawing groups (nitro) and highly active halogen (bromo and chloro) groups. *N*-methyl substituted indoles could also efficiently participate in the reaction, giving **3oa** in 60% yield.

Table 2. The scope of indoles used in direct C3 alkylations.[a]

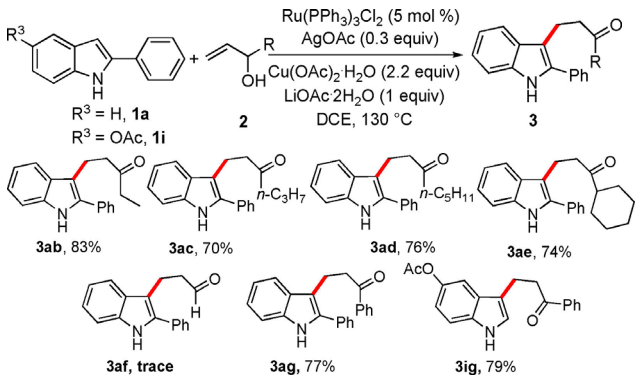


[a] Reaction conditions unless otherwise specified: 0.1 mmol of **1**, 5.0 equiv **2a**, 5 mol% $Ru(PPh_3)_3Cl_2$, 2.2 equiv $Cu(OAc)_2{\cdot}H_2O$, 0.3 equiv AgOAc, 1.0 equiv $LiOAc{\cdot}2H_2O$, 1.0 mL of DCE, 130 °C, 48 h, under Ar atmosphere. Isolated yield.

We then investigated the scope of substituted allylic alcohols with 2-phenyl indoles under $Ru(PPh_3)_3Cl_2$ catalytic conditions (Table 3). To our delight, the coupling of linear or cyclic α-alkyl substituted allylic alcohols **2b**–**2e** with **1a** was smooth, generating β-aryl ketones **3ab**-**3ae** as the single direct alkylation products in good yields. However, primary alcohol **2f** did not undergo coupling under these conditions. Moreover, α-aryl substituted allylic alcohol **2g** could also participate smoothly with **1a** and **1i** in the reaction to yield the corresponding products **3ag** and **3ig** in good yields.

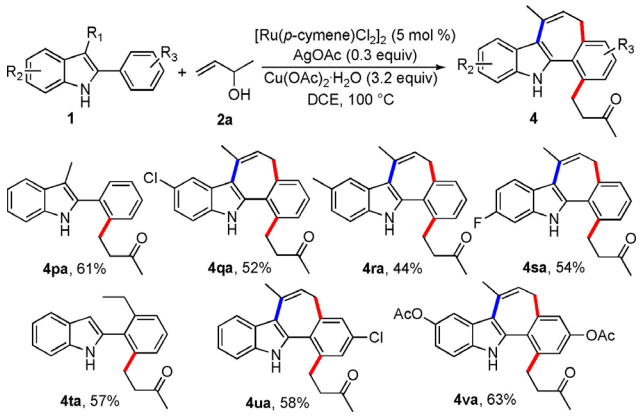
We next evaluated the scope of 2-phenyl indoles with **2a** in the cascade cyclization reaction under the $[Ru(p\text{-cymene})Cl_2]_2$ catalytic system (Table 4). When the C3-position of the indole ring has a methyl group, only a single-substituted oxidative alkylation product **4pa** was obtained. Formation of **4pa** indi-

Table 3. Substrate scope of allylic alcohols in direct C3 alkylations.[a]



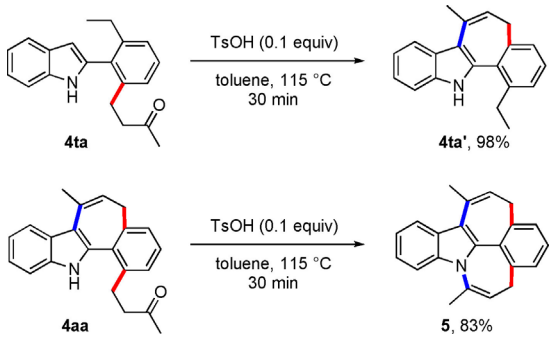
[a] Reaction conditions unless otherwise specified: 0.1 mmol of **1a**, 5.0 equiv **2**, 5 mol% of $Ru(PPh_3)_3Cl_2$, 2.2 equiv $Cu(OAc)_2{\cdot}H_2O$, 0.3 equiv AgOAc, 1.0 equiv $LiOAc{\cdot}2H_2O$, 1.0 mL of DCE, 130 °C, 48 h, under Ar atmosphere. Isolated yield.

