A Metal–Ligand Cooperative Pathway for Intermolecular Oxa-Michael Additions to Unsaturated Nitriles**

Sébastien Perdriau, Douwe S. Zijlstra, Hero J. Heeres, Johannes G. de Vries,* and Edwin Otten*

Abstract: An unprecedented catalytic pathway for oxa-Michael addition reactions of alcohols to unsaturated nitriles has been revealed using a PNN pincer ruthenium catalyst with a dearomatized pyridine backbone. The isolation of a catalytically competent Ru–dieneamido complex from the reaction between the Ru catalyst and pentenenitrile in combination with DFT calculations supports a mechanism in which activation of the nitrile through metal–ligand cooperativity is a key step. The nitrile-derived Ru-N moiety is sufficiently Brønsted basic to activate the alcohol and initiate conjugate addition of the alkoxy to the α,β-unsaturated fragment. This reaction proceeds in a concerted manner and involves a six-membered transition state. These features allow the reaction to proceed at ambient temperature in the absence of external base.

The chemistry of metal complexes bearing “non-innocent” ligands is receiving increasing attention because of its potential to expand the scope of reactivity beyond that which is possible with classical ligands. One particularly successful class of non-innocent ligands is based on a pincer scaffold with a central pyridine ring which can be dearomatized by deprotonation of an adjacent CH₂ group. The high reactivity of such dearomatized compounds towards a variety of X–H bonds (for example, X = H, OR, NR₂, RCOO) is driven in part by rearomatization of the pyridine ring. Milstein and co-workers have developed an impressive array of catalytic reactions using dearomatized PNN and PNP pincer complexes that make use of the metal–ligand cooperative (“bifunctional”) reactivity. It has been shown that the C=O bond in carbonyl compounds and CO can be activated in a similar fashion, leading to C–C and metal–O bond formation with concomitant rearomatization of the pincer backbone. More recently, this reaction was extended to include activation of nitrile C≡N bonds. Our group reported the ruthenium PNN pincer complex 1 (Scheme 1) to be an active olefin isomerization catalyst in the presence of iPrOH. In the course of these studies we found that non-conjugated nitriles such as 3-pentenenitrile (3-PN) do not only isomerize to the more stable α,β-unsaturated compounds, but also undergo unexpected oxa-Michael reactions. Although Michael additions with carbon nucleophiles are a well-established class of C=C bond-forming reactions, the analogous reactivity of oxygen nucleophiles (oxa-Michael addition) is less straightforward. This is due to the comparatively low nucleophilicity of alcohols and the reversibility of the oxa-Michael addition. Mechanistically, established pathways for oxa-Michael addition reactions involve the generation of reactive alkoxide nucleophiles through addition of a strong base, activation of the Michael acceptor by Lewis/Brønsted acids or (for α,β-unsaturated carbonyl compounds) organocatalysis via iminium intermediates. In contrast to α,β-unsaturated carbonyl acceptors, the corresponding nitriles have received considerably less attention because of their low reactivity towards conventional nucleophiles. The catalysis of oxa-Michael additions to unsaturated nitriles by transition-metal complexes (Ru,[12] Cu,[13] Ni,[14]) involves metal–alkoxide or metal–nitrile intermediates as a means of activating the Michael donor or acceptor, respectively. Despite these advances, the addition of nucleophiles containing heteroatoms to acrylonitriles remains challenging, in particular for β-substituted derivatives. Herein we report the dearomatized PNN-coordinated ruthenium complex 1 as an active catalyst for oxa-Michael additions to pentene- and butenenitriles under mild, additive-free conditions. The reaction is shown to proceed through...
a novel pathway that involves “bifunctional” activation of the nitrite.

