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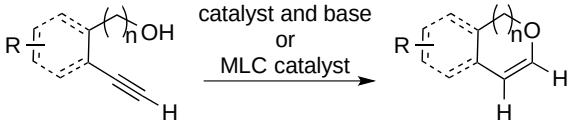
The first successful use of the $P^R_2N^{R'}_2$ (1,5-R'-3,7-R-1,5-diaza-3,7-diphosphacyclooctane) ligand family toward an organic synthesis is described. The precatalysts [Ru(Cp)($P^R_2N^{Bn}_2$)(MeCN)]PF_6 are active toward cyclization of ethynylbenzyl alcohol at low catalyst loading and mild temperatures. Catalyst performance however is limited by both low conscription and by competitive deactivation.

Oxygen heterocycles are important motifs in a variety of natural products and are used extensively as building blocks in synthesis.[1] Oxygen-containing iso-chromenes can be accessed through atom-economic catalytic cyclization of alkynyl alcohols with ruthenium (Scheme 1).[2] Mechanistically, this involves isomerization of a terminal alkyne to a metal vinylidene, followed by nucleophilic attack of the alcohol at the carbon alpha to the metal.[2c] Early examples of this transformation used a large excess of a base additive to mediate the required proton-transfer steps.[2a] Improved catalyst loadings and higher performance can be achieved by using a base as the solvent.[2c, 2d] An intermolecular base can be avoided if the catalyst contains an acid/base group on the ligand manifold to shuttle protons in an intramolecular fashion.[2f] Such metal-ligand cooperative (MLC) catalysts require low catalyst loadings and operate at moderate temperatures.



Scheme 1. Catalytic cyclization of alkynyl alcohols.[2a-f]

The bisphosphine $P^R_2N^{R'}_2$ (1,5-R'-3,7-R-1,5-diaza-3,7-diphosphacyclooctane) MLC ligand family are highly tunable through the R and R' substituents.[3] This property is exploited extensively in electrocatalytic transformations, including H_2 oxidation and production. Despite the growth of MLC catalytic processes for organic synthesis,[4] the $P^R_2N^{R'}_2$ ligands are yet to be exploited successfully in this realm. To address this, we recently studied the reactivity of [Ru(Cp)($P^{tBu}_2N^{Bn}_2$)(MeCN)]PF_6 (**1a**, Figure 1) with phenylacetylene.[5] The complex readily reacts with the alkyne to give a putative vinylidene, which is immediately and irreversibly deactivated at Cα by attack of the Lewis basic pendent nitrogen to give **2a**. This precludes the use of **1a** in catalytic alkyne functionalization strategies[6] that rely on intermolecular nucleophilic attack at this Cα position. We reasoned that cyclization via intramolecular nucleophilic attack would compete with deactivation. Herein, we report the first successful use of M($P^R_2N^{R'}_2$) complexes in a transformation for organic synthesis, specifically cyclization of alkynyl alcohols.

In addition to **1a**, the MLC complex **1b** and a control complex **3** – that lacks a pendent base in the dppp ligand backbone (dppp = 1,3-bisdiphenylphosphinopropane) – were prepared by ligand exchange with the ruthenium precursor [Ru(Cp)$(MeCN)_3$]PF_6. Complexes **1b** and **3** exhibited δ_{31P} of 38.4 and 37.4, respectively, that are in accord with previously reported **1a**[7] and RuCl(Cp)(dppp)[8] (cf. 52.6 and 38.7 ppm, respectively). The structure of **1b** and **3** were further characterized by ^1H and $^{13}C\{^1H\}$ NMR spectroscopy and MALDI MS. A crystal structure of **1b** was also obtained (See ESI).

