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Rh(III)-Catalyzed Tandem C−H Allylation and Oxidative Cyclization of Anilides: A New Entry to Indoles

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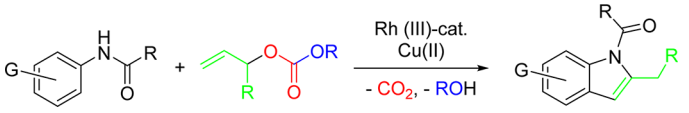
ABSTRACT



Rh^{III}-catalyzed tandem C−H allylation and oxidative cyclization of anilides with allyl carbonates in the presence of a slight excess of $AgSbF_6$ salt and $Cu(OAc)_2$ as oxidant affords easy, economical access to important bioactive 2-methylindoles. The new reaction supports a wide range of functional groups on the anilide substrate. A possible mechanism is proposed as a basis for its rational further development.

Indoles form a part of numerous bioactive natural products, pharmaceuticals, and organic materials[1] and have consequently attracted the continued interest of synthetic chemists for many years.[2] Prominent among methods developed for their preparation in recent decades have been transition-metal-catalyzed processes.[3] Originally, most of these catalytic approaches, such as the Larock[4] synthesis, required an *ortho*-disubstituted arene, which increased their overall complexity and reduced their overall atom economy. Recently, catalytic approaches involving monofunctionalized materials (typically, aniline derivatives), and cyclization to an unactivated C−H, have emerged as more efficient alternatives (Scheme 1).[5] Two general strategies have been successfully employed: (a) oxidative cyclization of enamines (path A)[6] and Yoshikai's imines[7] and Hartwig's oximes oxidative cyclizations[8] by formation of C−C or C−N bonds; and (b) the oxidative coupling of *N*-acetyl[9] or 2-pyrimidinyl anilines,[10] or of

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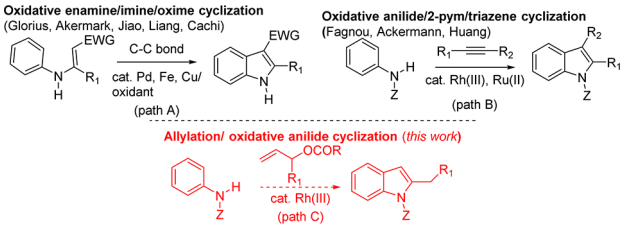
triazenyl arenes,[11] to internal alkynes (path B). Herein we describe a new strategy based on Rh-catalyzed tandem allylation and oxidative cyclization[12,13] of anilides[14] with allyl carbonates. This approach allows the synthesis of indoles with substituents at position 2 but not position 3 and is, thus, equivalent to an oxidative cyclization with *terminal* alkynes (path C, Scheme 1).

Scheme 1. General Catalytic Synthetic Strategies to Indoles Based on C−H Functionalization



We initiated our study by examining the cyclization of *N*-phenylacetamide (**1a**) with allyl methyl carbonate (**2a**) in DCE at 120 °C, using 1:2.5 [{Cp*$RhCl_2$}$_2$]/$AgSbF_6$ as the catalyst system and $Cu(OAc)_2 \cdot H_2O$ (2.1 equiv) as the oxidant (Table 1). To our delight, *N*-acetyl-2-methylindole (**3a**) was smoothly obtained in 66% yield after 20 h (entry 1). At 80 °C a lower yield of **3a** was obtained with a longer reaction time (entry 2), but the observation of a small amount of *N*-(2-allylphenyl)acetamide (**4a**)[15] (GCMS, ^{1}H NMR) was taken as indicating that the probable reaction course involves C−H bond allylation followed by oxidative cyclization. Screening of a range of solvents identified the tertiary alcohols *t*-BuOH and *tert*-amyl alcohol as the most appropriate, with yields of up to 82% being obtained at 120 °C (entries 3−7). The yield was lower using $AgBF_4$ instead of $AgSbF_6$ for chloride removal (entry 8), but was less sensitive to replacement of [{Cp*$RhCl_2$}$_2$]/$AgSbF_6$ by [Cp*Rh(CH_3CN)$_3$]SbF_6 as the catalyst system (entry 9).[16] By contrast, replacement of $Cu(OAc)_2 \cdot H_2O$ by AgOAc as the oxidant prevented the reaction (entry 10). Although allyl alcohol and allyl chloride showed no reactivity, allyl *tert*-butyl carbonate, allyl diethyl phosphate, allyl acetate, and allyl benzoate all afforded **3a**, albeit in lower yields than allyl methyl carbonate (entries 11−14). Interestingly, as the R group of **1** increased in size from methyl to *tert*-butyl, the yield of **3** decreased and that of **4** increased (entries 7 and 15−17). More expected was the detrimental effect of attenuating the Lewis basicity of the amide oxygen with a strongly electron-withdrawing group (entry 18). Rather surprisingly, increasing the starting concentration of **1a** to 0.2 M, as appears to be standard for similar Rh^{III}-catalyzed reactions,[9,12] reduced the yield of indole **3a** to ∼50% (entry 19), which may perhaps indicate partial inhibition of the catalyst by the product.[17]

