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Exploring Bis-Cyclometalated Ru(II) Complexes as Active Catalyst Precursors: Room-Temperature Alkene-Alkyne Coupling for 1,3-Diene Synthesis

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Late transition metal-mediated C–H bond activation has become a popular method to generate metal-carbon σ bonds in metallacycle synthesis. These cyclometalation reactions are usually facilitated by a heteroatom (X)-based functional group nearby the target C–H bond.^[1] Such directed C–H bond activation strategy has been widely used to generate cyclometalated late transition catalysts and catalyst precursors in various homogeneous catalytic processes.^[2] Among reported metallacycles as catalyst precursors, a dominant majority feature one 5- or 6-member chelating ring with a η^2 -[C,X] ligand as both anionic carbon-donor and neutral heteroatom-donor. By contrast, bis-cyclometalated late transition metal complexes with *two* η^2 -[C,X] ligands^[3] are rarely exploited as organometallic catalysts.^[4–6] We herein report the synthesis, structural characterization, and catalytic applications of several bis-cyclometalated ruthenium(II) complexes with η^2 -[C,N] and η^2 -[C,O] ligands. The potential of these ruthenacycles as catalyst precursors is demonstrated by

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a room-temperature catalytic alkene-alkyne coupling to synthesize $\alpha,\beta,\gamma,\delta$ -unsaturated esters and amides.

We have recently reported a bis-cyclometalated octahedral Ru(II) complex, $\{\text{Ru}(\eta^4\text{-cod})[\eta^2\text{-HN}=\text{C}(\text{C}_6\text{H}_5)\text{C}_6\text{H}_4]_2\}$ (**1a**), as a catalyst precursor in Ru(II)-catalyzed [3+2] carbocyclization between N-H ketimines and alkynes using a N-heterocyclic carbene ligand IPr (Scheme 1).^[7] The proposed mechanism involves carbon-carbon bond formation by alkyne insertion into the Ru–C σ bond of a ruthenacycle intermediate (**A**→**B**), presumably facilitated by the IPr ligand that has replaced cod ligand on Ru center. Thus, the substrate-derived $\eta^2\text{-[C,N]}$ imine ligands appear to play the dual role of actor ligand and spectator ligand, eventually incorporated into the cyclization product and replaced by incoming ketimine substrates via cyclometalation. It is noteworthy that **1a** did not react with alkyne substrates without added IPr ligand, suggesting significant ligand effect on its stability and reactivity. We envision that bis-cyclometalated **1a** and its structural analogs can be further explored as Ru(II) catalyst precursors with $\eta^2\text{-[C,X]}$ ligands *solely as spectator ligands* that occupy four of the six coordination sites and affect reactions occurring at the other two *cis*-coordination sites (Scheme 2, **C**). In particular, ancillary ligands (L) can be replaced by alkene/alkyne substrates via π -complexation (**C**→**D**), setting the stage for C–C bond formation by oxidative cyclization (**D**→**E**).^[8] The latter transformation is a key step in a number of Ru-catalyzed C–C coupling reactions such as alkene-alkyne (enyne) couplings for diene synthesis,^[9] [2+2] or [2+2+2] cycloadditions,^[10] and [2+2+1] cycloadditions such as the Pauson-Khand reaction.^[11] With easily accessible $\eta^2\text{-[C,X]}$ ligands via C–H activation, bis-cyclometalated Ru(II) complexes may serve as an attractive alternative to existing Ru catalysts,^[12] allowing modular catalyst design and tunable ligand effects on catalyst efficiency and selectivity.

