Metallacycles

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Hydroxy-Directed Ruthenium-Catalyzed Alkene/Alkyne Coupling: Increased Scope, Stereochemical Implications, and Mechanistic Rationale

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Abstract: *The recognition of the dual binding mode of propargyl and allyl alcohols to [Cp*Ru] fragments fostered the development of a highly regioselective intermolecular Alder-ene-type reaction of alkynes with 1,2-disubstituted alkenes. The increased substrate scope opens new perspectives in stereochemical terms. As the loaded catalyst is chiral-at-metal, stereochemical information is efficiently relayed from the propargylic site to the emerging C–C bond. This interpretation is based on the X-ray structure of the first Cp*Ru complex carrying an intact enyne ligand, and provides valuable insights into bonding and activation of the substrates. Computational data draw a clear picture of the principles governing regio- and stereocontrol.*

During the course of our investigations into alkyne *trans*-hydrogenation and *trans*-hydrometalation reactions we recognized a massive directing effect exerted by protic groups XH (X = O, NR) in the vicinity of the reacting π bond.[1–4] This effect originates from strong hydrogen bonding between the XH substituent and the polarized [Cp*Ru-Cl] entity of the catalyst as illustrated by complexes **1**–**4** (Figure 1).[5,6] Importantly, the crystal structure of **2** shows that a single [Ru-Cl] unit is capable of entertaining two hydrogen bonds at the same time.[5] Alternatively, an OR (R = H, Me) group can engage in a regular donor/acceptor interaction with the metal center and is capable of creating synergy with hydrogen bonding. The complexes **4** and **5** illustrate these possibilities.[6,7]

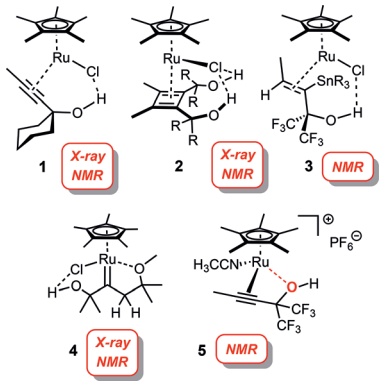
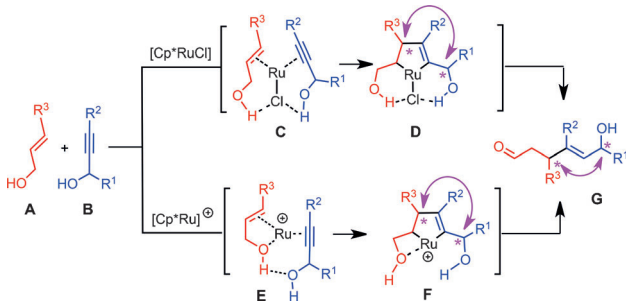


Figure 1. Experimentally confirmed peripheral hydrogen bonding and/or donor/acceptor interactions in Cp*Ru complexes comprising protic ligands. Cp* = pentamethylcyclopentadienyl.

Details apart, peripheral patterns as manifested in **1**–**5** impose directionality on the ligand sphere of a loaded catalyst. It is likely such preorganization can be advantageous beyond alkyne hydrometalation. Herein we show how such secondary interactions can be used to render alkene/alkyne coupling of the Alder-ene-type stereoselective while increasing the substrate scope of this valuable transformation.[8–10]

Ruthenium complexes such as $[CpRu(MeCN)_3]^+$ or [Cp*Ru(cod)Cl] are known to engender oxidative cyclization of alkenes and alkynes with formation of metallacycles, and lead to 1,4-dienes by selective elimination of the exocyclic β-H atom.[8,11–13] The broad scope of this reaction notwithstanding, it remains limited to the use of terminal olefins as substrates, except for intramolecular and hence entropically favored cases. Even amongst terminal olefins, the use of 1,1-disubstitued alkenes was accomplished only recently. They require a coordinating NHBoc group at the allylic position to assist in their binding to the catalyst.[14–16]

Under the proviso that formation of a peripheral hydrogen-bonding network of the types referred to above is fast compared with oxidative cyclization, one can envisage that neutral, as well as cationic [Cp*Ru] fragments, will preorganize a generic pair of unsaturated alcoholic substrates **A** and **B** in a head-to-head orientation (Scheme 1). Oxidative cyclization followed by elimination of the exocyclic β-H atom



Scheme 1. Peripheral interactions preorganize the ligands prior to alkene/alkyne coupling and allow stereochemical information to be relayed, no matter if neutral or cationic Cp*Ru complexes are used as catalysts. The Cp* ligand to ruthenium in the putative intermediates is not shown for clarity.

