Allylic Alcohols as Substrate for Ruthenium-Catalyzed C–C Coupling Allylation Reactions

Preliminary Communication

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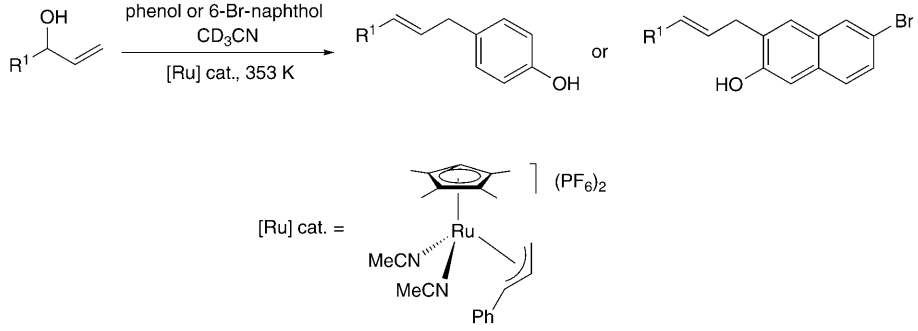
Allylic alcohols, rather than halides, acetates, or carbonates can be used directly in the *Friedel–Crafts*-type coupling with various phenols. The use of a Ru^{IV}, rather than a Ru^{II}, precursor promotes the formation of one H^+ per cycle so that a large excess of acid is never present in the reaction mixture. Consequently, the leaving group in the oxidative addition reaction is H_2O, thereby avoiding the production of an unnecessary by-product.

An increasing variety of metal-mediated catalytic transformations involving allyl compounds have been developed, and these tools are rapidly becoming indispensable in organic synthesis [1–5]. Generally, π- or σ-allyl species are regarded as important intermediates in these various transformations [6][7]. Typically, allyl sources such as halides, acetates, or carbonates have been employed since the allyl moiety often requires a 'leaving group' to be effective; however, the direct activation of an allyl alcohol is both economically and environmentally more desirable, in that the leaving group is not wasted.

One finds only a modest number of reports in which an allyl alcohol is employed as substrate [8–13], and *Akita* and co-workers [8] have summarized several mechanistic possibilities for the use of an alcohol, *e.g.*, either an oxidative addition reaction or a dehydration pathway. The former is not favored because the OH group is thought to be a poor leaving group. The latter mechanism works under acidic conditions; however, this often requires excess acid and/or severe reaction conditions [8].

We have recently shown [14] that $[Ru(Cp^*)(MeCN)_2)(\eta^3\text{-}PhCH{=}CHCH_2)](PF_6)_2$ ($Cp^* = 1,2,3,4,5$-pentamethylcyclopenta-1,3-dien-1-yl); **1**) facilitates *Friedel–Crafts* type aromatic allylation reactions of phenols and related arene compounds under relatively mild conditions, using allyl carbonate substrates. There is now a modest literature involving metal-catalyzed *Friedel–Crafts* reactions [15], but little involving ruthenium [16]. We report here an extension of this chemistry and show that the dicationic catalyst precursor **1**, which contains Ru^{IV} rather than Ru^{II}, affords the C–C coupling products starting from a selection of alcohols, as indicated in *Scheme 1*. The *Table* gives a list of the substrates and products tested. The reactions were, in many cases, fairly rapid (often complete conversion in less than 20 min) and regioselective in that the attack occurred at the least-substituted allyl C-atom, and proceeded to completion under relatively mild conditions in MeCN solution. Several of the tested alcohols

Scheme 1



reacted relatively slowly, *e.g.*, allyl alcohol; nevertheless, this reaction proceeded satisfactorily.

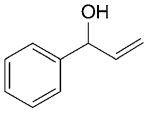
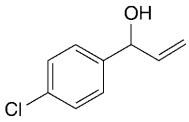
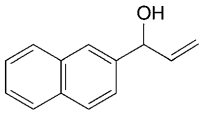
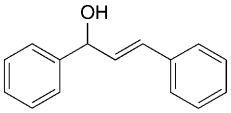
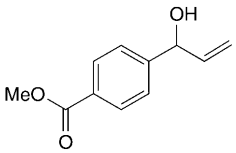
We suggest that the relative ease with which an allyl alcohol can be employed as substrate for this reaction derives from a mechanism which allows for the controlled release of one proton (see *Scheme 2*). Starting from the Ru^{IV} catalyst, the reaction proceeds *via a*) reductive attack of (for example) the phenol nucleophile to afford a Ru^{II} olefin complex such as **2**, followed by *b*) loss of H^+ to reform the aromatic moiety with concomitant dissociation of the product, thus opening a coordination position at Ru^{II}, *c*) olefin coordination of the allylic alcohol and O-protonation[1]) to afford **3**, and then *d*) oxidative addition with loss of H_2O (as the leaving group) to reform the Ru^{IV} catalyst. The proton is generated during the reduction of Ru^{IV} to Ru^{II}, and then 'consumed' as H_2O. Consequently, the use of the *higher-oxidation-state complex* as the starting precursor facilitates the controlled release of the proton, thereby avoiding a large excess of acid at any time.