As reported previously,^[7] complex **1a** was synthesized by room-temperature cyclometalation of benzophenone imine with a commercially available Ru(II) π -allyl complex $[(\text{cod})\text{Ru}(\eta^3\text{-methallyl})_2]$ in a 2:1 ratio (Scheme 3). A bis-cyclometalated ketone analog $\{\text{Ru}(\eta^4\text{-cod})[\eta^2\text{-OC}(\text{C}_6\text{H}_5)\text{C}_6\text{H}_4]_2\}$ (**1b**) was synthesized using benzophenone in a similar fashion, albeit with lower reactivity and requiring heating at 80 °C for complete conversion. The chelating cod ligand in both **1a** and **1b** could be replaced by two pyridine ligands via heating in neat pyridine at 60 °C to form bis(pyridine)-ligated **2a** and **2b** respectively. The solid-state structures of complexes **1a**,^[7] **1b**, **2a** and **2b** were determined by single crystal X-ray diffraction (see Supporting Information for details). All four of these bis-cyclometalated Ru(II) complexes displayed a near-octahedral Ru(II) center with two *cis* $\eta^2\text{-[C,X]}$ ligands, where the two N or O atoms were *trans* to each other and the two Ru–C σ bonds were *cis* to each other.^{[7][13]}

The catalytic activity of bis-cyclometalated Ru(II) complexes was evaluated by intermolecular alkene-alkyne coupling between diphenylacetylene (**3a**) and methyl acrylate (**4a**) to form a (2E,4Z)-1,3-diene product **5a** (Table 1).^{[9][14–16]} Using 5 mol% $[(\text{cod})\text{Ru}(\eta^3\text{-methallyl})_2]$ (**6**) as catalyst precursor and no added ligands led to only 12% conversion after heating at 80 °C for 24 hours in toluene (entry 1). By contrast, *in situ* generated ruthenacycle **1a** by pre-activation of **6** with 2 equivalents of benzophenone imine effectively promoted formation of **5a** in quantitative yield (entry 2). Compared to benzophenone imine ligand,

much lower reactivity was observed when catalyst pre-activation was carried out using other aromatic compounds that are capable of generating bis-cyclometalated Ru(II) complexes.^[13] For example, using 2-phenylpyridine and benzophenone ligands both result in lower than 10% conversion (entries 3,4; see Supporting Information for complete results).

Gratifyingly, the *in situ* formed **1a** was sufficiently active at room temperature, promoting quantitative formation of **5a** after 24 hours with 5 mol% catalyst loading (entry 5). To our best knowledge, this is the first example of room-temperature catalytic acrylate-alkyne coupling to form $\alpha,\beta,\gamma,\delta$ -unsaturated esters and complements other catalyst systems for mild enyne couplings.^{[15][16]} Notably, skipping the 80 °C pre-activation led to much lower catalyst reactivity (entry 6). Thus, isolated **1a** was used as catalyst precursor to further evaluate the solvent effect, with highest reactivity observed in toluene and THF solvents (entries 7-11). Under optimized conditions, room-temperature coupling between **3a** (1.0 equiv) and **4a** (2.0 equiv)^[17] proceeded smoothly in toluene solvent with 5.0 mol% **1a**, giving **5a** in quantitative yield by GC analysis (entry 7). The pyridine-ligated bis(imine) complex **2a** was less stable than **1a** in solution phase but displayed comparable catalytic activity (entry 13). By contrast, the bis(ketone) analogs **1b** and **2b** were virtually unreactive as catalyst precursors (entries 12 and 14). Such reactivity distinction is consistent with the mechanistic hypothesis that cod or pyridine ligands will be replaced by alkene/alkyne substrates (Scheme 2, **C**→**D**), thus having little effects on catalytic activity beyond the initial stage of catalyst pre-activation. On the other hand, the η^2 -[C,X] imine or ketone ligands are expected to stay on the Ru center throughout catalytic cycles and play a dominant role on catalyst activity.

