Fast, efficient Ru(IV)-catalysed regioselective allylation of indoles using allyl alcohol (without additives) under mild conditions†

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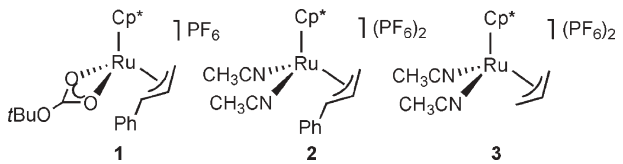
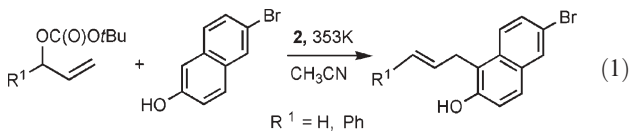
Received (in Cambridge, UK) 13th July 2007, Accepted 28th September 2007
First published as an Advance Article on the web 15th October 2007
DOI: 10.1039/b710763c

The new Ru(IV) salt, $[Ru(\eta^3\text{-}C_3H_5)(Cp^*)(CH_3CN)_2](PF_6)_2$, is an excellent catalyst for the regioselective allylation of a variety of indole compounds using allyl alcohol as substrate; there are *no co-catalysts* required in this chemistry and the yields and reaction conditions are very favorable.

Transition metal-catalysed allylation reactions continue to enjoy increasing popularity[1] as these can a) be based on a variety of metals, b) demonstrate regioselectivity to a branched isomer and c) be carried out in an enantioselective fashion with resulting high ee's.



We have recently noted[2] that a modest change in the structure of a Ru(IV) catalyst from the monocationic, **1**, to the dicationic, **2**, results in facile high yield Friedel–Crafts type C–C coupling reactions, under relatively mild conditions, rather than *O*-allylation, *e.g.* see eqn 1.

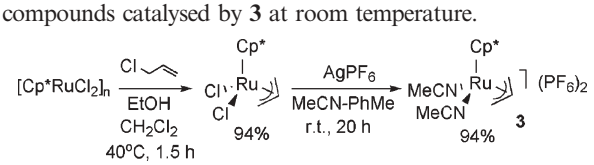


(1)

We show here that a slightly modified form of this catalyst, $[Ru(\eta^3\text{-}C_3H_5)(Cp^*)(CH_3CN)_2](PF_6)_2$, **3**, which can more readily be prepared in high yield, catalyses a C–C bond making reaction for indole compounds, *using allyl alcohol*, at room temperature, rather than carbonate, acetate or halogen substituted substrates.

There are *no additives* required in this indole chemistry in contrast to reports which use boron[3,4] or titanium co-catalysts.[5] Further, we offer evidence in support of a reaction mechanism and discuss what advantage **3** (or **2**) offers with respect to using alcohols as substrates.

Equation 2 shows the new synthesis[6] of the catalyst and Table 1 gives results for the reaction of allyl alcohol with substituted indole compounds catalysed by **3** at room temperature.



(2)

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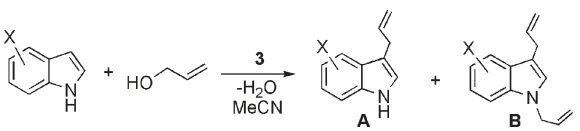
† Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/b710763c

The major product is the 3-substituted allyl compound with the double allylation product as the minor component. Using an excess of the alcohol results in complete conversion to the double allylation product (see entry 2). The use of 2-phenylindole as substrate (entry 11) slows the reaction only slightly and the product, 3-allyl-2-phenylindole, is obtained in excellent yield. The catalytic reactions with 1-methyl-substituted indole derivatives (see entries 12 and 13) afford exclusively the 3-allyl product. The observed regioselectivity at the indole 3-position is consistent with the known literature.[7,8] The observed yields and reaction times compare very favorably with the current Pd[3b,8]- or In[7]-catalysed literature reports using indole as nucleophile, which require 12–24 h, or higher temperatures, and do not always afford high yields.

Preparative experiments, on the 1 mmol scale, using the indole substrates in entries 11 and 13 afforded 91% and 96% yields of the new products, respectively (see ESI†).

Concentration dependent rate studies, using either indole or 5-hydroxyindole as reagent, reveal that this reaction is first order in the Ru-catalyst, first order in the indole compound and zero order in alcohol. Fig. 1, which gives a plot of the log of the relative rate *vs.* the Hammett substituent constant, shows that substitution of electron withdrawing groups at the 5-position decreases the

Table 1 Ru-catalysed allylation of indole compounds with allyl alcohol[a]



Run	Indole	Reaction time, h	Convn. %	A : B ratio
1	Indole	0.5	100	8 : 1
2[b]	Indole	12	100	Only B[b]
3	5-HO-indole	0.5	100	8 : 1
4	5-Me-indole	0.5	100	7 : 1
5	5-MeO-indole	0.5	100	7 : 1
6	5-Br-indole	3	100	6 : 1
7	5-Cl-indole	5.5	100	6 : 1
8	5-CN-indole	27	100	8 : 1
9	5-NO_2-indole	96	100	8 : 1
10	4-MeO-indole	0.5	100	5 : 1
11	2-Ph-indole	0.9	100	11 : 1
12	1-Me-indole	1	100	Only A[c]
13	1-Me-2-Ph-indole	0.5	100	Only A[c]

[a] Reaction conditions: allyl alcohol (0.07 mmol, unless otherwise stated), indole (0.07 mmol), catalyst (0.0035 mmol) in CD_3CN (0.5 ml), room temperature; the reaction was monitored *via* ^1H NMR at 296 K. [b] Four equivalents of allyl alcohol (with respect to indole) were used to induce complete conversion to B. [c] *N*-allylation blocked.

