Macrocyclic Pincers

International Edition: DOI: 10.1002/anie.201807028
German Edition: DOI: 10.1002/ange.201807028

Terminal Alkyne Coupling Reactions through a Ring: Mechanistic Insights and Regiochemical Switching

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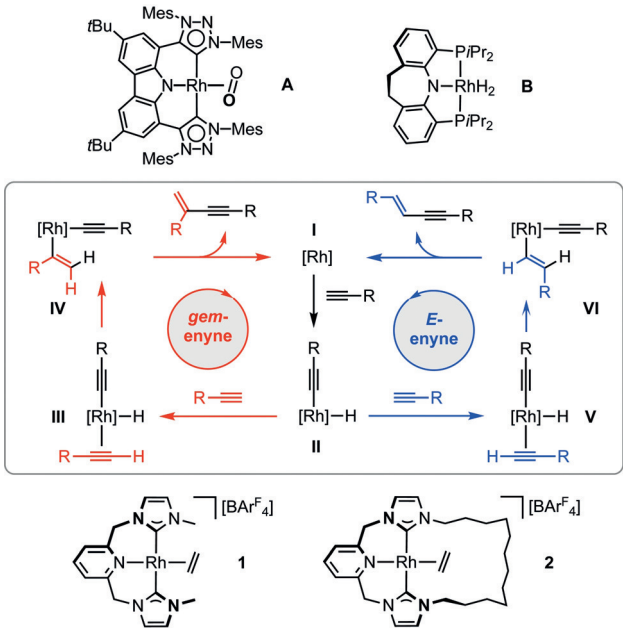
In memory of Andrew Brodie

Abstract: *The mechanism and selectivity of terminal alkyne coupling reactions promoted by rhodium(I) complexes of NHC-based CNC pincer ligands have been investigated. Synthetic and kinetic experiments support E- and gem-enyne formation through a common reaction sequence involving hydrometallation and rate-determining C–C bond reductive elimination. The latter is significantly affected by the ligand topology: Employment of a macrocyclic variant enforced exclusive head-to-head coupling, contrasting the high selectivity for head-to-tail coupling observed for the corresponding acyclic pincer ligand.*

The transition-metal-catalysed dimerisation of terminal alkynes into conjugated enynes is an attractive, atom-economic method for the preparation of versatile organic building blocks from readily accessible starting materials.[1,2] These reactions involve the formal addition of the C(sp)–H bond of one alkyne across the C≡C bond of the other, a process that can in principle result in three different regio- or stereochemical isomers: *gem*-, *E*-, and *Z*-enynes. With the additional possibility for the substrates to be consumed through competing metal-catalysed reaction pathways—for instance leading to butatrienes, arenes, or other polyenes—the widespread application of terminal alkyne coupling reactions in organic synthesis rests on the development of catalysts that can enforce high reaction control.[1,3] Despite the evaluation of a variety of transition-metal complexes, this remains a largely unfulfilled aspiration, with few catalysts capable of producing single enyne isomers with sufficiently high selectivity.[4]

Building on early landmarks,[5] rhodium-based catalysts are of notable contemporary interest.[6–9] Recent examples bearing anionic pincer ligands, in particular, show promising activity and product fidelity. For instance, Rh(CNC) complex **A** has been shown to be a highly selective precatalyst for the production of a range of *gem*-enynes (1 mol%, 80 °C),[6] while Rh(PNP) complex **B** principally affords *E*-enynes under similar conditions (1 mol%, 100 °C).[7] Although closely related Rh(PNP) and Rh(PCP) systems demonstrate reduced selectivity, they predominantly give mixtures of only *gem*- and *E*-enynes.[7,8] As previously asserted by Ozerov,[8] these observations implicate a common hydrometallation–reductive elimination mechanism for the aforementioned rhodium pincer complexes, a scheme that bifurcates on coordination of the second alkyne to afford either "head-to-tail" (*gem*) or "head-to-head" (*E*) coupled products (i.e., **II**→**III** vs. **II**→**V** in Scheme 1). The formation of *Z*-enynes instead typically evokes vinylidene intermediates.[1]

Motivated by these precedents and as part of our research exploring the organometallic chemistry of NHC-based pincer ligands,[10,11] we set about evaluating the use of rhodium complexes containing neutral lutidine-based CNC ligands in terminal alkyne coupling reactions. In particular, we were interested in ascertaining the capacity of macrocyclic variants for imparting additional reaction control. To this end, we herein describe our work contrasting the reactions of Rh^{I}



Scheme 1. Selected complexes and proposed mechanistic pathways for the rhodium pincer catalysed formation of *gem*- and *E*-enynes from terminal alkynes. $Ar^{F} = 3,5\text{-}(CF_3)_2C_6H_3$.