With the standard reaction conditions established, various internal alkynes and acrylic esters or amides were studied for Ru-catalyzed room-temperature alkene-alkyne coupling (Table 2). Coupling between **3a** and unsubstituted alkyl acrylates proceeded smoothly to form 1,3-diene products **5a-d** and **5f** in over 90% yields and with exclusive stereoselectivity for the (2E,4Z)-isomers. For phenyl acrylate coupling product **5e**, the yield was improved from 58% to 87% by replacing **1a** with bis(pyridine) ruthenacycle **2a** as the catalyst precursor. Such reactivity enhancement is likely due to facile catalyst activation by substrate replacement of more labile pyridine ligands compared to the chelating diene ligand. When coupling between **3a** and **4a** was scaled up from 0.2 mmol to 20 mmol, the loading of **1a** could be reduced to 1.0 mol% to acquire **5a** in 90% isolated yield (4.8 gram purified product) over 48 hours. Coupling between **3a** and N,N-dimethyl acrylamide gave product **5g** in 72% yield, while heating was needed to improve the yield of N,N-diethyl product **5h** to 85% at 60 °C. Compared to less reactive N,N-dialkylacrylamides, N-isopropyl- and N-*t*-butylacrylamide reacted with **3a** in good reactivity to form products **5i** and **5j**, although the latter required **2a** as catalyst precursor for satisfactory yield. The scope of alkyne substrates was studied by coupling reactions with methyl acrylate (**4a**) to give products **5k-v**. High reactivity and regioselectivity was observed for phenylacetylene derivatives with alkyl substituents (products **5k-s**), favoring the formation of 4-alkyl-5-aryl regioisomer in >10:1 selectivity. The mild reaction conditions allow good compatibility with functional groups such as acyl, formyl, and Br substituents (products **5p**, **5r** and **5s**), providing synthetic handles for further functional group transformations. Aliphatic internal alkynes such as 3-

hexyne and 4-octyne displayed lower reactivity than aromatic alkynes, and a 2:1 alkyne/acrylate stoichiometry was used to get coupling products **5t** and **5u** in moderate yields. Coupling between **4a** and terminal alkynes generally suffered from low reactivity and gave a complex mixture of products.^[18] Nevertheless, coupling between **4a** and phenylacetylene was effectively catalyzed by **2a** to form product **5v** with (E,E)-stereoselectivity in 65% isolated yield.^[14b]

Three types of reaction mechanism have been proposed for Ru-catalyzed alkene-alkyne couplings to form 1,3-dienes:^{[14][19]} (1) C–C bond formation by alkene-alkyne oxidative cyclization (Scheme 2), followed by β -H elimination and C–H reductive elimination (Path 1); (2) alkyne insertion into a Ru hydride, followed by alkene insertion into the resulting Ru-alkenyl linkage and subsequent β -H elimination (Path 2); (3) sp^2 C–H bond activation of alkene, followed by alkyne insertion into Ru alkenyl, and C–H bond formation by either reductive elimination or protonation of Ru–C bond (Path 3). Although the latter two pathways cannot be completely ruled out, the oxidative cyclization mechanism (Path 1) is most consistent with the observed regio- and stereochemistry in coupling products. In particular, high regioselectivity with non-symmetric alkyne substrates (products **5k-s**) supports C–C bond formation by oxidative cyclization (Path 1) or alkyne insertion into Ru-alkenyl linkage (Path 3), not by alkyne insertion into Ru–H linkage (Path 2).^[19] The complete lack of (2Z)-stereoisomers as coupling products also argues against the proposed alkene C–H activation stereochemistry in Path 3, which should favor (2Z)-isomers by ester- or amide-directed C–H activation/cyclometalation.

The proposed oxidative cyclization pathway has prompted us to extend our study to other mechanistically related C–C couplings using current catalyst system. Thus, **1a** was found to catalyze room-temperature dimerization of methyl acrylate with high efficiency and exclusive tail-to-tail regioselectivity (Eq. 1).^[17] In addition, a [2+2] norbornene/alkyne cycloaddition was effectively catalyzed by **1a** at 120 °C (Eq. 2), which further supports the proposed Ru(II)/Ru(IV) catalytic cycle involving oxidative cyclization.^{[19][20]}

In summary, we have developed a new class of bis-cyclometalated Ru(II) catalyst precursors with readily available η^2 -[C,X] ligands based on aromatic N–H ketimines and ketones. The catalytic activity of bis(imine) complex **1a** was demonstrated with several catalytic C–C coupling reactions by proposed Ru(II)/Ru(IV) catalytic cycles involving oxidative cyclization. A room-temperature alkene-alkyne coupling was promoted to form $\alpha,\beta,\gamma,\delta$ -unsaturated esters and amides with high regio- and stereoselectivities, good functional group tolerance, and very high catalyst efficiency in a representative gram-scale synthesis. The major limitation of current catalyst system is the limited scope of alkene substrates,^{[21][22]} which we aim to improve by a more systematic future study on structure-reactivity correlations in bis-cyclometalated Ru(II) complexes with various η^2 -[C,X] ligands.

