Oxa-Michael Additions

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

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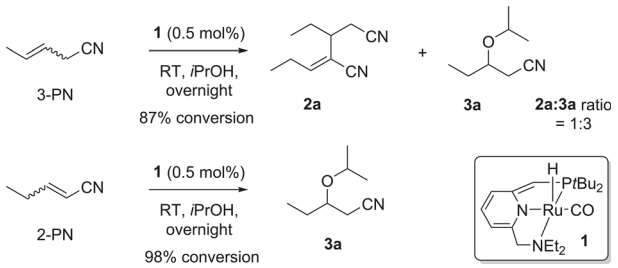
Abstract: *An unprecedented catalytic pathway for oxa-Michael addition reactions of alcohols to unsaturated nitriles has been revealed using a PNN pincer ruthenium catalyst with a dearomatized pyridine backbone. The isolation of a catalytically competent Ru–dieneamido complex from the reaction between 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 alkoxide 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.[1] 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 CH_2 group. The high reactivity of such dearomatized compounds towards a variety of X–H bonds (for example, X = H, OR, NR_2, 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.[2] It has been shown that the C=O bond in carbonyl compounds[3] and CO_2[4] 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.[5] Our group reported the ruthenium PNN pincer complex **1** (Scheme 1) to be an active olefin isomerization catalyst in the presence of *i*PrOH.[6] 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.[7] Mechanistically, established pathways for oxa-Michael addition reactions involve the generation of reactive alkoxide nucleophiles through addition of a strong base,[8] activation of the Michael acceptor by Lewis/Brønsted acids[9] or (for α,β-unsaturated carbonyl compounds) organocatalysis via iminium intermediates.[10] In contrast to α,β-unsaturated carbonyl acceptors, the corresponding nitriles have received considerably less attention because of their low reactivity towards conventional nucleophiles.[11] 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.[15] 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



Scheme 1. Catalytic addition of isopropanol to 2-pentenenitrile (2-PN) and 3-pentenenitrile (3-PN).

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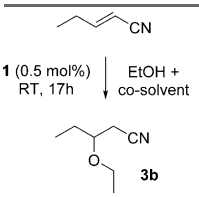
a novel pathway that involves "bifunctional" activation of the nitrile.

Reaction of 3-pentenenitrile (3-PN) with a catalytic amount of **1** (0.5 mol% catalyst, overnight at room temperature in *i*PrOH) 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,[16] whereas **3a** is the oxa-Michael addition product of *i*PrOH 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 *i*PrOH with KO*t*Bu as a base (0.5 and 2.5 mol% of KO*t*Bu 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^0 nanoparticles, other homogeneous "bifunctional" Ru complexes, and various Lewis acids failed to give conversion of 2-PN under these conditions.[17] Thus, **1** is distinctive in its ability to catalyze the conjugate addition of *i*PrOH 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 *i*PrOH) 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 *i*PrOH (Figure S1). A competition experiment was performed by carrying out the catalytic oxa-Michael addition in a 1:1 mixture of EtOH and *i*PrOH. 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–alkoxide[3a,6] and/or Ru–dihydride[18] 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]

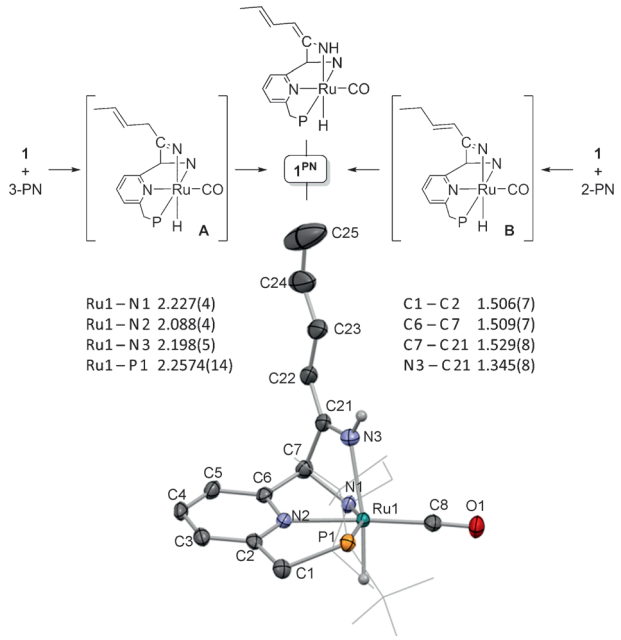
Table 1: Effect of co-solvents on the addition of ethanol to 2-pentenenitrile to form **3b**.