Table 4. The scope of indoles in cascade reactions.[a]



[a] Reaction conditions unless otherwise specified: 0.1 mmol of **1**, 5.0 equiv **2a**, 5 mol% of $[Ru(p\text{-cymene})Cl_2]_2$, 3.2 equiv $Cu(OAc)_2{\cdot}H_2O$, 0.3 equiv AgOAc, 1.0 mL of DCE, 100 °C, 48 h, under Ar atmosphere. Isolated yield.

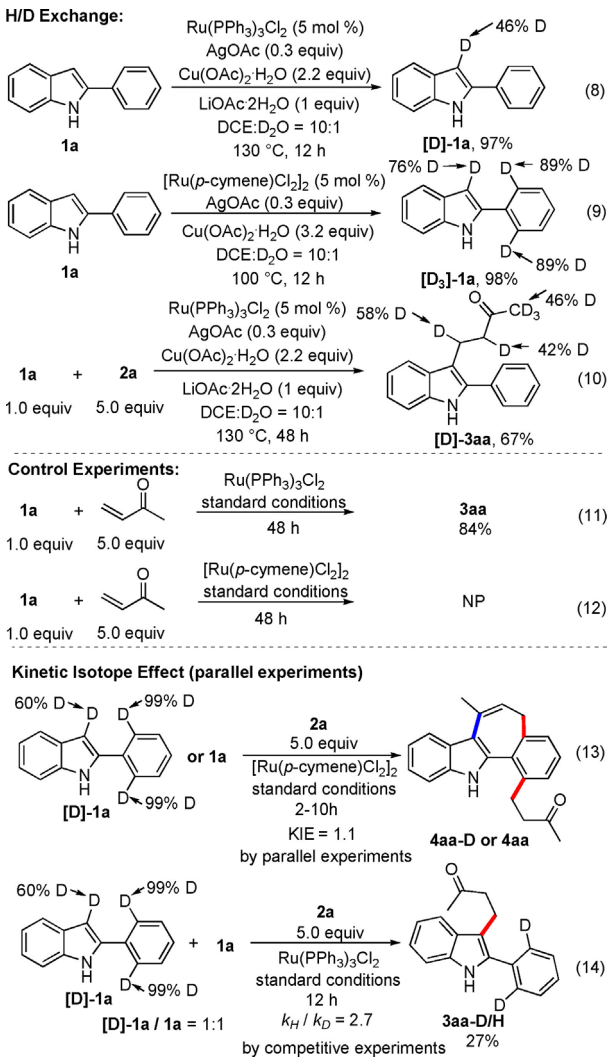
cates that dearomatization does not occur in preference to the formation of heterocycles, and construction of carbocycles is more favorable than heterocycles. The cascade reactions worked well for the groups on the phenyl ring of indole skeletons (**1q**–**1s**). However, when *ortho*-ethyl-substituted substrate **1t** was used, only single-substituted alkylation product **4ta** was isolated and no cyclization product was observed, probably owing to the influence of steric hindrance. Conversely, direct cyclization of **4ta** with TsOH could give the C–C bond formation product **4ta′** in 98% yield (Scheme 2). The substrates bearing different substituents at the *para* positions of the phenyl ring were tolerated in the catalyst systems (**1u** and **1v**). However, when the methyl group of allylic alcohol was changed to other substituents, such as H, phenyl, and cyclohexyl, no desired product was obtained. Surprisingly, the cyclization product **4aa** could be further converted into the quite



Scheme 2. Synthetic applications of compounds **4ta** and **4aa**.

unique fused heterocyclic compound **5** in 83% yield via nucleophillic addition and cyclization (Scheme 2).

