

Directed Catalytic Asymmetric Olefin Metathesis. Selectivity Control by Enoate and Ynoate Groups in Ru-Catalyzed Asymmetric Ring-Opening/Cross-Metathesis

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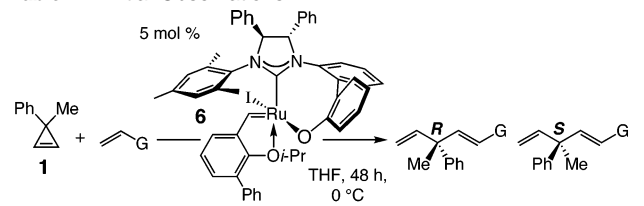
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Catalytic asymmetric olefin metathesis offers unique and efficient pathways for the synthesis of enantiomerically enriched molecules.¹ High enantioselectivity has been achieved through steric and/or electronic tuning of catalysts,^{1,2} as well as by manipulation of the structure of olefins.³ Herein, we demonstrate that α,β -unsaturated carbonyls within a cross partner can significantly *alter and enhance* enantioselectivity in asymmetric ring-opening/cross-metathesis (AROM/CM) reaction.

The present study arose as part of a program directed toward development of processes that deliver products of asymmetric cross-metathesis,⁴ particularly those with an all-carbon quaternary stereogenic center.^{3,5} We have probed the ability of chiral Ru complexes, developed in these laboratories, to promote AROM/CM^{2a,6} of cyclopropenes, a diverse and readily available class of substrates.⁷ Because of the near exclusive use of styrenes in previous investigations,^{4,6,8} our focus is on transformations that involve *non-styrenyl* alkenes as cross partners.

Key initial findings are summarized in Table 1. In the presence of 5 mol % chiral Ru complex **6**,⁶ reaction of cyclopropene **1** with styrene (**2**) delivers *R*-**7** in 93% ee and 90% yield (entry 1); with the less hindered 1-octene (**3**, entry 2), *R*-**8** is obtained in only 17% ee. Catalytic AROM/CM with *iso*-butyrate (**4**, entry 3) is noteworthy because, although it is not highly selective (30% ee), it furnishes the *S* isomer predominantly. More noteworthy is that when enoate **5** is used, *S*-**10** is generated in 85% ee and 77% isolated yield. Thus, an ester (**4**) or, more efficiently, an enoate (**5**) can significantly influence (enhance and reverse) the sense of asymmetric induction in an olefin metathesis process.

Table 1. Initial Observations



entry	G	product	<i>E:Z</i> ^a	yield (%) ^b	<i>R:S</i> ^a	ee (%) ^a
1	2 G = Ph	7	>20:1	90	96.5:3.5	93
2	3 G = <i>n</i> -hex	8	1.5:1	59	59.5:40.5	17
3	4 G = CH ₂ OCO <i>i</i> -Pr	9	3:1	59	35:65	30
4	5 G = CH ₂ OCO(Me)C=CH ₂	10	5:1	77	7.5:92.5	85

^a Determined by chiral HPLC analysis; selectivity of *E* olefin products.

^b Isolated yields of *E/Z* mixtures.

As illustrated in Table 2, substrates bearing a range of unsaturated carbonyl groups undergo catalytic AROM/CM, providing *E* alkene products in up to 98% ee. Several additional points are noteworthy: (1) Terminal (entry 1), trisubstituted (entries 2–4), and cyclic (entries 2, 3) olefins have a significant positive effect on enantioselectivity. (2) Minor *Z* olefin isomers are generated in lower ee (entries 2–4 and 6), with the *R* isomer predominating (same as

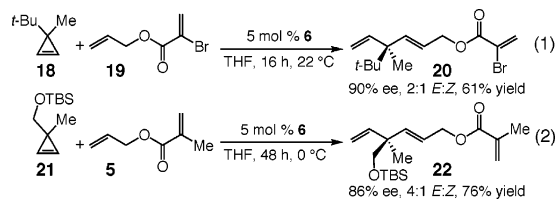
Table 2. Ru-Catalyzed AROM/CM Reactions of Cyclopropene **1**^a