Solvent (S)	GC conversion [%][a] 1 h	17 h
ethanol	30	92
isopropanol[b]	62	98
tert-amyl alcohol	94	>99
THF	97	>99
toluene	94	>99

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

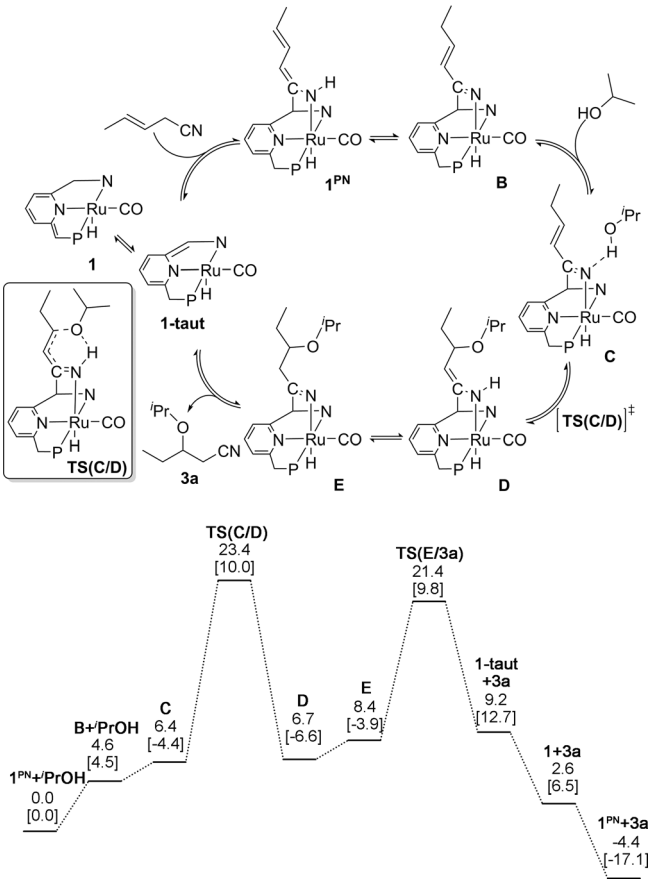
Having established that the oxa-Michael addition reaction is catalyzed by **1**, we focused on elucidating the reaction mechanism. A stoichiometric NMR-scale reaction between **1** and 2-PN or 3-PN in C_6D_6 resulted in the formation of a single new Ru species (**1^{PN}**), regardless of which pentenenitrile isomer is used (Scheme 2). In the ^{1}H NMR spectrum, a new resonance for the hydride appears at $\delta = -12.0$ ppm ($J_{PH} = 28.4$ 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[4b,18] 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 ^{1}H NMR spectrum ($\delta = 6.70$, 5.52, and 5.18 ppm) together with an N–H resonance at $\delta = 3.96$ ppm indicate formation of a pentenenitrile-



Scheme 2. Synthesis of compound **1^{PN}** and its molecular structure. Selected bond lengths [Å] are given and thermal ellipsoids are set at 50% probability. In the reaction scheme (top), the Et and *t*Bu substituents on the N and P sidearms, respectively, of the PNN pincer ligand are omitted for clarity. In the molecular structure, the P*t*Bu$_2$ and NEt$_2$ groups are drawn as a wire-frame model and H atoms (except the Ru–H and N–H) and the toluene solvate molecule are omitted for clarity.