Reaction of 3-pentenenitrile (3-PN) with a catalytic amount of 1 (0.5 mol% catalyst, overnight at room temperature in iPrOH) gave 87% conversion into a 1:3 mixture of compounds 2a and 3a (Scheme 1). Compound 2a is the result of α,β-dimerization of 3-PN,[10] whereas 3a is the oxa-Michael addition product of iPrOH to 2-pentenenitrile (2-PN). Using 2-PN as the substrate under identical conditions afforded 3a cleanly without concomitant formation of dimer 2a. To verify that the reaction was catalyzed by 1, we ran control experiments[17] in which both 2- and 3-PN were reacted in iPrOH with KOtBu as a base (0.5 and 2.5 mol% of KOtBu for the 2-PN and 3-PN reaction, respectively). However, these control experiments gave poor conversion (36 and 56%) into an approximately 1:1 mixture of 3a and the other pentenenitrile isomer. These results clearly establish that 1 has a role in the observed reactivity. A series of additional control experiments with Ru nanoparticles, other homogeneous “bifunctional” Ru complexes, and various Lewis acids failed to give conversion of 2-PN under these conditions.[13] Thus, 1 is distinctive in its ability to catalyze the conjugate addition of iPrOH to the β-substituted unsaturated nitrile isomers 2-PN and 3-PN at ambient temperature. In this context it should be noted that whereas 1 is known to catalyze the dehydrogenative coupling of alcohols to esters at elevated temperature (>115°C),[18] our room-temperature procedure completely suppresses this potential side reaction.

The reaction progress was monitored by GC analysis (0.5 mol% 1, 0.5 m unsaturated nitrile in iPrOH) and showed that addition to 2-PN occurs faster than to 3-PN. Additionally, for the 2-PN reaction there is negligible formation of the dimer 2a (see Figure S1 in the Supporting Information). With 3-PN as the substrate, catalyst deactivation causes the reaction to cease at approximately 85% conversion into a mixture of 2a and 3a. Although the deactivation pathway is currently unknown, it is likely that dimer 2a is involved: addition of 2a at the start of the reaction significantly slows down catalysis (Figure S2).

EtOH is also a suitable nucleophile but, contrary to expectation, the reaction is slower than with iPrOH (Figure S1). A competition experiment was performed by carrying out the catalytic oxa-Michael addition in a 1:1 mixture of EtOH and iPrOH. Surprisingly, the reaction is considerably faster in this mixture than in EtOH alone, and the product obtained is almost exclusively the EtOH addition product (3b:3a = 24:1). Screening other co-solvents for the EtOH addition gave similar results regardless of the nature of the co-solvent: protic and nonprotic polar (tert-amyl alcohol and THF) as well as nonpolar co-solvents (toluene) all lead to much faster oxa-Michael addition to form the EtOH addition product (Table 1, Figure S3). While the origin of this effect is at present not fully understood, it could be related to the (reversible) formation of catalytically inactive Ru–alkoxides[9] and/or Ru–dihydrides[15] species, the concentration of which is dependent on the alcohol used (Figure S4). A decreased EtOH content in the reaction mixture (by adding a co-solvent) may thus lead to an increase of catalytically competent Ru species and an enhanced reaction rate.[19]

<table>
<thead>
<tr>
<th>Solvent (S)</th>
<th>GC conversion [%][a]</th>
<th>1 h</th>
<th>17 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>ethanol</td>
<td>30</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>isopropanol[8]</td>
<td>62</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>tert-amyl alcohol</td>
<td>94</td>
<td>&gt;99</td>
<td></td>
</tr>
<tr>
<td>THF</td>
<td>97</td>
<td>&gt;99</td>
<td></td>
</tr>
<tr>
<td>toluene</td>
<td>94</td>
<td>&gt;99</td>
<td></td>
</tr>
</tbody>
</table>

[a] traces of 3-PN were also detected. [b] 4% (1 h) and 6% (17 h) of the isopropanol addition product was also obtained.