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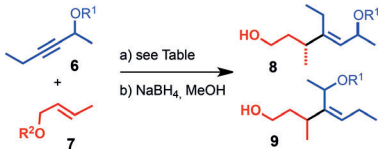
affords an enol in the first place, which tautomerizes to the corresponding aldehyde **G**. Since an interligand Ru-Cl···H-O hydrogen bond amounts to 2–8 kcal mol^{-1} of energetic gain,[6] it seemed reasonable to assume that otherwise unreactive 1,2-disubstituted alkenes might be suitable substrates, even in intermolecular settings. If so, the envisaged transformation provides an opportunity to relay chiral information from the propargylic site by a transiently chiral ruthenium atom to the newly developing stereocenter.[17–19]

Proof of principle was attained by reaction of the secondary propargyl alcohol **6** ($R^1 = H$) with crotyl alcohol (**7**, $R^2 = H$, 2 equiv) in CH_2Cl_2 in the presence of either catalytic $[Cp^*RuCl]_4$ (**10**) or $[Cp^*Ru(MeCN)_3]PF_6$ (**11**) (Table 1).[15] In either case, the 1,4-*anti*-configured product **8** was formed as the major isomer with appreciable levels of selectivity after reductive work up of the crude reaction mixture.[20] The neutral complex **10** led to the better stereochemical outcome, whereas its cationic sibling **11** was more imposing in regiochemical terms. This trend proved general (see below). In line with the proposed model emphasizing the critical role of hydrogen bonding, the conversion stalled upon protection of crotyl alcohol (entries 5 and 6); likewise, O-acylation of the propargylic partner basically halted the reaction (entry 3) or led to poor selectivity (entry 4). Additional support comes from the observation that the use of acetone or THF is detrimental when **10** is used as catalyst, since these solvents are hydrogen-bond acceptors and hence likely interfere with the crucial preorganization of the ligands.[21]

Table 1: Coupling of a propargyl and crotyl alcohol.[a]

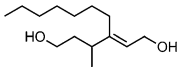
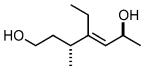
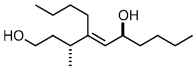
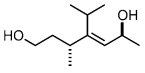
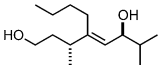
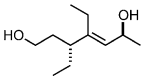
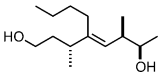
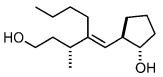
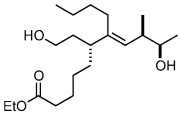
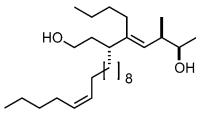


Entry	R^1	R^2	Catalyst	**8**/**9**[b]	d.r.[c]	Yield [%][d]
1	H	H	**10**	5:1	12:1	69
2	H	H	**11**	17:1	6:1	69
3	Ac	H	**10**	n.d.	n.d.	<20
4	Ac	H	**11**	3:1	2:1	quant (NMR)
5	H	Ac	**10**	–	–	–
6	H	Ac	**11**	–	–	–

[a] All reactions were carried out in CH_2Cl_2 at 0 °C using either $[Cp^*RuCl]_4$ (**10**, 2.5 mol %) or $[Cp^*Ru(MeCN)]PF_6$ (**11**, 10 mol %). [b] Determined by ^{1}H NMR spectroscopy. [c] The *anti/syn* ratio (HPLC) of the major regioisomer **8**. [d] Yield of isolated **8**, unless stated otherwise. n.d. = not determined.

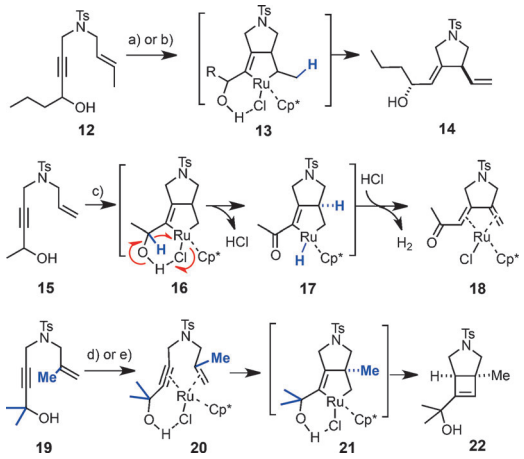
Table 2 compiles a number of representative cases. Various propargyl alcohols of different steric demand on either side of the triple bond reacted well (entries 1–9). Interestingly, homopropargyl alcohols afforded the expected head-to-head products with even better yields and selectivities (entries 10–13).[22] Likewise, variation of the allylic alcohol partner was possible, as long as its disubstituted alkene is *E*-configured (entries 9, 12, and 13). It is mechanistically telling that *Z*-crotyl alcohol derivatives did not react well (see below). Excellent results were observed for the functionalized products shown in entries 12 and 13, in which the allylic alcohol partner carried either a lateral ester substituent or an extra double bond. In the latter case, peripheral hydrogen bonding also engenders a noteworthy site selectivity, in that only the allylic alcohol subunit of the substrate took part in the coupling event whereas a regular alkene passed untouched (entry 13).

