Communication

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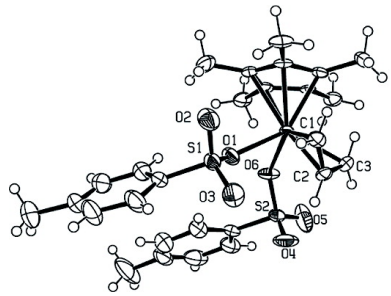

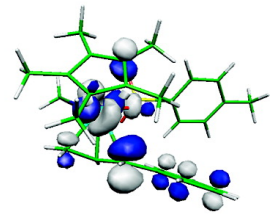

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Fast and Highly Regioselective Allylation of Indole and Pyrrole Compounds by Allyl Alcohols Using Ru-Sulfonate Catalysts

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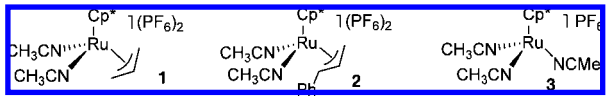
Indole and pyrrole moieties are important structural elements of many natural compounds of biological interest.[1] Therefore the development of efficient pathways for the functionalization of these compounds will facilitate access to pharmaceutically attractive molecules. An allyl group can be a synthetically useful building block and transition-metal catalyzed allylation chemistry continues to draw attention in that this reaction can be carried out using allyl carbonates or acetates together with palladium,[2] molybdenum,[3] or iridium catalysts.[4] However, these reactions are often slow, waste the leaving group, and require stoichiometric amounts of a base.

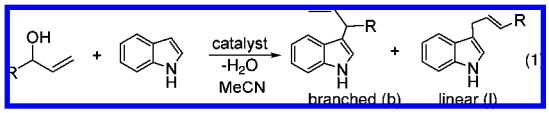
Some few papers report on the use of alcohols in the allylation of nitrogen heterocyles;[5,6] however, these reactions are sluggish and frequently require the use of Lewis acid additives in substantial amounts.[5] Further, there is no clear mechanistic picture with respect to when and with which catalysts alcohols can be employed.

We have recently reported[7,8] that several Ru(IV)- rather than Ru(II)-allyl catalysts, e.g., **1** or **2**, readily tolerate alcohols as substrates in acetonitrile solution and we have offered a mechanism to explain why this is so.[7,8]



We have now carried out new and related allylation reactions with several new Ru(IV) sulfonate catalysts and show that the new catalysts are more regioselective and even faster than either **1** or **2**.[8,9]

Reaction of indole with PhCH(OH)CH=CH_2 in the presence of the Trost catalyst, **3**, plus 1 equiv of *p*-toluenesulfonic acid (TSA), at ambient temperature, afforded 100% conversion to the products after 40 min with a b/l ratio of 9.5:1 (see eq 1). For the same



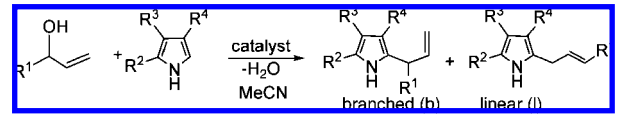
reaction, the Ru(IV) catalyst **1** requires 4.5 h and gives a b/l ratio of 2:1. Using indole with the larger (*o*-tolyl)CH(OH)CH=CH_2, the new sulfonic acid-based catalyst afforded 100% conversion to the products after only 20 min with a b/l ratio of 56:1 (!) while **1** required 50 min and gave a b/l ratio of 15:1. An alternative sulfonate source, camphor sulfonic acid (CSA), **4**, was also tested. Table 1 shows catalytic results based on the **3/4** combination for a series of alcohols using indole as nucleophile. The reactions of the various alcohols in Table 1 are all complete in less than 1 h and several of the entries (6−8) afford outstanding b/l ratios.

