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

Russell E. Giudici and Amir H. Hoveyda*

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467

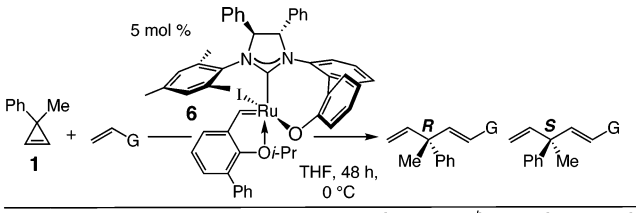
Received January 10, 2007; E-mail: amir.hoveyda@bc.edu

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

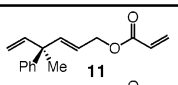
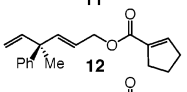
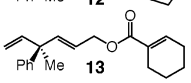
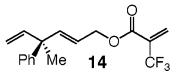
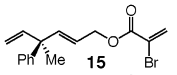
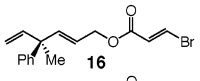
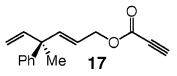


entry	G	product	*E*:*Z*[a]	yield (%)[b]	*R*:*S*[a]	ee (%)[a]
1	**2** G = Ph	**7**	>20:1	90	***96.5:3.5***	***93***
2	**3** G = *n*-hex	**8**	1.5:1	59	59.5:40.5	17
3	**4** G = CH_2OCOi-Pr	**9**	3:1	59	35:65	30
4	**5** G = $CH_2OCO(Me)C{=}CH_2$	**10**	5:1	77	***7.5:92.5***	***85***

[a] Determined by chiral HPLC analysis; selectivity of *E* olefin products. [b] Isolated yields of *E*/*Z* mixtures.

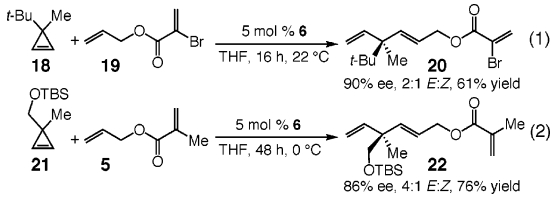
As illustrated in Table 2, substrates bearing a range of unsaturated carbonyl groups undergo catalytic AROM/CM, providing *E* alkene products in up to 98% ee. Several additional points are noteworthy: (1) Terminal (entry 1), trisubstituted (entries 2−4), and cyclic (entries 2, 3) olefins have a significant 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 **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 ^{1}H 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-metathesis[4] 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.

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

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

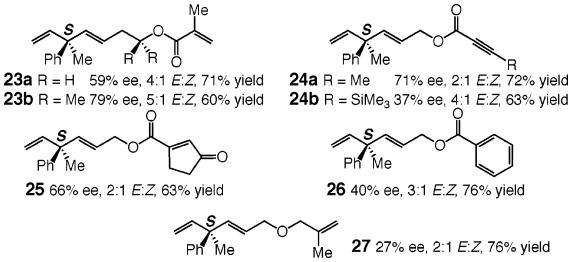
[a] Conditions: see Table 1. [b] Isolated yields of *E* and *Z* mixtures; all conversions >98%. [c] ^{1}H NMR analysis. [d] Chiral HPLC analysis (see the Supporting Information); assignment refers to major enantiomer.

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-



10.1021/ja070187v CCC: $37.00

Scheme 1. Probing the Origins of the Directing Effect[a]



[a] Same conditions as shown for Tables 1 and 2.

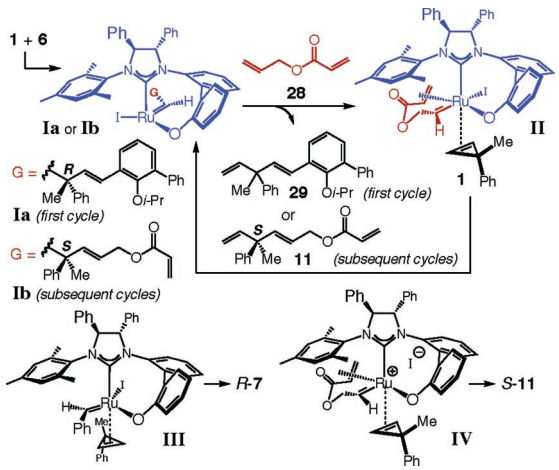
lyzed (aq LiOH, THF; 85−98% yield) to afford the corresponding alcohols; *E* and *Z* allylic alcohols are separated by chromatography to afford pure *E* olefins.

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 % PPh_3, 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, PPh_3 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-bonding[11] 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 metallacyclobutane[15] proceeds with inversion at the Ru center.[16] Reaction of **Ib** with a diene cross partner (e.g., **28**) gives **II** (Ru inversion). Enoate coordination[17] 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 study[20] 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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