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H-Bonding as a Control Element in Stereoselective Ru-Catalyzed Olefin Metathesis

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H-bonding is the key feature of many catalytic stereoselective transformations;[1] application of such interactions to the design of metal-catalyzed processes, however, is uncommon.[2] Polarization of a metal−halide bond toward the more electronegative atom renders late transition metal−halides, which are largely inert toward mild Brønsted acids, attractive candidates for serving as H-bonding partners.[3] One relevant class of catalysts consists of widely used Ru-based carbene dihalides (Figure 1).[4] We now demonstrate that H-bonding can be utilized to render Ru-catalyzed olefin metathesis stereoselective. The above concept is introduced through diastereoselective ring-opening/cross-metathesis (DROCM) reactions,[5] which are catalyzed by achiral Ru complexes and involve enantiomerically enriched allylic alcohols; these transformations allow for control of remote relative stereochemistry (1,4). H-bonding has been proposed to account for a small number of observations;[6a] to the best of our knowledge, however, such interactions have not been previously utilized in, nor has their nature been elucidated through, the design of catalytic stereoselective olefin metathesis processes.

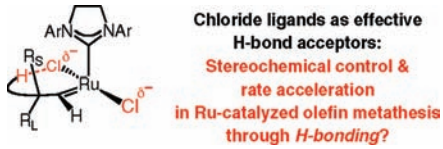


Figure 1

Whereas treatment of cyclopropene **2** with 1-octene and 0.5 mol % **1a** leads to 83% conversion after 4 h (~40% in 15 min), catalytic ROCM of allyl alcohol is complete in 5 min (Scheme 1, 56% yield). When enantiomerically enriched chiral allylic alcohol *R*-**3** (1.0 equiv, 95.5:4.5 enantiomeric ratio) is used, there is >98% conversion with 0.5 mol % **1a** after only 5 min. Importantly, *S*,*R*-**4** is obtained in 96:4 diastereomeric ratio (dr), 10:1 *E*:*Z* selectivity, and 87% yield. In contrast, reaction of the methyl ether derivative (Scheme 1) is far less facile (51% conv, 18 h) and proceeds with lower and the opposite sense of stereoselectivity: 79:21 dr is observed in favor of *R*,*R*-**5**; 25−30% cross partner homodimer is also generated (vs <10% with *R*-**3**). Formation of **6** is similarly inefficient (56% conv, 18 h; <2% conv in 5 min), and the *R*,*R*-diastereomer is again favored (91:9 dr).

Enantiomerically enriched allylic alcohols and cyclopropenes can be used in Ru-catalyzed DROCM reactions (dr ≥ 89:11, Table 1). Transformations proceed rapidly (5 min−4 h) in up to 11:1 *E*:*Z* selectivity. Catalytic processes involving an allylic alcohol bearing a relatively small substituent still proceed with high levels of stereochemical control (entries 2 and 5, Table 1). When PCy_3-containing variant of **1a** (Grubbs second-generation) is used, reaction with **3** reacts more slowly (28% conv vs >98% conv in 5 min); however, >98% conversion is observed in 90 min (95:5 dr, 7:1 *E*:*Z*).

The stereoselectivities in Scheme 1 and Table 1 can be explained through complexes **I**−**II** (Figure 2). Intramolecular H-bonding between the hydroxyl proton and a chloride ligand favors the complex where the stereogenic center's substituent (R) is situated away from the sterically demanding Mes groups.[7] Rotation of the bound cyclic olefin causes immediate collapse to the metallacyclobutane via **II**, affording the preferred diastereomer. The strong

Scheme 1. Effect of Hydroxyl Groups on Ru-Catalyzed ROCM

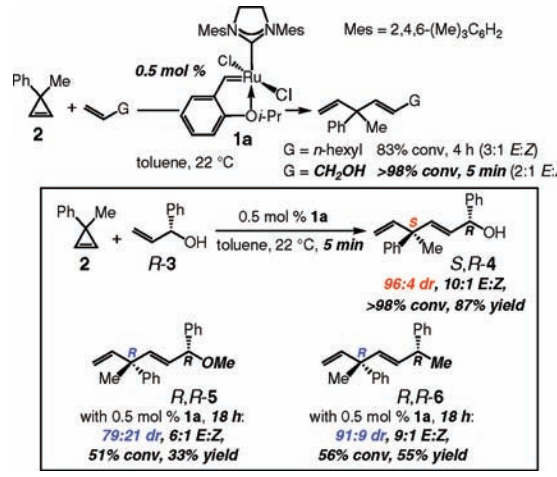
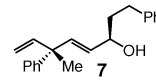
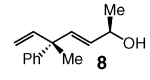
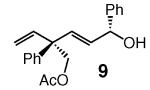
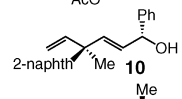
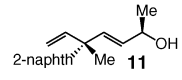
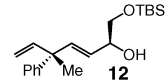


Table 1. Ru-Catalyzed DROCM Reactions with Cyclopropenes and Enantiomerically Enriched Allylic Alcohols[a]

entry	product	mol % **1a**; time	yield (%)[b]	*E*:*Z*[c]	dr[d]
1	 **7**	0.5; 15 min	80	4:1	91:9
2	 **8**	0.5; 15 min	64	6:1	95:5
3	 **9**	5.0; 4 h[e]	80	8:1	95:5
4	 **10**	0.5; 5 min	76	10:1	96:4
5	 **11**	0.5; 15 min	84	6:1	97:3
6	 **12**	0.5; 15 min	71	11:1	89:11

[a] See the Supporting Information (SI) for all experimental details, including enantiomeric purity of allylic alcohols used. [b] Yields of purified products (*E* and *Z* mixture). [c] Based on 400 MHz ^{1}H NMR analysis of unpurified mixtures. [d] Based on HPLC analysis of the major *E* olefin products (see the SI for details). [e] Reaction performed by slow addition of allylic alcohol (see the SI for details).

