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Direct propargylation of furan and arene by propargylic alcohols promoted by bisoxazoline–ruthenium catalysts

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The mononuclear [(arene)(bisoxazoline)ruthenium(II) (NCMe)][$(BF_4)_2$] complex 4 characterised by X-ray crystallography is a catalyst precursor for the propargylation of methylfuran and 1,3-dimethoxybenzene directly with propargyl alcohols incorporating terminal or internal alkyne bonds.

Introduction

Selective C–C bond formation catalysed by ruthenium catalysts is a developing area as it allows new combinations of molecules, especially with non-protected or activated groups.[1] Recently, ruthenium catalysts have promoted, besides the oxidative coupling of a variety of unsaturated substrates[2,3] and alkene metathesis,[4] several innovative reactions involving the activation of inert C–H bonds,[5] the activation of alkynes *via* vinylidene[6,7] or allenylidene intermediates,[7,8] tandem isomerisation–Claisen reactions[9] and cyclopropanation–ring closing metathesis of enynes[10] and dienynes.[11]

In this direction, Nishibayashi *et al.* have shown that the propargylation of alkenes, heterocycles and ketones, directly with propargyl alcohols, can be catalysed by bimetallic complexes of type Cp*RuCl(μ-SR)$_2$ClRuCp*[12] and [Cp*RuCl(μ-SR)$_2$(H$_2$O)RuCp*][OTf][13] but not by mononuclear complexes. For these systems the involvement of an allenylidene–ruthenium intermediate stabilized by the second Cp*Ru(SR)$_2$ moiety was suggested as the key catalytic step for the direct propargylation by propargyl alcohols bearing a terminal alkyne[12] whereas the involvement of an (η-propargyl)ruthenium species is proposed for the reactions involving internal alkynes.[13] The stoichiometric activation of propargyl alcohols by 16 electron mononuclear ruthenium species readily gives allenylidene–ruthenium complexes,[7,8] and it could be predicted that these mononuclear precursors should favour the direct propargylation of nucleophiles if an allenylidene intermediate was the key intermediate. Actually, preliminary communications have just reported that mononuclear complexes [Ru(metallyl)(CO)(dppf)][SbF_6][14] and [RuCl(CO)(PCy_3)(*p*-cymene)][OTf][15] catalyse propargylation with C–O and C–C bond formation, respectively and that a rhenium catalyst efficiently performs propargylation without a possible allenylidene intermediate.[16] Ruthenium as well as other metal complexes are also able to promote propargylation reactions with various propargylic derivatives and nucleophiles.[17]

Within the course of our study on bisoxazoline–ruthenium complexes in catalysis[9] we have found that these catalyst precursors are also able to perform direct propargylation of weak nucleophiles with propargyl alcohols. We now report that a mononuclear (bisoxazoline)(arene)ruthenium(II) complex catalyses the direct propargylation of furan and arene by propargyl alcohols with C–C bond formation in moderate yields, but we show that this feasible catalytic reaction does not involve an allenylidene intermediate, but rather an activation of the triple bond by coordination.

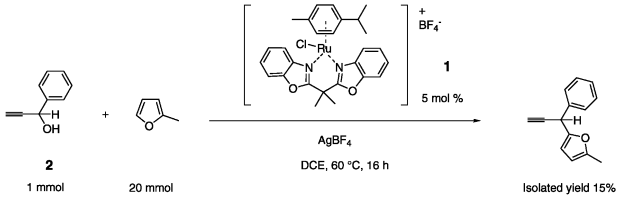
Results and discussion

The ionic (arene)(bisoxazoline)ruthenium(II) complex **1** has been shown to be an active catalyst for the tandem isomerisation–Claisen rearrangement reactions of allyl ethers, containing a 1,6-diene structure, into unsaturated aldehydes.[9] To evaluate its possible activation of propargylic alcohol into an allenylidene derivative, complex **1** (0.02 mmol) has been reacted *in situ* with one equivalent (0.02 mmol) of $AgBF_4$ in dichloroethane (DCE), as an attempt to generate a 16 electron intermediate, before addition of 1 mmol of propargylic alcohol **2** and 20 mmol of methylfuran. After 16 h at 60 °C, full conversion of **2** was observed and the derivative **3** corresponding to the direct propargylation of methylfuran was isolated in a modest yield of 15% due to the parallel formation of non identified polymeric products (Scheme 1).