Table 1. Allylation of Indole by Different Allyl Alcohols Catalyzed by the Trost Catalyst−CSA System at Room Temperature (See eq 1)[a]

run	R	reaction time, min	conversion %	l/b ratio
1	Ph	25	100	1:9
2	*p*-Cl-C_6H_4-	40	100	1:5
3	*p*-MeO-C_6H_4-	40	100	1:11.5
4	*o*-Cl-C_6H_4-	20	100	1:24
5	*o*-MeO-C_6H_4-	55	100	1:24
6	*o*-Me-C_6H_4-	20	100	1:49
7	mesityl	55	100	1:32
8	1-naphthyl	15	100	1:49
9	2-naphthyl	35	100	1:8
10	2-furyl	20	100	1:2.3
11[b,c]	H	50	100	

[a] CD_3CN (0.5 mL), indole (0.07 mM), allyl alcohol (0.07 mM), Trost cat (0.0035 mM), CSA (0.0035 mM). [b] 3-Allylindole/1,3-diallylindole ratio = 5:1. [c] 3-Butene-2-ol, 1,4-pentadiene-3-ol, and cinnamyl alcohol can be used as substrates, although the reactions are somewhat slower (see Supporting Information for details).

Table 2. Allylation of Pyrroles by Different Allyl Alcohols Catalyzed by the Trost Catalyst−CSA System at Room Temperature[a]



run	R^1	R^2	R^3	R^4	reaction time, min	conversion %	l/b ratio
1	*o*-Me-C_6H_4-	Et	H	H	5	100	only b
2	*o*-MeO-C_6H_4-	Et	H	H	≤7	100	1:71
3	*o*-Cl-C_6H_4-	Et	H	H	≤7	100	1:38
4	mesityl	Et	H	H	≤7	100	only b
5	1-naphthyl	Et	H	H	≤7	100	only b
6	Ph	Et	H	H	7	100	1:13
7	Ph	Me	Et	Me	35	100	1:22
8	Ph	Me	H	Me	12	100	1:12

[a] CD_3CN (0.5 mL), pyrrole (0.07 mM), allyl alcohol (0.07 mM unless otherwise stated), Trost cat (0.0035 mM), CSA (0.0035 mM).

We have also tested the **3/4** mixture as catalyst for a series of pyrroles and show these catalytic results in Table 2. These reactions are *even faster*, and, for entries 1−5, using 2-ethyl pyrrole, afford impressive b/l ratios.

It seemed obvious that the sulfonate anion was involved somehow, either as a noncoordinated anion or in the Ru-coordination sphere, and to clarify this issue, we have prepared several complexes starting from **5** and show the structure for one of these, the bis-sulfonate, **6**, in eq 2 and Figure 1. Clearly, the sulfonate anion is capable of coordination.

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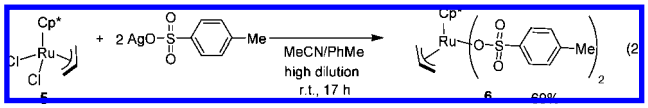
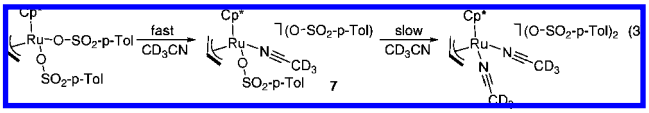
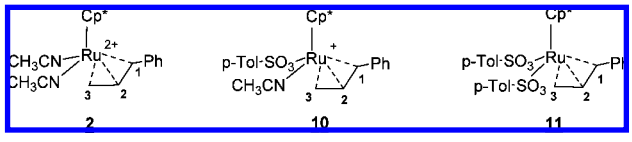


Since the optimum sulfonic acid/Ru ratio was found to be 1, we carried out experiments to determine the number of coordinated sulfonates under the reaction conditions. When complex **6** was allowed to react with indole only a modest amount of allylation product was found. Addition of CD_3CN to this reaction solution gave rapid conversion to the organic product, 3-allyl indole. When complex **6** was dissolved in CD_3CN (eq 3) rapid formation of the monosulfonated cationic complex, **7**, and slow appearance of the bis-nitrile, related to **1** was observed. These results suggest that cation **7** (or the CSA analogue **8**) is the active species in the catalytic chemistry.