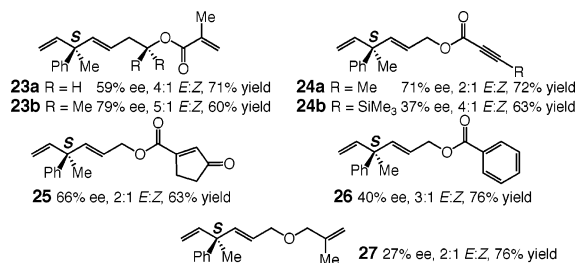
entry	product	yield (%) ^b	<i>E:Z</i> ^c	ee (%) ^d , config.; <i>E</i> (ee (%), config.; <i>Z</i>) ^d
1	11	71	4.5:1	85, <i>S</i>
2	12	72	5:1	90, <i>S</i> [47, <i>R</i>]
3	13	83	3:1	87, <i>S</i> [39, <i>R</i>]
4	14	63	6:1	82, <i>S</i> [31, <i>R</i>]
5	15	80	7:1	98, <i>S</i>
6	16	69	6:1	98, <i>S</i> [51, <i>R</i>]
7	17	65	4:1	86, <i>S</i>

^a Conditions: see Table 1. ^b Isolated yields of *E* and *Z* mixtures; all conversions >98%. ^c ¹H NMR analysis. ^d Chiral HPLC analysis (see the Supporting Information); assignment refers to major enantiomer.

7–8). (3) As indicated by the formation of **17** (86% ee, entry 7), an alkyne can influence a catalytic AROM/CM. (4) In addition to allowing access to products of high enantiomeric purity, coordinating groups can be used for further functionalization (e.g., conjugate additions, catalytic cross-metathesis or **15–16** in catalytic cross coupling). (5) In all instances, <2% of cyclic lactones from RCM of the diene cross partners is detected (400 MHz ¹H NMR). (6) Reactions are only slightly less selective at 22 °C (e.g., **13** is obtained in 83% ee, 3:1 *E/Z*, 71% yield). (7) Products shown in Table 1 can, in principle, be obtained by catalytic asymmetric cross-metathesis⁴ of 1,4-pentadienes bearing an all-carbon quaternary stereogenic center at the allylic C3 position. Such processes, however, would likely be inefficient, since the allylic all-carbon quaternary center renders the requisite acyclic substrates unreactive—a complication resolved by the strain of cyclopropenes.

Other cyclopropenes can be used (eqs 1 and 2); **18** and **21** undergo reaction to afford **20** and **22** in 90% and 86% ee, respectively. Three of the substituents of the stereogenic center in **22** are amenable to further functionalization. Products are hydro-



Scheme 1. Probing the Origins of the Directing Effect^a

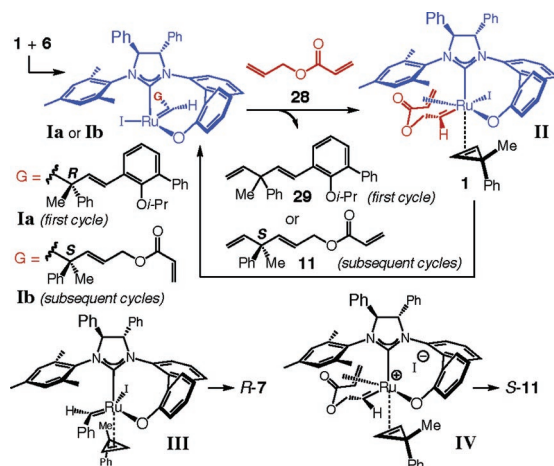
^a Same conditions as shown for Tables 1 and 2.

lyzed (aq LiOH, THF; 85–98% yield) to afford the corresponding alcohols; *E* and *Z* allylic alcohols are separated by chromatography to afford pure *E* olefins.