Subsequently, experiments were carried out to further investigate the catalytic mechanism (Scheme 3). When **1a** was conducted in DCE/D_2O in the absence of **2a** by using $Ru(PPh_3)_3Cl_2$ as the catalyst, deuterium was observed by NMR spectroscopy only at the C3-position of indole, which indicated that the alky-



Scheme 3. Preliminary mechanistic investigations.

lation is a direct C–H bond activation without chelation assistance [Scheme 3, Eq. (8)]. In contrast, *ortho*-positions of the phenyl ring were observed with 89% deuterium, which implies that the cascade cyclization underwent coordination of nitrogen [Scheme 3, Eq. (9)]. Deuteration at the α-position of carbonyl groups was observed, which might proceed by deuteration through keto–enol tautomerization [Scheme 3, Eq. (10)].[5e,8c,e] The reaction of **1a** with but-3-en-2-one could be conducted smoothly when $Ru(PPh_3)_3Cl_2$ was used as the catalyst, which implies that the oxidation of allylic alcohols to enones by $Ru(PPh_3)_3Cl_2$ at the first step is likely to occur.[7] However, the reaction was dramatically affected in the absence of $Cu(OAc)_2{\cdot}H_2O$,[12] which indicates that oxidant is very important in the catalytic system and the β-hydride elimination pathway might also exist [Scheme 3, Eq. (11)].[8] On the contrary, the reaction was very non-selective when **1a** was reacted directly with but-3-en-2-one in the $[Ru(p\text{-cymene})Cl_2]_2$ catalytic conditions, which implies that the reaction does not proceed through oxidation of allylic alcohols to enones [Scheme 3, Eq. (12)]. The deuterium kinetic isotopic effects were determined to be 1.1 and 2.7 in the $Ru(PPh_3)_3Cl_2$ and $[Ru(p\text{-cymene})Cl_2]_2$ catalytic conditions, respectively, which indicates that C–H bond cleavage might be involved in the rate-determining step [Scheme 3, Eqs. (13) and (14)].[12]

A plausible mechanism is proposed in Scheme 4. Under the $[Ru(p\text{-cymene})Cl_2]_2$ catalyst system (the cascade cyclization), ruthenium coordinates to the nitrogen and followed by C–H bond activation forms the Ru^{II} complex intermediate **I** in the first step. Then olefin insertion yields seven-membered complex **II**, which then undergoes β-H elimination and keto–enol tautomerism pathway to give alkylation intermediate **III** and a Ru^0 species; the latter is reoxidized by Cu^{II} to complete the catalytic cycle. Subsequently, the second alkylation process occurs to generate intermediate **IV**. Finally, dehydrative cyclization furnishes the final annulation product **4aa**.[13]

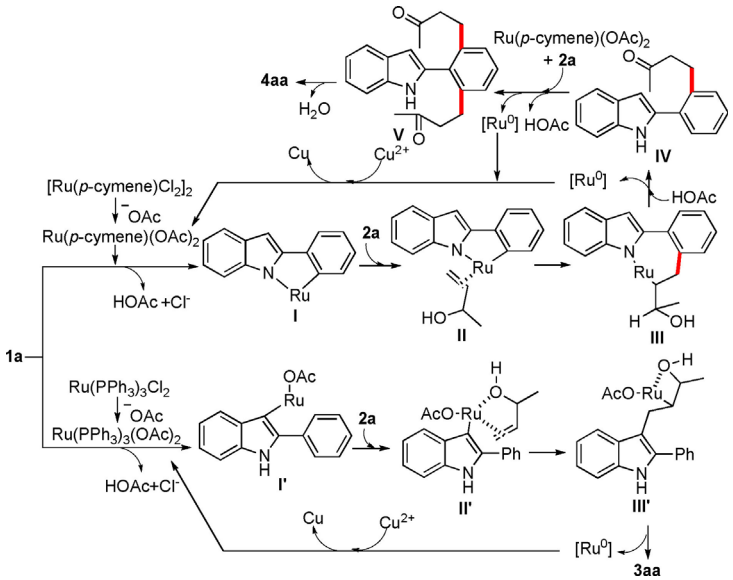
Under the $Ru(PPh_3)_3Cl_2$ catalyst system (direct C3 alkylation), the ruthenium catalyst first inserts into C(3)-H of an indole to form complex **I′**, which could be stabilized by oxygen and adjacent system to afford intermediate **II′**. Then intermediate **II′** undergoes olefin insertion to give ruthenium species **III′**. Finally, β-H elimination forms alkylation product **3aa**. However, the allylic alcohol **2a** converting into α,β-unsaturated enone in the presence of the ruthenium catalyst at the first step might be also possible, which is similar to Equation (1), Scheme 1.[7]