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Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201807028.

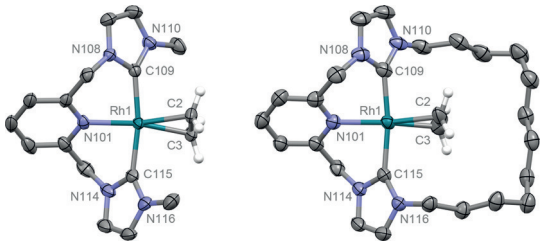


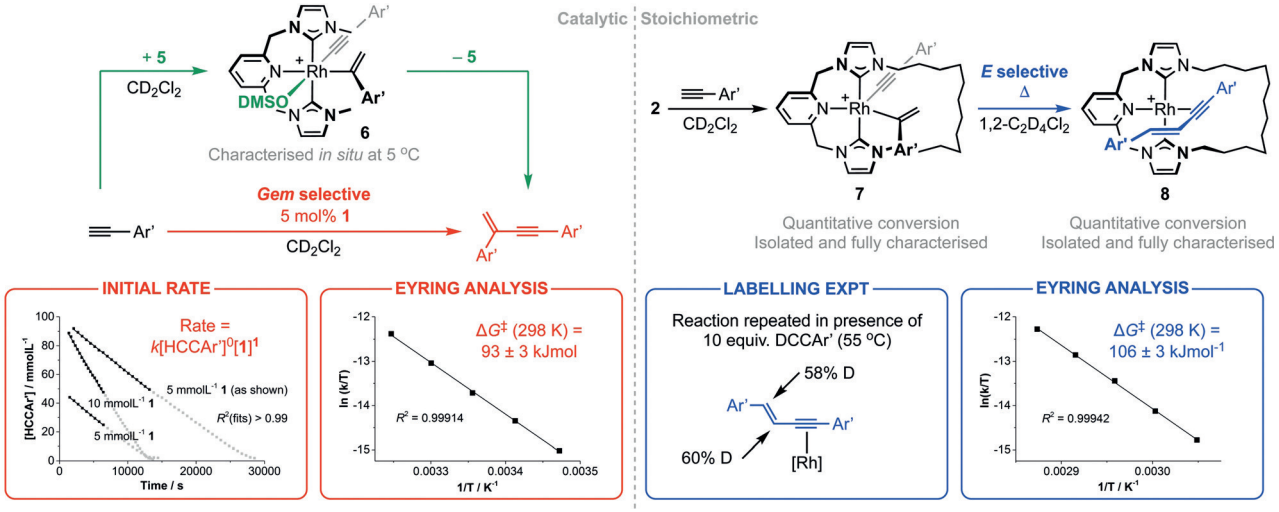
Figure 1. Solid-state structures of **1** and **2**. Thermal ellipsoids drawn at 50% probability; anions and most hydrogen atoms omitted for clarity. Selected data for **1**: Rh1–Cnt(C2,C3) 2.033(3) Å, C2–C3 1.373(4) Å, Rh1–N101 2.116(2) Å, Rh1–C109 2.037(2) Å, Rh1–C115 2.042(2) Å; Py-Rh-C=C twist 16.0(2)°; for **2**: Rh1–Cnt(C2,C3) 1.996(3) Å, C2–C3 1.363(5) Å, Rh1–N101 2.116(2) Å, Rh1–C109 2.042(3) Å, Rh1–C115 2.061(3) Å; Py-Rh-C=C twist 31.7(2)°.[13]