Table 2: Scope of the intermolecular hydroxy-directed alkene/alkyne coupling.[a]

Entry	Product	Cat.	Yield [%][b]	Regio-selectivity[c]	d.r.[d]
1		**10**	68	10:1	–
2		**10**	69	5:1	12:1
3		**11**	69	17:1	6:1
4		**10**	67	6:1	12:1
5		**11**	72	16:1	8:1
6		**10**	81[e]	8:1	10:1[f]
7		**11**	67[e]	5:1	4:1[f]
8		**10**[g]	70	6:1	9:1
9		**10**	67	5:1	13:1
10		**10**	92	>20:1	>20:1
11		**10**	86	11:1	>20:1
12		**10**	92	>20:1	>20:1
13		**10**	85	>20:1	>20:1

[a] Unless stated otherwise, all reactions were carried out in CH_2Cl_2 at 0 °C using either **10** (2.5 mol %) or **11** (10 mol %). For work up, the crude mixture was treated with $NaBH_4$ in MeOH for 1 h. [b] Yield of the isolated major regioisomer. [c] Determined by ^{1}H NMR spectroscopy after $NaBH_4$ reduction. [d] Diastereomeric ratio of the major regioisomer as determined by HPLC. [e] Mixture of diastereomerically pure regioisomers. [f] Determined after purification. [g] Using 3.5 mol % of the catalyst.

Valuable information can be deduced from the intramolecular reactions shown in Scheme 2. Although the use of internal alkenes in cyclizations has precedent,[8,23] the transformation of the enyne **12** into the product **14** is the first example to show that chiral information residing *exo* to the metallacycle is effectively transferred.[17] In contrast to the intermolecular cases compiled in Table 2, in which both substrates carry an OH group, only the chloride-containing precatalyst **10** proved functional with the substrate **12**, bearing a single protic site, whereas the cationic complex **11** was hardly selective. This result suggests that a propargylic OH interacts well with a polarized [Ru–Cl] unit but is more



Scheme 2. a) **10** (2.5 mol%), CH_2Cl_2, 0°C, 86%, d.r. = 11:1. b) **11** (10 mol%), CH_2Cl_2, 0°C, quant. (NMR), d.r. = 2:1. c) **10** (0.27 equiv), CH_2Cl_2, 0°C, **18** (35%, see text). d) **10** (12.5 mol%), CD_2Cl_2, 0°C, **22** (quant., NMR). e) **10** (0.125 equiv), [D_8]THF, 0°C, **20** (quant., NMR). THF = tetrahydrofuran, Ts = *p*-toluenesulfonyl.

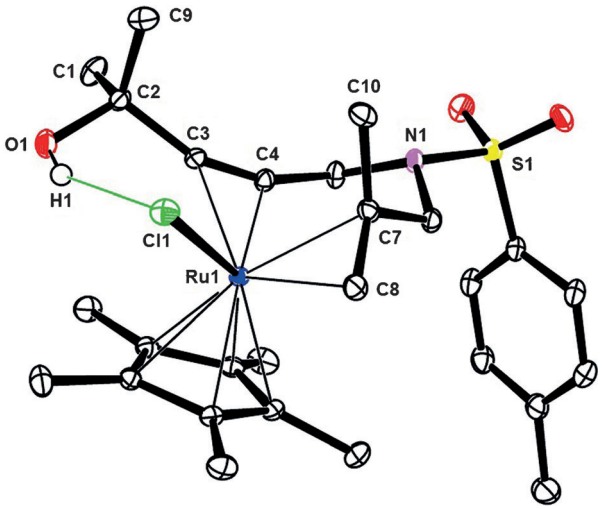


Figure 2. Structure of the complex **20** in the solid state.[33] Thermal ellipsoids shown at 50% probability.

reluctant to ligate the $[Ru]^+$ center in **11**, probably for simple geometric reasons.[24] That is why we propose the alignment shown in **E** to explain the intermolecular cases catalyzed by **11** (see Scheme 1), wherein the crotyl alcohol makes the primary contact to $[Ru]^+$.[25] This coordination, in turn, acidifies the OH proton and leads to peripheral hydrogen bonding with the incoming propargyl alcohol. The inverse scenario with the propargylic OH being docked onto the metal center is much less likely.