An attempt to isolate the 16 electron intermediate resulting from chloride abstraction by $AgBF_4$ of **1** was not successful. However, when the previous reaction was performed in the presence of acetonitrile the complex **4** was isolated in 70% yield and characterized (Scheme 2).

Complex **4** was purified by precipitation in diethyl ether to yield a bright yellow powder. Needles suitable for X-ray characterisation were obtained, and complex **4** was found to crystallise with one molecule of dichloroethane (Fig. 1).

Complex **4** was then used as a catalyst precursor (5 mol%) for the propargylation of methylfuran. When 2 equivalents of methylfuran were used, 60% conversion was reached after 24 h at 60 °C and again only 15% of **3** were isolated. A larger excess of methylfuran (10 eq. or 20 eq.) resulted in faster conversion of the substrate but without improvement of the isolated yield. The arene derivative **5** (5 eq.) was reacted with propargylic alcohol **2** in the presence of **4** (5 mol%) under the same



Scheme 1 Propargylation of methylfuran by *in situ* generated catalyst.

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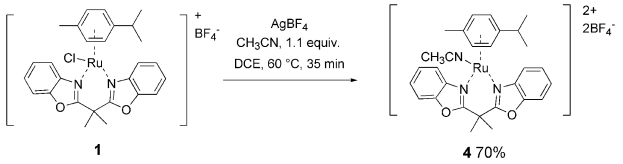


Scheme 2 Preparation of the dicationic, 18 electron complex **4**.

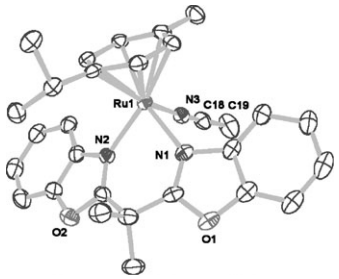


Fig. 1 Molecular structure of complex **4** (50% ellipsoid probability). H atoms, BF_4 anions and the solvent dichloroethane are omitted for clarity. Selected bond length (Å) and angles (deg): Ru1–N1, 2.095(3); Ru1–N2, 2.107(3); Ru1–N3, 2.054(4); N1–Ru1–N2, 82.72(14); N1–Ru1–N3, 82.39(14); N2–Ru1–N3, 86.32(13).

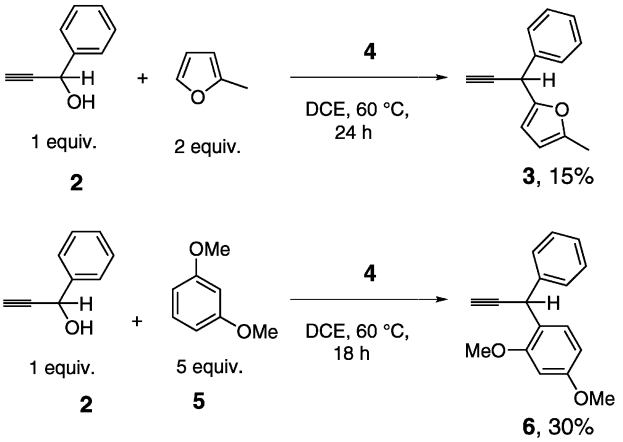
conditions at 60 °C for 18 h for complete conversion of **2** and derivative **6** was isolated in 30% yield (Scheme 3).

The above reactions, even if the yields remain modest, show that the well-defined mononuclear ruthenium catalyst precursor can activate propargylic alcohol and perform the propargylation of heterocyclic and aromatic compounds.

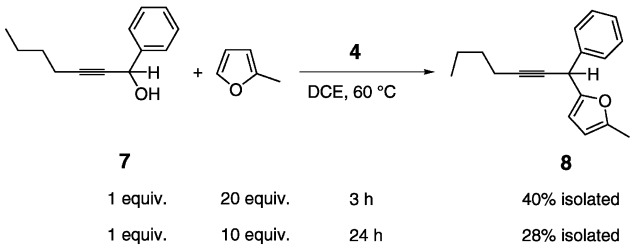
In order to understand the activation process and check the possible involvement of an allenylidene intermediate Ru=C=C=CHR, the related transformation of the propargylic alcohol **7**, which is unable to afford an allenylidene–ruthenium moiety with **4**, was attempted. Derivative **7** was reacted with an excess (20 eq.) of methylfuran in the presence of 5 mol% of **4** at 60°C for only 3 h and was completely converted to give the propargylated compound **8** with an increase in yield (40%) (Scheme 4). When only 10 eq. of methylfuran were used the reaction required 24 h for full conversion and the compound **8** was isolated in 28% yield.