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preference for DROCM to proceed through the H-bonded complex might be due to the resulting charge distribution within the Ru complex. As comparison of the calculated partial atomic charge values[8] for **I** and **III** (Figure 2) indicates, H-bonding between the hydroxyl and a Cl elevates electrophilicity at the carbene carbon (+0.41 in **I** vs +0.35 in **III**),[6a] while the electron density at the coordinating olefin is enhanced (+0.14 and +0.12 in **I** vs +0.24 and +0.13 in **III**). Such an increase in electron density differences between the carbene and alkene carbons facilitates metallacyclobutane formation. As indicated by **IV**, intermolecular H-bonding can accelerate the rate of cross-metathesis, leading to rapid release of the product.

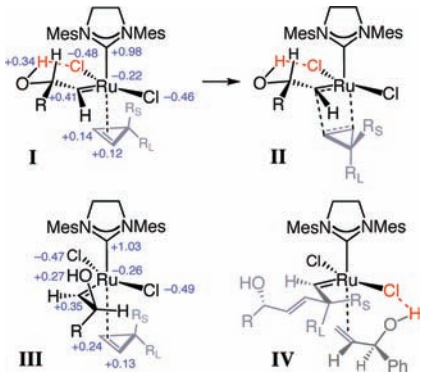
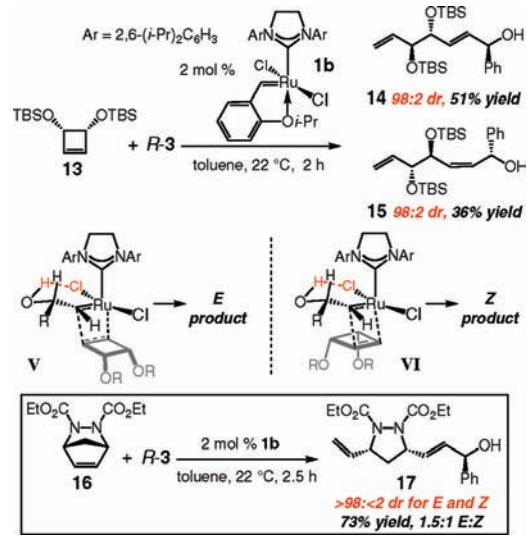


Figure 2. Models for Ru-catalyzed DROCM of cyclopropenes, including the charge values; OH−Cl distance in **I** = 2.064 Å; distances between OH and Cl atoms in **III** = 2.429 and 2.435 Å (see the SI for details).

When reaction of **2** with **3** (Scheme 1) is performed with 10 equiv of *t*-BuOH (0.5 mol % **1a**, 22 °C, tol), there is 38% conversion (vs >98%) after 5 min but stereoselectivity remains high (94.5:5.5 dr, 9:1 *E*:*Z*). With 10 equiv of H_2O, **4** is formed at a more similar rate as a reaction without an additive (88% conv in 5 min, 93.5:6.5 dr). Thus, while H-bonding between the sterically demanding alcohol and the chlorides of the Ru carbene renders the metal complexes such as **I** and **IV** more encumbered, *t*-BuOH and H_2O cannot disrupt[9] the intramolecular interaction (cf. **I**), as judged by the consistently high dr values. Finally, reversal and levels of selectivity observed for slow reactions that furnish **5**−**6** can be rationalized by intermediacy of a complex corresponding to **III** (OMe or Me vs OH), where minimization of allylic strain determines the stereochemical outcome.[10]

The significance of H-bonding to diastereoselectivity of ROCM is further underlined by reactions of other cyclic alkenes. As shown in Scheme 2, DROCM of cyclobutene **13** with *R*-**3**, catalyzed by **1b**,[11] delivers *E*-**14** in 51% yield and 98:2 dr along with an easily separable *Z*-**15** in 36% yield and 98:2 dr.[12] With 3-phenyl-1-butene as the cross partner (cf. **6**), the reaction proceeds with the opposite (and lower) sense of stereocontrol and at a slower pace (~40% yield, 14 h).[8] Thus, H-bonding, while ensuring exceptional stereoselectivity in reactions of cyclobutenes, cannot exert strong control over *E*:*Z* ratios. In contrast to quaternary carbon-bearing cyclopropenes, one face of the cyclobutene is relatively unhindered, allowing reaction via **VI** to become competitive (vs **V**, Scheme 2). The additional example, regarding the highly diastereoselective formation of **17**, and the observation that the minor *Z* isomer obtained in entry 2 of Table 1 is predominantly the *S*,*R*-product (80:20 dr; *E* isomer is *R*,*R*)[8] support the scenario posited in Scheme 2. Design of catalysts that promote high diastereoselectivity through H-bonding and furnish high *E*:*Z* selectivity is in progress.

Scheme 2



The strategies presented herein, not applicable to hydroxy-sensitive Mo-based complexes,[4] should prove to be of utility in the development of new strategies in Ru-catalyzed olefin metathesis.

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Supporting Information Available: Experimental procedures and spectral, analytical data for all reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Additional examples of DROCM with cyclobutenes are provided in the Supporting Information.

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