In addition to the results given in the *Table*, we also prepared and carried out the coupling reactions of several *para*-substituted 1,3-diphenylallyl alcohols (=α-(2-arylethenyl)benzenemethanols) **4** with 2,6-dimethylphenol as nucleophile, with the aim of understanding which electronic factors favor this transformation. In contrast to the catalytic data in the *Table*, these reactions were performed on a preparative scale by using 1 equiv. each of the reagents and 3 mol-% of catalyst. The products were isolated, purified, and fully characterized by 2D-NMR and mass spectroscopy. The yields of the products isolated from the reactions of **4b**–**d** were 72, 81, and 89%, respectively. Compounds **4b** and **4c** were purified by chromatography; however, this procedure was not necessary for **4d**. For further details, see the *Exper. Part.*

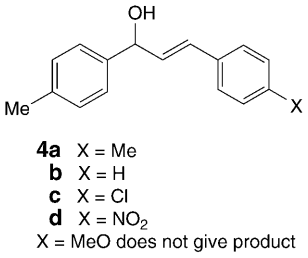
We found that the reactions of **4b**–**d** afforded a mixture of the two expected isomeric products in the ratios 1.38 : 1, 1.15 : 1, and 2.30 : 1, respectively. The major product results from attack of the phenol at the allyl terminus *proximate to the 4-methylphenyl moiety* (and not, *e.g.*, the allyl terminus close to the 4-Cl–C_6H_4 or 4-NO_2–C_6H_4 group). Presumably, the favored product is that in which the newly formed Ru–olefin bond

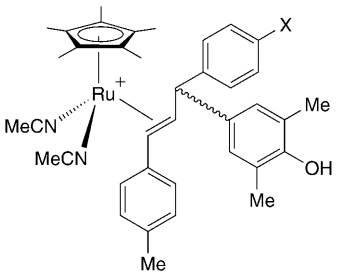
[1]) The sequence in which complexation/protonation occurs is not defined.

Table. *Selected Ru-Catalyzed C–C Bond-Formation Reactions, by Using Alcohol Precursors.* In MeCN at 353 K, with **1** as catalyst[a]).

Allylic substrate	Phenol derivative	Time [min]	Products[b])
	phenol	4	100 (10:6:84)
	6-bromonaphthalen-2-ol	8	94
	phenol	18	100 (13:6:81)
	4-methylphenol	9	100 (0:15:85)
	6-bromonaphthalen-2-ol	6	96
	phenol	10	100 (6:2:92)
	6-bromonaphthalen-2-ol	1	92
	phenol	1	100 (8:4:88)
	6-bromonaphthalen-2-ol	1	90
	phenol	800 (13 h)	*ca.* 60
	6-bromonaphthalen-2-ol	310	*ca.* 60
	6-bromonaphthalen-2-ol	125	100

[a]) Conditions: 0.07 mmol of allylic substrate, 0.21 mmol of the corresponding phenol derivative, and 0.002 mmol of catalyst (3 mol-%) in 0.5 ml of solvent at room temperature. [b]) Conversion in %; *o*/*m*/*p* ratio in parentheses, as determined by ^{1}H-NMR spectroscopy.





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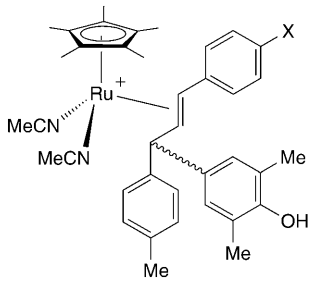