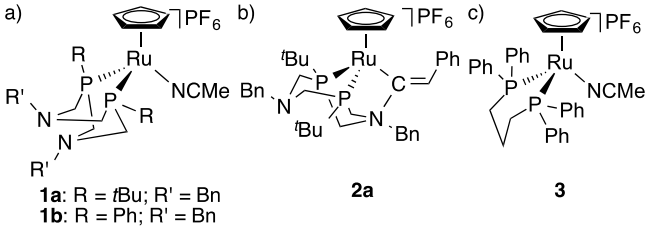


Figure 1 a) Ruthenium MLC catalysts employed in this study; b) known deactivation of **1a** on reaction with phenylacetylene; c) non-MLC control catalyst.

Cyclization catalysis was assessed with ethynylbenzyl alcohol (**4a**) with 5 mol% **1a** at 40 ˚C in acetone, CH_2Cl_2 and THF, and at 60 ˚C in MeCN (Figure 2). Gratifyingly, the MLC catalyst **1a** is active in the intramolecular cyclization reaction. Optimal

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†Electronic Supplementary Information (ESI) available: Synthetic procedures, NMR and IR spectroscopy and MALDI MS specta, additional catalysis graphs, crystallographic data. See DOI: 10.1039/x0xx00000x

catalyst performance was observed in acetone where a maximum conversion of 82% of benzopyran (**5a**) was achieved within 6 h. Conversion was slower in CH_2Cl_2 and THF, but final 24 h values were similar to acetone. Poor performance in MeCN (max 10% conv.) is likely due to suppressed lability of the coordinating MeCN ligand preventing substrate binding. Lowering the loading of **1a** to 1 and 0.1 mol% in acetone reveals that reasonable performance is achieved with the former. The catalyst loadings are in the range of the best known cyclization catalysts (1 – 5 mol%)[2b, 2f] whilst operating at a lower temperature (cf. 70 – 90 ˚C for known[2a-f] systems). A comparison of catalyst performance was conducted under optimal conditions of 1 mol% catalyst at 40 ˚C in acetone (Figure 2d). Catalyst **1b** with phenyl substituents on the phosphine donors leads to lower catalyst activity relative to the *t*Bu-substituted **1a**. No product is observed on treating **4a** with the dppp catalyst **3**, which is strong support that the pendent base of **1a** and **1b** is required for catalysis. The role of the base is likely to act as the proton shuttle, required for a MLC mechanism.

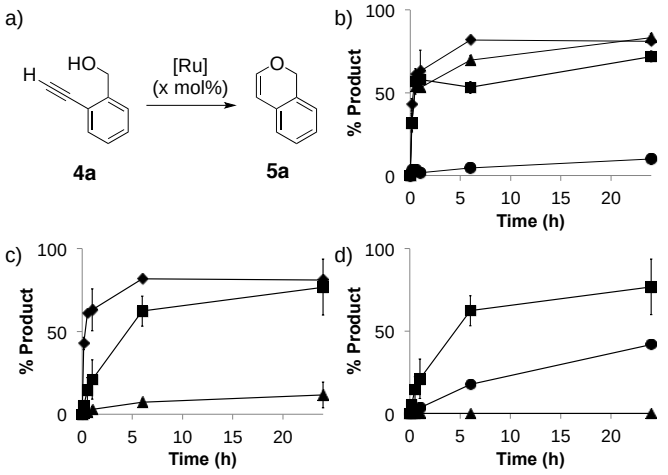
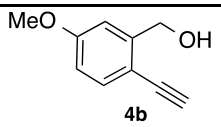
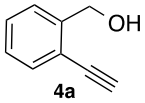


Figure 2. a) Cyclization of **4a** (150 mM) at 40 ˚C monitored over 24 h with [Ru] b) 5 mol% **1a** in acetone (◆), CH_2Cl_2 (▲), THF (■) and MeCN at 60 ˚C (●); c) 5 (◆), 1 (■), 0.1 (▲) mol% **1a** in acetone; d) 1 mol% **1a** (■), **1b** (●) and **3** (▲) in acetone.

