Rh-catalyzed Cyclization of Acetanilides with Allylic Carbonates: A New Entry to Indoles

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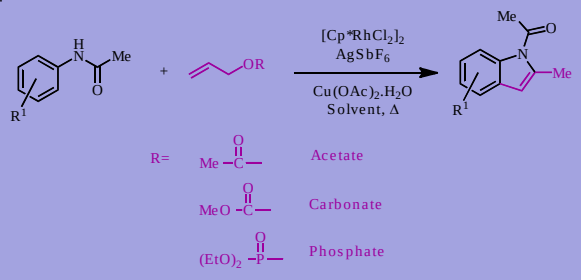
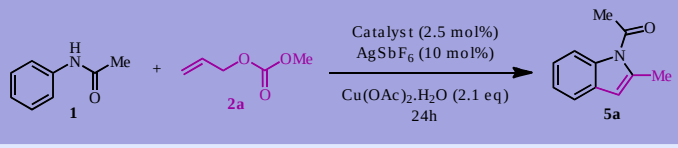
Task:F7

Objective

Indoles are found at the core of many pharmaceutical and biologically active compounds. Accordingly, the synthesis of indoles has been intensely studied over the last few decades.[1] Recently, Fagnou's group has reported a novel synthesis of highly substituted indoles based on Rh(III)-catalyzed C-H bond activation of acetanilides.[2] Herein, we report a novel cyclization to 2-substituted indoles by Rh(III)-catalyzed C-H bond functionalization of acetanilides with allylic acetates, carbonates and phosphonates.



Optimization



Entry	Catalyst	Solvent	T (ºC)	Yield (%)
1	$[Cp^*RhCl_2]_2$	DCE	120	66
2	$[Cp^*RhCl_2]_2$	*i*-PrOH	75	4
3	$[Cp^*RhCl_2]_2$	DCM	75	46
4	$[Cp^*RhCl_2]_2$	THF	105	58
5	$[Cp^*RhCl_2]_2$	*t*-BuOH	130	75
6	$[Cp^*RhCl_2]_2$	*t*-AmOH	120	82
7[a]	$[Cp^*RhCl_2]_2$	*t*-AmOH	120	1
8[b]	$[Cp^*RhCl_2]_2$	*t*-AmOH	120	15
9	$[Ru(p\text{-cymene})Cl_2]_2$	DCE	120	13
10	$[Ru(p\text{-cymene})Cl_2]_2$	*t*-AmOH	120	2
11	$[Ru(p\text{-cymene})Cl_2]_2$	MeOH	100	-

[a] Reaction was performed without $AgSbF_6$. [b]Reaction was performed without $Cu(OAc)_2.H_2O$.

Products

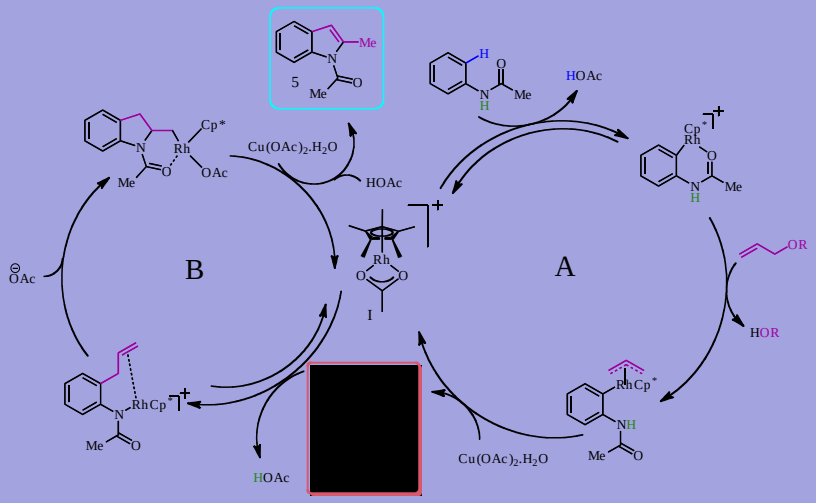
Substrates	5a R=Me, 6 R= Et	5b	5c
2a	82% (R=Me)	68%	76%
2b	12% (R=Et)	-	-
3a	68% (R=Me)	47%	58%
4a	49% (R=Me)	32%	42%

Products

Substrates	7	8 + 9
2a	42%	14%

Proposed Mechanism

The proposed cyclization of acetanilides with allylic derivatives in the presence of $[Cp^*RhCl_2]_2$ could be derived from two consecutive catalytic cycles **A** and **B**. First, C-H bond activation of the anilide followed by allyl activation would give *o*-allylanilide **5a'**. Secondly, N-H activation of **5a'** followed by alkene insertion, β–elimination and isomerization would lead to the observed indoles with recovery of the catalytic Rh species.



Acknowledgement: We thank the MICINN [Projects: CTQ 2011-28258, Consolider Ingenio 2010 (CSD 2007-00006)] and the Xunta de Galicia (CN 2011/054) for financial support. A.C thanks MICINN for a predoctoral FPI fellowship (BES 2009-024194).

References:

[1] (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689-6690. (b) Larock, R. C. Masuda, T. *Top. Organomet. Chem.* **2005**, *14*, 147-182.

[2] (a) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474-16475. (b) Huestis, M. P.; Chan, L. N.; Stuart, D. R.; Fagnou, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 1338-1341. (c) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 18326-18339.