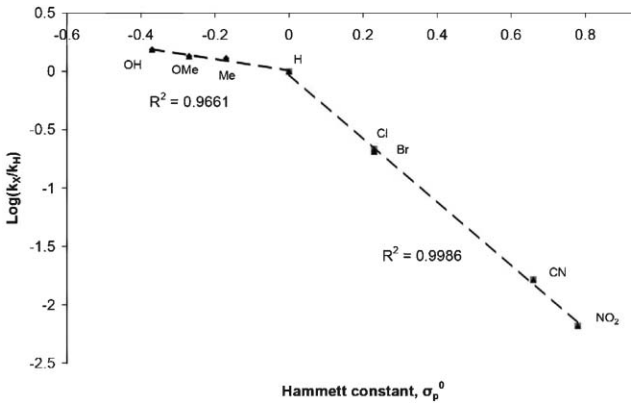
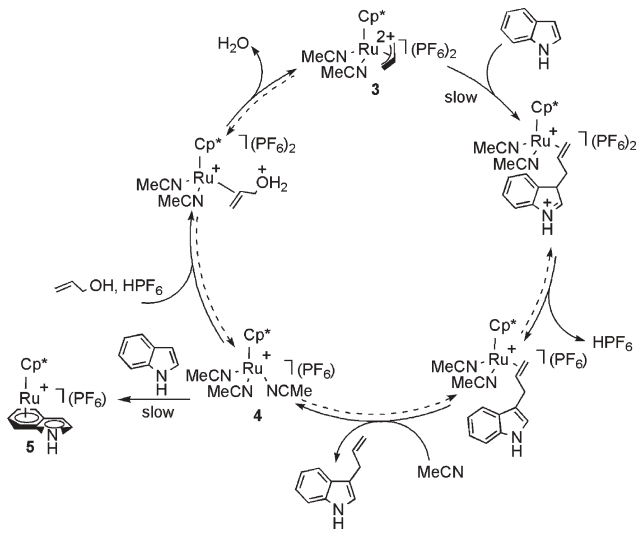


Fig. 1 Hammett plot for the allylation of 5-substituted indoles.



Scheme 1

reaction rate whereas electron donors accelerate the reaction slightly.[9]

Combining these data with the concentration studies gives rise to the proposed mechanism, shown in Scheme 1, in which attack of the indole on the Ru(IV) allyl salt is rate determining.

We believe that liberating a catalytic amount of H^+ per cycle permits the use of the alcohol as substrate. This *controlled release* of acid, due to the nucleophilic attack on the Ru(IV) catalyst precursor, eventually results in water as the leaving group in the oxidative addition reaction. One implication of this mechanism is that the use of a catalyst made up of $[Ru(Cp^*)(CH_3CN)_3](PF_6)$, **4**, plus additional acid should afford an active catalyst. We have carried out this experiment and, indeed, the catalysis works well; however, the use of **3** guarantees a controlled release of exactly one proton per catalytic cycle, whereas adding acid can result in either too much or not enough plus an unnecessary additional anion.

We have prepared the η^6-arene complex, **5**[10] (see Scheme 1), *via* the reaction of indole with salt **4**, and find that complex **5** does not catalyse the allylation reaction.

Summarizing, we have shown that a new Ru(IV) salt, **3**, is an excellent catalyst for the allylation of indoles using allyl alcohol as substrate. This substrate is both economically and environmentally preferable, in that the leaving group is not wasted. The mechanism has been established and involves the controlled release of one proton per catalytic cycle.

Notes and references

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6 **Synthesis of $[Ru(\eta^3\text{-}C_3H_5)(Cp^*)(MeCN)_2](PF_6)_2$ (3)**. Toluene (110 ml) was added to an acetonitrile (110 ml) solution of $[Ru(\eta^3\text{-}C_3H_5)(Cp^*)Cl_2]$[11] (0.565 g, 1.62 mmol) and $AgPF_6$ (1.640 g, 6.49 mmol). The reaction mixture was stirred at room temperature for 20 h after which time the solution was evaporated *in vacuo*. The resulting residue was dissolved in acetone (5 ml) and filtered through Celite. The resulting solid was washed with acetone (2 × 5 ml). The filtrate was evaporated *in vacuo*, and the residue washed with water (3 × 5 ml) to remove the remaining $AgPF_6$. After drying *in vacuo* the crude product was again dissolved in acetone (5 ml), filtered through Celite, evaporated and dried *in vacuo* to afford a brown solid (0.990 g, 94%). ^{1}H NMR (acetone-d_6, 400.13 MHz): δ = 2.02 (15H, s, C_5Me_5), 2.72 (6H, s, MeCN), 3.33 (2H, d, J = 11.1, *trans*-HC_{all}), 4.80 (2H, d, J = 6.3, *cis*-HC_{allyl}), 5.98 (1H, m, *central*-HC_{allyl}); ^{13}C NMR δ = 5.3 (*Me*CN), 10.5 (C_5Me_5), 73.6 (H_2C_{allyl}), 101.4 (HC_{allyl}), 111.7 (C_5Me_5), 135.23 (Me*C*N). Elemental analysis (%) calcd for $C_{17}H_{26}F_{12}N_2P_2Ru$: C 31.44, H 4.04, N 4.31; found: C 31.61, H 3.95, N 4.12.

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