In an attempt to study the selectivity-determining peripheral interactions in more detail, we reacted compound **15**, comprising a terminal rather than an internal alkene, with stoichiometric [Cp*RuCl] (Scheme 2). Since the resulting metallacycle **16** lacks exocyclic H atoms for β-hydride elimination, this intermediate was deemed amenable to spectroscopic and/or crystallographic characterization. However, the ^{13}C NMR spectrum suggested formation of four different carbonyl-containing products. The major one (**18**) was isolated as orange-red crystals and characterized by X-ray diffraction (see the solid-state structure in the Supporting Information). While the formation of a ruthenium diene complex per se is not surprising, the ligand constitution in **18** is unusual in that it mandates formal loss of H_2 either before or after cyclization; Scheme 2 shows a plausible scenario.

To block this unexpected escape route, the relevant protons in **15** were formally replaced by methyl groups (Scheme 2). As expected, exposure of enyne **19** to **10** in CD_2Cl_2 afforded a single ruthenium complex, which proved metastable and evolved into the cyclobutene **22**, presumably by reductive elimination of the metallacycle **21** and subsequent isomerization of the bridgehead olefin primarily formed.[26] Gratifyingly though, an intermediate derived from **19** was sufficiently long-lived in [D_8]THF to allow isolation in the crystalline form. To the best of our knowledge, **20** (Figure 2) is the first ruthenium complex comprising an intact enyne ligand.

The firm binding of the alkyne unit in **20** is manifested in the elongated C3–C4 distance [1.250(2) Å][27] and the bending of the acetylene away from linearity [C2-C3-C4 154.9(1)°]. As expected, coordination of the triple bond is supported by tight hydrogen bonding between the OH group and the chloride (2.342 Å).[28,29] Since the resulting chelate structure locks the adjacent methyl groups, C1 and C9, in different chemical environments, it is predisposed for relaying stereochemical information during cyclization from a propargylic center to the newly developing C–C bond. Note that the tetrahedral coordination sphere renders the Ru center in the piano-stool complex **20** chiral.[19] Binding of the alkene must also be appreciable as judged from the extended C7-C8 distance [1.406(2) Å].[27] Despite these clear signs of activation of either π system, the enyne has not yet succumbed to oxidative cyclization with formation of a planar ruthenacycle as evidenced from the significant tilting of the alkene against the alkyne unit (C3-C4···C7-C8 69.8°) and the nonbonding C4···C7 distance (2.637(3) Å). A clash between the pseudoaxial but slightly inwardly-bent methyl groups, C9 and C10, on the rim seems to prevent further contraction and hence spontaneous oxidative cyclization from occurring. NMR spectra recorded at −50°C show that these structural features are largely maintained in solution. Warming of the sample to ambient temperature, however, entails line broadening and is suggestive of rapid exchange between at least two species. We suppose that de-coordination/re-coordination of the alkene accounts for this dynamic phenomenon.[30] It is therefore readily understood why more highly substituted alkenes are handicapped substrates, particularly in intermolecular settings. They qualify, however, if a proximal OH group assists in binding (Table 2).

To understand the origin of the experimentally observed regio- and diastereoselectivity of the ruthenium-catalyzed coupling reaction with **7**, we performed density-functional theory (DFT) calculations at the SMD-M06L/def2-TZVP level of theory.[31] Achiral but-2-yn-1-ol and chiral pent-3-yn-2-ol were chosen as reaction partners. In the Supporting Information, we describe the computational methods, the

numerical results, and their interpretation in full detail. Here, we only summarize the most pertinent points.

The DFT study confirmed that peripheral hydrogen bonding is essential. Specifically, the head-to-head alignment (**1-A1**) with two interligand hydrogen bonds is 4.9 kcal mol^{-1} more stable than the head-to-tail complex **1-A1′** (Figure 3).