Using the optimal conditions of 1 mol% **1a** or **1b** at 40 ˚C the substrate scope was evaluated with the more challenging methoxy-substituted (**4b**) and alkyl-linked (**4c**) substrates (Table 1, Entries 1-4). In both cases, poor or no product yield was observed with either catalyst. This prompted catalytic testing at increased temperatures. Surprisingly, no improvement in yield is observed on conducting cyclization of **4a** at 54 ˚C (Table 1, Entries 5-8). In the case of the dppp catalyst **3**, the higher temperature still did not promote productive turnover (Table 1, Entries 9-10).

The poor conversion to cyclization product **5a** at higher temperatures suggested a competitive deactivation process is promoted under these conditions. To confirm this, ruthenium speciation was monitored by $^{31}P\{^1H\}$ NMR spectroscopy during catalysis (Figure 3). Reactions were conducted at 40 and 50 ˚C in acetone-d_6 with a slightly higher loading of **1a** (1.5 mol%) to achieve reasonable signal to noise. At 40 ˚C precatalyst **1a** is the dominant species over 95 min, representing ca. 71% of the initial integration. Thus conscription of **1a** into the catalytic cycle is low, presumably due to poor MeCN lability. Two minor species are observed at 70.8 and 71.1 ppm each in ca. 10% yield. At 50 ˚C, entry of **1a** into the catalytic cycle is increased as the proportion of the precatalyst is reduced significantly to ca. 30%. By 95 minutes the species found at 71.1 and 70.8 ppm are present in a 43 and 9% yield, respectively. The dominant species is assigned as the deactivation product **7a**, an analogue of the previously characterized deactivation species **2a** that has a very similar ^{31}P chemical shift (cf. δ_{31P} = 71.5 for **2a**).[5] By 7 h **7a** is observed in 84%, but greater conversion is not achieved on longer reaction times and attempts to isolate **7a** were unsuccessful. In situ NMR spectroscopy of the catalytic sample showed a correlation from the methylene protons of the $P^{tBu}{}_2N^{Bn}{}_2$ ring to a new carbon signal at 196.9 ppm. This is very similar to Cα in **2a** ($\delta_{C\alpha}$ = 195.7) and is significantly upfield of Cα for a vinylidene (ca. 350 ppm). This data, together with the poor catalytic performance when **7a** is dominant, supports assignment of this deactivation species. The third species found in the in situ experiments (δ_{31P} = 70.8) is tentatively assigned as an on-cycle catalyst intermediate, either a π-bound alkyne species (**6a**), a Ru–vinylidiene (**6a'**) or Ru–vinyloxonium species (**6a''**) (Figure 4). Assignment as **6a''** is favoured since analogues of **6a** and **6a'** were not observed on reaction of **1a** with phenylacetylene.[5]

Table 1. Catalyst comparison and substrate scope for cyclization.[a]

Entry	Substrate	[Ru]	Temp (˚C)	Yield (%)[b]
1	 **4b**	**1a**	40	22
2		**1b**	40	12
3	 **4c**	**1a**	40	0
4		**1b**	40	0
5	 **4a**	**1a**	40	77
6		**1a**	54	52[c]
7		**1b**	40	42
8		**1b**	54	34
9		**3**	40	0
10		**3**	54	0

[a] Conditions: 150 mM **4a**, 1 mol% [Ru], acetone, 24 h. [b] Determined by ^1H NMR spectroscopy by relative integration to an internal standard (dimethyl terephthalate). [c] Time = 2 h at which point max conversion is reached.

We postulated that rapid turnover with minimal deactivation could be achieved at low temperature by generating the active catalyst by halide abstraction. Cyclization of **4a** at 40 ˚C was conducted with 1 mol% of the neutral precatalyst $RuCl(Cp)(P^{tBu}{}_2N^{Bn}{}_2)$ treated with $TlPF_6$ to halide abstract in situ. A maximum conversion of 79% **5a** was reached within 1 h,

considerably faster than catalyst **1a** that requires 6 h to reach a similar conversion. However, the maximum conversion does not significantly exceed that found for **1a** (cf. 77% at 24 h). Thus, halide abstraction from RuCl(Cp)($P^{tBu}_2N^{Bn}_2$) gives faster catalysis via improved initiation, but overall yields are not improved as deactivation remains problematic. Rapid initiation and deactivation is likewise found at room temperature.