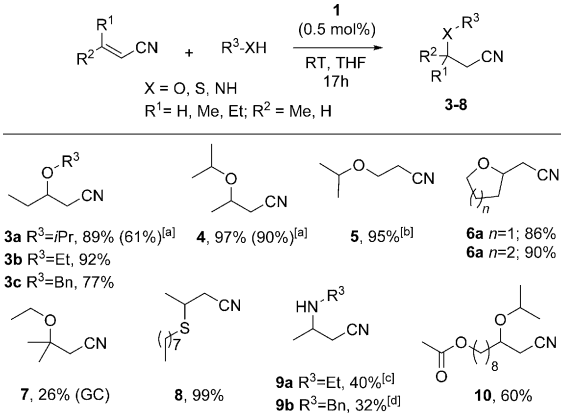
derived dieneamido fragment. It is likely that C≡N bond addition of 3- and 2-PN initially forms the intermediates **A** and **B**, respectively, which subsequently tautomerize to the thermodynamic product $\mathbf{1}^{\mathbf{PN}}$ (see Scheme 2 for structures of the intermediates). Related rhenium PNP pincer complexes were recently described by Milstein and co-workers for nitriles without a pendant C=C moiety.[5a] A single-crystal X-ray diffraction study on isolated $\mathbf{1}^{\mathbf{PN}}$ gave unequivocal confirmation of its formulation as a Ru dieneamido species (Scheme 2).[20] 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 rearomatized 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 $\mathbf{1}^{\mathbf{PN}}$ is the addition of the nitrile through C–C bond formation at the side of the pincer NEt_2 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_2 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.[4b,21]

Although **1** is known to react with *i*PrOH at low temperatures to give a Ru–alkoxide species, this reaction is not favorable at room temperature[6] and it is thus likely that catalysis of the oxa-Michael addition by **1** is initiated by activation of the nitrile. The observation that isolated $\mathbf{1}^{\mathbf{PN}}$ is also catalytically competent lends credence to this hypothesis. To further elaborate the mechanistic details, calculations were carried out at the DFT/TPSSTPSS level of theory.[22] While the reactive moiety in **1** is at the $PtBu_2$ pincer arm, nitrile addition to give $\mathbf{1}^{\mathbf{PN}}$ takes place at the NEt_2 pincer sidearm. 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 NEt_2 arm is favored over that at the $PtBu_2$ 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–dienamido compound $\mathbf{1}^{\mathbf{PN}}$ obtained experimentally (Scheme 2). Overall, the transformation from **1** + 3-PN to $\mathbf{1}^{\mathbf{PN}}$ is exergonic with $\Delta G_r = -7.0$ kcal mol^{-1}. Starting from 2-PN, a similar pathway is calculated and the same product is obtained. Subsequent calculations to determine a plausible oxa-Michael addition pathway starting from $\mathbf{1}^{\mathbf{PN}}$ 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 *i*PrOH with the Ru–N(ketimide) moiety (intermediate **C**), which leads to C–O bond formation via **TS(C/D)** ($\Delta G^{\ddagger} = 23.4$ 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 *i*PrOH 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 oxa-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 $\mathbf{1}^{\mathbf{PN}}$ leads to a cycle for which the overall thermodynamics are favorable ($\Delta G_r = -4.4$ kcal mol^{-1}; $\Delta H_r = -17.1$ kcal mol^{-1}). Experimentally, the stoichiometric reaction of **1** with **3a** leads to formation of $\mathbf{1}^{\mathbf{PN}}$ with liberation of *i*PrOH. This is in agreement with the DFT calculations and corroborates $\mathbf{1}^{\mathbf{PN}}$ as the catalyst resting state.



Scheme 3. DFT calculated pathway and corresponding reaction mechanism for the oxa-Michael addition of *i*PrOH to 3-PN. Values are relative Gibbs free energies (enthalpies in parentheses) in kcal mol^{-1}. On the PNN pincer ligand, *t*Bu groups on the P sidearm and Et groups on the N sidearm are omitted for clarity.