With the optimized procedure in hand, our attention turned to evaluating the scope and limitations of the reaction. Given the importance of the 2-methyl substituent in bioactive indoles,[18] we initially assessed the reactions of variously substituted acetanilides with allyl carbonate **2a** (Table 2). The reaction conditions optimized for **1a** also supported the tandem C−H allylation and oxidative cyclization of a variety of *para*-substituted acetanilides, affording *N*-acetyl-2-methylindoles **3b**−**h** in yields of 40−76%. Notably, better indole yields were found when electron-rich (**1b,c**) rather than electron-poor anilides (**1d**−**1h**) were employed; the latter substituents were valuable functional groups amenable for further decoration of the corresponding indoles **3d**−**h**.

The reaction of the benzannulated anilide **1i** was regioselective, affording the linear naphthylindole **3i** in fairly good yield. The regioselectivity for the less-hindered C−H bond was also excellent with *meta*-substituted anilides when electron-poor (**1j**−**l**), or when the substituent lacked a coordinating atom (**1m**), but not when the *meta*-substituent of an electron-rich anilide did contain a coordinating atom (**1n**). However, activation of the less-hindered C−H was reinforced by the additional presence of a second methoxy group in the *para* position, with acetanilide **1o** giving indole **3o** as the sole product.

Gratifyingly, dicyclization of the *meta*-diacetanilide **1p** (R^2 = NHCOMe) readily provided the fused *bis*-indole **3p** in 42% yield with excellent regioselectivity for the linear product. No conventional method affords the corresponding *bis*-indoles with such ease. Interestingly, this

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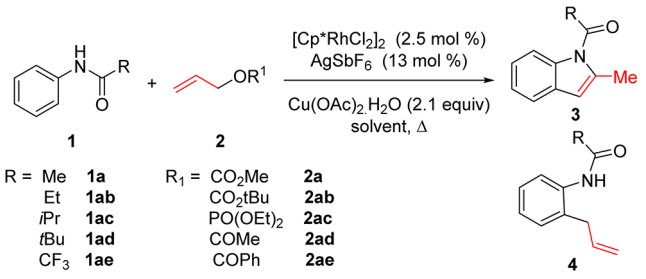
Table 1. Reaction Optimization[a]



entry	anilide	allyl source	solvent	temp (°C)	t (h)	yield of **3** (%)[b]
1	**1a**	**2a**	DCE	120	20	66
2	**1a**	**2a**	DCE	80	30	44[c]
3	**1a**	**2a**	DCM	75	24	46
4	**1a**	**2a**	THF	105	24	58
5	**1a**	**2a**	toluene	120	24	57
6	**1a**	**2a**	^{t}BuOH	130	24	75
7	**1a**	**2a**	^{t}AmOH	120	24	82
8[d]	**1a**	**2a**	^{t}AmOH	120	24	56
9[e]	**1a**	**2a**	^{t}AmOH	120	15	75
10[f]	**1a**	**2a**	^{t}AmOH	120	24	-
11	**1a**	**2ab**	^{t}AmOH	120	24	47
12	**1a**	**2ac**	^{t}AmOH	120	24	49
13	**1a**	**2ad**	^{t}AmOH	120	24	68
14	**1a**	**2ae**	^{t}AmOH	120	24	32
15	**1ab**	**2a**	^{t}AmOH	120	24	63
16	**1ac**	**2a**	^{t}AmOH	120	24	38
17	**1ad**	**2a**	^{t}AmOH	120	24	59[g]
18	**1ae**	**2a**	^{t}AmOH	120	24	–
19	**1a**	**2a**	^{t}AmOH	120	24	51[h]

[a] Typical conditions: **1**, 0.37 mmol; **2**, 0.41 mmol; [**1**] = 0.074 M. [b] Isolated yields. [c] ^{1}H NMR showed a small amount (< 5%) of **4a**. [d] Additive: $AgBF_4$ (13 mol %). [e] Catalyst: $[Cp^*Rh(CH_3CN)_3]SbF_6$ (5 mol %). [f] Oxidant: AgOAc (2.1 equiv). [g] Isolated yield of 2-allyl amide **4ad** and its 2-propenyl isomer **4ad′** (isomer ratio 10:1). [h] Conditions: **1a**, 0.37 mmol; **2a**, 0.41 mmol; [**1a**] = 0.2 M in t-AmOH (1.85 mL), 120 °C.