The anions of both TSA and CSA are relatively large. To distinguish between the steric and electronic effects associated with these complexed anions, we prepared the bis-methyl sulfonate complex, **9**, an analogue of **6**. Using **9** as catalyst for the allylation of indole with either $PhCH(OH)CH{=}CH_2$ or (*o*-tolyl)$CH(OH)CH{=}CH_2$ (in analogy with the experiments described above with **3** plus TSA) affords some clarity. With the phenyl alcohol, the reaction is finished in 35 min (about the same as TSA) with a b/l ratio of 10.5 (9.5 with TSA). For the *o*-tolyl alcohol the reaction is finished in 20 min (again, about the same as TSA) with a b/l ratio of 93:1 (!) (56 with TSA). The smaller sulfonate affords a larger and unprecedented regioselectivity, and consequently, it would appear that this improved selectivity is based on an electronic rather than a steric effect.

Density functional theory calculations[10] were performed on the three Ru(IV) complexes, **2**, **10**, and **11**, in order to probe the observed regioselectivity.[11] The calculated complexes show increasing Ru−allyl backdonation with the number of sulfonate anions in the complex, resulting in stronger and less asymmetric allyl coordination (i.e., with shorter Ru−C1 distances). Relevant metric and electronic parameters are provided as Supporting Information (Table S1). These results are in contrast to the regioselectivity observed for the allylation reaction. The calculations indicate that the presence of sulfonate ligands produce similar Ru−C3 bonds and more negative C1 atoms. Thus, the selectivity *is not due to attack on a weaker Ru−C(allyl) moiety*, and is certainly not charge driven.



The LUMO of the complexes offers a clue to the observed selectivity. Figure 2 shows the LUMO for **2**, the bis(nitrile), and **10**, the species with one sulfonate ligand, suggested by the experimental results as the possible active species.

Both orbitals are essentially equivalent in their general features and represent a Ru−allyl π^* orbital. In both cases there is an important contribution from C1, the substituted allyl carbon. However, there is a major difference in the *relative weight of the contribution for the two terminal allyl C-atoms*. For the sulfonate complex, **10**, the contribution of C3 is much diminished when compared to the contribution of C3, in the bis(nitrile) species, **2**. Thus, the preference

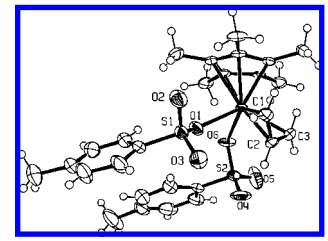


Figure 1. Structure of complex **6**.

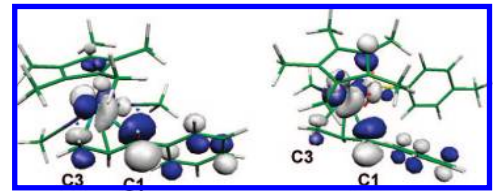


Figure 2. LUMO of $[RuCp^*(CH_2CHCHC_6H_5)(CH_3CN)_2]^{2+}$ (**2**, left) and of $[RuCp^*(CH_2CHCHC_6H_5)(CH_3CN)(CH_3C_6H_4SO_3)]^{+}$ (**10**, right). Note the difference in the C3 contributions.

for a nucleophilic attack on C1, yielding the branched product, appears to be related to the *relative contribution* of these two terminal C-atoms to the LUMO of the complex. The reaction is driven by orbital control, and the selectivity is dictated by the topology of the LUMO of the corresponding Ru(IV) complexes.

Concluding we have prepared new Ru-sulfonate allylation catalysts that are fast, efficient, in that they use alcohols as substrates, and afford unprecedented regioselectivity.

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Supporting Information Available: Complete ref 10b; additional experimental data and details of the calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The complex with one CH_3CN and one sulfonate has two diastereomers (**10** and **10′**). These were shown to be equally stable (within 0.1 kcal/mol). Additional metric and electronic information for all calculated complexes (**2**, **10**, **10′**, and **11**) are presented as Supporting Information (Table S1).

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