In summary, we have realized ruthenium(II)-catalyzed selective C–C coupling of allylic alcohols with free indoles for the synthesis of diverse C3-substituted indole derivatives. $Ru(PPh_3)_3Cl_2$ provides C3-substituted β-ketone indoles and $[Ru(p\text{-cymene})Cl_2]_2$ yields 5,12-dihydrobenzo[6,7] cyclohepta [1,2-*b*] indoles. The selective pathway may be attributed the difference in binding affinity of a metal center with but-3-en-2-ol. The presented conversions extend the diversity of heterocyclic scaffolds accessible from 2-phenyl indoles with allyl carbonates as shown previously.[11] Given the iniquitousness of the indoles, the reactions may find broader applications in the synthesis of related useful products.

Experimental Section

General procedure for synthesis of the C3-substituted β-ketone indoles: 2-Phenyl indole **1a** (0.05 mmol, 9.7 mg), but-3-en-2-ol **2a** (5.0 equiv, 22 μL), $Ru(PPh_3)_3Cl_2$ (5 mol%, 2.4 mg), AgOAc (0.3 equiv, 2.5 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.2 equiv, 22 mg) and $LiOAc{\cdot}2H_2O$ (1.0 equiv, 5.1 mg) were stirred in DCE (0.5 mL) at 130 °C for 48 h under Ar atmosphere. After completion, the reaction mixture was purified by flash chromatography eluting with petroleum ether and ethyl acetate (PE/EA = 100:1) to give the product **3aa** as yellow liquid (12.1 mg, 92%).

General procedure for synthesis of the annulated 2-phenyl indoles: 2-Phenyl indole **1a** (0.05 mmol, 9.7 mg), but-3-en-2-ol **2a** (5.0 equiv, 22 μL), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%, 1.5 mg), AgOAc (0.3 equiv, 2.5 mg) and $Cu(OAc)_2{\cdot}H_2O$ (3.2 equiv, 32 mg) were stirred in DCE (0.5 mL) at 100 °C for 48 h under Ar atmosphere. After completion, the reaction mixture purified by flash chromatography eluting with petroleum ether and ethyl acetate (PE/EA = 100:1) to give the product **4aa** as yellow liquid (9.5 mg, 60%).



Scheme 4. Plausible reaction mechanism.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: allylic alcohols · free indoles · ruthenium · selective C–C coupling · β-ketone indoles

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Coupling Reactions

*Y.-Q. Xia, C. Li, M. Liu, L. Dong**

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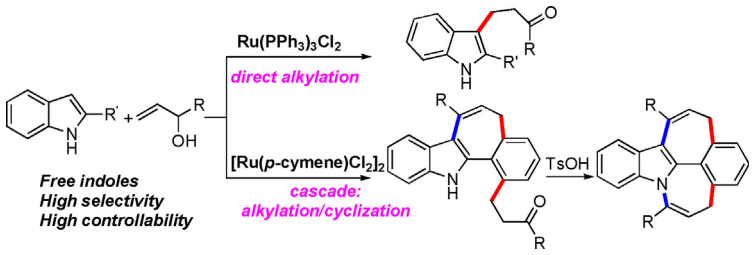
Ruthenium-Catalyzed Selective C–C Coupling of Allylic Alcohols with Free Indoles: Influence of the Metal Catalyst



R u C′ing this? Versatile reactive activities of allyl alcohols with free indoles in C–H functionalization reactions were investigated. Direct alkylation or cascade cyclization reactions were selectively controlled based on the particular catalyst system: $Ru(PPh_3)_3Cl_2$ provided C3-substituted β-ketone indoles, whereas $[Ru(p\text{-cymene})Cl_2]_2$ gave cyclized indoles.