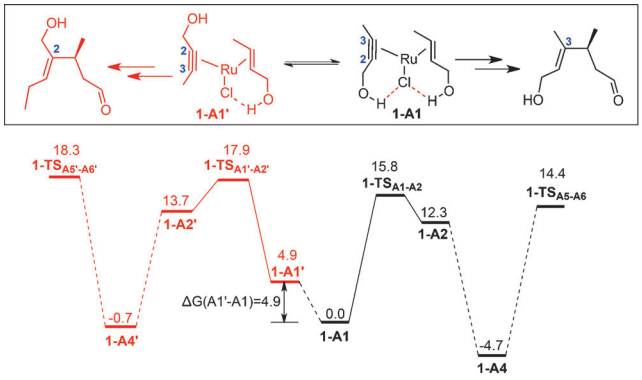


Figure 3. Relative free energies (kcal mol^{-1}) for key species governing the regioselectivity of the coupling reaction between 2-butyn-1-ol and crotyl alcohol. For the nature of the intermediates and transition states (TSs), see Figure 5. The Cp* ring on Ru is not shown for clarity.

Similar free-energy differences are found along the reaction path for the intermediates (**1-A4** vs. **1-A4′**, 4.0 kcal mol^{-1}) and the rate-limiting transition states (**1-TS$_{A5-A6}$** vs. **1-TS$_{A5'-A6'}$**, 3.9 kcal mol^{-1}), for the same reason. The observed regioselectivity is thus largely governed by the equilibrium between the two isomeric catalyst/substrates complexes and their relative free energies.

The DFT calculations also unraveled the origin of the observed 1,4-*anti* selectivity. Once again, hydrogen bonding plays an important role (Figure 4). In the initial step the alkyne may approach either the *Re*-face or the *Si*-face of **7** (Figure 4). In the former case (**1-TS$_{A1-A2}$-cf1**) the hydrogen bond between **7** and [Ru-Cl] is retained, whereas it is lost in the latter case (**1-TS$_{A1-A2}$-cf2**). Because this loss results in significant enthalpic penalty (7.6 kcal mol^{-1}), we considered only the *Re*-face approach when analyzing the origin of diastereoselectivity in the ruthenium-catalyzed coupling of pent-3-yn-2-ol and **7** in more detail. Comparison of the computed free-energy profiles shows that incorporation of a methyl substituent at the propargylic position separates the diastereomeric pathways in energetic terms (Figure 5): all transition states are lower in free energy on the route leading to the 1,4-*anti* isomer. In essence, it is the steric repulsion between the propargylic Me group and the Cp* ring which renders the formation of the 1,4-*syn*-isomer less favorable. Note that this methyl group is locked by the hydrogen bonding

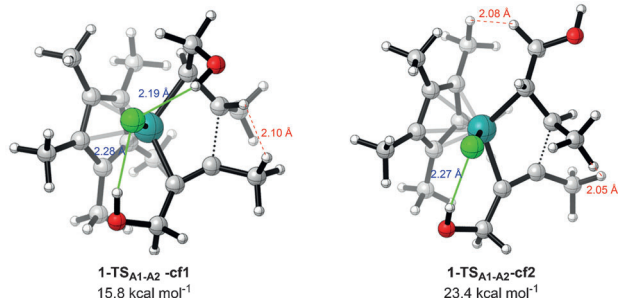


Figure 4. Molecular structures of the transition state conformers **1-TS$_{A1-A2}$-cf1** (left) and **1-TS$_{A1-A2}$-cf2** (right) for the reaction between 2-butyn-1-ol and crotyl alcohol. Interligand H-bonds are indicated by green lines and steric repulsions by red dashed lines. Free energies are given relative to **1-A1**.

array of the adjacent OH group with the chloride ligand on ruthenium (compare complex **20**). These steric effects are discussed in more detail in the Supporting Information, especially for **2-TS$_{A5-A6}$**.

The ruthenium-catalyzed coupling reaction itself follows the expected course (Figure 5), in that oxidative coupling via **2-TS$_{A1-A2}$** affords a high-energy metallacycle (**2-A2**) in the first place, which then relaxes by conformational changes to the more stable metallacycles **2-A3** (twisted) and **2-A4**. Only the latter is planar and stabilized by a direct O···Ru interaction. Product formation then mandates rotation of the exocyclic substituent derived from the alkene partner: an agostic interaction between the metal center and the exocyclic H-atom is in place in **2-A5** as a prelude to β-hydride elimination with formation of the enol **2-A6**. Interestingly, the computations suggest that concerted hydride elimination/reductive elimination via **2-TS$_{A5-A6}$** is favored over a stepwise process.[32]