ethylene complexes [Rh(CNC-Me)(C_2H_4)][BAr^F_4] (**1**) and [Rh(CNC-12)(C_2H_4)][BAr^F_4] (**2**) with a bulky terminal alkyne (Scheme 1; R = 3,5-*t*Bu$_2$C$_6$H$_3$ = Ar′). These novel and appreciably air-sensitive complexes were synthesised by employing reactions of the corresponding Cu^I transfer agents [Cu(CNC)][BAr^F_4] with [Rh(C_2H_4)$_2$Cl]$_2$,[11] and fully characterised in solution and the solid state (see the Supporting Information and Figure 1). Reinforcing the electronic similarities of the CNC-Me and CNC-12 ligands evident from these data, the corresponding Rh^I carbonyl derivatives [Rh(CNC-Me)(CO)][BAr^F_4] (**3**) and [Rh(CNC-12)(CO)][BAr^F_4] (**4**) have directly comparable carbonyl stretching frequencies (ν(CO) = 1980 cm^{-1}, **3**; 1978 cm^{-1}, **4**).[12]

Under comparably milder conditions to those employed for **A** and **B**, complex **1** was found to be an effective and selective precatalyst for the homocoupling of HC≡CAr′ in CD_2Cl_2, affording the *gem*-product Ar′C≡CC(CH_2)Ar′ exclusively until alkyne conversion reached > 90% (5 mol%, $t_{1/2}$ = 4.2 h, 25 °C; Scheme 2). At this point, nearing complete consumption of the alkyne, there was evidence for a subsequent metal-catalysed reaction of the enyne.[14] Ar′C≡CC(CH_2)Ar′ was, however, readily isolated in practically useful yield (73%) upon quenching the reaction with carbon monoxide at high alkyne conversion, sequestering the catalyst as **3**. Alternative use of [Rh(CNC-Me)($SOMe_2$)][BAr^F_4] (**5**) as the precatalyst maintained the exclusive *gem*-selectivity observed for **1**, but the homocoupling was an order of magnitude slower under equivalent conditions (5 mol%, 25 °C), presumably owing to reversible binding of dimethyl sulfoxide. Whilst use of **5** is detrimental to catalytic activity, it advantageously facilitated in situ investigation of the organometallic intermediates involved by NMR spectroscopy and ESI-MS. In this way, a single and persistent species was identified and, following additional interrogation under conditions more amenable to characterisation (33 mol%, 5 °C), assigned as Rh^{III} *gem*-alkenyl complex **6** (Scheme 2; cf. **IV** in Scheme 1). Notable spectroscopic features of **6** include C_1 symmetry, two 18H *t*Bu resonances, geminal alkene ^{1}H resonances at δ 3.21 and 4.79, and ^{13}C resonances at δ 101.9 (Rh<u>C</u>≡C, $^1J_{RhC}$ = 55 Hz) and 153.8 (Rh<u>C</u>(CH_2)Ar′, $^1J_{RhC}$ = 38 Hz) that display large ^{103}Rh coupling.[15] Isolation of **6** from solution was encumbered by facile reductive elimination of Ar′C≡CC(CH_2)Ar′.

These observations can be reconciled by a hydrometallation mechanism for the HC≡CAr′ homocoupling with the resting state **IV** (cf. **6**) and turnover-limiting C–C bond reductive elimination (i.e., **IV**→**I** in Scheme 1). Consistent with this suggestion, a kinetic analysis using the more active precatalyst **1** indicated that the homocoupling reaction is zero order in the alkyne substrate and first order in **1** (Scheme 2). Working within our conjecture, the activation barrier for the reductive elimination step was also determined through measurement of the temperature dependence of the reaction, affording $\Delta G^{\ddagger}$ (298 K) = 93 ± 3 kJ mol^{-1} ($\Delta H^{\ddagger}$ = 97 ± 1 kJ mol^{-1}, $\Delta S^{\ddagger}$ = 15 ± 5 J K^{-1} mol^{-1}; Scheme 2).

Paralleling the formation of **6**, reaction of **2** with 2.1 equiv of HC≡CAr′ in CD_2Cl_2 led to rapid and quantitative formation of Rh^{III} *gem*-alkenyl complex **7**, which was subsequently isolated and fully characterised (Scheme 2 and Figure 2). Presumably as a consequence of the confined metal coordination sphere evident in the solid state, **7** is appreciably dynamic in solution on the NMR timescale (500 MHz; see the Supporting Information). The spectroscopic characteristics nevertheless corroborate the structure of **7** in the solution



Scheme 2. Reactions of **1** and **2** with HC≡CAr′. [BAr^F_4]$^-$ counteranions omitted for clarity.