(1)

(2)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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21. The current catalyst system did not work with α - or β -substituted acrylates or less electron-deficient alkenes such as vinylarenes.
22. Preliminary results from DFT calculations suggest involvement of hydrogen-bonding interactions between cyclometalated imine NH moieties and carbonyl groups from acrylate substrates, which could contribute to the reactivity dependence on alkene substrates and classes of $\eta^2\text{-[C,X]}$ ligands. Results of this computational study on proposed catalytic mechanisms will be reported separately.

Scheme 1.

Proposed C-C bond formation by alkyne insertion into Ru-C bond of ruthenacycle intermediates for Ru(II)-catalyzed [3+2] imine/alkyne carbocyclization.^[7]

Scheme 2.

Envisioned C-C bond formation by oxidative cyclization with bis-cyclometalated Ru(II) complexes having two η^2 -[C,X] ligands

Scheme 3.

Synthesis of bis-cyclometalated Ru(II) complexes with η^2 -[C,N] benzophenone imine and η^2 -[C,O] benzophenone ligands.

Table 1

Development of the catalytic reactions.^[a]

Entry	Ru Catalyst	Ligand	Solvent	Method ^[b]	Temp.	Yield (%) ^[c]
1	[Ru(cod)(C ₄ H ₇) ₂] (6)	none	toluene	A	80 °C	12
2	6	Ph ₂ C=NH	toluene	B	80 °C	>98
3	6	2-phenylpyridine	toluene	B	80 °C	8
4	6	Ph ₂ C=O	toluene	B	80 °C	<5
5	6	Ph ₂ C=NH	toluene	B	r.t.	>98
6	6	Ph ₂ C=NH	toluene	A	r.t.	15
7	1a	none	toluene	A	r.t.	>98
8	1a	none	THF	A	r.t.	96
9	1a	none	DME	A	r.t.	66
10	1a	none	DMF	A	r.t.	93
11	1a	none	hexane	A	r.t.	82
12	1b	none	toluene	A	r.t.	<2
13	2a	none	toluene	A	r.t.	>98
14	2b	none	toluene	A	r.t.	<2

^a Conditions: **3a** (0.20 mmol, 1 equiv), **4a** (2.0 equiv), Ru catalyst (0.05 equiv), ligand (0.10 equiv), solvent (0.5 mL), room temperature (20-22 °C) or 80 °C, 24 h.

^b Mixing methods: (A) All components were mixed without pre-activation; (B) Ru precursor **6** and the ligand were added to toluene and stirred at 80 °C for 30 min; the mixture was then cooled down to room temperature and added with substrates **3a** and **4a**.

^c GC yields with *n*-dodecane as internal standard.

Table 2

Scope of the catalytic alkene-alkyne coupling.^[a] ^a Conditions: **3** (0.20 mmol, 1.0 equiv), **4** (2.0 equiv), **1a** (0.050 equiv), toluene (0.5 mL), 20–22 °C, 24h; averaged isolated yields of two runs.^b Isolated yield under scale-up conditions: **3** (20 mmol, 1.0 equiv), **4** (2.0 equiv), **1a** (0.010 equiv), toluene (6.0 mL), 22 °C, 48h.^c Using **2a** as catalyst precursor.^d Reactions at 60 °C^e Combined yield of two regioisomers (ratios determined by NMR analysis); structure of major isomer is shown.^f Using 0.20 mmol methyl acrylate as limiting reagent and 2.0 equiv of alkyne.^g Isolated yield for the major stereoisomer in 5:1 selectivity; minor isomer was not purified.