Analogously, a reaction performed with **7** and 5 eq. of the arene **5** led to the derivative **9** isolated in 60% yield (Scheme 5).

These experiments demonstrate that the direct propargylation with **4** of methylfuran or arene **5** can take place without involving an allenylidene intermediate. Moreover, the propargylation with **7** is much more efficient than with **2** containing a terminal C≡C bond. As the conversion in both cases is similar, it is likely that parallel transformations (decomposition or polymerisation) of **2** or of the formed products **3** or **6**, are faster than those of **7**, **8** or **9**.



Scheme 3 Propargylation of furan and arene derivatives with a propargylic alcohol bearing a terminal alkyne.



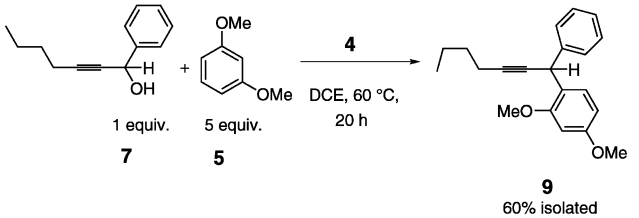
Scheme 4 Propargylation of methylfuran with a propargylic alcohol bearing an internal alkyne.

We can thus suggest that the propargylation takes place *via* an activation process analogous to that of the Nicholas reaction consisting in the stoichiometric nucleophilic substitution of propargylic alcohol with the help of cobalt carbonyl complex.[18] Activation of **4** is supposed to take place by decoordination of the acetonitrile ligand rather than arene decoordination since free *p*-cymene was never observed when the reaction mixtures were analysed by GC-MS. The resulting 16 electron ruthenium intermediate arising from **1** or **4** (Ru = [Ru(bisoxazoline)(*p*-cymene)]$^{2+}$(BF_4^-)$_2$) can coordinate the C≡C bond leading to the intermediate **A** (Scheme 6).

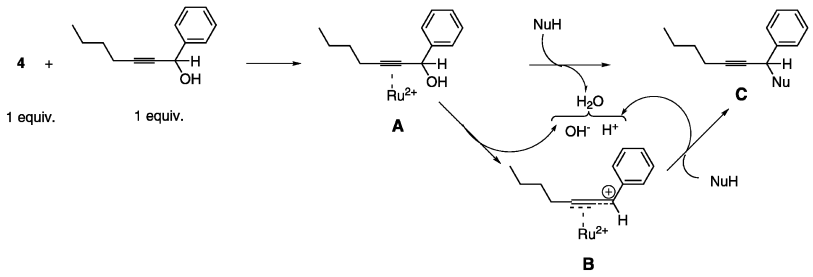
This coordination should enhance the nucleofugacity of the hydroxide in **A**, stabilizing the resulting α carbenium ion **B** and allowing the nucleophilic addition at the α-carbon of the coordinated C≡C bond. The high electrophilicity of the intermediate **B** may explain side reactions occurring by addition of propargylic alcohol to this intermediate. An attempt to demonstrate the involvement of a species like **A** was conducted by monitoring with ^{1}H NMR the stoichiometric reaction between **4** and **7** at 60 °C and 80 °C. It resulted in the formation of the propargylic ether **10** by addition of **7** as a nucleophile on its intermediate of type **B** (Scheme 7).

Conclusion

A monometallic dicationic ruthenium–bisoxazoline complex was found to catalyse the propargylation, directly with propargyl alcohols, of methylfuran and 1,3-dimethoxybenzene. The choice of the substrate **7** has allowed us to discard an activation pathway involving a ruthenium–allenylidene intermediate. An activation process *via* the Nicholas model can rather be suggested. However, two different reaction pathways depending on the nature of the substrate can not be discarded. Although the yields are modest these preliminary results are encouraging since bisoxazoline ligands allow a wide range of steric and electronic modifications that should be orientated to provide higher catalytic activity. Furthermore, bisoxazoline ligands play a crucial role in enantioselective catalysis[19] which has potential for the transformation presented here.



Scheme 5 Propargylation of dimethoxybenzene with a propargylic alcohol bearing an internal alkyne.



Scheme 6 Proposed activation process of propargyl alcohol.