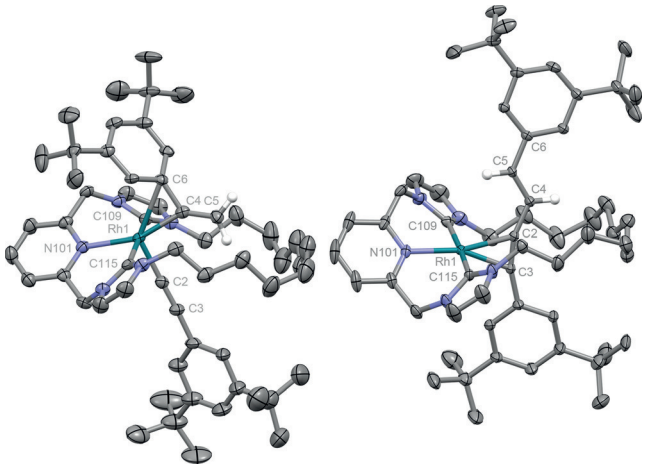
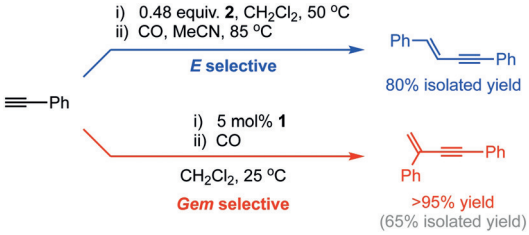


Figure 2. Solid-state structures of **7** and **8**. Thermal ellipsoids drawn at 50% and 30% probability, respectively; anions, minor disordered components (1×*t*Bu group in **7**; 1×Ar′ and 1×CH_2CH_2 group in **8**), solvent molecules, and most hydrogen atoms omitted for clarity. Selected data for **7**: Rh1–C2 1.940(5) Å, C2–C3 1.204(8) Å; Rh1-C2-C3 176.6(5)°; Rh1–C4 1.983(5) Å, C4–C5 1.310(8) Å; Rh1-C4-C5 140.1(4)°, C2-Rh1-C4 96.6(2)°; Rh1–C6 2.435(5) Å, Rh1–N101 2.228(5) Å, Rh1–C109 2.066(5) Å, Rh1–C115 2.075(6) Å; for **8**: Rh1–Cnt(C2,C3) 1.981(3) Å, C2–C3 1.255(4) Å, C2–C4 1.425(4) Å, C4–C5 1.338(4) Å; C2-C4-C5 124.7(3)°; Rh1–N101 2.105(2) Å, Rh1–C109 2.052(3) Å, Rh1–C115 2.042(3) Å; Py-Rh-C≡C twist 38.7(2)°.[13]

phase, for instance, the presence of germinal ^{1}H resonances at δ 5.57 and 5.76 alongside doublets in the ^{13}C NMR spectrum at δ 85.0 (Rh<u>C</u>≡C, $^1J_{RhC} = 72$ Hz) and 157.7 (Rh<u>C</u>(CH_2)Ar′, $^1J_{RhC} = 27$ Hz). While the intricacies of the spectroscopic data diverge, the most meaningful difference between **6** and **7** is the significantly enhanced stability of the latter, macrocyclic variant. Reminiscent of active-metal-template methods used in the construction of interlocked molecules,[16] **7** does however undergo C–C bond reductive elimination through the annulus of the bound CNC-12 ligand when heated in the higher-boiling-point solvent 1,2-$C_2D_4Cl_2$. Curiously, the resulting mechanically entrapped hydrocarbon product is not the *gem*-enyne Ar′C≡CC(CH_2)Ar′, expected for a single reaction step and through extrapolation of the reactivity established for **1** and **5**, but instead the alternative *E*-regioisomer *E*-Ar′C≡CCH=CHAr′ (Scheme 2).[17] The associated Rh^{I} adduct **8** is formed quantitatively and was isolated from solution and comprehensively characterised, including in the solid state by single-crystal X-ray diffraction (see the Supporting Information and Figure 2).

