

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

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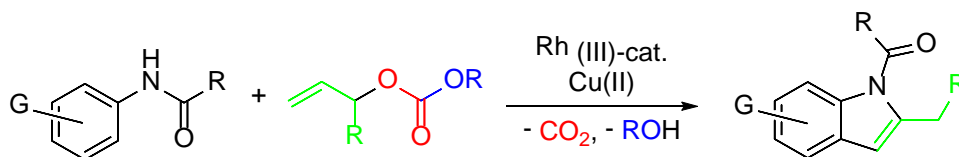
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Received Date (will be automatically inserted after manuscript is accepted)

ABSTRACT



Rh^{III}-catalyzed tandem C-H alkylation and oxidative cyclization of anilides with allyl carbonates in the presence of a slight excess of AgSbF₆ 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 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 Larock⁴ 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

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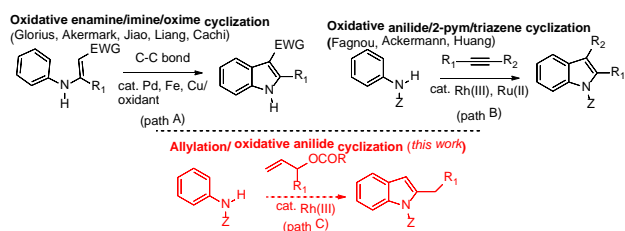
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been successfully employed: a) oxidative cyclization of enamines (Path A)⁶ and Yoshikai's imines⁷ and Hartwig's oximes oxidative cyclizations⁸ by formation of C-C or C-N bonds; and b) the oxidative coupling of *N*-acetyl⁹ or 2-pyrimidinyl anilines¹⁰ anilines, or of 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 anilides¹⁴ 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*RhCl₂]₂]/AgSbF₆ as catalyst system and Cu(OAc)₂·H₂O (2.1 equiv) as 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 in a longer reaction time (entry 2), but the observation of a small

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(14) Substrates other than secondary amides (tosylamide, urethane, urea and several tertiary amides) all failed to produce appreciable yields of indole under presumably favorable conditions (see Supporting Information for details).

amount of *N*-(2-allylphenyl)acetamide (**4a**)¹⁵ (GCMS, ¹H 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 *t*-amyl alcohol as the most appropriate, yields of up to 82% being obtained at 120°C (entries 3-7). Yield was lower using AgBF₄ instead of AgSbF₆ for chloride removal (entry 8), but was less sensitive to replacement of [{Cp*RhCl₂]₂]/AgSbF₆ by [Cp*Rh(CH₃CN)₃]/SbF₆ as catalyst system (entry 9).¹⁶ By contrast, replacement of Cu(OAc)₂·H₂O by AgOAc as oxidant prevented reaction (entry 10). Although allyl alcohol and allyl chloride showed no reactivity, allyl *t*-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 about 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 evaluation of 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

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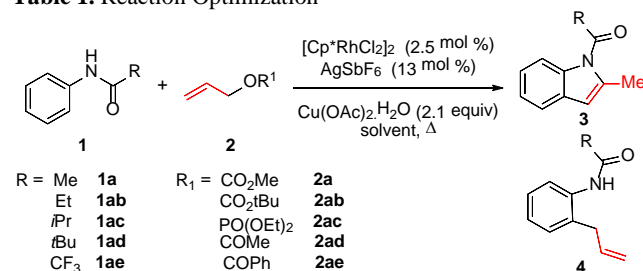
(16) Reactions at lower temperature using O₂ as oxidant gave incomplete transformations. See ref 9.

(17) A small amount (< 3%) of starting acetanilide **1a** was observed at the end of the reaction. For a related inhibition by substrate, see: Tauchert, M. E.; Incarvito, C. D.; Rheingold, A. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 1482-1485.

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fairly good yield. 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 *para* position, acetanilide **1o** giving indole **3o** as the sole product.

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	<i>t</i> BuOH	130	24	75
7	1a	2a	<i>t</i> AmOH	120	24	82
8 ^d	1a	2a	<i>t</i> AmOH	120	24	56
9 ^e	1a	2a	<i>t</i> AmOH	120	15	75
10 ^f	1a	2a	<i>t</i> AmOH	120	24	-
11	1a	2ab	<i>t</i> AmOH	120	24	47
12	1a	2ac	<i>t</i> AmOH	120	24	49
13	1a	2ad	<i>t</i> AmOH	120	24	68
14	1a	2ae	<i>t</i> AmOH	120	24	32
15	1ab	2a	<i>t</i> AmOH	120	24	63
16	1ac	2a	<i>t</i> AmOH	120	24	38
17	1ad	2a	<i>t</i> AmOH	120	24	59 ^g
18	1ae	2a	<i>t</i> AmOH	120	24	-
19	1a	2a	<i>t</i> AmOH	120	24	51 ^h

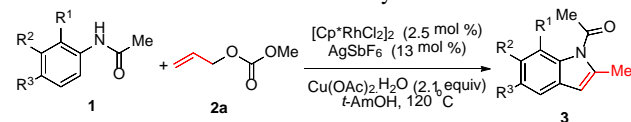
^aTypical conditions: **1**, 0.37 mmol; **2**, 0.41 mmol; [**1**] = 0.074 M. ^bIsolated yields. ^c¹H NMR showed a small amount (<5%) of **4a**. ^dAdditive: AgBF₄ (13 mol %). ^eCatalyst: [Cp*Rh(CH₃CN)₃]SbF₆ (5 mol %). ^fOxidant: AgOAc (2.1 equiv). ^gIsolated yield of 2-allyl amide **4ad** and its 2-propenyl isomer **4ad'** (isomer ratio 10:1). ^hConditions: **1a**, 0.37 mmol; **2a**, 0.41 mmol; [**1a**] = 0.2 M in *t*-AmOH (1.85 mL), 120 °C.