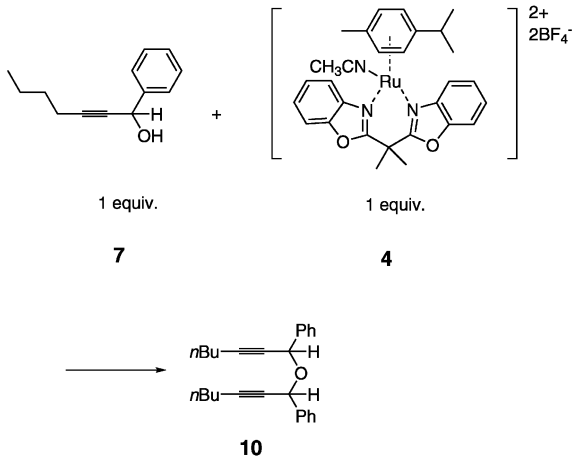
Experimental

General

All manipulations were performed under an inert atmosphere of argon using standard Schlenk tube technique. Commercially available methylfuran, dimethoxybenzene, phenylpropargyl alcohol and dichloroethane were distilled prior to use and stored under argon. Compound **7** was prepared by classical *n*BuLi deprotonation of 1-hexyne followed by condensation with benzaldehyde. Products **3**[12b] and **8**[13] were characterised by GC-MS and showed ^{1}H and ^{13}C NMR analyses consistent with those described in the literature. NMR spectra were obtained using a Bruker 300 MHz spectrometer. Proton and carbon assignments were done by using HMBC and HMQC sequences.

Synthesis

Complex 4. To 46 mg (0.24 mmol, 1.2 eq.) of $AgBF_4$ in a dried Schlenk tube filled with argon was added *via* cannula a solution of 122 mg (0.2 mmol, 1 eq.) of **1** dissolved in 40 ml of dichloroethane and 13 µl (0.24 mmol, 1.2 eq.) of CH_3CN. The reaction was stirred for 35 min at 60 °C resulting in the precipitation of a white solid (AgCl). This solid was filtered and the filtrate concentrated to half volume before being added to 30 ml of diethyl ether to precipitate the desired compound as a bright yellow powder. Precipitation was repeated to obtain complex **4** free of dichloroethane although a trace amount of this solvent was always present in the compound hindering elemental analysis (yield 0.44 g, 70%). ^{1}H NMR (300.131 MHz, CD_2Cl_2) δ: 1.26 (d, 6H, 6.7 Hz, CH(CH_3)$_2$), 2.12 (s, 6H, NC–CH_3, CCH_3), 2.28 (s, 3H, CCH_3), 2.92 (heptet, 1H, 6.7 Hz, CH(CH$_3$)$_2$), 6.31 (d, 5.4 Hz, 2H, CHar), 6.42 (d, 5.4 Hz, 2H, CHar), 7.71–7.84 (m, 6H, CHar), 7.97 (d, 8.0 Hz, 2H, CHar). ^{13}C NMR (75.475 MHz, CD_2Cl_2) δ: 3.5 (*C*H$_3$CN), 18.5 (*C*H$_3$ *p*-cymene), 22.4 (CCH$_3$), 23.0 (2*C*H$_3$ *p*-cymene), 28.6 (CCH$_3$), 32.2 (*C*H(CH$_3$)$_2$), 40.8 (*C*(CH$_3$)$_2$), 85.7, 86.3 (*C*H *p*-cymene), 105.7 (*C*CH$_3$ *p*-cymene), 117.2 (*C*CH(CH$_3$)$_2$) *p*-cymene), 111.2, 118.6, 127.7, 128.5 (*C*HAr), 130.1 (*C*≡N, weak), 139.3, 149.8 (*C*ar), 166.7 (*C*=N). HRMS (ESI CH_2Cl_2, M^{++} BF_4^-): calcd. 642.1502, found 642.1505.



Scheme 7 Stoichiometric activation of **7** by **4**.