The formation of **8** from **7** necessitates a multistep mechanism starting with β-H abstraction and terminating with reductive elimination from a Rh^{III} *E*-alkenyl alkynyl species. Moreover, on the basis of a labelling experiment, which involved heating **7** in the presence of excess DC≡CAr′ and resulted in significant D incorporation into both positions of the enyne core, exchange and reversible C(sp)–H activation of both alkyne components must occur: **IV**⇌**III**⇌**II**-(⇌**I**)⇌**V**⇌**VI**→**8** (Scheme 1 and Scheme 2). No intermediates were observed when the conversion of **7** into **8** was followed in situ by ^{1}H NMR spectroscopy, with the reaction following ideal first-order kinetics across a wide temperature range (328–348 K). On the basis of these data, we assign reductive elimination as the rate-determining step, with an associated barrier of $\Delta G^{\ddagger}(298\,K) = 106 \pm 3\,kJ\,mol^{-1}$ ($\Delta H^{\ddagger} = 119 \pm 1\,kJ\,mol^{-1}$, $\Delta S^{\ddagger} = 44 \pm 4\,J\,K^{-1}\,mol^{-1}$).

Reflecting on these results from a fundamental perspective, the observation, structural elucidation, and onward (orthogonal) reactivity of **6** and **7** provide convincing evidence for a common hydrometallation–reductive elimination mechanism for the formation of *gem*- and *E*-enynes by rhodium pincer promoted terminal alkyne coupling. In the case of the lutidine-based CNC ligands employed in this study, product-forming reductive elimination appears to be rate-determining. The energetics of this step are, however, significantly perturbed when performed through the aperture of the macrocyclic CNC-12 ligand. By comparison to the acyclic congener CNC-Me, the steric constraints imposed by the flexible ring raise the barrier for C–C bond reductive elimination from a Rh^{III} *gem*-alkenyl alkynyl species relative to the alternative Rh^{III} *E*-alkenyl alkynyl intermediate by at least $\Delta G^{\ddagger}(298\,K) = 13 \pm 6\,kJ\,mol^{-1}$, triggering a switch in product selectivity. These observations provide new insight into how terminal alkyne coupling reactions can be controlled and, more generally, showcase an unconventional approach for tuning the reactivity of pincer ligands.[18] As a proof-of-concept demonstration of how this knowledge could be applied, the orthogonal selectivity of acyclic **1** and macrocyclic **2** can be exploited to prepare both PhC≡CC(CH_2)Ph (catalytically) and *E*-PhC≡CCH=CHPh (stoichiometrically) from HC≡CPh in high yield (Scheme 3, see the Supporting Information for full details). Our future work is focused on exploring the application of these lutidine-based CNC ligands in catalysis, supramolecular, and organometallic chemistry.



Scheme 3. Preparation of PhC≡CC(CH_2)Ph and *E*-PhC≡CCH=CHPh.

Acknowledgements

We thank the European Research Council (ERC, grant agreement 637313; C.M.S., M.R.G., A.B.C.), the University of Warwick (R.E.A.), and the Royal Society (UF100592, UF150675; A.B.C.) for financial support. Crystallographic (**1**, **3**, **8**) and high-resolution mass-spectrometry data were collected using instruments purchased through support from Advantage West Midlands and the European Regional Development Fund. Crystallographic data for **2**, **5**, **7**, and [Cu(CNC-12)][BAr^F_4] were collected using an instrument that received funding from the ERC under the European Union's Horizon 2020 research and innovation programme (Grant Agreement No. 637313).

Conflict of interest

The authors declare no conflict of interest.

Keywords: C–C coupling · enynes · macrocyclic ligands · pincer ligands · rhodium

How to cite: *Angew. Chem. Int. Ed.* **2018**, *57*, 12003–12006
Angew. Chem. **2018**, *130*, 12179–12182

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[12] Carbonyl complexes **3** and **4** are readily prepared by reaction of **1** and **2**, respectively, with carbon monoxide (see the Supporting Information for details and the solid-state structure of **3**).

[13] CCDC 1849620–1849626 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[14] Balance tetramer formed. Full details will be published in due course.

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Manuscript received: June 18, 2018
Revised manuscript received: July 7, 2018
Accepted manuscript online: July 13, 2018
Version of record online: August 20, 2018