Gratifyingly, dicyclization of the *meta*-diacetanilide **1p** (R² = 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 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*-substituted acetanilides **1q-s** were significantly less reactive than **1a-p**, giving indoles **3q-s** in only low yields.¹⁹

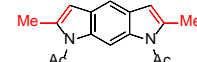
(19) In contrast to the good yields obtained in the cyclization of *ortho*-substituted acetanilides with alkynes (see ref 9). This difference may

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 ₃ H ₇ NO-		42
3h	H	H	CF ₃	44	3q	Me	H	H	6
3i	H	-C ₄ H ₉ -		68	3r	OMe	H	H	27
3j^b	H	E	H	50	3s	Ph	H	H	29

^aSee Table 1 for typical conditions. ^bE = CO₂Me. ^cMixture (1.6:1) of 6-OMe and 4-OMe isomers. ^d



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-methylpropenyl 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 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-d₅** 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-d₅** to the standard reaction conditions with and without allyl carbonate **2a** (Scheme 3b), 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} Furthermore, 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 AgSbF₆ were

indicate the pursuit of different mechanistic pathways following cyclorhodation of the anilide.

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

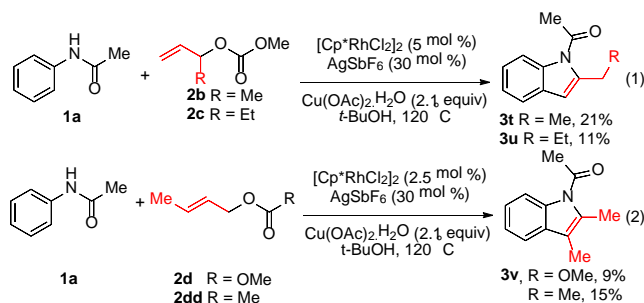
(21) See Supporting Information for details.

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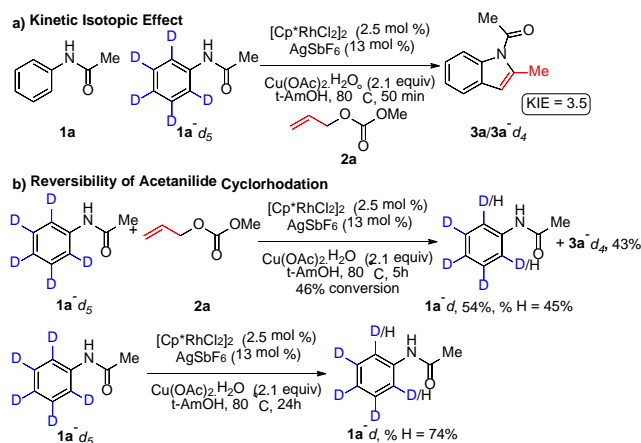
(23) For a review, see: Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118-1126.

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

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 Rh-C

(24) Reaction under standard conditions (except for the absence of Cu(OAc)₂ or AgSbF₆) afforded only 10–14% yields of indole **3a**.

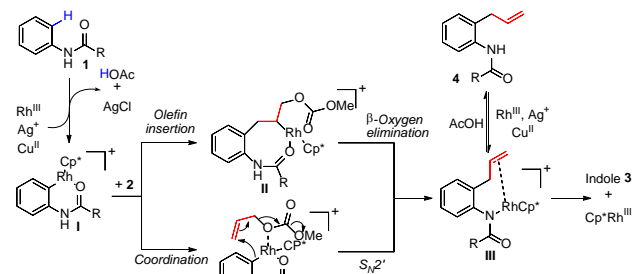
(25) (a) Reaction performed without AgSbF₆ or Cu(OAc)₂ gave only 14% yield of indole **3a**. No cyclization occurred in the presence of Cu(OAc)₂ alone. See Supporting Information for details. (b) For comparison, Pd-catalyzed oxidative cyclization of anilide **4a** to indole **3a** affords only a 25% conversion rate and a 14% isolated yield; see ref. 15c.

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

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 Alternatively, 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*-amidorrhodation^{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 for details).

Other plausible alternative paths involving π-allyl formation²⁹ seem to be ruled out by the finding that 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**.

Scheme 4. Proposed Catalytic Cycle



In conclusion, we have developed an Rh^{III}-catalyzed direct intermolecular tandem C-H allylation and oxidative cyclization of acetanilides with allyl carbonates (see Supporting Information, Section 7, for a comparison with

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(30) For the nucleophilic substitution mechanism in Rh (III) chemistry, see: (a) Yang, L.; Correia, C. A.; Li, C.-J. *Adv. Synth. Catal.* **2011**, *353*, 1269–1273. (b) Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2011**, *14*, 656–659. (c) Ng, K.-H.; Zhou, Z.; Yu, W.-Y. *Org. Lett.* **2011**, *14*, 272–275.

allylation of benzamides). This reaction, which requires a slight excess of AgSbF_6 as salt and $\text{Cu}(\text{OAc})_2$ as 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.

Acknowledgment. This work was supported by MICINN [projects CTQ2011-28258 and Consolider Ingenio 2010 (CSD2007-00006)] and Xunta de Galicia (projects CN2011/054 and EM 2012/051). We thank M. J. Cotón for preliminary experiments. A.C. thanks Ministerio de Ciencia e Innovación for a FPI predoctoral fellowship.

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>.