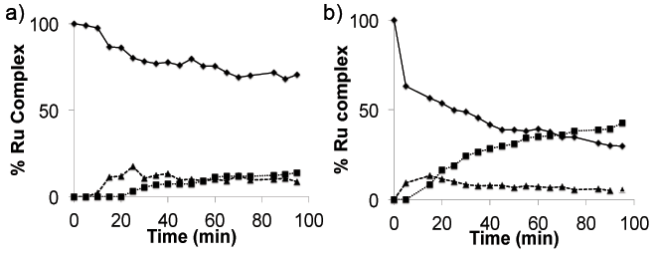


Figure 3. In situ observation of **1a** (◆; δ_{31P} = 53.9), **6a/6a'/6a''** (▲; δ_{31P} = 70.8), **7a** (■; δ_{31P} = 71.1) by $^{31}P\{^1H\}$ NMR spectroscopy relative to an internal standard (O=PPh_3) over 95 min at a) 40 ˚C and b) 50 ˚C.

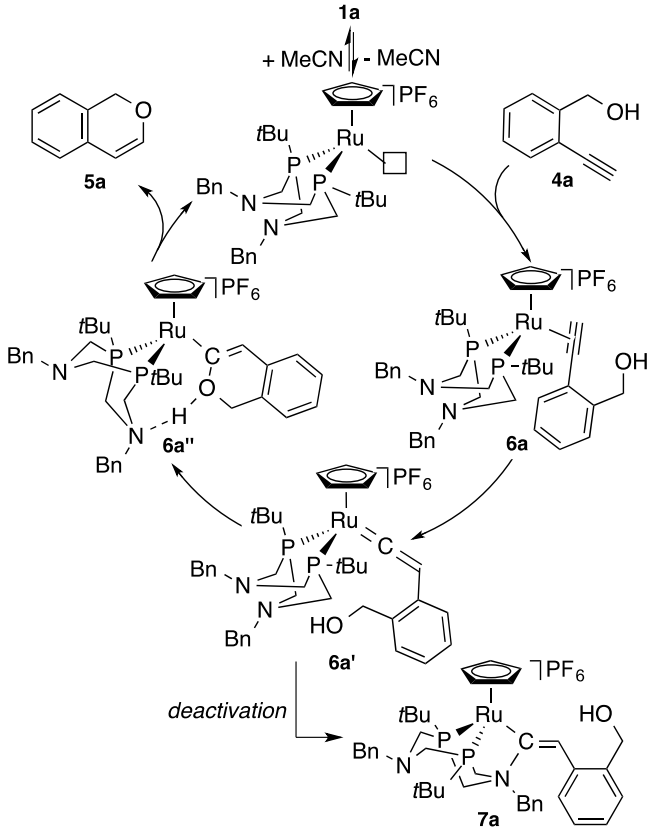


Figure 4. Postulated mechanism for the cyclization of 2-ethynylbenzyl alcohol (**4a**) with catalyst **1a**. The box (□) represents an open coordination site.

Conclusions

The cationic precatalysts [Ru(Cp)($P^R_2N^{Bn}_2$)(MeCN)]PF_6 (**1a**: R = *t*Bu; **1b**: R = Ph) are active for the cyclization of ethynylbenzyl alcohol (**4a**) under milder conditions than known catalysts. This represents the first successful example of the MLC $P^R_2N^{R'}_2$ ligand family used in an organic transformation. In situ catalyst studies revealed that competitive catalyst deactivation is a major challenge to increasing performance and expanding the substrate scope. Thus, the pendent amine of the $P^R_2N^{R'}_2$ ligand is both beneficial by promoting cooperative catalysis and detrimental by deactivating the active vinylidene intermediate. The balance of these two roles must be considered for future catalyst designs and in other applications of these complexes.

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