Having established that the oxa-Michael addition reaction is catalyzed by 1, we focused on elucidating the reaction mechanism. A stoichiometric NMR-scale reaction between 1 and 2-PN or 3-PN in C6D6 resulted in the formation of a single new Ru species (1PN), regardless of which penteninitrile isomer is used (Scheme 2). In the 1H-NMR spectrum, a new resonance for the hydride appears at δ = −12.0 ppm (JHH = 28.4 Hz). The occurrence of the signal at this chemical shift is indicative of a complex with a ligand which is bound trans to the Ru–H[19,20] and the position of the signals attributable to the protons of the pyridine ring is consistent with rearomatization of the ligand. The appearance of three new signals in the olefinic region of the 1H-NMR spectrum (δ = 6.70, 5.52, and 5.18 ppm) together with an N–H resonance at δ = 3.96 ppm indicate formation of a pentenenitrile-

![Scheme 2](https://example.com/scheme2.png)

**Table 1**: Effect of co-solvents on the addition of ethanol to 2-pentenenitrile to form 3b.

**Reference**


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derived dieneamido fragment. It is likely that C≡N bond addition of 3- and 2-PN initially forms the intermediates A and B, respectively, which subsequently tautomerize to the thermodynamic product 1PN (see Scheme 2 for structures of the intermediates). Related rhenium PNP pincer complexes were recently described by Milstein and co-workers for nitriles without a pendant C=C moiety.[8a] A single-crystal X-ray diffraction study on isolated 1PN gave unequivocal confirmation of its formulation as a Ru dieneamido species (Scheme 2).[8b] The length of the new C=C bond between the carbon of the ligand and that of the nitrile (C7−C21 1.529(8) Å) is in the range expected for a C=C single bond, and the structural parameters within the pincer backbone are consistent with a dearomatized ligand. Within the fragment derived from pentenenitrile, the long N3−C21 bond of 1.345(8) Å and short C21−C22 and C23−C24 bonds are typical of the bond lengths expected for a dieneamido moiety.

A noteworthy feature of 1PN is the addition of the nitrile through C−C bond formation at the side of the pincer NEt group, whereas in the starting material 1 the reactive moiety is at the P sidearm of the PNN ligand. Sanford and co-workers and Zhang and Liu observed that CO activation by 1 gives C−C bond formation at the P sidearm as the kinetic product, which converts into a thermodynamically more stable compound in which a C−C bond is formed at the N sidearm.[10,21]

Although 1 is known to react with iPrOH at low temperatures to give a Ru−alkoxide species, this reaction is not favorable at room temperature[10] and it is thus likely that catalysis of the oxo-Michael addition by 1 is initiated by activation of the nitrile. The observation that isolated 1PN is also catalytically competent lends credence to this hypothesis. To further elaborate the mechanistic details, calculations were carried out at the DFT/TPSS level of theory.[22] While the reactive moiety in 1 is at the PrBu nitrogen sidearm, nitrile addition to give 1PN takes place at the N≡N bond. Calculations were performed starting from both 1 and its tautomer 1-taut, which was calculated to be 6.6 kcal mol⁻¹ higher in energy.[21] The calculations indicate that the experimentally detected addition to the N≡N bond is favored over that at the PrBu nitrogen sidearm, both kinetically and thermodynamically.[23] Activation of the C≡N bond in 3-PN initially forms the Ru−ketimido species A, which subsequently tautomerizes to form the more stable Ru−diennamido compound 1PN obtained experimentally (Scheme 2). Overall, the transformation from 1−3-PN to 1PN is endergonic with ∆G_i = −7.0 kcal mol⁻¹. Starting from 2-PN, a similar pathway is calculated and the same product is obtained. Subsequent calculations to determine a plausible oxo-Michael addition pathway starting from 1PN identified the Ru−ketimido tautomer B that has the requisite α,β-unsaturated motif for conjugate addition (Scheme 3).[24] The reaction is calculated to proceed by hydrogen bonding of iPrOH with the Ru−N(ketimide) moiety (intermediate C), which leads to C−O bond formation via TS(C/D) (∆G° = 23.4 kcal mol⁻¹). Two salient features of this key step are worthy of mention: a) the bond-forming reaction occurs through a concerted mechanism via a six-membered transition state, and b) the Brønsted basicity of the ketimido N atom increases the nucleophilicity of iPrOH which leads to facile C−O bond formation. In a subsequent step, the resulting Ru−eneamido complex D is tautomerized to its Ru−ketimido analogue E. This liberates the organic oxo-Michael addition product 3a by retro-addition and regenerates the dearomatized ruthenium PNN starting material 1. While this last transformation is endergonic, capture of a new pentenenitrile substrate to form 1PN leads to a cycle for which the overall thermodynamics are favorable (∆G_i = −4.4 kcal mol⁻¹; ∆H_i = −17.1 kcal mol⁻¹). Experimentally, the stoichiometric reaction of 1 with 3a leads to formation of 1PN with liberation of iPrOH. This is in agreement with the DFT calculations and corroborates 1PN as the catalyst resting state.