***Crystal data for* 4.** $RuC_{31}H_{35}Cl_2N_2O_3 2BF_4$, M = 827.21, monoclinic, $P21/c$, a = 14.4571(4), b = 16.0168(4), c = 16.1516(5) Å, β = 112.092(1)°, V = 3465.4(2) Å^3, Z = 4, λ(Mo Kα) = 0.710 73 Å, μ = 6.84 cm^{-1}, F(000) = 1672, T = 120 K. 7953 reflections collected on a NONIUS Kappa CCD; Independent reflections, 7953 [R(int)=0.0000], Reflections observed ($>2\sigma$), 6062. Final R indices [$I > 2\sigma(I)$], $R1$ = 0.0596 $wR2$ = 0.1546. R indices (all data), $R1$ = 0.0826 $wR2$ = 0.1750.†

2,4-Dimethoxy-1-(1-phenylprop-2-ynyl)benzene, 6. A vacuum dried Schlenk tube was charged under argon with 132 mg (1 mmol, 1 eq.) of **2** and 36 mg (0.05 mmol, 5 mol%) of **4**; 5 ml of dichloroethane and 0.69 g (5 mmol, 5 eq.) of 1,3-dimethoxybenzene **5** were added and the reaction was stirred at 60 °C for 18 h. Solvent evaporation followed by chromatography purification on SiO_2 using heptane–ethyl ether (9 : 1, v/v) as eluant afforded 75 mg (yield 0.3 mmol, 30%) of **6** as a colorless oil. ^{1}H NMR (300.131 MHz, $CDCl_3$) δ: 2.41 (d, 1H, 1.6 Hz, ≡CH), 3.81 (s, 6H, OCH_3), 5.43 (d, 1H, 1.6 Hz, ≡CCH), 6.47 (d, 1H, 2.4 Hz, CH), 6.52 (dd, 1H, 2.4 Hz, 8.4 Hz, CH), 7.19–7.35 (m, 3H, CH), 7.40–7.47 (m, 3H, CH). ^{13}C NMR (75.475 MHz, $CDCl_3$) δ: 35.4 (≡C*C*H), 55.4 (O*C*H$_3$), 55.6 (O*C*H$_3$), 71.3 (≡*C*H), 85.5 (≡*C*), 98.7 (*C*H), 104.6 (*C*H), 122.3 (C_{ar}), 122.9 (*C*H), 126.6 (*C*H), 127.7 (*C*H), 128.3 (*C*H), 129.4 (*C*H), 141.5 (C_{ar}), 157.1 (C_{ar}), 160.0 (C_{ar}). HRMS (EI): calcd. 252.1150, found 252.1165. Anal for $C_{17}H_{16}O_2$. calcd: C, 80.93; H, 6.39; found: C, 80.86; H, 6.59%.

2,4-Dimethoxy-1-(1-phenylhept-2-ynyl)benzene, 9. A vacuum dried Schlenk tube was charged under argon with 188 mg (1 mmol, 1 eq.) of **7** and 36 mg (0.05 mmol, 5 mol%) of **4**; 5 ml of dichloroethane and 0.69 g (5 mmol, 5 eq.) of 1,3-dimethoxybenzene **5** were added and the reaction was stirred at 60 °C for 20 h. Fractionated distillation afforded 0.2 g (yield 0.60 mmol, 60%) of **9** as a light brown oil. ^{1}H NMR (200.130 MHz, $CDCl_3$) δ: 0.94 (t, 3H, 6.8 Hz, CH_3), 1.35-1.65 (m, 4H, CH_2), 2.29 (td, 2H, 2.2 Hz, 6.9 Hz, CH_2), 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 5.38 (bt, 1H, 2.2 Hz, ≡CCH), 6.40–6.65 (m, 3H, CH), 7.10–7.50 (m, 5H, CH). ^{13}C NMR (75.475 MHz, $CDCl_3$) δ: 13.7 (*C*H$_3$), 18.7 (*C*H$_2$), 22.1 (*C*H$_2$), 31.2 (*C*H$_2$), 35.6 (≡C*C*H), 55.4 (O*C*H$_3$), 55.5 (O*C*H$_3$), 81.3 (≡*C*), 83.6 (≡*C*), 98.6 (*C*H), 104.5 (*C*H), 123.7 (C_{ar}), 126.2 (*C*H), 127.7 (*C*H), 128.2 (*C*H), 129.4 (*C*H), 142.9 (C_{ar}), 157.0 (C_{ar}), 159.7 (C_{ar}). HRMS (EI): calcd. 308.1776, found 308.177 63. Anal. for $C_{21}H_{24}O_2$. calcd: C, 81.78; H, 7.84; found: C, 82.00; H, 8.00%.

† CCDC reference numbers 249962. See http://www.rsc.org/suppdata/nj/b5/b501305d/ for crystallographic data in CIF or other electronic format.

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