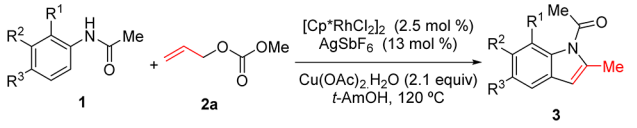
regioselectivity, attributable to activation of the two less-hindered C−H bonds, contrasts with the regioselectivity for the angular product that is found in the oxidative cyclization of the analogous *meta*-diimines.[7]

Not unexpectedly, the *ortho*-susbtituted acetanilides **1q**−**s** were significatively less reactive than **1a**−**p**, giving indoles **3q**−**s** in only low yields.[19]

The new reaction proved to be less versatile as regards the allyl partner. Anilide **1a** underwent no reaction whatsoever with internal and *Z*-substituted allyl carbonates such as 2-methylallyl or *Z*-2-pentenyl methyl carbonates (**2e,f**), and with their branched isomers, 1-methyl-2-propenyl methyl carbonate (**2b**) and 1-ethyl-2-propenyl methyl carbonate (**2c**) afforded only low yields of the 2-alkylindoles **3t** and **3u** (Scheme 2, eq 1). However, useful mechanistic information emerged when *E*-2-butenyl carbonate **2d** and acetate **2dd** gave the 2,3-dimethyl

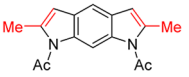
(19) This is in contrast to the good yields obtained in the cylization of ortho-substituted acetanilides with alkynes (see ref 9). This difference may indicate the pursuit of different mechanistic pathways following cyclorhodation of the anilide.

Table 2. Indoles **3b**−**s** by Rh^{III}-Catalyzed Cyclization of Substituted Acetanilides **1b**−**s** with Allyl Carbonate **2a**[a]



ind	R^1	R^2	R^3	%	ind	R^1	R^2	R^3	%
3b	H	H	Me	68	**3k**	H	Cl	H	62
3c	H	H	OMe	76	**3l**	H	CF_3	H	40
3d[b]	H	H	E	46	**3m**	H	Me	H	59
3e	H	H	F	65	**3n**	H	OMe	H	49
3f	H	H	Cl	62	**3o**[c]	H	OMe	OMe	44
3g	H	H	I	40	**3p**[d]	H	$-C_5H_7NO-$		42
3h	H	H	CF_3	44	**3q**	Me	H	H	6
3i	H	$-C_4H_4-$		68	**3r**	OMe	H	H	27
3j[b]	H	E	H	50	**3s**	Ph	H	H	29

[a] See Table 1 for typical conditions. [b] E = CO_2Me. [c] Mixture (1.6:1) of 6-OMe and 4-OMe isomers. [d]



disubstituted indole **3v** (albeit in very low yield) instead of the alternative product, the monosubstituted indole **3t** (eq 2).[20]

Further mechanistic insight was sought as follows. First, the kinetic isotope effect was measured using **1a** and **1a**-d_5 as substrates.[21] A KIE of 3.5 suggested that the C−H bond cleavage is involved in the rate-limiting step[9b,22] and may be effected by a concerted metalation−deprotonation (CMD) mechanism (Scheme 3a).[23] The reversibility of C−H activation was shown by the results of subjecting deuterated acetanilide **1a**-d_5 to the standard reaction conditions with and without allyl carbonate **2a** (Scheme 3b), with 45% of *ortho* deuterium being replaced by hydrogen in the former case and 74% in the latter (note that C−H activation of **1a** with internal alkynes is irreversible).[9,12,22b] Furthemore, relative reactivities of allyl carbonate **2a** and 1-phenyl-1-butyne were compared in a competition experiment with **1a** which afforded exclusively the corresponding indole derived from the internal alkyne.[21] Both $Cu(OAc)_2$ and $AgSbF_6$ were necessary for achievement of indole yields suggestive of catalysis.[24] Finally, the smooth conversion of 2-allylacetanilide **4a** to indole **3a** under the standard conditions (isolated yield 48%)[25] suggested that *ortho*-allylation and oxidative cyclization are discrete steps in the catalytic cycle.[26]

(20) However, no reaction was observed with cinnamyl acetate as the cyclization partner.

(21) See Supporting Information for details.

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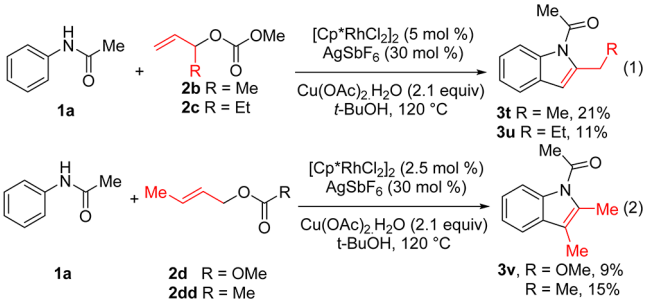
(23) For a review, see: Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118–1126.