Anticipating that this novel metal−ligand cooperative pathway for oxo-Michael addition through activation of the nitrile could be quite versatile, we performed a preliminary screening of the substrate scope using a 1:1 mixture of alcohol/THF as the solvent. The products obtained are shown in Scheme 4. In all cases, control experiments in the absence of 1 gave poor conversion and low yields of addition products.[17] Addition of primary or secondary aliphatic alcohols ROH to 2-PN afforded 3-alkoxypentenamides 3 which in each case were isolated in good yield (R = iPr (3a), 89%; Et (3b), 92%; Bn (3c), 77%). The butenenitrile
isomers crotonitrile and allyl cyanide both react with iPrOH to form the expected product 4 which was isolated in more than 90% yield. For the more reactive substrate acrylonitrile, the iPrOH addition product 5 was isolated in 95% yield using a catalyst loading as low as 0.07 mol%. Intramolecular reactions also proceeded smoothly, as shown by the high-yield cyclization of 6-hydroxy-2-hexenitriii and 7-hydroxy-2-heptenitriii to the corresponding 2-(tetrahydrofuran)- and 2-(tetrahydropropyl)acetonitriles 6a–b, respectively. β-Disubstituted conjugate acceptors (3-methylcrotonitrile) or tertiary O-containing nucleophiles (R = α-amyl, Ad) do not go to completion (7, 26% conversion) or give no conversion at all. The poor reactivity of these encumbered systems likely relates to unfavorable reaction energetics which acts by transferring Brønsted basic character to the nitrile N atom upon addition of the C≡N bond through metal–ligand cooperativity. The isolation of a catalytically competent Ru–dieneamido complex 1PN together with DFT calculations support a new mechanistic route for efficient hetero-Michael addition chemistry that takes place under mild, additive-free conditions.

**Experimental Section**

Synthesis of 3-isopropoxypentanenitrile (3a): A Schlenk flask was charged with 2-pentenenitrile (537 mg, 6.6 mmol), a 1:1 mixture of isopropanol/THF (13.2 mL), and pentadecane (83 mL) as the internal standard. Catalyst 1 (15 mg, 0.033 mmol) was added and the reaction was stirred at room temperature for 17 h. After quenching by exposure to air, all volatile components were condensed under high vacuum into a clean flask to separate them from the catalyst residue and pentadecane. The solvent was then evaporated by rotary evaporation (40°C, ca. 200 mbar) to yield 3a as a colorless oil in 89% yield (825 mg, 5.85 mmol). 1H NMR (200 MHz, CDCl3): \( \delta = 3.68 \) (sept, 1H, \( J = 6.1 \), CH/CHC=CH), 3.53 (quint, 1H, \( J = 6.0 \), CH/CHC=CH), 2.44 (d, 2H, \( J = 5.7 \), CH/CHC=CH), 1.59 (m, 2H, CH/CH=CH/CH/CH), 1.17 (d, 3H, \( J = 6.2 \), CH/CHC=CH), 1.13 (d, 3H, \( J = 6.1 \), CH/CHC=CH), 0.92 ppm (t, 3H, \( J = 7.3 \), CH/CHC=CH). 13C NMR (75 MHz, CDCl3): \( \delta = 118.1 \) (CN), 74.0 (CH/CHC=CH), 71.0 (CH/CHC=CH), 28.0 (CH/CHC=CH), 23.6 (CH/CHC=CH), 23.0 and 22.5 ((CH/CHC=CH), 9.7 ppm (CH/CHC=CH). HRMS (ESI) calcd. for C11H14O2N [M+H]+ 174.12264, found 174.12255.

**Keywords:** homogeneous catalysis · Michael addition · non-innocent ligands · pincer ligands · ruthenium

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