Anticipating that this novel metal–ligand cooperative pathway for oxa-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-alkoxypentanenitriles **3** which in each case were isolated in good yield (R = *i*Pr (**3a**), 89%; Et (**3b**), 92%; Bn (**3c**), 77%). The butenenitrile



Scheme 4. Products of hetero-Michael additions to α,β-unsaturated nitriles catalyzed by **1** with yields of isolated products given. [a] Yield of isolated product when starting from 3-alkenenitrile. [b] Reaction with 0.07 mol% catalyst. [c] 5 days at 40°C. [d] 3 days at 60°C. Bn = benzyl.

isomers crotonitrile and allyl cyanide both react with *i*PrOH to form the expected product **4** which was isolated in more than 90% yield. For the more reactive substrate acrylonitrile, the *i*PrOH 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-hexenenitrile and 7-hydroxy-2-heptenenitrile to the corresponding 2-(tetrahydrofuranyl)- and 2-(tetrahydropyranyl)acetonitriles **6a/b**, respectively. β-Disubstituted conjugate acceptors (3-methylcrotonitrile) or tertiary O-containing nucleophiles (R = *t*-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 ($\Delta G_r \geq 0$ based on DFT calculations). The phenols PhOH and *p*-NO_2-C_6H_4OH also fail to give conversion of 2-PN, which is likely due to formation of stable, catalytically inactive Ru–aryloxide species.[6,25] The importance of the nitrile in these oxa-Michael reactions was confirmed by the lack of reaction between ethanol and methyl crotonate. Other heteroatom-containing nucleophiles were subsequently tested. The addition of 1-octanethiol to crotonitrile is complete within 1 h at room temperature (**8**, 99% yield), whereas the addition of amines is less efficient, as shown for ethyl- and benzyl amine (**9a**/**9b**). Conversion into the aza-Michael addition products is slow (**9a**: 54% after 5 days at 40°C; **9b**: 39% after 3 days at 60°C), and the products were isolated in 40 and 32% yields, respectively. To investigate possible substrate inhibition in the aza-Michael addition reaction, crotonitrile was reacted with a 1:1 mixture of EtOH and $EtNH_2$. The catalyst is active and highly chemoselective for the addition of alcohol over amine,[26] with 94% conversion obtained after 1 h and less than 2% of amine addition product **9a** detected. This conclusively shows that no substrate inhibition takes place. Finally, using our novel base-free procedure we were able to obtain the acetyl-substituted oxa-Michael addition product **10**. The attempted KO*t*Bu-catalyzed synthesis of **10** resulted in rapid loss of the acetyl group by transesterification. These data provide further evidence for the distinctive properties of **1** as a catalyst in Michael additions.

In conclusion, the PNN pincer ruthenium complex **1** serves as an efficient catalyst for the oxa-Michael addition of alcohols to β-substituted unsaturated nitriles. The dearomatized pincer backbone in **1** is of central importance to the measured reactivity, 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 $\mathbf{1}^{PN}$ 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 μL) 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). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.68 (sept, 1H, J = 6.1, CH_3CHCH_3), 3.53 (quint, 1H, J = 6.0, CH_2CHCH_2), 2.44 (d, 2H, J = 5.7, $CHCH_2CN$), 1.59 (m, 2H, CH_3CH_2CH), 1.17 (d, 3H, J = 6.2, CH_3CHCH_3), 1.13 (d, 3H, J = 6.1, CH_3CHCH_3), 0.92 ppm (t, 3H, J = 7.3, CH_3CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 118.1 (CN), 74.0 (CH_2CHCH_2), 71.0 (CH_3CHCH_3), 28.0 (CH_3CH_2CH), 23.6 ($CHCH_2CN$), 23.0 and 22.5 ($(CH_3)_2CH$), 9.7 ppm (CH_3CH_2). HRMS (ESI) calcd. for $C_8H_{16}ON$ [M+H^+] 142.12264, found 142.12255.

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

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[23] Catalysis by substrate activation at the $PtBu_2$ arm is calculated to give intermediates/transition states that are significantly higher in energy and we conclude that this is not a likely reaction channel (see the Supporting Information).
[24] Compound **B** is the direct cycloaddition product of **1** and 2-PN, while its formation from **1** and 3-PN likely involves $\mathbf{1}^{\mathbf{PN}}$ as an intermediate.
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