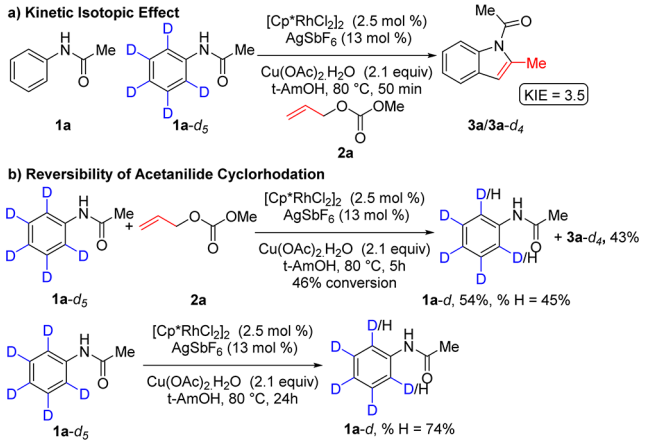
(24) Reaction under standard conditions (except for the absence of $Cu(OAc)_2$ or $AgSbF_6$) afforded only 10−14% yields of indole **3a**.

(25) (a) The reaction performed without $AgSF_6$ or $Cu(OAc)_2$ gave only a 14% yield of indole **3a**. No cyclization occurred in the presence of $Cu(OAc)_2$ alone. See Supporting Information for details. (b) For comparison, Pd-catalyzed oxidative cyclization of anilide **4a** to indole **3a** affords only a 25% conversion rate and a 14% isolated yield; see ref 15c.

Scheme 2. Synthesis of Indoles **3t**–**u** by Cyclization of **1a** with Substituted Allyl Partners

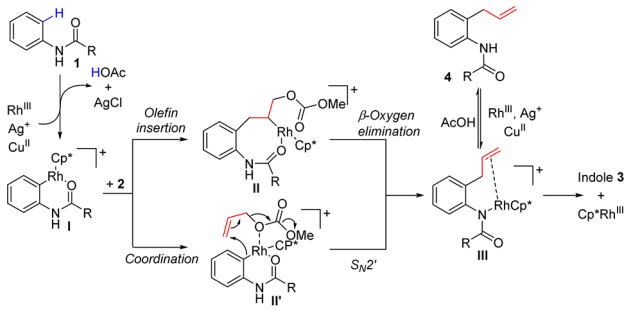


Scheme 3. Mechanistic Experiments



The above findings are compatible with the mechanism sketched in Scheme 4. We hypothesize that after initial formation of the previously proposed rhodacycle **I**,[9] migratory insertion of the allyl double bond into the Rh–C bond[12,13b,27] affords a seven-membered rhodacycle **II** with the carbonate oxygen chelating to the metal. β-Oxygen elimination gives the new olefin-coordinated Rh^{III} species **III** (oxidative Mizoroki–Heck/β-elimination pathway).[28]

Scheme 4. Proposed Catalytic Cycle



Alternatively, the same species **III** could be formed by coordination of the allyl-bearing carbonate oxygen to Rh^{III} species **II**′ which facilitates an intramolecular S_N2' process. *Syn*-amidorhodation[25b] in **III**, followed by β-hydrogen elimination and isomerization, then releases the observed product, the 2-substituted indole **3**. Finally, the reduced Cp^*Rh^I catalyst is oxidized back to the active species by catalytic copper(II) acetate. The appearance of small amounts of 2-allylanilide **4** is attributable to protonolysis of intermediate **III** (see Supporting Information (SI) for details).

Other plausible alternative paths involving π-allyl formation[29] seem to be ruled out by the finding that the reaction of **1a** with allyl carbonate **2d** gives 2,3-dimethylindole **3v** instead of 2-ethylindole **3t**, which would be sterically more accessible for a π-allyl intermediate.[30] The formation of **III** would also explain why increasing the size of the amide group reduces the yield of **3** (through steric hindrance) and favors the accumulation of **4**.

In conclusion, we have developed a Rh^{III}-catalyzed direct intermolecular tandem C–H allylation and oxidative cyclization of acetanilides with allyl carbonates (see SI, Section 7, for a comparison with allylation of benzamides). This reaction, which requires a slight excess of $AgSbF_6$ as the salt and $Cu(OAc)_2$ as the oxidant, supports a wide range of functional groups in the anilide substrate and provides unprecedented ease of access to important 2-methyl indoles. It is equivalent to the never-achieved cyclization of an *N*-substituted aniline substrate with terminal alkynes.

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Supporting Information Available. Experimental procedures, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) The lower yield (48%) relative to the standard reaction with acetanilide **1a** (82%) may indicate the greater ability of **1a** to compete with the indole **3a** for catalyst binding relative to **4a**.

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