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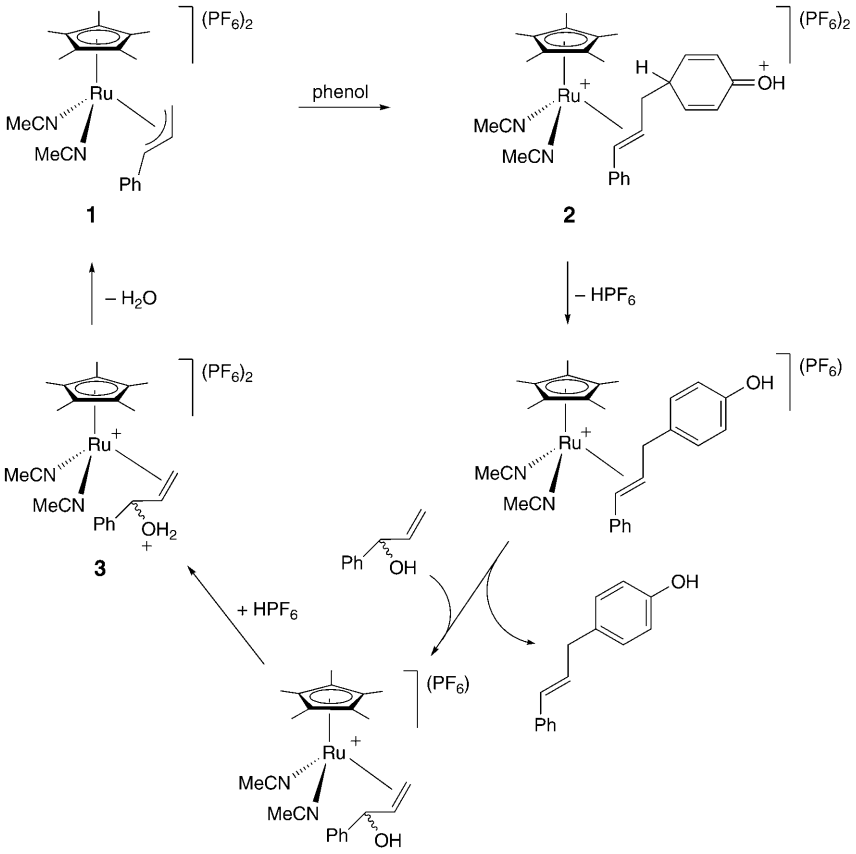
derives from the most-electron-donating aryl moiety, *i.e.*, complex **5** is slightly favored relative to **6**. One might have expected the preferred attack of the phenol nucleophile to take place at the electron-poorer terminal allyl carbon; however this is not the case.

Scheme 2



Interestingly, for X = MeO in **4**, we did not observe the formation of product. This is consistent with the observations that the substrate alcohols **7** and **8**, react only very slowly[2]) with 6-bromonaphthalen-2-ol to afford the C–C coupling products, even after 24 h at 353 K in MeCN.

7 (10% conversion) **8** (12% conversion)

[2]) This relative lack of reactivity most likely arises from the formation of an η^6-arene complex which is stable, and observable, under these conditions, due to the strongly electron-donating MeO group.

Concluding, the selection of a [Ru^{IV}(allyl)] catalyst precursor, rather than a more readily available Ru^{II} species, permits the use of the economically and environmentally more favorable alcohol (rather than a carbonate or acetate) substrate in the C–C coupling reaction described.

Experimental Part

*2,6-Dimethyl-4-[(2*E*)-1-(4-methylphenyl)-3-(4-nitrophenyl)prop-2-enyl]phenol and 2,6-Dimethyl-4-[(2*E*)-3-(4-methylphenyl)-1-(4-nitrophenyl)prop-2-enyl]phenol.* To a soln. of (2*E*)-1-(4-methylphenyl)-3-(4-nitrophenyl)prop-2-en-1-ol (**4d**; 71.6 mg, 0.266 mmol) in MeCN (2 ml) was added [Ru(Cp*)$(MeCN)_2(\eta^3$-PhCH=$CHCH_2)](PF_6)_2$ (**1**; 6.0 mg, 0.008 mmol; 3 mol-%) and 2,6-dimethylphenol (32.5 mg, 0.266 mmol). The resulting brown suspension was stirred at 353 K overnight. Filtration through silica gel and subsequent washing of the silica gel with AcOEt removed the Ru-catalyst. The mixed solvent was then evaporated to afford the crude product as a yellow powder. This material was washed with hexane and dried *i.v.*: 148 mg (89%) of the product as a mixture of isomers (for **4b** and **4c**, it was necessary to chromatograph the crude product to obtain a pure material). ^{1}H- and ^{13}C-NMR: a selection of assignments is given in the *Figure*. MS: 373 (M^+), 358 ($[M-Me]^+$), 251 ($[M-C_6H_4NO_2]^+$), 236 ($[M-Me-C_6H_4NO_2]^+$). Anal. for $C_{24}H_{23}NO_3$: C 77.19, H 6.21, N 3.75; found: C 76.52, H 6.18, N 3.83.

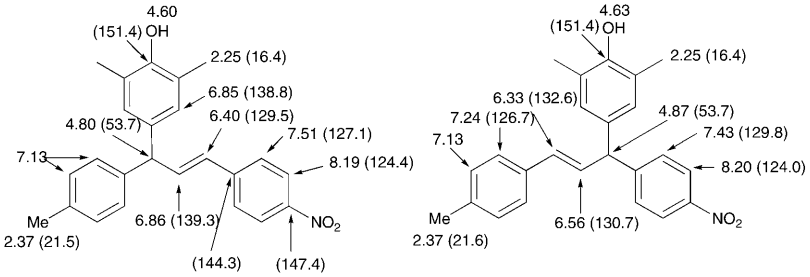


Figure. *Selection of ^{1}H- and ^{13}C-NMR assignments for 2,6-dimethyl-4-[(2*E*)-1-(4-methylphenyl)-3-(4-nitrophenyl)prop-2-enyl]phenol and 2,6-dimethyl-4-[(2*E*)-3-(4-methylphenyl)-1-(4-nitrophenyl)prop-2-enyl]phenol*

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