A rationale regarding the above findings relates to the affinity of NHC-coordinated Ru for enoates and ynoates.⁹ This scenario is supported by the observation that in the presence of 10 mol % PPh₃, AROM/CM of **1** and **5** (>98% conversion 48 h) leads to *S*-**10** in 40% ee (vs 85% ee). The phosphine can compete for Ru binding (reversible) with the resident enoate; alternatively, PPh₃ may conjugatively add (also reversible) to the enoate, thus diminishing Ru complexation.¹⁰ Such a model (**II** and **IV**, Scheme 2) suggests that chelation of a more distal enoate would be entropically less favored. Homologous triene **23a** is thus formed in 59% ee, and **23b**, which benefits from the organizing effects of a *gem*-dimethyl, is obtained in 79% ee. Also consistent is that the increase in the size of ynoate substituents leads to lower ee: in contrast to alkyne **17** (entry 7, Table 2; 86% ee), Me- and Si-substituted **24a** and **24b** are formed in 71% and 37% ee, respectively.

The involvement of Ru-enoate chelation suggests that ligand-to-metal donation as well as Ru → enoate back-bonding¹¹ is critical. Significant reduction of π Lewis basicity thus discourages enoate-Ru chelation and lowers ee: γ -ketoester *S*-**25** is formed in 66% ee (vs **12** in 90% ee). Similarly, when the distal alkene is the less Lewis basic (η^2) phenyl group, (*S*)-**26** is generated in 40% ee. Strong diminution of π Lewis acidity can also be detrimental to selectivity: diallyl ether *S*-**27** (Scheme 1) is obtained in 27% ee (vs 85% ee for *S*-**10**). The exceptionally high ee observed for vinylbromides (entries 5, 6, Table 2), particularly **15** (98% ee), may be partly due to the halogen serving as a σ -donor (i.e., Br → Ru chelation). Halogen-metal chelation is particularly favorable with *d*⁶ octahedral complexes (e.g., **II** in Scheme 2).¹² Studies to clarify this possibility are in progress.

Preliminary mechanistic models are presented in Scheme 2. The catalytic cycle is initiated by the reaction of **6** with **1**, affording

Scheme 2. Preliminary Mechanistic Models

Ia.¹³ Because of the bidentate NHC, formation of **Ia** (and **29**)¹⁴ or **Ib** via a metallacyclobutane¹⁵ proceeds with inversion at the Ru center.¹⁶ Reaction of **Ib** with a diene cross partner (e.g., **28**) gives **II** (Ru inversion). Enoate coordination¹⁷ affords a *Z* carbene, causing the approach of cyclopropene proximal to the biphenylate ligand (alternative mode blocked by the chelated olefin), with the smaller Me pointing syn to the complex.¹⁸ Reaction of **1** with **II** results in another Ru inversion and initiates a fresh catalytic cycle. Benzylidene **III** (**Ia** + styrene) reacts via an *E* carbene, causing **1** to approach from the less hindered direction, leading to the opposite sense of enantioselectivity (e.g., *R*-7). The minor *E* alkene enantiomers, *Z* olefins, and aliphatic **8** likely arise through *non-coordinated* variants of **II** and **III** (i.e., via *E* and *Z* carbenes, as the barrier to carbene rotation is low).¹⁷

Chelation with Ru may involve a η^2 or η^4 complexation; the latter mode could entail Ru–I dissociation (**IV** → *S*-**11**) to allow for substrate coordination. Cationic Ru complexes have been shown to serve as olefin metathesis catalysts.¹⁹ The lability of Ru–halogen bonds finds support in facile conversion of Ru chlorides to iodides,^{2,6} and a recent study²⁰ illustrates that with the achiral Ru complexes bearing a bidentate carbene,²¹ halogen ligands readily exchange at 22 °C.

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Supporting Information Available: Experimental procedures and spectral and 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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