Furthermore, the DFT results explain the poor performance of *Z*-crotyl alcohol as compared to *E*-crotyl alcohol. A clash between the terminal Me group in *Z*-crotyl alcohol with

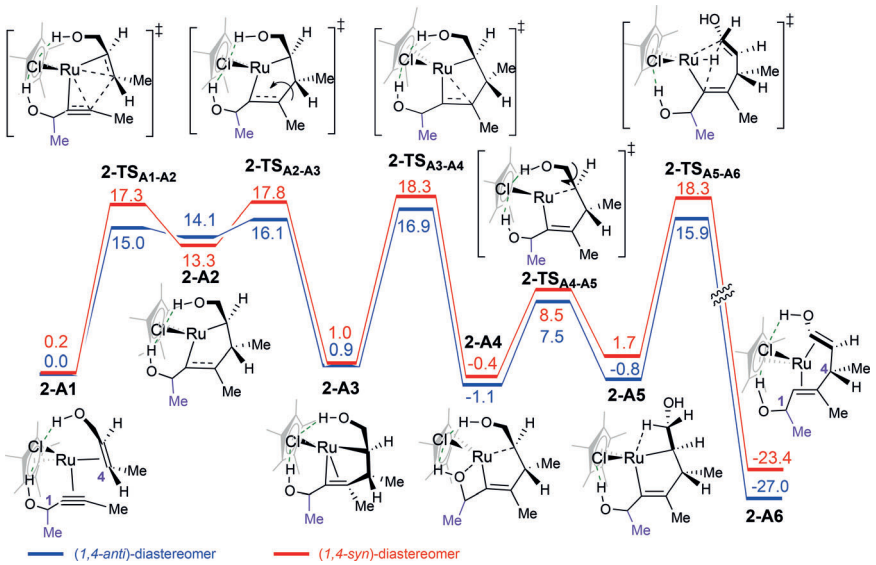


Figure 5. Free-energy profile (kcal mol^{-1}) for the diastereoselective ruthenium-catalyzed coupling of pent-3-yn-2-ol and crotyl alcohol.

the alkyne as well as a distortion of the nascent metallacycle raise the activation barrier for C–C-coupling by no less than 8 kcal mol^{-1}.[32]

Overall, this investigation shows how insights into the origins of hydroxy-directed *trans*-hydrometalations of unsymmetrical alkynes could be translated into a productive Alder-ene reaction of extended scope. As the loaded catalyst is chiral at ruthenium, stereochemical information is effectively relayed from the propargylic site to the newly formed C–C bond. The isolation of the first Cp*Ru complex, endowed with an intact enyne ligand, together with in-depth computational studies draws a clear picture of the underlying mechanism. Further studies into transformations benefitting from secondary interactions in the periphery of the chosen catalysts are underway and will be reported in due course.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkynes · hydrogen bonds · metallacycles · reaction mechanisms · ruthenium

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[20] The 1,4-*anti* assignment was rigorously proven for the product shown in Table 2, entry 8, by chemical correlation with a compound of known stereochemistry (for details, see the Supporting Information). All other compounds were assigned by analogy.

[21] The reactions catalyzed by the cationic complex **11** are also less selective in acetone, although the effect is not as dramatic. This observation suggests that the direct coordination of the OH of crotyl alcohol to the metal center is less sensitive to competition.

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[29] The importance of this secondary interaction is further illustrated by the fact that the methyl ether derived from **19** does not form a defined adduct on treatment with **10**.
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[32] See the Supporting Information for details.
[33] CCDC 1523565 (**18**) and 1523566 (**20**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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Communications

Metallacycles

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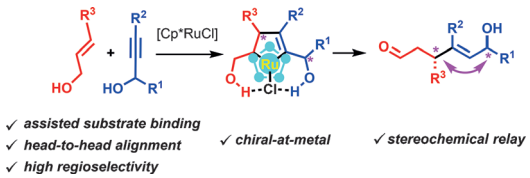
Hydroxy-Directed Ruthenium-Catalyzed Alkene/Alkyne Coupling: Increased Scope, Stereochemical Implications, and Mechanistic Rationale



Peripheral but quintessential: The ability of hydroxy groups to engage in interligand hydrogen bonding with the polarized [Ru-Cl] unit of a catalyst powers highly regioselective alkene/alkyne coupling reactions. Stereochemical information is relayed from the propargylic site to the nascent C—C-bond through chiral-at-metal ruthenium intermediates.